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Association of serum copper, zinc and selenium levels with risk of metabolic syndrome: A nested case-control study of middle-aged and older Chinese adults

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ABSTRACT

Trace elements, such as copper, zinc and selenium, have been linked to the development of metabolic syndrome. However, previous studies concerning these trace elements in association with metabolic syndrome have presented conflicting results in different countries. The aim of this study was to analyse the association between serum copper, zinc and selenium concentrations and the risk of metabolic syndrome among middle-aged and older Chinese adults. We performed a nested case-control study that included 349 individuals who developed metabolic syndrome (125 males and 224 females) during a 3-year follow-up and 349 controls matched by baseline age (± 1 years), sex and area. Serum trace element concentrations were measured using atomic absorption spectrometry. The median serum selenium levels in males and females in the metabolic syndrome group were 82.2 (13.4) μg/L and 82.6 (11.1) μg/L, respectively, which were significantly higher than the serum selenium levels in the control group ($p = 0.001$ and $p < 0.001$). After adjusting for potential confounders, the odds ratios of risk for metabolic syndrome in the highest tertile of serum selenium levels were 2.72 [95% confidence interval (CI) 1.43–5.20; p for trend 0.002] for males and 5.30 (95% CI 3.31–8.74; p for trend < 0.001) for females, respectively, compared with the lowest tertile. In addition, serum selenium levels were positively correlated with postprandial plasma glucose in both genders (for males: odds ratio 2.42; 95% CI 1.27–4.61; for females: odds ratio 2.11; 95% CI 1.32–3.37) and negatively associated with high-density lipoprotein in only females (odds ratio 3.21; 95% CI 1.75–5.91). These results suggest that higher levels of serum selenium might be an independent risk factor for metabolic syndrome, especially in relation to elevated postprandial plasma glucose and reduced high-density lipoprotein levels. However, we failed to demonstrate an association between copper or zinc status and metabolic syndrome or its components.

1. Introduction

Metabolic syndrome (MetS) is a cluster of abnormalities that typically involve abdominal obesity, dysglycaemia, elevated blood pressure, elevated triglyceride (TG) levels, and low high-density lipoprotein cholesterol (HDL-C) levels. People with MetS are at high risk for developing cardiovascular disease and type 2 diabetes mellitus (T2DM). Parallelling with the ageing of population, changing of lifestyle and dietary habits and growing epidemic of obesity, the prevalence of MetS is increasing rapidly in China; a recent survey demonstrated that 33.9% (31.0% of men and 36.8% of women) of adults in China have MetS [1].

Numerous studies have supported the notion that oxidative stress represents a central mechanism of MetS by either triggering or aggravating the biochemical processes related to MetS [2]. Several MetS components are characterized by an increased production of reactive oxygen species and reactive nitrogen species [3]. Copper (Cu), zinc (Zn), and selenium (Se) are trace elements that play important roles in immunity, glucose and lipid metabolism, and cardiovascular function [4–6]. Moreover, Cu, Zn, and Se are essential cofactors of antioxidant enzymes [Cu, Zn-superoxide dismutase (CuZnSOD) and Se-glutathione peroxidase] that are involved in the maintenance of redox balance and protect cells from oxidative damage. On this basis, whether changes in Cu, Zn, and Se homeostasis are related to the risk of MetS is worth studying. However, the current findings regarding these trace elements

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in association with MetS are inconsistent across countries and regions. Several case-control observational studies have revealed an inverse association between antioxidant supplementation and serum concentrations of antioxidants and MetS [7–9], while a prospective survey conducted in France did not demonstrate a benefit of antioxidant intake on the risk of MetS after 7.5 years of follow-up [10]. Plasma Cu, Zn, and Se levels were not clearly associated with MetS in Croatian adults [11], but cross-sectional and prospective studies have suggested that higher serum Cu, Zn, or Se levels are related to MetS or its components [12–15]. To date, little evidence is available for several trace elements (Cu, Zn, and Se) in relation to MetS components and risk of MetS in Chinese adults. Hence, in this nested case-control study, we aimed to investigate the association between baseline serum Cu, Zn, and Se status and the risk of MetS and its components of middle-aged and older Chinese population; we assessed the risk separately for both genders.

