General Psychiatry

J-shaped association between dietary thiamine intake and the risk of cognitive decline in cognitively healthy, older Chinese individuals

Chengzhang Liu,[1,2,3] Qiguo Meng,[1,2] Yuanxiu Wei,[1,2] Xinyue Su,[1,2] Yuanyuan Zhang,[3] Panpan He,[3] Chun Zhou,[3] Mengyi Liu,[3] Ziliang Ye,[3] Xianhui Qin [1,2,3]

To cite: Liu C, Meng Q, Wei Y, *et al*. J-shaped association between dietary thiamine intake and the risk of cognitive decline in cognitively healthy, older Chinese individuals. *General Psychiatry* 2024;**37**:e101311. doi:10.1136/gpsych-2023-101311

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101311).

Received 22 August 2023
Accepted 16 November 2023

For numbered affiliations see end of article.

Correspondence to
Dr Xianhui Qin;
pharmaqin@126.com

ABSTRACT

Background The prospective association of dietary thiamine intake with the risk of cognitive decline among the general older adults remains uncertain.

Aims To investigate the association between dietary thiamine intake and cognitive decline in cognitively healthy, older Chinese individuals.

Methods The study included a total of 3106 participants capable of completing repeated cognitive function tests. Dietary nutrient intake information was collected through 3-day dietary recalls and using a 3-day food-weighed method to assess cooking oil and condiment consumption. Cognitive decline was defined as the 5-year decline rate in global or composite cognitive scores based on a subset of items from the Telephone Interview for Cognitive Status–modified.

Results The median follow-up duration was 5.9 years. There was a J-shaped relationship between dietary thiamine intake and the 5-year decline rate in global and composite cognitive scores, with an inflection point of 0.68 mg/day (95% confidence interval (CI): 0.56 to 0.80) and a minimal risk at 0.60–1.00 mg/day of dietary thiamine intake. Before the inflection point, thiamine intake was not significantly associated with cognitive decline. Beyond the inflection point, each unit increase in thiamine intake (mg/day) was associated with a significant decrease of 4.24 (95% CI: 2.22 to 6.27) points in the global score and 0.49 (95% CI: 0.23 to 0.76) standard units in the composite score within 5 years. A stronger positive association between thiamine intake and cognitive decline was observed in those with hypertension, obesity and those who were non-smokers (all $p<0.05$).

Conclusions This study revealed a J-shaped association between dietary thiamine intake and cognitive decline in cognitively healthy, older Chinese individuals, with an inflection point at 0.68 mg/day and a minimal risk at 0.60–1.00 mg/day of dietary thiamine intake.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Research findings on the relationship between dietary thiamine intake and cognitive function in the general older population are inconsistent and are based mainly on the evidence from cross-sectional and case–control studies. The prospective association of dietary thiamine intake with the risk of cognitive decline in the general older population remains uncertain.

WHAT THIS STUDY ADDS

⇒ In cognitively healthy, older Chinese individuals, there was a J-shaped association between dietary thiamine intake and cognitive decline, with an inflection point at 0.68 mg/day and a minimal risk at 0.60–1.00 mg/day.

⇒ Beyond the inflection point, the positive association of dietary thiamine intake with cognitive decline was significantly stronger in those with obesity, hypertension and those who were non-smokers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study highlights the importance of maintaining optimal dietary thiamine intake levels in the general older population to prevent cognitive decline.

INTRODUCTION

Dementia is one of the leading causes of death and disability and is projected to affect 139 million people worldwide by 2050,[1] resulting in a substantial social and economic burden.[2] Given that there is currently no cure for dementia, preventing cognitive decline is particularly important, especially through targeting easily modifiable nutritional and behavioural factors in the population.

Thiamine (vitamin B_1) is an essential water-soluble B vitamin involved in energy metabolism, neurotransmitter synthesis and secretion. Previous clinical trials with small sample sizes have reported that thiamine treatment (5–600 mg/day) can improve cognitive function in patients with cognitive impairment or mild dementia (n=70),[3] in maintenance haemodialysis patients with cognitive impairment (n=50)[4] and in patients with alcohol dependence (n=107).[5] Of note,

these trials mainly focused on the effects of high-dose thiamine supplementation or intramuscular injection,[3–5] rather than dietary thiamine derived from foods in the general population. However, findings on the association between dietary thiamine intake and cognitive function in the older population were inconsistent and mainly based on the evidence from cross-sectional and case–control studies.[6–9] Therefore, the prospective association of dietary thiamine intake with the risk of cognitive decline in the general older population remains uncertain. To address these knowledge gaps, this study aimed to investigate the relationship between dietary thiamine intake and cognitive decline in cognitively healthy, older Chinese individuals.

METHODS

This research used data from the China Health and Nutrition Survey (CHNS), a public database. The data and study materials can be found on its official website (http://www.cpc.unc.edu/projects/china). Each CHNS participant provided written informed consent.[10]

Population and study design

Details of the study design and key results of CHNS have been previously published.[11–13] Briefly, CHNS is an ongoing multipurpose longitudinal open cohort study initiated in 1989, with follow-up conducted every 2–4 years. A multistage, random cluster approach was used to draw the sample from nine provinces or autonomous cities. The provinces include Heilongjiang (enrolled in 1997), Liaoning, Shandong, Henan, Jiangsu, Hubei, Hunan, Guizhou and Guangxi, and the three largest autonomous cities were Beijing, Shanghai and Chongqing, with the latter enrolled in 2011. By 2011, the provinces included in CHNS represented 47% of China's population.[11] The CHNS follow-up rounds were completed in 1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011 and 2015.

