


Review Article

The Relationship between Serum Zinc Level and Heart Failure: A Meta-Analysis

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Zinc is essential for the maintenance of normal cellular structure and functions. Zinc dyshomeostasis can lead to many diseases, such as cardiovascular disease. However, there are conflicting reports on the relationship between serum zinc levels and heart failure (HF). The purpose of the present study is to explore the relationship between serum zinc levels and HF by using a meta-analysis approach. PubMed, Web of Science, and OVID databases were searched for reports on the association between serum zinc levels and HF until June 2016. 12 reports with 1453 subjects from 27 case-control studies were chosen for the meta-analysis. Overall, the pooled analysis indicated that patients with HF had lower zinc levels than the control subjects. Further subgroup analysis stratified by different geographic locations also showed that HF patients had lower zinc levels than the control subjects. In addition, subgroup analysis stratified by HF subgroups found that patients with idiopathic dilated cardiomyopathy (IDCM) had lower zinc levels than the control subjects, except for patients with ischemic cardiomyopathy (ICM). In conclusion, the results of the meta-analysis indicate that there is a significant association between low serum zinc levels and HF.

1. Introduction

Zinc is an important trace element in the body. It plays a critical role in maintaining cellular structure and functions and is also involved in gene expression and cell growth and differentiation as a catalytic and structural cofactor [1]. Zinc deficiency accompanies many health conditions, such as renal disease, gastrointestinal disorders, alcoholism, sickle cell anemia, some cancer types, AIDS, and aging [2, 3]. The extracellular and intracellular levels of zinc are also related to cardiovascular health [4, 5]. According to Little et al., plasma zinc levels decrease with age and have a strong association with increasing cardiovascular disease (CVD); thus, there is an association between zinc deficiency and increased CVD [4]. Moreover, recent advances in cardiac biology and pathophysiology have highlighted the critical contribution of perturbations in zinc homeostasis to myocardial ischemia/reperfusion injury and the role of zinc signaling in cardioprotection against ischemia/reperfusion injury [2, 6].

Heart failure (HF) is one of the most frequent causes of death worldwide. Recently, there has been emerging evidence

suggesting that micronutrient dyshomeostasis is associated with HF [7]. Many studies have attempted to explore the relationship between changes in serum zinc level in HF patients; however, conflicting results have been obtained. Some studies found significantly lower serum zinc levels in HF patients than in the control groups [8–16], whereas other works reported that the serum zinc levels were not significantly different between the HF patients and the control subjects [17–19]. Therefore, a comprehensive and critical meta-analysis of previous studies is carried out in the present work to draw a clearer, evidence-based conclusion on the association between serum zinc levels and HF.

2. Materials and Methods

2.1. Search Strategy. A systematic literature search of PubMed, Web of Science, and OVID databases was done until June 2016 with the use of medical subject headings (MeSH) or free text words. The search keywords were “zinc” or “Zn” 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.

2.2. Inclusion and Exclusion Criteria. Three authors (Xuefang Yu, Lei Huang, and Jinyan Zhao) 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 (Xuefang Yu and Lei Huang) independently selected eligible studies for possible inclusion in the meta-analysis. Any disagreement regarding study inclusion was resolved by discussion with Jinyan Zhao 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 zinc levels and HF, and (4) providing sufficient data on zinc levels in both HF patients and control subjects. The exclusion criteria were (1) obviously irrelevant study, (2) animal study, (3) review or case report, and (4) not providing data on zinc levels in either HF patients or control subjects.

2.3. Data Extraction and Quality Assessment. All data were extracted independently by two reviewers (Bo Bian and Wei Yao) according to the inclusion and exclusion criteria. Specifically, the following data were extracted: authors' names, year of publication, country, number of subjects, and data on serum zinc levels. Any inconsistencies or discrepancies in the extracted information were resolved by discussion between the two reviewers, with a third author (Zhaoqun Wang) providing input.

The quality of all the included studies was evaluated by using the Newcastle-Ottawa Scale (NOS). 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 (Xianming Wu and Jingjing Huang) assessed the quality of studies independently.

2.4. Statistical Analysis. The statistical analysis was carried out by using Stata 12, and statistical significance was 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 chi-square and I^2 -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, and a fixed-effects model was applied; otherwise, a random-effects model was used.

Subgroup analysis was done to determine associations between serum zinc levels and other relevant study characteristics, which may be possible sources of heterogeneity. Sensitivity analysis was carried out with one study removed at a time to assess whether the results could be affected markedly by a single study. Publication bias was measured by using Begg's test and visualization of funnel plots.

3. Results

Figure 1 shows the detailed steps of the literature selection. A total of 549 primary reports were identified by using the aforementioned search terms. After a series of assessments, 12 eligible articles with 1453 subjects from 27 case-control studies were chosen for the meta-analysis. Table 1 presents the detailed characteristics of the included studies.

3.1. Serum Zinc Levels and HF. There were 12 studies that assessed the association between serum zinc levels and HF. First, the heterogeneity among the included studies was assessed. The results showed a high statistical heterogeneity ($I^2 = 76.5\%$; $p < 0.001$) (Table 2); thus, a random-effects model was used. The results of the random-effects meta-analysis indicated that HF patients had lower zinc levels than the control subjects [SMD: -0.740 ; 95% CI: $-0.987, -0.493$] (Figure 1).

3.2. Subgroup Analysis. The subgroup analysis showed that the geographic locations and etiologies of HF [idiopathic dilated cardiomyopathy (IDCM) and ischemic cardiomyopathy (ICM)] had some influence on the serum zinc levels in HF patients and control subjects.

Further subgroup analysis stratified by different geographic locations found that HF patients had lower zinc levels than the control subjects [Europe: SMD: -0.832 and 95% CI: $-1.119, -0.545$; Asia: SMD: -0.408 and 95% CI: $-0.761, -0.055$; America: SMD: -1.920 and 95% CI: $-2.456, -1.384$] (Figure 2). In addition, the subgroup analysis stratified by HF subgroups found that patients with IDCM [SMD: -0.562 ; 95% CI: $-0.804, -0.320$] and other HF patients [SMD: -0.924 ; 95% CI: $-1.267, -0.581$] had lower zinc levels than the control subjects, except for ICM patients [SMD: -0.577 ; 95% CI: $-1.353, 0.199$] (Figure 3). Table 3 provides a summary of subgroup analysis results.

