Original Article

Association between serum copper and heart failure: a meta-analysis

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Background and Objectives: Copper dyshomeostasis can lead to many diseases, including cardiovascular disease. However, there are conflicting reports on the relationship between serum copper and heart failure (HF). To explore the relationship between serum copper levels and HF by performing a meta-analysis. **Methods and Study Design:** The PubMed and ScienceDirect databases until June 2019 were searched for reports on the association between serum copper levels and HF. **Results:** A total of thirteen studies including 1504 subjects were chosen for the meta-analysis. The pooled analysis indicated that patients with HF had higher serum copper than the control subjects [standardized mean difference (SMD), 0.982; 95% confidence interval (CI), (0.679, 1.285)]. Subgroup analysis stratified by different geographic locations found that HF patients had higher copper than the control subjects in Asia and Europe [Asia: SMD, 0.948 and 95% CI, (0.569, 1.327); Europe: SMD, 1.275 and 95% CI, (0.633, 1.917)], but not in America [America: SMD, 0.637 and 95% CI, (-0.109, 1.383)]. Additionally, subgroup analysis revealed that patients with ischemic cardiomyopathy (ICM) [SMD, 1.171; 95% CI, (0.717, 1.624)], idiopathic dilated cardiomyopathy (IDCM) [SMD, 0.569; 95% CI, (0.097, 1.042)] and other types of HF [SMD, 1.152; 95% CI, (0.594, 1.710)] all had higher copper levels than controls. Further subgroup analysis stratified by Newcastle–Ottawa Scale (NOS) scores also found higher serum copper in patients with HF than controls within each subgroup. **Conclusions:** Our meta-analysis identified a significant association between high serum copper and HF.

Key Words: copper, Cu, heart failure, meta-analysis

INTRODUCTION

Copper, an important trace element for humans, plays a critical role in the oxidant/antioxidant. Copper dyshomeostasis can lead to cardiovascular disease, numerous studies support the possibility that high copper concentration may increase the risk for cardiovascular disease.[1] Copper is being increasingly recognized as an essential mediator of the development and progression of myocardial infarction, coronary artery disease and atherosclerosis.[1,2] Additionally, experimental studies have examined the consequences of copper deficiency in the cardiovascular system. According to Zheng et al copper supplementation restores cytochrome c oxidase (CCO) activity and promotes myocardial angiogenesis, regression of cardiac hypertrophy and the recovery of cardiac contractile function.[3]

Heart failure (HF) is one of the most frequent causes of death worldwide. Recently published evidence has suggested that micronutrient dyshomeostasis is associated with HF.[4] Many studies have attempted to explore the relationship between changes in serum copper level in HF patients; however, their results have been conflicting. Some studies have found significantly higher serum copper levels in patients with HF than in control groups,[5-13] whereas other works reported that the serum copper levels did not differ significantly between patients with HF and controls.[14-16] Therefore, we performed a comprehensive and critical meta-analysis of previous studies to determine a clearer, evidence-based conclusion concerning the association between serum copper levels and HF.

METHODS

Search strategy

A systematic search of the PubMed and ScienceDirect databases until June 2019 was performed using medical subject headings (MeSH) or free text words. The search keywords were “copper” or “Cu” and “heart failure”. The references cited in the studies and in review articles were also reviewed to identify additional works that were not captured by the database search. Only published studies with full-text reports were included.

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Inclusion and exclusion criteria

Three authors (Lei Huang, Ronghuan Shen, Hao Rong) carried out the search independently. Titles and abstracts were screened for subject relevance, and studies that could not be definitely excluded based on the abstract information were selected for full-text screening. Two authors (Longfei Huang, Jing Yu) independently selected eligible studies for possible inclusion in the meta-analysis. Any disagreement regarding study inclusion was resolved by discussion with Lei Huang toward reaching a consensus.

The appropriateness of the studies was assessed. The criteria for inclusion in the analysis were: (1) human study, (2) case-control or cohort study or randomized clinical trial, (3) focus on the association between serum copper levels and HF; and (4) provides sufficient data on copper levels in both patients with HF and controls. The exclusion criteria were: (1) obviously irrelevant study; (2) animal study; (3) review or case report; and (4) failure to provide data on copper levels in either patients with HF or controls.[17]

Data extraction and quality assessment

All data were extracted independently by two reviewers (Longfei Huang, Jing Yu) according to the inclusion and exclusion criteria. Specifically, the following data were extracted: first author, year of publication, country, number of participants, and data on serum copper. Any inconsistencies or discrepancies in the extracted information were resolved by discussion between the two reviewers, with a third author (Ronghuan Shen) providing input.

