Biological Trace Element Research
https://doi.org/10.1007/s12011-019-01979-x

Association Between Copper, Zinc, Iron, and Selenium Intakes and TC/HDL-C Ratio in US Adults

Xiaoyu Ma[1] · Shan Jiang[1] · Shoumeng Yan[1] · Meng Li[1] · Changcong Wang[1] · Yingan Pan[1] · Chong Sun[1] · Lina Jin[1] · Yan Yao[1] · Bo Li[1]

Received: 9 September 2019 / Accepted: 5 November 2019

Abstract

The trace minerals zinc, copper, iron, and selenium are essential micronutrients, and because of their antioxidant activity, they are hypothesized to improve cardiovascular health. However, their associations with different risk levels for cardiovascular diseases are less clear. Data from the National Health and Nutrition Examination Survey 2007–2014 were used. In this study, the ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) was used as a risk marker for cardiovascular disease, and a ratio ≥ 5 was considered to indicate high risk. A total of 7597 adults (3673 men and 3924 women) were included, and 15.9% of the participants had a high risk of cardiovascular disease. Using quantile regression analysis, we found the negative correlation between zinc, copper, iron, and selenium intakes and TC/HDL-C. The effects of copper and zinc were enhanced with increasing quantiles of risk levels. In addition, the difference in the associations of the trace minerals was sex-dependent. The correlation between iron and cardiovascular risk in males was stronger than those in females, while that of copper was weaker than that in females. Moreover, a significant nonlinear relationship between selenium and the TC/HDL-C ratio was only found in females, and this relationship was U-shaped. Our findings suggest that among healthy adults in the US, zinc, copper, iron, and selenium intakes are inversely associated with cardiovascular disease risk, and the effect is enhanced with increasing quantiles of risk levels, with magnitudes differing by sex. Therefore, trace minerals may have the ability to prevent cardiovascular disease.

Keywords Zinc · Copper · Iron · Selenium · Cardiovascular disease · Trace minerals

Introduction

Cardiovascular disease (CVD) is a great challenge for public health worldwide and is the leading cause of death in the United States (> 800 000, or approximately 1 in 3 overall deaths/y) [1, 2]. Studies have demonstrated that lipid metabolism indicators, such as the ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C), are potent predictors of CVD incidence, and a TC/HDL-C ratio ≥ 5 is considered to indicate high risk [3–5]. Oxidative stress was shown to alter lipid metabolism, and underlie the mechanism of CVD [6–9]. Recently, some studies have shown that antioxidants might improve lipid metabolism by acting on oxidative stress [10, 11]. Although minerals have antioxidant activity, their association with lipids remains controversial. In addition, limited published research has examined the

✉ Bo Li
li_bo@jlu.edu.cn

Xiaoyu Ma
maxy17@mails.jlu.edu.cn

Shan Jiang
jiangs17@mails.jlu.edu.cn

Shoumeng Yan
yansm17@mails.jlu.edu.cn

Meng Li
lm17@mails.jlu.edu.cn

Changcong Wang
wangcc18@mails.jlu.edu.cn

Yingan Pan
panya18@mails.jlu.edu.cn

Chong Sun
sunchong17@mails.jlu.edu.cn

Lina Jin
jinln@jlu.edu.cn

Yan Yao
yaoyan@jlu.edu.cn

[1] Department of Epidemiology and Biostatistics, School of Public Health, Jilin University, Changchun 130021, China

Published online: 19 November 2019

relationships of minerals with the TC/HDL-C ratio cardiovascular disease risk predictor.