3.3. Sensitivity Analysis and Publication Bias. The sensitivity analysis showed that no individual study had an extreme influence on the pooled effect (Table 4). The publication bias was measured by using Begg's test, which showed no evidence of significant publication bias ($p = 0.868$), and by visualizing the funnel plot, which was symmetrical (Figure 4).

4. Discussion

Our meta-analysis included 12 reports with 1453 subjects from 27 case-control studies. The results showed that the serum zinc levels in HF patients were significantly lower than those in control subjects. This supported the supposition that there is some difference in zinc levels between HF patients and controls. In the subgroup analysis, the lower serum zinc levels in HF patients compared with control subjects were observed in different geographic locations (Europe, Asia, and America) and in IDCM and other HF patients. However, no significant difference in serum zinc levels was found in ICM patients, which could be due to the limited number of studies included in the analysis.

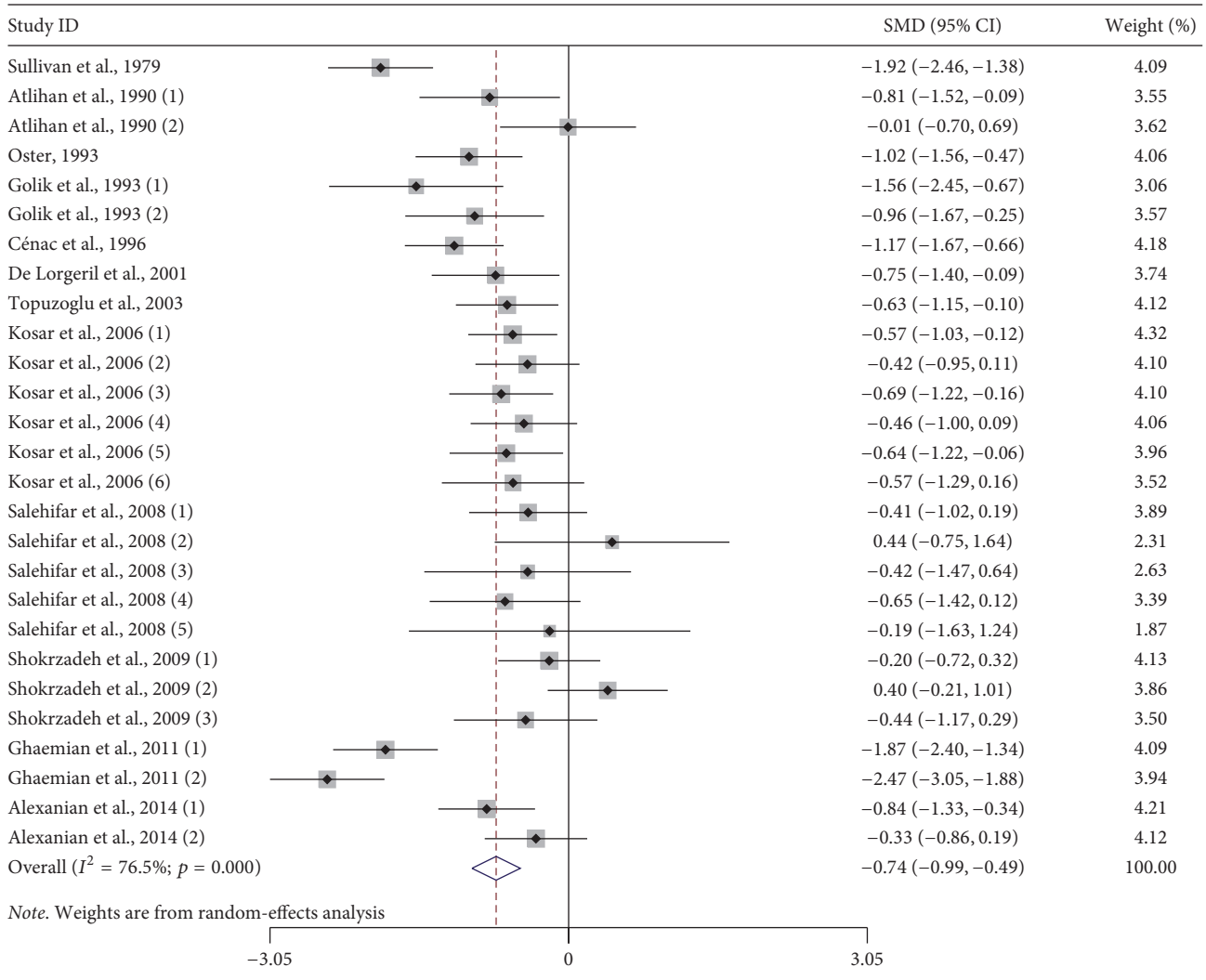


FIGURE 1: Forest plot of studies on zinc levels in HF patients versus control subjects. The combined SMD and 95% CIs were calculated by using a random-effects model.

The mechanisms underlying the association between serum zinc levels and HF are still not fully understood. One underlying explanation for this meta-analysis showing is that micronutrient dyshomeostasis (such as zinc, copper, and Zn/Cu ratio dyshomeostasis) is associated with HF. The zinc and copper levels in the body affect each other, and decreased zinc levels are associated with deterioration of copper homeostasis and function [20]. For instance, decreased zinc levels, increased copper levels, and decreased Zn/Cu ratios have been observed in many diseases, such as rheumatoid arthritis, ICM, and thyroid carcinoma [19, 21, 22]. Moreover, a decreased Zn/Cu ratio and the subsequent systemic oxidative stress explained the more extensive atherosclerosis in some aged patients [23]. Indeed, previous studies have suggested that HF incidence and prevalence rates increased with advancing age [24]. Plasma zinc levels were found to decrease with age [3] and plasma cu to zinc ratio (CZr) was higher in hospitalized elderly subjects than in their

healthy counterparts [25]. According to Malavolta et al., increments of CZr reflect increased inflammatory status or decreased nutritional status with subsequent appearance of some degenerative age-related diseases [26]. Thus, we speculated that lower levels of zinc in HF patients may be associated with advancing age or increasing of CZr due to age.