2. Subjects and methods

2.1. Study population

The Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study was a multicentre prospective study designed primarily to evaluate the association between diabetes and the risk of cancer among Chinese individuals. The methodology of the study has been described in detail elsewhere [16,17]. Briefly, 259,657 participants aged 40 years and older were recruited from 2011 to 2012 from 25 communities in China, of which we randomly recruited 5088 eligible individuals from Wenzhou City [18]. At the baseline visit, fasting and postprandial serum samples were obtained from each subject and analysed for total cholesterol (TC), TGs, HDL-C, low-density lipoprotein cholesterol (LDL-C) and blood glucose. The samples were collected and stored at −80 °C until analysis. Information about the demographic characteristics, lifestyle factors, and medical history was collected, and the details of the anthropometric measurements have been reported previously [18]. A repeat investigation was conducted between September 1 and October 31, 2014, and 67.7% of individuals from the baseline visit participated.

All protocols of this study were approved by the ethical review committee of the first affiliated hospital of Wenzhou Medical University. All subjects from this study provided their written informed consents at baseline and the follow-up stages.

2.2. Ascertainment of metabolic syndrome and selection of the control group

Incident MetS cases were identified in participants who were MetS-free at baseline (2011) and newly diagnosed with MetS during the follow-up examination (between October 1, 2011, and October 31, 2014). In total, we determined 349 eligible cases (125 males and 224 females). The controls were selected by random sampling from the same source of 2076 participants who did not develop MetS during the follow-up period. Each case was singly matched to a control by gender, age (± 1 years) and area at baseline. Fig. 1 presents a flowchart describing the selection of the study population.

2.3. Metabolic syndrome definition

MetS was defined based on the Chinese guidelines for the prevention and treatment of dyslipidaemia in adults (2007) as presentation of three or more of the following components: 1) waist circumference > 90 cm in men and > 85 cm in women; 2) serum TG concentration ≥1.7 mmol/l (150 mg/dl) or treatment for high TGs; 3) HDL-C < 1.04 mmol/l (40 mg/dl) or treatment for low HDL-C; 4) systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg or current use of antihypertensive drugs; and 5) fasting plasma glucose (FPG) ≥6.1 mmol/l (110 mg/dl), postprandial plasma glucose (PPG) ≥7.8 mmol/l (140 mg/dl), previous diagnosis of T2DM, or use of antidiabetic drugs [19].

2.4. Determination of trace elements

Serum Cu and Zn were measured by flame atomic absorption spectrometry (SpectrAA240FS; Varian, USA) with deuterium background correction, and Se was measured by graphite furnace atomic absorption spectroscopy (SpectrAA240Z; Varian, USA) with Zeeman background correction. We followed a standard operating procedure for the collection, processing, and storage of blood samples in both study stages as previously described [18]. We used the wet acid digestion method to digest blood samples. Standard solutions of Cu (500 μg/mL), Zn (500 μg/mL) and Se (100 μg/mL) were prepared by dilution of certified standard solutions (National Institute of Metrology, China). A Pd $(NO_3)_2$ solution (10.0 g/L) (Merck, Darmstadt, Germany) was used to prepare a matrix modifier for Se detection. We used the Seronorm™ Trace Elements Serum (batch number: 201405, Sero AS, Norway) as a reference material to evaluate the accuracy and precision of the detection. The settings of the atomic absorption spectrometer for Cu, Zn and Se measurements were as follows: Cu: wavelength 324.8 nm, lamp current 4.0 mA, slit width 1.0 nm; Zn: wavelength 213.9 nm, lamp current 5.0 mA, slit width 0.2 nm; and Se: wavelength 196.0 nm, lamp current 10.0 mA, slit width 1.0 nm. The flow rate was 13.5 L/min for air (oxidant) and 2.0 L/min for acetylene for Cu and Zn measurements, and a standard addition technique was used for Se quantification with a standard addition concentration of 25 μg/L [20].