In 1997, 2000, 2004 and 2006, cognitive function was assessed repeatedly for participants aged ≥55 years who were capable of completing cognitive function tests, representing the cognitively healthy, older Chinese population. We conducted a prospective cohort based on the four rounds of data. Participants with only one survey wave were excluded. Of the remaining participants with at least two rounds of survey data (n=3119), the first survey round was considered as the baseline. In addition, 13 participants with extreme dietary energy data (male: >4200 or <600 kcal/day; female: >3600 or <500 kcal/day) were also excluded.[14] The final analysis included a total of 3106 participants (figure 1).

Dietary nutrient intakes

Dietary measurements in CHNS have been previously published.[11 14] Briefly, both individual and household-level dietary data were collected in each survey round. Individual diet data were collected by trained investigators through a 24-hour dietary recall on three consecutive days randomly allocated from Monday to Sunday. The allocated days were almost evenly distributed across the week for each sampling unit. Given that cooking oil and condiments are integral to Chinese cuisine and are added during cooking and preparation, their consumption was assessed by examining changes in household inventory over the same 3 days with a weighting technique. Specifically, on each of the three consecutive days, interviewers conducted a household visit to weigh and record the household food inventories, including food purchased and discarded, as well as individuals' proportion of food consumption. The cooking oil and condiments consumed at the household level were allocated to each individual according to their consumption proportion. Nutrient intake was calculated using the Chinese food composition tables. The accuracy of the 24-hour dietary recall designed to assess energy and nutrient intake has been validated.[15]

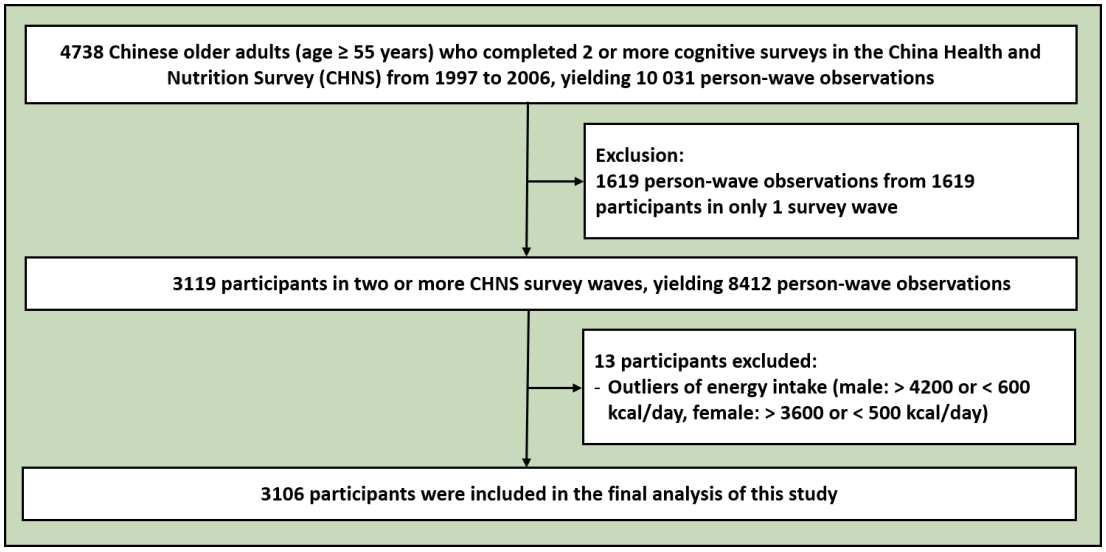

Figure 1 Flowchart of the study.

In our study, 3-day average intakes of dietary macronutrients and micronutrients in each round were calculated. Furthermore, to represent the long-term nutrient status of each participant and minimise within-person variation, the cumulative average intake of each nutrient was calculated for each participant using all results up to the last visit and was used in the final analysis.

Covariate measurements

After the participants had rested for 5 min, seated blood pressure was measured by trained research staff using a mercury manometer following standard procedures. 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 three independent measures were used in the analysis.

Demographic and lifestyle information was obtained through questionnaires at each follow-up survey, including age, sex, smoking, alcohol consumption, occupation, education level, urban or rural residency, region, concomitant conditions and drug use. Height and weight were measured following standard procedures with calibrated equipment. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Physical activity was collected by staff-administered questionnaires exploring all occupational, transportation, domestic and leisure activities in adults.

Assessment of cognitive function decline

A subset of items from the Telephone Interview for Cognitive Status–modified (TICS-m)[16] was used to measure cognitive performance. The TICS-m can be administered both over the telephone and through face-to-face interviews[17] and has been approved as a strong predictor of cognitive decline,[18] dementia and mild cognitive impairment,[19] even among people with low levels of education or illiteracy.[20] The cognitive test consists of three simple tasks, including immediate and delayed recall of a 10-word list (0–10 points for each), counting backward from 20 (0–2 points) and serial seven subtraction five times from 100 (0–5 points), to evaluate verbal memory, attention and calculation, respectively. A higher score in each item indicates better cognitive function, and the global cognitive score ranges from 0 to 27 points. Moreover, to eliminate the influence of the score proportion of the three components on the global score, a composite score in standard units by averaging z scores of verbal memory and other items was also conducted.

During face-to-face interviews, all items used to test cognitive performance were read and/or interpreted in detail by trained and qualified staff. Therefore, as reported in a previous study,[17] participants' vision and literacy skills may not affect their cognitive assessment. However, participants unable to complete the cognitive assessment due to various reasons, such as severe cognitive impairment, were excluded from the study.