Zinc is an important component of superoxide dismutase (SOD). Manganese SOD and copper-zinc SOD, as metal-binding proteins and enzymes, have highly efficient antioxidant mechanisms and a preventive effect on the occurrence of free radical induced injury. Zinc deficiency has been found to be associated with lower SOD activity [27] and greater susceptibility to oxidative injury [28]. In HF, irrespective of the etiology, oxidative stress is important and correlates with the severity of symptoms and signs [29, 30]. Furthermore, some studies have reported a reduction of antioxidant defenses in HF patients [31–33]. Thus, in HF patients, these defenses (such as copper-zinc SOD) could be overwhelmed,

TABLE I: Characteristics of subjects in included studies.

Studies	Country	Number of participants		Age (year)		Subgroups of HF	Score
		HF	Controls	HF	Controls		
Sullivan et al., 1979	USA	42	37	NA	NA	ICM	6
Atlihan et al., 1990 (1)	Turkey	29	11	2.3 ± 1.5	3.1 ± 2.8	NA	6
Atlihan et al., 1990 (2)	Turkey	29	11	2.3 ± 1.5	3.1 ± 2.8	NA	6
Oster, 1993	Germany	20	50	53 ± 8	50.5 ± 7.2	IDCM	8
Golik et al., 1993 (1)	Israel	9	20	63.8 ± 6	48.7 ± 8	NA	8
Golik et al., 1993 (2)	Israel	15	20	64.9 ± 5	48.7 ± 8	NA	8
Cénac et al., 1996	France	35	36	NA	NA	NA	7
De Lorgeril et al., 2001	France	21	18	27–76	34–68	CHF	7
Topuzoglu et al., 2003	Turkey	54	20	18–75	21–73	IDCM	6
Kosar et al., 2006 (1)	Turkey	54	30	62 ± 10	56 ± 8	CHF	8
Kosar et al., 2006 (2)	Turkey	26	30	62 ± 10	56 ± 8	IDCM	8
Kosar et al., 2006 (3)	Turkey	28	30	62 ± 10	56 ± 8	ICM	8
Kosar et al., 2006 (4)	Turkey	24	30	62 ± 10	56 ± 8	NA	8
Kosar et al., 2006 (5)	Turkey	20	30	62 ± 10	56 ± 8	NA	8
Kosar et al., 2006 (6)	Turkey	10	30	62 ± 10	56 ± 8	NA	8
Salehifar et al., 2008 (1)	Iran	18	27	49.06 ± 8.88	42.30 ± 8.99	IDCM	8
Salehifar et al., 2008 (2)	Iran	3	27	49.06 ± 8.88	42.30 ± 8.99	IDCM	8
Salehifar et al., 2008 (3)	Iran	4	27	49.06 ± 8.88	42.30 ± 8.99	IDCM	8
Salehifar et al., 2008 (4)	Iran	9	27	49.06 ± 8.88	42.30 ± 8.99	IDCM	8
Salehifar et al., 2008 (5)	Iran	2	27	49.06 ± 8.88	42.30 ± 8.99	IDCM	8
Shokrzadeh et al., 2009 (1)	Iran	30	27	57.17 ± 8.88	42.3 ± 8.99	ICM	7
Shokrzadeh et al., 2009 (2)	Iran	17	27	57.17 ± 8.88	42.3 ± 8.99	ICM	7
Shokrzadeh et al., 2009 (3)	Iran	10	27	57.17 ± 8.88	42.3 ± 8.99	ICM	7
Ghaemian et al., 2011 (1)	Turkey	38	40	70.1 ± 9.2	64.9 ± 4.7	NA	8
Ghaemian et al., 2011 (2)	Turkey	40	40	66.7 ± 11.5	64.9 ± 4.7	NA	8
Alexanian et al., 2014 (1)	Greece	81	21	69.22 ± 11.09	57.0 ± 19.11	NA	8
Alexanian et al., 2014 (2)	Greece	44	21	67.50 ± 11.17	57.0 ± 19.11	NA	8

creating an antioxidant deficit, particularly in cases when the activity of these oxidoreductases is dependent on the zinc concentrations.

According to Tousoulis et al., proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor- α (TNF- α), are elevated in states of HF and are related to long-term prognosis [34]. IL-1, IL-6, and TNF- α have been found to increase metallothioneins (MTs), which bind zinc from plasma and tissues, resulting in reduced zinc bioavailability [35]. Excessive catecholamine- and PTH-induced intracellular and intramitochondrial Ca^{2+} accumulation in HF has been found to be coupled with increased intracellular Zn^{2+} due to increased Zn^{2+} entry and nitric oxide-induced release of inactive Zn^{2+} bound to MT-1 [16, 36]. Thus, we speculated that elevated inflammatory markers in HF further induce MT-1 and consequently lower zinc levels.

In addition, HF may be associated with zinc deficiency through other mechanisms: reduced dietary intake (due to anorexia, nausea, and premature satiety with eating), reduced absorption due to gastrointestinal edema and impaired motility, increased intestinal zinc losses (protein-losing enteropathy), and excessive urinary excretion due to the use of diuretics [37]. Moreover, zinc deficiency frequently accompanies

many health conditions, such as diabetes mellitus (DM), aging, and hypertension [2, 38]. The majority of HF patients are older, and many of them have various comorbidities, such as DM and hypertension, which may further impair zinc homeostasis. Cellular senescence was discovered as strong driver of atherosclerosis and heart failure [39, 40]. Recent observation performed on long-term culture of primary endothelial cells suggests that zinc deficiency may lead to accumulation of senescent cells and to vascular pathology as well as to heart failure [41]. Also, in HF patients, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) results in increased urinary zinc excretion and zinc deficiency [37].

