Iron, Zinc and Copper from Cereal Food Sources and Cognitive Performance in Older Adults in China

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Abstract

Background: We aimed to determine the risk factors associated with cognitive performance in older adults in China.

Methods: A longitudinal study was conducted in a group of 1,898 adults aged 60 yr and over in China, Cognitive score was determined by a modified Telephone Interview for Cognitive Status (TICSM). The dietary intake of iron (Fe), zinc (Zn) and copper (Cu) from cereal source foods (CSF) were calculated by using Food Frequency Questionnaire (FFQ) and Chinese Food Composition Tables. Descriptive statistics and multivariate mixed regression models were utilized to explore the association between the intake of these elements and cognitive function.

Results: The mean dietary intakes of Fe, Zn and Cu from CSF were 12.01, 6.90 and 1.30 mg/d respectively. Compared with participants in the high-cognitive group, those in the low-cognitive group had lower total dietary intakes of Fe, Zn and Cu. However, with respect to ratios of CSF-Zn, CSF-Fe and CSF-Cu to their respective total values, participants in the low-cognitive group had significantly higher ratios than those in the high-cognitive group. The results of multivariate mixed regression model revealed that although total dietary Zn intake was positively linked with cognitive function, the CSF-Zn/Zn ratio was negatively associated with cognitive performance.

Conclusion: Excessive intake of Zn from a specific food source, such as CSF, was found to be negatively associated with cognitive status. Avoiding over-intake of Zn from CSF foods and diversifying intake of Zn from different food sources seemed to protect individuals from cognitive decline.

Keywords: Iron; Zinc; Copper; Cognitive; Cereal; Diet; China

Introduction

One of the most severe challenges that China currently faces is the unprecedented aging of population. It is projected that by the year 2100, Chinese adults aged 65 and over will grow to 324 million and account for roughly 32% of China's total population (1). This demographic change will produce profound implications on healthy aging in China, as aging is commonly accompanied by increased health risks in various domains (2). One of those risks that draws widespread concern among health researchers and professionals is decline of cognitive function.

Cognitive health plays a critical role in the normal performance of daily functions, thereby significantly affecting the quality of life of the elderly people. Evidence indicates that cognitive decline commences from age 50 and accelerates after age 65 (3). If without any interventions, cognitive decline may gradually progress into Alzheimer's disease (AD). It is estimated that patients with AD may reach 23.3 million in 2030 in China (4). Given this reality, scholars have shown significant interests in researching how to take interventions to prevent cognitive decline or impairment with aging (5-7). Of these interventions, diets are of particular interest as it may offer a relatively simple way of intervention to produce positive outcomes in cognitive functioning (8, 9). Trace elements, such as iron (Fe), zinc (Zn) and copper (Cu), are essential in regulating numerous biological reactions and physiological functions in a human body. A homeostasis of these trace elements is required to maintain a proper cell functioning, especially in the central nervous system, where trace elements play critical roles in a series of biological functions. Disturbed homeostasis of trace elements was found to be associated with the pathogenesis of many neurodegenerative disorders, including Alzheimer's and Parkinson's disease (10).

Cereals are major components of human diet, providing essential nutrients for human being (11). China is the world's leading cereals producer, with rice and wheat accounting for approximately 28.3% and 17.0% of global production (12). The traditional Chinese diet is typically characterized by a high intake of cereals, plant-based foods and a low intake of meats and fat (13,14). Compared to meat, cereals were inexpensive and provided primary sources of calories, energy and protein for habitants in low-income countries like China. Nearly all cereals were consumed domestically in China, thus cereal consumption had significant effects on the health status of Chinese population. Insufficient or excessive intakes of trace elements from diet were found to be associated with Alzheimer's disease (15, 16).

The purpose of the present study was to assess the association between trace elements intake from cereal source foods (CSF) and cognitive function among older Chinese adults using data from the China Health and Nutrition Survey (CHNS).

Methods

Ethical Considerations
This research uses data from China Health and Nutrition Survey (CHNS). All participants in CHNS signed written informed consent.