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of all the included studies. This assessment tool focused on three aspects: participant selection, comparability, and exposure. Studies that satisfied all the items on the scale were given nine stars. Two authors (Lei Huang, Hao Rong) assessed the quality of studies independently.[18]

Statistical analysis

Statistical analysis was carried out by using Stata 12, statistical significance being set at $p<0.05$. The standardized mean difference (SMD) and 95% confidence intervals (CI) were calculated. A random effects or fixed effects model was used to calculate the pooled SMD in the presence or absence of heterogeneity, respectively. Statistical heterogeneity was measured by applying the χ^2 and I^2 tests. I^2 value less than 50% or p greater than 0.10 was considered to denote insignificant heterogeneity and a fixed effects model was applied; otherwise, a random effects model was used.[2]

Subgroup analysis was performed to determine associations between serum copper levels and other relevant study characteristics that may been sources of heterogeneity. Sensitivity analysis was carried out by removing one study at a time to assess whether the results were affected markedly by any single study. Publication bias was measured by using Begg's test and visualization of funnel plots.[18]

RESULTS

Figure 1 shows the detailed steps for selecting published reports. A total of 412 primary reports were identified by using the aforementioned search terms. After the above-described series of assessments, 13 eligible articles with 1504 subjects were chosen for the meta-analysis. The characteristics of the included studies were presented in Table 1. Among the 13 studies, 2 were conducted in America, 7 were conducted in Asian countries and the remaining 4 were in Europe countries.

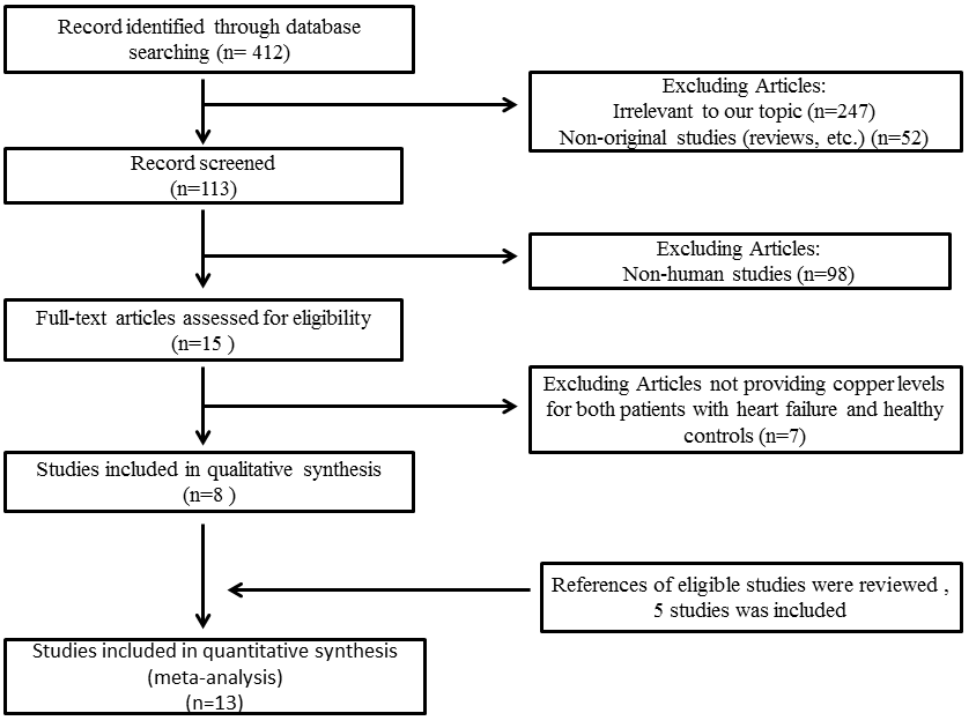


Figure 1. Flow diagram of the literature search.