To the best of our knowledge, this is the first meta-analysis to evaluate the association between zinc levels and HF. The sensitivity analysis showed that excluding any study from the pooled analysis did not vary the results substantially. Publication bias was also absent, as determined by funnel plot visualization and Begg's test. 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. Second, heterogeneity could not be eliminated because of methodological diversity

TABLE 2: Summary of studies included in the analysis of serum zinc levels for subjects with HF versus control subjects.

Author	HF			Controls			Weight (%)	SMD (95% CI)
	Number	Zn concentration (mean ± SD)	Number	Zn concentration (mean ± SD)	Number	Zn concentration (mean ± SD)		
Sullivan et al., 1979	42	0.74 ± 0.11 µg/ml	37	0.97 ± 0.13 µg/ml	4.09	-1.920 (-2.456, -1.384)		
Atlihan et al., 1990 (1)	29	92.9 ± 18.9 µg/100 ml	11	107.5 ± 15.7 µg/100 ml	3.55	-0.806 (-1.523, -0.089)		
Atlihan et al., 1990 (2)	29	107.4 ± 17.2 µg/100 ml	11	107.5 ± 15.7 µg/100 ml	3.62	-0.006 (-0.700, 0.688)		
Oster, 1993	20	745 ± 195 µg/l	50	931 ± 178 µg/l	4.06	-1.017 (-1.563, -0.4710)		
Golik et al., 1993 (1)	9	11.5 ± 1.53 µmol/L	20	16 ± 3.3 µmol/L	3.06	-1.557 (-2.446, -0.667)		
Golik et al., 1993 (2)	15	13.2 ± 2.3 µmol/L	20	16 ± 3.3 µmol/L	3.57	-0.960 (-1.668, -0.251)		
Cénac et al., 1996	35	0.9 ± 0.21 µg/ml	36	1.17 ± 0.25 µg/ml	4.18	-1.168 (-1.672, -0.664)		
De Lorgetil et al., 2001	21	0.82 ± 0.12 mg/l	18	0.9 ± 0.09 mg/l	3.74	-0.746 (-1.398, -0.094)		
Topuzoglu et al., 2003	54	81.42 ± 15.4 µg/dl	20	92.51 ± 22.8 µg/dl	4.12	-0.628 (-1.151, -0.105)		
Kosar et al., 2006 (1)	54	555 ± 104 µg/l	30	620 ± 130 µg/l	4.32	-0.571 (-1.026, -0.116)		
Kosar et al., 2006 (2)	26	568 ± 116 µg/l	30	620 ± 130 µg/l	4.1	-0.420 (-0.951, 0.111)		
Kosar et al., 2006(3)	28	542 ± 92 µg/l	30	620 ± 130 µg/l	4.1	-0.689 (-1.219, -0.158)		
Kosar et al., 2006 (4)	24	565 ± 107 µg/l	30	620 ± 130 µg/l	4.06	-0.457 (-1.001, 0.087)		
Kosar et al., 2006 (5)	20	543 ± 106 µg/l	30	620 ± 130 µg/l	3.96	-0.636 (-1.216, -0.056)		
Kosar et al., 2006 (6)	10	553 ± 66 µg/l	30	620 ± 130 µg/l	3.52	-0.568 (-1.295, 0.159)		
Salehifar et al., 2008 (1)	18	0.97 ± 0.25 mg/l	27	1.12 ± 0.42 mg/l	3.89	-0.414 (-1.017, 0.189)		
Salehifar et al., 2008 (2)	3	1.3 ± 0.09 mg/l	27	1.12 ± 0.42 mg/l	2.31	0.444 (-0.754, 1.642)		
Salehifar et al., 2008 (3)	4	0.95 ± 0.26 mg/l	27	1.12 ± 0.42 mg/l	2.63	-0.418 (-1.474, 0.637)		
Salehifar et al., 2008 (4)	9	0.87 ± 0.24 mg/l	27	1.12 ± 0.42 mg/l	3.39	-0.649 (-1.419, 0.121)		
Salehifar et al., 2008 (5)	2	1.04 ± 0.06 mg/l	27	1.12 ± 0.42 mg/l	1.87	-0.194 (-1.631, 1.243)		
Shokrzadeh et al., 2009 (1)	30	1.05 ± 0.28 mg/l	27	1.12 ± 0.42 mg/l	4.13	-0.198 (-0.719, 0.323)		
Salehifar et al., 2009 (2)	17	1.27 ± 0.29 mg/l	27	1.12 ± 0.42 mg/l	3.86	0.399 (-0.214, 1.012)		
Shokrzadeh et al., 2009 (3)	10	0.95 ± 0.27 mg/l	27	1.12 ± 0.42 mg/l	3.5	-0.439 (-1.172, 0.294)		
Ghaemian et al., 2011 (1)	38	24.7 ± 27.6 µg/dl	40	70.9 ± 21.6 µg/dl	4.09	-1.870 (-2.405, -1.336)		
Ghaemian et al., 2011 (2)	40	23.2 ± 16.8 µg/dl	40	70.9 ± 21.6 µg/dl	3.94	-2.465 (-3.050, -1.881)		
Alexanian et al., 2014 (1)	81	74.27 ± 15.87 µg/dl	21	87.9 ± 17.85 µg/dl	4.21	-0.837 (-1.331, -0.343)		
Alexanian et al., 2014 (2)	44	81.51 ± 19.73 µg/dl	21	87.9 ± 17.85 µg/dl	4.12	-0.334 (-0.857, 0.189)		

