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Trace element status in type 2 diabetes: A meta-analysis

Namrata Sanjeevi,

Postdoctoral Fellow, Health Behavior Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, 6710B Rockledge Drive Room 3165A, MSC 7004, Bethesda, MD 20817, USA, namratas@utexas.edu

Jeanne Freeland-Graves,

Department of Nutritional Sciences, The University of Texas at Austin, 1 University Station A2703, Austin, TX 78712, USA, jfg@mail.utexas.edu

S. Natasha Beretvas, and

Department of Educational Psychology, The University of Texas at Austin, 1 University Station D5800, Austin, TX 78712, USA, tberetvas@austin.utexas.edu

Prageet K. Sachdev

Department of Nutritional Sciences, The University of Texas at Austin, 1 University Station A2703, Austin, TX 78712, USA, prageet@utexas.edu

Abstract

Introduction—Type 2 diabetes is a chronic metabolic disorder that has been associated with alterations in the status of trace elements, including zinc, copper, iron and manganese. However, clinical studies reporting statuses of these trace elements in type 2 diabetes patients compared to controls have shown conflicting results.

Objective—This meta-analysis aimed to summarize the existing literature on the statuses of zinc, copper, iron, and manganese in Type 2 diabetes mellitus patients.

Methods—A literature search of Embase, PubMed, EBSCOHost, ScienceDirect, Scopus, Cochrane library and Web of Science electronic databases was conducted to find studies published from 1970 to November 2016 that compared the trace elements of interest between type 2 diabetic patients and healthy controls. Keywords used were type 2 diabetes, diabetes, hyperglycemia, insulin, glucose, HbA1c, trace elements, micronutrients, zinc, manganese, copper, ceruloplasmin, iron and ferritin. The bias corrected Hedges' g, was utilized as the effect sizes. Due to the biological interaction between trace elements, it is important to collectively evaluate the statuses of these minerals in type 2 diabetes. Thus, the robust variance estimation method was chosen to handle dependency between multiple outcomes.

Correspondence to: Jeanne Freeland-Graves.

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Results—A total of 52 studies met the inclusion criteria, amounting to 98 effect sizes. Diabetic patients (n=20183) had significantly lower zinc status when compared to controls (effect size = −1.73, p<0.01); whereas copper (effect size = 1.10, p<0.05) and ferritin levels (effect size = 1.05, p<0.01) were significantly higher. Although not significant, ceruloplasmin (effect size = 1.85, p=0.06) and iron (effect size = 1.42, p=0.06) levels were higher, and manganese (effect size = 0.27, p=0.34) was lower in patients.

Conclusion—Results from this meta-analysis indicate lower zinc status accompanied by increased copper and ferritin levels in patients with type 2 diabetes when compared to controls.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that arises due to absolute or relative lack of insulin production by the beta-cells of the pancreas. Impaired secretion of this protein affects glucose metabolism, and consequently, results in hyperglycemia. (1) Unregulated levels of blood glucose can lead to several debilitating conditions such as nephropathy, neuropathy, retinopathy, cardiovascular disease, stroke, and amputations of extremities.(2) About 90 to 95% of the patients are affected by type 2 diabetes (2) which is characterized primarily by insulin resistance, hyperinsulinemia, and beta-cell dysfunction.(3)

Trace elements facilitate numerous biochemical reactions (4), including those related to insulin and glucose metabolism. The transport of zinc into the beta-cells of the pancreas is essential for insulin production and its efficient packaging into vesicles.(5) Moreover, zinc finger protein 407 (6) and zinc-alpha2-glycoprotein (7, 8) have been shown to enhance the expression of the Glucose transporter type 4 (GLUT 4) protein in adipocytes and skeletal muscles, thereby mediating insulin-induced glucose uptake into these cells. Manganese is another trace element involved in carbohydrate metabolism.(9) Animal studies have indicated an association of manganese with optimal insulin synthesis and secretion.(10) Manganese also increases the binding of insulin to its receptor, thereby facilitating the physiological action of this hormone.(11) In a study conducted by Baly et al., manganese deficient rats had diminished insulin-stimulated glucose oxidation in the adipose tissue, and fewer insulin receptors compared to controls.(12) In contrast, elevated levels of copper (13) and iron (14, 15) have been linked to increased oxidative stress, which in turn could lead to insulin resistance, impaired glucose tolerance, and type 2 diabetes.(16) Consistently, greater copper and iron statuses have been associated with increased insulin resistance in humans. (17, 18) Thus, copper and iron also are important while investigating trace element status in type 2 diabetes.

Research comparing zinc, manganese, copper and iron levels between type 2 diabetes patients and healthy individuals have reported inconsistent results. For example, some studies have indicated greater levels of these trace elements in type 2 diabetes patients compared to controls (4, 19, 20); whereas other investigations have demonstrated reduced status. (20–25) Thus, this meta-analysis aimed to summarize the existing literature on difference in zinc, manganese, copper and iron levels between type 2 diabetic and nondiabetic individuals. Ceruloplasmin and ferritin levels were additionally utilized to indicate copper and iron statuses, respectively. It is hypothesized that diabetic patients will

have lower zinc and manganese concentrations, and elevated copper and iron statuses compared to nondiabetic controls.

