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RESEARCH

High Copper Intake Is Associated with Decreased Likelihood of Abdominal Aortic Calcification in Middle-Aged and Older US Adults

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Abstract

The purpose of our study was primarily to investigate the relationship between dietary copper intake and abdominal aortic calcification (AAC) in US adults. We used data from the National Health and Nutrition Examination Survey (NHANES) 2013–2014 for our analysis. Multivariate linear regression analysis was used to explore the relationship between copper intake and AAC scores. We also used multivariate logistic regression analysis to explore the association between copper intake and the risk of AAC and severe AAC. We also examined whether there was a nonlinear relationship between copper intake and AAC scores and risk of AAC and severe AAC using restricted cubic splines (RCS) analysis. In addition, we also performed subgroup analysis and interaction tests. A total of 2897 participants were recruited in this study. The mean AAC score of the participants was 1.46 ± 0.11, and the prevalence of AAC and severe AAC among the participants was 28.53% and 7.68%, respectively. In the fully adjusted model, a negative association of copper intake with AAC scores ($\beta = -0.16$, *95%CI*: $-0.49 \sim 0.17$) and the risk of AAC (*OR* = 0.85, *95% CI*: 0.61–1.19) and severe AAC (*OR* = 0.82, *95% CI*: 0.49–1.38) was observed. Compared to participants in the lowest tertile of copper intake, participants in the highest tertile of copper intake had a 0.37-unit decrease in mean AAC score ($\beta = -0.37$, *95% CI*: -0.90–0.15) and a significant 38% and 22% decrease in risk of AAC (*OR* = 0.62, *95% CI*: 0.41–0.95) and severe AAC (*OR* = 0.78, *95% CI*: $0.34 - 1.77$), respectively. The results of subgroup analyses and interaction tests suggested no significant differences in AAC scores and AAC risk between the different strata. In contrast, the risk of severe AAC was significantly dependent on the patients' diabetes status. Increased copper intake was associated with decreased AAC scores and decreased likelihood of AAC and severe AAC.

Keywords Copper intake · Abdominal aortic calcification · Vascular calcification, Cross-sectional study

Introduction

Vascular calcification (VC) is a pathological process of abnormal deposition of calcium, phosphorus, and other mineral components in the walls of blood vessels, commonly found in the aorta, coronary arteries, and aortic valves [1–3]. VC is common in patients with diabetes [4] and chronic kidney disease (CKD) [5–7]. Coronary artery calcification score could predict all-cause mortality and risk of cardiovascular events in patients with type 2 diabetes [8]. In patients with stage CKD 3–5, moderate to severe coronary artery calcification was associated with an increased risk of cardiovascular events [9]. One study suggested that vascular calcification was also an independent predictor of cardiovascular events in patients receiving peritoneal dialysis [10].

Abdominal aortic calcification (AAC) has received increasing attention in recent years. The prevalence of AAC has been reported to be 28.8% in adults in the USA [11]. Advanced age was associated with an increased incidence of AAC, and the prevalence of AAC has been reported to be as high as about 96% in older women aged 85 years or older [12]. AAC was thought to be associated with poor cardiovascular prognosis in pre-dialysis CKD patients [13]. AAC has also been used to predict the risk of adverse cardiac and cerebrovascular events and the occurrence of left ventricular

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remodeling in dialysis patients [14, 15]. Even in the general population, AAC remained significantly associated with long-term cardiovascular events and mortality [16]. Kauppila et al. proposed a method to grade and score calcification of the abdominal aorta by lateral lumbar spine radiographs, which can effectively assess the severity of AAC [17]. Subsequently, Kidney Disease: Improving Global Outcomes (KDIGO) recommended the use of the AAC score to manage arterial calcification in peritoneal dialysis patients [18].

Copper is an important micronutrient for human health and development, since copper cannot be synthesized in the body, it must be obtained daily from foods such as animal offal, nuts, and legumes and from drinking water [19, 20]. Copper is particularly important for the development of the brain, bones, and other organs [21]. In addition, copper can also be used as a cofactor component of enzymes such as cytochrome C oxidase and superoxide dismutase to participate in processes such as energy metabolism and redox mechanisms in the body [22, 23]. One study found that serum copper concentrations were significantly higher in patients with atherosclerosis and showed a positive correlation with the severity of the disease [24]. A study investigating copper and cardiovascular disease risk factors demonstrated a significant positive association between serum copper concentrations and total cholesterol and glycated hemoglobin (HbA1c) levels [25]. In another study, dietary copper intake levels were negatively associated with the risk of myocardial infarction, and this negative association was more pronounced in older women, smokers, and overweight individuals [26]. The researchers also found that inadequate copper intake was not associated with hospitalization and mortality rates in outpatients with heart failure [27]. Plasma copper concentration was also found to be positively associated with the risk of first stroke episode in patients with hypertension [28]. Another study found that an increase in dietary copper intake reduced the risk of stroke [29].