2.5. Statistical analysis

The baseline characteristics of the individuals with MetS and controls are described as the means (SD), percentages or medians (interquartile range). Comparisons between the individuals with MetS and the controls were carried out using either a t-test, Chi-squared test or Mann-Whitney *U* test based on the characteristics of the data. We computed odds ratios (ORs) and 95% CIs for the risk of MetS in tertiles of serum concentrations of Cu, Zn and Se using conditional logistic regression analysis and controlling for matching variables (age, area and gender); the following models were used: model 1, unadjusted, and model 2, adjusted for potential confounders including smoking habit, alcohol consumption, physical activity and medication usage (medications for cardiovascular or cerebrovascular diseases and neurological or mental disorders) at baseline. Logistic regressions were performed simultaneously for Cu and Zn because their metabolisms are closely related. We further examined the relationship between MetS components as the dependent variable and baseline serum Se as the independent variable using logistic regression analysis.

3. Results

3.1. General characteristics of study subjects stratified by metabolic syndrome and non-metabolic syndrome

This study was carried out with 349 individuals with MetS and 349 MetS-free controls (both groups included 125 men and 224 women) with complete data on MetS components and serum Cu, Zn and Se concentrations. The baseline characteristics of the participants are described and compared separately for each gender in Table 1. Participants in the MetS group were more likely to have a greater waist circumference, waist-hip ratio, serum TG level, and PPG level and a lower HDL-C level; these associations were observed in both genders. Women tended to have higher SBP levels, and men tended to have higher FPG levels compared with the levels in the control groups. No significant difference was observed regarding physical activity, smoking habits or alcohol consumption between the MetS and non-MetS groups. The median serum Se concentrations in male and female individuals with

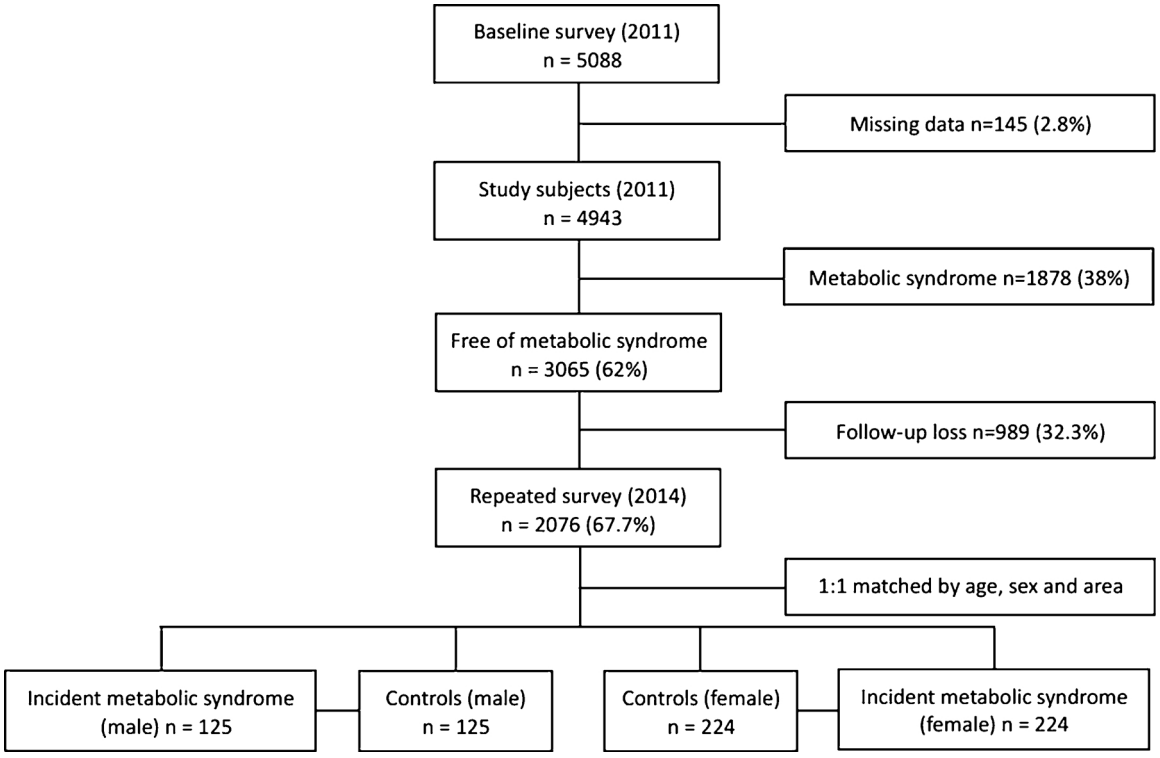

Fig. 1. Flowchart of study population.