A secondary goal of this research is to explore the influence of age, body mass index (BMI) and gender on the primary outcomes of interest by a moderator analysis. It is well established that age > 45 years, (26) gender (27) and overweight/ obesity (28) may influence trace element concentrations in humans, and are associated with a higher incidence of type 2 diabetes.(29–31) Moreover, the presence of fat depots around organs has been reported to negatively impact the status of minerals when compared to subcutaneous fat. Consequently, gender may influence the development of type 2 diabetes since the incidence of visceral adiposity is higher in men as compared to women.(32)

MATERIAL AND METHODS

Search Strategy

A literature search of Embase, PubMed, EBSCOHost, ScienceDirect, Scopus, Cochrane library and Web of Science electronic databases was conducted to identify studies published between 1970 and November 2016 investigating trace element concentrations in type 2 diabetes mellitus patients and healthy controls. Keywords used were type 2 diabetes, diabetes, hyperglycemia, insulin, glucose, HbA1c, trace elements, micronutrients, zinc, manganese, copper, ceruloplasmin, iron and ferritin.

Data Extraction

Two investigators independently carried out the literature search and recorded the data in the database. The studies recorded by each investigator were then matched to remove duplicate studies. The titles and abstracts were read for each retrieved record to select studies meeting the inclusion criteria. The reference lists of all the retrieved studies also were reviewed by each investigator to minimize the chance of missing relevant studies.

Inclusion and Exclusion Criteria

The inclusion criteria for the studies that were retrieved using the search terms were: a) use of a cross-sectional or case-control design b) reporting of plasma/ serum values of zinc/ copper/ ceruloplasmin/ iron/ ferritin/ manganese of type 2 diabetic patients and healthy controls and b) absence of any diabetes-related complications in patients.

Studies were excluded if: a) they reported statistics jointly for patients with and without complications in type 2 diabetes group; b) the text was not available in English; and c) adequate information was not available in the text to calculate effect sizes.

All articles were assessed based on the inclusion/exclusion criteria and any disagreements were resolved by discussion with a nutrition professor having expertise in field of trace elements.

Statistical analysis

The author, year and country for investigations that met the inclusion criteria were identified. The primary outcome, status of trace elements (zinc, copper, iron and manganese), in the control and diabetic groups were extracted. Other characteristics included for the analysis were type of biomarker (serum/plasma), age, BMI, and percentage of men in the control and diabetic arms. Difference in BMI between the control and diabetic groups was documented. The weighted average of age and proportion of males were determined, with the number of participants in each group representing the weights.

The primary studies reported trace element status in varying units of concentrations. Thus, a standardized mean difference, the bias corrected Hedges' *g*, (33) was utilized as the effect size for the meta-analysis. The hypothesis to be tested was that the status of zinc and manganese would be lower in diabetic subjects, whereas that of copper, ceruloplasmin, and iron and ferritin would be higher. Since these trace elements have been shown to interact with each other, the use of a univariate model to determine their effect sizes could inflate Type I error rates. Methods utilized to handle dependency of multiple related outcomes in meta-analysis included robust variance estimation (RVE) method and generalized least squares (GLS) estimation. Unlike GLS estimation, the RVE approach does not require use of the correlations between pairs of multivariate outcomes. Thus, the RVE method was chosen for this meta-analysis due to the lack of reporting of correlations between trace elements in the primary studies.

Computations in the ensuing section were performed using the Statistical Package for Social Sciences (SPSS Version 22, Armonk, NY, 2013). The standard deviations of the trace element biomarker values in the control and diabetic groups, and the associated sample sizes were used to calculate the pooled sample variances. Trace element values of the diabetic subjects were subtracted from the controls when calculating effect sizes. Negative effects indicated that the trace element levels were lower in the diabetic arm as compared to the nondiabetic control. The resulting differences were divided by the pooled sample variances to compute Hedges *g*, to which the small-sample bias correction was applied. Bias-corrected Hedges *g*, thus obtained, represented the effect size for each study. The variance and 95% confidence intervals estimates for the effect sizes were calculated using the associated standardized mean difference and sample sizes in each group.

The statistical software, R with macro robumeta, were used to calculate the pooled average effect size and variance using the RVE method to apply Tipton's (34) small sample bias correction. Statistics reported were 95% CIs, and two-sided Z-statistic to assess the statistical significance of the pooled average effect size. The effects of type of biomarker, age, difference in BMI, and percent males were evaluated by including these variables in the mixed-effects, meta-regression model. Publication bias was assessed by visualization of funnel plots. The I^2 statistic was used to assess heterogeneity across studies. Cut-off values of 0, 25, 50 and 75% indicated no, low, moderate and high heterogeneity. A symmetrical funnel plot evidence for lack of publication bias in the meta-analysis. The Egger's regression test also was performed, with $p<0.05$ suggesting significant publication bias.

RESULTS

Literature search

Table/Figure 1 illustrates the flow diagram of the screening involved in the selection of articles for the meta-analysis. A total of 97 articles were retrieved, with a final number of 52 case-control studies (1, 4, 19, 20, 22–25, 35–79) with 20183 participants were included in the meta-analysis.

Summary of included studies

The characteristics of the included studies are presented in Table/Figure 2. The number of included studies reporting values for zinc, copper, ceruloplasmin, iron, ferritin, and manganese were 25, 20, 12, 9, 16 and 7, respectively. A few investigations reported mean trace element levels separately for men and women, thereby resulting in two effect sizes per study. Thus, the total number of effect sizes for zinc, copper, ceruloplasmin, iron, ferritin and manganese were 27, 21, 12, 10, 19 and 9, respectively.