The CHNS is an open household-based cohort survey performed in nine provinces in China between 1989 and 2011. For the purpose of this study, only participants in 2004 and 2006 (We aimed to examine the long-term effects of CSF, therefore a long-time span of data was more convincing) aged 60+yr were enrolled. In these two waves there were 31,170 participants, 1,427 of them were under 60 yr old and were then excluded. Overall, 27,836 participants with missing values on cognitive tests or dietary intake were excluded. Participants with implausible energy intake (<600 or > 6000 kcal/day for female; <800 or > 8000 kcal/day for male) (n=9) were also excluded (17). Thus, the final subjects for the analysis of trace elements and cognitive function were 1,898 participants aged 60 and over (1,044 men and 854 women). Of these participants, 868 attended both surveys, and 1,030 attended at least one survey. Informed consent was obtained from all participants.

Cognitive score
Cognitive score was the outcome variable in this study. The cognitive screening items utilized in CHNS were a subset of modified Telephone Interview for Cognitive Status (TICSM), which were administered face-to-face among CHNS participants, aged 55 yr and over (18). The cognitive scores used in this study were calculated as a sum of immediate and delayed recall of a 10-word list, counting backwards from 20, and serial 7's subtractions. The total cognitive score ranged

from 0 to 27, with high scores indicating better cognitive performance. The validity of the TICS cognitive score has been previously established in China as well as in other countries (19, 20).

Dietary intake

The CSF-Zn/Zn ratio was calculated as the ratio of CSF zinc with respect to the total zinc. CSF-Fe/Fe and CSF-Cu/Cu ratios were computed similarly. In multivariate regression analysis, CSF-Zn/Zn, CSF-Fe/Fe and CSF-Cu/Cu ratios were used as the primary predictor variables, with total Fe, Zn and Cu intakes being evaluated as secondary predictor variables.

Cereal source foods (CSF) in this paper was defined as the grains of wheat, rice, corn, barley, millet, and other cereal grains as well as the flour and relevant products of them (such as wheat flour, wheat noodle, and wheat bread etc.). The dietary data were recorded by trained CHNS interviewers using Food Frequency Questionnaire (FFQ) through face-to-face interviews (21).

The food recall data was utilized in this research to derive individual daily average intakes (grams) of specific food items, which were then extrapolated into daily trace element intakes according to Chinese Food Composition Tables (22, 23). In addition, in order to better feature the core foods of the Chinese diet we grouped food items into 15 major groups: 1) cereals; 2) tubers; 3) legume; 4) vegetables; 5) fruit; 6) meat; 7) eggs; 8) fish and shrimp; 9) dairy; 10) nuts; 11) fast foods; 12) cooking oil; 13) beverage; 14) alcohol; 15) condiments. The individual average daily macronutrients intakes such as energy (kcal), fat (grams), carbohydrate (grams), and protein (grams) were also available in the dietary data of CHNS.

The K-means cluster analysis based on Euclidean distance was performed to derive dietary patterns using the daily intake of these 15 food groups. The number of clusters was varied (from 2 to 6) to determine the optimal number of clusters with reasonable sizes. We identified 2 dietary patterns in this population based on K-means cluster analyses. We labelled them Dietary Pattern 1 (DP1), Dietary Pattern 2 (DP2) respectively. Dietary patterns are frameworks that people tend to

follow when choosing what to eat. The DP1 had higher intakes of condiments but lower intakes of fish, meat, dairy products and vegetables. The DP2 had higher mean intakes of fish, meat, vegetables and fruits. Data of mean food group consumption for each cluster is available upon request.

Covariates

We included the following variables as covariates: dietary pattern, daily energy intake (kcal), protein intake (grams), fat intake (grams) and carbohydrate intake (grams), age, gender, education (0= illiterate/primary school; 1= junior middle school; 2= high middle school or higher), individual annual income, urban community (yes or no), physical activity (1=weekly time>=30 min, 0=otherwise), smoking (0=non-smokers; 1=ex-smokers; 2=current smokers), alcohol drinking (yes or no), hypertension (1= systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, 0=otherwise), BMI(Body Mass Index), self-reported diabetes mellitus and stroke (yes or no).

The Chinese Dietary Reference Intakes

The Chinese Dietary Reference Intakes (Chinese DRIs) was created by the Chinese Nutrition Society. The DRIs offered Estimated Average Requirements (EARs), Recommended Nutrient Intakes (RNIs), Adequate Intakes (AIs) and Tolerable Upper Intake Levels (ULs) for nutrient intakes for infant, children, adolescent, pregnant women, breastfeeding women, and old people.

