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Serum copper and the risk of cardiovascular disease death in Finnish men

Nzechukwu M. Isiozor [a,*], Setor K. Kunutsor [b,c], Dorothea Vogelsang [d], Ifeanyichukwu Isiozor [e], Jussi Kauhanen [f], Jari A. Laukkanen [a,f,g]

[a] Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[b] National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, United Kingdom
[c] Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, University of Bristol, United Kingdom
[d] Faculty of Health, Medicine and Life Sciences, Maastricht University, Netherlands
[e] Federal Medical Centre, Owerri, Nigeria
[f] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
[g] Central Finland Health Care District, Department of Internal Medicine, Jyvaskyla, Finland

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Abstract *Background and aims:* Copper (Cu) is a component of enzymes catalyzing oxidation-reduction reactions. With the persisting burden of cardiovascular disease (CVD), there is evident need to identify biomarkers and potential risk factors for CVD. We therefore examined the association between serum Cu levels and the risk of CVD death in Finnish men and across different body mass index (BMI) categories.

Methods and results: This Finnish prospective study is based on 1911 men aged 42–60 years who were free of coronary heart disease at baseline. Cu concentrations (mg/l) were determined using atomic absorption spectrometer and categorized into quartiles (<1.0; 1 to <1.1; 1.1 to <1.21; ≥1.21). Participants were categorized into normal weight <25 kg/m^2, pre-obesity 25–29.9 kg/m^2, and obesity >30 kg/m^2. The association between Cu and CVD death was analyzed using multivariable Cox regression models. During a median follow-up of 25.8 years, 358 CVD deaths occurred. The risk of CVD death increased continuously with increasing Cu levels (for non-linearity, $p = 0.64$). Using the first quartile as reference after adjustment for covariates, the hazard ratios (HR) (95% confidence interval (CI)) for CVD death for Cu concentrations in second, third and fourth quartiles were 1.45(1.05–2.01), 1.69(1.25–2.27), and 1.68(1.23–2.29), respectively. Obese men in the third quartile of serum Cu concentrations had highest risk of CVD death (HR (95%CI) 2.71(1.27–5.78)).

Conclusion: Elevated serum Cu level was associated with increased risk of CVD death across all BMI categories in middle-aged and older Finnish men. Serum Cu may have prognostic implication for CVD mortality risk; however, further studies are needed.

* Corresponding author. Institute of Clinical Medicine University of Eastern Finland, Yliopistonranta 1, 70211 Kuopio, Finland.
E-mail address: nzechukwu.isiozor@uef.fi (N.M. Isiozor).

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1. Introduction

Cardiovascular disease (CVD) remains a leading cause of mortality worldwide [1]. Despite the decline in mortality from coronary heart disease (CHD) over the years, CVD still accounts for 36% of all mortality in Finland [2] - causing 1 in every 5 deaths in men and 1 in 6 for women [3]. As the burden of CVD persists, biomarkers or potential risk factors that can promptly predict CVD risk need to be further explored and identified to ensure adequate management and improve cardiovascular health.

Copper (Cu), a component of enzymes that catalyze oxidation-reduction reactions, is an essential micronutrient and trace element in humans [4]. However, due to its potential role in atherogenesis, higher Cu concentrations may pose increased cardiovascular risk [5,6]. Higher serum Cu levels have been reported in patients with myocardial infarction [7]. Moreover, recent studies suggest that high levels of serum Cu can be a risk factor for heart failure [8] and stroke [9,10], with a stronger association among participants with elevated body mass index (BMI) [10].

In a recent meta-analysis, higher serum Cu concentration has been strongly linked with obesity [11]. Most serum Cu are bound to ceruloplasmin, which has been reported to be higher in obese patients [12]. This likely explains increased Cu deposits in adipose tissues. There is overwhelming evidence of an association between obesity or BMI and increased CVD risk [13–15], however, the possibility that serum Cu levels contribute to this risk remains unclear.

Apart from Ford et al.'s study in a US general population [16] and Grammar and colleagues' research in coronary angiography patients in Germany [17], to our knowledge, longitudinal studies assessing the association between serum Cu and CVD death are sparse. There is limited data on the relationship between serum Cu and CVD in the general population. Additionally, long-term prospective studies reporting the association between serum Cu and the risk of CVD death across different BMI categories are not existent. Therefore, we sought to examine the prospective association between serum Cu levels and the risk of death from CVD using a representative sample of the general population of men in Finland with no history of CHD at baseline. Our second objective was to investigate how the association varied across different BMI categories.

