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Serum Levels of Copper and Zinc in Patients with Rheumatoid Arthritis: a Meta-analysis

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Abstract Many publications with conflicting results have evaluated serum levels of copper (Cu) and zinc (Zn) in patients with rheumatoid arthritis (RA). To derive a more precise estimation of the relationship, a meta-analysis was conducted. Relevant published data were retrieved through PubMed, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical Database (CBM) before September 20, 2014. Weighted mean difference (WMD) with a 95 % confidence interval (95 % CI) was calculated using STATA 11.0. A total of 26 studies, including 1444 RA cases and 1241 healthy controls, were collected in this meta-analysis. Pooled analysis found that patients with RA had a higher serum level of Cu and a lower serum Zn level than the healthy controls (Cu (μg/dl), WMD=31.824, 95 % CI=20.334, 43.314; Zn (μg/dl), WMD=−12.683, 95 % CI=−19.783, −5.584). Subgroup analysis showed that ethnicity had influence on the serum level of Cu (μg/dl) (Caucasian, WMD=43.907, 95 % CI=35.090, 52.723, $P<0.001$; Asian, WMD=14.545, 95 % CI=−12.365, 41.455, $P=0.289$) and Zn (μg/dl) (Caucasian, WMD=−11.038, 95 % CI=−23.420, 1.344, $P=0.081$; Asian, WMD=−14.179, 95 % CI=−18.963, −9.394, $P<0.001$) in RA and healthy controls. No evidence of publication bias was observed. This meta-analysis suggests that increased serum level of Cu and decreased serum level of Zn are generally present in RA patients.

Keywords Zinc · Copper · Rheumatoid arthritis · Meta-analysis

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by inflammation of the synovial membrane and progressive destruction of the articular cartilage and bone [1]. The most prominent feature is symmetrical joint swelling of the feet, hands, and knees [2]. The progressive disability has impacted people's quality of life seriously [3]. Besides, many of its risk factors have not yet been established. Some researchers have focused on the role of trace elements, including copper (Cu) and zinc (Zn) [4, 5].

Cu and Zn are trace elements that are essential for many biological processes in animals and humans. They are integral functional components of many enzymes and transcriptional regulatory proteins, which play important roles in the biochemistry of the body [6].

In recent years, a great number of studies have been performed on the possible role of trace elements in the etiology and pathogenesis of RA. Effects of Cu and Zn on RA were studied in many investigations which showed enhanced Cu serum level and decreased Zn plasma level occur in RA patients [7, 8]. However, some investigators found no differences and even lower Cu serum or plasma content in comparison with healthy group [9–11]. And other investigators found normal or higher serum or plasma Zn levels in RA compared with control group in their studies [12, 13]. Such a controversy motivated us to carry out this meta-analysis and explore the change of serum levels of Cu and Zn among RA patients.

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Methods

Search Strategy

PubMed, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical Database (CBM) were searched, and last search was updated on September 20, 2014. The searching keywords were as follows: "serum copper" or "plasma copper" or "copper" or "serum zinc" or "plasma zinc" or "zinc," and "rheumatoid arthritis" or "RA". Language was limited to English or Chinese. We also reviewed the references cited in the studies and review articles to avoid missing studies. Only published studies with full-text articles were included.

Selection Criteria

Studies eligible for this meta-analysis had to meet all the following inclusion criteria: (1) human study, (2) case-control study or cohort study or randomized clinical trial, (3) the language was either in English or Chinese, and (4) provided sufficient data of serum level of Cu or Zn for both RA and control subjects.

The exclusion criteria were as follows: (1) researches that did not meet the inclusion criteria and (2) the study reported useless or duplicated data.

Data Extraction

All data were extracted independently by two reviewers (Lihong Xin and Xiao Yang) according to the selection criteria. The following data were extracted: first author, year of publication, country, language, number of subjects, and data on serum Cu or Zn. When the extracted information was inconsistent, discrepancies were resolved by discussion between the two reviewers, with a third author (Guoqi Cai) input.