MetS were 82.2 (13.4) μg/L and 82.6 (11.1) μg/L, respectively, which were significantly higher than the concentrations in the control group ($p = 0.001$ and $p < 0.001$). In addition, male participants with MetS were more prone to have lower baseline serum Zn levels compared with the control group ($p = 0.011$).

3.2. Associations between serum levels of copper, zinc or selenium and risk of metabolic syndrome

As shown in Table 2, higher serum Se concentrations at baseline were correlated with a high risk of MetS. In female subjects, there were statistically significant increases in the risk for MetS in the T2 and T3 groups compared with the risk of MetS in the T1 group [T2 vs. T1, OR 3.85, 95% CI (2.36–6.28); T3 vs. T1, OR 5.48, 95% CI (3.33–9.01)]. Similarly, increasing tertiles of serum Se levels were positively correlated with the risk of MetS in male subjects (T3 vs. T1, OR 2.63, 95% CI 1.40–4.93). All trends persisted in model 2 after adjusting for potential confounders. However, serum Cu and Zn concentrations were not associated with the risk of MetS in either gender in the univariate or multivariate models.

Table 1
Baseline characteristics of individuals with metabolic syndrome and the matched controls.

Characteristic	Male			Female		
	MetS (n = 125)	Controls (n = 125)	P-value	MetS (n = 224)	Controls (n = 224)	P-value
Age, y	65.35 (7.86)	65.33 (7.82)	m.v.	63.10 (7.19)	63.02 (7.15)	m.v.
BMI, kg/m^2	24.55 (2.69)	23.83 (3.89)	0.086	24.51 (3.13)	23.08 (3.27)	< 0.001
WC, cm	87.5 (7.4)	84.9 (6.9)	0.004	85.0 (8.3)	80.7 (8.8)	< 0.001
WHR	0.90 (0.05)	0.88 (0.05)	0.014	0.89 (0.05)	0.87 (0.07)	< 0.001
TGs, mmol/L	1.73 (1.15)	1.30 (0.57)	< 0.001	1.57 (0.82)	1.30 (0.57)	< 0.001
HDL-C, mmol/L	1.26 (0.26)	1.40 (0.32)	< 0.001	1.42 (0.28)	1.56 (0.29)	< 0.001
FPG, mmol/L	5.60 (5.12-6.20)	5.31 (5.00-5.84)	0.013	5.30 (5.00-5.80)	5.29 (4.99-5.60)	0.061
PPG, mmol/L	6.90 (6.00-10.30)	6.40 (5.00-7.90)	0.001	7.20 (6.23-8.60)	6.40 (5.60-7.58)	< 0.001
SBP, mmHg	134.7 (19.0)	130.3 (16.5)	0.052	131.5 (18.2)	126.4 (17.5)	0.003
DBP, mmHg	80.5 (11.8)	77.7 (9.2)	0.042	78.2 (10.5)	76.5 (10.1)	0.071
Physical activity score	26.20 (25.60-27.55)	26.00 (25.28-27.80)	0.349	25.80 (25.50-26.70)	25.80 (25.25-26.65)	0.156
Current smoker, n %	48 (38.4)	48 (38.4)	1.000	6 (2.7)	2 (0.9)	0.151
Alcohol consumption, n %	54 (43.2)	39 (31.2)	0.051	15 (6.7)	10 (4.5)	0.302
Cu, mg/L	0.91 (0.11)	0.90 (0.11)	0.603	0.95 (0.12)	0.94 (0.12)	0.383
Zn, mg/L	0.95 (0.16)	1.01 (0.18)	0.011	0.97 (0.18)	1.00 (0.19)	0.176
Se, μg/L	82.2 (13.4)	77.0 (9.7)	0.001	82.6 (11.1)	74.4 (11.3)	< 0.001

Data are expressed as the mean (SD), percentages or medians (interquartile range) based on the characteristic of the data. P-values were obtained from the t-test, Mann-Whitney *U* test or Chi-squared test.
BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; m.v., matching variable.

Table 2
Association between baseline levels of serum copper, zinc and selenium and risk of metabolic syndrome.