Table 1. Characteristics of subjects in included studies

Author	Country	HF number	HF Cu concentration	Controls number	Controls Cu concentration	subgroups of HF	NOS Score
Sullivan JF 1979	UAS	42	1.38±0.33 μg/ml	37	1.06±0.3 μg /ml	ICM	7
Singh MM 1985(1)	India	11	205±17.6 μg %	13	171±14.1 μg %	ICM	6
Singh MM 1985(2)	India	10	203±16.6 μg %	13	171±14.1 μg %	ICM	6
Singh MM 1985(3)	India	2	208±16.3μg %	13	171±14.1 μg %	ICM	6
Atlihan F 1990(1)	Turkey	29	174±26.6 μg/100mL	11	114±16.2 μg/100 mL	Other	6
Atlihan F 1990(2)	Turkey	29	151±27.3 μg/100mL	11	114±16.2 μg/100 mL	Other	6
Oskar 1993	Germany	20	1544±280 μg/L	50	1111±340 μg/L	IDCM	8
Cénac A 1996	France	32	2.03±0.37 μg /mL	32	1.23±0.2 μg /mL	Other	7
de Lorgeril M 2001	France	21	1.15±0.34 mg/L	18	0.97±0.09 mg/L	Other	7
Sérgio da Cunha 2002	Brazil	30	1.2±0.4 mg/L	30	1.1±0.4 mg/L	IDCM	7
Topuzoglu G 2003	Turkey	54	172±47.6 μg/dL	20	117±31.3 μg/dL	IDCM	6
Kosar F 2006(1)	Turkey	54	880±185 μg/L	30	644 ±179 μg/L	Other	8
Kosar F 2006(2)	Turkey	26	886±143 μg/L	30	644 ±179 μg/L	IDCM	8
Kosar F 2006(3)	Turkey	28	874±146 μg/L	30	644±179 μg/L	ICM	8
Kosar F 2006(4)	Turkey	24	861±156 μg/L	30	644 ±179 μg/L	Other	8
Kosar F 2006(5)	Turkey	20	895±133 μg/L	30	644±179 μg/L	Other	8
Kosar F 2006(6)	Turkey	10	936±97 μg/L	30	644±179 μg/L	Other	8
Salehifar E 2008(1)	Iran	18	1.33±0.2 mg/L	27	1.31±0.23 mg/L	IDCM	8
Salehifar E 2008(2)	Iran	3	1.12±0.16 mg/L	27	1.31±0.23 mg/L	IDCM	8
Salehifar E 2008(3)	Iran	4	1.32±0.29 mg/L	27	1.31±0.23 mg/L	IDCM	8
Salehifar E 2008(4)	Iran	9	1.43±0.12 mg/L	27	1.31±0.23 mg/L	IDCM	8
Salehifar E 2008(5)	Iran	2	1.28±0.05 mg/L	27	1.31±0.23 mg/L	IDCM	8
Shokrzadeh M 2009(1)	Iran	30	1.54±0.52 mg/L	27	1.31±0.24 mg/L	ICM	7
Shokrzadeh M 2009(2)	Iran	17	1.65±0.54 mg/L	27	1.31±0.24 mg/L	ICM	7
Shokrzadeh M 2009(3)	Iran	10	1.36±0.35 mg/L	27	1.31±0.24 mg/L	ICM	7
Ghaemian A 2011(1)	Iran	38	66.6±25 μg/dL	40	77.6±6.4 μg/dL	Other	8
Ghaemian A 2011(2)	Iran	40	72±44.3 μg/dL	40	77.6±6.4 μg/dL	Other	8
Alexanian I 2014(1)	Greece	81	118±35.4 μg/dL	21	92.7±17.0 μg/dL	Other	8
Alexanian I 2014(2)	Greece	44	121±33.9 μg/dL	21	92.7±17.0 μg/dL	Other	8

HF: heart failure; IDCM: idiopathic dilated cardiomyopathy; ICM: ischemic cardiomyopathy; NOS: Newcastle–Ottawa Scale.

Serum copper levels and HF

Thirteen studies that assessed the association between serum copper and HF were identified. First, the heterogeneity of the included studies was assessed and highly significant heterogeneity identified (I^2=84.1%; p<0.001); thus, a random effects model was used. The results of the random effects meta-analysis indicated that HF patients had higher copper levels than the control subjects [SMD, 0.982, 95% CI, (0.679, 1.285)] (Figure 2A).

Subgroup analysis

Subgroup analysis showed that the geographic locations, etiologies of HF [idiopathic dilated cardiomyopathy (IDCM) and ischemic cardiomyopathy (ICM)] and NOS scores were significantly associated with serum copper levels in HF patients and control subjects.

