

J-shaped association between dietary zinc intake and new-onset hypertension: a nationwide cohort study in China

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Abstract We aimed to investigate the relationship of dietary zinc intake with new-onset hypertension among Chinese adults. A total of 12,177 participants who were free of hypertension at baseline from the China Health and Nutrition Survey were included. Dietary intake was assessed by three consecutive 24-h dietary recalls combined with a household food inventory. Participants with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or diagnosed by a physician or under antihypertensive treatment during the follow-up were defined as having new-onset hypertension. During a median follow-up duration of 6.1 years, 4269 participants developed new-onset hypertension. Overall, the association between dietary zinc intake and new-onset hypertension followed a J-shape (P for non-linearity < 0.001). The risk of new-onset hypertension significantly decreased with the increment of dietary zinc intake (per mg/day: hazard ratio (HR) 0.93; 95% confidence interval (CI) 0.88–0.98) in participants with zinc intake < 10.9 mg/day, and increased with the increment of zinc intake (per mg/day: HR 1.14; 95% CI 1.11–1.16) in participants with zinc intake ≥ 10.9 mg/day. In conclusion, there was a J-shaped association between dietary zinc intake and new-onset hypertension in general Chinese adults, with an inflection point at about 10.9 mg/day.

Keywords dietary zinc intake; new-onset hypertension; general population; CHNS

Introduction

Hypertension is the leading cause of cardiovascular disease and premature death [1–3], affecting more than a billion individuals worldwide [4]. Nearly half of Chinese adults aged 35–75 years had hypertension [5,6]. Therefore, a better understanding of the modifiable risk factors of hypertension would aid in the prevention and management of hypertension and its related diseases. Recently, the relations of trace minerals with hypertension have received considerable interest [7].

Zinc is the second most abundant transition metal in the body after iron. Through its presence in various enzymes and proteins, zinc plays a major role in normal cell

structure and catalytic functions, especially in the immune and central nervous systems [7,8]. The associations between serum or urine zinc levels and hypertension had been examined mainly in previous cross-sectional and case-control studies [9–12]. However, the findings were inconsistent, including inverse or no significant relations. Consistently, only a few previous cross-sectional studies [13–18] had evaluated the associations between dietary zinc intake and hypertension, and also reported inconsistent results. Of note, only one previous study [19] evaluated the prospective association between dietary zinc intake and hypertension. However, this study had a relatively small sample size and only included men. Therefore, a definitive conclusion could not be drawn. Moreover, no previous study used dietary zinc data continuously, which may provide more granular information and allow for the

possibility of a nonlinear association between zinc intake and new-onset hypertension. As such, to date, the relationship of dietary zinc intake with new-onset hypertension remains uncertain.

To address the above important knowledge gaps, the present study aimed to investigate the prospective association between dietary zinc intake and the risk of new-onset hypertension in the general population using data from the China Health and Nutrition Survey (CHNS), a national health and nutrition survey in China.

Methods

Population and study design

Details on the study design and major results of the CHNS have been described previously [20–26]. CHNS is an ongoing, national, prospective open-cohort study in China. CHNS began in 1989, with a total of 10 rounds (1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011, and 2015) already completed. By 2011, the CHNS included 12 provinces/autonomous regions and 288 communities, which constituted 47% of China's population [20].

The current study is based on seven rounds of CHNS data from 1997 to 2015. We excluded participants who were pregnant, aged < 18 years, or with missing blood pressure (BP) data. Among the remaining participants, those who were surveyed in at least two study rounds ($n = 15\,774$; 61 612 person-waves) were included, and the first survey round was considered as the baseline. Furthermore, hypertensive participants (defined as having a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or previously diagnosed by a physician or under antihypertensive treatment at baseline), or those with missing dietary zinc data or implausible dietary energy data (men, > 4200 or < 600 kcal/day; women, > 3600 or < 500 kcal/day) were excluded [27]. Finally, a total of 12 177 participants were included in the final analysis (Fig. S1).

The Institutional Review Boards of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety, and the Chinese Center for Disease Control and Prevention approved the study. Each CHNS participant provided their written informed consent. The data and study materials that support the findings of this study can be found at the official website of CHNS.

Dietary nutrient intakes

Both individual and household level dietary data in the CHNS were collected by trained research staff through face-to-face interview in each survey round. The dietary intake was recorded by three consecutive 24-h recalls at

the individual level, in combination with using a 3-day food-weighed method to assess cooking oil and condiment consumption at the household level. The three consecutive days were randomly allocated from Monday to Sunday and are almost equally balanced across the seven days of the week for each sampling unit [28]. Twenty-four-hour dietary recall is a common survey method for dietary assessment and had been used in a series of important cohorts [29,30]. The accuracy and reproducibility of 24-h dietary recall designed to assess energy and nutrient intake has been validated [31–33]. Food consumption data were converted into nutrient intake and total energy using Chinese food composition tables (FCTs). The 1991 FCT was utilized to calculate the nutrient values for the dietary data of 1997 and 2000 surveys. The 2002/2004 version (two books combined) was used for the 2004, 2006, 2009, and 2011 surveys.

