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The association of serum zinc and copper with hypertension: A meta-analysis

Zhaoying Li, Weijing Wang, Hui Liu, Suyun Li, Dongfeng Zhang*

Department of Epidemiology and Health Statistics, The Medical College of Qingdao University, Qingdao, Shandong Province, China

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ABSTRACT

Objective: The association of serum zinc (Zn), copper (Cu) with the risk of hypertension (HT) remains controversial. Therefore, we conducted a meta-analysis to explore the relationships.

Methods: We searched relevant literatures on PubMed and Web of Science up to September 2018. Pooled standard mean difference (SMD) with corresponding 95% confidence interval (CI) was calculated by random effects model.I^2 was used to evaluate heterogeneity among studies.

Results: 25 articles of serum Zn and 22 articles of serum Cu were included in meta-analysis. HT patients had lower serum Zn [SMD (95%CI): -0.612(-0.951, -0.274), z = 3.54, $P_{for\ z} < 0.001$; $I^2 = 97.0\%$, $P_{for\ I^2} < 0.001$], whereas no significant difference of serum Cu was shown between HT patients and controls [SMD (95%CI): 0.153(-0.101, 0.407)]. Also, male HT patients had lower serum Zn [SMD (95%CI): -1.443(-2.868, -0.017), z = 1.98, $P_{for\ z} = 0.047$; $I^2 = 98.8\%$, $P_{for\ I^2} < 0.001$]. In subgroup analysis, a lower serum Zn was observed in HT patients in studies conducted in Europe [-1.066(-1.759, -0.374)], in case-control studies [-0.718(-1.294, -0.142)], in matched case-control studies [-0.939(-1.646, -0.233)] and studies involving treated patients [-1.416(-2.195, -0.638)]. Meanwhile, a higher serum Cu was found in HT patients in studies conducted in Africa [1.96(1.402, 2.518)], and in matched case-control studies [0.655(0.204, 1.107)].

Conclusion: The present meta-analysis indicates that serum Zn level in HT patients was significantly lower than that in controls, while no significantly different serum Cu level was found between HT patients and controls. Future studies are needed to confirm these results in future research.

1. Introduction

Hypertension (HT), as a public health challenge worldwide, can increase the risk of several diseases, such as chronic renal disease, dementia, stroke or coronary artery disease, etc. [1–5]. HT is considered to be the leading risk factor for death in the world, causing an estimated 7.5 million deaths per year [6,7]. Besides, it is predicted that the number of adults with HT in 2025 will increase by 1.56 billion [8]. Therefore, prevention, treatment, and control of HT should receive much attention.

Abuse of alcohol, physical inactivity, mental stress, and genetic factors may increase the risk of HT [7,9], whereas higher consumption of seafood, fruits, and vegetables may reduce the risk of HT due to the antioxidant ingredients [10,11]. Zinc (Zn) and copper (Cu) as important antioxidant ingredients, are sufficient in these food [12], and may be associated with HT through reducing oxidative stress and involving in lipid metabolism [13–16]. Previous studies have explored the relationship between serum Zn, Cu and HT, but the results were conflicting and inconsistent. Some studies had discovered a higher serum Zn level in HT patients compared with controls [17–21], whereas others found contrary results [22–30]. Besides, several studies expressed no significant difference between HT patients and controls [27,31–40]. As for Cu, some studies found a higher serum Cu level in HT patients than controls [21,23,24,26,31,32,38], however, inverse results were reported in other studies [17–19,25,28,37,40]. Meanwhile, some studies didn't find significant associations [20,22,27,33–36,41].

Given that individual study may have insufficient power to obtain a more credible conclusion, the present meta-analysis was conducted to: firstly, examine the association of serum Zn, Cu levels with HT risk; secondly, explore the potential between-study heterogeneity; and investigate the potential publication bias finally.

* Corresponding author at: Department of Epidemiology and Health Statistics, Medical College, Qingdao University, No. 38 Dengzhou Road, Qingdao 266021, China.

E-mail addresses: zhangdf1961@126.com, zhangdongfeng@qdu.edu.cn (D. Zhang).

