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Common trace metals in rheumatoid arthritis: A systematic review and meta-analysis

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ABSTRACT

Introduction: Environmental risk factors regrading rheumatoid arthritis (RA) have not been explored extensively. Selenium (Se), zinc (Zn) and copper (Cu) nutrients were reported to associate with RA, but the results were inconsistent. Therefore, we conduct present study to meta-analyze the relationship between serum Se, Zn and Cu and RA and review the potential mechanisms.

Methods: PubMed, Web of Science and Cochrane Library were comprehensively searched till October 1, 2018 for pertinent studies. Standard mean differences (SMDs) and 95% confident intervals (CIs) were calculated according to random effects model.

Results: Finally 41 literatures were included. Meta-analysis of 16 studies involving 806 RA patients and 959 health controls showed that serum Se (SMD = −1.04, 95% CI = −1.58 to −0.50) was decreased in RA patients, and 23 literatures with 1398 patients and 1299 controls reported serum Zn (SMD = −1.20, 95% CI = −1.74 to −0.67) was decreased. But serum Cu (SMD = 1.26, 95% CI = 0.63 to −1.89) was increased with 26 studies including 1723 patients and 1451 controls. Meta-regression reported that steroid use was positively related to serum level of Se in RA (β = 0.041, 95% CI = 0.002 to 0.079). Differences in serum Se, Zn and Cu between rheumatoid arthritis patients and controls were all related with the geographical distribution.

Conclusions: Patients with RA have significant decreased serum Se and Zn and increased serum Cu than health controls, suggesting potential roles of Se, Zn and Cu in the pathogenesis of RA. Patients and rheumatologist should give enough attention to the monitor of these elements during follow up.

1. Introduction

Rheumatoid arthritis (RA) is a common chronic, destructive inflammatory arthritis, characterized with progressive cartilage, bone and joint destruction. The disease mainly involves synovial small and large joints such as fingers, elbows, shoulders, keens and ankles. The most common feature of RA is the thickening and hyperplasia of synovial line alongside with permanent inflammatory, causing severe disability and early death [1]. Approximately 1% of adult population is affected by RA worldwide, making RA a big public health challenge and social burden [2,3]. Although the exactly pathogenesis of RA remains obscure, interaction between genetic and environmental factors is widely accepted accounting for the attack and development of RA [4–8]. Factors like HLA-DRB1, smoking and infection are widely reported to associate with RA [9–13]. Meanwhile, environmental factors as female hormones and trace elements like selenium (Se), zinc (Zn), and copper (Cu) are argued to play roles in the pathogenesis of RA.

Trace mental elements, like Se, Zn, and Cu, have been recognized as one of these factors, and their homeostasis is essential to regulate different aspects for inflammatory and immune systems. As essential micronutrient related to the oxidant defense system, Se is reported to play crucial roles in activation, differentiation, and proliferative capacity of immune cells and antioxidant defense [14]. Likewise, Zn is demonstrated to participate in cell cycle progression, cell maturation and differentiation [15]. Studies also indicate that Cu could influence the oxidant defense system acted as catalytic cofactors and coordinated with Se and Zn [16–19]. Abnormal trace metals concentrations are also associated with expression of genes regulating bone metabolism, inflammatory response, and transcriptional regulation, like inducible nitric oxide synthase, cyclooxygenase-2, and matrix metalloprotease 2,

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potentially associated with RA [20–23]. Besides, patients with RA are reported to associate with inadequate nutrient status of various trace metals and vitamins [24,25]. Previous studies also indicate that these abnormal trace metals homeostasis status may related to rheumatoid arthritis [26,27], but the results were inconsistent. Previously, study comprehensive reviewed association between RA and micronutrients is still devoid. Taking into account of these factors, we take this study to systematic review the authentic relationship between Se, Zn and Cu and RA.

2. Material and methods

This study was performed as a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard [28] (see Supplementary Table S1) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for systematic reviews of observational studies [29] (see Supplementary Table S2). In accordance with PICOs scheme, the review question of present study was whether the serum levels of Se, Zn and Cu of RA patients were different from health controls.

2.1. Search strategy and selection criteria

To identify literatures regarding the association between serum levels of Se, Zn and Cu and RA, two reviewers (Yubo Ma, Xu Zhang) independently searched PubMed, Web of Science and Cochrane Library from inception to October 1, 2018 using the strategy detailed in Supplementary Fig. S1. Pertinent studies were also hand searched according to the bibliographies of eligible studies and reviews. Where necessary, corresponding author was contacted for full-text and elaborate data. Studies were eligible for inclusion if they: (a) had a cohort, cross-sectional or case-control study design; (b) were written in English; (c) reported the elaborate data regarding serum levels of Se, Zn or Cu in both RA patients and healthy controls. The most comprehensive study containing the largest sample size was included only for duplicate publications.