TABLE 3: Subgroup analyses of zinc level and heart failure (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						
Europe	16	-0.832 (-1.119, -0.545)	<0.001	5.68	76.1%	<0.001
Asia	10	-0.408 (-0.761, -0.055)	2.27	0.023	51.0%	0.031
America	1	-1.920 (-2.456, -1.384)	<0.001	7.02	NA	NA
Subgroups of HF						
ICM patients	5	-0.577 (-1.353, 0.199)	1.46	0.145	88.9%	<0.001
IDCM patients	8	-0.562 (-0.804, -0.320)	4.55	<0.001	0.0%	0.504
Other HF patients	14	-0.924 (-1.267, -0.581)	5.28	<0.001	78.6%	<0.001

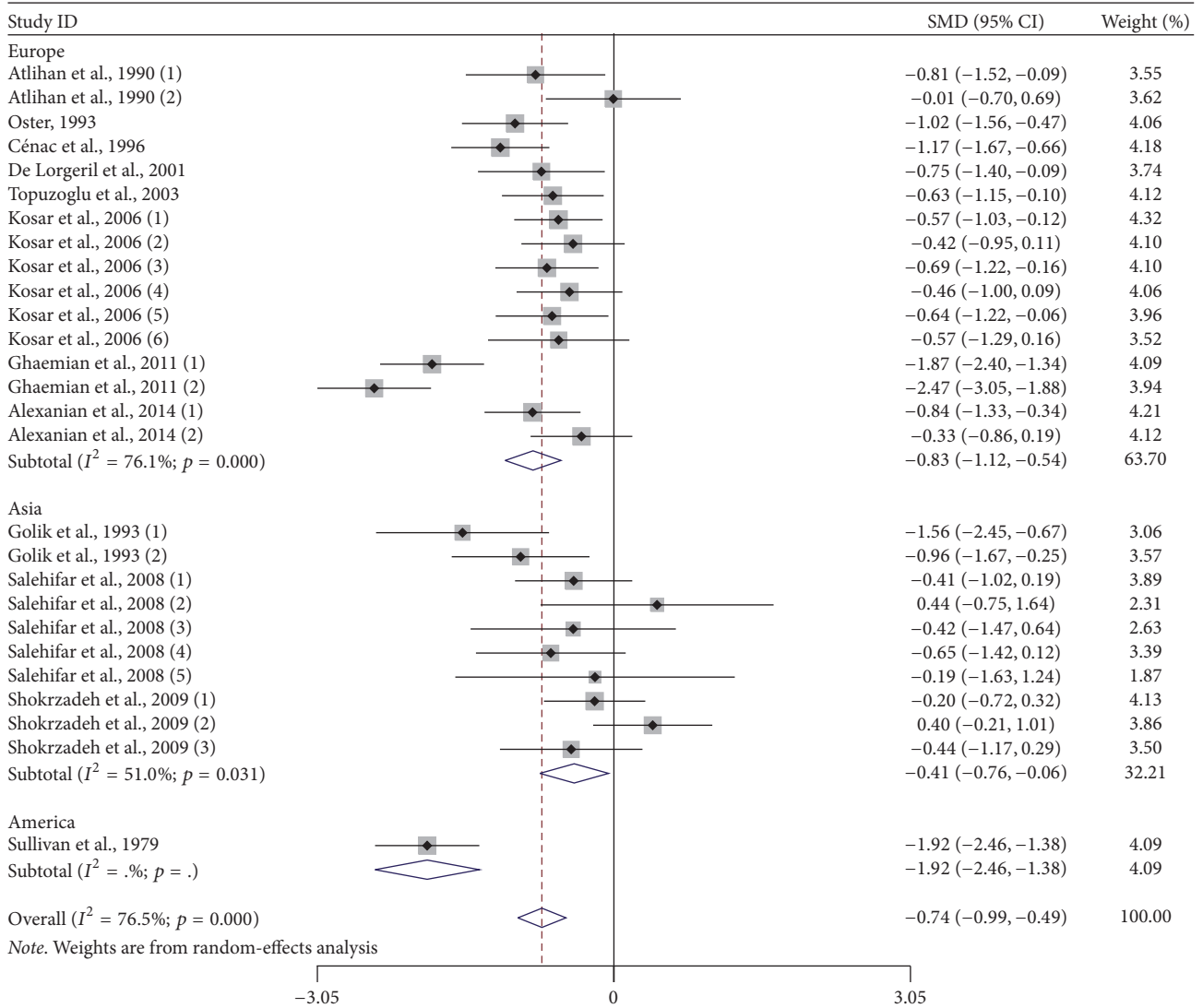


FIGURE 2: Subgroup analysis of studies on zinc levels in HF patients versus control subjects stratified by geographic location.

between studies; thus, the conclusion should be conservative. In addition, because of limited data, we did not analyze the zinc levels in other tissues; this might affect the comprehensive interpretation of the zinc levels in HF patients. Therefore, better designed studies are required to verify the results and further assess the role of zinc in the progress of HF.

5. Conclusions

In conclusion, the results of the meta-analysis indicate that there is a significant association between low serum zinc levels and HF. Meanwhile better designed studies are required to verify the results and further assess the role of zinc in the progress of HF.