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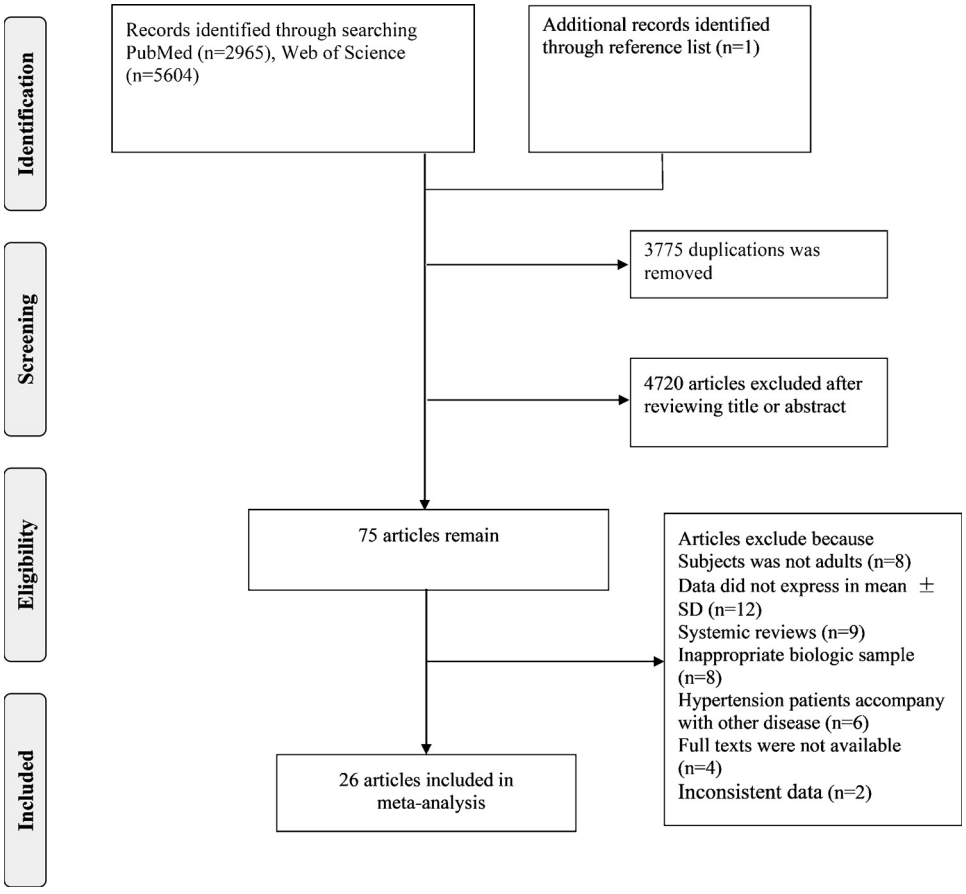

Fig. 1. Flow diagram of the literature search.

2. Material and method

2.1. Search strategy

We searched the relevant literatures on PubMed, Web of Science up to date of September 2018 published in both Chinese and English. Search terms includes “trace element”, “zinc”, “copper”, “Zn”, “Cu”, and “hypertension”, “high blood pressure”, “systolic pressure”, “diastolic pressure”. Moreover, references of relevant literatures were reviewed to identify additional studies which were not captured by databases research.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria were as follows: (1) observational studies; (2) the outcome was diagnosed essential hypertension (Table S1 in supplementary material); (3) biological samples were from blood; (4) measurement of serum Zn and Cu should be available, such as atomic absorption spectrometer, inductively coupled plasma spectrometry, or proton-induced X-ray emission; (5) data were expressed as mean ± standard deviation (SD) or standard error mean (SEM); (6) adult subjects without occupational metal exposures; (7) the controls were normotensives.

The following exclusion criteria were used if: (1) hypertensive subjects that with any other concomitant diseases or secondary hypertension; (2) subjects were pregnant or in lactation; (3) subjects attacked by stroke, myocardial infarction, arrhythmia, and cardiac dysfunction recently.

If data were duplicated in more than one study, the most recent one was adopted. Studies searching and data extraction were conducted independently by two investigators with disagreements being resolved through discussion.

2.3. Data extraction

The following data were extracted from each included literature: first author(year), county(continent) where study was performed, study types, groups, gender, mean age or range, sample size, mean ± SD of both hypertensive patient and controls, data unit, blood sample type, treated status, test methods, fasting status, and matched factors. If just standard error mean (SEM) was available, SD was calculated by the formula of $SEM = SD/\sqrt{n}$. The data from different groups in accordance to the severity of disease were also extracted.

2.4. Statistical analyses

Standard mean difference (SMD) with corresponding 95% confidence interval (CI) was used to evaluate the association between serum Zn, Cu level and the risk of HT. The SMD was the ratio of the mean difference to the pooled standard deviation. I^2 was used to assess the heterogeneity among studies. In the presence of substantial heterogeneity, the random effect model (REM) was adopted as the pooling method. Meta-regression was performed with restricted maximum likelihood estimation to access the potentially vital covariates [42]. We conducted an influence analysis to access whether the result could be affected markedly after removing one individual study. Funnel plot and Egger's linear regression test were used to appraise publication bias. All statistical analyses were performed with Stata 15.0 (Stata Corporation, College Station, TX, USA). All reported probabilities (*P*-values) were two-sided with $P < 0.05$ considered statistically significant.