Statistical Analysis

The statistical analysis was conducted using STATA 11.0 (StataCorp, College Station, TX, USA), and $P<0.05$ was considered to be statistically significant. The weighted mean difference (WMD) and 95 % confidence interval (CI) were calculated. Before calculating the WMD, we used the unified unit, and doing the unit conversion to microgram per deciliter. Besides, in some articles, the data was only available for male and female, separately. Combined data was calculated using the following formulas:

$$\overline{x} = \frac{x_1 n_1 + x_2 n_2}{n_1 + n_2}; \quad (1)$$

$$s_c^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2} \quad (2)$$

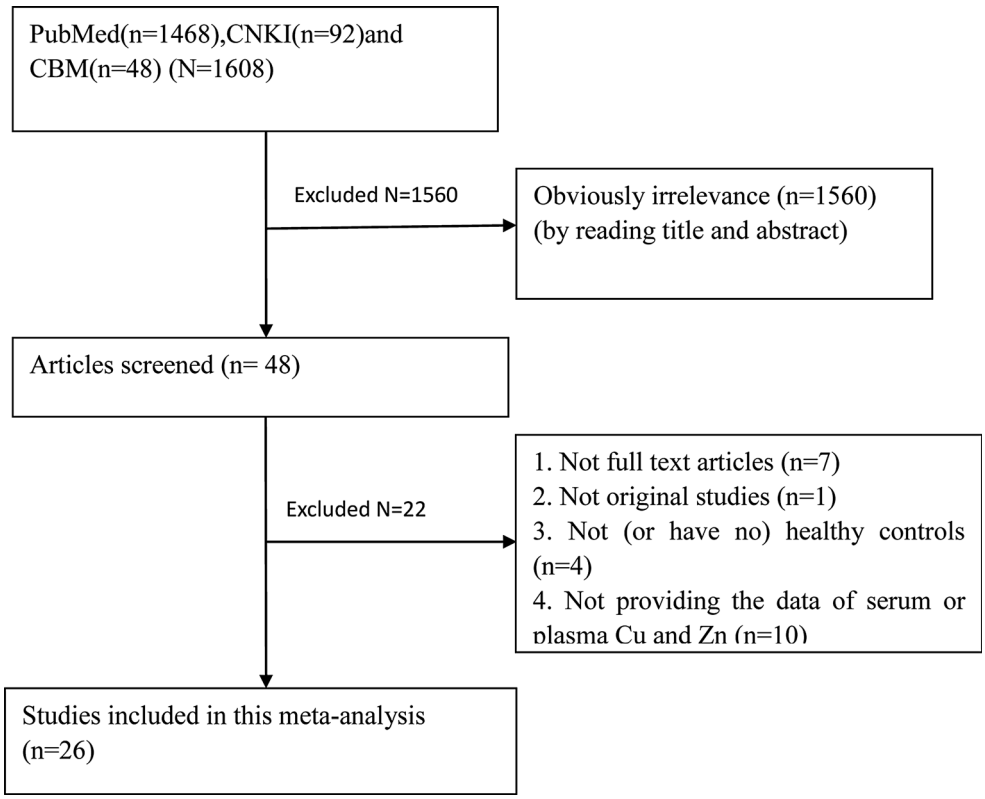

Fig. 1 Flow diagram for study selection progress

With $\bar{x}$ being the pooled mean of the data in male (x_1) and female (x_2) groups, s_c being the pooled standard deviation of the standard deviation in male (s_1) and female (s_2) groups, and n_1 and n_2 being the sample size of male and female, respectively.

Statistical heterogeneity was measured using the chi-square and *I*-square tests. If the I^2 value was less than 50 % or the *P* value was greater than 0.10, significant heterogeneity was not considered [14]; therefore, a fixed effects model was used. Otherwise, random effects model was adopted.

Subgroup analysis was used to identify associations between the serum level of Cu or Zn and other relevant study characteristics, which may be the possible sources of heterogeneity. Grouping criteria were on basis of ethnicity and blood components. Sensitivity analyses were performed by sequential omission of individual studies. Begg's test was also used to statistically assess the publication bias ($P \leq 0.10$ was considered to be representative of statistically significant publication bias [15]).

Results

Eligible Studies

A total of 1608 studies were identified using the aforementioned search terms. After a series of assessments, 26 eligible studies, including 1444 RA cases and 1241 healthy controls were chosen for the meta-analysis. The flow chart of study selection is summarized in Fig. 1. And the detailed characteristics of the included studies are summarized in Table 1.

