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J-shaped association between dietary copper intake and all-cause mortality: a prospective cohort study in Chinese adults

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Abstract

The association between dietary Cu intake and mortality risk remains uncertain. We aimed to investigate the relationship of dietary Cu intake with all-cause mortality among Chinese adults. A total of 17 310 participants from the China Health and Nutrition Survey, a national ongoing open cohort of Chinese participants, were included in the analysis. Dietary intake was measured by three consecutive 24-h dietary recalls in combination with a weighing inventory over the same 3 d. The average intakes of the 3-d dietary macronutrients and micronutrients were calculated. The study outcome was all-cause mortality. During a median follow-up of 9·0 years, 1324 (7·6 %) participants died. After adjusting for sex, age, BMI, ever alcohol drinking, ever smoking, education levels, occupations, urban or rural residents, systolic blood pressure, diastolic blood pressure and the intakes of fat, protein and carbohydrate, the association between dietary Cu intake and all-cause mortality followed a J-shape ($P_{\text{for nonlinearity}} = 0{\cdot}047$). When dietary Cu intake was assessed as quartiles, compared with those in the first quartile (<1·60 mg/d), the adjusted hazard ratios for all-cause mortality were 0·87 (95 % CI (0·71, 1·07)), 0·98 (95 % CI (0·79, 1·21)) and 1·49 (95 % CI (1·19, 1·86)), respectively, in participants in the second (1·60–<1·83 mg/d), third (1·83–<2·09 mg/d) and fourth (≥2·09 mg/d) quartiles. A series of subgroup analyses and sensitivity analyses showed similar results. Overall, our findings emphasised the importance of maintaining optimal dietary Cu intake levels for prevention of premature death.

Key words: **Dietary copper intake: All-cause mortality: General Chinese adults: China Health and Nutrition Survey: J-shape**

Cu, an essential mineral nutrient, plays important roles in many metabolic processes, including neuropeptide synthesis, antioxidant defense and immunologic functions[1,2]. At the same time, Cu can also be toxic in excessive amounts via oxidation and production of free radicals[3,4], which have the potential to cause oxidative damage to lipids, proteins, DNA and other molecules. Accordingly, a recent study in general Chinese adults found that there was a U-shaped relation of dietary Cu intake with new-onset hypertension[5], which is one of the most important causes of morbidity and mortality. However, although mortality is the most important indicator of health, findings about the relation between Cu levels and mortality risk from prospective cohort studies are still mixed and limited[6–13]. Some studies had examined the association between blood Cu concentrations and the risk of mortality, but the results were inconsistent[9–13]. The prior studies[6–8] that examined the relation of dietary Cu intake and mortality also reported discrepant findings. Of note, few related studies, using the dietary Cu intake data continuously, have been conducted, which may provide more granular information and allow for the possibility of non-linear relation of dietary Cu intake and mortality. Overall, to date, the association between dietary Cu intake and mortality risk remains uncertain.

To provide evidence to bridge the above knowledge gaps, our current study aimed to evaluate the association between

Abbreviations: BMI, body mass index; CHNS, China Health and Nutrition Survey; CIs, confidence intervals; Cu, copper; DBP, diastolic blood pressure; HRs, hazard ratios; SBP, systolic blood pressure; SDs, standard deviations.

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dietary Cu intake and the risk of all-cause mortality in general population, using data from the China Health and Nutrition Survey (CHNS) – a national ongoing open cohort in China.

Methods

Population and study designs

The data and materials that support the discoveries of this study are available at the official website (http://www.cpc.unc.edu/projects/china) of the CHNS, which is an ongoing multipurpose, prospective open-cohort project initiated in 1989 in China, with a response rate of 88 % at individual level[14]. The CHNS was scheduled for follow-up every 2 to 4 years, with its implementation in 1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011 and 2015, respectively. By 2011, twelve provinces/autonomous cities and 288 communities were included, and people in these areas consisted of 47 % of the Chinese population[15]. The cohort profile and some of the major findings had been reported elsewhere[14–20] in detail.

