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A PROSPECTIVE ASSOCIATION OF NUT CONSUMPTION WITH COGNITIVE FUNCTION IN CHINESE ADULTS AGED 55+ _ CHINA HEALTH AND NUTRITION SURVEY

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Abstract: *Objectives:* We aimed to investigate the association of nut intake with cognitive function in Chinese adults aged 55 and over. *Design:* This was a prospective open cohort study with repeated measurements of diet and cognition scores. *Participants/settings:* 4822 adults aged 55 and over participating in the China Health Nutrition Survey during 1991-2006. *Measurements:* Global cognitive function measured repeatedly in 1997, 2001, 2004, and 2006 using a subset of modified Telephone Interview for Cognitive Status; poor cognitive function was defined as cognition score<7. Nut consumption was collected using 3-day 24 recall method in 1991, 1993, and at surveys of cognition assessment. *Statistical analyses performed:* Multilevel mixed effect linear regression and logistic regression analysis were conducted to assess the association with cognitive function. *Results:* The unadjusted cognitive score decreased by 0.29 (95% CI 0.22-0.28) with one-year aging during 1997-2006. Nut intake of more than 10g/d was associated with higher cognition score by 0.63 points (95% CI 0.15-1.12) or 40% less likely to have poor cognitive function (OR 0.60, 95% CI 0.43-0.84) after adjusted for demographic, lifestyle behavioural, BMI, and energy intake. *Conclusions:* Nut consumption was inversely associated with cognition decline.

Key words: Nut consumption, cognition function, prospective association, China Nutrition and Health Survey.

Introduction

Preventing and managing highly prevalent chronic diseases including dementia, in addition to cardiometabolic conditions has become a challenge for public health and medical services in the rapidly aging China in recent decades (1, 2). Dementia is manifested by significantly more decline in cognition function such as thinking, reasoning, and remembering, than what occurs with normal aging. Studies have indicated that cognition decline involves oxidative stress (3), inflammations (4), and impaired endothelial function (5). While there is no targeted and effective treatment or cures for age-related cognition decline and neurogenerative diseases, more focus has been on dietary approaches to maintain or prevent cognition decline (6).

Nuts are a good source of unsaturated fatty acids, and are rich in fibre, minerals (potassium, calcium, and magnesium), vitamins (folate and E), phytosterols, and polyphenols. The effect of nut consumption on cognition function has been reviewed in a synthesis of 32 randomised control trials (7). These trials, lasting mostly for 3 months, indicated that nut consumption, especially walnut, improved significantly the endothelial function marked by flow-mediated dilation of 0.8% (7). Twelve intervention studies indicated that mixed nut consumption of 10-193g per day from 4 weeks to 2 years in healthy participants significantly reduced inflammatory markers of C reactive protein (CRP) by 5-75% (8). A prospective cohort study in the US using data from the Nurses' Health Study reported long-term consumption of mixed nuts more than 20g per day is associated with an increased global composite cognition score compared to non-consumers in older women aged 70 years over (9). The Doetinchem Cohort Study followed 2690 middle-aged men and women for 5 years and observed a positive association between cognition outcomes and nut consumption (10).

While studies about the effect/association of nut consumption on/with cognition have emerged, it has not yet been clarified in the general older population in China. The China Health and Retirement Longitudinal Study (CHARLS) reported that the cognitive score declined sharply with age and that the pattern differed by gender, education, residential region, and family economic resources, among those aged over 45 years, but nut consumption was not available to facilitate the investigation (1). China Health and Nutrition Surveys (CHNS) data suggested that nut consumption is becoming more common during the past two decades (11) and cognition function was assessed in a subgroup aged 55+. Using the available information, we aimed to assess the association of nut consumption with cognitive function among this population.

Methods

Study design and study sample

This is a longitudinal study based on repeated measurements of dietary intake during 1991-2006 and cognitive function in 1997-2006 using CHNS data.