Table 1
Characteristics of 26 included studies of zinc (Zn) and copper (Cu).

Author year	Country continent	Trait	Study types	Group	Mean age /range	Sex	N	Mean (Zn)	SD (Zn)	Mean (Cu)	SD (Cu)	Data unit	Blood sample	Treated	Test method	Fasting	Match
Thind, G S (1974)	USA (NA)	Zn	CC	control	33.1	C	15	113	17.8	—	—	μg/100mL	plasma	No	AAS	No	—
				HT	40.5		10	120.5	33.2	—	—						
Olatunbosun, D. A. (1976)	Nigeria (AF)	Zn, Cu	CC	control	NA*	C	37	1.07	0.122	1.01	0.182	mg/L	serum	Yes	AAS	No	—
				HT	51.5		48	1.09	0.127	1.38	0.28						
Sullivan, J. F. (1979)	USA (NA)	Zn, Cu	CC	control	NA*	M	37	0.97	0.13	1.06	0.3	μg/mL	serum	NA*	AAS	Yes	age
				HT	20-80		9	0.7	0.15	1.29	0.28						
Khan, S. H. (1984)	Pakistan (AS)	Zn, Cu	CC	control	42.6	C	30	1107	268.38	1556	301.25	μg/L	serum	NA*	AAS	No	socio-economic status
				HT	52.7		28	1110	327.36	1907	253.99						
Uza, G. (1984)	Romania (EU)	Zn, Cu	CC	control	53.1	C	65	18.46	7.18	17.14	0.72	mmol/L	serum		AAS	No	—
				AstageI	45.75		16	21.75	9.04	16.65	0.97			Yes			
				AstageII	47.36		64	21.58	9.68	17.16	1.13			Yes			
				AstageIII	62.71		20	14.83	3.98	17.56	0.78			Yes			
				BstageI	42.2		12	19.09	5.65	16.57	1.18			No			
				BstageII	49.9		22	18.13	3.52	17.35	0.44			No			
				BstageIII	61.1		7	14.73	1.9	18.74	1.13			No			
Vivoli, G. (1987)	Italy (EU)	Zn, Cu	CC	control	37.8	M	63	90.32	19.95	113.05	23.3	μg/100mL	serum	No	AAS	No	sex, occupation, age, smoking habits, BMI
				HT	38.3		63	92.84	19.07	118.11	31.98						
Vivoli, G. (1995)	Italy (EU)	Zn, Cu	CC	control	49.5	C	31	87	15.26	81	16.2	μg/100mL	serum	No	AAS	Yes	sex, age, smoking habits
				HT	49.6		31	83	14.03	84	23.55						
Bergomi, M. (1997)	Italy (EU)	Zn, Cu	CC	control	49.32	C	60	866	130.13	933	162.67	μg/L	serum	No	AAS	Yes	sex, age, smoking habits
				HT	49.68		60	850	127.81	976	211.46						
Russo, C. (1998)	Italy (EU)	Zn, Cu	CC	control	45.9	C	100	14.84	1.9	16.9	2.3	mmol/L	plasma	No	AAS	No	age, sex
				HT	47.7		105	17.47	4.6	15.7	3.4						
Akanle, O. A. (1999)	Nigeria (AF)	Zn, Cu	CC	control	51.5	C	18	4.5	0.82	1.12	0.27	mg/L	NA*	Yes	PIXE	No	age, socio-economic status
				HT	52.5		16	5.34	1.4	1.82	0.41						
Li, J. (1999)	China (AS)	Zn, Cu	CC	control	51.5	C	102	0.015	0.005	0.015	0.004	mmol/L	serum	No	ICPS	Yes	age, sex hypertensive family history
				HT	51.6		102	0.016	0.005	0.015	0.004						
He, Bangping (2003)	China (AS)	Zn, Cu	CC	control	68.4	C	30	10.08	1.89	14.32	3.74	μmmol/L	serum	NA*	AAS	Yes	—
				HT	66.7		42	11.68	1.06	12.97	1.29						
Canatan, H. (2004)	Turkey (AS)	Zn, Cu	CC	control	39.9	C	50	89.62	23.79	81.5	15.48	μg/dL	plasma	No	AAS	Yes	BMI, age
				HT	40.5		35	75.34	13.33	117.51	36.73						
Liu, W. M. (2004)	China (AS)	Zn, Cu	CC	control	67.2	C	52	12.3077	3.6535	15.625	3.1833	μmmol/L	serum	NA*	AAS	Yes	—
				HT	57.8		48	15.2823	1.9072	12.9794	3.4814						
Kedzierska, K. (2005)	Poland (EU)	Cu	CC	control	NA	M	11	—	—	1.12	0.26	mg/L	plasma	No	AAS	No	—
				HT	NA		15	—	—	1.016	0.193						
Yu, Feng (2005)	China (AS)	Zn, Cu	CC	control	55.9	C	32	11.855	2.622	4.46	1.145	μg/mL	NA*	NA*	ICP-MS	Yes	—
				HT	63.1		47	9.55	3.976	3.759	1.956						
Pavao, M. L. (2006)	Portugal (EU)	Zn, Cu	CS	control	20-60	M	50	1.02	0.17	0.99	0.52	μg/L	serum	No	AAS	Yes	—
				HT	20-60		7	0.95	0.18	1.23	0.63						
Taneja, S. K. (2007)	India (AS)	Zn, Cu	CC	control	49.88	M	250	0.177	0.16	0.063	0.158	mg/dL	serum	NA*	AAS	Yes	number, age, and sex
				HT	49.84		250	0.46	0.16	0.035	0.158						
Afridi, H. I. (2014)	Pakistan (AS)	Zn	CC	control	30-60	M	84	10.7	2.1	—	—	mg/L	NA*	partly	AAS	No	age, socioeconomic status
				HT	30-60	M	137	8.3	1.6	—	—						
				control	30-60	F	82	11.5	1.6	—	—						
				HT	30-60	F	120	8.5	1.2	—	—						
Afridi, H. I. (2015)	Ireland (EU)	Zn	CC	control	30-50	M	18	10.6	2.16	—	—	mg/L	NA*	partly	ICP-AES	No	age, sex
				HT	30-50	M	21	7.05	0.92	—	—						
				control	30-50	F	24	9.69	1.39	—	—						
				HT	30-50	F	17	6.08	0.75	—	—						
Okoduwa, S. I. (2015)	Nigeria (AF)	Zn, Cu	CC	control	52.1	C	50	15.55	1.84	13.82	0.9899	μmol/L	serum	No	AAS	Yes	age, sex and BMI
				HT	46.7		50	14.59	2.05	16.15	0.9899						
Suarez-Varela, M.M (2015)	Span (EU)	Zn	CS	control	20-59	C	139	13.39	4.35	—	—	μmol/L	serum	No	ICP-MS	No	—
				HT	20-59		21	12.32	3.19	—	—						