2. Methods

2.1. Study population

We used population-based data from the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study in eastern Finland, comprising men aged 42–60 years at baseline [18]. The KIHD study was designed to investigate risk factors for developing CVD and other chronic diseases among middle-aged and older men and women living in Kuopio and the surrounding communities in eastern Finland [19]. The baseline examinations were done between March 1984 and December 1989 from randomly selected and eligible participants (3235 men) from the national population register among which 2682 men volunteered to participate in the study [19]. Men with missing data on serum Cu (109), BMI (9), serum high-density lipoprotein cholesterol (HDL-C) (11), systolic blood pressure (4) and alcohol intake (3) were excluded. Additional 635 men who had history of CHD at baseline were further excluded, since CHD remains a major cause of CVD death for Finns [20]. A final cohort of 1911 men were involved in this current study (Supplement Fig. 1; the comparison between included and excluded participants is shown in Supplement Table 1). All the participants in the study gave written informed consent and the study protocol is in conformity with the ethical guidelines of the 1975 Helsinki Declaration. The Research Ethics Committee of the University of Eastern Finland, Kuopio approved the KIHD research protocol with reference number 143/97.

2.2. Measurements

A self-administered questionnaire was mailed to each participant prior to their visit to the study centre. The participants were then invited to the study centre for interviews and clinical examination. A trained research nurse was responsible for interviewing all the study participants, who also went through health examinations. Information on education, income, occupation type, smoking status, alcohol consumption and previous medical condition was obtained using detailed questionnaires and was cross-checked by a physician during medical examination. During physical examination, weight, height and blood pressure were also measured. Adulthood socioeconomic status (SES) was assessed as a combined measure of income, education, occupation, occupational prestige, material standard of living, and housing conditions [21]. The SES scale generated ranges from score 0 through 25; 0 indicating the highest, and 25 the lowest SES. Body mass index was calculated as the weight in kilograms divided by height in meters squared (kg/m^2). Resting blood pressure was measured with a random-zero sphygmomanometer (Hawskley, UK) between 8 and 10 in the morning after 5 and 10 minutes of rest in a seated position.

Participants were required to abstain from alcohol for 3 days, smoking for 12 hours and eating for 12 hours prior to collection of blood samples between 8 and 10 a.m. After the subject had rested for 30 minutes in the supine position, blood sample was drawn from the antecubital vein with Terumo Venoject VT-100PZ vacuum (Terumo Corp., Tokyo), without the use of tourniquet using Cu-free needles and tubes for collection and storage. Serum Cu concentrations were determined using Atomic Absorption Spectrometer from frozen samples stored at −20 °C [6]. All daily batches had control serum samples. Reference standards were dissolved in 5% glycerol using acetylene-air (1:4) flame technique with a PerkinElmer (Norwalk, Connecticut, United States) 306 atomic absorption spectrometer used for measurements. The between-batch coefficient of variation was 4.0%. The cholesterol contents

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of serum lipoprotein fractions and triglycerides were measured enzymatically (CHOD-PAP method, Boehringer Mannheim). The HDL-C and its subfractions were separated from fresh serum samples using ultracentrifugation and precipitation [22].

2.3. Determination of follow-up events

All deaths that occurred from study enrolment to end of 2014 were checked against hospital documents, health centre wards and death certificates. Information sources included interviews, hospital documents, death certificates, autopsy reports and medico-legal reports. All CVD deaths were ascertained by computer linkage to the national health death registry using the Finnish personal identification code. The CVD deaths were coded according to cause of death related to the ICD-9 (International Classification of Diseases, Ninth Revision, Code numbers 390–459) or the ICD-10 (code numbers I00–I99). The documents related to death were cross-checked in detail by two physicians. The Independent Events Committee, masked to clinical data, performed classification of deaths [23].