In recent years, researchers have shown that better diet control can improve cardiovascular health [12, 13]. Nutritional antioxidants such as zinc, copper, iron, and selenium, which are essential micronutrients for the body, can be ingested in the diet or through supplements [14]. As one of the most common antioxidants, zinc plays a substantial role in metabolic syndrome [15]. The association between zinc deficiency and the development of CVD has been supported by numerous studies [16, 17]. Studies have demonstrated that dietary zinc supplementation may reduce total cholesterol, but the role of dietary zinc supplementation in HDL is controversial [18]. Moreover, dietary copper deficiency has been associated with inflammation and a variety of CVDs [19]. Copper and zinc are important components of extracellular superoxide dismutase (EC SOD), which is an antioxidant that acts against oxidative stress [20, 21]. Studies have shown that zinc intake is associated with EC SOD activity [22, 23]. In addition, some studies have shown that excessive zinc intake may affect copper status, which might have adverse consequences on blood lipids [24, 25]. Iron is important in regulating cellular function and oxidative stress [26]. Regarding iron, Mark J Sarnak MD et al. identified anemia as an independent risk factor for CVD [27]. Meroño T et al. showed that iron-deficiency anemia was associated with oxidative stress and functionally deficient HDL particles [28]. Selenium is required for selenoproteins and glutathione-peroxidase (GPX), which had antioxidant activity [29]. Several studies have demonstrated that selenium deficiency may increase the risk of CVD [30, 31]. Joachim Bleys et al. found that elevated serum selenium was associated with elevated serum concentrations of TC [32].

In particular, the development of dyslipidemia is a long and continuous process. Thus, in logistic regression, some information might be lost when hyperlipidemia is viewed as a categorical variable. Additionally, the distribution of lipids is nonnormal. Compared with linear regression, quantile regression has great advantages when predicting an entire distribution, such as when analyzing extreme data. In addition, most studies focus on the effects of dietary supplementation on hyperlipidemia but neglect the roles of dietary supplementation on normal people. Therefore, we used quantile regression to analyze the effect of trace minerals from diet and supplements on the levels of CVD risk; we particularly analyzed the effect on low risk levels to explore "early prevention."

Materials and Methods

Data Collection and Study Population

National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey that uses a complex multistage probabilistic sampling method and that is designed to provide a representative sample of the US noninstitutionalized civilian population. The NHANES database includes publicly available data released in 2-year cycles and is available from the NHANES website. The data from 4 cycles of NHANES (2007–2008, 2009–2010, 2011–2012, and 2013–2014) were combined for the present analyses. Out of a total of 40,617 participants in the 2007–2014 NHANES, we chose 23,482 individuals who were not younger than 20 years old. Among these individuals, we excluded pregnant women (n = 247). Additionally, we excluded participants who did not participate in the dietary interview (n = 2439), who did not have a whole blood lipid examination (n = 11,322), and who were missing lifestyle data (including BMI and smoking (n = 85)). Additionally, we excluded patients who used blood-lipid lowering prescription medicines (n = 1805). Ultimately, this study was limited to participants aged 20 years and older and included a total of 7597 participants (3673 males and 3924 females).

Lipid Assessment

Laboratory methods are described in detail in NHANES documentation. Briefly, the Roche Modular P chemical analyzer (enzymatic method) was used to determine the total cholesterol and high density lipoprotein levels of all participants 20 years and older. Then TC and HDL were used to obtain the TC/HDL-C ratio. The NHANES quality assurance and quality control (QA/QC) protocols meet the 1988 Clinical Laboratory Improvement Act mandates. According to the National Cholesterol Education Program Adult Treatment Panel III [33]: a high TC/HDL-C ratio is ≥ 5.

Dietary and Supplement Intake Assessment

The dietary intake interviews included total nutrient intake and dietary supplement intake. All participants participated in two 24-hour total nutrient recall interviews. The first recall interview was conducted in person in the Mobile Examination Center (MEC), and the second interview was conducted through telephone 3 to 10 days later. In our study, we used the average total mineral nutrient intake if the individual completed two 24-hour recalls. Otherwise, we used the data from the first 24-hour recall. Additional, we used an average of 30 days of dietary mineral supplement intake to assess the participants' dietary supplement intake level. Notably, NHANES does not account for the influence of soil selenium levels on the selenium content of many foods. According to the NHANES documentation, all analyses incorporated these dietary weights and provided nationally representative estimates of dietary intake.