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Country	Ethnicity	Language	Research type	Case (*n*)	Control (*n*)	Detected in serum/plasma		
								Cu	Zn	both
Li [11]	2014	China	Asian	English	Case-control	60	60			Y
Strecker [7]	2013	Poland	Caucasian	English	Case-control	74	30	Y		
Mierzecki [12]	2011	Poland	Caucasian	English	Case-control	74	30		Y	
Ala [9]	2009	Iran	Asian	English	Case-control	40	40			Y
Yazar[a] [13]	2005	Turkey	Asian	English	Case-control	25	25			Y
Qian [16]	2004	China	Asian	Chinese	Case-control	10	45			Y
Silverio Amancio [17]	2003	Brazil	Caucasian	English	Case-control	41	23			Y
Wanchu[a] [18]	2002	India	Asian	English	Case-control	39	22			Y
Louro [19]	2000	Spain	Caucasian	English	Case-control	40	95	Y		
Tuncer[a] [8]	1999	Turkey	Asian	English	Case-control	38	20			Y
Zhang[a] [20]	1997	China	Asian	Chinese	Case-control	15	20			Y
Wang [21]	1990	China	Asian	Chinese	Case-control	40	52			Y
Marrella[a] [22]	1990	Italy	Caucasian	English	Case-control	77	25	Y		
Dijkmans [23]	1987	Netherlands	Caucasian	English	Case-control	36	18		Y	
Cimmino [24]	1986	Italy	Caucasian	English	Case-control	33	85		Y	
Morgenstern [10]	1983	Israel	Asian	English	Case-control	30	30			Y
Conforti [25]	1983	Italy	Caucasian	English	Case-control	88	34	Y		
Banford [26]	1982	England	Caucasian	English	Case-control	85	49	Y		
Scudder [27]	1978	England	Caucasian	English	Case-control	100	100	Y		
Aiginger [28]	1978	Austria	Caucasian	English	Case-control	12	7	Y		
Aaseth [29]	1978	Norway	Caucasian	English	Case-control	23	30			Y
Mcmurray [30]	1975	England	Caucasian	English	Case-control	146	45	Y		
Hansson [31]	1975	Finland	Caucasian	English	Case-control	79	130/132[b]			Y
Kennedy[a] [32]	1975	Scotland	Caucasian	English	Case-control	113	100		Y	
Niedermeier [33]	1971	America	Caucasian	English	Case-control	105	105			Y
Niedermeier [34]	1965	America	Caucasian	English	Case-control	21	19	Y		

[a] The levels of Cu/Zn were detected in plasma

[b] The number of controls for the detection of Zn level

Level of Serum Cu

Among the 26 studies included, 22 studies [7–11, 13, 16–22, 25–31, 33, 34] had data of the serum or plasma Cu level. As significant heterogeneity was found (I^2=98.7 %, P<0.001), a random effect model was used. The results showed that patients with RA had a higher serum level of Cu than the healthy controls (WMD=31.824, 95 % CI=20.334, 43.314) (μg/dl) (Fig. 2).

Level of Serum Zn

There were 16 studies [8–10, 12, 13, 16–18, 20, 21, 23, 24, 29, 31–33] assessed the serum or plasma Zn level. Heterogeneity among the included articles was examined first. The results showed a high statistical heterogeneity among studies (I^2=96.6 %, P<0.001). So, a random effect model was used. The results indicated that compared with healthy controls, patients with RA had a lower serum level of Zn (WMD=−12.683, 95 % CI=−19.783, −5.584) (μg/dl) (Fig. 3).

Subgroup Analysis

The subgroup analysis showed that ethnicity had influence on the serum level of Cu (μg/dl) (Caucasian, WMD=43.907, 95 % CI=35.090, 52.723, P<0.001; Asian, WMD=14.545, 95 % CI=−12.365, 41.455, P=0.289) and Zn (μg/dl) (Caucasian, WMD=−11.038, 95 % CI=−23.420, 1.344, P=0.081; Asian, WMD=−14.179, 95 % CI=−18.963, −9.394, P<0.001) in RA patients and healthy controls (Figs. 4 and 5), and the pooled results showed no significant difference in serum and plasma (Table 2).