Pooled average effect size for zinc, copper, ceruloplasmin, iron, ferritin and manganese

The Forest plots in Tables/Figures 3–8 depict the average pooled effect size, 95% CI and statistical significance for zinc, copper, ceruloplasmin, iron, ferritin and manganese, respectively. For investigations that report separate values for men and women, a weighted average of the effect size was calculated with the number in each gender as weights. Zinc levels were significantly lower in type 2 diabetic subjects when compared to non-diabetic individuals (pooled effect size = −1.73, $p<0.01$), whereas that for copper (pooled effect size = 1.10, $p<0.05$) and ferritin (pooled effect size = 1.05, $p<0.05$) were significantly higher. Patients diagnosed with type 2 diabetes also had higher values for ceruloplasmin (pooled effect size = 1.85, $p=0.06$) and iron (pooled effect size = 1.42, $p=0.06$), but lower manganese concentrations (pooled effect size = −0.27, $p=0.34$) than nondiabetic controls. However, these effect sizes were not significant. The I^2 statistic for the meta-analysis was 97.6%.

Moderator analysis

The influence of biomarker type for quantification of trace element status, age, gender and BMI on effect size were carried out as separate, additional analyses. The weighted average of age and percentage of men were used to represent age and gender, respectively, with the number of individuals in the control and diabetic groups serving as the weights. The weighted mean of the difference in BMI also was used as a moderator.

Z-statistics for testing the type of biomarker, age, gender and BMI as moderator effects were −0.504, −0.219, 0.982, and 0.459 respectively. Furthermore, none of the moderators had a significant influence on any of the effect sizes.

Publication bias

Figure 8 indicates a fairly symmetrical funnel plot. Furthermore, the Egger's regression showed no evidence for significant publication bias in the included studies.

DISCUSSION

This meta-analysis found that zinc and manganese concentrations were lower in type 2 diabetic individuals compared to nondiabetic controls; while levels of copper, ceruloplasmin, iron and ferritin were higher. However, the bias-corrected Hedges *g* was not significant for ceruloplasmin, iron and manganese. The inconsistent findings between copper and ceruloplasmin, and iron and ferritin could due to difference in the number of studies investigating levels of these biomarkers. It is important to note that the greatest effect size was observed for ceruloplasmin, followed by iron. The smaller number of studies reporting ceruloplasmin and iron values could have resulted in lower statistical power, and subsequently, non-significant effect sizes. The use of plasma vs serum, age, BMI, and gender did not significantly influence the effect sizes in the present meta-analysis.

The results of this meta-analysis suggest possible zinc deficiencies and elevated copper and iron (as indicated by ferritin) statuses in type 2 diabetic individuals. The findings are comparable to previous research which demonstrates abnormal metabolism of zinc in type 2 diabetes patients, marked by malabsorption and increased urinary losses of this micronutrient.(80) Further, the greater ceruloplasmin (40, 81) and lower transferrin (40) levels observed in type 2 diabetic individuals could result in elevated levels of free copper and iron, respectively. Increased levels of these transition metals have been linked to greater oxidative stress,(82) and subsequently, increased insulin resistance and type 2 diabetes (16). The concomitant decrease in trace elements that function as antioxidants, such as zinc (83) and manganese, (84, 85) may cause an impaired scavenging mechanism of free radicals, and may further exacerbate the prognosis of diabetes. Collectively, these results indicate the need for cohort studies to explore the role of these trace elements in the progression of type 2 diabetes.

The results of this meta-analysis are subject to certain limitations. Since the meta-analysis did not include longitudinal studies, it is not possible to establish causal inferences on the association between altered trace element status and type 2 diabetes. Another limitation is that the results could have been influenced by exclusion of articles that lacked availability of text in English. Further, the high level of heterogeneity in this meta-analysis could have affected the validity of the overall pooled effect size estimate. Nevertheless, the analysis is strengthened by the use of a model that handles dependency between multiple outcomes.

CONCLUSION

In conclusion, this meta-analysis found altered levels of trace minerals in type 2 diabetes patients in comparison with controls. Inadequate zinc and a concurrent excess of copper and iron levels may be associated with an increased level of oxidative stress, and may exacerbate the condition. Longitudinal studies could help in understanding the association between trace element variations and onset and progression of type 2 diabetes.