Covariates

In addition to blood lipid index and dietary, we also investigated the influence of potential confounding factors, which included demographic characteristics: age (analyzed as continuous variable), sex (male and female), race (non-Hispanic White, non-Hispanic Black, and other race); anthropometric characteristics: BMI; and behavioral characteristics: smoking status (having smoked at least 100 cigarettes throughout life or not) and physical activity (the individuals' physical activity intensity level in a typical week was classified into three levels: sedentary, moderate, and vigorous).

Statistical Analysis

We used quantile regression in R version 3.5.0 for data analysis. The distribution of blood lipids was different, so we analyzed men and women separately. Additionally, the distributions of dietary intake and lipids were nonnormal. The descriptive characteristics of the male and female groups are shown as the median (quartile) and frequency (percentage) for continuous and categorical variables, respectively. Chi square tests were used to compare the percentages of categorical variables. Then, a rank sum test was performed to analyze the differences between males and females in continuous variables. Finally, QR in the quantreg package was used to estimate the relationship between the different percentiles of TC/HDL-C distribution and mineral intake. All statistical tests were 2-sided and a P value < 0.05 was considered statistically significant.

Results

Descriptive Characteristics of Participants by Sex

Overall, 7597 adults aged ≥ 20 years with complete information were included in the analysis. As shown in Fig. 1, dietary mineral intake and TC/HDL-C were nonnormally distributed. Tables 1 and 2 show the basic characteristics of the participants. Among the participants, 1250 had a high risk status of TC/HDL-C ≥ 5 (15.9%), with a difference between males (22.1%) and females (10.2%). Significant differences in demographics (race, smoking, and physical activity) between males and females ($P < 0.001$) were found. Additionally, there were significant differences in terms of iron, zinc, copper, and selenium intake between females and males ($P < 0.001$). Moreover, as shown in Table 3, the distributions of the TC/HDL-C ratio were different between males and females. Therefore, the QR model was used to separately analyze the relationship between TC/HDL-C and dietary elements for males and females.

QR Statistics Relationship Between Dietary Mineral Intake and TC/HDL-C in Males

Table 4 shows the QR coefficients and P values of the relationship between TC/HDL-C and dietary mineral intake (iron, zinc, copper, and selenium) in males. After adjusting for age, race, BMI, smoking, and physical activity, we found that iron intake was negatively associated with TC/HDL-C in males at all normal levels. The intake of zinc was negatively associated with TC/HDL-C. Moreover, the intake of copper was negatively associated with TC/HDL-C, with a stronger correlation. In particular, we found that copper was also correlated at abnormal levels, but the validity of this finding needs to be examined. However, the intake of selenium in males was not correlated with the TC/HDL-C distribution.

QR Statistics Between Dietary Mineral Intake and TC/HDL-C in Females

The relationship between dietary intake and TC/HDL-C in females is shown in Table 5. Similar to males, after adjusting for age, race, BMI, smoking, and physical activity, we found that iron and zinc intakes were negatively associated with TC/HDL-C in higher quantiles among individuals with normal levels. In addition, the intake of copper was negatively associated with TC/HDL-C at all normal levels, and this association was stronger with increasing quantiles. Additionally, the intake of selenium was negatively associated with TC/HDL-C in most of the normal quantiles. We found that the relationship was nonlinear, with the correlation coefficient fluctuation changing.

Comparison of QR Statistics Correlation Between Mineral Dietary Intake and TC/HDL-C in Males and Females

Figure 2 shows that the nonlinear correlation of iron in males was stronger than that in females, so iron may be more effective in regulating lipid levels in males. In contrast, the copper correlation in males was weaker than that in females, so copper may be more effective at improving lipid levels in healthy females and in individuals in high quantiles. Copper had a negative association with high TC/HDL-C ratio only in males. In addition, selenium was only associated in females, and the relationship was nonlinear and appeared U-shaped.