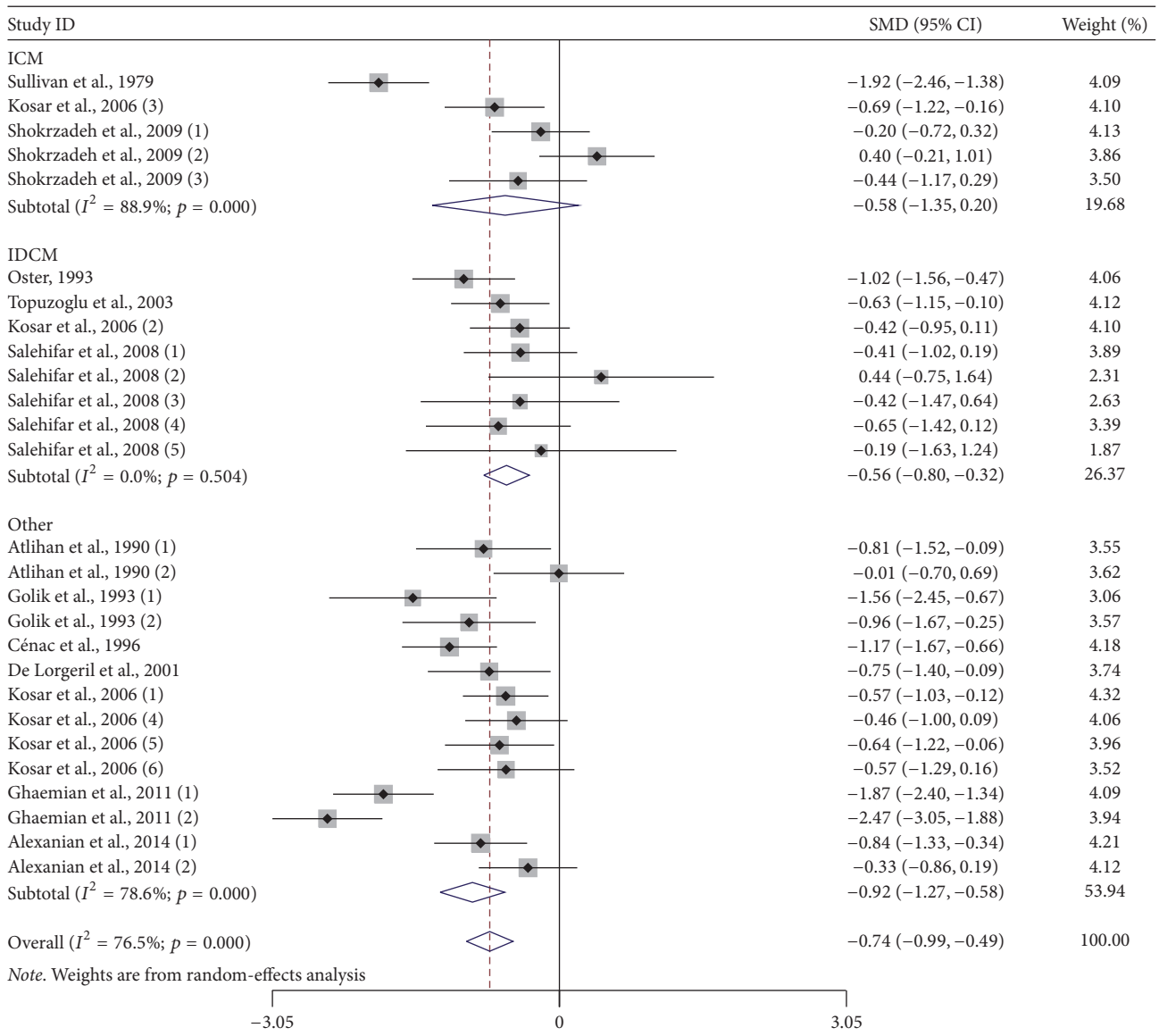


FIGURE 3: Subgroup analysis of studies on zinc levels in HF patients versus control subjects stratified by HF subgroups.

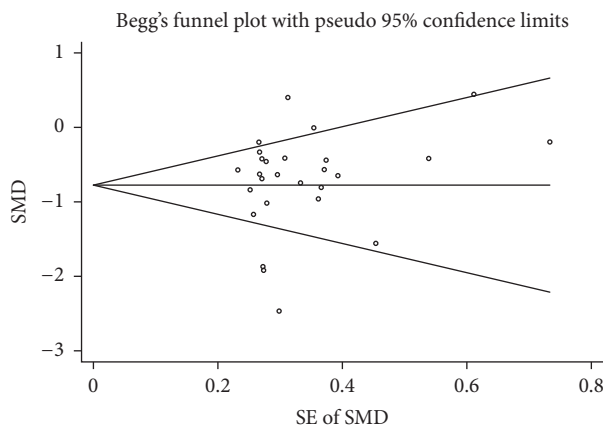


FIGURE 4: Funnel plot of studies on zinc levels in HF patients versus control subjects.

TABLE 4: The heterogeneity of the included studies through sensitivity analysis.

Excluded studies	SMD (95% CI)	I ²	p value
Sullivan et al., 1979	-0.692 (-0.929, -0.456)	72.90%	<0.001
Atlihan et al., 1990 (1)	-0.737 (-0.993, -0.482)	77.40%	<0.001
Atlihan et al., 1990 (2)	-0.768 (-1.018, -0.518)	76.30%	<0.001
Oster, 1993	-0.728 (-0.985, -0.470)	77.20%	<0.001
Golik et al., 1993 (1)	-0.715 (-0.965, -0.464)	76.70%	<0.001
Golik et al., 1993 (2)	-0.732 (-0.987, -0.476)	77.30%	<0.001
Cénac et al., 1996	-0.721 (-0.977, -0.465)	76.90%	<0.001
De Lorgeril et al., 2001	-0.739 (-0.996, -0.483)	77.40%	<0.001
Topuzoglu et al., 2003	-0.744 (-1.002, -0.486)	77.30%	<0.001
Kosar et al., 2006 (1)	-0.747 (-1.006, -0.487)	77.20%	<0.001
Kosar et al., 2006 (2)	-0.753 (-1.010, -0.497)	77.00%	<0.001
Kosar et al., 2006 (3)	-0.741 (-1.000, -0.483)	77.40%	<0.001
Kosar et al., 2006 (4)	-0.752 (-1.008, -0.495)	77.10%	<0.001
Kosar et al., 2006 (5)	-0.744 (-1.001, -0.486)	77.30%	<0.001
Kosar et al., 2006 (6)	-0.746 (-1.001, -0.491)	77.30%	<0.001
Salehifar et al., 2008 (1)	-0.753 (-1.008, -0.497)	77.10%	<0.001
Salehifar et al., 2008 (2)	-0.769 (-1.016, -0.521)	76.50%	<0.001
Salehifar et al., 2008 (3)	-0.749 (-1.001, -0.496)	77.30%	<0.001
Salehifar et al., 2008 (4)	-0.743 (-0.998, -0.488)	77.40%	<0.001
Salehifar et al., 2008 (5)	-0.751 (-1.001, -0.500)	77.20%	<0.001
Shokrzadeh et al., 2009 (1)	-0.764 (-1.017, -0.511)	76.30%	<0.001
Salehifar et al., 2009 (2)	-0.788 (-1.028, -0.549)	73.90%	<0.001
Salehifar et al., 2009 (3)	-0.751 (-1.005, -0.496)	77.20%	<0.001
Ghaemian et al., 2011 (1)	-0.694 (-0.932, -0.456)	73.30%	<0.001
Ghaemian et al., 2011 (2)	-0.676 (-0.891, -0.460)	67.60%	<0.001
Alexanian et al., 2014 (1)	-0.735 (-0.994, -0.476)	77.40%	<0.001
Alexanian et al., 2014 (2)	-0.757 (-1.013, -0.502)	76.80%	<0.001