In the current analyses, 3-day average intakes of dietary macronutrients and micronutrients in each round were calculated. The cumulative average intake values of each nutrient from baseline to the last visit before the date of new-onset hypertension or the end of follow-up were further calculated to represent long-term dietary intake and minimize within-person variation. In this study, we evaluated energy-adjusted nutrient intake for dietary zinc using the residual method [34].

Assessments of BP and covariates

After the patients had rested for 5 min, seated BP measurements were obtained by trained research staff using a mercury manometer, following the standard method and with appropriately sized cuffs at each follow-up survey. The mean SBP and DBP of three independent measures were used in the analysis.

Information on age, sex, residence, region, education level, physical activity, occupation, smoking, and drinking status was obtained from the questionnaires at each follow-up survey. Height and weight were measured following a standard procedure with calibrated equipment. The body mass index (BMI) was calculated as weight (kg) by height squared (m^2). In the 2009 wave of CHNS, blood samples were collected and assessed in a national central laboratory in Beijing (medical laboratory accreditation certificate ISO 15189:2007), China. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. The levels of physical activity were the product of the self-reported time spent in each activity multiplied by the specific metabolic equivalent values [35].

Study outcome

New-onset hypertension was defined as mean SBP

≥ 140 mmHg and/or mean DBP ≥ 90 mmHg or diagnosed by a physician or currently under antihypertensive treatment during the follow-up [35–37].

The follow-up time was calculated by the middle date between the following survey when a participant was first identified with new-onset hypertension and the nearest survey before. For those free of hypertension in all following surveys, the last survey date was used to calculate the follow-up time.

Statistical analysis

Baseline characteristics were presented as means (SDs) for continuous variables or proportions for categorical variables by zinc quartiles. Differences in characteristics were compared using ANOVA tests or chi-square tests accordingly.

The incidence rates of hypertension, expressed as per 1000 person-years, were calculated as the number of new hypertension cases divided by the person-years of follow-up. The relation of dietary zinc intake with new-onset hypertension was estimated using Cox proportional hazards models (hazard ratio (HR) and 95% confidence interval (CI)) without and with adjustments for baseline SBP, DBP, demographic variables (age, sex, education levels, occupations, urban or rural residence), hypertension risk factors (BMI, smoking, and drinking status), sodium-to-potassium intake ratio (Na/K), and energy intake. We applied a two-piecewise regression model to examine the threshold effect of the dietary zinc intake on the study outcome using a smoothing function. The inflection point was determined using the likelihood-ratio test and bootstrap resampling method. We additionally performed restricted cubic spline Cox regression with four knots (5th, 35th, 65th, 95th percentiles of dietary zinc intake) to test for linearity and explore the shape of the dose–response relation of zinc intake and new-onset hypertension.

As additional exploratory analyses, possible modifications on the association of dietary zinc intake and new-onset hypertension were evaluated by stratified analyses and interaction testing.

A two-tailed $P < 0.05$ was considered to be statistically significant in all analyses. R software version 3.6.1 was used for all data analyses.

Results

Study participants and baseline characteristics

As illustrated in the flowchart (Fig. S1), a total of 12 177 participants were included in the current study. The average age of the study population was 41.2 (SD, 14.2) years. A total of 5698 (46.8%) of the participants were male. The mean dietary zinc intake was 11.2 (SD, 2.0)

mg/day. The median number of dietary zinc measurements was 2 (interquartile range, 1–4) times (Fig. S2).

The baseline characteristics of study participants are presented by quartiles of dietary zinc intake in Table 1 and Table S1. Participants with higher dietary zinc intake were older, more likely to be male, urban residents, smokers and drinkers, and living in the south region; had higher education levels; had higher intakes of protein, seafood, nuts, red meat, vitamin A, riboflavin, niacin, vitamin C, copper, magnesium, iron, and potassium; were less likely to be female; and had lower BMI, physical activity levels, and Na/K and lower intakes of fat, carbohydrate, whole grain, and sodium.

Association between dietary zinc intake and new-onset hypertension

During a median follow-up of 6.1 years (interquartile range, 3.6–11.4 years), 4269 (44.9 per 1000 person-years) participants developed new-onset hypertension. Among them, 826 were diagnosed with hypertension by a physician, 526 reported the use of antihypertensive treatment during follow-up, and 3923 had a new-onset mean SBP ≥ 140 mmHg and/or mean DBP of ≥ 90 mmHg during follow-up. Some of the patients met at least two of the above three criteria.

Overall, the association between dietary zinc intake (Fig. 1) and the risk of new-onset hypertension followed a J-shape (P for non-linearity < 0.001). Accordingly, in the threshold effect analysis, the risk of new-onset hypertension significantly decreased with the increment of dietary zinc intake (per mg/day: HR, 0.93; 95% CI, 0.88–0.98) in participants with zinc intake < 10.9 mg/day and increased with the increment of dietary zinc intake (per mg/day: HR, 1.14; 95% CI: 1.11–1.16) in participants with zinc intake ≥ 10.9 mg/day (Table 2). Consistently, when dietary zinc intake was assessed as quartiles, the risk of new-onset hypertension was higher in participants in the first quartile (< 10.0 mg/day: HR, 1.09; 95% CI, 1.01–1.18) and fourth quartile (≥ 12.2 mg/day: HR, 1.42; 95% CI, 1.32–1.53) compared with those in the second to third quartiles (10.0 to < 12.2 mg/day) (Table 3).