2.2. Methodological quality assessment and data extraction

Newcastle-Ottawa Scale (NOS) for case-control study was used for methodological quality assessment with maximum score of nine, and the quality score higher than three was considered as acceptable (see Supplementary Table S3). In order to analyze the review question and explore potential factors influencing the homeostasis of Se, Zn and Cu, following characteristics of the included studies were independently extracted by two reviewers (Yubo Ma, Xu Zhang): first author's name, publication year, methods for serum concentration determination and laboratory control, country and continent of research and study quality score; number, age, gender distribution, and serum levels of Se, Zn or Cu of RA patients and healthy controls; diagnosis criteria, disease duration, and proportion of people with steroid use of RA patients. Any discrepancy during these processes was resolved with consensus via discussing.

2.3. Statistical analysis

Since studies used different scales and methods, the standard mean difference (SMD) and 95% confidence interval (CI), based on either fixed effect model or random effects model, were applied to evaluate the difference of serum levels of Se, Zn and Cu between RA patients and healthy controls. In some articles, the data was only available for subgroups separately, as male and female or active and inactive patients. Combined data was calculated using the following formulas:

$$\bar{x} = \frac{x_1 n_1 + x_2 n_2}{n_1 + n_2}$$

$$S_c^2 = \frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}$$

With $\bar{x}$ and S_c being the pooled mean and standard deviation of the means and standard deviations in group 1 (x_1, S_1) and group 2 (x_2, S_2), and n_1 and n_2 being the sample sizes of group 1 and group 2, respectively.

Fixed effect model was used to calculate the SMD if between studies heterogeneity was insignificant, otherwise, random effects model was applied [30]. The significance of pooled SMD between groups was assessed by Z-test. Between studies heterogeneity was calculated according to Cochran's Q statistic, and I^2 test was also used complemented to quantify the degree of inconsistency by calculating the percentage of total between studies variation due to heterogeneity rather than chance [31]. Any significant heterogeneity was defined as $P < 0.05$ of Cochran's Q test and $I^2 < 50\%$. Subgroup analysis and meta-regression were used to explore the potential factors affecting the homeostasis of Se, Zn and Cu for categorical and continuous variables respectively. Sensitivity analysis was also used to assess the stability of effect size through omitting each enrolled study consecutively. Funnel plot, Begg's rank correlation test and Egger's linear regression were performed to assess publication bias qualitatively and quantitatively [32]. Any $P < 0.05$ was considered statistically significant, and all data analyses were conducted by R software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Search results and characteristics of studies

A total of 3555 literatures were identified from PubMed (n = 1053), Web of Science (n = 2299), Cochrane Library (n = 182) and references hand search (n = 21). Eighty-nine full texts were ultimately reviewed after duplicate publication remove and abstract screening detailed in Fig. 1. The finally meta-analysis included 41 literatures [27,33–72]. Among them, 16 [27,33–37,48–55,71,72], 23 [27,33–47,56–60,70,71] and 27 [27,33–47,61–71] articles presented the data of Se, Zn and Cu respectively. All of the included articles have assessed with acceptable quality scores (greater than three) conducted mainly in Europe and Asia with the earliest study published in 1975. These studies examined the serum levels of the three elements using different methods, most with atomic absorption spectrometry. These data were detailed in Table 1. The methods for laboratory control of included studies were reported in Supplementary Tables S3, S4.

3.2. Se among patients and controls

Sixteen studies have evaluated the serum levels of Se in 806 RA patients and 959 health controls [27,33–37,48–55,71,72]. Significant difference of serum Se between groups was detected with SMD = −1.04 (95% CI = −1.58 to −0.50, $Z = -3.77$, $P < 0.001$), accompanied with significant heterogeneity (I^2 = 95.6%; Q = 343.55, $P < 0.001$) (Fig. 2). Meta-regression analyses have indicated that factors as publication year, study quality score, sample size and age, female proportion and disease duration have no impact on the serum level of Se, but the steroid use was positively related to serum level of Se (β = 0.041, 95% CI = 0.002 to 0.079, $Z = 2.08$, $P = 0.037$) (Table 2). Meanwhile, we found that the serum Se levels were different across continents (Q = 6.40, $P = 0.041$, Table 3). Patients with RA lived in Asia (SMD = −0.1576, 95% CI = −1.0204 to 0.7051, $Z = -0.36$, $P = 0.720$) and North America (SMD = −0.52, 95% CI = −1.09 to 0.05, $Z = -1.78$, $P = 0.074$) have relative lower, but insignificant, serum Se. On the contrary, the serum Se was significantly decreased in RA patients of Europe (SMD = −1.61, 95% CI = −2.46 to −0.77, $Z = -3.75$, $P < 0.001$). Sensitive analysis demonstrated that the result of the meta-analysis was stable (Supplementary Fig. S2).