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- [1] J. M. Berg and Y. Shi, "The galvanization of biology: a growing appreciation for the roles of zinc," *Science*, vol. 271, no. 5252, pp. 1081-1085, 1996.
- [2] C. T. Chasapis, A. C. Loutsidou, C. A. Spiliopoulou, and M. E. Stefanidou, "Zinc and human health: an update," *Archives of Toxicology*, vol. 86, no. 4, pp. 521-534, 2012.
- [3] A. S. Prasad, "Discovery of human zinc deficiency: Its impact on human health and disease," *Advances in Nutrition*, vol. 4, no. 2, pp. 176-190, 2013.
- [4] P. J. Little, R. Bhattacharya, A. E. Moreyra, and I. L. Korichneva, "Zinc and cardiovascular disease," *Nutrition Journal*, vol. 26, no. 11-12, pp. 1050-1057, 2010.
- [5] M. Foster and S. Samman, "Zinc and redox signaling: Perturbations associated with cardiovascular disease and diabetes mellitus," *Antioxidants & Redox Signaling*, vol. 13, no. 10, pp. 1549-1573, 2010.
- [6] Z. Xu and J. Zhou, "Zinc and myocardial ischemia/reperfusion injury," *BioMetals*, vol. 26, no. 6, pp. 863-878, 2013.
- [7] K. T. Weber, W. B. Weglicki, and R. U. Simpson, "Macro- and micronutrient dyshomeostasis in the adverse structural remodelling of myocardium," *Cardiovascular Research*, vol. 81, no. 3, pp. 500-508, 2009.
- [8] J. F. Sullivan, A. J. Blotcky, M. M. Jetton, H. K. Hahn, and R. E. Burch, "Serum levels of selenium, calcium, copper magnesium, manganese and zinc in various human diseases," *Journal of Nutrition*, vol. 109, no. 8, pp. 1432-1437, 1979.
- [9] F. Atlihan, T. Soylemezoglu, A. Gokce, G. Guvendik, and O. Satici, "Zinc and copper in congestive heart failure," *Turkish Journal of Pediatrics*, vol. 32, pp. 33-38, 1990.
- [10] O. Oster, "Trace element concentrations (Cu, Zn, Fe) in sera from patients with dilated cardiomyopathy," *Clinica Chimica Acta*, vol. 214, no. 2, pp. 209-218, 1993.
- [11] A. Cénac, M. Simonoff, and A. Djibo, "Nutritional status and plasma trace elements in peripartum cardiomyopathy. A comparative study in Niger," *Journal of Cardiovascular Risk*, vol. 3, no. 6, pp. 483-487, 1996.
- [12] M. De Lorgeril, P. Salen, M. Accominotti et al., "Dietary and blood antioxidants in patients with chronic heart failure. Insights into the potential importance of selenium in heart failure," *European Journal of Heart Failure*, vol. 3, no. 6, pp. 661-669, 2001.
- [13] G. Topuzoglu, A. R. Erbay, A. B. Karul, and N. Yensel, "Concentrations of Copper, Zinc, and Magnesium in Sera from Patients with Idiopathic Dilated Cardiomyopathy," *Biological Trace Element Research*, vol. 95, no. 1, pp. 11-17, 2003.