Discussion

Our findings further support the effect of antioxidant minerals on CVD. We used quantile regression which clearly shows the relationship between trace minerals and different risk levels indicated by TC/HDL-C; the analysis was adjusted for age,

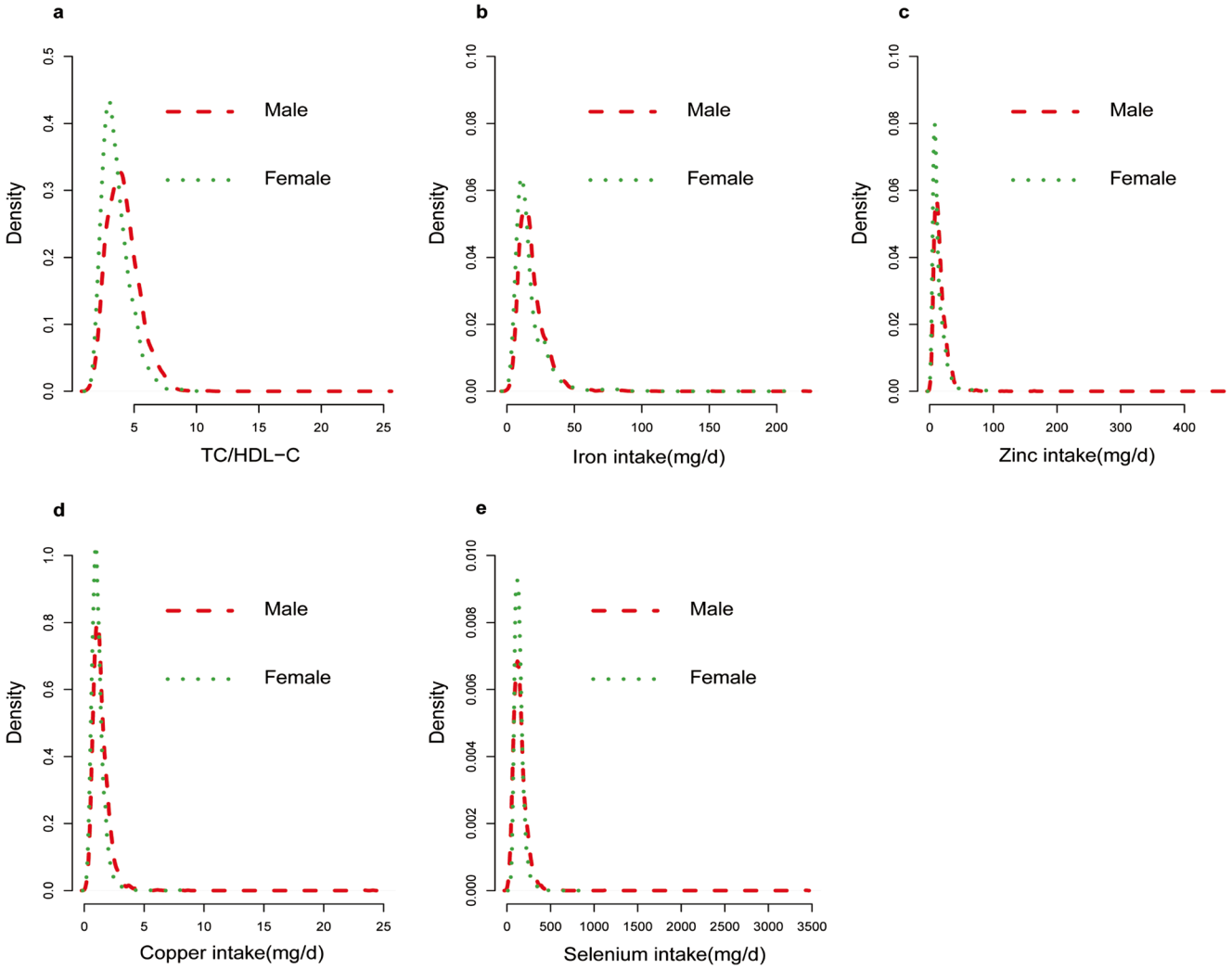

Fig. 1 The distribution of TC/HDL-C ratio (**a**), iron (**b**), zinc(**c**), copper (**d**), and selenium (**e**)