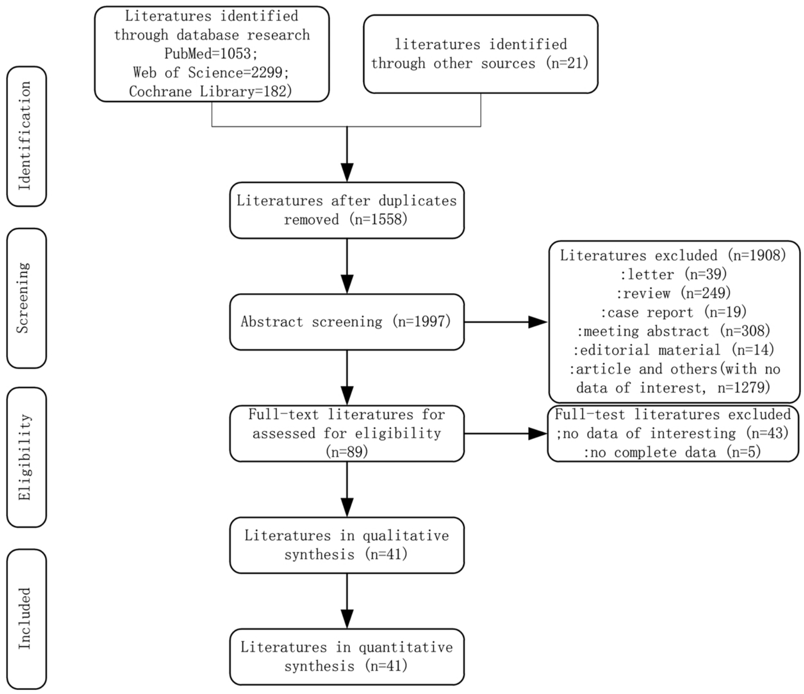

Fig. 1. Flow chart of the literature search and study selection.

Funnel plot (Fig. 3) was visually asymmetry with Egger test ($t = -3.57$, $P = 0.003$) and Begg test ($Z = -2.88$, $P = 0.004$) showing the publication bias (Supplementary Figs. S3, S4).

3.3. Zn among patients and controls

The serum levels of Zn were reported in 23 literatures with 1398 RA patients and 1299 health controls [27,33–47,56–60,70,71]. Significant decreased serum Zn was also found in RA patients (SMD = −1.20, 95% CI = −1.74 to −0.67, $Z = -4.41$, $P < 0.001$) (Fig. 2). Meta-regression analyses found that none of above mentioned continuous factors was associated serum Zn (Table 2). Subgroup analysis also found that serum Zn of RA patients in different continents were different ($Q = 13.23$, $P = 0.004$, Table 3). Serum Zn was significantly decreased in RA patients of Asia (SMD = −1.31, 95% CI = −2.34 to −0.28, $Z = -2.50$, $P = 0.013$) and Europe (SMD = −1.40, 95% CI = −2.13 to −0.67, $Z = -3.76$, $P < 0.001$). Sensitive analysis demonstrated stable result (Supplementary Fig. S2). The visually asymmetry funnel plot (Fig. 3), Egger test ($t = -1.52$, $P = 0.142$) and Begg test ($Z = -2.03$, $P = 0.042$) also reported publication bias (Supplementary Figs. S3, S4).

3.4. Cu among patients and controls

Twenty-six studies including 1723 patients and 1451 controls reported serum level of Cu [27,33–47,61–71]. Different with Se and Zn, serum Cu was significantly increased in RA patients compared with controls (SMD = 1.26, 95% CI = 0.63 to −1.89, $Z = 3.92$, $P < 0.001$) (Fig. 2). Through meta-regression and subgroup analysis, we find that patients with RA under different diagnosis criteria have different serum Cu ($Q = 9.95$, $P = 0.007$), and disease duration was positively related to the increased serum Cu ($\beta = 0.5601$, $P = 0.042$) (Tables 2 and 3). Similarly, patients in different continents have different serum levels of Cu ($Q = 8.49$, $P = 0.037$). Serum Cu was not significantly increased in patients of Asia (SMD = 0.77, 95% CI = −0.27 to 1.80, $Z = 1.45$, $P = 0.145$) and North America (SMD = 0.09, 95% CI = −0.72 to 0.90, $Z = 0.21$, $P = 0.830$). The result was also reliable according sensitive analysis (Supplementary Fig. S2). Funnel plot (Fig. 3), Egger test ($t = 2.88$, $P = 0.008$) and Begg test ($Z = 2.11$, $P = 0.042$) indicated publication bias (Supplementary Figs. S3, S4).

4. Discussion

Tremendous studies have explored potential genetic pathogenic factors of RA, but studies concerning nutritional factors were still devoid. Therefore, we conduct the present study to comprehensively review and meta-analyze the association between trace micronutrients and RA. We found that people with RA exhibited decreased serum Se and Zn concentrations and increased serum Cu concentration.