However, the relationship between copper intake and AAC has not been reported previously. Therefore, we used the data from the National Health and Nutrition Examination Survey (NHANES) 2013–2014 to explore the relationship between copper intake and AAC scores and the risk of AAC and severe AAC. The authors hypothesized that a higher copper intake was negatively associated with AAC scores and the risk of AAC and severe AAC.

Materials and Methods

Study Population

The National Health and Nutrition Examination (NHANES) survey is a national cross-sectional survey study based on the US population with the primary purpose of assessing the health and nutritional status of the US population. Participants underwent standardized household interviews and health screenings at mobile examination centers to assess their physical status and laboratory tests to collect their laboratory-related data. The NHANES used a complex stratified, multilevel probability cluster sampling design, resulting in the recruitment of a highly representative sample of the US population. The NHANES study protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. All participants provided written informed consent. The detailed NHANES study design and data are publicly available at https://www.cdc.gov/nchs/nhanes/.

We used the 2013–2014 NHANES survey cycle to assess the correlation between dietary copper intake and AAC because this was the only survey cycle that contained complete data on both copper intake and AAC scores. Data on AAC scores were obtained by dual-energy X-ray absorptiometry scanning (DXA), and we excluded participants under the age of 40 years because only those aged 40 years and older underwent DXA.

We initially included 10,175 participants in this study, and after excluding data from participants under the age of 40 years ($n=6360$), as well as from lack of dietary copper intake ($n=514$) and AAC scores ($n=404$), a total of 2897 subjects were included in our final analysis (Fig. 1).

Assessment of Copper Intake

All NHANES participants were eligible to participate in two 24-h dietary recall interviews. The first dietary recall interview was collected in person at the mobile testing center.

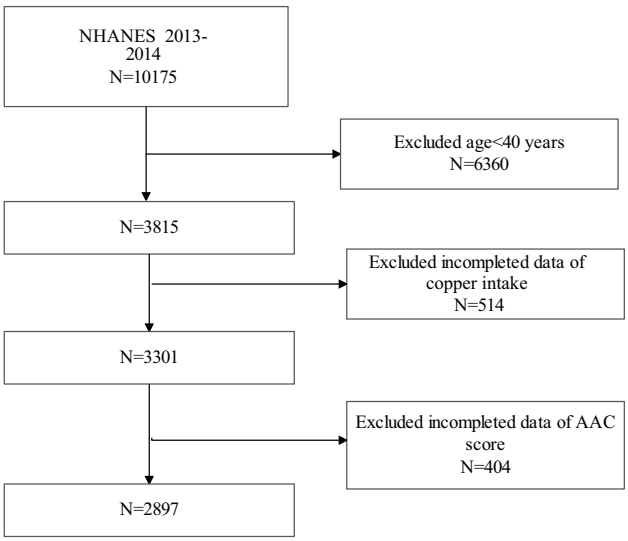

Fig. 1 Flowchart of the sample selection from National Health and Nutrition Examination Survey (NHANES) 2013–2014

The second interview was collected by telephone 3–10 days later. Dietary intake of copper was obtained from the total nutrient intake file, which contains the total nutrients for all foods and beverages. The average copper intake from two 24-h recalls was used in our analysis.

Definition of Abdominal Aortic Calcification

The AAC score is an assessment system proposed by Kauppila et al. by quantifying the lumbar lateral images obtained by DXA [17]. The total AAC score ranges from 0 to 24. We used the AAC score to assess the severity of abdominal aortic calcification, where a higher AAC score represented a more severe calcification of the abdominal aorta. Based on previous studies, the authors defined participants with an AAC score of 6 or more as having severe AAC [30, 31].

Selection of Covariates

The covariates included in our analysis included age, sex, race, education levels, ratio of family income to poverty (PIR), body mass index (BMI), total cholesterol, total energy intake, hypertension, diabetes (DM), alcohol consumption, and smoking status. BMI was classified as <25, 25–29.9, and ≥ 30 kg/m2, which corresponded to normal weight, overweight, and obesity for all participants. Hypertension was defined based on a self-reported diagnosis of hypertension, diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg, or the use of antihypertensive medications [32]. DM was defined base on a self-reported diagnosis of diabetes mellitus, 2-h plasma glucose ≥ 200 mg/dL in an oral glucose tolerance test, HbAlc $\geq 6.5\%$, use of oral hypoglycemic agents, or fasting glucose ≥ 126 mg/dL [33]. All details regarding these variables are available on the website at www.cdc.gov/nchs/nhanes/.