2.4. Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the participants overall and according to the outcome status (Yes and No CVD death). Baseline characteristics were presented as means (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and number and percentages for categorical variables. Differences in baseline characteristics across outcome status were assessed using a *t*-test for continuous variables and chi-squared test for categorical variables. Cohen's d and Cramer's V tests were performed as well. The shapes of the relationships between serum Cu and the risk of CVD death were explored using restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles in multivariable adjusted models. Multivariable Cox regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of CVD mortality using baseline serum Cu levels after confirmation of no major departure from the proportionality assumptions using Schoenfeld residuals [24]. Serum Cu levels were categorized into quartiles, with the lowest and highest serum Cu concentrations in the 1st and 4th quartiles respectively, thus, quartile 1: $<$1.0 mg/l; quartile 2: 1 to $<$1.1 mg/l; quartile 3: 1.1 to $<$1.21 mg/l; and quartile 4: $\geq$1.21 mg/l. Three BMI categories were used to further group the participants into normal weight BMI $<$25 kg/m^2, pre-obesity BMI 25–29.9 kg/m^2, and obesity $\geq$30 kg/m^2 (including all the classes). As only two participants had BMI $<$18.5 kg/m^2, no underweight group was created.

Three models were used to estimate the HRs. The first model was adjusted for age and BMI (excluded in analysis according to BMI categories). The second model was model 1 plus C-reactive protein, serum zinc, HDL-C and total cholesterol (i.e., blood-based markers). The third model included blood pressure, SES, alcohol consumption, smoking status, and history of type 2 diabetes in addition to the covariates in model 2. These covariates were selected due to their role as risk factor as well as their potential as confounders. In a subsidiary analysis, men with history of CVD (including CHD) at baseline were excluded. Microsoft windows software, SPSS Statistics 27 (IBM Corp., Chicago, IL, USA 9) and Stata version 12 (Stata Corp, College Station, TX) were used to perform the statistical analyses. Two-sided p value < 0.05 was considered statistically significant.

3. Results

The baseline characteristics of included participants are shown in Table 1. The mean (SD) age and serum Cu level at baseline for the 1911 men were 52.5 (5.3) years and 1.1 (0.2) mg/l, respectively. Most participants were pre-obese at baseline. After a median follow-up of 25.8 years, 358 CVD deaths were recorded, and most deaths occurred in pre-obese men.

Participants who died from CVD were older. Their mean systolic blood pressure, BMI and total cholesterol were higher than that of survivors. The mean serum Cu level was also higher among the deceased in comparison with survivors, i.e., 1.2 mg/l vs. 1.1 mg/l ($p < 0.01$). Comparing the highest versus lowest serum Cu quartiles for all participants, the HR (95% CI) for CVD death was 2.28 (1.70–3.08) after adjustment for age and BMI. The association was minimally attenuated on further adjustment for blood levels of C-reactive protein, serum zinc, HDL-C and total cholesterol, 1.94 (1.42–2.64); and on full adjustment for, blood pressure, SES, alcohol intake, smoking status, and history of type 2 diabetes, 1.68 (1.23–2.29) (Table 2). The restricted cubic spline curve for all participants showed that the risk of CVD death increased continuously with increasing Cu levels (for non-linearity, $p = 0.64$) (Fig. 1A), indicating a linear graded association. Fig. 1B, C and D illustrate the association between the different BMI strata and risk of CVD death using cubic spline curves (p for non-linearity for normal, pre-obese and obese men are 0.003, 0.23, and 0.008 respectively).

Further analyses on serum Cu across the different BMI categories showed consistent strong association with the risk of CVD death among pre-obese men in the highest quartile of serum Cu compared with those in lowest quartile (Table 2), with HRs (95% CI) of 2.64 (1.70–4.12) and 1.95 (1.23–3.10) in the age-adjusted and fully adjusted models, respectively. A graded increase in the HRs among men in the different BMI categories in relation to the 4th versus 1st quartiles of serum Cu was observed in the age-adjusted and fully adjusted models. Similar trend could not be observed in the model adjusted for blood-based markers (model 2) (Table 2). Obese men in the 3rd quartile of serum Cu had highest risk of CVD death with HR (95% CI) of 2.71 (1.27–5.78) (Table 2).

In a sensitivity analysis excluding men with CVD history at baseline, the findings were qualitatively similar. In the age-adjusted model (model 1), the risk of CVD death increased across the different BMI groups, with obese men

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Table 1 Baseline characteristics of the KIHD study participants.