Table 1 Descriptive characteristics of categorical variables of participants by sex

Variable	Male			Female			χ^2	P^b
	n	%	95% CI[a]	*n*	%	95% CI[a]		
Race							10.349	0.025
Non-Hispanic white	1618	66	(62, 69.8)	1730	66.9	(63.4, 70.2)		
Non-Hispanic black	696	9.8	(8.2, 11.7)	773	11.5	(9.7, 13.6)		
Other	1359	24.1	(20.9, 27.7)	1421	21.6	(19.0, 24.5)		
Smoking							147.48	< 0.001
yes	1900	50.6	(47.5, 53.7)	1382	36.8	(34.1, 39.6)		
no	1773	49.4	(46.3, 52.5)	2542	63.2	(60.4, 65.9)		
Physical activity							483.821	< 0.001
high	421	12.1	(10.4, 13.9)	111	2.8	(2.2, 3.6)		
medium	1404	41.2	(38.5, 44.0)	1007	27.9	(25.4, 30.6)		
low	1848	46.7	(44.0, 49.5)	2806	69.2	(66.5, 71.8)		
TC/HDL-C ≥ 5%[c]	836	22.1	(20.2, 24.1)	414	10.2	(9.0, 11.6)	199.875	< 0.001

[a] 95% confidence interval by number of case

[b] *P* value by χ^2 test

[c] A ratio of total cholesterol to high-density lipoprotein cholesterol ≥ 5

Table 2 Descriptive characteristics of continuous variables of participants by sex

Variable	Male		Female		*t*	*P*[b]
	mean	95% CI[a]	mean	95% CI[a]		
Age	43.19	(42.28, 44.11)	45.31	(44.53, 46.09)	122.191	< 0.001
BMI	28.14	(27.79, 28.49)	28.62	(28.26, 28.99)	223.285	< 0.001
Iron intake(mg/d)	19.41	(18.90, 19.91)	17.87	(17.13, 18.62)	94.243	< 0.001
Zinc intake(mg/d)	17.56	(16.86, 18.27)	14.39	(13.89, 14.90)	69.652	< 0.001
Copper intake(mg/d)	1.48	(1.44, 1.51)	1.18	(1.15, 1.21)	98.743	< 0.001
Selenium intake(mcg/d)	154.37	(150.03, 158.71)	110.86	(107.82, 113.89)	97.914	< 0.001
HDL (mmol/L)	49.15	(48.37, 49.92)	59.29	(58.51, 60.09)	181.198	< 0.001
Triglyceride (mmol/L)	125.59	(121.67, 129.51)	110.86	(106.57, 113.63)	78.198	< 0.001
LDL (mmol/L)	118.11	(116.35, 119.87)	116.87	(115.36, 118.37)	174.297	< 0.001
Total (mmol/L)	192.39	(190.28, 194.49)	198.19	(196.21, 200.18)	222.507	< 0.001
ApoB	0.92	(0.91, 0.94)	0.89	(0.88, 0.91)	159.638	< 0.001
TC/HDL-C[c]	4.16	(4.09, 4.22)	3.54	(3.49, 3.59)	160.006	< 0.001

[a] 95% confidence interval by geometric mean

[b] *P* value by *t* test

[c] Ratio of total cholesterol to high-density lipoprotein cholesterol

race, BMI, smoking, and physical activity. We found that the dietary intake of iron, zinc, and copper was negatively correlated with TC/HDL-C levels. And, the effects of copper and zinc tended to be stronger when the risk increased. In addition, the correlation between iron and CVD risk in males was stronger than that in females, while the association of copper was weaker than that in females. A nonlinear negative correlation between selenium and TC/HDL-C ratio was only found in females.