Similar trends were also found for different components of new-onset hypertension, including physician-diagnosed hypertension, use of antihypertensive treatment during follow-up, and new-onset mean SBP ≥ 140 mmHg and/or mean DBP ≥ 90 mmHg during follow-up (Table S2).

We further performed a series of sensitivity analyses to test the robustness of the association. First, further adjustments for the intakes of vitamin A, riboflavin, niacin, vitamin C, sodium, copper, magnesium, and iron did not substantially change the results (Table S3). Second, further adjustments for the intakes of seafood,

Table 1 Population characteristics by quartiles of dietary zinc intake

Characteristics	Zinc intake (mg/day)				P value
	Q1 (< 10.0)	Q2 (10.0 to < 11.0)	Q3 (11.0 to < 12.2)	Q4 (\geq 12.2)	
N	3044	3044	3044	3045	
Age (years)	41.0 (14.3)	41.2 (14.1)	40.5 (14.0)	42.1 (14.3)	< 0.001
Male (<i>n</i> (%))	1358 (44.6)	1317 (43.3)	1421 (46.7)	1602 (52.6)	< 0.001
BMI (kg/m ²)	22.7 (3.1)	22.3 (3.1)	22.2 (3.0)	22.4 (3.1)	< 0.001
SBP (mmHg)	114.1 (11.3)	113.9 (11.5)	113.1 (11.4)	114.4 (11.4)	< 0.001
DBP (mmHg)	74.2 (8.0)	74.2 (7.9)	73.8 (7.7)	74.5 (7.7)	0.003
Current smoking (<i>n</i> (%))	883 (29.1)	886 (29.3)	895 (29.5)	1024 (33.8)	< 0.001
Current alcohol drinking (<i>n</i> (%))	971 (32.2)	947 (31.4)	1033 (34.4)	1187 (39.5)	< 0.001
Self-report diabetes (<i>n</i> (%))	29 (1.0)	35 (1.2)	39 (1.3)	50 (1.7)	0.100
Urban residence (<i>n</i> (%))	903 (29.7)	1057 (34.7)	1109 (36.4)	1336 (43.9)	< 0.001
eGFR (mL/min/1.73 m ²)	88.0 (16.0)	84.7 (16.1)	84.3 (16.4)	82.5 (16.8)	< 0.001
Physical activity, MET-h/week	162.7 (140.1)	161.0 (139.7)	162.2 (135.6)	142.1 (127.4)	< 0.001
Regions (<i>n</i> (%))					< 0.001
Central	1699 (55.8)	1416 (46.5)	1247 (41.0)	1220 (40.1)	
North	710 (23.3)	723 (23.8)	565 (18.6)	486 (16.0)	
South	635 (20.9)	905 (29.7)	1232 (40.5)	1339 (44.0)	
Occupation (<i>n</i> (%))					< 0.001
Famer	1171 (39.0)	1196 (39.8)	1122 (37.1)	859 (28.5)	
Worker	312 (10.4)	351 (11.7)	404 (13.4)	390 (12.9)	
Unemployed	829 (27.6)	738 (24.5)	697 (23.0)	773 (25.6)	
Other	687 (22.9)	723 (24.0)	802 (26.5)	993 (32.9)	
Education (<i>n</i> (%))					< 0.001
Illiteracy	588 (19.7)	599 (20.1)	533 (17.9)	485 (16.2)	
Primary school	631 (21.1)	593 (19.9)	584 (19.6)	519 (17.4)	
Middle school	1030 (34.5)	1024 (34.3)	979 (32.8)	958 (32.0)	
High school or above	737 (24.7)	767 (25.7)	889 (29.8)	1028 (34.4)	
Dietary intake					
Energy (kcal/day)	2236.7 (535.0)	2135.9 (500.1)	2150.3 (505.1)	2189.5 (522.8)	< 0.001
Fat (g/day)	81.3 (33.6)	71.0 (28.0)	70.6 (26.9)	74.3 (27.8)	< 0.001
Carbohydrate (g/day)	315.2 (102.6)	311.0 (94.1)	311.4 (99.8)	304.4 (101.0)	< 0.001
Protein (g/day)	61.0 (17.1)	63.1 (16.2)	67.4 (16.7)	75.8 (21.0)	< 0.001
Sodium (g/day)	5.4 (3.1)	4.9 (2.7)	5.0 (2.9)	4.8 (3.3)	< 0.001
Potassium (g/day)	1.5 (0.5)	1.6 (0.4)	1.7 (0.5)	1.9 (0.8)	< 0.001
Na/K	3.7 (2.4)	3.3 (1.9)	3.1 (2.0)	2.7 (1.8)	< 0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MET, metabolic equivalent; Na/K, sodium-to-potassium.