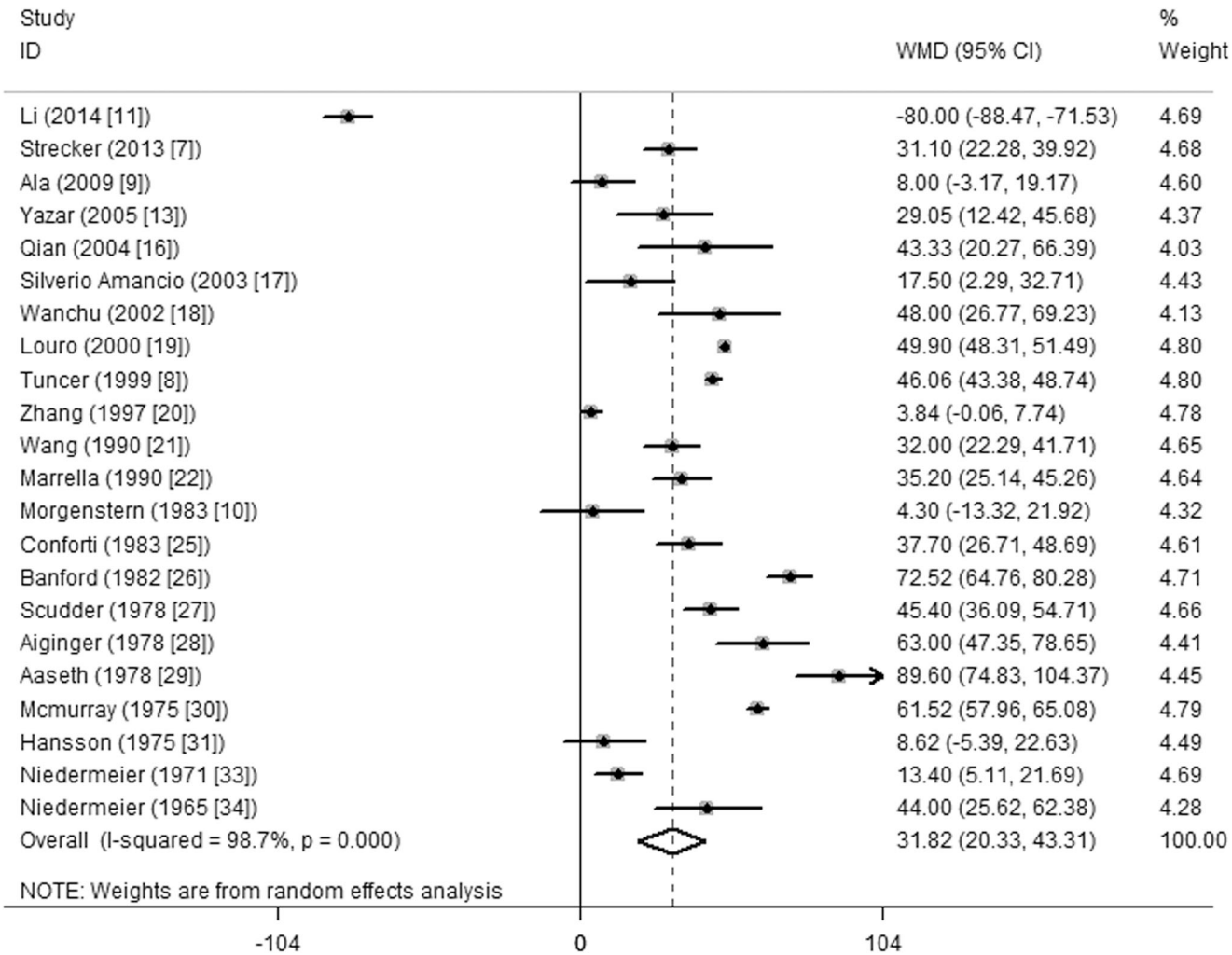

Fig. 2 Forest plot of studies in serum Cu for patients with RA versus healthy controls. The combined WMD and 95 % CI were calculated using the random effects model