Statistical Analysis

Statistical analysis was performed using appropriate sampling weights according to NHANES analysis guidelines and considering complex multi-stage clustering surveys. Continuous variables were presented as mean with standard deviation, and categorical variables were presented as percentages. Weighted Student's *t*-test (continuous variables) or a weighted chi-square test (categorical variables) was employed to assess the differences among participants grouped by copper intake and AAC. To examine the association between copper intake and AAC, multivariable linear regression used AAC score as a continuous variable and logistic regression used the risk of AAC (AAC score >0) and severe AAC (AAC score >6) as dichotomous variables in three different models. No covariates were adjusted for in Model 1, and in Model 2, age, sex, and race were adjusted. In Model 3, adjustments were made for sex, age, race, education levels, PIR, BMI, total cholesterol, total energy intake, hypertension, DM, alcohol consumption, and smoking status. Subgroup analysis on the associations of copper intake with AAC scores and the risk of AAC and severe AAC was conducted with stratified factors including age, sex, race, diabetes, hypertension, BMI, and smoking status. In addition, an interaction term was added to test the heterogeneity of associations between the subgroups. Restricted cubic spline (RCS) is a popular way to explore the nonlinear relationship in regression models flexibly and is widely used in epidemiology and clinical trials. RCS analysis (with three piecewise points) was performed to evaluate the nonlinear associations between copper intake and AAC scores and the risk of AAC and severe AAC. All analysis was performed using R version 4.2.1 (http://www.R-project.org, The R Foundation). $p<0.05$ was considered statistically significant.

Results

Baseline Characteristics of Participants

The weighted baseline characteristics of the included individuals are shown in Table 1. A total of 2897 participants were enrolled in our study, with a mean age of 57.47 ± 0.28 years, of which 52.42% were female and 47.58% were male. The mean AAC score of the participants was 1.46 ± 0.11, and the prevalence of AAC and severe AAC among the participants was 28.53% and 7.68%, respectively. In the lowest copper intake tertile participants, the prevalence of AAC and severe AAC was 32.26% and 10.50%, respectively. Participants in the highest copper intake tertile showed the lowest rate of AAC (23.54%) and severe AAC (5.28%). Among the copper intake tertiles, age, total energy intake, gender, race, education, PIR, BMI, hypertension, diabetes, alcohol consumption, and smoking status were statistically significant (all $p<0.05$). Compared to the lowest copper intake group, participants with increased copper intake were more likely to be male, less likely to have hypertension and diabetes, more likely to be never smokers and former smokers, more educated, had lower household poverty, were more likely to be normal weight and overweight, and had higher total energy intake. There were no statistically significant differences in serum creatinine, serum uric acid, and total cholesterol between the tertiles (all $p>0.05$).

The Association Between Copper Intake and Increased AAC Scores

Our findings suggested that higher copper intake was associated with decreased AAC scores (Table 2). The

Table 1 Baseline characteristics of the study population

Copper intake	All participants	Tertile 1	Tertile 2	Tertile 3	*p* value
Age (year)	57.47 (0.28)	58.11 (0.29)	58.20 (0.49)	56.17 (0.45)	**0.003**
Serum creatinine (mg/dl)	0.92 (0.01)	0.93 (0.02)	0.91 (0.01)	0.93 (0.01)	0.47
Serum uric acid (umol/L)	321.36 (1.82)	326.91 (3.33)	315.92 (4.26)	322.08 (3.70)	0.09
Total cholesterol (mmol/L)	5.06 (0.01)	5.10 (0.03)	5.07 (0.05)	5.02 (0.04)	0.50
Total energy (Kcal/d)	2066.68 (20.92)	1409.63 (27.10)	1966.17 (29.35)	2744.78 (48.22)	**< 0.0001**
Copper intake (mg/d)	1.24 (0.02)	0.64 (0.01)	1.09 (0.01)	1.93 (0.03)	**< 0.0001**
AAC score	1.46 (0.11)	1.86 (0.20)	1.42 (0.11)	1.15 (0.09)	**0.001**
Sex (%)					**< 0.0001**
Female	52.42 (0.03)	64.26 (1.51)	54.78 (2.47)	39.64 (2.08)	
Male	47.58 (0.03)	35.74 (1.51)	45.22 (2.47)	60.36 (2.08)	
Races (%)					**< 0.001**
Mexican American	6.74 (0.01)	6.09 (1.72)	6.84 (1.63)	7.22 (1.68)	
Non-Hispanic Black	9.99 (0.01)	13.88 (1.79)	8.54 (1.11)	8.04 (1.55)	
Non-Hispanic White	71.92 (0.07)	69.94 (3.30)	74.30 (2.98)	71.25 (3.59)	
Others	11.35 (0.01)	10.09 (1.10)	10.31 (1.21)	13.49 (1.52)	
PIR (%)					**< 0.0001**
< 1	10.81 (0.01)	16.01 (2.21)	9.59 (1.53)	9.40 (1.50)	
1–4	45.04 (0.03)	52.28 (1.97)	48.32 (3.57)	43.45 (2.98)	
> 4	38.31 (0.05)	31.71 (2.30)	42.09 (4.12)	47.15 (4.11)	
Educational levels (%)					**< 0.0001**
Less than 9th grade	4.70 (0.01)	5.40 (1.23)	4.34 (0.77)	4.46 (0.69)	
9–11th grade	10.04 (0.01)	13.45 (1.50)	9.01 (1.15)	8.11 (1.50)	
High school graduate	21.52 (0.02)	24.06 (2.14)	22.42 (2.12)	18.37 (1.47)	
Some college or AA degree	30.52 (0.02)	34.47 (2.19)	29.36 (2.58)	28.24 (1.47)	
College graduate or above	33.21 (0.04)	22.62 (2.74)	34.87 (3.24)	40.82 (2.49)	
BMI (%)					**0.02**
Normal weight	26.43 (0.02)	22.33 (1.85)	26.12 (1.50)	30.61 (1.71)	
Overweight	37.13 (0.03)	36.54 (2.44)	37.41 (2.30)	37.73 (1.62)	
Obesity	36.09 (0.02)	41.13 (2.18)	36.47 (2.25)	31.66 (1.97)	
Smoke (%)					**< 0.001**
Never	54.61 (0.04)	52.41 (2.40)	56.48 (2.40)	54.71 (2.39)	
Former	28.31 (0.03)	24.35 (1.68)	28.84 (2.05)	31.26 (2.20)	
Now	17.04 (0.02)	23.24 (2.26)	14.68 (1.79)	14.02 (1.06)	
Alcohol use (%)	80.19 (0.05)	76.17 (2.16)	82.17 (1.31)	81.72 (1.56)	**0.01**
DM (%)	18.52 (0.01)	22.84 (1.64)	17.95 (1.73)	15.31 (1.07)	**0.003**
Hypertension (%)	50.52 (0.03)	56.38 (1.63)	50.96 (1.72)	44.94 (1.72)	**< 0.0001**
AAC (%)	28.53 (0.02)	32.26 (3.04)	30.23 (2.20)	23.54 (1.58)	**0.004**
Severe AAC (%)	7.68 (0.01)	10.50 (1.28)	7.60 (0.99)	5.28 (0.71)	**0.001**