Subgroup analysis stratified by geographic location found that HF patients had higher copper levels than the control subjects in Asia and Europe [Asia: SMD, 0.948 and 95% CI, (0.569, 1.327); Europe: SMD, 1.275 and 95% CI, (0.633, 1.917)], but not in America [America: SMD, 0.637 and 95% CI, (-0.109, 1.383)] (Figure 2B). In addition, subgroup analysis stratified by HF subgroups found that patients with ICM [SMD, 1.171; 95% CI, (0.717, 1.624)], IDCM [SMD, 0.569; 95% CI, (0.097, 1.042)] and other HF patients [SMD, 1.152; 95% CI, (0.594, 1.710)] had higher copper levels than the control subjects (Figure 2C). Further subgroup analysis stratified by NOS scores also found serum copper levels higher than the control subjects [NOS=6: SMD, 1.171 and 95% CI, (0.717, 1.624); NOS=7: SMD, 0.569 and 95% CI, (0.097, 1.042); NOS=8: SMD, 1.152 and 95% CI, (0.594, 1.710)] (Figure 2D). Table 2 provides a summary of subgroup analysis results.

Sensitivity analysis and publication bias

The sensitivity analysis showed that no individual study had an extreme influence on the pooled effect (Table 3). According to a funnel plot (Figure 3), which was symmetrical, and Begg's test, there was no significant publication bias (p=0.088).

DISCUSSION

In the present meta-analysis of a total of 13 eligible articles, with a combined patient population of 1504 participants, we first assessed the association between serum copper and HF. To the best of our knowledge, this is the first meta-analysis to estimate the association between copper levels and HF. We made sure to minimize the bias by means of study procedure. Not only did we search PubMed and ScienceDirect databases to identify potential studies, but also we manually examined all reference lists from relevant studies. We found that serum copper was significantly higher in patients with HF than in control subjects, which supports the proposition that copper levels differ between patients with HF and controls. Subgroup analysis showed higher serum copper levels in patients with HF than in controls in Asia and Europe; however, there was no significant difference in serum copper levels between these groups in America. This discrepancy may be attributable to the limited number of studies included in the analysis. Our results showed the geographical paradox, therefore a trans-regional multicenter study is needed for the investigation of the interrelationship between copper levels and HF of different human races or regions.

The mechanisms underlying the association between serum copper levels and HF are still not fully understood. One possibility is that micronutrient dyshomeostasis (such as zinc, copper, and zinc/ copper ratio dyshomeostasis) is associated with HF. Amounts of zinc and copper in the body affect each other. For instance, decreased zinc levels, increased copper levels, and decreased zinc/ copper ratios have been observed in many diseases, including rheumatoid arthritis, ICM, and thyroid carcinoma, among others.[13,19,20] Moreover, a decreased zinc/ copper ratio and the subsequent systemic oxidative stress explained the more extensive atherosclerosis in some aged patients.[21] Some studies have reported that oxidative stress is important, correlating with the severity of manifestations of HF[22,23] and with impairment of antioxidant defenses in these patients.[24-26] Copper is an essential cofactor in a variety of metal-binding proteins and enzymes, including copper–zinc superoxide dismutase (zinc-copper SOD), that have highly efficient antioxidant mechanisms and a preventive effect on the occurrence of free radical-induced injury. It was also reported that the zinc/ copper ratio dyshomeostasis (for example, decreased zinc levels, increased copper) has been found to be associated with lower SOD activity[27] and greater susceptibility to oxidative injury.[28] Thus, in patients with HF, antioxidant defenses such as zinc-copper SOD could be overwhelmed, creating an antioxidant deficit, particularly when the activity of the oxidoreductase in question is dependent on copper levels.

The high serum copper in HF probably reflect a significant increase in ceruloplasmin (Cp), which binds up to 95 % of the circulating serum copper.[29] Cp has been shown to have multiple roles in copper transportation, coagulation, angiogenesis, defense against oxidant stress, and iron homeostasis.[30] In addition to transporting copper, Cp oxidizes Fe(II) to Fe(III) (ferroxidase) to be incorporated into transferrin, exerts antioxidant glutathione–peroxidase activity, and scavenges reactive oxygen species (ROS),[31] thus possibly being fundamentally involved in protection from iron-mediated free radical injury.[32] Cp has also been shown to have NO oxidase activity in vivo, converting NO, which is a potent short living vasodilator and anti-oxidant, to the less active reservoir form of nitrite. High concentrations of Cp may decrease available plasma NO, thus enhancing reactive oxidant species formation and oxidative cell injury. Recent studies have demonstrated that high concentrations of Cp are associated with increased risk of developing HF.[29,33,34] We speculate that HF may be associated with high Cp concentrations as a result of the high serum copper levels.