The CHNS study is an ongoing open prospective household-based cohort study conducted in nine provinces in China (12, 13). CHNS uses a multistage random-cluster sampling process to select samples in both urban and rural areas. Nine waves of diet data collection during 1989-2011 have been completed. In

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1997, 2000, 2004 and 2006 surveys, cognitive screen tests were conducted in the group aged 55+. In total, 4822 participants attended the cognitive screen tests at least once. Among them, 2303 (47%) people entered the surveys in 1997, 836 (17%) started in 2000, 1031 (21%) were new participants in 2004, while 652 (14%) had their first cognition test in 2006. To sum up, more than two thirds (n=3229) had the cognition test at least twice, and 795 completed all 4 test rounds. Participants who completed at least one cognitive screening test were included in the analysis.

The survey was approved by the institutional review committees of the University of North Carolina (USA) and the National Institute of Nutrition and Food Safety (China). Informed consent was obtained from all participants. The response rate based on those who participated in 1989 and remained in the 2006 survey was >60%.

Outcome variable

The primary outcome was a cognitive score summed from the cognitive screening items used in CHNS. It is comprised of a subset of items from the Telephone Interview for Cognitive Status–modified (14). The tool has been used in other population studies in China to assess cognitive function (15). The test was conducted during a face to face interview with survey questionnaires. The cognition screening included immediate and delayed recall of a 10-word list (score 10 for each), counting backward from 20 (score 2), and serial 7 subtraction (score 5). The total global cognitive score ranges from 0 to 27. A high cognitive score represents a better cognition. We use a score below 7 as the cut-off for a poor cognitive function as it marked the first quintile and equivalent to the prevalence of cognitive impairment in Chinese population (16).

Exposure variables: cumulative mean nut intake

At each round of the survey, individual dietary intake data were collected by a trained investigator conducting a 24h dietary recall on each of 3 consecutive days. In addition, foods and condiments in the home inventory, foods purchased from markets or picked from gardens, and food waste were weighed and recorded by interviewers at the beginning and end of the three-day survey period. Detailed description of the dietary measurement has been published previously (12). Food consumption data was converted to nutrient intake using the Chinese Food Composition Table (17). The dietary assessment method has been validated for energy intake (18).

Nuts in this study were from the "nut and seed" group in Chinese Food Composition Table (17). They were walnut, chestnut, pine nut, almond, hazelnut, flax seed, peanut, lotus seed, sunflower seed, pumpkin seed, watermelon seed, and sesame.

We calculated a cumulative average intake of nuts for each individual at each round to reduce variation within individuals and to represent long term habitual intake (19). For example, the cumulative average nut intake in 1997 was the intake in 1991, 1993 and 1997. The nut consumption was categorized by a cut point of 10 grams/day into "0, 0.1-9.9, >=10" based on the distribution (6-9% of the population) and the existing evidence of long-term nut consumption of 10-193g/d (8).

Covariates

Sociodemographic and lifestyle factors were collected at each survey using a structured questionnaire. The following constructed variables were included to reflect socioeconomic status: education (low: illiterate/primary school; medium: junior middle school, and high: high middle school or higher), per capita annual family income (recoded into tertiles as low, medium and high), urbanization levels (recoded into tertiles as low, medium and high) (12).

Height, weight and blood pressure were measured at each round. Overweight/obesity was defined as BMI ≥25 kg/m^2. Hypertension was defined as systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg or having known hypertension.

Physical activity level (metabolic equivalent of task, (MET)) was estimated based on self-reported activities (including occupational, domestic, transportation, and leisure time physical activity) and duration using a Compendium of Physical Activities. Smoking status was categorized as non-smokers, ex-smokers and current smokers. Alcohol drinking, and self-reported diabetes were coded as yes or no.

Statistical analysis

Sample characteristics at the first cognition assessment were presented and compared by nut intake categories using ANOVA for continuous measures or chi-square test for categorical ones.