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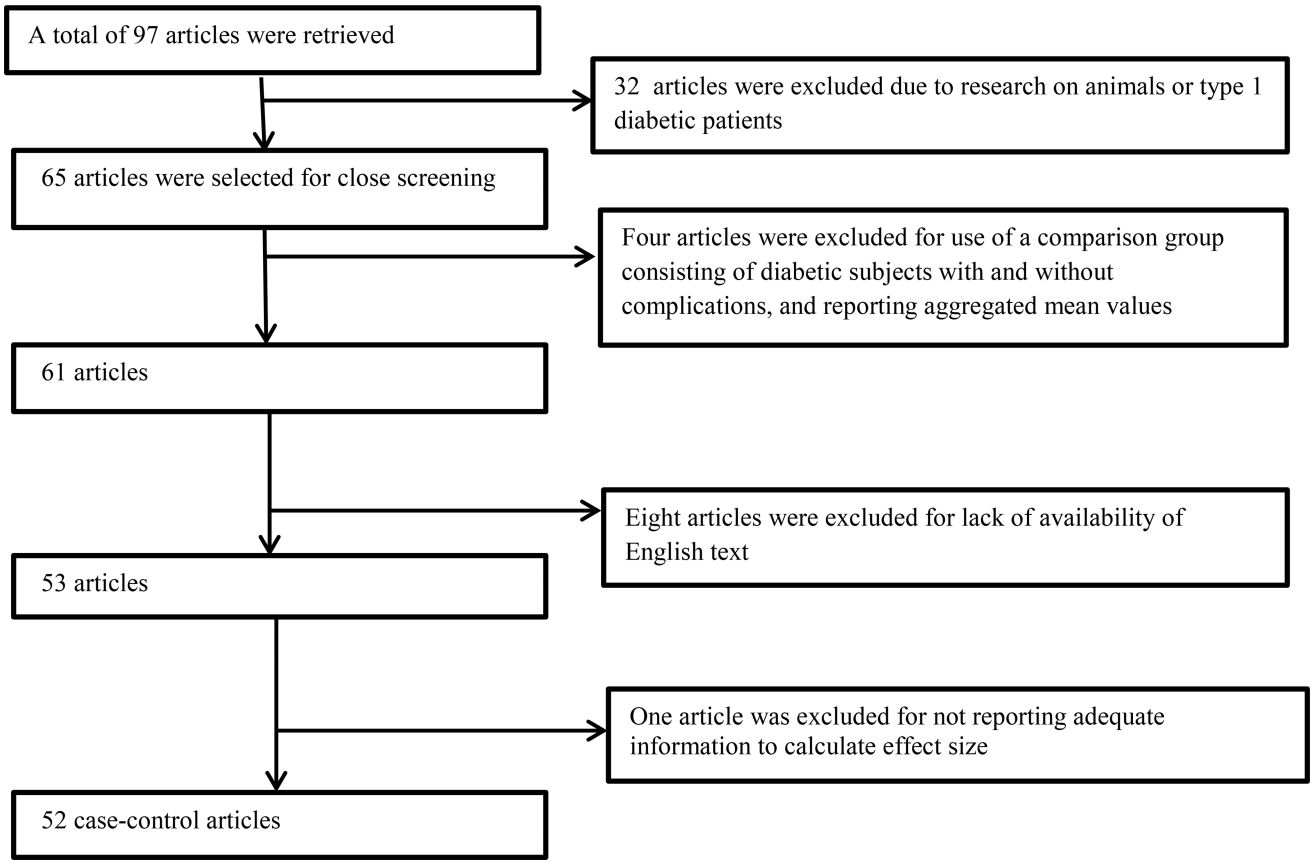

Figure 1.
Flow diagram of the screening process involved in inclusion of articles

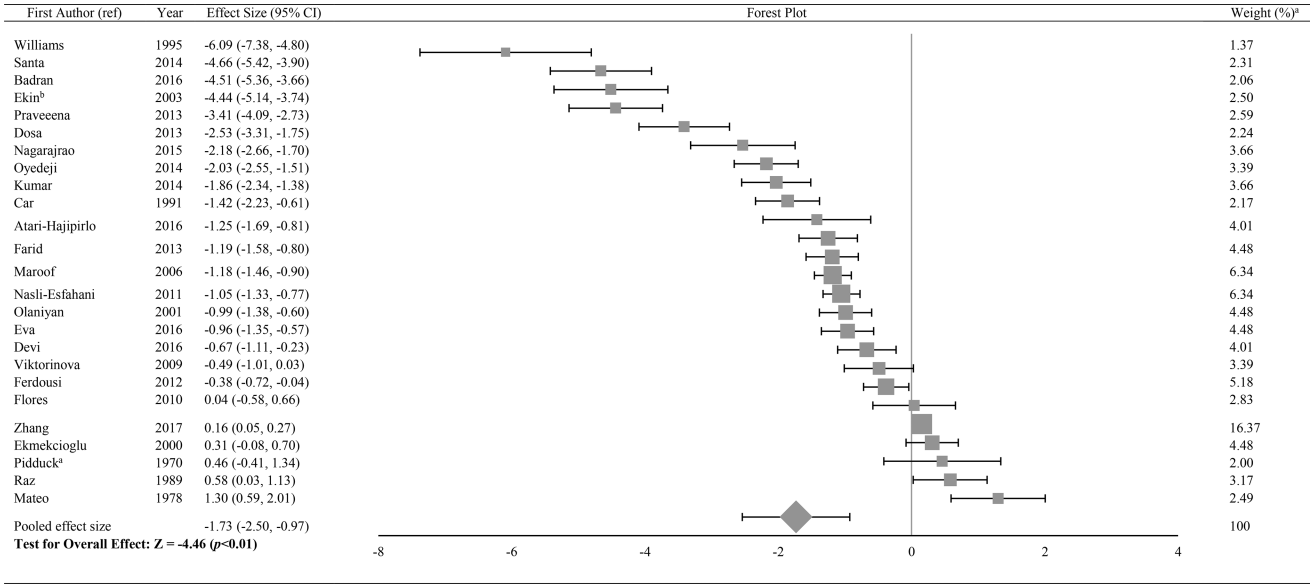

Figure 2.