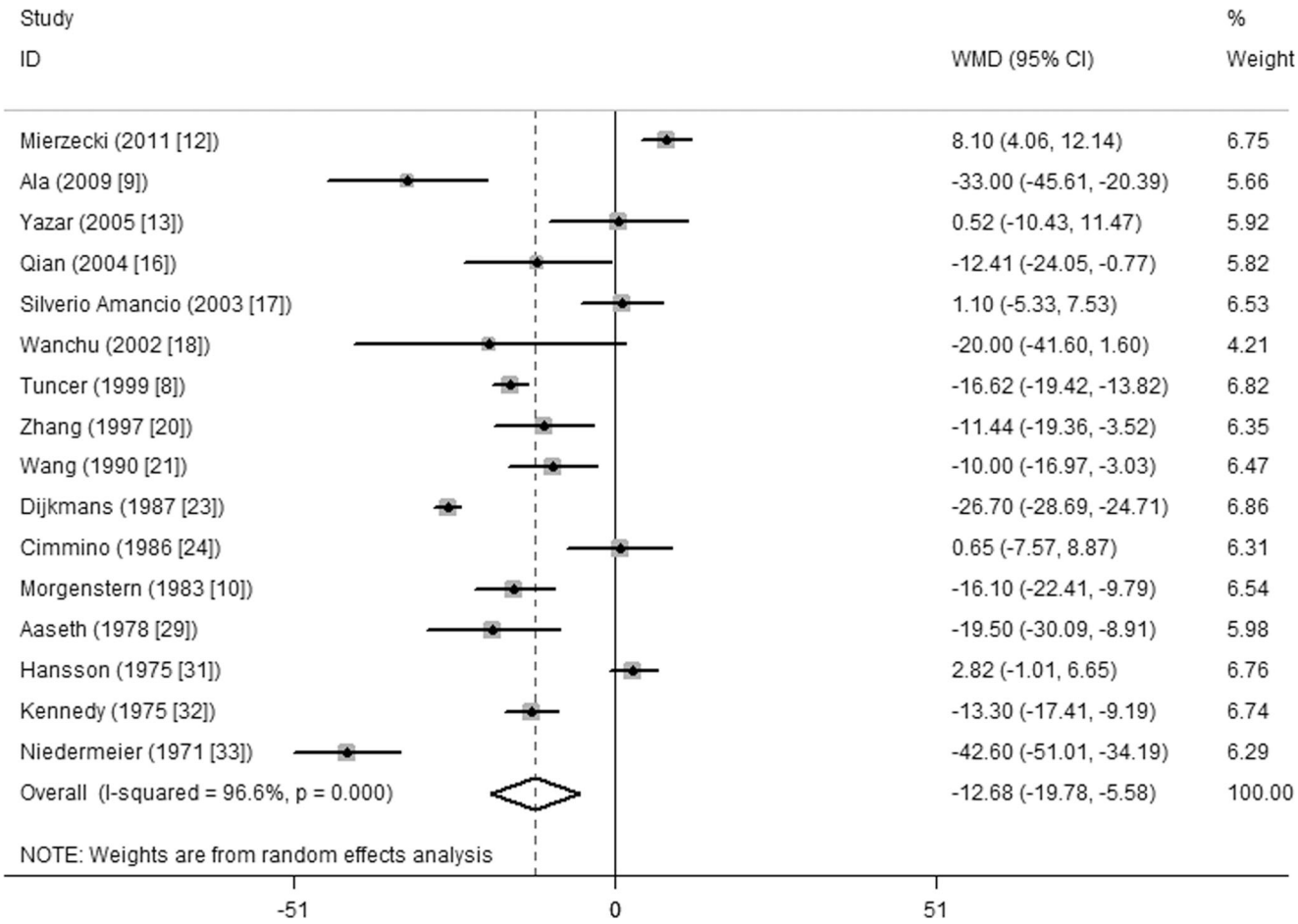

Fig. 3 Forest plot of studies in serum Zn for patients with RA versus healthy controls. The combined WMD and 95 % CI were calculated using the random-effects model

Sensitivity Analysis and Publication Bias

Sensitivity analysis showed that no individual study had extreme influence on the pooled effect (data not shown). Publication bias was measured using Begg's test, and there was no evidence revealing publication bias for Cu (Begg's test: P= 0.155) or Zn (Begg's test: P=0.315).

Discussion

The result of this meta-analysis indicated that the high serum level of Cu was observed in RA patients. This result is in keeping with some studies showing that among RA patients the mean Cu level was significantly higher in serum, compared with the control group [7, 16, 17, 19, 21]. Cu homeostasis is mainly regulated by SLC31/CTR (solute-linked carrier, SLC; copper transporter, CTR). The members A1 (CTR1) and A2 (CTR2) of the SLC31 family of solute carriers act to regulate the intracellular Cu ion concentration within a certain range [35]. In the blood, Cu is predominantly present in the plasma, where it is major bound to ceruloplasmin (Cp) and other Cu-binding proteins [36, 37]. During the inflammatory process in RA, some inflammatory biomarkers such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) can upregulate the synthesis and secretion of Cp in hepatocytes [38–40]. As a result, the concentration of Cu increases when Cp was transferred from hepatocytes to blood serum. It seems that it could explain why the patients with RA have higher serum Cu level, even though some authors found inconsistent results [9–11, 20, 31].

The outcome also suggested that serum level of Zn was lower in RA than healthy controls. This finding is consistent with previous studies [9, 10, 16, 21, 23, 29, 33]. Zn is an indispensable trace element in the body and is considered as crucial for immune responses [41]. Its homeostasis is tightly controlled by Zn transporter family members: the SLC30s/ZnTs (Zn transporter, ZnT) and SLC39s/ZIPs (Zrt/Irt-like protein, ZIP) families contribute to Zn ion influx and efflux, respectively [35, 42]. Zn ion is absorbed through the intestinal