Tertile 1, 2, 3, copper intake tertiles; *PIR* ratio of family income to poverty, *BMI* body mass index, *DM* diabetes, *AAC* abdominal aortic calcification
P values with statistical significance have been bolded

correlation between copper intake and AAC score was significant in both our crude model ($\beta = -0.34$, *95% CI*: $-0.46 \sim -0.21$) and the minimally adjusted model ($\beta = -0.25$, *95% CI*: $-0.46 \sim -0.04$). The negative association between copper intake and AAC score remained stable in the fully adjusted model ($\beta = -0.16$, *95%CI*: $-0.49 \sim 0.17$), which indicated that each unit increase in copper intake was associated with a 0.16 unit decrease in AAC score. When the authors considered copper intake as tertiles, participants in the highest tertile of copper intake had a mean AAC score decrease of 0.37 units ($\beta = -0.37$, *95% CI*: -0.90–0.15) compared to participants in the lowest tertile. Participants in the middle copper intake tertile also exhibited a decrease in mean

Table 2 Multivariate logistic regression models of AAC scores with copper intake

AAC scores	*β* (*95%CI*)		
	Model 1	Model 2	Model 3
Continuous	−0.34 (−0.46, −0.21), **$p < 0.0001$**	−0.25 (−0.46, −0.04), **$p = 0.02$**	−0.16 (−0.49, 0.17), **$p = 0.03$**
Categories			
Tertile 1	Reference	Reference	Reference
Tertile 2	−0.44 (−0.85, −0.03), **$p = 0.04$**	−0.47 (−0.91, −0.02), **$p = 0.04$**	−0.32 (−0.77, 0.12), **$p = 0.04$**
Tertile 3	−0.72 (−1.06, −0.38), **$p < 0.001$**	−0.52 (−0.94, −0.09), **$p = 0.02$**	−0.37 (−0.90, 0.15), **$p = 0.01$**

Model 1: No covariates were adjusted

Model 2: Age, sex, and race were adjusted

Model 3: Age, sex, education levels, PIR, BMI, total cholesterol, total energy intake, hypertension, DM, alcohol consumption, and smoking status were adjusted

P values with statistical significance have been bolded

AAC scores compared to participants in the lowest tertile ($\beta = -0.32$, *95% CI*: −0.77–0.12).

The Negative Association Between Copper Intake and the Risk of AAC and Severe AAC

We also investigated the association of copper intake with the risk of AAC in three different models (Table 3). We observed a negative association between copper intake and the risk of AAC in both the crude and minimally adjusted models, although this correlation was not consistent with statistical significance. In contrast, in the fully adjusted model, we observed that each 1-unit increase in copper intake was associated with a 15% decrease in the risk of AAC (*OR* = 0.85, *95% CI*: 0.61–1.19). When we further adjusted copper intake from a continuous variable to a categorical variable, the risk of AAC decreased by 38% in participants in the highest tertile of copper intake compared to the lowest tertile of copper intake (*OR* = 0.62, *95% CI*: 0.41–0.95).

For severe AAC, we also observed a negative association between copper intake and the increased likelihood of severe AAC with statistical significance (Table 4). In both the crude and minimally adjusted models, the authors found that participants with higher copper intake exhibited a lower risk of severe AAC (Model 1: *OR* = 0.60, *95% CI*: 0.44–0.81; Model 2: *OR* = 0.68, *95% CI*: 0.47–0.98). In the fully adjusted model, the authors observed that participants with higher copper intake were 18% less likely to have severe AAC (Model 3: *OR* = 0.82, *95% CI*: 0.49–1.38). This correlation remained statistically significant when we considered copper intake as tertiles. Participants in the highest tertile had a 22% lower risk of severe AAC compared to those in the lowest tertile of copper intake (Model 3: *OR* = 0.78, *95% CI*: 0.34–1.77).