	Male				Female			
	T1	T2	T3	P_{trend}	T1	T2	T3	P_{trend}
Cu								
Cutoff level (mg/L)	< 0.87	0.87–0.94	> 0.94		< 0.90	0.90–0.98	> 0.98	
Median (mg/L)	0.79	0.91	1.02		0.83	0.93	1.04	
Total (n)	82	89	79		158	142	148	
Cases (n)	43	42	40		75	69	80	
Model 1	1 (ref.)	0.81 (0.44-1.48)	0.93 (0.50-1.73)	0.820	1 (ref.)	1.06 (0.67-1.67)	1.30 (0.83-2.04)	0.251
Model 2	1 (ref.)	0.80 (0.43-1.47)[a]	0.91 (0.49-1.70)[a]	0.768	1 (ref.)	1.00 (0.63-1.58)[a]	1.28 (0.81-2.01)[a]	0.303
Zn								
Cutoff level (mg/L)	< 0.90	0.90–1.03	> 1.03		< 0.91	0.91–1.04	> 1.04	
Median (mg/L)	0.82	0.97	1.19		0.79	0.98	1.16	
Total (n)	84	87	79		149	143	156	
Cases (n)	47	43	35		79	72	73	
Model 1	1 (ref.)	0.77 (0.42-1.40)	0.63 (0.34-1.16)	0.139	1 (ref.)	0.90 (0.57-1.42)	0.78 (0.50-1.22)	0.279
Model 2	1 (ref.)	0.79 (0.43-1.46)[b]	0.66 (0.35-1.24)[b]	0.196	1 (ref.)	0.88 (0.55-1.39)[b]	0.79 (0.50-1.24)[b]	0.303
Se								
Cutoff level (μg/L)	< 74.4	74.4–84.4	> 84.4		< 73.3	73.3–81.5	> 81.5	
Median (μg/L)	68.1	79.2	90.5		66.7	78.2	89.5	
Total (n)	83	83	84		149	149	150	
Cases (n)	37	31	57		39	86	99	
Model 1	1 (ref.)	0.74 (0.40-1.38)	2.63 (1.40-4.93)**	0.002	1 (ref.)	3.85 (2.36-6.28)***	5.48 (3.33-9.01)***	< 0.001
Model 2	1 (ref.)	0.72 (0.38-1.35)	2.72 (1.43-5.20)**	0.002	1 (ref.)	3.88 (2.37-6.33)***	5.30 (3.31-8.74)***	< 0.001

Data are presented as ORs (95% CIs). Median levels are the medians in each tertile of the case groups. ** $p < 0.01$, *** $p < 0.001$. P-values are from the comparison with the first tertile category (T2 or T3 vs. T1). Model 1: unadjusted. Model 2: adjusted for potential confounders including smoking habit, alcohol consumption, physical activity and medication use at baseline. [a] In this model serum zinc was further included as a covariate. [b] In this model serum copper was further included as a covariate.

3.3. Associations between serum levels of selenium and metabolic syndrome components

Table 3 shows the associations between the baseline serum Se levels and MetS components at follow-up. Serum levels of Se were positively correlated with blood glucose in both genders (for males: T3 vs. T1, OR 2.96; 95% CI 1.56–5.62; for females: T3 vs. T1, OR 2.12; 95% CI 1.33–3.38) and negatively correlated with HDL-C in only females (OR 3.22; 95% CI 1.76–5.89) in model 1. The associations remained significant after adjusting for multiple potential risk factors. We did not observe a significant association between Se levels and other MetS components after adjusting for multiple confounders. Regarding blood glucose levels, we further studied the relationships between baseline Se levels and FPG and PPG concentrations. The upper tertile of serum Se (T3: > 84.4 μg/L for males and > 81.5 μg/L for females) was associated with an increased risk of elevated PPG levels (defined as PPG ≥ 7.8 mmol/L) compared with the risk associated with the lowest tertile (T1: < 74.4 μg/L for males and < 73.3 μg/L for females) (for males: T3 vs. T1, OR 2.42; 95% CI 1.27–4.61; for females: T3 vs. T1, OR 2.11; 95% CI 1.32–3.37). However, no significant association between

Table 3
Association between baseline serum levels of selenium and risk of metabolic syndrome components stratified by gender.