According to Tousoulis et al., concentrations of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, are high in individuals with HF and are related to long-term prognosis.[35] IL-1 and TNF-α concentrations have been found to correlate positively with copper in patients with active rheumatoid arthritis (RA).[19] Thus, we speculated that elevated inflammatory markers in HF further induced by higher lev-

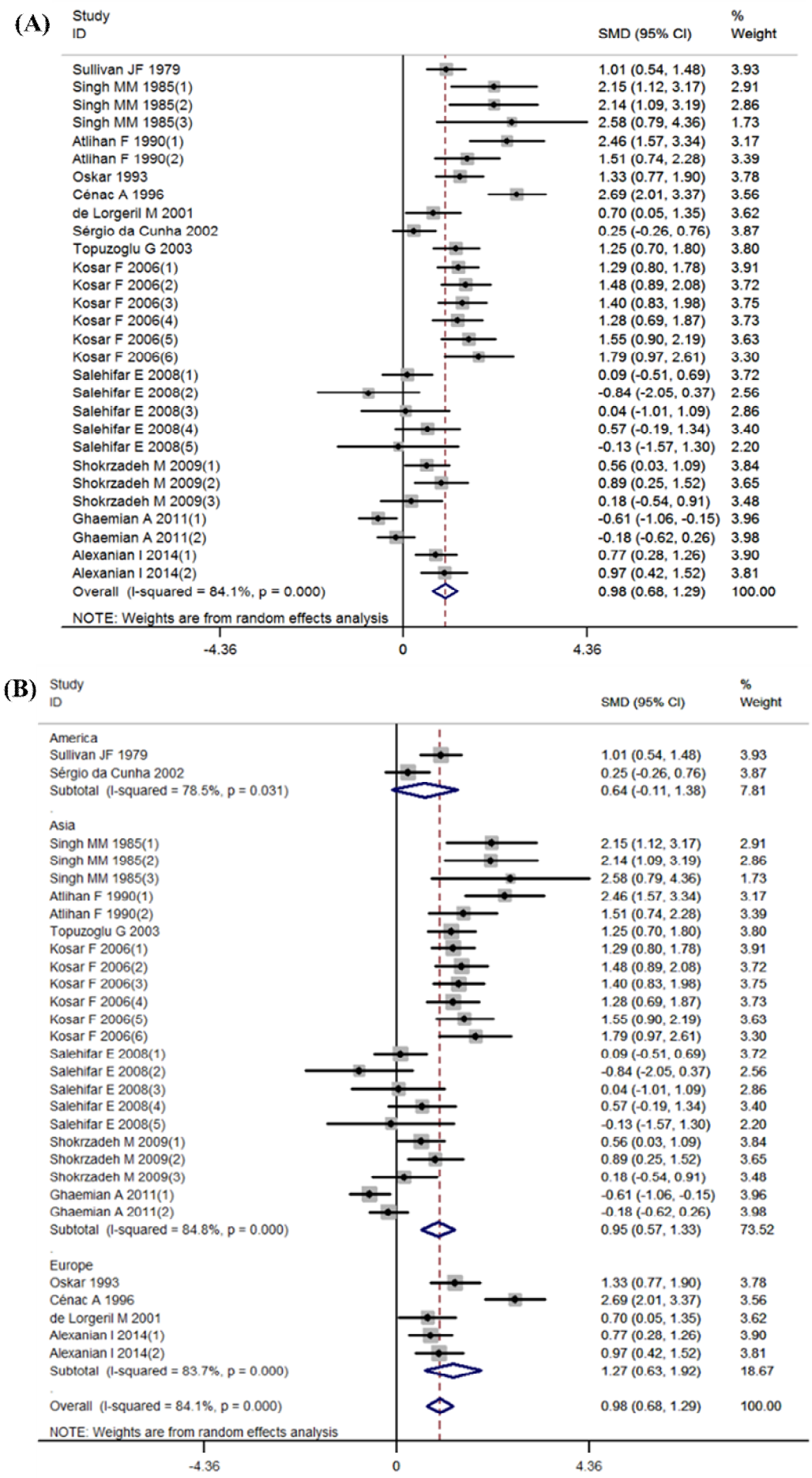
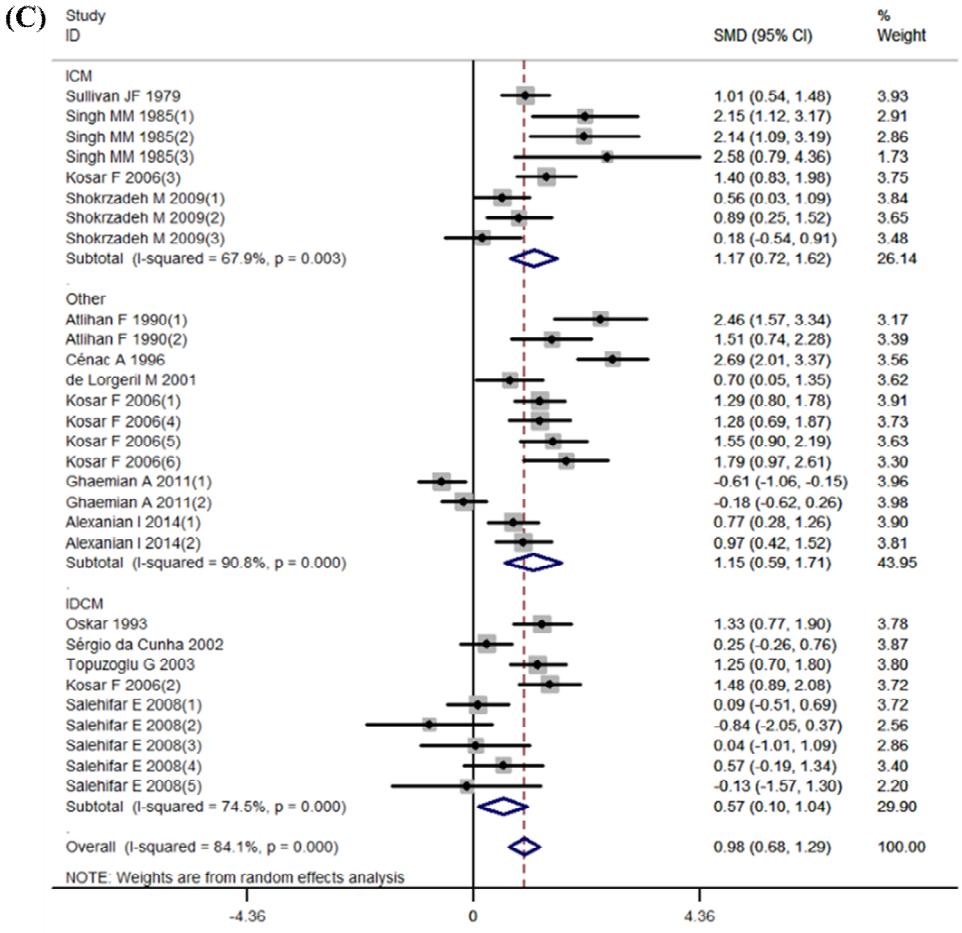