The 5-year decline rate in global or composite cognitive scores, which was used to assess the decline of cognitive function, was calculated as the baseline score minus the last survey score, then divided by the follow-up time (in years) and multiplied by 5. A positive value represents a decline in cognitive function, while a negative value represents an increase in cognitive function.

Statistical analysis

For continuous variables with normal and non-normal distributions, the population characteristics were presented as mean (standard deviation (SD)) and median (25th percentile, 75th percentile), respectively. Differences by categories of dietary thiamine intake (<0.40, [0.40, 0.60), [0.60, 0.80), [0.80, 1.00), [1.00, 1.20), [1.20, 1.40), ≥1.40 mg/day) were compared using analysis of variance, or the Kruskal-Wallis test, accordingly. For categorical variables, the population characteristics were presented as proportions; differences by categories of dietary thiamine intake were compared using χ^2 tests.

A restricted cubic spline function was applied to display the relationship between dietary thiamine intake and the 5-year decline rate in global or composite cognitive scores. A two-piecewise linear regression was performed to examine the threshold effect of dietary thiamine intake using R package of *segmented*. The inflection point was determined using the likelihood ratio test and the bootstrap resampling method. The relationship of dietary thiamine intake with the 5-year decline rate in global or composite scores was estimated by linear regression models (β and 95% confidence interval (CI). The models included adjustments for sociodemographic characteristics (age, sex, occupation, region and urban or rural residency), known dementia risk factors (smoking, alcohol consumption, BMI, self-reported diabetes, SBP, DBP, antihypertensive medication, physical activity and education level),[21] the dietary intake factors (fibre, sodium, potassium, carbohydrate, protein and fat) associated with cognitive function[22–24] and the baseline global cognitive score. Possible modifications of the association between thiamine intake and the 5-year decline rate in global or composite cognitive scores were evaluated by stratified analyses and interaction testing.

Several sensitivity analyses were performed to assess the robustness of the key findings. First, to exclude the confounding effects of total energy intake, the association between energy-adjusted thiamine intake, calculated using the nutrient residual model, and cognitive decline was further examined. Second, to exclude the influence of food consumption, the intake of whole grains, legumes, unprocessed red meat and processed red meat was further included in the adjustments. Third, considering the potential confounding effect of other dietary B vitamins due to similar food sources, we further adjusted the dietary intakes of riboflavin and niacin in the regression models. Lastly, considering that some participants had more than two cognitive measurements, a mixed linear regression model was applied to capture the information from the multiple measurements to

assess the relationship between dietary thiamine and cognitive decline. To eliminate false positives caused by multiple tests, the Benjamini-Hochberg method was used to further calculate the multiple testing corrected p values (P-BH) in regression and subgroup analysis.

All analyses were performed using R software (V.3.6.3), and a two-sided p<0.05 was considered statistically significant.

RESULTS

Characteristics of the study participants

A total of 3106 participants were included in this study (figure 1). The mean age was 63.1 (7.0) years, and the average intake of thiamine was 0.93 (0.32) mg/day.

The characteristics of the study population are presented in online supplemental table 1. Participants with a higher dietary thiamine intake were younger, more likely to be male, smokers, alcohol drinkers and farmers. Moreover, those with a higher dietary thiamine intake had higher BMI, physical activity, education, better cognitive function, lower SBP and higher intakes of fibre, sodium, potassium, carbohydrates, protein and fat.

The relationship between dietary thiamine intake and cognitive decline

The median follow-up time was 5.9 years (25th–75th percentiles: 2.0, 8.8). The distribution of decline rates in the global and composite cognitive scores approximates a normal distribution (online supplemental figure 1). There was a J-shaped relationship between dietary thiamine intake and the 5-year decline rate in both global and composite cognitive scores (online supplemental figure 2A,B), with an inflection point at 0.68 (95% CI: 0.56 to 0.80) mg/day (table 1). Before the inflection point, thiamine intake was not significantly associated with cognitive decline. Beyond the inflection point, each unit increase in thiamine intake (mg/day) was associated with a significant decrease of 4.24 (95% CI: 2.22 to 6.27) points in global score and 0.49 (95% CI: 0.23 to 0.76) standard units in the composite score within 5 years.

To further explore the optimal intake range of dietary thiamine for maintaining cognitive function, the value of thiamine intake was further categorised

Table 1 The relationship between dietary thiamine intake and cognitive decline using two-piecewise linear regression*

Inflection point, mg/day Estimate (95% CI)	n	Mean (SD)	β (95% CI)	P value	R^2
Decline rate in global cognitive scores, points/5 years					
Model 1					
0.67 (0.51 to 0.82)					0.270
<0.67	570	2.89 (11.13)	−7.43 (−18.79 to 3.93)	0.200	
≥0.67	2536	2.09 (11.12)	3.10 (1.35 to 4.85)	**<0.001**	
Model 2					
0.68 (0.56 to 0.80)					0.312
<0.68	617	2.80 (10.95)	−7.13 (−18.77 to 4.50)	0.230	
≥0.68	2489	2.09 (11.16)	4.24 (2.22 to 6.27)	**<0.001**	
Decline rate in composite cognitive scores, SU/5 years					
Model 1					
0.66 (0.52 to 0.81)					0.256
<0.66	527	0.43 (1.47)	−0.90 (−2.50 to 0.70)	0.271	
≥0.66	2579	0.29 (1.43)	0.33 (0.10 to 0.55)	**0.005**	
Model 2					
0.68 (0.56 to 0.80)					0.297
<0.68	617	0.40 (1.46)	−1.00 (−2.56 to 0.56)	0.208	
≥0.68	2489	0.29 (1.44)	0.49 (0.23 to 0.76)	**<0.001**	

p values less than 0.05 are shown in bold.
*Model 1 was adjusted for age, sex, global score, as well as the intakes of carbohydrate, protein and fat. Model 2 was further adjusted for smoking, alcohol consumption, BMI, SBP, DBP, education level, occupation, region, urban or rural residency, self-reported diabetes, antihypertensive medicine, physical activity, as well as the intakes of fibre, sodium and potassium.
BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; SU, standard units by averaging z scores.