Selenium is an essential micronutrient that plays crucial roles in wide ranges of physiological processes including innate and adaptive immune responses. Se acts as 21st amino acid, selenocysteine, through incorporated into proteins via specific transfer RNA. The effects of dietary selenium on the immune function were mainly based on the insertion of Se into a family of seleno-proteins containing 25 members [14,73,74]. Some members of selenoprotein family could affect immune cell function as enzymes involved in redox reactions like glutathione peroxidases [75,76]. Studies also reported that selenium deficiency could induce higher levels of inflammatory cytokines in various tissues and immune incomplete leading to increased susceptibility to infection [77,78]. Likewise, Zn plays a pivotal role in the regulation of innate and adaptive immunity [79]. Severe deficit of Zn was reported to associate with decreased T helper cell to cytotoxic T cell ratio, increased monocytes cytotoxicity and reduced natural killer cell activity [80–82]. Cu as a redox active metal often takes functions with Zn in the form of copper–zinc superoxide dismutase. Cu and Zn could work collaboratively in immune responses, and the imbalance of them was associated with humoral immune response and infections [83,84]. Additionally, Cu/Zn ratio, an indicator independent with sex and age [34], was also reported to associate with oxidative stress and inflammatory response and acted as a biomarker of various diseases [84–88]. Previously, only two studies reported that Cu/Zn ratio was associated with RA, but the conclusions were contrary [34,45]. Further studies focusing on Cu/Zn ratio in RA patients are necessary.

Animal experiments also supported that Se and Zn supplementation may be beneficial for RA patients. Studies reported that Se supplements

Table 1
Characteristics of included studies.