Figure 2. Forest plot of studies in copper levels for subjects with HF versus control subjects. The combined SMD and 95% confidence intervals (CIs) were calculated using the random-effects model (A); Subgroup analysis of studies in levels of copper for subjects with HF versus control subjects. Stratified by geographical location (B). Stratified by subgroups of HF (C). Stratified by NOS scores (D).



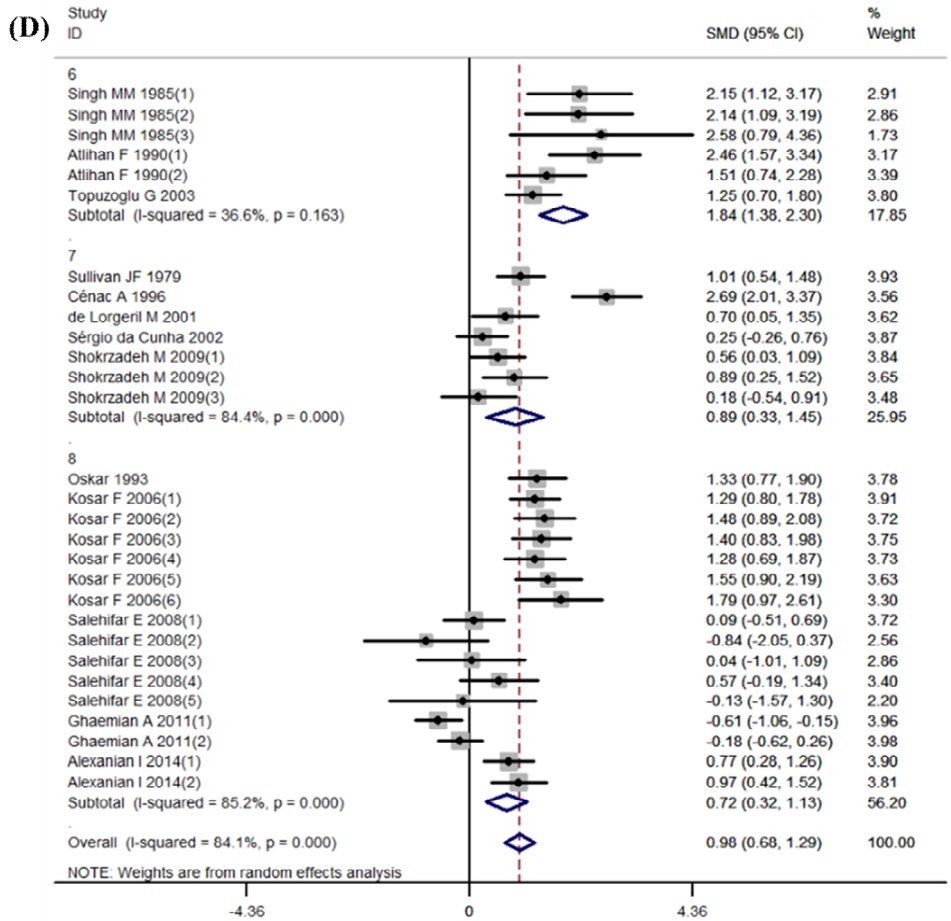


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Table 2. Subgroup analyses of copper levels and HF

Subgroup	Number of Studies	SMD (95% CI)	Test of SMD = 0		Heterogeneity	
			Z	*p* for Z	I^2	*p* for I^2
Geographical location						
America	2	0.637 (-0.109, 1.383)	1.67	0.094	78.5%	0.031
Asia	22	0.948 (0.569, 1.327)	4.90	<0.001	84.8%	<0.001
Europe	5	1.275 (0.633, 1.917)	3.89	<0.001	83.7%	<0.001
Subgroups of HF						
ICM patients	8	1.171 (0.717, 1.624)	5.06	<0.001	67.9%	0.003
IDCM patients	9	0.569 (0.097, 1.042)	2.36	0.018	74.5%	<0.001
Other HF patients	12	1.152 (0.594, 1.710)	4.05	<0.001	90.8%	<0.001
NOS						
6	6	1.171 (0.717, 1.624)	7.79	<0.001	36.6%	0.163
7	7	0.569 (0.097, 1.042)	3.10	0.002	84.4%	<0.001
8	16	1.152 (0.594, 1.710)	3.50	<0.001	85.2%	<0.001

HF: heart failure; IDCM: idiopathic dilated cardiomyopathy; ICM: ischemic cardiomyopathy; NOS: Newcastle–Ottawa Scale; SMD: standardized mean difference; CI: confidence intervals.