Variables are presented as mean (SD) or *n* (%).

nuts, red meat, vegetable, legume, and whole grain also did not materially alter the findings (Table S3). Third, further adjustment for the physical activity levels also did not substantially change the results (Table S4). Moreover, among participants with blood sample measurements in 2009 wave, further adjustment for eGFR levels did not materially alter the results (Table S4).

Stratified analyses by potential effect modifiers

We further performed exploratory subgroup analyses to assess the associations between dietary zinc intake and new-onset hypertension in two groups of participants separated by the inflection point of zinc intake (10.9 mg/day).

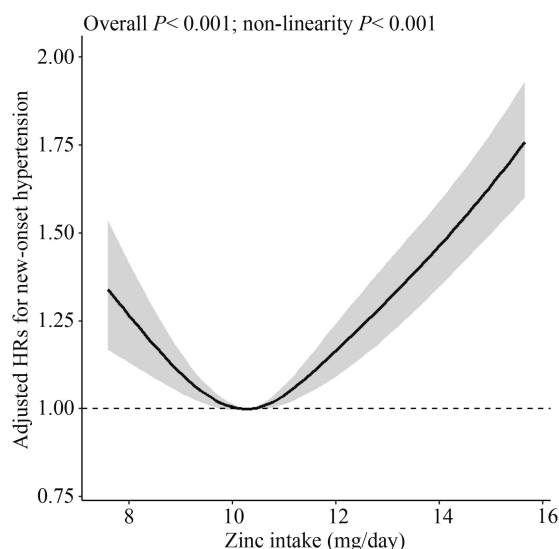


Fig. 1 Relation of dietary zinc intake with risk of new-onset hypertension. Adjusted for age, sex, body mass index (BMI), smoking and drinking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), education levels, occupations, urban or rural residence, sodium-to-potassium intake ratio (Na/K), and energy intake.

None of the variables, including age, sex, BMI, SBP, Na/K, fat, protein, carbohydrate, copper intake, and self-reported diabetes, significantly modified the association

between dietary zinc intake and new-onset hypertension (Fig. 2 and Fig. S3). The *P* values for interactions for smoking status; intakes of protein, carbohydrate, and vitamin A among participants with dietary zinc intake ≥ 10.9 mg/day; and intakes of fat, niacin, and riboflavin intake among participants with dietary zinc intake < 10.9 mg/day were lower than 0.05. After being corrected for multiple comparisons with the use of the Bonferroni procedure, only the *P* values for interactions for fat intake (*P*-interaction = 0.003) among participants with dietary zinc intake < 10.9 mg/day and carbohydrate intake (*P*-interaction = 0.004) among participants with dietary zinc intake ≥ 10.9 mg/day remained significant. However, due to the similar directionality of most of the associations, these results may not have significant clinical implications.

Discussion

In this relatively large-scale, nationally prospective cohort of Chinese adults, we first observed a J-shaped relationship of dietary zinc intake and new-onset hypertension with the inflection points at 10.9 mg/day.

Few previous studies [19] have examined the association between dietary zinc intake and new-onset hypertension. Kunutsor and Laukkanen [19] reported no

Table 2 Threshold effect analyses of dietary zinc intake on the risk of new-onset hypertension using two-piecewise regression models

Zinc intake (mg/day)	<i>n</i>	Cases (incidence rate)	Crude model		Adjusted model	
			HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
< 10.9	5899	2034 (43.6)	0.88 (0.84–0.92)	< 0.001	0.93 (0.88–0.98)	0.003
≥ 10.9	6278	2235 (46.1)	1.14 (1.12–1.16)	< 0.001	1.14 (1.11–1.16)	< 0.001

Incident rate is presented as per 1000 person-years of follow-up.

Adjusted for age, sex, body mass index (BMI), smoking and drinking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), education levels, occupations, urban or rural residence, sodium-to-potassium intake ratio (Na/K), and energy intake.

Table 3 Association between dietary zinc intake and the risk of new-onset hypertension

Zinc intake (mg/day)	<i>n</i>	Cases (incidence rate)	Crude models		Adjusted models	
			HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Quartiles						
Q1 (< 10.0)	3044	1045 (46.3)	Ref			
Q2 ($10.0 - < 11.0$)	3044	1044 (40.4)	0.87 (0.80–0.94)	0.001	0.92 (0.84–1.00)	0.060
Q3 ($11.0 - < 12.2$)	3044	975 (37.8)	0.81 (0.74–0.89)	< 0.001	0.91 (0.83–1.00)	0.042
Q4 (≥ 12.2)	3045	1205 (57.4)	1.25 (1.15–1.36)	< 0.001	1.30 (1.19–1.42)	< 0.001
Categories						
Q1 (< 10.0)	3044	1045 (46.3)	1.19 (1.11–1.28)	< 0.001	1.09 (1.01–1.18)	0.024
Q2–3 ($10.0 - < 12.2$)	6088	2019 (39.1)	Ref		Ref	
Q4 (≥ 12.2)	3045	1205 (57.4)	1.49 (1.39–1.60)	< 0.001	1.42 (1.32–1.53)	< 0.001

Incidence rate is presented as per 1000 person-years of follow-up.