The current study included seven rounds of the CHNS data from 1997 to 2015. Person-waves were calculated as the sum of waves for each individual from entry to the last visit prior to the date of death, date of loss to follow-up or the end of follow-up. As shown in online Supplementary Fig. 1, among a total of 94 532 person-waves, we first excluded participants who were pregnant, <18 years of age (17 672 person-waves). Among the remaining participants, those who were surveyed in at least two study rounds were included (*n* 17 517, 68 057 person-waves), and the first survey round is considered as baseline. The included population did not differ in most of the baseline characteristics from those excluded (*n* 8443, 8443 person-waves) (online Supplementary Fig. 1, online Supplementary Table 1). Furthermore, individuals with missing dietary Cu intake, or with extreme dietary energy intakes (<600 kcal or >4200 kcal/d for males and <500 kcal or >3600 kcal/d for females) were also excluded[21]. At last, a total of 17 310 participants were included in the final analysis (online Supplementary Fig. 1).

The CHNS was approved by the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention and Institutional Review Boards at the University of North Carolina at Chapel Hill. Each participant provided written informed consent.

Assessments of dietary nutrient intakes

Dietary data in the study were obtained by well-trained nutritionists through an interview face to face in each survey round. The dietary diets were repeatedly assessed via three consecutive 24-h dietary recalls at the individual level and a food-weighing approach over the same 3 d at the household level. The three consecutive days were distributed from Monday to Sunday randomly and were almost equally in balance across the 7 d of the week. Nutrient intakes were calculated using the China food composition tables. The accuracy of 24-h dietary recall designed to evaluate the intake of energy and nutrient has been proven[22,23]. In each round, the average intakes of the 3-d dietary macronutrients and micronutrients were calculated.

Moreover, the cumulative average intake values of each nutrient were calculated for each subject, using all results up to the last visit prior to the date of death, or using all results among those alive throughout the follow-up (number of waves included during follow-up, median: 3·3; interquartile range, 2·0–5·0), to reflect long-term intake levels and minimise within-person variation. In our study, the residual method[24] was used to assess energy-adjusted intake for dietary Cu.

Assessments of covariates

Information on socio-demographic characteristics (age, sex, urban/rural residents, regions, education levels and occupations) and lifestyle behaviours (smoking and alcohol drinking status) were obtained through the structured questionnaires. Ever smokers and ever alcohol drinkers included former and current smokers and former and alcohol drinkers, respectively. Height and weight were measured based on a standard procedure with calibrated equipment. BMI was calculated as one's weight in kilograms divided by the square of his height in metres (kg/m^2).

Seated blood pressure was measured by trained research staff after the participants had rested for 5 min, using a mercury manometer, following the standard method. Triplicate measurements on the same arm were taken in a quiet and bright room. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the measures in three independent days were used in analysis.

Study outcome

The study outcome was all-cause mortality. In each wave, information on health and death for every participant was recorded. The death status was recorded based on the report of household members in each survey wave. If someone died, household members were asked for the exact time of death. For any deaths reported more than once in different waves, the first report was chosen.

Statistical analysis

Population characteristics, presented as means (SD) for continuous variables and proportions for categorical variables according to quartiles of energy-adjusted dietary Cu intake, were compared by χ^2 tests for categorical variables and ANOVA tests for continuous variables.

The year of each participant's first entry into the survey was considered as baseline. The follow-up person-time for each participant was calculated from baseline until the time of death, the last survey round before the participant's departure from the survey or the end of the latest survey, whichever came first. Cox proportional-hazards model was used to estimate the relation of energy-adjusted dietary Cu intake with all-cause mortality, without and with adjustments for sex (males and females), age in years, BMI in kg/m^2, ever alcohol drinking (yes and no), ever smoking (yes and no), education levels (illiteracy, primary school, middle school and high school or above), occupations (farmer, worker, unemployed and other), urban or rural residents (urban and rural), SBP in mmHg, DBP in mmHg, as well

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as the intakes of fat in g/d, protein in g/d and carbohydrate in g/d. To assess the proportional-hazards assumption, the significance of the interaction between exposures and follow-up time was assessed, and no clear evidence of violation was detected. Restricted cubic spline with three knots (at the 25th, 50th and 75th percentiles of energy-adjusted dietary Cu intake) was performed to test for linearity and visualise the dose–response relation of Cu intake and all-cause mortality.