Forest plot of effect size estimates and its 95% confidence intervals representing difference in zinc levels between healthy and diabetic subjects

[a]The weight of each study indicates its influence on the pooled effect size. A higher percentage weight is shown by a larger box and narrower confidence interval for the respective study in the forest plot

[b]Data represented as weighted average of the effect size for men and women

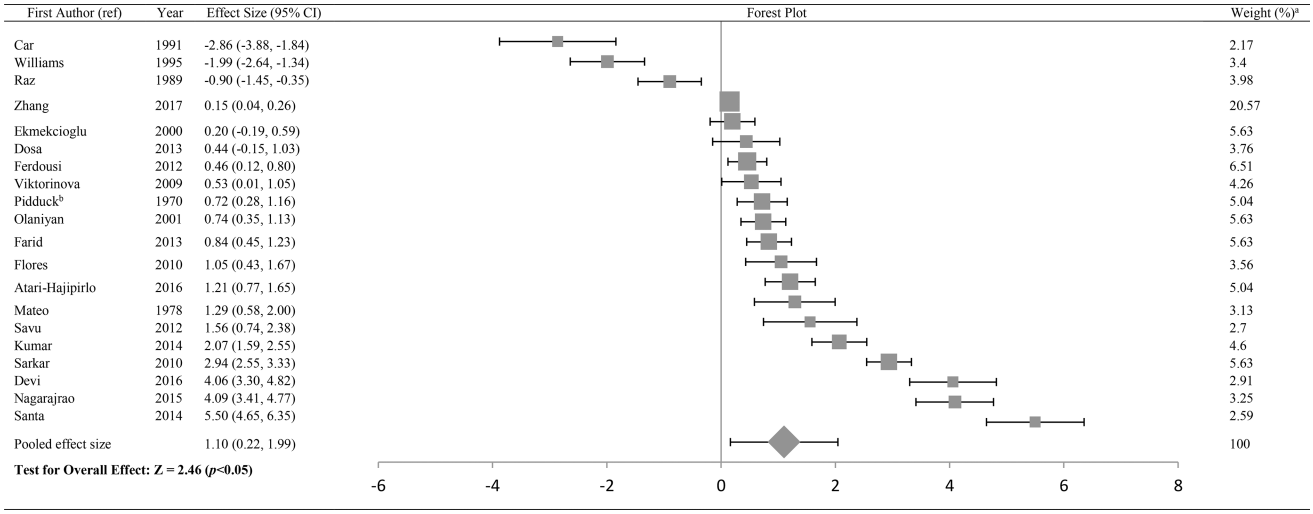

Figure 3.

Forest plot of effect size estimates and its 95% confidence intervals representing difference in copper levels between healthy and diabetic subjects

[a]The weight of each study indicates its influence on the pooled effect size. A higher percentage weight is shown by a larger box and narrower confidence interval for the respective study in the forest plot

[b]Data represented as weighted average of the effect size for men and women

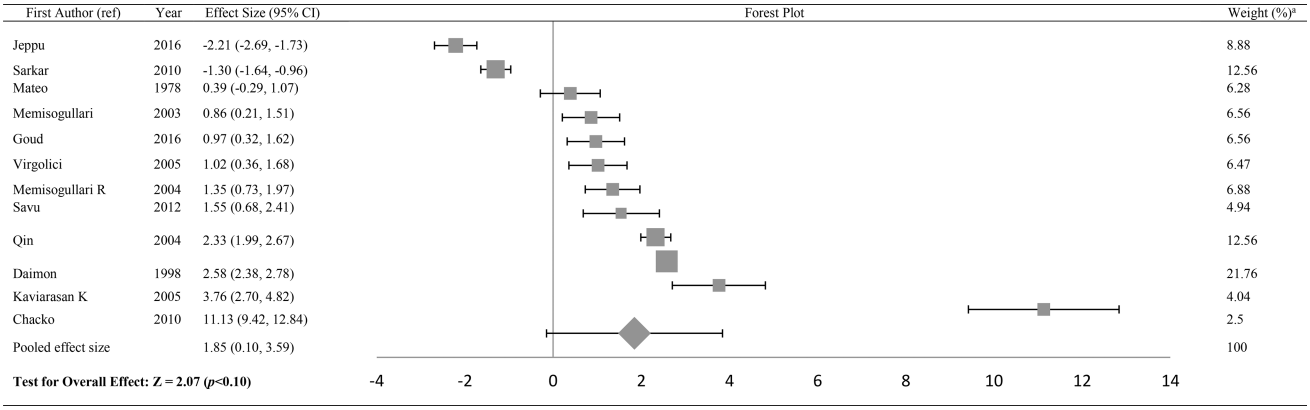

Figure 4.