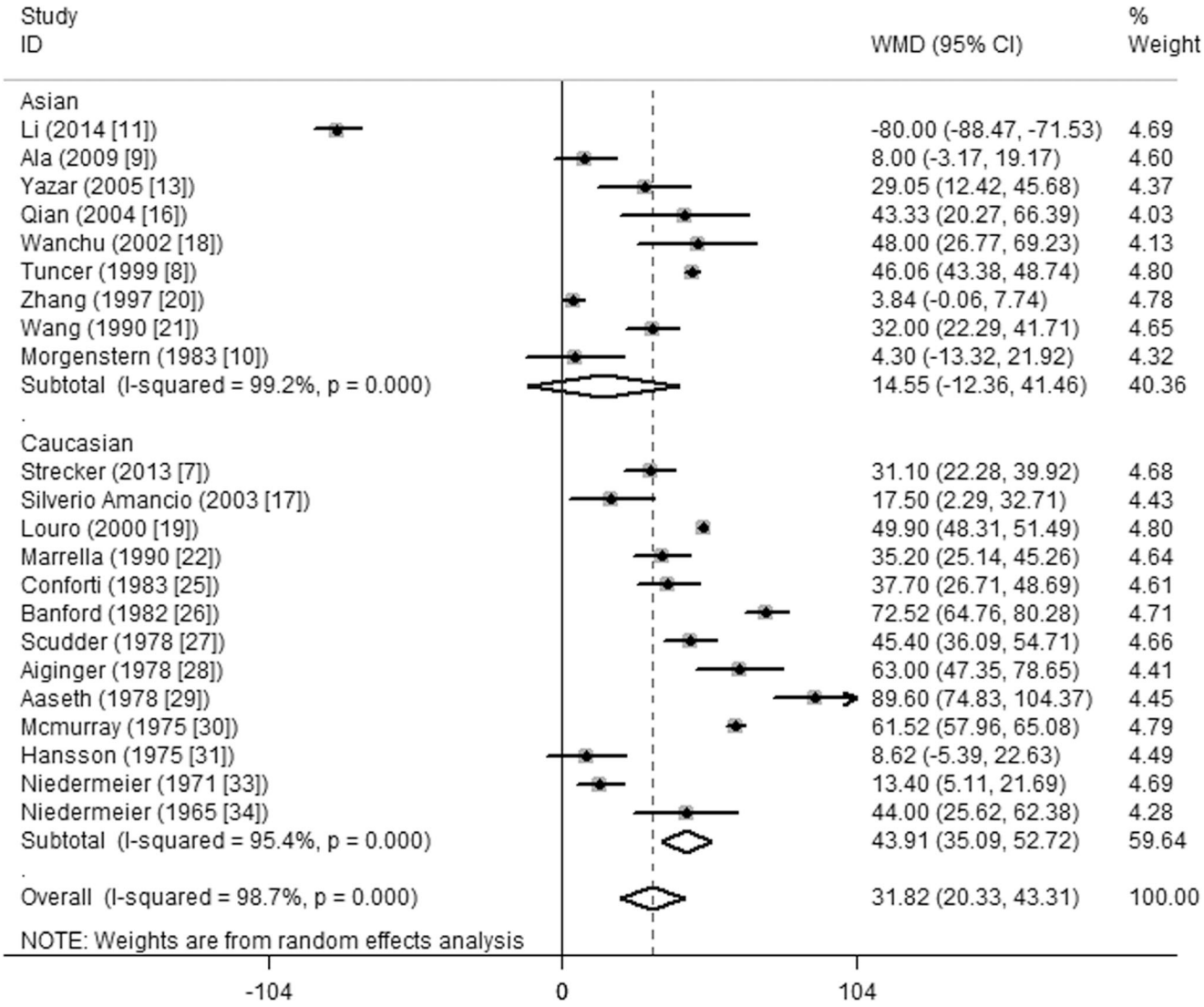

Fig. 4 Forest plots of relationship between ethnicity and serum Cu level

Zn transporters such as ZIP4 and ZnT1. Next, it is taken into peripheral or somatic cells by ZIP14. Finally, the incorporated Zn ion is delivered within the cell by intracellular Zn transporters such as ZIP13 and ZnT5 [42]. During the inflammatory response, pro-inflammatory cytokines (for example, IL-6, which was considered as an important role in the progress of inflammation in RA [43]), can upregulate the Zn importer ZIP14 in the liver, resulting in Zn influx and binding of Zn, which probably contributed to the decrease of serum Zn [38, 44]. Milanino et al. also reported the serum or plasma Zn level in chronic models of inflammation (adjuvant arthritis of the rat) was significantly decreased, while the Zn accumulation in the liver was three to four times higher than that observed in acutely inflamed animals [45]. Therefore, it seems to suggest that inflammation essentially promotes a redistribution of Zn between plasma and liver. However, in our study, we did not analyze the Zn level in the liver because of the restriction of data in the included studies. Beyond that, white blood cells release leukocyte endogenous neurotransmitter to promote the synthesis of liver to release a series of defensive reaction substance in the infection, such as fibrin and α_2-acute globulin, and the process would consume Zn [20]. RA, as a chronic systemic inflammatory disease, was closely associated with the infection and abnormal immune [20]. So, we speculate that all of the above lead to the decrease of serum Zn in RA patients.