Adjusted for age, sex, body mass index (BMI), smoking and drinking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), education levels, occupations, urban or rural residence, sodium-to-potassium intake ratio (Na/K), and energy intake.

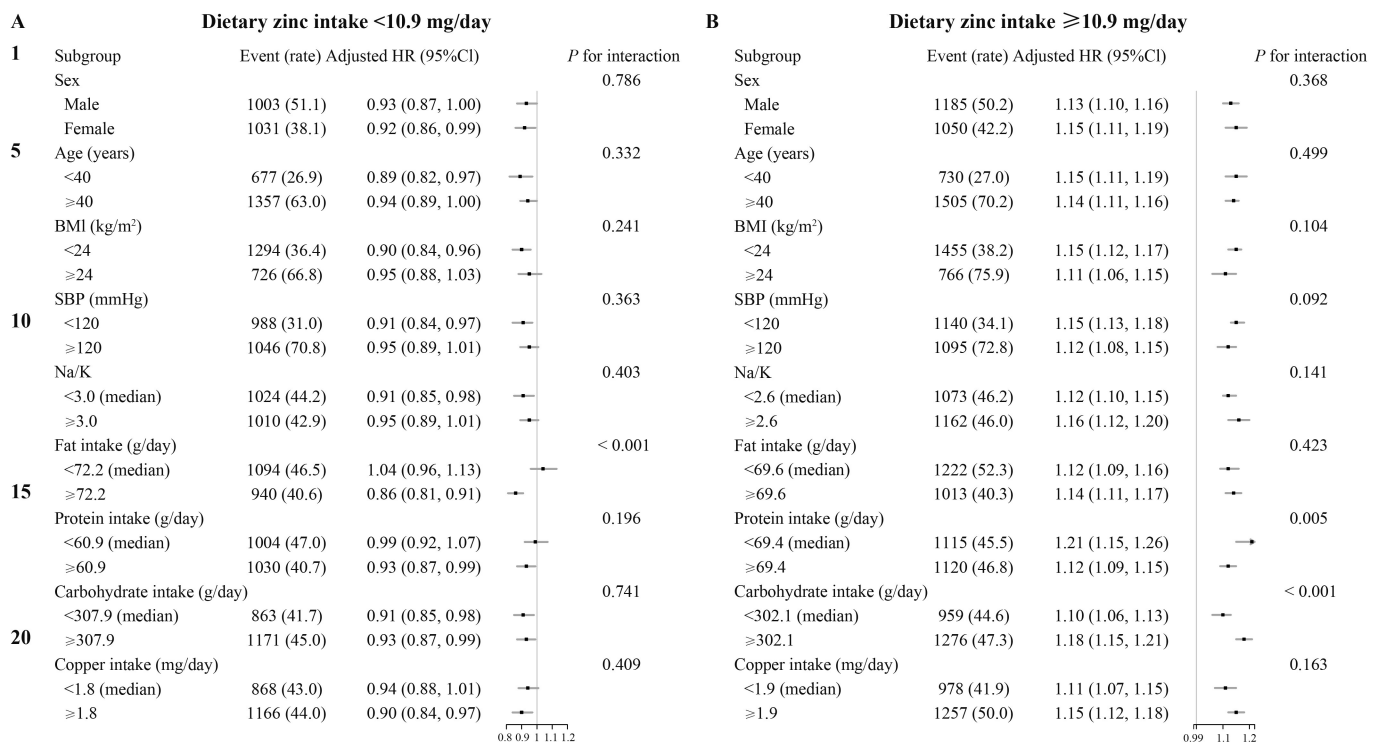


Fig. 2 Stratified analyses by potential effect modifiers for the association between dietary zinc intake and new-onset hypertension in various subgroups divided by 10.9 mg/day. (A) Zinc intake < 10.9 mg/day. (B) Zinc intake ≥10.9 mg/day. Incidence rate is presented as per 1000 person-years of follow-up. Adjusted, if not stratified, for age, sex, body mass index (BMI), smoking and drinking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), education levels, occupations, urban or rural residence, sodium-to-potassium intake ratio (Na/K), and energy intake.

evidence of an association of dietary zinc intake with the risk of hypertension among 1652 adult male participants in Eastern Finland. However, when dietary zinc intake was assessed as quartiles, this study found that compared with participants in the first quartile, the adjusted HRs (95% CI) of new-onset hypertension in the second, third, and fourth quartiles were 0.83 (0.56–1.23), 1.19 (0.81–1.76), and 1.34 (0.83–2.16), respectively. Although the comparisons were not significant, the lowest risk of new-onset hypertension was found in those in the second quartile. That is to say, this study also showed a J-shaped relation between dietary zinc intake and new-onset hypertension. Nevertheless, this study had a relatively small sample size and only included male participants. Therefore, a clear conclusion could not be drawn. Our current study, with a prospective design, relatively large sample size, and relatively accurate dietary nutrition measurement of 24-h dietary recall, provided an opportunity to assess the continuous association between dietary zinc intake and new-onset hypertension in the general population.