To date, several epidemiological studies reported the association between dietary zinc intake and lipids with controversial conclusions. In the present study, the association between dietary zinc and TC/HDL-C was negative in high quantile. Some studies have demonstrated that the intake of zinc has positive effects on plasma lipid parameters [15, 18]. However, several studies have shown that zinc supplementation can decrease HDL concentrations [34, 35]. Some of the negative results may result from high-dose zinc supplements affecting copper status [25, 36]. Compared with previous studies, we chose a complex predictor. It has been shown that a simple indicator has not provided comprehensive; for example, simply increasing the HDL-C concentration did not reduce the risk of CVD [4, 5, 37]. Consistent with present results, a previous study reported a significant reduction in the TC/HDL-C ratio after zinc supplementation [38]. The biological mechanism of zinc was found to be the suppressing of reactive oxygen species production, the reduction in oxidative stress, and the participation in lipid metabolism [15, 39]. Therefore, zinc supplementation might play a preventive role and reduce CVD.

In the current study, dietary copper intake was inversely associated with the predictor of CVD. Similar to our findings, research has shown that increasing copper intake could reduce the risk of CVD [40]. In addition, it has been reported that low copper concentrations may influence serum lipids through oxidative stress processes [41, 42]. However, in contrast with our study, a study demonstrated a weaker positive association between serum copper and 10-year coronary risk [43]. It was

Table 3 Quantiles of TC/HDL-C by sex

Variable	Quantiles								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
male									
TC/HDL-C ratio[a]	2.633	3.024	3.37	3.693	3.991	4.298	4.67	5.149	5.832
female									
TC/HDL-C ratio[a]	2.351	2.641	2.869	3.105	3.342	3.618	3.943	4.381	5.042

[a] A ratio of total cholesterol to high-density lipoprotein cholesterol ≥ 5 indicates high risk

Table 4 Quantile regression coefficient (*P* value) of iron, zinc, copper, selenium, and TC/HDL in males (NHANES, 2007–2014) [a]

Minerals	Quantiles [b]								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Iron	− 5.72 (0.05)	− 7.91 (0.024)	− 6.79 (0.045)	− 7.93 (0.017)	− 8.94 (0.004)	− 7.37 (0.017)	− 10.55 (0.001)	− 9.02 (0.13)	− 7.17 (0.25)
Zinc	− 0.02 (0.99)	− 0.91 (0.66)	− 3.54 (0.14)	− 4.16 (0.18)	− 4.26 (0.21)	− 6.27 (0.021)	− 6.75 (0.049)	− 6.55 (0.09)	− 6.82 (0.09)
Copper	− 0.01 (0.89)	− 0.04 (0.34)	− 0.07 (0.06)	− 0.11 (0.017)	− 0.13 (0.002)	− 0.14 (0.003)	− 0.15 (0.014)	− 0.12 (0.07)	− 0.18 (0.004)
Selenium	− 0.01 (0.99)	− 0.12 (0.74)	− 0.21 (0.55)	− 0.32 (0.29)	− 0.41 (0.15)	− 0.52(0.11)	− 0.62 (0.08)	− 0.71 (0.19)	− 0.95 (0.16)

[a] Adjusted for age, race, BMI, smoking, and physical activity

[b] Quantile regression coefficient and *P* value

suggested that serum copper levels can be increased by inflammation, even in the presence of moderate copper deficiency [44, 45]. In addition, other research using logistic regression showed that copper and zinc concentrations were not associated with metabolic syndrome [46]. We used QR model, which, unlike logistic regression analysis, can obtain the correlation of all levels, not just 2 categories. In addition, we found a negative correlation in males with abnormal levels, which might have a therapeutic effect.

Iron is essential for the oxidative metabolism of lipids, as demonstrate by clinical and animal experiments. A large prospective cohort study demonstrated that anemia was an independent risk factor for CVD [27]. In the present study, iron was strongly negatively correlated with TC/HDL-C in males at almost all normal levels, and the association was stronger than that in females. The correlation disappeared when the TC/HDL-C was abnormal. In previous studies, a negative correlation between hemoglobin concentration and the risk of CVD has been observed [47, 48]. In addition, a study found that hemoglobin may be affected by factors other than iron status [27].Therefore, iron might be used as a dietary supplement to prevent CVD.