(*continued on next page*)

Table 1 (*continued*)

Author year	Country continent	Trait	Study types	Group	Mean age /range	Sex	N	Mean (Zn)	SD (Zn)	Mean (Cu)	SD (Cu)	Data unit	Blood sample	Treated	Test method	Fasting	Match
Suryana, A. L. (2015)	Indonesia (AS)	Zn, Cu	CS	control	40-70	C	15	10.9	5.08	58.47	22.03	μmol/L	serum	NA*	AAS	No	—
				HT	40-60		15	9.96	2.88	41.37	18.39						
Cikim, G (2017)	Turkey (AS)	Zn, Cu	CC	control	50-55	M	27	131.3	7.9	116.8	9.4	μg/dL	serum	No	AAS	Yes	—
				HT	50-55		26	111.4	18.2	81.8	11.2						
Yao, J. (2018)	USA (NA)	Zn, Cu	CS	control	> 18	C	10178	82.03	15.4	117.76	30.36	μg/dL	serum	Yes	ICP-MS	No	—
				HT	> 18		7633	82.34	15.5	121.8	26.78						
Guzel, S. (2018)	Turkey (AS)	Zn, Cu	CS	control	51.18	C	30	172.55	45.47	172.55	45.47	μg/dL	serum	Yes	AAS	Yes	—
				HT	53.83		60	179.13	34.06	179.13	34.06						

NA: North America. AF: Africa. AS: Asia. EU: Europe. CC: case-control study. CS: cross-sectional study. HT: hypertension. C: combined M: male. F: female. SD: standard deviation. NA*: not available. AAS: Atomic Absorption Spectrometer. PIXE: proton-induced X-ray emission. ICPS: inductively coupled plasma spectrometry. ICP-MS: Inductively coupled plasma mass spectrometer. ICP-AES: inductively coupled plasma–atomic emission spectrometry. BMI: body mass index.