Characteristics Mean (SD) or Median [IQR]	All participants N = 1911	CVD death (Yes) N = 358	CVD death (No) N = 1553	P-value	Cohen's d/Cramér's V tests
Age, years	52.5 (5.3)	54.4 (4.4)	52.0 (5.4)	<0.01	−0.44
Serum copper, mg/l[a]	1.1 (0.2)	1.2 (0.2)	1.1 (0.2)	<0.01	−0.34
Serum C-reactive protein, mg/l	1.2 [0.7–2.2]	1.7 [0.8–3.0]	1.1 [0.6–2.1]	<0.01	−0.26
Serum zinc, mg/l	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.08	0.10
BMI, kg/m^2	26.8 (3.5)	27.5 (4.1)	26.6 (3.3)	<0.01	−0.27
HDL-C, mmol/l[b]	1.3 (0.3)	1.3(0.3)	1.3(0.3)	0.24	0.07
Total cholesterol, mmol/l[b]	5.9 (1.1)	6.0 (1.1)	5.8 (1.0)	<0.01	−0.20
Systolic blood pressure, mmHg	134.4 (16.6)	141.0 (17.4)	132.9 (16.1)	<0.01	−0.49
Socioeconomic status	11.7 (5.1)	12.8 (5.0)	11.4 (5.1)	<0.01	−0.27
Alcohol intake/week, g	32.2 [6.6–90.4]	32.5 [4.8–111.3]	32 [6.9–88]	<0.01	−0.19
Proportion (%)					
History of diabetes	90 (4.7)	36 (10.1)	54 (3.5)	<0.01	0.12
Smokers	569 (29.8)	129 (36)	440(28.3)	<0.01	0.07
BMI categories				<0.01	0.09
Normal weight	627 (32.8)	98 (27.4)	526 (33.9)		
Pre-obesity	986 (51.6)	181 (50.6)	805 (51.8)		
Obese	298 (15.6)	79 (22.1)	219 (14.1)		

BMI, body mass index; CVD, cardiovascular disease; g, gram; HDL-C, high density lipoprotein; IQR, interquartile range; mg/l, milligram per litre; mmHg, millimeter of mercury; SD, standard deviation.
Normal weight BMI <25 kg/m^2, pre-obesity BMI 25–29.9 kg/m^2, and obesity ≥30 kg/m^2.
The socioeconomic status (SES) scale ranges from 0 through 25; 0 indicating the highest, and 25 the lowest SES.
[a] 1 mg/L = 15.737 μmol/l
[b] mmol/l × 38.6 = mg/dl.

in the 4th quartile of serum Cu levels having significantly higher risk of CVD death compared to those in the 1st quartile. In other adjusted models across the 4th quartile, the risk of CVD death did not significantly change. In the fully adjusted model (model 3), however, significant association between serum Cu and CVD death was observed in normal and pre-obese men within the 3rd quartile of serum Cu when compared to those within the 1st quartile (Supplement Table 2).

4. Discussion

In this prospective cohort study of Finnish men, we assessed the association of serum Cu levels with the risk of CVD death. We identified higher serum Cu levels to be significantly associated with an increased risk of CVD death in Finnish men. This was independent of several risk factors. On further exclusion of men with history of CVD at baseline, the direct significant association between serum Cu level (per unit increment) and the risk of CVD death did not change. When considering all the covariates, the risk of CVD death was higher in obese and pre-obese individuals within the 3rd quartile of serum Cu concentrations. For men without history of CVD at baseline, there was significantly higher risk of CVD death among the pre-obese in the 3rd quartile of serum Cu compared to those in the 1st quartile. These results are in accordance with earlier studies that have shown that higher levels of serum Cu or ceruloplasmin are associated with increased risk of cardiovascular events and death [6,7,9,10,16,25–28].

Our findings are consistent with the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study [16] and a large coronary angiography patients' study [17]. Furthermore, studies report serum Cu concentration to be higher in obesity [11,12]. With obesity being a known risk factor for CVD [14,15] and its predisposition to higher serum Cu levels, this is in line with our findings which suggest elevated serum Cu levels, particularly within the 3rd quartile, are associated with higher risk of CVD death in pre-obese and obese men. The latter could indicate that even the highest serum Cu level may not pose the worst CVD mortality risk in pre-obese and obese people. This furthermore creates the need for a threshold level of serum Cu to be identified; also considering that Cu deficiency has been linked to increased risk of CVD [29,30]. Although tight regulation of serum Cu may be essential in controlling cardiovascular events, higher levels of Cu and BMI could be revealing future risk of CVD. Additionally, serum Cu levels may be of use in monitoring therapeutic progress of CVD. Based on our results, we propose that serum Cu could potentially be a biomarker for CVD death, and that the regulation of its levels could be beneficial for cardiovascular health, particularly among pre-obese and obese individuals. However, the biochemical mechanism underlying this relation needs further investigation.