Serum level of Se	Male				Female			
	T1	T2	T3	P_{trend}	T1	T2	T3	P_{trend}
Increased waist circumference								
MetS/controls	38/45	27/56	43/41		69/80	76/73	87/63	
Model 1	1(ref.)	0.57 (0.30-1.07)	1.24 (0.68-2.28)	0.459	1(ref.)	1.21 (0.77-1.90)	1.60 (1.01-2.53)*	0.044
Model 2	1(ref.)	0.57 (0.30-1.07)	1.23 (0.67-2.27)	0.490	1(ref.)	1.20 (0.76-1.90)	1.53 (0.96-2.42)	0.072
Elevated triglycerides								
MetS/controls	27/56	22/61	33/51		38/111	59/90	55/95	
Model 1	1(ref.)	0.75 (0.38-1.46)	1.34 (0.71-2.53)	0.342	1(ref.)	1.92 (1.17-3.14)*	1.69 (1.03-2.78)*	0.042
Model 2	1(ref.)	0.74 (0.38-1.45)	1.29 (0.68-2.44)	0.422	1(ref.)	1.92 (1.17-3.15)*	1.66 (1.01-2.74)*	0.050
Reduced HDL-C								
MetS/controls	29/54	23/60	33/51		18/131	38/111	46/104	
Model 1	1(ref.)	0.71 (0.37-1.38)	1.21 (0.64-2.26)	0.539	1(ref.)	2.49 (1.35-4.61)**	3.22 (1.76-5.89)***	< 0.001
Model 2	1(ref.)	0.71 (0.37-1.38)	1.20 (0.64-2.27)	0.547	1(ref.)	2.53 (1.36-4.68)**	3.21 (1.75-5.91)***	< 0.001
Elevated blood glucose								
MetS/controls	38/45	45/38	60/24		69/80	81/68	97/53	
Model 1	1(ref.)	1.40 (0.76-2.58)	2.96 (1.56-5.62)**	0.001	1(ref.)	1.38 (0.88-2.18)	2.12 (1.33-3.38)**	0.002
Model 2	1(ref.)	1.40 (0.76-2.58)	3.08 (1.61-5.89)**	0.001	1(ref.)	1.38 (0.87-2.18)	2.10 (1.31-3.35)**	0.002
Elevated blood pressure								
MetS/controls	51/32	42/41	62/22		77/72	82/67	94/56	
Model 1	1(ref.)	0.64 (0.35-1.19)	1.77 (0.92-3.41)	0.093	1(ref.)	1.14 (0.73-1.81)	1.57 (0.99-2.49)	0.056
Model 2	1(ref.)	0.63 (0.33-1.18)	1.93 (0.97-3.81)	0.066	1(ref.)	1.14 (0.72-1.80)	1.49 (0.94-2.38)	0.094

Data are presented as ORs (95% CIs). Serum levels of selenium in T1, T2 and T3 were < 74.4 μg/L, 74.4–84.4 μg/L, > 84.4 μg/L in males and < 73.3 μg/L, 73.3–81.5 μg/L, > 81.5 μg/L in females, respectively. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. P-values are from the comparison with the first tertile category (T2 or T3 vs. T1). Model 1: unadjusted. Model 2: adjusted for potential confounders including smoking habit, alcohol consumption, physical activity and medication use at baseline.

Table 4
Association between baseline serum selenium levels and risk of elevated fasting plasma glucose and postprandial plasma glucose at follow-up in both genders.

Serum level of Se[a]		High FPG[b]		Normal FPG		p[¥]	OR(95% CI)[§]	High PPG[c]		Normal PPG		p[¥]	OR(95% CI) [§]
		n	%	n	%			n	%	n	%		
						0.213						0.020	
	T1	16	19.3	67	80.7		1 (ref.)	38	45.8	45	54.2		1 (ref.)
Male	T2	17	20.5	66	79.5		1.03 (0.48-2.24)	43	51.8	40	48.2		1.19 (0.64-2.22)
	T3	25	29.8	59	70.2		1.69 (0.81-3.50)	56	66.7	28	33.3		2.42 (1.27-4.61)**
	P_{trend}						0.125						0.001
						0.183						0.005	
	T1	14	9.4	135	90.6		1 (ref.)	67	45.0	82	55.0		1 (ref.)
Female	T2	23	15.4	126	84.6		1.79 (0.88-3.63)	76	51.0	73	49.0		1.30 (0.83-2.06)
	T3	24	16.0	126	84.0		1.90 (0.94-3.85)	95	63.3	55	36.7		2.11 (1.32-3.37)**
	P_{trend}						0.078						0.002