Statistical Analysis

For sample descriptive analysis, we examined baseline characteristics of participants. In addition, we divided baseline participants into low and high cognitive groups on the basis of standard deviations from mean cognitive score: with low-cognition as being 1.0 standard deviation (SD) below the mean, and high-cognition as being 1.0 SD above the mean. We further compared differences between low and high cognitive groups. Chi-square tests were used to compare differences between groups for categorical varia-

bles, and *t*-tests were utilized for continuous variables.

For multivariate regression analysis, we employed linear mixed-effects models to evaluate the relationship between CSF-Zn, CSF-Fe and CSF-Cu and cognitive performance. In our primary multivariate regression analysis, model 1 used the CSF-Fe/Fe ratio as a single predictor after adjusting for age, sex, education, annual income, community type, physical activity, smoking status, alcohol drinking, BMI, hypertension, diabetes, stroke, dietary patterns, as well as energy, protein, fat and carbohydrate intakes; model 2 replaced CSF-Fe/Fe by CSF-Zn/Zn in model 1; model 3 substituted the CSF-Cu/Cu for CSF-Fe/Fe in model 1; model 4 added CSF-Zn/Zn as another

predictor to model 1; model 5 included CSF-Cu/Cu in model 1; model 6 added CSF-Cu/Cu to model 2; and model 7 added CSF-Cu/Cu to model 4. In addition, for the purpose of comparison, in the multivariate mixed model regression analysis, total dietary intakes of Fe, Zn and Cu were used in models 1b to 7b as predictors to substitute for the respective predictors of ratios in models 1 to 7 to repeat the same analysis.

Results

The selected socio-characteristics of all subjects, low and high cognitive ones at baseline (2004) are presented in Table 1.

Table 1: Baseline sample characteristics of adults aged 60 and over [mean (SD) or %]

Variables	All n=1356	Low Cognitive n=240	High Cognitive n=190	P*
Cognitive score (range = 0-27)	13.04 (6.37)	2.98 (2.29)	22.39 (2.27)	<0.001
Age (yr)	67.92 (6.06)	70.49 (6.67)	66.13 (4.99)	<0.001
Gender (male %)	55.31	44.17	66.32	<0.001
Education (%)				<0.001
Illiterate/primary school	68.14	90.83	45.79	
Junior middle school	14.75	5.83	18.95	
High middle school or higher	17.11	3.34	35.26	
Smoking (%)				0.004
Non-smoker	62.83	70.83	55.26	
Ex-smoker	8.55	6.25	10.53	
Current smoker	28.61	22.92	34.21	
Cereal intake (g/day)	501.19 (254.87)	505.36 (265.14)	500.31 (221.95)	0.833
Dietary Pattern 1	71.17	72.50	68.42	0.356
Dietary Pattern 2	28.83	27.50	31.58	
Urban community type (% yes)	41.89	27.92	49.47	<0.001
Individual annual income (1,000 ¥)	6.57 (6.77)	3.83 (4.18)	9.08 (8.03)	<0.001
BMI (kg/m2)	23.22 (3.69)	21.98 (3.29)	24.22 (3.81)	<0.001
Physical activity (% yes)	11.95	2.5	11.58	<0.001
Alcohol drinking (% yes)	31.71	25.42	36.32	0.015
Hypertension (% yes)	10.62	13.75	11.58	0.503
Diabetes (% yes)	3.47	2.50	4.74	0.209
Stroke (% yes)	3.98	5.42	1.58	0.037

*tests for differences between low and high cognitive groups

The mean ± SD cognitive score of full sample was 13.04 ± 6.37, with mean ± SD cereal intake

5.01 ± 2.55 100 g/d. The majority of subjects (68.14%) had a relatively low education level (il-

literate and primary education). A very high proportion of participants were current smokers (28.61%), alcohol drinkers (31.71%) and followers of Dietary Pattern 1 (71.17%). Subjects of high-cognitive group were more likely to be younger, urban dwellers, more physically active, and had higher education, income, and BMI compared with low-cognitive group. However, there was no significant difference in cereal intakes and dietary patterns between these two groups.

The dietary intake of trace elements and macronutrients of subjects at baseline are displayed in Table 2. In the full sample, the mean ± SD dietary intakes of Fe, Zn and Cu from CSF were 12.01 ± 7.50, 6.90 ± 3.59 and 1.30 ±0.78 mg/day respectively. Although in the full sample the average total dietary intakes of Fe, Zn and Cu from all foods (35.78, 17.92 and 3.44 mg/day with *P*-values 0.003, 0.001, 0.002 respectively) were within ULs, they were significantly higher than AIs or RNIs.