To further explore the correlation between copper intake and AAC score and risk of AAC and severe AAC, we used RCS analysis (Figs. 2, 3, 4). Our results showed no nonlinear correlation between copper intake and AAC score (*p* nonlinear = 0.3859) and risk of AAC (*p* nonlinear = 0.6694) and severe AAC (*p* nonlinear = 0.4106).

Table 3 Multivariate logistic regression models of AAC with copper intake

AAC	*OR* (*95%CI*)		
	Model 1	Model 2	Model 3
Continuous	0.84 (0.69, 1.02), $p = 0.07$	0.87 (0.68, 1.10), $p = 0.20$	0.85 (0.61, 1.19), **$p = 0.03$**
Categories			
Tertile 1	Reference	Reference	Reference
Tertile 2	0.91 (0.70, 1.18), $p = 0.44$	0.87 (0.67, 1.14), $p = 0.28$	0.87 (0.65, 1.17), $p = 0.33$
Tertile 3	0.65 (0.49, 0.85), **$p = 0.004$**	0.68 (0.47, 0.97), **$p = 0.04$**	0.62 (0.41, 0.95), **$p = 0.03$**

Model 1: No covariates were adjusted

Model 2: Age, sex, and race were adjusted

Model 3: Age, sex, education levels, PIR, BMI, total cholesterol, total energy intake, hypertension, DM, alcohol consumption, and smoking status were adjusted

P values with statistical significance have been bolded

Table 4 Multivariate logistic regression models of severe AAC with copper intake

Severe AAC	*OR* (*95%CI*)		
	Model 1	Model 2	Model 3
Continuous	0.60 (0.44, 0.81), ***p* = 0.003**	0.68 (0.47, 0.98), ***p* = 0.04**	0.82 (0.49, 1.38), ***p* = 0.04**
Categories			
Tertile 1	Reference	Reference	Reference
Tertile 2	0.70 (0.48, 1.03), $p = 0.07$	0.67 (0.44, 1.04), $p = 0.07$	0.79 (0.42, 1.48), $p = 0.07$
Tertile 3	0.47 (0.34, 0.66), ***p* < 0.001**	0.56 (0.34, 0.90), ***p* = 0.02**	0.78 (0.34, 1.77), ***p* = 0.03**

Model 1: No covariates were adjusted

Model 2: Age, sex, and race were adjusted

Model 3: Age, sex, education levels, PIR, BMI, total cholesterol, total energy intake, hypertension, DM, alcohol consumption, and smoking status were adjusted

P values with statistical significance have been bolded

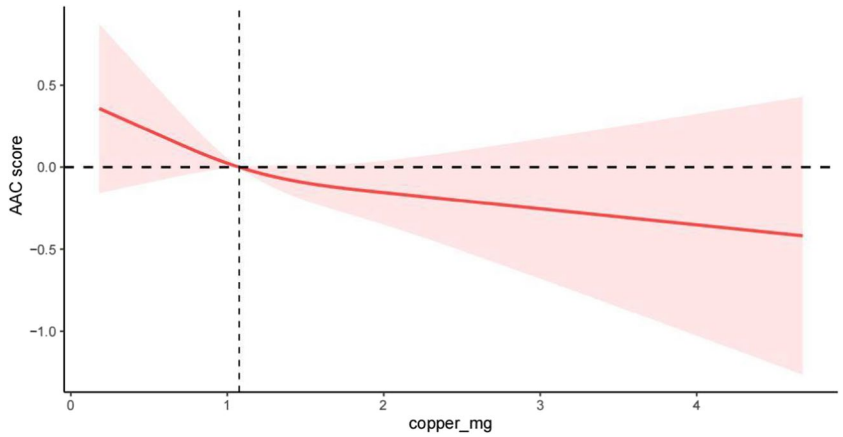

Fig. 2 The restricted cubic spline (RCS) analysis between copper intake and AAC scores (p nonlinear = 0.3859)

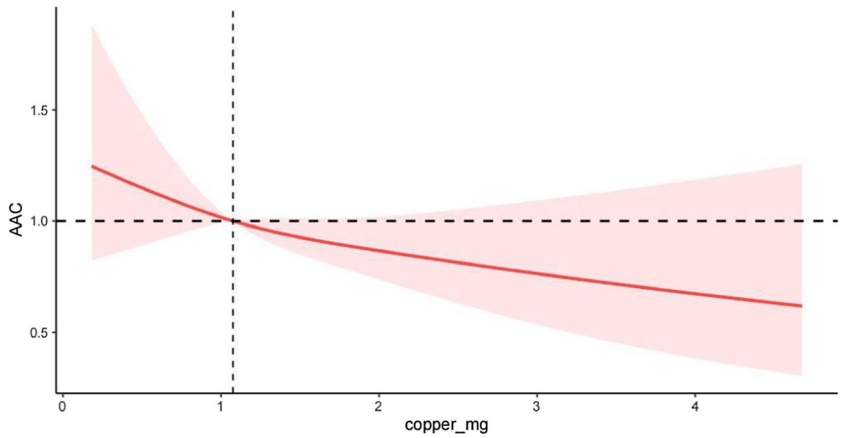

Fig. 3 The restricted cubic spline (RCS) analysis between copper intake and AAC. (p nonlinear = 0.6694)

Subgroup Analysis

For the association between copper intake and AAC scores and the risk of AAC, we did not find any statistically significant relationship (Fig. 5, 6).