Furthermore, possible modifications of the association between energy-adjusted dietary Cu intake and all-cause mortality were evaluated for the following variables: sex (males or females), age (<45 or ≥45 years), BMI (<24 or ≥24 kg/m^2), ever alcohol drinkers (no or yes), ever smokers (no or yes), SBP (<120 or ≥120 mmHg), Zn intake (<10·7 (median) or ≥10·7 mg/d), protein intake (<64·2 (median) or ≥64·2 g/d), carbohydrate intake (<293·4 (median) or ≥293·4 g/d) and fat intake (<71·0 (median) or ≥71·0 g/d). Interactions between subgroups and dietary Cu intake were examined by likelihood ratio testing.

Sensitivity analyses were additionally conducted to examine the robustness of the results. First, further adjustments for the intakes of major food sources of Cu, including legumes, nuts, vegetables, fruits, seafoods and whole grains. Second, other micronutrients that are known as traditional or suspected risk factors for all-cause mortality, or related to energy-adjusted dietary Cu intake, were further adjusted, including dietary intakes of Na, potassium, Zn, Ca, Fe, Mg, Se, vitamin A, vitamin B_1, vitamin B_2, vitamin E and niacin. Third, we have further explored the association between dietary Cu intake (without energy adjustment) and all-cause mortality. Fourth, instead of using the cumulative average of diet, the association between baseline energy-adjusted dietary intake and all-cause mortality was also examined.

A two-tailed $P < 0·05$ was set to be statistically significant, and Bonferroni corrections were performed for multiple comparisons in Table 1 and Supplementary Table 2. Statistical analyses were performed by using R software, version 4.0.5 (http://www.R-project.org).

Results

Study participants and population characteristics

As shown in the flow chart (online Supplementary Fig. 1), a total of 17 310 participants were included in the current study. The average age of the study participants was 44·0 (SD 15·9) years. The mean dietary Cu intake was 1·9 (SD 0·5) mg/d.

Population characteristics of the study participants by dietary Cu intake quartiles are presented in Table 1 and Supplementary Table 2. Participants with higher dietary Cu intake were less likely to be urban residents and live in south regions, tended to have lower fat intake levels and higher intakes of carbohydrate, protein, potassium, Ca, Mg, Fe, Zn, Se, vitamin B_1, legumes, nuts, vegetables, fruits, seafoods and whole grains.

Association between energy-adjusted dietary copper intake and risk of all-cause mortality

A total of 1324 (7·6 %) participants died during a median follow-up duration of 9·0 years (interquartile range, 4·1–15·2 years). Overall, the association between energy-adjusted dietary Cu intake and the risk of all-cause mortality followed a J-shape (Fig. 1, $P_{\text{for nonlinearity}} = 0·047$). Accordingly, when energy-adjusted dietary Cu intake was assessed as quartiles, compared with those in the first quartile (<1·60 mg/d), the adjusted hazard ratios for all-cause mortality were 0·87 (95 % CI (0·71, 1·07)), 0·98 (95 % CI (0·79, 1·21)) and 1·49 (95 % CI (1·19, 1·86)), respectively, in participants in the second (1·60–<1·83 mg/d), third (1·83–<2·09 mg/d) and fourth (≥2·09 mg/d) quartiles (Table 2).

Further adjustments for the intakes of legumes, nuts, vegetables, fruits, seafoods and whole grains or dietary intakes of Na, potassium, Zn, Ca, Fe, Mg, Se, vitamin A, vitamin B_1, vitamin B_2, vitamin E and niacin did not materially alter the results (online Supplementary Table 3). Similar results were found for the relation of dietary Cu intake without energy adjustment (online Supplementary Fig. 2) and baseline energy-adjusted dietary Cu intake with all-cause mortality (online Supplementary Table 4).