Author [reference number]	Year	Region	Continent	Cases			Controls			Disease duration (Y)	Steroid use (%)	Diagnosis criteria	Quality	Detected element and measurement		
				N	Age (Y)	Female proportion (%)	N	Age (Y)	Female proportion (%)					Selenium	Zinc	Copper
Aaseth J [33]	1978	Norway	Europe	23	NA	NA	30	NA	NA	NA	NA	ARA	6	NAA	FAAS	FAAS
Sahebari M [34]	2015	Iran	Asia	110	44.7	85.3	100	41.5	14.7	0.33	72.7	ACR	7	EAAS	FAAS	FAAS
Afridi HI[27]	2015	Ireland	Europe	53	NA	49.1	52	NA	NA	NA	NA	ACR	7	ICP-MS	ICP-MS	ICP-MS
Yazar M [35]	2005	Turkey	Asia	25	47.4	56.0	25	48.2	52.0	NA	NA	ACR	7	EAAS	EAAS	EAAS
Li J [36]	2014	China	Asia	60	48.6	46.7	60	49.0	48.3	2.13	NA	ACR	8	FAAS	FAAS	FAAS
Bacon MC [37]	1900	America	North America	34	10.2	61.8	9	8.9	44.4	4.98	23.7	ARA	7	EAAS	FAAS	FAAS
Niedermeier W [38]	1971	America	North America	105	51	NA	105	31	NA	9.4	NA	NA	5	NA	EAAS	EAAS
Banford JC [39]	1982	England	Europe	85	NA	74.1	49	NA	55.1	NA	NA	ARA	6	NA	FAAS	EAAS
Morgenstern H [40]	1983	Israel	Asia	30	62.3	80.0	30	62.3	80.0	NA	NA	NA	7	NA	AAS	AAS
Zoli A [41]	1998	Italy	Europe	57	52.2	100	20	53	100	3.4	NA	ARA	7	NA	CA	CA
Tuncer S [42]	1999	Turkey	Asia	39	36.2	81.6	22	34.2	90	8.42	NA	ARA	6	NA	FAAS	FAAS
Wanchu A [43]	2002	India	Asia	39	36.2	79.5	22	34.2	63.6	4.65	NA	ACR	7	NA	FAAS	FAAS
Silverio Amancio OM [44]	2003	Brazil	South America	41	11.3	51.2	23	9.9	56.5	NA	NA	ACR	7	NA	FAAS	FAAS
Ala S [45]	2009	Iran	Asia	40	43.7	87.5	40	41.5	87.5	NA	NA	NA	6	NA	FAAS	FAAS
Ullah Z [46]	2016	Pakistan	Asia	61	42.7	77.0	61	43.3	77.0	5.15	NA	ACR	7	NA	FAAS	FAAS
Afridi HI [47]	2013	Pakistan	Asia	202	NA	44.1	203	NA	48.3	NA	NA	ACR	6	NA	FAAS	FAAS
Pemberton PW [48]	2009	England	Europe	46	57	100	58	56	100	NA	35	NA	4	STFA	NA	NA
Witkowska AM [49]	2003	Poland	Europe	37	49	100	18	44	100	8.3	18.9	ACR	7	EAAS	NA	NA
Knekt P [50]	2000	Finland	Europe	122	45.8	68.9	357	45.8	68.9	NA	NA	ACR	8	EAAS	NA	NA
Heliovaara M [51]	1994	Finland	Europe	14	55	42.9	27	55	44.4	NA	NA	ARA	6	EAAS	NA	NA
Kose K [52]	1996	Turkey	Asia	60	51.1	73.3	60	NA	66.7	9.6	NA	ARA	7	EAAS	NA	NA
Jacobsson L [53]	1990	Sweden	Europe	41	57	66.7	57	57	43.9	7.79	NA	ARA	7	EAAS	NA	NA
O'Dell JR [54]	1991	America	North America	122	55.5	NA	29	38.9	NA	NA	NA	ACR	7	NAA	NA	NA
Borglund M [55]	1988	Sweden	Europe	7	NA	100	5	NA	100	16	NA	NA	6	EAAS	NA	NA
Mierzecki A [56]	2011	Poland	Europe	74	39.8	73.0	30	38.2	73.3	8.51	NA	ACR	7	NA	FAAS	NA
Dijkmans BA [57]	1987	Netherland	Europe	36	61.5	80.6	18	44	55.6	NA	NA	ARA	6	NA	FAAS	NA
Cimmino MA [58]	1986	Italy	Europe	33	59.1	66.7	85	48.5	52.9	7.1	NA	NA	4	NA	FAAS	NA
Pandey SP [59]	1985	India	Europe	28	29.67	57.1	31	NA	NA	NA	NA	ARA	7	NA	FAAS	NA
Kennedy AC [60]	1975	Scotland	Europe	113	51.9	58.4	100	NA	NA	12.9	37.2	ARA	8	NA	FAAS	NA
Chakraborty M [61]	2015	India	Asia	50	NA	76	50	NA	NA	NA	NA	ACR	6	NA	NA	CA
Strecker D [62]	2013	Poland	Europe	74	39.8	73.0	30	38.2	73.3	7.7	50.0	ACR	6	NA	NA	FAAS
Louro MO [63]	2000	Spain	Europe	40	44.7	75.0	95	NA	NA	NA	NA	NA	6	NA	NA	FAAS
Marrella M [64]	1990	Italy	Europe	77	NA	NA	25	NA	NA	NA	NA	ARA	5	NA	NA	FAAS
Youssef AA [65]	1983	England	Europe	60	63	NA	14	58	NA	NA	NA	ARA	7	NA	NA	FAAS
Scudder PR [66]	1978	England	Europe	100	NA	60	100	NA	60	NA	NA	NA	4	NA	NA	FAAS
Aiginger P [67]	1978	Austria	Europe	12	57	100	7	40	100	NA	NA	NA	4	NA	NA	NA
McMurray W [68]	1975	England	Europe	146	NA	67.1	45	NA	60.0	NA	44.5	NA	6	NA	NA	FAAS
Scudder P [69]	1976	England	Europe	50	NA	74	50	NA	78	NA	NA	NA	6	NA	NA	NA
Hansson L [70]	1975	Finland	Europe	78	NA	51.3	132	NA	28.0	NA	NA	NA	5	NA	FAAS	FAAS
Onal S [71]	2011	Turkey	Europe	32	50	34.4	52	NA	NA	7.36	NA	ACR	7	EAAS	EAAS	EAAS
Hannonen P [72]	1985	Finland	Europe	20	NA	NA	20	NA	NA	NA	NA	NA	4	NA	NA	NA

AAS: atomic absorption spectrophotometry; ACR: American College of Rheumatology criteria; ARA: American Rheumatism Association criteria; CA: colorimetric assays; EAAS: electrothermal atomic absorption spectrometry; FAAS: flame atomic absorption spectrophotometry; ICP-MS: inductively coupled plasma-mass spectrometer; N: number; NA: not available; NAA: neutron activation analysis; STFA: single-tube fluorimetric assay; Y: year.