Serum Cu is an important trace element that plays a role in oxidation-reduction reactions of enzymes [4]. The exact mechanism linking excess serum Cu to CVD is unclear. Copper produces oxygen radicals through a 'Fenton-like' reaction (the production of reactive oxygen species via the catalytic decomposition of hydrogen peroxide) [31,32]. High Cu levels can thus cause imbalances in the oxidant-antioxidant system activating reactive oxygen species and reactive nitrogen species [33]. Copper is also involved in many physiological processes including angiogenesis [34] through the regulation of hypoxia-inducible factor-1(HIF-1) activity [35]. Copper toxicity leading to oxidative stress can cause cellular damage [36]

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Table 2 Association of Serum copper and the risk of CVD death among men without history of CHD at baseline.

Events/Total		Model 1				Model 2				Model 3			
Serum copper (mg/l)		All participants, N = 1911	Normal weight N = 627	Pre-obese N = 986	Obese N = 298	All participants, N = 1911	Normal weight N = 627	Pre-obese N = 986	Obese N = 298	All participants, N = 1911	Normal weight N = 627	Pre-obesity N = 986	Obese N = 298
		HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value	HR (95% CI); p-value
Quartile 1	76/609	1	1	1	1	1	1	1	1	1	1	1	1
Quartile 2	71/401	1.50 (1.09−2.07); 0.014	1.03 (0.59−1.81); 0.908	1.88 (1.18 −3.00); 0.008	1.90 (0.83 −4.34); 0.129	1.45 (1.05 −2.01); 0.025	0.99 (0.56 −1.74); 0.959	1.82 (1.14 −2.92); 0.012	1.55 (0.67 −3.57); 0.306	1.45 (1.05 −2.01); 0.026	1.03 (0.58 −1.83); 0.921	1.78 (1.11−2.85); 0.017	1.74 (0.75−4.06); 0.201
Quartile 3	107/473	1.87 (1.39−2.51); <0.001	0.88 (0.49−1.55); 0.650	2.47 (1.61 −3.80); <0.001	2.96 (1.43 −6.09); 0.003	1.75 (1.30 −2.36); <0.001	0.82 (0.46 −1.48): 0.514	2.34 (1.52 −3.61); <0.001	2.55 (1.23 −5.27); 0.012	1.69 (1.25 −2.27); 0.001	0.75 (0.41 −1.36); 0.340	2.25 (1.46−3.50); <0.001	2.71 (1.27−5.78); 0.010
Quartile 4	104/428	2.28 (1.70 −3.08); <0.001	1.87 (1.13−3.11); 0.016	2.64 (1.70 −4.12); <0.001	2.92 (1.41 −6.05); 0.004	1.94 (1.42 −2.64); <0.001	1.63 (0.65 −2.80); 0.075	2.26 (1.43 −3.57): <0.001	1.90 (0.88 −4.08); 0.102	1.68 (1.23 −2.29); 0.001	1.11 (0.63 −1.96); 0.711	1.95 (1.23−3.10); 0.005	2.03 (0.91−4.52); 0.083
Per unit increment (mg/l)	358/1911	6.04 (3.50−10.41); <0.001	5.91 (2.20−15.88); <0.001	5.45 (2.47 −12.00); <0.001	8.56 (2.68 −27.31); <0.001	4.00 (2.23 −7.17); <0.001	4.53 (1.58−13.00); 0.005	3.47 (1.49 −8.09); 0.004	2.90 (0.75 −11.20); 0.123	2.87 (1.57 −5.22); 0.001	2.88 (0.90 −9.22); 0.074	2.51 (1.05−5.99); 0.038	2.41 (0.62−9.42); 0.207

CI confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; $p < 0.05$, statistically significant.
Copper quartiles: quartile 1, <1.0 mg/l; quartile 2, 1 to <1.1 mg/l; quartile 3, 1.1 to <1.21 mg/l; quartile 4, ≥1.21 mg/l.
Model 1, adjusted for age and body mass index (BMI, excluded in analysis across BMI categories).
Model 2, model 1 + C-reactive protein, serum zinc, high density lipoprotein cholesterol and total cholesterol.
Model 3, model 2 + systolic blood pressure, socioeconomic status, alcohol consumption, smoking status, and history of type 2 diabetes.