3. Results

3.1. Characteristics of studies

As shown in Fig. 1, 8570 articles were identified. After removing the duplications and irrelative articles, 75 articles were included. 49 articles excluded because: subjects of eight articles were not adults; twelve express the data in correlation coefficient, odds ratio, or relative risk; nine were systemic reviews; eight provided urine, hair or nail samples; patients of six articles accompanied with other diseases; four full texts were not available; and two were about unmatched data between text and table. Ultimately, a total of 26 eligible articles [17–41,43] were included in meta-analyses. Of these studies, twenty-five were about serum Zn level and twenty-two were about serum Cu level. Nineteen were case–control studies [17–25,27,28,30–32,34–36,41,43], and seven were cross-sectional studies [26,29,33,37,38,40,44]. Eighteen articles [17–19,21,23,24,27,28,31,32,34–38,40,43,44] reported the results for combined HT patients (without information for gender distribution), and six articles [20,22,25,26,33,41] reported the results only for male HT patients, and 2 articles [29,30] reported the results for both male and female HT patients. Thirteen studies were matched case-control studies [17,18,20–24,29,30,32,35,36]. Zn and Cu levels were determined by atomic absorption spectrophotometer in twenty studies [17–20,22–27,29,31–35,37,40,43], inductively coupled plasma spectrometry in five studies [28,30,36,38,44], and proton-induced X-ray emission in one study [21]. Major confounding factors included age, body mass index (BMI), sex, or socioeconomic status. More details are shown in Table 1.

3.2. Serum or plasma Zn level and HT

Twenty-five studies involving 9129 cases and 11,888 controls assessed the association between serum Zn levels and HT risk in our meta-analysis.

The serum Zn levels was significantly lower in HT patients compared with controls [SMD (95%CI): -0.612(-0.951, -0.274), z = 3.54, $P_{for\ z} < 0.001$; $I^2 = 97.0\%$, $P_{for\ I}{}^2 < 0.001$] (Fig. 2), especially in male [SMD (95%CI): -1.443(-2.868, -0.017), z = 1.98, $P_{for\ z} = 0.047$; $I^2 = 98.8\%$, $P_{for\ I}{}^2 < 0.001$] (Fig. 3).

For subgroup analysis by continent, a lower serum Zn level was found in HT in Europe [SMD (95%CI): -1.066(-1.759, -0.374)]. With regard to study types, a statistically significant relationship was found in case-control studies [-0.718(-1.294, -0.142)]. The association was also significant in studies with treated patients [-1.416(-2.195, -0.638)]. Furthermore, a statistically significant relationship was found in matched case-control studies [-0.939(-1.646, -0.233)]. The details of subgroup analysis are summarized in Table 2.

3.3. Serum or plasma Cu level and HT

Twenty-two studies with 8716 patients and 11,383 controls assessed the association between serum Cu levels and HT risk.

Although serum Cu level was found higher in HT patients, there was no statistically significant difference between HT patients and controls [SMD (95%CI): 0.153(-0.101, 0.407), z = 1.18, $P_{for\ z} = 0.187$; $I^2 = 93.0\%$, $P_{for\ I}{}^2 < 0.001$] (Fig. 4).

A higher serum Cu level was found in HT patients in Africa [1.960(1.402, 2.518)]. Also, a statistically significant relationship was found in matched case-control studies [0.655(0.204, 1.107)]. The details of subgroup analysis are summarized in Table 2.

3.4. Meta-regression results

To explore the between-study heterogeneity in the analysis, we performed univariate meta-regression with the covariates of continent, gender, treated status, study types, fasting status, test method, and