The association between repeated nut intake and cognitive function either as continuous or categorical outcome was assessed using multilevel mixed effect linear or logistic regression models with "mixed" or "melogit" command in STATA. A set of models were used: Model 1 adjusted for age, gender; Model 2 further adjusted for socioeconomic status of income, urbanization, education; Model 3 adjusted for behavioural factors of smoking, alcohol drinking, and physical activity; Model 4 adjusted for energy/macronutrients/selected vitamins (vitA, vitB, vitC vitE), and health factors of overweight/obesity, hypertension, and self-reported diabetes. The cognition score or poor cognition was modelled as a function of fixed effects, whereas individual participants variables were modelled as random effects. Both the intercept and slope were fitted with random-effects components to account for interindividual differences in baseline measures and rate of change (20). Categorical variables included in the models as dummies using the first category as reference as shown in Table 1. The association was expressed as beta coefficient (slope of the linear models) or odds ratio (relative odds from logistic models). A positive coefficient of nut

Table 1
Population characteristics at the first cognition assessment during 1997-2006 by nut intake (g/day) in China Health and Nutrition Survey (N=4822)

	intake 0 (n=4367)	0.1-9.9 (n=121)	>=10 (n=334)	p
Mean age (years SD)	62.9 (7.6)	67.2 (8.0)	62.0 (7.0)	<0.001
Sex				<0.001
Men	2046 (46.9%)	53 (43.8%)	197 (59.0%)	
Women	2318 (53.1%)	68 (56.2%)	137 (41.0%)	
Urbanization				<0.001
Low	1191 (27.3%)	15 (12.4%)	58 (17.4%)	
Medium	1228 (28.1%)	41 (33.9%)	81 (24.3%)	
High	1945 (44.6%)	65 (53.7%)	195 (58.4%)	
Income				<0.001
Low	1414 (32.8%)	32 (26.9%)	75 (22.7%)	
Medium	1333 (30.9%)	37 (31.1%)	82 (24.8%)	
High	1562 (36.2%)	50 (42.0%)	173 (52.4%)	
Education				<0.001
Low	2857 (74.2%)	78 (72.2%)	182 (59.5%)	
Medium	543 (14.1%)	12 (11.1%)	58 (19.0%)	
High	449 (11.7%)	18 (16.7%)	66 (21.6%)	
Overweight/obesity				0.11
No	2856 (72.5%)	81 (70.4%)	208 (67.1%)	
Yes	1083 (27.5%)	34 (29.6%)	102 (32.9%)	
Hypertension				0.49
No	2628 (65.3%)	71 (61.7%)	199 (62.8%)	
Yes	1394 (34.7%)	44 (38.3%)	118 (37.2%)	
Self-reported diabetes				0.143
No	3,781 (96.9%)	106 (93.8%)	291 (96.0%)	
Yes	121 (3.1%)	7 (6.2%)	12 (4.0%)	
Smoking				0.088
Non-smoker	2899 (67.7%)	89 (74.2%)	204 (62.4%)	
Ex-smokers	155 (3.6%)	6 (5.0%)	13 (4.0%)	
Current smokers	1227 (28.7%)	25 (20.8%)	110 (33.6%)	
Alcohol drinker				<0.001
No	2925 (69.6%)	88 (73.9%)	172 (53.3%)	
Yes	1277 (30.4%)	31 (26.1%)	151 (46.7%)	
Median METS (IQR)	15.1 (6.5-30.4)	13.3 (5.5-23.2)	16.2 (7.7-34.4)	0.004
Mean energy (Kcal/d SD)	2103.3 (827.6)	1970.1 (580.2)	2272.6 (666.7)	
Mean protein intake (g/d SD)	63.1 (23.6)	62.5 (24.4)	73.5 (23.8)	<0.001
Mean fat intake (g/d SD)	66.6 (69.3)	66.9 (33.9)	83.6 (42.3)	<0.001
Mean carbohydrate intake (g/d SD)	307.6 (110.7)	275.5 (82.8)	292.5 (90.2)	<0.001
Median vitamin A (μg/d IQR)	99.0 (24.0-256.4)	149.8 (56.0-335.4)	101.2 (23.4-334.0)	<0.001
Median thiamine (mg/d IQR)	0.8 (0.6-1.2)	0.8 (0.6-1.0)	1.0 (0.8-1.4)	0.001
Median vitamin C (mg/d IQR)	68.2 (43.8-102.6)	64.8 (38.6-96.8)	74.4 (47.6-105.4)	0.004
Median vitamin E (mg/d IQR)	8.8 (5.8-13.4)	9.0 (6.4-15.0)	14.4 (10.2-20.6)	0.001
Mean global cognitive score (SD)	13.2 (6.7)	12.6 (6.7)	15.0 (6.0)	<0.001
Global cognitive function categories				<0.001
>=7	3281 (82.2%)	89 (78.1%)	283 (91.6%)	
<7	710 (17.8%)	25 (21.9%)	26 (8.4%)	