On the other hand, RA, as a systemic autoimmune disease, characterized by a chronic inflammatory reaction leading to progressive destruction of the joints [46], could also be affected by the level of Cu and Zn. In many biochemical processes, Cu is an essential bioelement which plays a key role in the cell's physiology, as a cofactor or an integral part of a number of enzymes, participating in anti-oxidative processes [7, 37]. There has study reported that serum Cu correlated well with

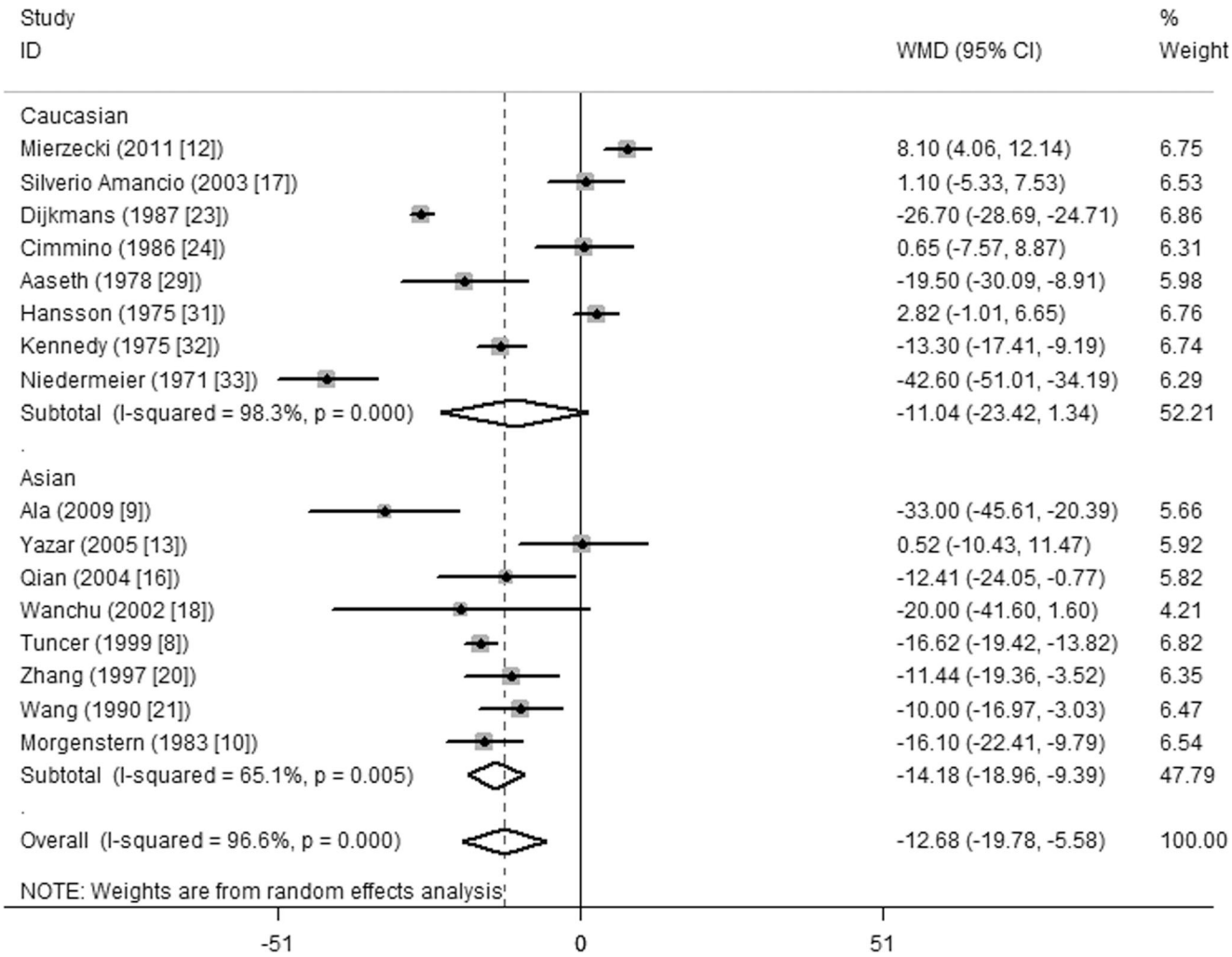

Fig. 5 Forest plots of relationship between ethnicity and serum Zn level

Table 2 Effects by subgroup analysis

Subgroups	No. of studies	WMD (95 % CI)	*P* value	Test of heterogeneity	
				I^2 (%)	*P* value
Cu					
Serum/plasma					
Serum	17	31.788 (16.674, 46.901)	<0.001	98.7	<0.001
Plasma	5	32.029 (8.120, 55.939)	0.009	98.7	<0.001
Ethnicity					
Caucasian	13	43.907 (35.090, 52.723)	<0.001	95.4	<0.001
Asian	9	14.545 (−12.365, 41.455)	0.289	99.2	<0.001
Zn					
Serum/plasma					
Serum	11	−13.169 (−23.820, −2.518)	0.015	97.7	<0.001
Plasma	5	−12.665 (−17.334, −7.995)	<0.001	62.1	0.032
Ethnicity					
Caucasian	8	−11.038 (−23.420, 1.344)	0.081	98.3	<0.001
Asian	8	−14.179 (−18.963, −9.394)	<0.001	65.1	0.005

the overall disease activity in RA [47]. Cu as a necessary mineral for bone development and maintenance, it is responsible for appropriate cartilage mineralization, formation of elastin and collagen structure, creation of bony trabeculation structures, and the crosslinking of collagen and elastin [7, 48, 49]. Besides, it plays an important role for immune response, including the production of IL-2 by activated lymphocytic cells, and supports the activity and effectiveness of humoral and cellular immunity [39]. All of these evidences support the view that Cu has important influence on RA.

The importance of Zn nutrition has been known for a long time. It is involved in many aspects of cellular metabolism and is an integral component of proteins involved in cell structures and stabilization of cell membranes [50]. The role of Zn in the immune system is also essentially important. There has evidence that Zn deficiency affects cells involved in both innate and adaptive immunity at the survival, proliferation and maturation levels. These cells include monocytes, and polymorphonuclear, natural killer, T, and B cells [51]. Moreover, Zn deficiency induces pro-inflammatory cytokine IL-1β secretion [52]. And simultaneous evaluation of circulating cytokines and Zn status showed that the reduced circulating Zn correlates with increased IL-6, IL-8, and TNF-α levels [53]. In summary, Zn deficiency affects many aspects of the immune system. Besides, Zn is a