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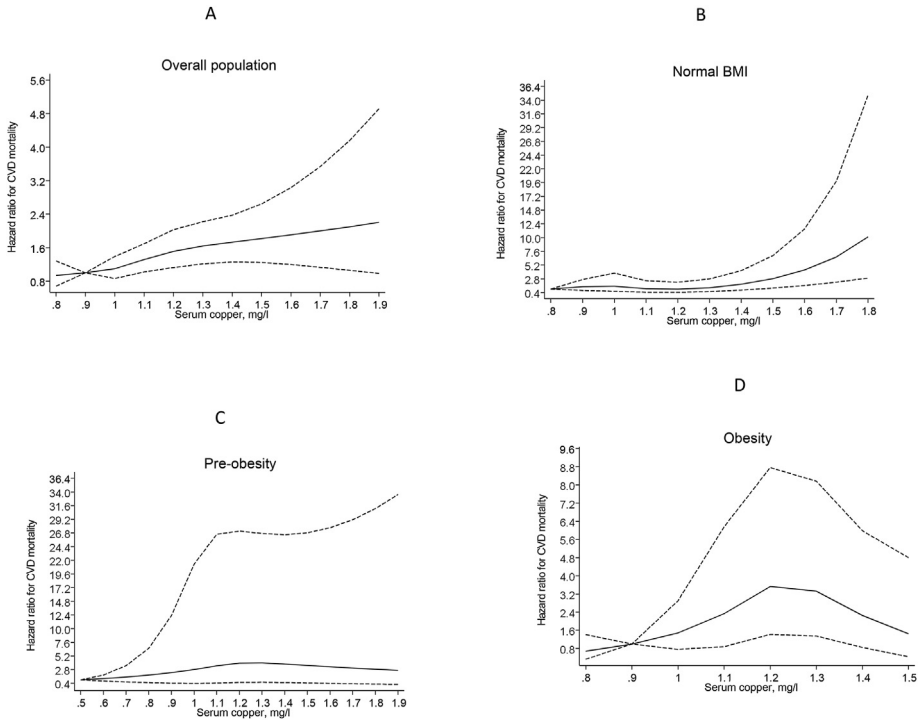

Figure 1 Cubic spline curves of hazard ratios for cardiovascular disease (CVD) mortality against serum copper concentrations. The dashed lines represent the 95% confidence intervals.

which might affect angiogenesis. Following liver, brain, and kidney, the myocardium is one of the organs with the highest Cu concentrations [37]. Therefore, any chronic toxicity effect of Cu might also have cardiovascular consequences. Should angiogenesis be affected by the chronic injury; cardiovascular events may be inevitable. Thus, in case of ischemia, Cu homeostasis in the myocardium is essential to promote myocardial regeneration [35].

Some limitations of this study warrant mentioning. It is important to note that despite the exclusion of men with a history of CHD at baseline, the possibility of other inflammatory processes being the cause of elevated serum Cu at the time of sample collection might not be ruled out. This is because Cu is necessary for ceruloplasmin function, which is an acute-phase reactant protein that is elevated during inflammation, infection, and diseases such as CVD and diabetes [27,36]. Furthermore, dietary pattern, exercise or urinary excretion prior to sample collection may alter serum Cu level [38–40]. This may be the rationale of leukocyte Cu measurement being considered more reliable in assessing Cu function in relation to health [41,42]. Another limitation is the use of a single sample serum Cu measurement at baseline, which can possibly vary among the participants over the period of follow-up. Finally, the results are based on Finnish men and therefore cannot be generalized to women and other population groups and ethnicities. Nevertheless, the strength of this study lies in its large-scale prospective cohort design with high response rate, and the participants being a representative sample of the population of middle-aged men in Eastern Finland. Participants were well characterized and followed up during the study period with credible ascertainment of CVD mortality. No loss to follow-up was recorded. The long follow-up period was adequate to determine the risk for CVD death.

5. Conclusion

Higher serum Cu level was associated with increased risk of CVD death in middle-aged Finnish men. After adjusting for other risk factors, men with obesity in the 3rd quartile of serum Cu levels had the highest risk of CVD death. Serum Cu may be a potential prognostic marker or risk factor for CVD mortality. Future research will be required in order to investigate whether Cu chelation therapy is beneficial for cardiovascular health and whether serum Cu levels can be used to monitor response to CVD treatment.

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Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2022.09.024.

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