Forest plot of effect size estimates and its 95% confidence intervals representing difference in ceruloplasmin levels between healthy and diabetic subjects

[a]The weight of each study indicates its influence on the pooled effect size. A higher percentage weight is shown by a larger box and narrower confidence interval for the respective study in the forest plot

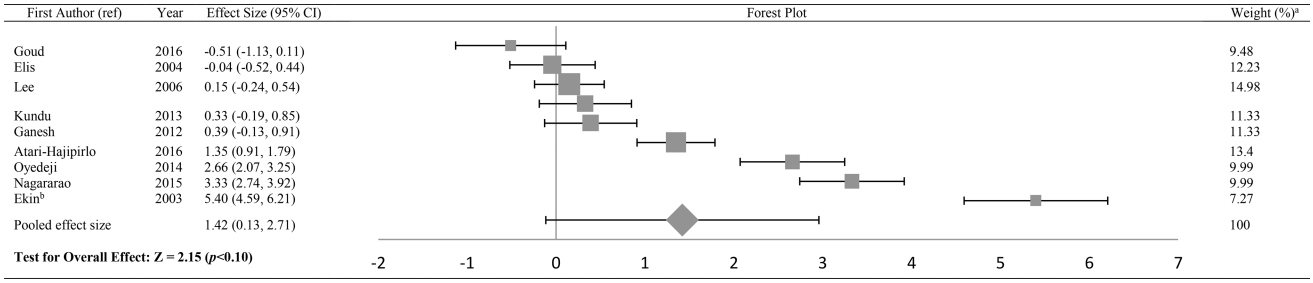

Figure 5.

Forest plot of effect size estimates and its 95% confidence intervals representing difference in iron levels between healthy and diabetic subjects

[a]The weight of each study indicates its influence on the pooled effect size. A higher percentage weight is shown by a larger box and narrower confidence interval for the respective study in the forest plot

[b]Data represented as weighted average of the effect size for men and women

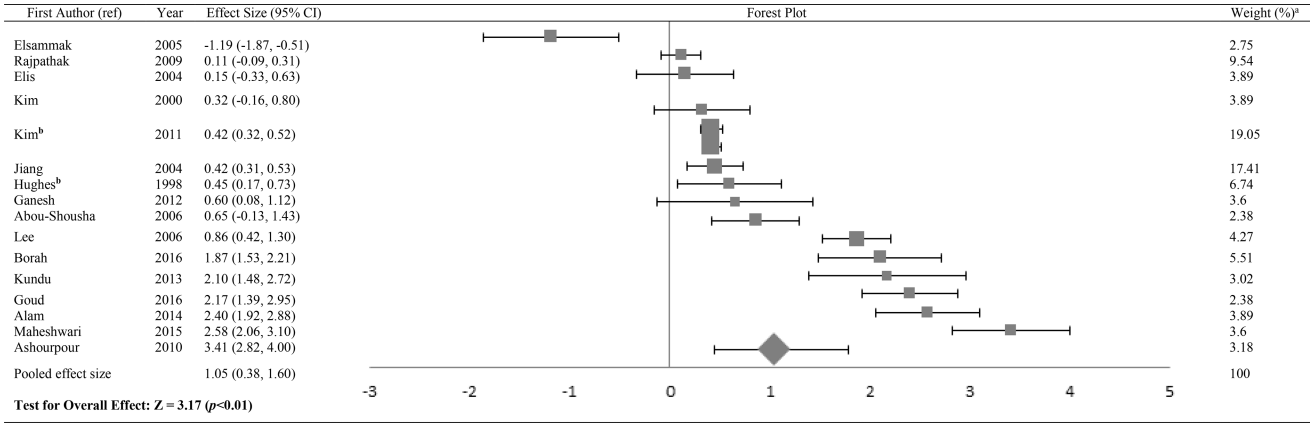

Figure 6.

Forest plot of effect size estimates and its 95% confidence intervals representing difference in ferritin levels between healthy and diabetic subjects

[a]The weight of each study indicates its influence on the pooled effect size. A higher percentage weight is shown by a larger box and narrower confidence interval for the respective study in the forest plot

[b]Data represented as weighted average of the effect size for men and women

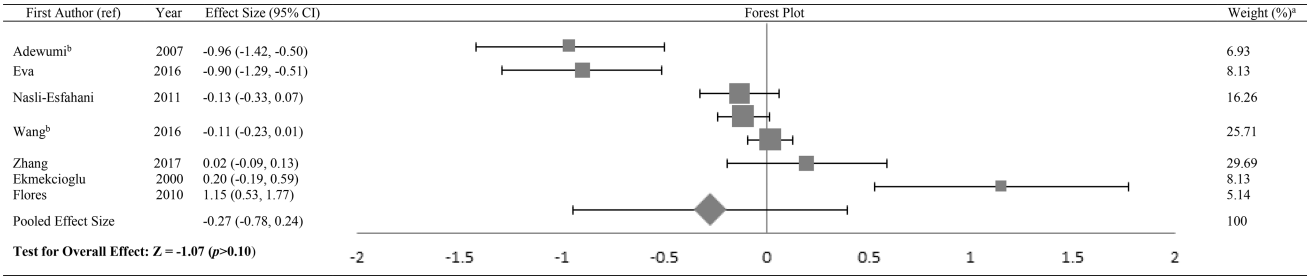

Figure 7.