Our study provides some new insights in this field. Overall, we found a J-shaped relation between dietary zinc intake and new-onset hypertension. First, among participants with dietary zinc intake < 10.9 mg/day, the risk of new-onset hypertension significantly decreased

with the increment of dietary zinc intake. Zinc plays an important role in nitric oxide system (NOS) activity because NOS contains zinc, and the stabilization of NOS activity in artery walls could improve endothelial function and induce endothelium-mediated vasodilation [38,39]. Moreover, zinc deficiency was found to reduce the vasodilatation reaction to bradykinin and prostacyclin [40]. In addition, zinc deficiency could lead to a decline in taste acuity, thus increasing salt intake and BP [7].

Second, the risk of new-onset hypertension significantly increased with the increment of dietary zinc intake in participants with dietary zinc ≥10.9 mg/day. In animal models, zinc is known to inhibit the adenosine triphosphate-dependent calcium pump, which causes an outpour of calcium ions from the cell [41], leading to a rise of free calcium ions in the smooth muscles of the vascular wall, subsequently resulting in increased wall tension and hypertension. Furthermore, zinc was demonstrated to cause accumulation of 1,4,5-triphosphoinositol-5-phosphatase (InsP₃) and promote the release of intracellular calcium, leading to the increase of the arterial muscular layer tension and the proliferation of smooth muscle cells [42]. Zinc protoporphyrin IX could also block the heme oxygenase–carbon monoxide system and inhibit the nitrogen oxide vasodilatation effect, leading to a rise in BP [18]. These findings from animal

models may partly explain the increased BP levels associated with higher zinc intake in our current study. However, further mechanistic studies are required to unravel the pathways involved in the association.

Third, we detected a minimal hypertension risk at 10.0 to 12.2 mg/day of dietary zinc intake. This value was relatively lower than that in Western countries. In the Eastern Finland population [19], a non-significant lower risk of new-onset hypertension was found in those with dietary zinc intake of 11.87 to 14.32 mg/day (second quartile). The discrepancy may possibly be partly due to the different food patterns. In China, the main food sources of dietary zinc are grains, red meat, vegetables, legumes, and seafood [17]. However, dairy products are one of the main food sources of dietary zinc in Western countries [43]. These food products may help to attain an optimal dietary zinc intake level. Nevertheless, our study was conducted in the Chinese population. More studies are needed to further investigate our findings in different populations. Moreover, although plant foods, which are high in phytates, may possibly affect the absorption of dietary zinc [44], our study showed that further adjustments for a series of plant foods did not substantially change our findings.

Of note, the relation of hypertension with zinc intake might be ascribed to other nutrients or some unknown components of the main dietary sources of zinc. However, our study showed that adjustments for other major nutrients or major food groups, including seafood, nuts, red meat, and whole grain, did not materially alter the findings. These results indicated that the association of zinc intake and new-onset hypertension may be independent of these factors.

The limitations of the present study should also be noted. First, although we had adjusted for several dietary and non-dietary covariates to reduce the confounding effects, unmeasured and residual confounding such as renal function remained possible. Second, we have no detailed information on dietary supplement use. However, data from the 2010–2012 China Nutrition and Health Surveillance [45], a nationally representative cross-sectional study covering all 31 provinces, autonomous regions, and municipalities in China, showed that only 0.71%, 0.03%, and 0.21% of the Chinese population reported using nutrient, multi-mineral, and zinc supplements, respectively. Due to the low supplement proportion of nutrients, especially zinc, we speculate that our results may not be materially altered by the use of dietary supplements. Third, serum zinc level was not available in the CHNS study. As such, we could not examine the correlation between serum zinc level and dietary zinc consumption. Fourth, our study was conducted in Chinese. Whether the observed findings can be extrapolated to other populations needs further

investigation. Therefore, further confirmation of our findings in more studies is essential.

Conclusions

We first observed a J-shaped relationship of dietary zinc intake and new-onset hypertension, with an inflection point at about 10.9 mg/day and minimal risk at 10.0 to 12.2 mg/day of dietary zinc intake. If further confirmed, our data provide some evidence for maintaining the optimal dietary zinc intake levels for the primary prevention of hypertension.

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Compliance with ethics guidelines

Panpan He, Huan Li, Mengyi Liu, Zhuxian Zhang, Yuanyuan Zhang, Chun Zhou, Ziliang Ye, Qimeng Wu, Min Liang, Jianping Jiang, Guobao Wang, Jing Nie, Fan Fan Hou, Chengzhang Liu, and Xianhui Qin declare no conflict of interest. The Institutional Review Boards of the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety, and the Chinese Center for Disease Control and Prevention, approved the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Electronic Supplementary Material Supplementary material is available in the online version of this article at <https://doi.org/10.1007/s11684-022-0932-3> and is accessible for authorized users.