Stratified analyses by potential effect modifiers

Due to the similar mortality risks in the 1–3 quartiles of dietary Cu, we combined the three quartiles into one group in the stratified analyses. Stratified analyses were performed to further assess the relations of energy-adjusted dietary Cu intake (≥2·09 mg/d (the 4 quartile) v < 2·09 (the 1–3 quartiles) mg/d) with the risk of all-cause mortality in total participants and various subgroups.

A significantly higher risk of all-cause mortality was found in participants in the fourth quartile of dietary Cu intake (≥2·09 mg/d) (HR 1·58; 95 % CI (1·37, 1·82)), compared with those in the 1–3 quartiles. Moreover, a stronger positive association between Cu intake and all-cause mortality was found in those with higher SBP ($P_{\text{for interaction}} = 0·04$), lower dietary fat intake ($P_{\text{for interaction}} = 0·02$) and higher dietary carbohydrate intake ($P_{\text{for interaction}} = 0·03$). None of other variables, including sex, age, BMI, ever smokers, ever alcohol drinkers, Zn intake and protein intake, significantly modified the association between energy-adjusted dietary Cu intake and all-cause mortality (Fig. 2).

Discussion

In this prospective cohort of Chinese adults, we observed that there was a nonlinear, J-shaped association between energy-adjusted dietary Cu and all-cause mortality, where the rate of all-cause mortality seemed to plateaued at less than 2·09 mg/d, beyond which the rate monotonically increased.

The role of dietary Cu intake on the risk of all-cause mortality had been reported in a few previous studies and reported inconsistent results[6–8]. In the British National Diet and Nutrition Survey, higher dietary intakes of Cu (measured by a 4-d weighed diet estimate and without energy adjustment) were associated with lower all-cause mortality (HR 0·91; 95 % CI (0·84, 1·00)) in 1054 community-living participants aged 65 years and over during a follow-up period of 13–14 years[6]. In the National Health and Nutrition Examination Survey from 1999 to 2010[7], there was no significant association between dietary Cu intake

Table 1. Population characteristics by quartiles of energy-adjusted dietary copper intake (Numbers and percentages; mean values and standard deviations)

	Energy-adjusted dietary copper intake, mg/d								
	Q1 (<1·60)		Q2 (1·60–<1·83)		Q3 (1·83–<2·09)		Q4 (≥2·09)		
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*P* value*
n	4328		4327		4327		4328		
Male	2337	54·0	2025	46·8	1943	44·9	2183	50·4	<0·001
Age, year									<0·001
Mean	42·8		44·7		44·5		43·8		
SD	15·3		16·2		15·8		15·9		
BMI, kg/m^2									0·02
Mean	23·0		22·8		22·8		22·8		
SD	3·4		3·4		3·3		3·3		
Ever smokers	1484	34·5	1277	29·7	1312	30·5	1360	31·6	<0·001
Ever alcohol drinkers	1604	37·5	1444	33·9	1410	33·1	1605	37·6	<0·001
Systolic blood pressure, mmHg									0·22
Mean	120·8		120·1		120·1		120·3		
SD	17·6		18·2		17·8		17·4		
Diastolic blood pressure, mmHg									0·07
Mean	77·6		77·4		77·9		78·0		
SD	10·8		10·7		11·0		10·8		
Self-reported diabetes	99	2·3	106	2·5	79	1·9	101	2·4	0·21
Self-reported hypertension	338	7·9	325	7·6	332	7·7	351	8·2	0·75
Urban residents	1882	43·5	1736	40·1	1507	34·8	1526	35·3	<0·001
Education									<0·001
Illiteracy	636	14·9	936	22·2	1038	24·7	952	22·7	
Primary school	732	17·2	830	19·7	902	21·5	807	19·2	
Middle school	1455	34·1	1331	31·5	1250	29·8	1305	31·1	
High school or above	1440	33·8	1126	26·7	1004	23·9	1137	27·1	
Regions									<0·001
Central	1996	46·1	1952	45·1	2035	47·0	2369	54·7	
North	538	12·4	707	16·3	1153	26·6	1305	30·2	
South	1794	41·5	1668	38·5	1139	26·3	654	15·1	
Occupations									<0·001
Farmer	932	21·7	1377	32·1	1669	39·1	1605	37·5	
Worker	563	13·1	532	12·4	415	9·7	458	10·7	
Unemployed	1404	32·7	1320	30·7	1174	27·5	1214	28·4	
Other	1393	32·5	1064	24·8	1011	23·7	1005	23·5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Dietary intakes									
Energy, kcal/d	2226·5	542·5	2046·8	496·1	2034·0	481·2	2182·4	510·9	<0·001
Fat, g/d	93·3	31·6	72·0	22·9	65·7	23·3	65·9	25·7	<0·001
Carbohydrate, g/d	281·2	94·9	287·3	90·4	298·3	89·4	325·5	103·2	<0·001
Protein, g/d	65·4	18·8	62·4	17·1	62·5	16·4	71·9	20·4	<0·001