component of matrix metalloproteases, which are responsible for matrix remodeling and have a central role in bone destruction [51]. What is more important, it is now well established that activated T and B cells, and their products including IL-1β, IL-6, and TNF-α play an important role in the pathogenesis of RA [40, 54]. For these reasons, Zn nutritional defect is linked to a large number of diseases and particularly to immune diseases, including RA.

Subgroup analysis by ethnicity revealed that serum Cu level had no difference between RA and healthy controls in Asian population, while serum level of Zn had no statistical difference between RA and control groups in Caucasian population. This may be on account of the difference of race and environment. Sensitivity analysis showed that the corresponding pooled WMD and 95 % CI were not conspicuously altered with any single study excluded. Besides, no significant publication bias of Cu and Zn were observed, suggesting good stability and reliability.

In this study, we excluded some studies [11, 55] because we consider that their data is abnormal. As we all know, zinc is trace element, which is extremely low in our body, and its serum normal level is only 66–110 μg/dl [56]. But in these studies, the data seriously exceeded the standard in healthy controls, so we consider these data as outliers, and did not include them in the analysis.

To the best of our knowledge, this is the first meta-analysis providing the pooled estimates of the difference of serum Cu and Zn levels between RA patients and healthy controls. However, the possible limitations of our study should be considered. First, some too old studies were included in the meta-analysis, which might weaken the quality of the results. In addition, because of the restriction of data, we did not analyze Cu and Zn levels in other tissues, and this may affect the comprehensive interpretation of the levels of Cu and Zn in RA. Beyond that, our results indeed showed increased level of serum Cu and decreased level of serum Zn in RA patients, but we could not confirm the roles played by Cu and Zn in the etiology and pathogenesis of RA. Therefore, more well-designed studies are required to verify the results and assess the role of Cu and Zn in the progress of RA.

Conclusions

In conclusion, this meta-analysis demonstrates that increased levels of serum Cu and decreased levels of serum Zn generally exist in RA patients, and further studies of higher quality may lead to more solid conclusions.

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Conflicts of interest None of the authors has any conflicts of interest to declare.

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