References

- Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol* 2020; 16(4): 223–237
- Qin X, Huo Y. H-Type hypertension, stroke and diabetes in China: opportunities for primary prevention. *J Diabetes* 2016; 8(1): 38–40
- GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392(10159): 1923–1994
- WHO. (2013) A global brief on hypertension. 2013. Available at WHO website
- Li Y, Yang L, Wang L, Zhang M, Huang Z, Deng Q, Zhou M, Chen Z, Wang L. Burden of hypertension in China: a nationally representative survey of 174,621 adults. *Int J Cardiol* 2017; 227: 516–523
- Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, Cheng X, Mu L, Zhang H, Liu J, Su M, Zhao H, Spatz ES, Spertus JA, Masoudi FA, Krumholz HM, Jiang L. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). *Lancet* 2017; 390(10112): 2549–2558
- Mohammadifard N, Humphries KH, Gotay C, Mena-Sánchez G, Salas-Salvadó J, Esmailzadeh A, Ignaszewski A, Sarrafzadegan N. Trace minerals intake: risks and benefits for cardiovascular health. *Crit Rev Food Sci Nutr* 2019; 59(8): 1334–1346
- Bergomi M, Rovesti S, Vinceti M, Vivoli R, Caselgrandi E, Vivoli G. Zinc and copper status and blood pressure. *J Trace Elem Med Biol* 1997; 11(3): 166–169
- Li Z, Wang W, Liu H, Li S, Zhang D. The association of serum zinc and copper with hypertension: a meta-analysis. *J Trace Elem Med Biol* 2019; 53: 41–48
- Darroudi S, Saberi-Karimian M, Tayefi M, Tayefi B, Khashyрманesh Z, Fereydouni N, Haghghi HM, Mahmoudi AA, Kharazmi-Khorassani J, Gonoodi K, Esmaeili H, Mohammadpour AH, Ferns GA, Ghayour-Mobarhan M. Association between hypertension in healthy participants and zinc and copper status: a population-based study. *Biol Trace Elem Res* 2019; 190(1): 38–44
- Bastola MM, Locatis C, Maisiak R, Fontelo P. Selenium, copper, zinc and hypertension: an analysis of the National Health and Nutrition Examination Survey (2011–2016). *BMC Cardiovasc Disord* 2020; 20(1): 45
- Wu W, Jiang S, Zhao Q, Zhang K, Wei X, Zhou T, Liu D, Zhou H, Zeng Q, Cheng L, Miao X, Lu Q. Environmental exposure to metals and the risk of hypertension: a cross-sectional study in China. *Environ Pollut* 2018; 233: 670–678
- Yao B, Wang Y, Xu L, Lu X, Qu H, Zhou H. Associations between copper and zinc and high blood pressure in children and adolescents aged 8–17 years: an exposure-response analysis of NHANES 2007–2016. *Biol Trace Elem Res* 2020; 198(2): 423–429
- Yao J, Hu P, Zhang D. Associations between copper and zinc and risk of hypertension in US adults. *Biol Trace Elem Res* 2018; 186(2): 346–353
- Kim J. Dietary zinc intake is inversely associated with systolic blood pressure in young obese women. *Nutr Res Pract* 2013; 7(5): 380–384
- Kim MH, Choi MK. Seven dietary minerals (Ca, P, Mg, Fe, Zn, Cu, and Mn) and their relationship with blood pressure and blood lipids in healthy adults with self-selected diet. *Biol Trace Elem Res* 2013; 153(1–3): 69–75
- Wang Y, Jia XF, Zhang B, Wang ZH, Zhang JG, Huang FF, Su C, Ouyang YF, Zhao J, Du WW, Li L, Jiang HR, Zhang J, Wang HJ. Dietary zinc intake and its association with metabolic syndrome indicators among Chinese adults: an analysis of the China nutritional transition cohort survey 2015. *Nutrients* 2018; 10(5): 572
- Ho M, Baur LA, Cowell CT, Samman S, Garnett SP. Zinc status, dietary zinc intake and metabolic risk in Australian children and adolescents; Nepean longitudinal study. *Eur J Nutr* 2017; 56(7): 2407–2414
- Kunutsor SK, Laukkanen JA. Serum zinc concentrations and incident hypertension: new findings from a population-based cohort study. *J Hypertens* 2016; 34(6): 1055–1061
- Zhang B, Zhai FY, Du SF, Popkin BM. The China health and nutrition survey, 1989–2011. *Obes Rev* 2014; 15(Suppl 1): 2–7
- Liu M, Zhou C, Zhang Z, Li Q, He P, Zhang Y, Li H, Liu C, Qin X. Inverse association between riboflavin intake and new-onset hypertension: a nationwide cohort study in China. *Hypertension* 2020; 76(6): 1709–1716
- Zhou C, Liu C, Zhang Z, Liu M, Zhang Y, Li H, He P, Li Q, Qin X. Variety and quantity of dietary protein intake from different sources and risk of new-onset diabetes: a nationwide cohort study in China. *BMC Med* 2022; 20(1): 6
- Zhang Z, Liu M, Zhou C, He P, Zhang Y, Li H, Li Q, Liu C, Qin X. Evaluation of dietary niacin and new-onset hypertension among Chinese adults. *JAMA Netw Open* 2021; 4(1): e2031669
- He P, Li H, Liu M, Zhang Z, Zhang Y, Zhou C, Li Q, Liu C, Qin X. U-shaped association between dietary zinc intake and new-onset diabetes: a nationwide cohort study in China. *J Clin Endocrinol Metab* 2022; 107(2): e815–e824
- Zhou C, Zhang Z, Liu M, Zhang Y, Li H, He P, Li Q, Liu C, Qin X. Dietary carbohydrate intake and new-onset diabetes: a nationwide cohort study in China. *Metabolism* 2021; 123: 154865
- Liu M, Liu C, Zhang Z, Zhou C, Li Q, He P, Zhang Y, Li H, Qin X. Quantity and variety of food groups consumption and the risk of diabetes in adults: a prospective cohort study. *Clin Nutr* 2021; 40(12): 5710–5717
- Seidemann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, Folsom AR, Rimm EB, Willett WC, Solomon SD. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health* 2018; 3(9): e419–e428
- Data Collection—China Health and Nutrition Survey (CHNS). 2022. Available from the website of Data Collection—China Health and Nutrition Survey (CHNS)
- Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, Iqbal R, Kumar R, Wentzel-Viljoen E, Rosengren A, Amma LI, Avezum A, Chifamba J, Diaz R, Khatib R, Lear S, Lopez-Jaramillo P, Liu X, Gupta R, Mohammadifard N, Gao N, Oguz A, Ramli AS, Seron P, Sun Y, Szuba A, Tsolekile L, Wielgosz A, Yusuf R, Hussein Yusufali A, Teo KK, Rangarajan S, Dagenais G, Bangdiwala SI, Islam S, Anand SS, Yusuf S; Prospective Urban Rural Epidemiology (PURE) study investigators. Associations of

- fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* 2017; 390(10107): 2050–2062
30. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* 1999; 149(6): 531–540
 31. Zhai F, Guo X, Popkin BM, Ma L, Wang Q, Shuigao WY, Ge JAK. Evaluation of the 24-hour individual recall method in China. *Food Nutr Bull* 1996; 17(2): 1–7
 32. Zhai FY, Du SF, Wang ZH, Zhang JG, Du WW, Popkin BM. Dynamics of the Chinese diet and the role of urbanicity, 1991–2011. *Obes Rev* 2014; 15(Suppl 1): 16–26
 33. Xue H, Yang M, Liu Y, Duan R, Cheng G, Zhang X. Relative validity of a 2-day 24-hour dietary recall compared with a 2-day weighed dietary record among adults in South China. *Nutr Diet* 2017; 74(3): 298–307
 34. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986; 124(1): 17–27
 35. Li Q, Li R, Zhang S, Zhang Y, He P, Zhang Z, Liu M, Zhou C, Li H, Liu C, Qin X. Occupational physical activity and new-onset hypertension: a nationwide cohort study in China. *Hypertension* 2021; 78(1): 220–229
 36. Zhang Y, Liu M, Zhou C, Zhang Z, He P, Li Q, Liu C, Qin X. Inverse association between dietary vitamin A intake and new-onset hypertension. *Clin Nutr* 2021; 40(5): 2868–2875
 37. He P, Li H, Liu C, Liu M, Zhang Z, Zhang Y, Zhou C, Li Q, Ye Z, Wu Q, Jiang J, Wang G, Liang M, Nie J, Hou FF, Qin X. U-shaped association between dietary copper intake and new-onset hypertension. *Clin Nutr* 2022; 41(2): 536–542
 38. Li H, Förstermann U. Nitric oxide in the pathogenesis of vascular disease. *J Pathol* 2000; 190(3): 244–254
 39. Moncada S. Nitric oxide in the vasculature: physiology and pathophysiology. *Ann N Y Acad Sci* 1997; 811(1 Atherosclerosis): 60–69
 40. Browning JD, Reeves PG, O'Dell BL. Zinc deficiency in rats reduces the vasodilation response to bradykinin and prostacyclin. *J Nutr* 1987; 117(3): 490–495
 41. Vezzoli G, Elli AA, Tripodi G, Bianchi G, Carafoli E. Calcium ATPase in erythrocytes of spontaneously hypertensive rats of the Milan strain. *J Hypertens* 1985; 3(6): 645–648
 42. Berridge MJ. Regulation of ion channels by inositol trisphosphate and diacylglycerol. *J Exp Biol* 1986; 124(1): 323–335
 43. O'Neil CE, Keast DR, Fulgoni VL, Nicklas TA. Food sources of energy and nutrients among adults in the US: NHANES 2003–2006. *Nutrients* 2012; 19; 4(12): 2097–2120
 44. Ma G, Li Y, Jin Y, Zhai F, Kok FJ, Yang X. Phytate intake and molar ratios of phytate to zinc, iron and calcium in the diets of people in China. *Eur J Clin Nutr* 2007; 61(3): 368–374
 45. Gong W, Liu A, Yao Y, Ma Y, Ding C, Song C, Yuan F, Zhang Y, Feng G, Chen Z, Ding G. Nutrient supplement use among the Chinese population: a cross-sectional study of the 2010–2012 China nutrition and health surveillance. *Nutrients* 2018; 10(11): 1733