Table 3. The heterogeneity of the included studies through sensitivity analysis

Excluded studies	SMD (95 % CI)	I^2	*p* value
Sullivan JF 1979	0.982 (0.664, 1.300)	84.6%	<0.001
Singh MM 1985(1)	0.947 (0.642, 1.252)	84.1%	<0.001
Singh MM 1985(2)	0.948 (0.643, 1.253)	84.1%	<0.001
Singh MM 1985(3)	0.954 (0.650, 1.258)	84.3%	<0.001
Atlihan F 1990(1)	0.933 (0.633, 1.233)	83.5%	<0.001
Atlihan F 1990(2)	0.964 (0.654, 1.274)	84.4%	<0.001
Oster O 1993	0.969 (0.656, 1.282)	84.4%	<0.001
Cénac A 1996	0.916 (0.628, 1.204)	81.7%	<0.001
de Lorgeril M 2001	0.994 (0.680, 1.307)	84.6%	<0.001
Sérgio da Cunha 2002	1.012 (0.700, 1.324)	84.1%	<0.001
Topuzoglu G 2003	0.972 (0.658, 1.287)	84.5%	<0.001
Kosar F 2006(1)	0.971 (0.656, 1.286)	84.4%	<0.001
Kosar F 2006(2)	0.963 (0.652, 1.275)	84.3%	<0.001
Kosar F 2006(3)	0.966 (0.654, 1.279)	84.3%	<0.001
Kosar F 2006(4)	0.971 (0.658, 1.285)	84.5%	<0.001
Kosar F 2006(5)	0.961 (0.651, 1.271)	84.3%	<0.001
Kosar F 2006(6)	0.955 (0.647, 1.262)	84.2%	<0.001
Salehifar E 2008(1)	1.017 (0.708, 1.326)	84.0%	<0.001
Salehifar E 2008(2)	1.029 (0.727, 1.331)	83.9%	<0.001
Salehifar E 2008(3)	1.010 (0.702, 1.318)	84.4%	<0.001
Salehifar E 2008(4)	0.997 (0.685, 1.309)	84.6%	<0.001
Salehifar E 2008(5)	1.007 (0.701, 1.314)	84.5%	<0.001
Shokrzadeh M 2009(1)	1.000 (0.685, 1.315)	84.5%	<0.001
Shokrzadeh M 2009(2)	0.987 (0.673, 1.301)	84.6%	<0.001
Shokrzadeh M 2009(3)	1.011 (0.702, 1.321)	84.3%	<0.001
Ghaemian A 2011(1)	1.045 (0.767, 1.323)	79.6%	<0.001
Ghaemian A 2011(2)	1.029 (0.731, 1.328)	82.3%	<0.001
Alexanian I 2014(1)	0.992 (0.675, 1.309)	84.6%	<0.001
Alexanian I 2014(2)	0.984 (0.667, 1.300)	84.6%	<0.001

SMD: standardized mean difference; CI: confidence intervals.

els of copper.

To the best of our knowledge, this is the first meta-analysis to evaluate the association between copper levels and HF. The sensitivity analysis showed that excluding any one study from the pooled analysis did not substantially affect the results. There was also insignificant publication bias, as determined by funnel plot visualization and Begg's test. However, our study did have some limitations. Some articles included in the meta-analysis did not provide the data of serum copper levels in relevant control group. First, to explore the relationship between serum copper levels among heart failure and healthy controls, we used the data of serum copper levels in relevant control group. We referred to the articles and made meta-analysis the same way as the reference methods, which allowing a much greater possibility of reaching more comprehensive conclusion. Second, some long ago published studies were included in the meta-analysis, possibly weakening the quality of the results. We expect new studies to verify our findings in the near future. Moreover, there was significant heterogeneity because the studies used diverse methodologies; thus, conclusions should be drawn with caution. In addition, we had insufficient data to analyze amounts of copper in other tissues and could not therefore comprehensively interpret the significance of copper levels in patients with HF. Better designed studies are required to verify our findings and further assess the role of copper in the development and pro-

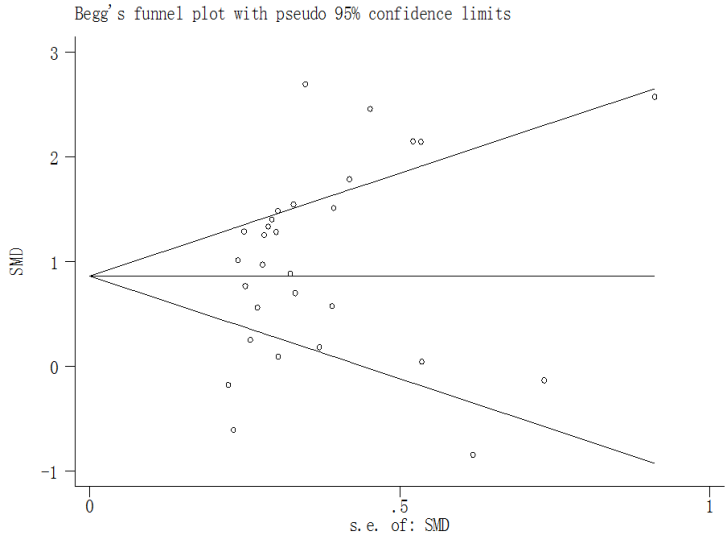

Figure 3. Funnel plot for studies in copper levels for subjects with HF versus control subjects.

gression of HF.

Conclusion

In conclusion, this meta-analysis and systematic review provided strong evidence that serum copper and HF have close-knit and significant association. Analyses demonstrated that patients with HF had a higher serum copper than healthy controls. Meanwhile better designed studies are required to verify the results and further assess the role of copper in the progress of HF.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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