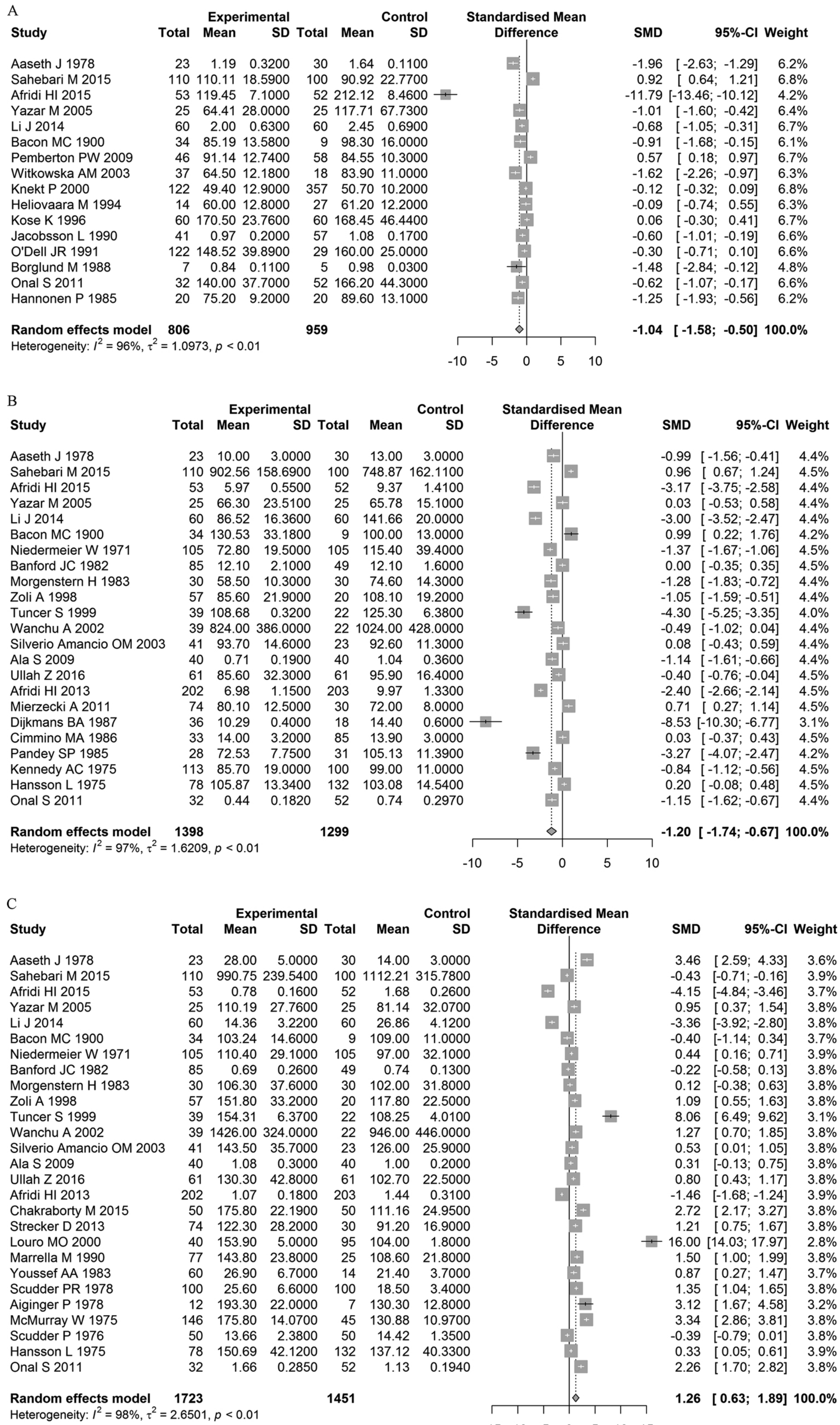

Fig. 2. Forest plots of serum trace metal in RA patients compared with controls: A. serum selenium; B. serum zinc; C. serum copper.

could reduce inflammatory cells recruit and pro-inflammatory cytokines release, and improve inflammatory manifestations in arthritis mice model [89,90]. Clinical study proved that antioxidants could improve disease activity significantly [91]. Whereas, study also reported controversial results that Se supplementation can not perform clinical benefit on RA [92]. These inconsistent results may due to the

Table 2
Results of meta-regression analyses.