[a] Serum selenium levels in T1, T2 and T3 were < 74.4 μg/L, 74.4–84.4 μg/L, > 84.4 μg/L in males and < 73.3 μg/L, 73.3–81.5 μg/L, > 81.5 μg/L in females, respectively.
[b] Defined as FPG ≥ 6.1 mmol/L.
[c] Defined as PPG ≥ 7.8 mmol/L.
** p < 0.01.
¥ P value for Chi-squared test.
§ Adjusted for potential confounders including smoking habit, alcohol consumption, physical activity and medication use at baseline.

baseline serum Se levels and FPG was found in either men or women (Table 4).

4. Discussion

Our study provides evidence that Se is positively associated with a higher risk of MetS in a middle-aged and older Chinese population. The relationship appears to be stronger among females, demonstrating a dose-response relationship with a 5.30-fold risk of MetS in the highest tertile of serum Se levels compared to the risk in the lowest serum Se tertile after adjusting for potential confounding risk factors (p for trend < 0.001). In addition, serum Se levels were positively correlated with the risk of elevated PPG levels at the follow-up stage in both genders. We also observed an inverse association between baseline Se concentrations and HDL-C levels in women. However, no clear association was found between serum Cu or Zn levels and the risk of MetS.

Zn is a trace element that is essential for many metabolic processes and has antioxidant and anti-inflammatory properties that protect against MetS-associated oxidative stress [4]. Low serum Zn or insufficient Zn intake seems to lead to MetS or a greater number of its components [21,22]. However, Zn was not substantially associated with MetS in either gender in European participants [13], which is in accordance with our results. Zn supplementation did not affect the risk of MetS in a prospective study, although the occurrence of MetS increased as baseline serum Zn concentrations increased [10]. The lack of association between serum Zn levels and MetS may be due to the opposite effects of Zn on different parameters of MetS (positive association between serum Zn levels and TG and negative association between Zn levels and HDL-C and glucose tolerance) [21,23].

Cu is both a pro-oxidant and an antioxidant. Similar to Zn, the antioxidant role of Cu has been attributed to increased CuZnSOD activity. Cu ions participate in radical reactions that may induce oxidative damage to DNA under the condition of excess Cu. Cu intake at particular doses in healthy middle-aged volunteers showed an antioxidant effect in protecting red blood cell membranes from free-radical-mediated oxidation [24], but Simona Bo et al. did not recommend Cu supplementation considering its association with inflammation and markers of oxidative stress [5]. From our data, the lack of association between serum Cu levels and MetS is in line with the result reported in Iranian subjects [25].

Regarding Se, we found an association between increased serum Se concentrations and the risk of MetS at follow-up in both genders, and the association remained significant after adjusting for smoking habit, alcohol consumption, physical activity and medication use at baseline. In the IMMIDIET study, female participants with higher levels of plasma Se showed an elevated risk of MetS, although no meaningful association was observed in males [13]. Similar results were found in a case-control study [15]. A study conducted in Lebanese adults showed that plasma Se levels correlated positively with all components of MetS [26]. Nevertheless, serum levels of Se did not differ significantly between subjects with and without MetS in the Third National Health and Nutrition Examination Survey or the SU.VI.MAX trial [10,27].

In terms of the association between Se and HDL-C, the results have not been consistent. Some studies have revealed a positive association [26,28–30], while others refer to a negative correlation [31,32], and many other researchers have not found clear correlations [15,33,34]. Different epidemiological research methods as well as different sample sizes may partially account for some of those inconsistencies. In our study, we found a negative association between serum Se levels and follow-up HDL-C concentrations in women but not in men. The median age of women in this study was approximately 63 years at baseline, suggesting that postmenopausal women with higher serum Se levels are more prone to have lower HDL-C levels. A potential menopausal effect was corroborated by an observational survey conducted in Japanese women [35]. However, the mechanisms involved in the association between serum Se levels and lipid profiles, especially HDL-C, have not been completely clarified. A possible explanation is a link between selenoprotein and lipoprotein metabolism [29]. Apolipoprotein receptors mediate the uptake of selenoproteins in different organs, such as the brain and kidneys [36], while selenoproteins in turn regulate plasma cholesterol levels, liver apolipoprotein E concentrations and gene expression involved in cholesterol biosynthesis [37].