For the risk of severe AAC, a negative association was found in non-diabetes participants ($OR = 0.693$) (Fig. 7). In addition, the interaction term reported the influence of diabetes on the association between copper intake and severe AAC (p for interaction = 0.004) (Fig. 7). However,

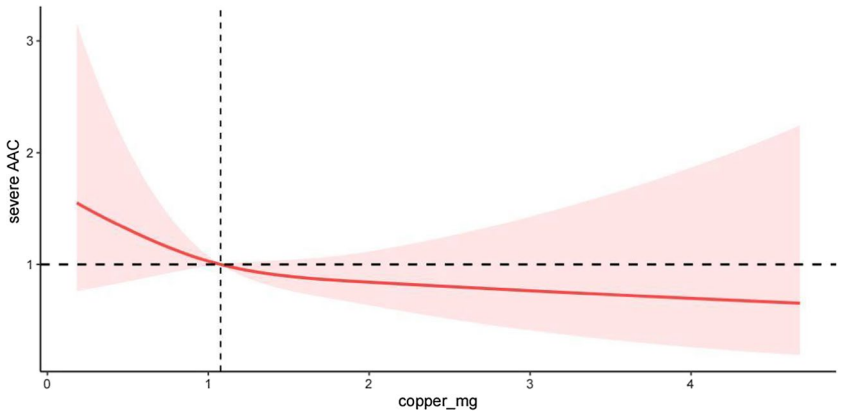

Fig. 4 The restricted cubic spline (RCS) analysis between copper intake and severe AAC. (p nonlinear = 0.4106)

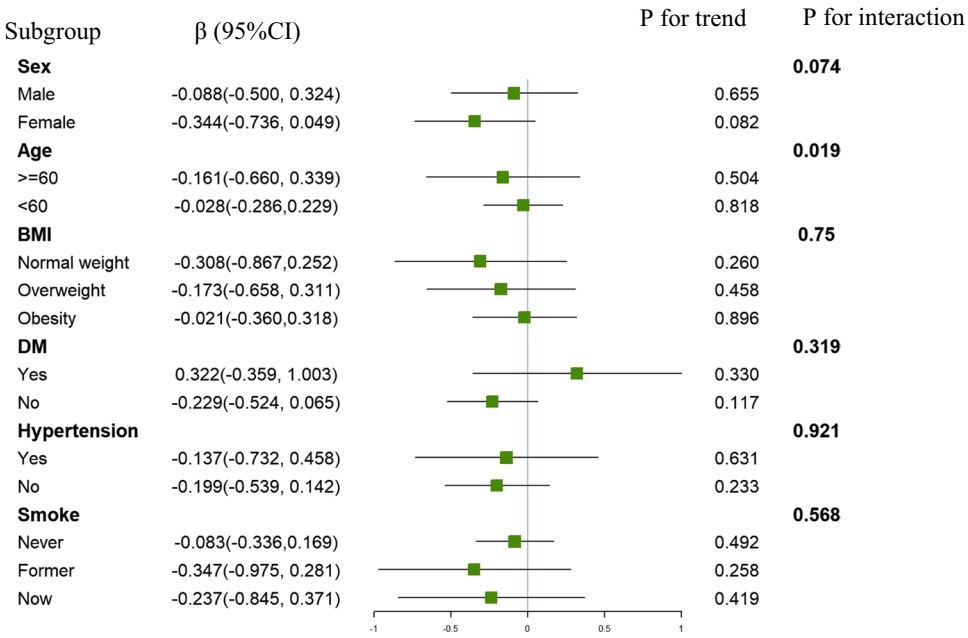

Fig. 5 Subgroup analysis for the association between copper intake and AAC score

the interaction test showed that this negative association between copper intake and the risk of severe AAC was not significantly influenced by age, sex, BMI, hypertension, and smoking status (pP for interaction > 0.05).

Discussion

In this cross-sectional study of 2897 participants, we observed that participants with higher copper intake had lower AAC scores and lower risk of AAC and severe AAC. The results of subgroup analyses and interaction tests demonstrated that the association between copper intake and AAC scores and risk of AAC was similar across different populations. In contrast, the association between copper intake and risk of severe AAC was significantly dependent on the participants' diabetes status. Clinicians should be aware of copper intake in patients at risk for AAC.