Table 2 The relationship between dietary thiamine intake and cognitive decline*

Thiamine intake, mg/day	n	Mean (SD)	Model 1 β (95% CI)	Model 1 P value	Model 1 P-BH	Model 2 β (95% CI)	Model 2 P value	Model 2 P-BH
Decline rate in global cognitive scores, points/5 years								
Group 1								
<0.40	30	2.63 (13.14)	0.61 (–2.95 to 4.18)	0.736	0.736	0.98 (–2.95 to 4.92)	0.625	0.625
[0.40, 0.60)	284	3.26 (11.10)	0.69 (–0.64 to 2.03)	0.310	0.466	1.08 (–0.37 to 2.53)	0.144	0.216
[0.60, 0.80)	843	2.32 (10.76)	Ref			Ref		
[0.80, 1.00)	905	1.84 (10.52)	0.17 (–0.77 to 1.11)	0.727	0.736	0.45 (–0.57 to 1.48)	0.386	0.463
[1.00, 1.20)	547	2.15 (11.95)	1.17 (0.00 to 2.34)	**0.049**	0.099	1.58 (0.30 to 2.86)	**0.015**	**0.031**
[1.20, 1.40)	269	2.99 (10.98)	2.19 (0.66 to 3.73)	**0.005**	**0.031**	3.51 (1.82 to 5.21)	**<0.001**	**<0.001**
≥1.40	228	1.48 (12.55)	2.08 (0.22 to 3.93)	**0.028**	0.085	3.25 (1.18 to 5.33)	**0.002**	**0.006**
R^2			0.269			0.312		
Group 2								
<0.60	314	3.20 (11.29)	0.62 (–0.64 to 1.88)	0.334	0.334	0.91 (–0.46 to 2.28)	0.194	0.194
[0.60, 1.00)	1748	2.07 (10.63)	Ref			Ref		
[1.00, 1.20)	547	2.15 (11.95)	1.07 (0.08 to 2.06)	**0.034**	0.051	1.29 (0.22 to 2.36)	**0.018**	**0.027**
≥1.20	497	2.30 (11.74)	2.02 (0.79 to 3.24)	**0.001**	**0.004**	3.05 (1.70 to 4.41)	**<0.001**	**<0.001**
R^2			0.269			0.312		
Decline rate in composite cognitive scores, SU/5 years								
Group 1								
<0.40	30	0.39 (1.72)	0.11 (–0.36 to 0.58)	0.640	0.685	0.14 (–0.37 to 0.66)	0.586	0.586
[0.40, 0.60)	284	0.47 (1.50)	0.11 (–0.06 to 0.29)	0.203	0.304	0.15 (–0.04 to 0.34)	0.113	0.170
[0.60, 0.80)	843	0.33 (1.40)	Ref			Ref		
[0.80, 1.00)	905	0.27 (1.37)	0.03 (–0.10 to 0.15)	0.685	0.685	0.06 (–0.07 to 0.19)	0.382	0.459
[1.00, 1.20)	547	0.30 (1.53)	0.13 (–0.02 to 0.29)	0.089	0.194	0.19 (0.02 to 0.36)	**0.026**	0.051
[1.20, 1.40)	269	0.38 (1.38)	0.23 (0.03 to 0.43)	**0.026**	0.157	0.39 (0.17 to 0.62)	**<0.001**	**0.003**
≥1.40	228	0.19 (1.62)	0.21 (–0.04 to 0.45)	0.097	0.194	0.36 (0.09 to 0.63)	**0.010**	**0.030**
R^2			0.255			0.296		
Group 2								
<0.60	314	0.46 (1.52)	0.10 (–0.06 to 0.27)	0.219	0.219	0.13 (–0.05 to 0.31)	0.153	0.153
[0.60, 1.00)	1748	0.30 (1.38)	Ref			Ref		
[1.00, 1.20)	547	0.30 (1.53)	0.12 (–0.01 to 0.25)	0.076	0.113	0.15 (0.01 to 0.29)	**0.033**	**0.049**
≥1.20	497	0.29 (1.50)	0.20 (0.04 to 0.36)	**0.014**	**0.043**	0.33 (0.15 to 0.51)	**<0.001**	**<0.001**
R^2			0.255			0.296		

p values less than 0.05 are shown in bold.
*Model 1 was adjusted for age, sex, global score, as well as the intakes of carbohydrate, protein and fat. Model 2 was further adjusted for smoking, alcohol consumption, BMI, SBP, DBP, education level, occupation, region, urban or rural residency, self-reported diabetes, antihypertensive medicine, physical activity, as well as the intakes of fibre, sodium and potassium.
BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; P-BH, multiple testing corrected p values by Benjamini-Hochberg method; SBP, systolic blood pressure; SD, standard deviation; SU, standard units by averaging z scores.

by the cut-off points of 0.40, 0.60, 0.80, 1.00, 1.20 and 1.40 mg/day. For the 5-year decline rate in the composite cognitive score, compared with participants with thiamine intake of 0.60–<1.00 mg/day, β (95% CI) was 0.13 (–0.05 to 0.31), 0.15 (0.01 to 0.29) and 0.33 (0.15 to 0.51) in those with thiamine intake of <0.60, 1.00–<1.20 and ≥1.20 mg/day, respectively (table 2). Similar patterns were observed for the global cognitive scores. Moreover, multiple test correction had no significant effect on the results.