Q, quartile.
* A $P < 0·0014$ was set to be statistically significant.

Table 2. The association between energy-adjusted dietary copper intake and the risk of all-cause mortality (Cases and incident rate; hazard ratio and 95 % confidence intervals)

				Crude model			Adjusted model†		
Energy-adjusted dietary Cu intake, mg/d	*n*	Cases	Incident rate*	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Quartiles									
Q1 (<1·60)	4328	198	5·4	Ref			Ref		
Q2 (1·60–<1·83)	4327	305	6·7	1·20	1·00, 1·43	0·05	0·87	0·71, 1·07	0·20
Q3 (1·83–<2·09)	4327	369	7·6	1·33	1·12, 1·59	0·001	0·98	0·79, 1·21	0·85
Q4 (≥2·09)	4328	452	10·4	1·86	1·57, 2·20	<0·001	1·49	1·19, 1·86	<0·001

Q, quartile.
* Incident rate is presented per 1000 person-years of follow-up.
† Adjusted for sex, age, BMI, ever alcohol drinking, ever smoking, education levels, occupations, urban or rural residents, systolic blood pressure (SBP), diastolic blood pressure (DBP), as well as dietary intakes of fat, protein and carbohydrate.

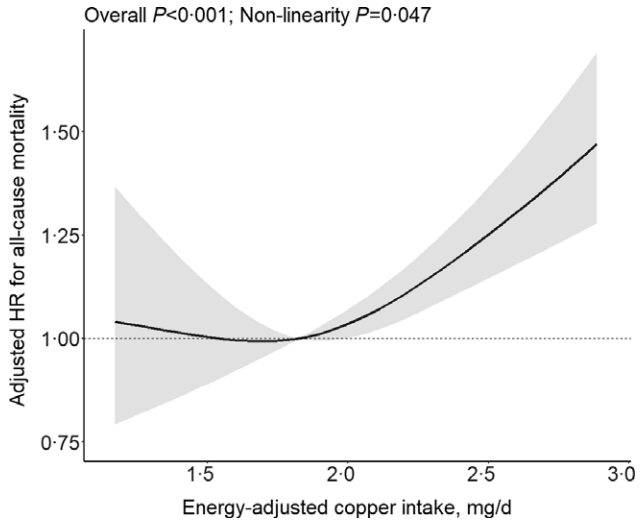

Fig. 1. Relation of energy-adjusted dietary Cu intake with risk of all-cause mortality based on restricted cubic splines. *Adjusted for sex, age, BMI, ever alcohol drinking, ever smoking, education levels, occupations, urban or rural residents, systolic blood pressure (SBP), diastolic blood pressure (DBP), as well as dietary intakes of fat, protein and carbohydrate.