According to our results, the dietary intake of selenium has a beneficial effect on improving the lipid level in females. Similar to our findings, several studies concluded that low selenium concentration was associated with an increased risk of CVD, but the relationship has not been defined [31]. However, another study revealed that there was no association between serum selenium levels and CVD mortality but selenium may prevent CVD only at intake levels below those in the United States [32]. In fact, the antioxidant activity of selenium has been demonstrated in epidemiological studies and animal experiments, and this antioxidant activity might regulate lipid levels [31, 49–51]. Numerous studies have demonstrated that the mechanism of protective function of selenium is that selenoprotein reduces oxidative stress and prevents oxidative damage by restoring the expression and enzymatic activity of glutathione peroxidases [50, 52]. No significant association was found in males, which is in agreement with

Table 5 Quantile regression coefficient (*P* value) of iron, zinc, copper, selenium, and TC/HDL in females (NHANES, 2007–2014) [a]

Minerals	Quantiles [b]								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Iron	0.68 (0.69)	− 0.64 (0.61)	− 1.37 (0.31)	− 2.61 (0.043)	− 4.26 (0.004)	− 5.29 (0.007)	− 7.03 (0.001)	− 8.41 (0.028)	− 4.08 (0.27)
Zinc	− 0.70 (0.78)	− 1.51 (0.52)	− 0.23 (0.93)	− 1.50 (0.42)	− 3.20 (0.12)	− 5.83 (0.007)	− 7.74 (0.003)	− 13.40 (<0.001)	− 9.32 (0.07)
Copper	− 0.10 (0.016)	− 0.11 (0.004)	− 0.11 (0.014)	− 0.14 (<0.001)	− 0.15 (0.006)	− 0.17 (0.001)	− 0.17 (0.002)	− 0.21 (0.005)	− 0.14 (0.13)
Selenium	− 0.75 (0.07)	− 1.18 (0.003)	− 1.32 (0.001)	− 1.43 (0.002)	− 1.25 (0.019)	− 1.53 (0.005)	− 0.80 (0.16)	− 1.50 (0.027)	− 0.58 (0.66)