A series of sensitivity analyses were performed to test the robustness of the association. First, results from the threshold analysis did not substantially change when thiamine intakes were tested in the energy-adjusted form (online supplemental table 2). Second, similar patterns were found with further adjustments for other B vitamins (riboflavin and niacin) (online supplemental table 3) or food consumptions (whole grain, legume, unprocessed red meat and processed red meat) (online supplemental table 4). Lastly, the mixed linear regression analysis for participants who underwent more than two cognitive assessments also found that participants with a dietary thiamine intake

Subgroups	N	Decline rate in global cognitive scores, points/5 years				Decline rate in composite cognitive scores, SU/5 years			
		mean (SD)	β (95%CI)	P-interaction	P-BH	mean (SD)	β (95%CI)	P-interaction	P-BH
Age, years				0.745	0.932			0.506	0.759
<60.2	1245	1.80 (12.35)	4.55 (2.26 to 6.83)			0.26 (1.56)	0.56 (0.26 to 0.86)		
⩾60.2	1244	2.39 (9.83)	4.07 (1.33 to 6.81)			0.33 (1.31)	0.43 (0.07 to 0.79)		
R-square			0.312				0.295		
Sex				0.947	0.947			0.730	0.821
male	1295	2.27 (11.48)	4.28 (1.97 to 6.59)			0.32 (1.44)	0.47 (0.17 to 0.77)		
female	1194	1.90 (10.80)	4.18 (1.50 to 6.87)			0.27 (1.43)	0.53 (0.18 to 0.88)		
R-square			0.317				0.301		
Hypertension				**0.030**	0.090			**0.024**	0.071
no	1371	2.04 (11.69)	2.78 (0.42 to 5.15)			0.29 (1.50)	0.30 (-0.01 to 0.60)		
yes	992	2.25 (10.66)	5.87 (3.32 to 8.43)			0.30 (1.38)	0.72 (0.38 to 1.05)		
R-square			0.318				0.302		
BMI, kg/m^2				**0.003**	**0.030**			**0.003**	**0.014**
<24	1480	2.06 (10.99)	2.92 (0.62 to 5.22)			0.30 (1.42)	0.30 (-0.00 to 0.60)		
24–<28	626	2.18 (11.64)	4.64 (1.68 to 7.60)			0.30 (1.48)	0.60 (0.22 to 0.99)		
⩾28	216	2.93 (11.04)	11.79 (6.71 to 16.88)			0.35 (1.48)	1.45 (0.79 to 2.12)		
R-square			0.321				0.305		
Smoking				**0.019**	0.086			**0.003**	**0.014**
no	1651	2.26 (10.90)	5.62 (3.29 to 7.95)			0.31 (1.43)	0.72 (0.42 to 1.03)		
yes	836	1.77 (11.67)	2.29 (-0.32 to 4.90)			0.26 (1.45)	0.17 (-0.17 to 0.51)		
R-square			0.319				0.304		
Alcohol drinking				0.202	0.454			0.203	0.456
no	1588	2.30 (11.44)	5.06 (2.67 to 7.45)			0.32 (1.49)	0.60 (0.29 to 0.91)		
yes	873	1.77 (10.77)	3.25 (0.72 to 5.79)			0.24 (1.35)	0.37 (0.03 to 0.70)		
R-square			0.318				0.301		
Carbohydrate, g/day				0.828	0.932			0.833	0.833
<306.2	1244	2.07 (10.11)	3.47 (0.62 to 6.32)			0.29 (1.32)	0.47 (0.09 to 0.84)		
⩾306.2	1245	2.12 (12.13)	3.82 (1.54 to 6.11)			0.30 (1.55)	0.42 (0.12 to 0.72)		
R-square			0.319				0.303		
Protein, g/day				0.742	0.932			0.632	0.813
<64.1	1244	2.53 (11.18)	3.94 (0.18 to 7.70)			0.35 (1.47)	0.49 (-0.00 to 0.98)		
⩾64.1	1245	1.66 (11.13)	3.28 (1.20 to 5.36)			0.23 (1.41)	0.36 (0.09 to 0.64)		
R-square			0.315				0.298		
Fat, g/day				0.379	0.683			0.513	0.759
<69.8	1244	2.44 (10.92)	3.59 (1.06 to 6.12)			0.34 (1.43)	0.43 (0.10 to 0.76)		
⩾69.8	1245	1.75 (11.39)	4.85 (2.43 to 7.27)			0.25 (1.44)	0.56 (0.24 to 0.87)		
R-square			0.319				0.302		