(using 24-h diet recalls and without energy adjustment) and all-cause mortality in 30 899 USA adults aged 20 years or older during a median follow-up of 6·1 years. A previous study[8] in the Warsaw region during spring 1999–31 December 2003 found that the all-cause mortality was higher among subgroup of elderly men with lower intake of Cu, which was collected using a 3-d record method, in 146 male participants. Overall, the above studies suggested that the association between dietary Cu intake and all-cause mortality remains uncertain. Of note, most of the previous studies did not consider the possible modifying effect of other dietary nutrients or other components of the primary dietary sources of Cu. More importantly, most of the previous studies reported mortality risk based on the categories of dietary Cu intake. Few related studies, using the dietary Cu intake data continuously, have been conducted, which may allow for presenting the non-linear association between Cu intake and all-cause mortality and provide more granular information. With a prospective cohort design, a relatively longer follow-up period and the use of three consecutive 24-h dietary recalls, our current study provided an opportunity to examine the continuous association between energy-adjusted dietary Cu intake and all-cause mortality in Chinese general population, with relatively comprehensive adjustments for a number of potential confounding factors and a series of stratified analyses.

Of note, the Cu levels (median: 1·83 mg/d) in our current study were higher than the dietary reference intakes for Cu (0·9 mg/d in adults)[9] of the Institute of Medicine and also was higher than that in French adults (means: male: 1·53 mg/d and female: 1·30 mg/d)[25] or USA adults (means:1·4 mg/d)[7]. The higher dietary Cu intake may be related to the different dietary habits of adults in Western countries and China. Chinese diets tend to include large amounts of grains and legumes[26], which are major sources of dietary Cu[27], while Western diets are animal-based and rich in red and processed meats[28]. It is giving us an opportunity to explore the association between relatively high levels of dietary Cu intake and all-cause mortality.

Our study yields some new insights. First, there was a nonlinear relation of Cu intake with all-cause mortality. Higher risk of all-cause mortality was found only in the highest quartile of Cu intake, and the effect of dietary Cu intake on the risk of all-cause mortality seemed to plateau in those in the 1–3 quartiles of dietary Cu intake, who may already have an adequate Cu intake. Consistently, our previous study also showed that in Chinese hypertensive patients, a significantly higher risks of first stroke were found in participants in the four quartile of plasma Cu, compared with those in the first quartile[29]. Higher Cu may participate in reactions that result in the production of highly reactive oxygen species, leading to DNA damage, and direct oxidation proteins[3,30,31]. Moreover, Cu concentrations were directly associated with high-sensitivity C-reactive protein levels[32]. In addition, Cu may manifest the detrimental effects by substituting other metal cofactors from their natural ligands[30,33]. Therefore, in excess of cellular demand, Cu can be detrimental.

We also found that SBP and dietary intakes of fat and carbohydrate may modify the relation between dietary Cu intake and all-cause mortality. A stronger positive association was found in those with higher SBP, lower dietary fat intake and higher carbohydrate intake, which suggested some protection against the apparent harm of high dietary Cu intake by lower SBP, higher fat intake and lower carbohydrate intake. However, in view of multiple testing and similar directionality of the associations, more studies are need to confirm our results and further examine the underlying mechanisms.

Notably, the relation of dietary Cu intake with all-cause mortality might be attributed to other components or some unclear nutrients of the primary dietary sources of Cu. However, our study showed that further adjustments for other major nutrients or the major food sources of Cu did not materially change our findings. In addition, a series of stratified analyses showed similar associations. These findings suggested that the relationship of Cu intake with all-cause mortality may be at least partly independent of these factors.

Potential limitations warrant consideration. First, although a number of dietary and non-dietary covariates had been adjusted, unmeasured and residual confounding factors remain possible. Second, there was no detailed data about dietary supplement use in our study. However, only 0·71 %, 0·03 % and 0·11 % of the Chinese population were reported taking nutrient supplements, multi-mineral and Cu supplements, respectively, according to the 2010–2012 China Nutrition and Health Surveillance[34] – a nationally representative and comprehensive cross-sectional study covering China's thirty-one provinces, autonomous regions and municipalities. Given the low supplement proportion of nutrients, especially Cu, we speculated that our results may not be materially altered by the limited usage of dietary supplements. Third, the current study depended on the Cu data from the China food composition tables, which is unlikely to be able to account for regional variation in Cu contents of foods that might be caused by local conditions, including soil and water Cu concentration, slurry/manure spreading, agricultural and industrial contamination. Fourth, the data for cause-specific mortality in CHNS are lacking, which may provide additional implications