Element	Variables	Coefficient (SE)	95% CI	Z	P
	Selenium				
Selenium	Publication year	−0.0112 (0.0266)	−0.0633, 0.0409	−0.421	0.674
Selenium	Age of cases	0.0139 (0.0182)	−0.0218, 0.0496	0.762	0.446
Selenium	Female proportion of cases	0.0335 (0.0398)	−0.0446, 0.1116	0.841	0.400
Selenium	N of cases	0.0111 (0.0195)	−0.0271, 0.0494	0.572	0.568
Selenium	N of controls	0.0043 (0.0087)	−0.0127, 0.0214	0.499	0.618
Selenium	N of participants	0.0037 (0.0065)	−0.0091, 0.0165	0.567	0.571
Selenium	Disease duration	−0.1054 (0.0630)	−0.2288, 0.0180	−1.6738	0.094
Selenium	Quality	−0.2021 (0.6306)	−1.4380, 1.0339	−0.321	0.749
Selenium	Steroid use	0.0406 (0.0195)	0.0024, 0.0789	2.083	0.037*
	Zinc				
Zinc	Publication year	−0.0133 (0.0167)	−0.0460, 0.0194	−0.798	0.425
Zinc	Age of cases	−0.0474 (0.0347)	−0.1154, 0.0207	−1.365	0.172
Zinc	Female proportion of cases	−0.0003 (0.0276)	−0.0545, 0.0539	−0.012	0.991
Zinc	N of cases	0.0038 (0.0103)	−0.0163, 0.0239	0.373	0.710
Zinc	N of controls	0.0041 (0.0092)	−0.0140, 0.0221	0.442	0.658
Zinc	N of participants	0.0021 (0.0050)	−0.0077, 0.0120	0.425	0.671
Zinc	Disease duration	−0.0713 (0.1374)	−0.3407, 0.1981	−0.519	0.604
Zinc	Quality	0.0301 (0.4490)	−0.8498, 0.9100	0.067	0.947
Zinc	Steroid use	0.0106 (0.0402)	−0.0682, 0.0894	0.263	0.792
	Copper				
Copper	Publication year	−0.0006 (0.0291)	−0.0575, 0.0564	−0.020	0.984
Copper	Age of cases	0.0042 (0.0731)	−0.1390, 0.1475	0.058	0.954
Copper	Female proportion of cases	0.0643 (0.0454)	−0.0247, 0.1532	1.417	0.157
Copper	N of cases	−0.0190 (0.0166)	−0.0516, 0.0136	−1.142	0.253
Copper	N of controls	−0.0049 (0.0159)	−0.0361, 0.0263	−0.308	0.758
Copper	N of participants	−0.0066 (0.0087)	−0.0237, 0.0105	−0.757	0.449
Copper	Disease duration	0.5601 (0.2748)	0.0215, 1.0986	2.038	0.042*
Copper	Quality	−0.9491 (0.6976)	−2.3164, 0.4182	−1.361	0.174
Copper	Steroid use	−0.0082 (0.0623)	−0.1303, 0.1138	−0.132	0.895

*: $P < 0.05$; CI: confident interval; N: number; SE: standard error.

Table 3
Results of subgroup analyses.

Subgroups	N	SMD	95%CI	Z	P	Test of heterogeneity		Subgroup differences	
						I^2	P	Q	P
Selenium									
Region								6.40	0.041*
Asia	4	−0.1576	1.0204, 0.7051	−0.36	0.720	95.2%	< 0.001		
Europe	10	−1.6149	−2.4597, −0.7700	−3.75	< 0.001	97.7%	< 0.001		
North America	2	−0.5202	−1.0915, 0.0512	−1.78	0.074	47.7%	0.167		
Diagnosis criteria								2.36	0.308
ACR	8	−1.5110	−2.4060, −0.6160	−3.31	< 0.001	97.5%	< 0.001		
ARA	5	−0.6720	−1.3260, −0.0181	−2.01	0.044	86.8%	< 0.001		
NA	3	−0.6473	−2.1234, 0.8287	−0.86	0.390	92.1%	< 0.001		
Zinc									
Region								13.23	0.004*
Asia	9	−1.3117	−2.3409; −0.2824	−2.50	0.013	98.1%	< 0.001		
Europe	11	−1.3982	−2.1267, −0.6696	−3.76	< 0.001	96.6%	< 0.001		
North America	2	−0.2160	−2.5222, 2.0903	−0.18	0.854	96.8%	< 0.001		
South America	1	0.0804	−0.4304, 0.5912	NA	NA	NA			
Diagnosis criteria								4.27	0.118
ACR	10	−0.8800	−1.8500, 0.0900	−1.78	0.075	98.2%	< 0.001		
ARA	8	−2.0259	−3.0809, −0.9708	−3.76	< 0.001	96.6%	< 0.001		
NA	5	−0.6992	−1.4358, 0.0374	−1.86	0.063	94.7%	< 0.001		
Copper									
Region								8.49	0.037*
Asia	10	0.7664	−0.2661; 1.7988	1.45	0.145	98.3%	< 0.001		
Europe	14	1.8851	0.9297; 2.8406	3.87	< 0.001	98.2%	< 0.001		
North America	2	0.0888	−0.7223; 0.8999	0.21	0.830	77.1%	0.037		
South America	1	0.5309	0.0116; 1.0503	NA	NA	NA			
Diagnosis criteria								9.95	0.007*
ACR	10	0.0351	−1.0066; 1.0767	0.07	0.974	98.5%	< 0.001		
ARA	7	1.8841	0.6752; 3.0930	3.05	0.002	96.5%	< 0.001		
NA	9	2.2654	1.2433; 3.2876	4.34	< 0.001	98.1%	< 0.001		

ACR: American College of Rheumatology criteria; ARA: American Rheumatism Association criteria; N, number of studies; NA: not available; SMD, standard mean difference.