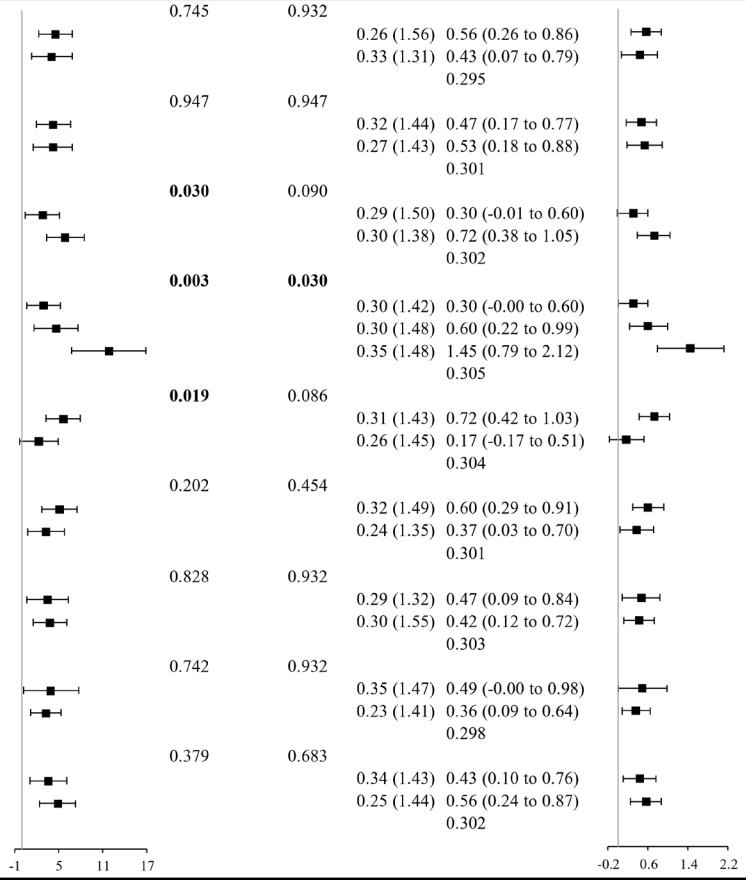

Figure 2 Subgroup analyses for the association between dietary thiamine intake and the 5-year decline rate in cognitive scores in participants with dietary thiamine intake higher than the inflection point (0.68 mg/day). (Adjusted, if not stratified, for age, sex, global score, smoking, alcohol consumption, BMI, SBP, DBP, education level, occupation, region, urban or rural residency, self-reported diabetes, antihypertensive medication, physical activity, as well as the intakes of fibre, sodium, potassium, carbohydrate, protein and fat. Hypertension was defined as SBP≥140 mm Hg or DBP≥90 mm Hg, or diagnosed by a physician, or currently under antihypertensive treatment.) BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; P-BH, multiple testing corrected p values by Benjamini-Hochberg method; SBP, systolic blood pressure; SD, standard deviation; SU, standard units by averaging z scores.

of 0.71–<1.02 mg/day had the lowest cognitive decline rate (online supplemental table 5).

Stratified analyses

Stratified analyses were performed in those with thiamine intake higher than the inflection point (0.68 mg/day) (figure 2). The positive association between thiamine intake and cognitive decline was stronger in those with hypertension (vs non-hypertension), obesity (BMI≥28, vs 24–<28 vs <24 kg/m^2) and non-smokers (vs smokers) (all p interaction <0.05). However, after multiple test correction, the modifying effect of hypertension (P-BH=0.090) and smoking on the decline rate in global cognitive scores became non-significant (P-BH=0.086), and the modifying effect of hypertension on the decline rate in composite cognitive scores became non-significant (P-BH=0.071).

None of the other variables, including age, sex, alcohol consumption and the intake of fat, protein and carbohydrate, significantly modified the linear positive association between dietary thiamine intake and cognitive decline.

DISCUSSION

Main findings

In this study, we found a J-shaped association between dietary thiamine intake and cognitive decline in cognitively healthy, older Chinese individuals, with an inflection point at 0.68 mg/day and a minimal risk at 0.60–1.00 mg/day of dietary thiamine intake. Dietary thiamine intake was not significantly associated with cognitive decline before the inflection point. However, a significant and positive association with cognitive decline emerged after the inflection point, especially in individuals with obesity, hypertension and those who were non-smokers.

Several previous clinical trials with small sample sizes reported that thiamine treatment (5–600 mg/

day) can improve cognitive function in patients with cognitive impairment or mild dementia (n=70),[3] in hemodialysis patients with cognitive impairment (n=50)[4] and in patients with alcohol dependence (n=107).[5] However, due to the small sample sizes and high-risk participants included, the conclusions of these clinical trials cannot be used to infer the effect of dietary thiamine intake on cognitive function in the general population. In addition, only a few previous cross-sectional and case–control studies with limited sample sizes have investigated the relationship between dietary thiamine intake and cognition in older adults, and these have reported inconsistent results.[6–9] As such, the association of dietary thiamine intake with the risk of cognitive function in the general older population remains unknown. Our current study, with a perspective study design, a relatively larger sample size and adjustments for a series of important confounding factors, provided an opportunity to examine the dose–response association of dietary thiamine intake with cognitive function in the general older population.

Our study provides several novel insights. First, we established a J-shaped relationship between dietary thiamine intake and cognitive decline, with an inflection point at 0.68 mg/day of dietary thiamine intake. Before the inflection point, the cognitive decline rate showed a decreasing trend with increased dietary thiamine intake, although the results were not significant, probably due to the small sample size. Thiamine deficiency may lead to an insufficient supply of energy to the neurons of the brain and decreased acetylcholine signalling in the brain, which may impair cognitive function.[25 26] As such, maintaining optimal thiamine intake is necessary for cognitive function in older adults. However, beyond the inflection point of dietary thiamine intake, thiamine intake was significantly positively associated with cognitive decline. This finding is consistent with our recent studies, which found that long-term excessive intake of thiamine was associated with an increased risk of new-onset diabetes[14] and new-onset hypertension[27] in the general population. This series of studies consistently shows that excessive intake of thiamine may have adverse health effects on Chinese adults. Of note, both diabetes and hypertension are risk factors for cognitive decline or dementia.[21] Moreover, thiamine can regulate acetylcholine levels by inhibiting the activity of cholinesterase.[25] High levels of acetylcholine in the brain can adversely affect cognition.[26] Therefore, we speculate that high levels of dietary thiamine intake may lead to cognitive decline by inducing elevated levels of acetylcholine in the brain. More research is needed to confirm our results and further explore the underlying mechanisms.