Table 2: Baseline sample dietary nutrients intake [mean (SD)]

Variables	All (n=1356)	Low Cognitive (n=240)	High Cognitive (n=190)	AI	UL	P-value
CSF Fe Intake (mg/day)	12.01(7.50)	12.89 (8.13)	12.09 (6.65)	-	-	0.271
CSF Zn Intake (mg/day)	6.90 (3.59)	7.26 (3.70)	6.82 (2.79)	-	-	0.178
CSF Cu Intake (mg/day)	1.30 (0.78)	1.35 (0.75)	1.35 (0.73)	-	-	0.957
Total Fe Intake (mg/day)	35.78 (21.73)	33.08 (18.74)	39.04 (22.89)	15	50	0.003
Total Zn Intake (mg/day)	17.92 (8.46)	16.12 (7.09)	19.42 (10.12)	11.5 (RNI)	37	<0.001
Total Cu Intake (mg/day)	3.44 (2.02)	3.12 (1.55)	3.72 (2.43)	2	8	0.002
CSF-Fe/Total-Fe Ratio	0.38 (0.19)	0.43 (0.20)	0.36 (0.18)			<0.001
CSF-Zn/Total-Zn Ratio	0.42 (0.19)	0.49 (0.19)	0.40 (0.18)			<0.001
CSF-Cu/Total-Cu Ratio	0.43 (0.20)	0.48 (0.21)	0.42 (0.19)			0.003
Energy Intake (kcal/day)	2085.91(652.18)	2032.29(656.93)	2182.45(695.60)	1700~2200	-	0.022
Carbohydrate Intake (g/day)	299.81 (108.43)	309.49 (111.43)	306.71 (107.85)	-	-	0.794
Fat Intake (g/day)	66.80 (35.65)	58.12 (36.36)	72.17 (34.40)	20~30	-	<0.001
Protein Intake (g/day)	64.17 (24.00)	59.84 (21.13)	66.86 (25.56)	65~75	-	0.002

No significant differences in average intakes of CSF-Fe, CSF-Zn and CSF-Cu were found between different cognitive groups at baseline. Compared with participants in the high-cognitive group, those in the low-cognitive group had lower *total* intakes of Fe, Zn and Cu. However, with respect to shares of CSF-Fe, CSF-Zn and CSF-Cu in their respective total values, participants in the low-cognitive group had significantly higher shares of these three elements from CSF compared to those in the high-cognitive group.

In the full baseline sample, the mean ± SD dietary intakes of energy, carbohydrate, fat and protein were 2085.91± 652.18 kcal/day, 299.81 ± 108.43 g/day, 66.80 ± 35.65 g/day, and 64.17 ± 24.00 g/day, respectively. Although in the full

sample average energy and protein intakes were within AIs, mean fat intake was considerably higher than the AIs. Compared with participants in the low-cognitive group, those in the high-cognitive group had significant higher energy, fat and protein intakes.

In our multivariate mixed model (Table 3), the CSF-Zn/Zn ratio, no matter used as a single predictor or as one combined with any one or all of the other ratio predictors, was consistently found to be negatively associated with cognitive performance. Although the corresponding ratios of Fe and Cu, if used as single predictors, were negatively linked with cognitive function, the association disappeared if they were combined with any other ratio predictors.

Table 3: Multivariate mixed model results (intake ratios as predictors)

Variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
CSF-Fe/Total-Fe Ratio	-2.64** (0.70)			-0.013 (1.21)	-2.19 (1.11)		-0.16 (1.35)
CSF-Zn/Total-Zn Ratio		-3.86** (0.83)		-3.84** (1.44)		-4.05** (1.23)	-3.94** (1.51)
CSF-Cu/Total-Cu Ratio			-2.20** (0.67)		-0.55 (1.07)	0.21 (0.99)	0.27 (1.11)

** $P<0.01$; Numbers in parenthesis are SD; All models were adjusted for age, sex, education, annual income, community type, physical activity, smoking status, alcohol drinking, BMI, hypertension, diabetes, stroke, dietary patterns, as well as energy, protein, fat and carbohydrate intakes.