- [14] F. Kosar, I. Sahin, C. Taskapan et al., "Trace element status (Se, Zn, Cu) in heart failure," *Anadolu Kardiyol Derg* 6, pp. 216–220, 2006.
- [15] A. Ghaemian, E. Salehifar, R. Jalalian et al., "Zinc and copper levels in severe heart failure and the effects of atrial fibrillation on the zinc and copper status," *Biological Trace Element Research*, vol. 143, no. 3, pp. 1239–1246, 2011.
- [16] I. Alexanian, J. Parissis, D. Farmakis et al., "Clinical and echocardiographic correlates of serum copper and zinc in acute and chronic heart failure," *Clinical Research in Cardiology*, vol. 103, no. 11, pp. 938–949, 2014.
- [17] A. Golik, N. Cohen, Y. Ramot et al., "Type II diabetes mellitus, congestive heart failure, and zinc metabolism," *Biological Trace Element Research*, vol. 39, no. 2-3, pp. 171–175, 1993.
- [18] E. Salehifar, M. Shokrzadeh, A. Ghaemian, S. Aliakbari, and S. S. Saeedi Saravi, "The study of Cu and Zn serum levels in idiopathic dilated cardiomyopathy (IDCMP) patients and its comparison with healthy volunteers," *Biological Trace Element Research*, vol. 125, no. 2, pp. 97–108, 2008.
- [19] M. Shokrzadeh, A. Ghaemian, E. Salehifar, S. Aliakbari, S. S. S. Saravi, and P. Ebrahimi, "Serum zinc and copper levels in ischemic cardiomyopathy," *Biological Trace Element Research*, vol. 127, no. 2, pp. 116–123, 2009.
- [20] D. B. Milne, C. D. Davis, and F. H. Nielsen, "Low dietary zinc alters indices of copper function and status in postmenopausal women," *Nutrition Journal*, vol. 17, no. 9, pp. 701–708, 2001.
- [21] A. Zoli, L. Altomonte, R. Caricchio et al., "Serum zinc and copper in active rheumatoid arthritis: Correlation with interleukin 1 β and tumour necrosis factor α ," *Clinical Rheumatology*, vol. 17, no. 5, pp. 378–382, 1998.
- [22] M. Kucharzewski, J. Braziewicz, U. Majewska, and S. Gózdź, "Copper, zinc, and selenium in whole blood and thyroid tissue of people with various thyroid diseases," *Biological Trace Element Research*, vol. 93, no. 1-3, pp. 9–18, 2003.
- [23] A. Mezzetti, S. D. Pierdomenico, F. Costantini et al., "Copper/zinc ratio and systemic oxidant load: Effect of aging and aging-related degenerative diseases," *Free Radical Biology & Medicine*, vol. 25, no. 6, pp. 676–681, 1998.
- [24] J. R. Wu, D. K. Moser, D. A. Dewalt, M. K. Rayens, and K. Dracup, "Health Literacy Mediates the Relationship between Age and Health Outcomes in Patients with Heart Failure," *Circulation: Heart Failure*, vol. 9, no. 1, 2016.
- [25] S. Belbraouet, H. Biaudet, A. Tébi, N. Chau, K. Gray-Donald, and G. Debry, "Serum Zinc and Copper Status in Hospitalized vs. Healthy Elderly Subjects," *Journal of the American College of Nutrition*, vol. 26, no. 6, pp. 650–654, 2007.
- [26] M. Malavolta, F. Piacenza, A. Basso, R. Giacconi, L. Costarelli, and E. Mocchegiani, "Serum copper to zinc ratio: Relationship with aging and health status," *Mechanisms of Ageing and Development*, vol. 151, pp. 93–100, 2015.
- [27] M. Ruz, K. R. Cavan, W. J. Bettger, P. W. F. Fischer, and R. S. Gibson, "Indices of iron and copper status during experimentally induced, marginal zinc deficiency in humans," *Biological Trace Element Research*, vol. 34, no. 2, pp. 197–212, 1992.
- [28] S. R. Powell, "The Antioxidant Properties of Zinc," *Journal of Nutrition*, vol. 130, no. 5, pp. 1447S–1454S, 2000.
- [29] Z. Ungvári, S. A. Gupte, F. A. Recchia, S. Bátkai, and P. Pacher, "Role of oxidative-nitrosative stress and downstream pathways in various forms of cardiomyopathy and heart failure," *Current Vascular Pharmacology*, vol. 3, no. 3, pp. 221–229, 2005.
- [30] A. Wykretowicz, J. Furmaniuk, J. Smielecki et al., "The oxygen stress index and levels of circulating interleukin-10 and interleukin-6 in patients with chronic heart failure," *International Journal of Cardiology*, vol. 94, no. 2-3, pp. 283–287, 2004.
- [31] R. Demirbag, R. Yilmaz, O. Erel, U. Gultekin, D. Asci, and Z. Elbasan, "The relationship between potency of oxidative stress and severity of dilated cardiomyopathy," *Canadian Journal of Cardiology*, vol. 21, no. 10, pp. 851–855, 2005.
- [32] H. Takano, Y. Zou, H. Hasegawa, H. Akazawa, T. Nagai, and I. Komuro, "Oxidative Stress-Induced Signal Transduction Pathways in Cardiac Myocytes: Involvement of ROS in Heart Diseases," *Antioxidants & Redox Signaling*, vol. 5, no. 6, pp. 789–794, 2003.
- [33] M. Itoh, S. Oh-Ishi, H. Hatao et al., "Effects of dietary calcium restriction and acute exercise on the antioxidant enzyme system and oxidative stress in rat diaphragm," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 287, no. 1, pp. R33–R38, 2004.
- [34] D. Tousoulis, N. Papageorgiou, A. Briasoulis, C. Antoniades, and C. Stefanadis, "The failure of immunomodulation therapy in heart failure: Does the statins "paradigm" prove the rule?" *Current Vascular Pharmacology*, vol. 8, no. 1, pp. 114–121, 2010.
- [35] E. Mocchegiani, M. Muzzioli, C. Cipriano, and R. Giacconi, "Zinc, T-cell pathways, aging: Role of metallothioneins," *Mechanisms of Ageing and Development*, vol. 106, no. 1-2, pp. 183–204, 1998.
- [36] N. Efeovbokhan, S. K. Bhattacharya, R. A. Ahokas et al., "Zinc and the prooxidant heart failure phenotype," *Journal of Cardiovascular Pharmacology*, vol. 64, no. 4, pp. 393–400, 2014.
- [37] N. Cohen and A. Golik, "Zinc balance and medications commonly used in the management of heart failure," *Heart Failure Reviews*, vol. 11, no. 1, pp. 19–24, 2006.
- [38] H. I. Afridi, T. G. Kazi, N. Kazi et al., "Distribution of copper, iron, and zinc in biological samples of Pakistani hypertensive patients and referent subjects of different age groups," *Clinical Laboratory*, vol. 59, no. 9-10, pp. 959–967, 2013.
- [39] B. G. Childs, D. J. Baker, T. Wijshake, C. A. Conover, J. Campisi, and J. M. Van Deursen, "Senescent intimal foam cells are deleterious at all stages of atherosclerosis," *Science*, vol. 354, no. 6311, pp. 472–477, 2016.
- [40] A. B. Gevaert, H. Shakeri, A. J. Leloup et al., "Endothelial Senescence Contributes to Heart Failure with Preserved Ejection Fraction in an Aging Mouse Model," *Circulation: Heart Failure*, vol. 10, no. 6, Article ID e003806, 2017.
- [41] M. Malavolta, L. Costarelli, R. Giacconi et al., "Changes in Zn homeostasis during long term culture of primary endothelial cells and effects of Zn on endothelial cell senescence," *Experimental Gerontology*, vol. 99, pp. 35–45, 2017.