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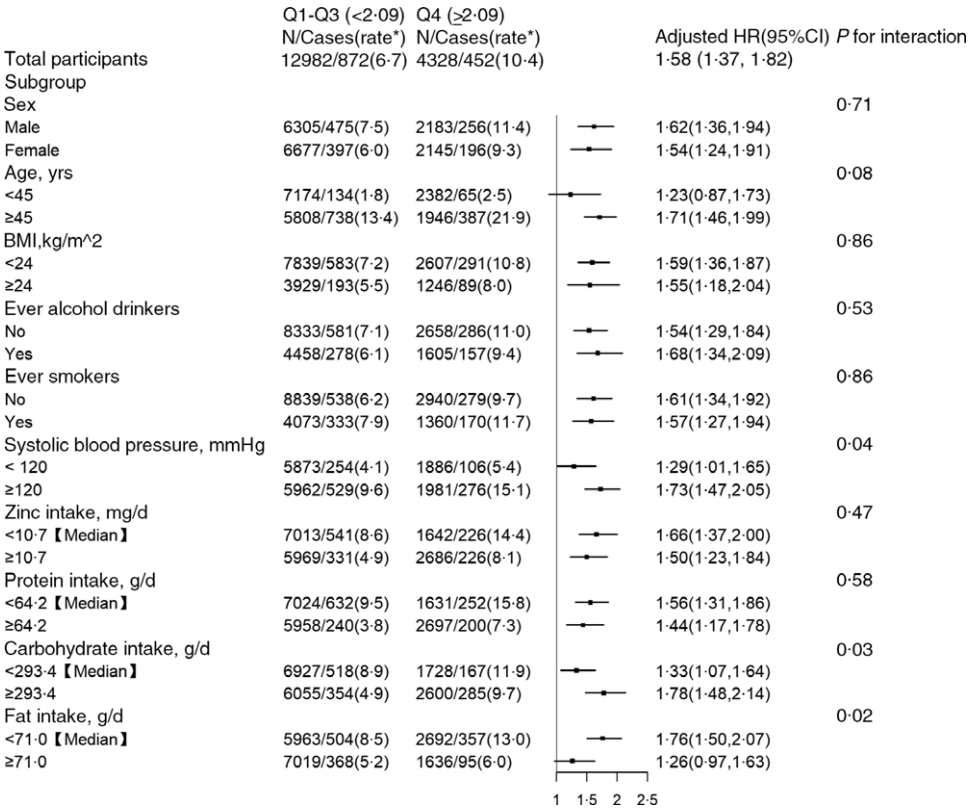

Fig. 2. Stratified analyses by potential effect modifiers for the associations between energy-adjusted dietary Cu intake and the risk of all-cause mortality in various subgroups. *Incident rate is presented per 1000 person-years of follow-up. Adjusted, if not stratified, for sex, age, BMI, ever alcohol drinking, ever smoking, education levels, occupations, urban or rural residents, systolic blood pressure (SBP), diastolic blood pressure (DBP), as well as dietary intakes of fat, protein and carbohydrate.

for health promotion and prevention. Last but not least, our study was conducted in general Chinese population, whether the findings can be extrapolated to other populations with different characteristics needs further investigations. Owing to these limitations, further confirmation of the reported findings in future studies is necessary.

Conclusions

In the current study, there was a J-shaped association between dietary Cu intake and the risk of all-cause mortality in general Chinese adults. If further confirmed, we need to pay more attention to maintaining optimal dietary Cu intake levels for the prevention of premature death.

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Dr. X. Q. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. X. G., C. L. and X. Q. designed the research; X. G., P. H., M. L., C. Z., Q. M., Y. Z., C. Z., S. Y., Y. Z., Z. Y., R. L., Q. W. and X. Q. conducted the research; X. G., C. Z., C. Z. and C. L. performed the data management and statistical analyses; X. G. and X. Q. wrote the manuscript; all authors reviewed/edited the manuscript for important intellectual content. All authors read and approved the final manuscript.

There are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522002732

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