Second, the positive association between thiamine intake and cognitive decline was stronger in individuals with hypertension, obesity and non-smokers. Hypertension and obesity are established risk factors for cognitive decline,[21] which could impair cognitive function by affecting cerebrovascular structure and central inflammation, respectively. Our findings suggest that hypertension and obesity have a synergistic effect with high thiamine intake on the risk of cognitive decline, emphasising the importance of avoiding excessive thiamine intake for those with hypertension and obesity. We also found that the positive association between thiamine intake and cognitive decline was significantly weaker in smokers. Nicotine has been reported to have certain cognitive enhancement effects.[28] Nicotine may enhance the signal-to-noise ratio or facilitate synaptic plasticity in specific neural circuits by binding to the nicotinic acetylcholine receptor.[28] As such, we speculate that nicotine may partly attenuate the detrimental effects of high dietary thiamine intake. However, after multiple test correction, the modifying effect of hypertension and smoking became non-significant, suggesting that our findings are hypothetical and need to be further evaluated by more studies.

Third, our results suggest the optimal dietary thiamine intake range for the lowest risk of cognitive decline in older adults to be 0.60–1.00 mg/day, which is slightly lower than the optimal dietary thiamine intake ranges for new-onset diabetes (0.75–1.10 mg/day)[14] and new-onset hypertension (0.76–1.13 mg/day)[27] in our previous studies. This is likely due to the older age of the current study population than in the previous two studies (mean age, 41.2–43.1 years), resulting in a lower basal metabolic rate and, consequently, a lower thiamine requirement. In addition, the recommended nutrient intake (RNI) of dietary thiamine for older Chinese (≥50 years) is 1.2–1.4 mg/day,[29] which is higher than our findings. However, it is important to note that the RNI was established based on those with energy intakes of 2600 kcal/day,[29] which is much higher than our study population (mean, 2076 kcal/day). People with higher energy intake also have higher thiamine requirements, which may explain the discrepancy between dietary thiamine RNI and our findings. After adjusting for energy intake, the RNI of dietary thiamine in the older population in China is 0.46 mg/1000 kcal, and the optimal dietary thiamine intake range in our current study is 0.3–0.5 mg/1000 kcal, covering the dietary thiamine RNI.

Limitations

Our study has several limitations. First, being an observational analysis, despite adjustments for important risk factors for cognitive decline, the possibility of residual confounding due to unmeasured or unknown factors could not be completely eliminated. Second, CHNS did not provide information on the use of thiamine supplements. However, the 2010–2012 China Nutrition and Health Surveillance, a nationally representative cross-sectional study, showed that

the proportions of people using nutrient supplements, multivitamins and vitamin B supplements were 0.71%, 0.03% and 0.21% in the Chinese population, respectively.[30] Considering these low proportions, we believe that dietary supplement use is unlikely to significantly alter the findings of our study. Third, while 24-hour dietary recall is one of the most widely used approaches for assessing dietary intake, it only captures dietary information on specific days and may be subject to recall bias. Lastly, this study focused on the older population in China, and further research is needed to determine whether the observed results can be extrapolated to other populations. Overall, further research is needed to validate our findings.

Implications

In conclusion, we first found a J-shaped association between dietary thiamine intake and cognitive decline in cognitively healthy, older Chinese individuals, with an inflection point at 0.68 mg/day and a minimal risk at 0.60–1.00 mg/day of dietary thiamine intake. If substantiated by further research, our study highlights the importance of maintaining optimal dietary thiamine intake levels in the general older population to prevent cognitive decline.

Author affiliations
[1]Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, Anhui, China
[2]Institute of Biomedicine, Anhui Medical University, Hefei, Anhui, China
[3]Division of Nephrology, Nanfang Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease; State Key Laboratory of Organ Failure Research; Guangdong Provincial Institute of Nephrology, Guangdong Provincial Key Laboratory of Renal Failure Research, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, Guangzhou, Guangdong, China

Contributors CL and XQ designed and conducted the research, performed the data management and statistical analyses and wrote the manuscript. All authors reviewed/edited the manuscript for important intellectual content. All authors read and approved the final manuscript. XQ is the guarantor.

Funding This study was funded by National Key Research and Development Program of China (2022YFC2009600, 2022YFC2009605). National Natural Science Foundation of China (81973133).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the institutional review boards (IRB) 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. We are unable to provide the IRB reference number because it could not be obtained from the official website of CHNS (http://www.cpc.unc.edu/projects/china). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data analysed in this study are from CHNS. Data are publicly available and can be downloaded from CHNS website: https://www.cpc.unc.edu/projects/china.