To the best of our knowledge, this is the first study to assess the relationship between copper intake and AAC, and the results of this study reflect that copper intake is associated with a lower risk of vascular calcification. Previous studies have reported the effects of circulating copper levels and copper intake on cardiovascular disease (CVD). Kunutsor SK et al. conducted a prospective study of 2492 Finnish men and found a positive association between high serum copper levels and increased risk of atherosclerotic CVD in middle-aged men, but the authors did not observe an association between serum copper and venous thromboembolism [34]. Another study by Isiozor NM et al. of 1911 middle-aged Finnish men showed that serum copper levels were positively associated with the risk of death from CVD, and this positive association was more pronounced in obese men [35]. Shi et al. reported a positive association of plasma copper with all-cause mortality and CVD mortality, suggesting that plasma copper levels may serve as a

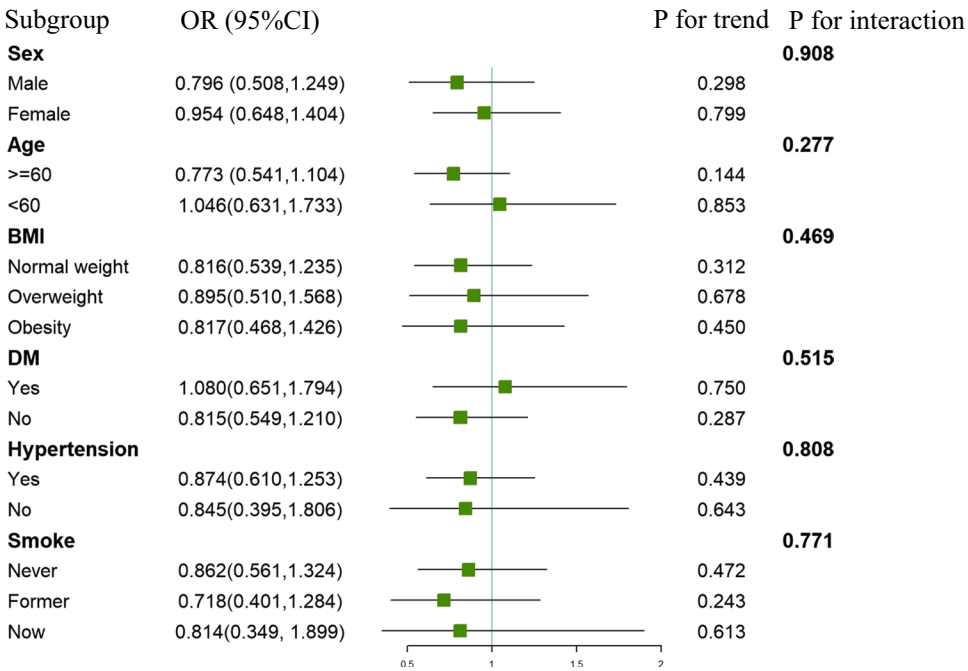

Fig. 6 Subgroup analysis for the association between copper intake and AAC

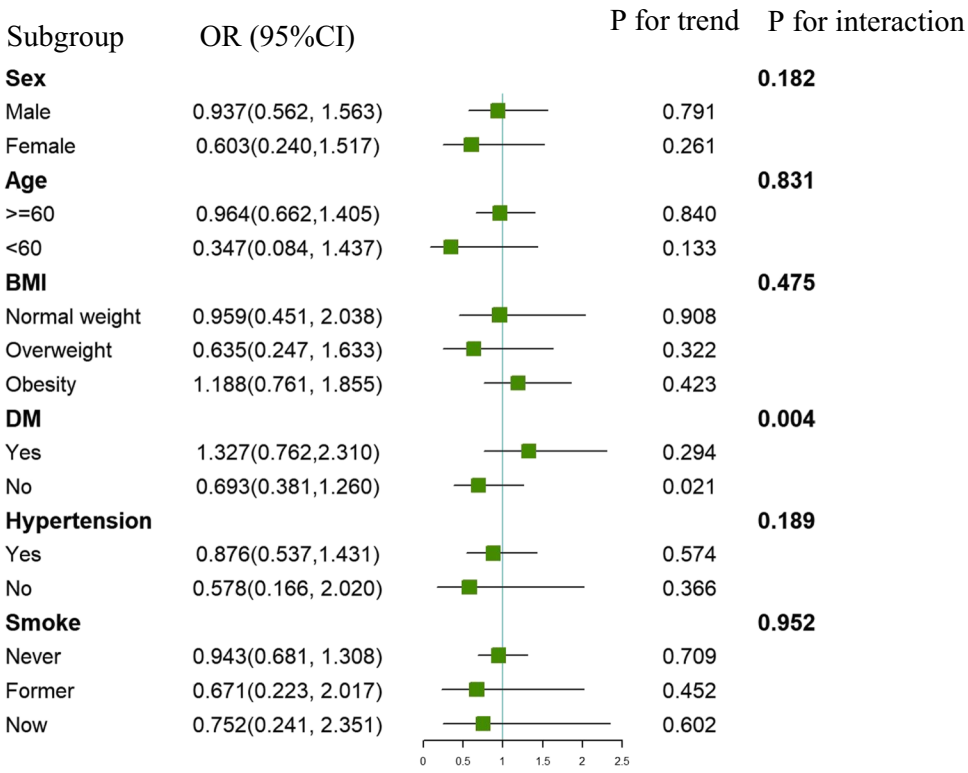

Fig. 7 Subgroup analysis for the association between copper intake and severe AAC