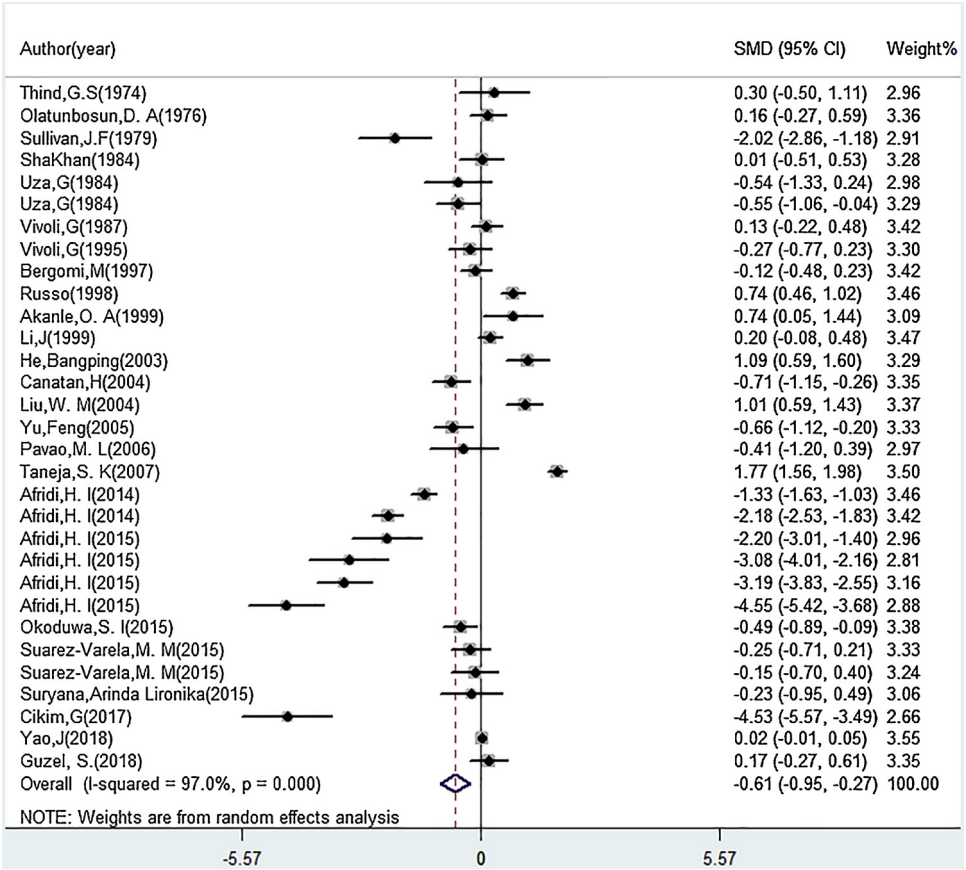

Fig. 2. Forest plot of standard mean difference (SMD) with corresponding 95% confidence interval (CI) of studies on serum zinc levels in total hypertension (HT) and normotensive controls. The size of grey box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95%.

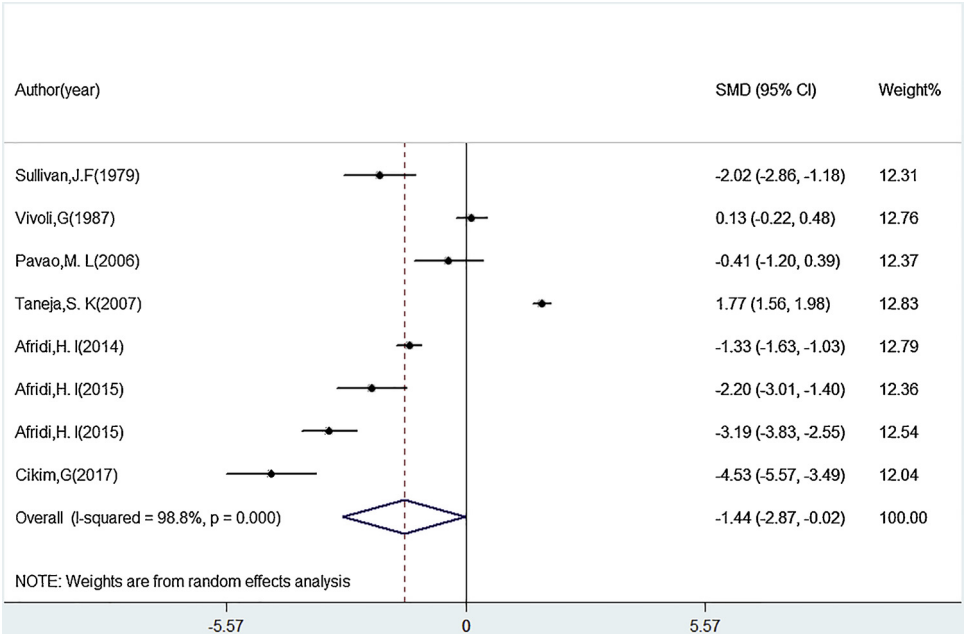

Fig. 3. Forest plot of standard mean difference (SMD) with corresponding 95% confidence interval (CI) of studies on serum zinc levels in male hypertension (HT) and male normotensive controls. The size of grey box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95%.

matched factors.

A high heterogeneity among studies was found in the present meta-analysis between serum Zn and HT risk (I^2_{Zn} = 97.0%). And gender contributed 22.05% (P = 0.005) and blood sample types contributed 24.69% (P = 0.005) to the heterogeneity of serum Zn and HT risk, respectively.

A high heterogeneity among studies was also found in Cu analysis (I^2_{Cu} = 93.0%). Continent contributed 39.54% (P = 0.002) and matched

Table 2
Subgroup analysis of zinc, copper level and hypertension (HT).