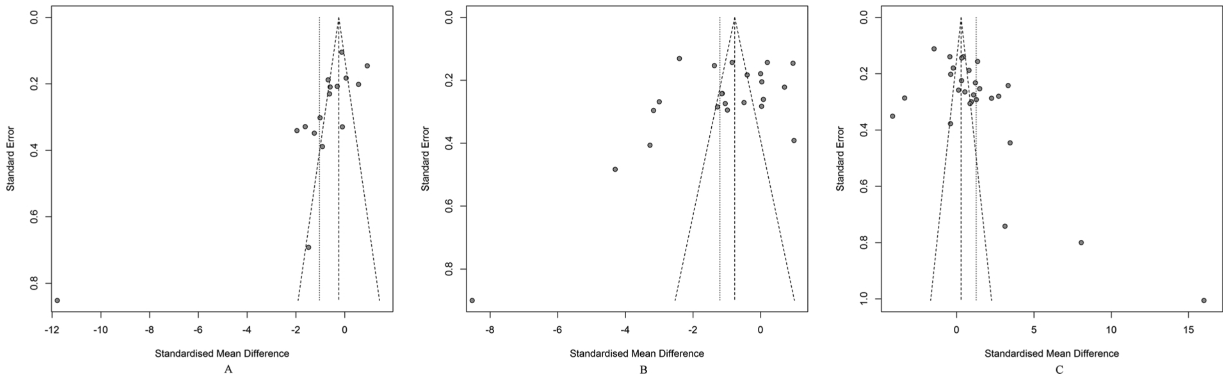

Fig. 3. Funnel plots of serum trace metal in RA patients compared with controls: A. serum selenium; B. serum zinc; C. serum copper.

different dose of Se supplement, Se status before supplementation as well as the characteristics of patients and controls. Similarly, Simkin PA reported that oral Zn sulphate may improve the clinical manifestations and disease activity of RA patients [93]. Combination use of Zn and coenzyme Q10 was reported to decrease inflammatory cytokines and improve the joint organic damage by regulating the balance between helper T 17 cells and regulatory T cells in mice model. The long-term deficiency of these elements was reported to increase the risk of large ranges of diseases as myocardiopathy, autoimmune diseases and cancers, as Se, Zn and Cu were also known to be involved in a wide range of biological processes [94]. We also hypothesize that the critical cardiovascular risk of RA may be related to the decreased Se in some extent. Hence, regular monitor of these micronutrients are necessary for RA patients.

We also find that corticosteroid use was associated with elevated serum Se in RA patients in meta-regression. The potential reason may concerning that steroid could effectively suppress inflammation response of RA patients and reduce the assumption of Se of abnormal inflammation and immunity processes. The conclusion was consistent with the result of McMillan DC that plasma Se was significantly lower from minor to modest and major inflammation [95]. This finding also in some extent proves that Se could play roles in the pathogenesis of RA. Serum Zn and Cu were reported not associated with corticosteroid use. Conclusions of previous studies about association between Zn and Cu steroid use were contradictory [96–100]. The potential underlying reasons were still obscure now, and prospective studies may be helpful. At the same time, we find the longer disease duration was associated with higher serum Cu, which indicates that Cu may takes part in the development of RA, and the study was requisite for the exploring of authentic mechanism. But we should also notice that weather the elevated serum Cu was induced by the abnormal metabolic status of Se and Zn.

In subgroup analyses we found that patients have differential serum Se, Zn and Cu across continents, and serum trace metals of some patients have similar levels with controls in specific continents. The result was consistent with the phenomenon that different countries and continents have different soil environment, and the abundance of Se was divergent, which may significant influence the enrichment of Se in human body. Besides, people in different continents have diverse dietary patterns, which will influence the nutritional habits across populations, partly contributing to the differential concentration. And another potential reason may be that the genetic background of patients was not strict consistent across races. Subgroups as North America and South America only have one or two included studies, which influenced the reliability and generation of our results. Cross-regional studies are necessary for the verification of the results. Even with these evidences, studies also reported that RA patients have a relative deficient dietary nutrients intake like folic acid, vitamin E, Cu, Zn and Se [24,25,101]. The findings indicated that the association between RA and Se, Zn or Cu may not causal, but because of the inadequate dietary intake of patients. Therefore, prospective and fundamental mechanical studies should be implemented to explore the mechanism underlying.

There also some limitations in our study should be concerned. First, some characteristics have not included in meta-regression and subgroup analyses due to insufficient data as biologics and non-steroid anti-inflammatory drugs use, and disease activity of RA patients, potentially accounting for the significant heterogeneity. Second, present study only can provide observational and correlative evidence for study design of observational nature. Third, these are significant publication bias in the meta-analysis, which will limit the stabilization of the results. And further exploring of the gray literatures should be taken to minimize the publication bias on our review. Lastly, the significant heterogeneity may limit the generalizability of the pooled results.

5. Conclusion

Patients with RA have significant decreased serum Se and Zn and increased serum Cu than health controls, suggesting potential roles of Se, Zn and Cu in the pathogenesis of RA. Patients and rheumatologist should give enough attention to the monitor of these elements during follow up.

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Declarations of Competing Interest

None.

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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.2019.07.007.

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