To provide insight to associations between intakes of Fe, Zn and Cu and cognitive scores, total dietary intake of these three elements were used as predictor variables in secondary analyses. Regression results (Table 4) showed that total dietary Zn intake was positively associated with cognitive scores. No similar associations were found for total intakes of Fe and Cu.

Table 4: Multivariate mixed model results (total intakes as predictors)

Variable	Model 1b	Model 2b	Model 3b	Model 4b	Model 5b	Model 6b	Model 7b
Total Fe	0.001 (0.005)			-0.007 (0.006)	-0.002 (0.006)		-0.007 (0.006)
Total Zn		0.06** (0.02)		0.07** (0.02)		0.07** (0.02)	0.07** (0.02)
Total Cu			0.08 (0.07)		0.09 (0.08)	-0.03 (0.08)	-0.001 (0.084)

** $P<0.01$; Numbers in parenthesis are SD; All models were adjusted for same confounders as listed in Table 3

Discussion

To the best of our knowledge, this population-based study was the first to explore whether these three trace elements, specifically from CSF, were linked with cognitive function among older adults in China.

In our baseline sample descriptive analysis, the estimated mean daily CSF intake among older adults was similar to those reported in previous studies in China (24). Consistent with previous study, the average daily consumption of CSF was found to be higher than recommended level (25). Previous researches (26, 27) on the association between CSF consumption and cognitive status produced mixed results: while some studies indicated that higher CSF consumption were associated with better cognitive performance (26); higher intakes of CSF, especially rice, might be associated with poor cognitive performance (27). Dietary intake of Zn was usually adequate among old adults (28). Although in our study the average total intakes of Fe, Zn and Cu from all food sources were within ULs, they were significantly higher than AIs or RNIs among old adults in China.

The present study also demonstrated that total dietary intakes of Fe, Zn and Cu were significantly lower among low-cognitive participants compared to high-cognitive ones. We speculated that causes of lower intakes of these three elements among low-cognitive participants might be low consumption of foodstuff besides cereals, since no significant differences in the average con-

sumption of cereals were observed between different cognitive groups.

Low or excessive intakes of trace elements were associated with poor cognitive performance in older adults (29). Specifically, disruptions in zinc homeostasis played a critical role in the pathogenesis of AD (30). Of all human organs, the brain has the highest zinc content. Zinc is the structural or catalytic component of approximately 70% of proteins in the brain (31). Alterations in zinc concentrations from normal levels may induce various devastating diseases (32). Increasing evidence showed that excess zinc could cause neuronal death, depletion of cellular energy, loss of mitochondrial membrane potential (33).

Moreover, soil contamination may affect the quality of dietary intake of trace elements. China is one of those countries with the largest amount of polluted soil. It was common to observe crops being grown in polluted soil in China. Significant accumulation of heavy metals was found in wheat plants grown in polluted soils (34). As a result, consumption of crops grown in polluted soils may induce deleterious effects on homeostasis of trace elements.

The results of our multivariate mixed model analysis demonstrated that although total Zn intake was *positively* correlated with cognitive function, the CSF-Zn/Zn ratio was *negatively* associated with cognitive performance. In other words, although total dietary Zn intake benefited cognitive function, if dietary Zn came predominantly from CSF, then it would be detrimental to cognitive health. This result implied that avoiding excessive intake of Zn solely from CSF foods and diversifying intake of Zn from different food sources seemed to be of critical importance for cognitive health. However, no similar associations were found for Fe and Cu after adjusting for all confounders in the present study.

This study has certain limitations. First, the time span covered in this study was relatively short, so a causal relationship conclusion should be cautious. Second, the trace element levels, as measured in dietary intake based on food frequency questionnaire in this study, might be biased, as many other factors, such as soil contamination, were not taken into consideration.

Conclusion

We examined the association between dietary Fe, Zn and Cu intake and cognitive performance. The excessive intake of Zn from a specific food source, such as cereal source foods, was negatively associated with cognitive performance, and such an association was often concealed when total Zn intake was used as a predictor. Although the mechanism behind the negative association of CSF-Zn and cognitive function was complex and needed further investigations, avoiding over-intake of Zn from CSF foods and diversifying intake of Zn from different food sources seemed to protect individuals from cognitive decline. These findings may provide health professionals and researchers with new information to implement interventions or make policy decisions to promote cognitive health.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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