Subgroups	N of Studies Studies	SMD(95%CI)	Test of SMD = 0		Heterogeneity		Studies
			Z	*P* for Z	I^2	*P* for I^2	
Zn							
Continent							
Africa	3	0.089(-0.565, 0.743)	0.27	0.790	81.2	0.005	[21,24,31]
North America	3	−0.525(-1.677, 0.626)	0.89	0.371	91.3	< 0.001	[22,38,44]
Asia	12	−0.415(-1.259, 0.429)	0.96	0.335	98.3	< 0.001	[18,19,20,23,25,28,29,32,36,37,40]
Europe	13	−1.066(-1.759, -0.374)	3.54	0.003	95.8	< 0.001	[17,26,27,30,33,34,35,45]
Design							
CC	22	−0.718(-1.294, -0.142)	2.44	0.015	97.2	< 0.001	[17,18,19,20,21,22,23,24,25,27,28,30,31,32,34,35,36,44]
CS	9	−0.478(-1.033, 0.078)	1.69	0.092	96.5	< 0.001	[26,29,33,37,38,40,45]
Treated or not							
yes	13	−1.416(-2.195, -0.638)	3.56	< 0.001	98.0	< 0.001	[21,27,29,30,31,38,40]
no	11	−0.370(-0.766, 0.026)	1.83	0.067	90.4	< 0.001	[17,23,24,25,26,33,34,35,36,44,45]
NA	7	0.174(-0.744, 1.092)	0.37	0.710	96.6	< 0.001	[18,19,20,22,28,32,37]
Match							
yes	17	−0.939(-1.646, -0.233)	2.61	0.009	98.1	< 0.001	[17,20,21,22,23,24,29,30,32,33,34,35,36]
no	14	−0.163(-0.466, 0.140)	1.19	0.233	90.2	< 0.001	[18,19,25,26,27,28,31,37,38,40,44,45]
Cu							
Continent							
Africa	3	1.96(1.402, 2.518)	6.89	< 0.001	62.5	0.070	[21,24,31]
North America	2	0.344(-0.238, 0.926)	1.16	0.247	64.1	0.095	[22,38]
Asia	10	−0.367(-0.873, 0.139)	1.31	0.189	93.7	< 0.001	[18,19,20,23,25,28,32,36,37,40]
Europe	8	0.035(-0.208, 0.279)	0.28	0.776	51.8	0.043	[17,26,27,33,34,35,41]
Design							
CC	19	0.203(-0.190, 0.596)	1.01	0.312	94.	< 0.001	[17,18,19,20,21,22,23,24,25,27,28,31,32,33,34,35,36,41]
CS	4	−0.120(-0.564, 0.324)	0.53	0.597	74.8	0.008	[26,37,38,40]
Treated or not							
yes	5	0.678(-0.017, 1.373)	1.91	0.056	92.8	< 0.001	[21,27,31,38,40]
no	11	0.051(-0.522, 0.624)	0.17	0.861	94.7	< 0.001	[17,23,24,25,26,33,34,35,36,41]
NA	7	−0.126(-0.583, 0.332)	0.54	0.590	86.9	< 0.001	[18,19,20,22,28,32,37]
Match							
yes	11	0.655(0.204, 1.107)	2.84	0.004	93.9	< 0.001	[17,20,21,22,23,24,32,33,34,35,36]
no	12	−0.345(-0.784, 0.094)	1.54	0.123	92.7	< 0.001	[18,19,25,26,27,28,31,37,38,40,41]