predictor of cardiometabolic risk [36]. Some studies have reported a positive association between dietary copper intake and CVD mortality, regardless of the gender of the participants; in contrast, zinc intake was significantly associated with decreased CVD mortality in men [37]. In a study by Ma et al. exploring copper intake and cardiovascular disease risk levels, a significant negative correlation was found between copper intake and the ratio of total cholesterol to HDL cholesterol, and this correlation was more pronounced in women [38]. Some studies have also shown that copper deficiency could lead to myocardial hypertrophy and an increased risk of valve regurgitation [39]. However, some studies have not

concluded that increased copper intake improved long-term cardiovascular health indicators, although increased copper intake has a significant increase in copper enzyme activity [40]. He et al. found a U-shaped association between copper intake and new-onset hypertension, with participants having a significantly lower risk of new-onset hypertension when copper intake did not exceed 1.57 mg/day, yet an increased risk of new-onset hypertension when copper intake exceeded this safe range [41]. In our study, consistent with most studies, we observed that increased copper intake was independently associated with lower AAC scores and a decreased risk of AAC and severe AAC, suggesting that copper intake may have a potentially beneficial effect on cardiovascular health. Although the association between dietary copper intake and calcification is less well studied, previous studies have revealed the influence of dietary factors on calcification. Zaragatski E et al. found that vitamin K supplementation attenuated calcification and endothelial hyperplasia in CKD rats [42]. Peralta-Ramírez A et al. demonstrated that in high phosphorus-induced human vascular smooth muscle cells, vitamin E also showed an effective attenuation of calcification [43]. In addition, the investigators also found that the severity of AAC increased when serum selenium concentrations exceeded 143 μg/L [44].

The underlying mechanism for this negative association between copper intake and AAC is not well understood. The common pathogenesis of VC mainly includes inflammatory cytokine release, extracellular matrix degradation, autophagy inhibition, endoplasmic reticulum stress, and mitochondrial dysfunction [45]. Interleukin (IL)-1β could contribute to the development of vascular calcification by activating the expression of the Wnt/β-catenin signaling pathway, thereby upregulating the expression levels of osteogenic genes in human aortic smooth muscle cells [46]. In a model of phosphate-induced calcification in vascular smooth muscle cells (VSMCs), the authors observed that the autophagic process was inhibited and calcium deposition increased [47]. Decreased mitochondrial membrane potential and reduced ATP production, accompanied by structural disruption of mitochondria and increased reactive oxygen species (ROS) production, were observed in the inorganic phosphate-induced calcification model of VSMCs [48]. Protein carbamylation also occurred during calcification of VSMCs, which led to downregulation of mitochondrial membrane potential and activation of oxidative stress, a process that promoted calcification [49]. Other investigators have also found that oxidative stress induced by mitophagy deficiency can accelerate the calcium deposition process in VSMCs [50]. Insufficient intake of copper may impair extracellular defenses against superoxide [51]. Copper intake not only activates autophagy by inhibiting the mTOR signaling pathway and regulating the expression of autophagy-related factors but also enhances catalase enzyme activity [52, 53]. Dietary copper deficiency may lead to the inhibition of cytochrome c oxidase activity and increased mitochondrial production of hydrogen peroxide [54, 55]. Those may be the possible mechanisms by which copper intake can slow down calcification, and more research is still needed to clarify these insights in the future.

This study has several strengths. First, the study is based on data from NHANES, a national population-based sample, and the sample selection and sample size are sufficiently representative. Second, we adjusted for confounding covariates to reduce confounding bias and to ensure that our findings are more reliable. Nevertheless, our study still has some unavoidable limitations. First, the design of the cross-sectional study did not allow us to obtain a causal relationship between copper intake and AAC. Second, although we have adjusted for some potential covariates, we still cannot guarantee that we have completely excluded other covariates that may cause confounding, such as the use of certain medications and whether patients have comorbidities. Finally, because of the NHANES study design, participants under the age of 40 years did not receive DXA screening, so we were unable to further explore the association between copper intake and AAC in a wide range of age groups. The NHANES database is data for the US population only, and our results may not be widely applicable worldwide.

Conclusion

This study found that increased copper intake was associated with decreased AAC scores and a lower likelihood of AAC and severe AAC. The current findings suggest that clinicians should be concerned about copper intake in patients at risk for AAC. However, further large prospective studies are needed to verify the validity of the authors' findings.

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Author Contribution CL analyzed the data and wrote the primary manuscript. DL reviewed and revised the manuscript. All the authors have approved the manuscript for publication.

Data Availability Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics Approval The studies involving human participants were reviewed and approved by NCHS Research Ethics Review Board (ERB).

Consent to Participate Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Conflict of Interest The authors declare no competing interests.

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