Forest plot of effect size estimates and its 95% confidence intervals representing difference in manganese levels between healthy and diabetic subjects

[a]The weight of each study indicates its influence on the pooled effect size. A higher percentage weight is shown by a larger box and narrower confidence interval for the respective study in the forest plot

[b]Data represented as weighted average of the effect size for men and women

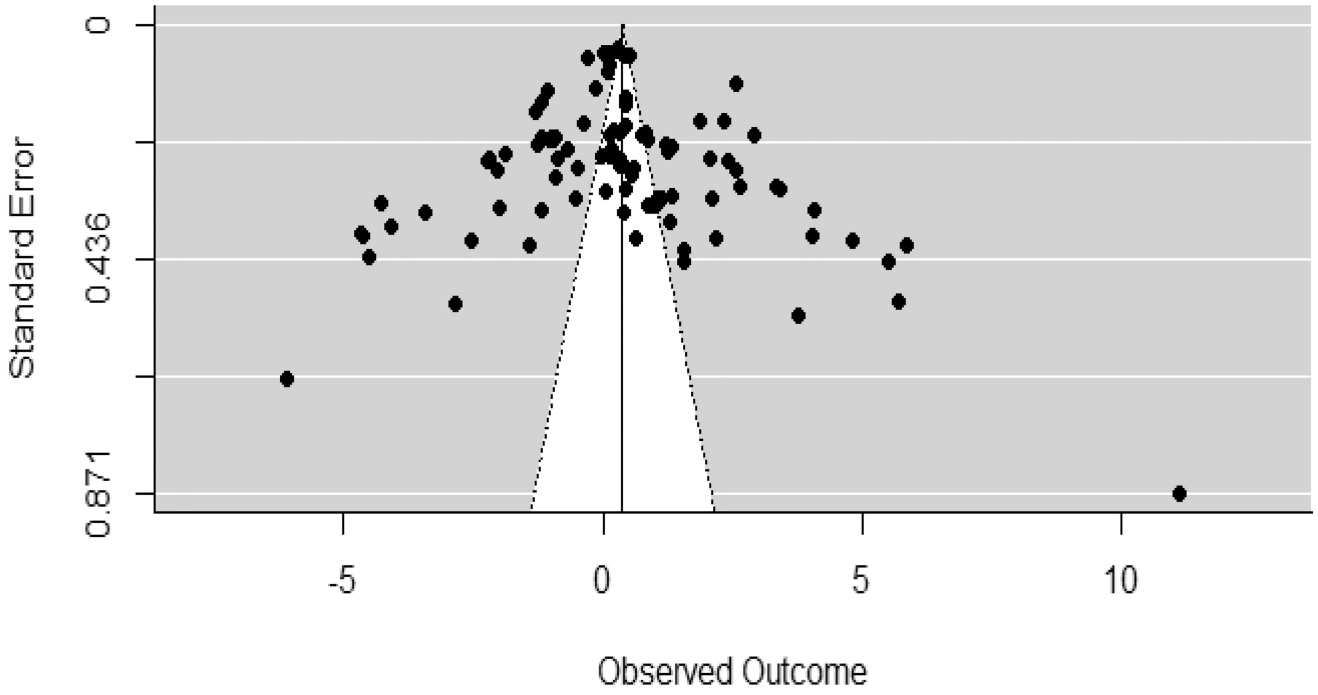

Figure 8.
Funnel plot

Table 1

Characteristics of studies included

First Author	Year	Country	Biomarker	Age[a]	Proportion of males[a]	Difference in body mass index[b]	Sample size		Effect size					
							Control	Diabetic	Zinc	Copper	Ceruloplasmin	Iron	Ferritin	Manganese
Pidduck	1970	England	Plasma	52.95	100	_[c]	40	36	5.71	0.18	--	--	--	--
Pidduck	1970	England	Plasma	57.43	0	--	46	42	-4.07	1.26	--	--	--	--
Mateo	1978	Spain	Serum	--	--	--	10	49	1.2	1.29	0.39	--	--	--
Raz	1989	Israel	Serum	50.51	49.15	1.7	21	38	0.58	-0.9	--	--	--	--
Car	1992	Yugoslavia	Serum	45.5	46.67	4.3	15	15	−1.42	−2.86	--	--	--	--
Williams	1995	UK	Plasma	51.55	46.15	--	26	26	−6.09	−1.99	--	--	--	--
Hughes	1998	Singapore	Serum	--	100	1.3	248	72	--	--	--	--	0.44	--
Hughes	1998	Singapore	Serum	--	0	1.5	282	54	--	--	--	--	0.46	--
Daimon	1998	Japan	Serum	57.05	--	--	158	637	--	--	2.58	--	--	--
Ekmekcioglu	2000	Austria	Plasma	67.05	--	0	50	53	0.31	0.2	--	_[d]	--	0.2
Kim	2000	Korea	Serum	57.03	46.67	2.4	25	50	--	--	--	--	0.32	--
Olaniyan	2001	Nigeria	Serum	57.03	39.81	--	50	53	−0.99	0.74	--	--	--	--
Ekin	2003	Turkey	Serum	56.98	0	1.2	29	108	−4.27	_[d]	--	5.86	--	_[d]
Ekin	2003	Turkey	Serum	56.28	100	1.6	21	92	−4.64	_[d]	--	4.83	--	_[d]
Memisogullari	2003	Turkey	Serum	--	--	--	18	21	--	--	0.86	--	--	--
Memisogullari	2004	Turkey	Serum	54.49	--	--	21	29	--	--	1.35	--	--	--
Qin	2004	China	Serum	--	--	--	110	104	--	--	2.33	--	--	--
Elis	2004	Israel	Serum	63	40.59	--	40	29	--	--	--	−0.04	0.15	--
Jiang	2004	USA	Plasma	56.45	0	4.1	716	698	--	--	--	--	0.42	--
Elsammak	2005	Egypt	Serum	--	--	--	18	22	--	--	--	--	−1.19	--
Kaviarasan	2005	India	Plasma	54.24	--	5.21	18	20	--	--	3.76	--	--	--
Virgolici	2005	Romania	Plasma	53.4	50	11.4	20	20	--	--	1.02	--	--	--
Al-Maroof	2006	Iraq	Serum	45.73	--	1.69	133	101	−1.18	--	--	--	--	--
Abou-Shousha	2006	Egypt	Serum	48.52	0	--	10	20	--	--	--	--	0.65	--
Lee	2006	Korea	Serum	58.6	67.35	--	47	48	--	--	--	0.15	0.86	--
Adewumi	2007	Nigeria	Serum	46.67	100	6.25	50	28	--	_[d]	--	--	--	−0.89