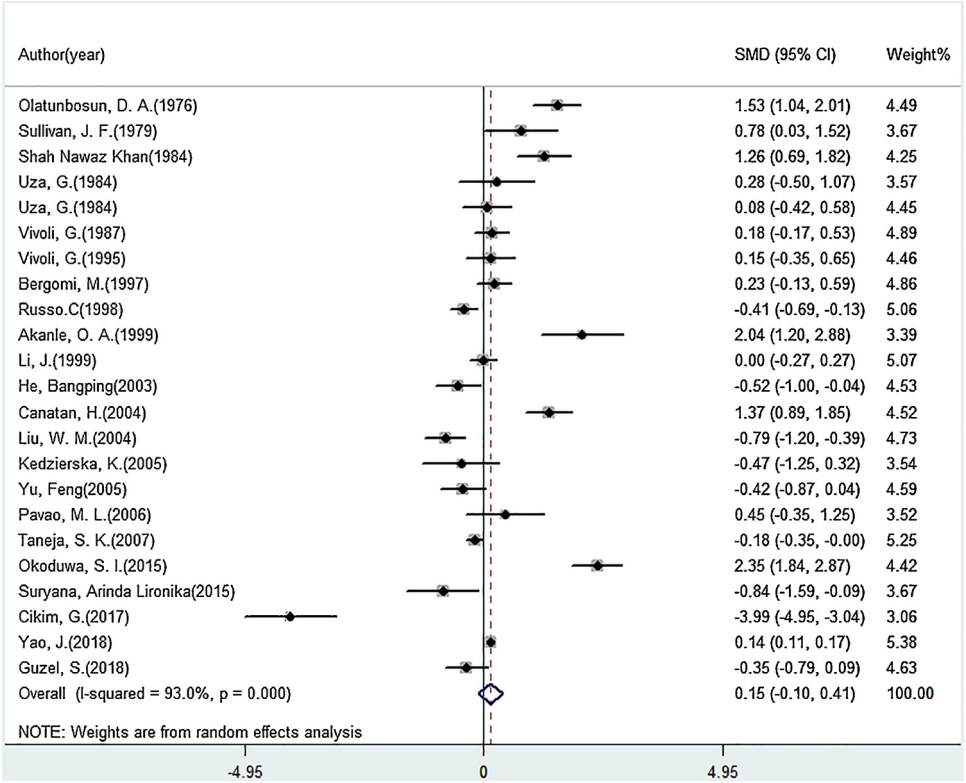

Fig. 4. Forest plot of standard mean difference (SMD) with corresponding 95% confidence interval (CI) of studies on serum copper levels in total hypertension (HT) and normotensive controls. The size of grey box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95%.

factor contributed 17.65% ($P = 0.033$) to the heterogeneity of serum Cu and HT risk.

3.5. Influence analysis and publication bias

In influence analysis, no individual study had an excessive effect on the associations of serum Zn, Cu levels with HT risk. Egger's test suggested no publication bias of Zn analysis ($P = 0.099$) and Cu analysis ($P = 0.970$).

4. Discussion

Our meta-analysis contained 26 studies, of which 25 were for Zn. Our results indicated that serum Zn level in HT patients was significantly lower than that in controls especially in male HT patients. Furthermore, in subgroup analysis, a lower serum Zn level was observed in HT patients in studies conducted in Europe, in case-control studies, in matched case-control studies, and studies involving treated patients. In the 22 studies on Cu, the results indicated that there was no significantly difference of serum Cu levels between HT patients and controls. In subgroup analysis, a significantly higher serum Cu level was observed in HT patients in Africa, and in matched case-control studies.

The mechanisms behind the association between serum Zn and HT were still not thoroughly clear. Zn was considered to be an antioxidant based on the increase in the levels of free oxygen radicals when serum Zn decreased [45]. Superoxide dismutase (SOD) is the first line of defense against oxidative stress serving as antioxidant enzymes to prove and cope with injury from oxidative damage, and maintain redox homeostasis [46,47]. Zn forms the prosthetic group of SOD. Alteration of its levels may affect the activity of the enzyme [48]. Therefore, the increase in superoxide ultimately could lead to the impairment and dysfunction of endothelial structure, consequently, the hypertension [49]. Meanwhile, Zn exerts an inhibiting effect on the ATP-dependent calcium pump that promotes the outpour of calcium ions from the cell, resulting in the outpouring of Ca^{2+} from cell [50]. Increased Ca^{2+} in smooth muscular layer of vessels caused an increase of the arterial wall tension [51].

Between-study heterogeneity is common in meta-analysis. It is essential to explore the sources of between-study heterogeneity. Strong evidence of high between-study heterogeneity was found in our meta-analysis between serum Zn, Cu level and HT. Meta-regression indicated that gender contributed 22.05% and blood sample type contributed 24.69% of between-study heterogeneity in Zn analysis. Continent contributed 39.54% and matched factors contributed 17.65% of between-study heterogeneity in Cu analysis. However, we did not find other covariates as the important contributors to the between-study heterogeneity.

There are some strengths in our meta-analysis: Firstly, a large number of participants was included in our study, allowing a much greater possibility of reaching a credible conclusion. Secondly, we included 13 studies matched potential confounders such as age, BMI, and sex, and obtained significant results, which can reduce the effects of confounding factors and reach a credible result.

However, limitations might also exist in present study: Firstly, the confounders were diverse in matched case-control studies, which might affect the stability of results. Secondly, although a significantly higher serum Cu level was observed in HT patients in matched case-control studies, the association was not significant in total results. Also, we found significant higher copper levels in HT patients in three African studies, and this might due to two of three matched studies. Since the inconsistent results in matched and African studies in serum Cu analysis, further researches and more participants are needed. Finally, methods of blood pressure measuring varied among studies, which might affect the observed association.

In conclusion, results from this meta-analysis showed that serum Zn level in HT patients was significantly lower than that in controls, while no significantly different serum Cu level was found between HT patients and controls. Also, we found the inconsistent results in matched and African studies in serum Cu analysis. Therefore, further studies are required to confirm the associations.

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Declaration of interests

None to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jtemb.2019.01.018.

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