[a] Adjusted for age, race, BMI, smoking, and physical activity

[b] Quantile regression coefficient and *P* value

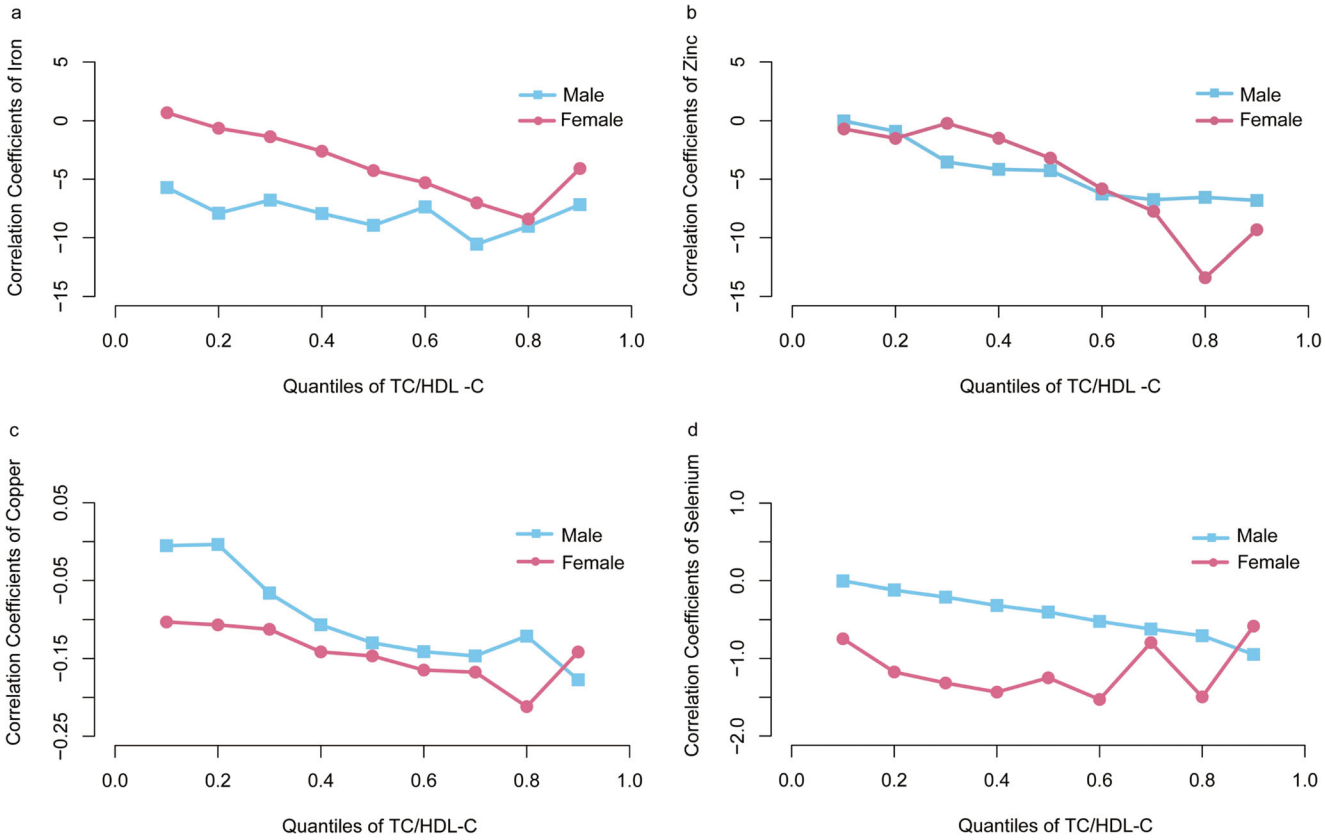

Fig. 2 Comparison of correlation coefficients of the relationships of iron (**a**), zinc (**b**), copper (**c**), and selenium (**d**) with TC/HDL-C ratio by sex

the results of the study conducted in Europe [46]. Why does selenium have sex diversity? The reasons may be that the functions of sex hormones or the alcohol and smoking behaviors may have different effects in males and females. Importantly, it has been shown that the biosynthesis of selenoenzymes and selenoproteins displays sex-specific differences in a dose-dependent manner [53]. Moreover, a previous study of NHANES 2011–2012 participants showed that the association with HDL might be potentially U-shaped [29]. We used QR analysis and found that the relationship between selenium and TC/HDL-C was nonlinear and that the correlation coefficient fluctuated, exhibiting a U-shaped relationship. Therefore, selenium supplementation may be associated with reducing CVD risk in females but none with reducing CVD risk in males.

There are limitations to this study. First, the NHANES is a cross-sectional survey; thus, we cannot examine cause–effect or time–effect relationships between trace minerals and CVD. Additionally, NHANES only examines total intake of minerals. Bioavailability is not addressed. In addition, the dietary data were collected through a self-reported method, which may result in retrospective bias, but the errors do not relate to variations in lipid status discordance. Fortunately, this study used a large nationally representative sample of adults in the US. We adjusted for the variables that may affect the associations between minerals and lipids. In addition, we used quantile regression, which can reveal the correlations of variables at different levels.

Conclusions

Our findings suggest that among US adults, zinc, copper, iron, and selenium intakes are inversely associated with CVD risk, and the effect is enhanced as the quantiles of risk levels increase, but the magnitudes differ by sex. Therefore, trace minerals may have the ability to prevent CVD.

Funding Information This work was supported by the National Natural Science Foundation of China (No. 81973129).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval NHANES is a publicly available data set and all participants in NHANES provide written informed consent, consistent with the approval by the National Center for Health Statistics Institutional Review Board.

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