First Author	Year	Country	Biomarker	Age[a]	Proportion of males[a]	Difference in body mass index[b]	Sample size		Effect size					
							Control	Diabetic	Zinc	Copper	Ceruloplasmin	Iron	Ferritin	Manganese
Adewumi	2007	Nigeria	Serum	44.12	0	3.43	40	62	--	--[d]	--	--	--	−1.03
Viktorinova	2009	Slovak	Plasma	42.49	47.46	0.55	34	25	−0.49	0.53	--	--	--	--
Rajpathak	2009	USA	Serum	50.3	36.4	1.5	280	280	--	--	--	--	0.11	--
Flores	2010	Mexico	Serum	--	--	--	12	76	0.04	1.05	--	--	--	1.15
Sarkar	2010	India	Plasma	54.39	62.19	--	78	123	--	2.94	−1.3	--	--	--
Ashourpour	2010	Iran	Serum	53.29	--	0.29	53	54	--	--	--	--	3.41	--
Chacko	2010	India	Serum	--	52.87	--	47	40	--	--	11.13	--	--	--
Nasli-Esfahani	2011	Iran	Serum	50.6	34.96	--	151	150	−1.05	--[d]	--	--	--	−0.13
Kim	2011	Korea	Serum	51.27	100	0.8	3384	727	--	--	--	--	0.3	--
Kim	2011	Korea	Serum	50.17	0	2.2	3869	327	--	--	--	--	0.54	--
Ferdousi	2012	Bangladesh	Serum	--	--	5.15	60	60	−0.38	0.46	--	--	--	--
Savu	2012	Romania	Plasma	40.99	41	--	15	15	--	1.56	1.55	--	--	--
Ganesh	2012	India	Serum	42.7	38.35	−1.86	30	30	--	--	--	0.39	0.6	--
Praveeena	2013	India	Serum	--	--	--	40	40	−3.41	--	--	--	--	--
Farid	2013	Saudi Arabia	Serum	59.51	100	--	55	55	−1.19	0.84	--	--	--	--[d]
Dosa	2013	Romania	Plasma	--	--	3.86	17	30	−2.53	0.44	--	--	--	--
Kundu	2013	India	Serum	--	--		30	30	--	--	--	0.33	2.1	--
Santa	2014	India	Serum	--	--	5.42	40	60	−4.66	5.5	--	--	--	--
Oyedeji	2014	Nigeria	Plasma	--	0	--	35	50	−2.03	--[d]	--	2.66	--	--
Kumar	2014	India	Serum	48.5	74	--	50	50	−1.86	2.07	--	--	--	--
Alam	2014	Pakistan	Serum	40.4	--	--	44	67	--	--	--	--	2.4	--
Nagarajrao	2015	Saudi Arabia	Serum	49.43	55.24	0.04	58	47	−2.18	4.09	--	3.33	--	--
Maheshwari	2015	India	Serum	48.28			50	50			--		2.58	
Badran	2016	Egypt	Serum	52.88	57.89	0.96	36	40	−4.51	--[d]	--	--[d]	--	--[d]
Atari-Hajipirlo	2016	Iran	Serum	52.46	53.12	--	50	46	−1.25	1.21	--	1.35	--	--
Wang	2016	China	Serum	67.58	100	0.87	529	289	--	--	--	--	--	0.15
Wang	2016	China	Serum	67.63	0	−2	751	494	--	--	--	--	--	−0.29
Devi	2016	India	Serum	--	47.5	--	40	40	−0.67	4.06	--	--	--	--
Goud	2016	India	Serum	--	--	--	20	20	--	--	0.97	−0.51	2.17	--

First Author	Year	Country	Biomarker	Age[a]	Proportion of males[a]	Difference in body mass index[b]	Sample size		Effect size					
							Control	Diabetic	Zinc	Copper	Ceruloplasmin	Iron	Ferritin	Manganese
Jeppu	2016	Malaysia	Serum	--	--	--	50	50	--	--	−2.21	--	--	--
Borah	2016	India	Serum	53.93	56.5	2.17	92	92	--	--	--	--	1.87	--
Eva	2016	Banglade	Serum	47.79	54	0.36	50	50	−0.96	--	--	--	--	−0.9
Zhang	2017	China	Serum	55.91	34.68	1.2	1327	510	0.16	0.15	--	--	--	0.02

[a] Represents the weighted average where the weights are the number of individuals in control and diabetic groups

[b] Represents the difference in the body mass index between diabetic and control groups

[c] Not reported in the primary study

[d] Data did not meet the inclusion criteria