With respect to glucose metabolism, we found that both men and women with higher baseline serum Se concentrations were more likely to have higher blood glucose levels after a 3-year follow-up, which is similar to what has been described in other studies [30,38–40]. The Third National Health and Nutrition Examination Survey (NHANES III), a large cross-sectional study conducted in 8876 U.S. adults, showed a positive association between serum Se levels and the prevalence of diabetes [40]. Saverio Stranges et al. used data from the Olivetti Heart Study and indicated that there was a higher proportion of individuals with diabetes in the highest tertile of baseline Se concentrations compared to the proportion of diabetes in the lowest tertile [30]. However, an increased incidence of dysglycaemia was found to be associated with lower plasma Se concentrations during a 9-year follow-up in French elderly men [41]. In addition, data from the SELECT (the Selenium and

Vitamin E Cancer Prevention Trial) study, a randomized controlled trial, showed a statistically nonsignificant increase in T2DM among participants in the Se supplementation group compared with participants in the placebo group after 5.5 years of follow-up (relative risk 1.07, p = 0.16) [42]. These discrepancies from human studies suggest that there may be a non-linear relationship between serum Se and T2DM: serum Se levels are positively associated with T2DM when individuals have relatively low (< 97.5 μg/L) or high serum Se levels (> 132.5 μg/L) [43]. In our study, the average serum Se levels were 82.2 μg/L and 82.6 μg/L in males and females, respectively, but the median baseline serum Se level was 135 μg/L in the SELECT trial, which may already exceed a threshold of risk; thus, an additional supplementation of Se may result in little extra risk. Another point worth mentioning is that in the SELECT study, the definition of diabetes was based on self-reported data or medication usage rather than measurements of biomarker data. In addition, different study designs, relative selectivity of participants, diverse forms of Se supplementation, and use of different diabetes diagnostic criteria may give rise to the inconsistencies in the current results.

To obtain a clearer picture of the association between dysglycaemia and serum Se status, we further divided elevated blood glucose into FPG and PPG. To the best of our knowledge, our research is the first to reveal that individuals with higher baseline serum Se levels had a significantly higher risk of elevated PPG levels during a 3-year follow-up period in both genders. However, we did not find a relationship between serum Se levels and FPG concentrations. Previous studies have shown that insulin resistance (IR), including muscle and hepatic IR, is the primary cause of elevated PPG levels, combined with defective insulin secretion, leading to hyperglycaemia after a glucose load [44,45]. The biological mechanism underlying the association between Se and IR has not been well established. Se exerts most of its biological functions through selenoprotein P (SeP), a liver-derived secretory protein that is involved in IR. The results from in vitro and in vivo experiments suggest that SeP disturbs the insulin signalling pathway in liver and muscle by reducing insulin-stimulated phosphorylation of insulin receptors and protein kinase B (Akt) and reduces insulin sensitivity by lowering the phosphorylation of AMP-activated protein kinase (AMPK), leading to IR and the development of T2DM [46,47].

Several limitations of our study need to be mentioned. First, with a response rate of only 67.7%, loss to follow-up can be a source of bias. Most of the non-responders were elderly individuals living alone without family members or participants who had inconveniences that prevented them from attending the repeated survey; hence, we may have underestimated the incidence of MetS in the general population. Second, baseline intake data were not included as a covariate in this study; thus, we cannot eliminate the influence of unmeasured dietary factors on our results. However, M Ghayour-Mobarhan et al. [48] revealed a modest relationship between serum Cu, Zn and Se concentrations and dietary intake. Third, this study was confined to middle-aged and elderly southern Chinese residents and may not be generalizable to other populations.

5. Conclusions

In conclusion, our results show that higher levels of serum Se might increase the risk of MetS, elevated PPG and reduced HDL-C levels. However, we did not observe a substantial association between Cu or Zn status and MetS or its components.

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Competing interests

The authors declare no conflict of interest.

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