ORCID iD
Xianhui Qin http://orcid.org/0000-0001-7812-7982

REFERENCES

1 He W, Goodkind D, Kowal PR. *An aging world: 2015*. Bureau Washington, DC: United States Census, 2016.
2 Ren R, Qi J, Lin S, *et al*. The China Alzheimer report 2022. *Gen Psychiatr* 2022;35:e100751.
3 Gibson GE, Luchsinger JA, Cirio R, *et al*. Benfotiamine and cognitive decline in Alzheimer's disease: results of a randomized placebo-controlled phase IIa clinical trial. *J Alzheimers Dis* 2020;78:989–1010.
4 Lu R, Fang Y, Zhou Y, *et al*. A pilot study of thiamin and folic acid in hemodialysis patients with cognitive impairment. *Ren Fail* 2021;43:766–73.
5 Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. *Alcohol Clin Exp Res* 2001;25:112–6.
6 Ortega RM, Requejo AM, Andrés P, *et al*. Dietary intake and cognitive function in a group of elderly people. *Am J Clin Nutr* 1997;66:803–9.
7 Lee L, Kang SA, Lee HO, *et al*. Relationships between dietary intake and cognitive function level in Korean elderly people. *Public Health* 2001;115:133–8.
8 Requejo AM, Ortega RM, Robles F, *et al*. Influence of nutrition on cognitive function in a group of elderly, independently living people. *Eur J Clin Nutr* 2003;57 Suppl 1:S54–7.
9 Aparicio Vizuete A, Robles F, Rodríguez-Rodríguez E, *et al*. Association between food and nutrient intakes and cognitive capacity in a group of institutionalized elderly people. *Eur J Nutr* 2010;49:293–300.
10 China Health and Nutrition Survey. Household- and individual-level data of the China health and nutrition survey. 2019. Available: https://www.cpc.unc.edu/projects/china [Accessed 23 Aug 2019].
11 Zhang B, Zhai FY, Du SF, *et al*. The China Health and Nutrition Survey, 1989-2011. *Obes Rev* 2014;15 Suppl 1:2–7.
12 Zhang Z, Liu M, Zhou C, *et al*. Evaluation of dietary niacin and new-onset hypertension among Chinese adults. *JAMA Netw Open* 2021;4:e2031669.
13 Liu M, Zhou C, Zhang Z, *et al*. Inverse association between riboflavin intake and new-onset hypertension: a nationwide cohort study in China. *Hypertension* 2020;76:1709–16.
14 Liu C, Meng Q, Zu C, *et al*. U-shaped association between dietary thiamine intake and new-onset diabetes: a nationwide cohort study. *QJM* 2022;115:822–9.
15 Zhai F, Guo X, Popkin BM, *et al*. Evaluation of the 24-hour individual recall method in China. *Food Nutr Bull* 1996;17:1–7.
16 Brandt J, Welsh KA, Breitner JC, *et al*. Hereditary influences on cognitive functioning in older men: a study of 4000 twin pairs. *Arch Neurol* 1993;50:599–603.
17 Fong TG, Fearing MA, Jones RN, *et al*. Telephone interview for cognitive status: creating a crosswalk with the mini-mental state examination. *Alzheimers Dement* 2009;5:492–7.
18 Crimmins EM, Kim JK, Langa KM, *et al*. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *J Gerontol B Psychol Sci Soc Sci* 2011:i162–71.
19 Knopman DS, Roberts RO, Geda YE, *et al*. Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology* 2010;34:34–42.
20 Georgakis MK, Papadopoulos FC, Beratis I, *et al*. Validation of TICS for detection of dementia and mild cognitive impairment among individuals characterized by low levels of education or illiteracy: a population-based study in rural Greece. *Clin Neuropsychol* 2017;31:61–71.
21 Livingston G, Huntley J, Sommerlad A, *et al*. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet* 2020;396:413–46.

22 Prokopidis K, Giannos P, Ispoglou T, *et al*. Dietary fiber intake is associated with cognitive function in older adults: data from the national health and nutrition examination survey. *Am J Med* 2022;135:e257–62.
23 Kou C, Zhao X, Fan X, *et al*. Dietary sodium/potassium intake and cognitive impairment in older patients with hypertension: data from NHANES 2011-2014. *J Clin Hypertens* 2023;25:534–44.
24 Muth A-K, Park SQ. The impact of dietary macronutrient intake on cognitive function and the brain. *Clin Nutr* 2021;40:3999–4010.
25 Meador KJ, Nichols ME, Franke P, *et al*. Evidence for a central cholinergic effect of high-dose thiamine. *Ann Neurol* 1993;34:724–6.
26 Mineur YS, Picciotto MR. The role of acetylcholine in negative encoding bias: too much of a good thing? *Eur J Neurosci* 2021;53:114–25.
27 Zhang Y, Zhang Y, Yang S, *et al*. U-shaped relation of dietary thiamine intake and new-onset hypertension. *Nutrients* 2022;14:3251.
28 Valentine G, Sofuoglu M. Cognitive effects of nicotine: recent progress. *Curr Neuropharmacol* 2018;16:403–14.
29 Chinese Nutrition Society. *Reference intake of dietary nutrients for Chinese residents (2013)*. Science Press, 2014.
30 Gong W, Liu A, Yao Y, *et al*. Nutrient supplement use among the Chinese population: a cross-sectional study of the 2010-2012 China Nutrition and Health Surveillance. *Nutrients* 2018;10:1733.

Chengzhang Liu obtained his bachelor's degree in science in 2010 from Northeast Agricultural University in Heilongjiang Province, China. He focused on medical-related bioinformatics research at BGI in Shenzhen, China from 2010 to 2016. From 2016 to 2021, he engaged in epidemiology and statistics related to hypertension at the Shenzhen Evergreen Medical Institute in China. Currently, he is a postgraduate student at the Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China. His main research interests include the impact of nutrition and lifestyle factors on chronic non-communicable diseases, such as hypertension, diabetes, stroke, dementia, cognitive decline and depression.