Numbers in the table as means (SD or Inter Quarter Range) for continuous variables and number (%) for categorical ones; P from one-way ANOVA for age, mean daily energy/nutrients, cognition; K-Wallis test for micronutrients, physical activity METS; Chi-square test for categorical variables; Nut intake categorized using cumulative mean in 1991-2006 corresponding to the first cognition assessment.

Table 2
Regression coefficients or odds ratios (95% CI) for cognitive function by nuts intake among participants aged 55 +s in China Health and Nutrition Survey during 1997-2006 (N=4822)

	Model 1	Model 2	Model 3	Model 4	Sensitivity analysis
Global cognitive function score (beta coefficient)					
0	Reference (0.0)				
0.1-9.9	0.43 (-0.07-0.94)	0.05 (-0.43-0.53)	0.38 (-0.14-0.92)	0.29 (-0.25-0.83)	-0.07 (-0.90-0.76)
>=10.0	1.27 (0.80-1.73)	0.58 (0.13-1.03)	0.75 (0.27-1.23)	0.63 (0.15-1.12)	0.99 (0.05-1.93)
Poor global cognition function (<7 relative to >=7) (OR)					
0	Reference (1.0)				
0.1-9.9	0.96 (0.76-1.22)	1.08 (0.86-1.36)	0.91 (0.69-1.20)	0.99 (0.74-1.31)	1.22 (0.81-1.84)
>=10.0	0.49 (0.47-0.76)	0.65 (0.50-0.86)	0.56 (0.41-0.78)	0.60 (0.43-0.84)	0.54 (0.30-0.97)

Beta coefficient from mixed effect linear regression model and OR from mixed effect logistic regression model; Nut intake categorized using cumulative mean from 1991-2006; corresponding to the first cognition assessment; Model 1 adjusted for age, gender; Model 2 further adjusted for urbanization, education, and household income; Model 3 further adjusted for smoking, alcohol drinking, and physical activity; Model 4 further adjusted for BMI, hypertension, self-reported diabetes, energy/macronutrients/micronutrients intake; Sensitivity analysis included 795 participants attending all the surveys during 1997-2006 in Model 4; All the adjusted variables treated as time-varying covariates.

suggests that the factor was associated with increased cognition score, while OR>1 indicates the factor is positively associated with poor cognitive function.

To test the interaction between nut intake and other covariates (demographic, or socioeconomic factors, or BMI, or hypertension), a product term of these two variables was put in the regression model. Sensitivity analysis was conducted by including participants attended all 4 rounds of the survey between 1997 and 2006 (n=795).

All the analyses were performed using STATA 14.2 (Stata Corporation, College Station). Statistical significance was considered when p<0.05 (two sided).

Results

A total of 4822 adults aged 55+ years participated at least one cognition assessment during 1997-2006. 814 participants (16.9%) reported having nuts intake with an inter quartile range (IQR) of 5.53-20 g/d. Peanut was the most frequently consumed in the nut group (84.2%), and consumed fresh, or roasted, or fried. Other nuts reported included chestnut, sunflower seed, pumpkin seed, and walnut.

Table 1 showed the sample characteristics by nut intake at the first cognition test. Adults reporting high nut intake were younger compared to non-consumers. Those from highly urbanized area or having higher education or family income had higher nut intake. Nut intake did not differ by body weight, blood pressure, self-reported diabetes, and smoking. High nut consumers had higher macronutrient and vitamin intake compared to non-consumers or less consumers. The mean global cognitive score was 15.0 (95% CI 14.4-15.7) in higher consumers, significantly higher than less consumers (mean 12.6, 11.4-13.9) or non-consumers (mean 13.2, 95% CI 13.0-13.4). The proportion of poor cognitive function was 8.4% among high consumers, significantly lower than 17.8% in non-consumers or 21.9% in less consumers.

During the study period, global cognition score decreased significantly, and the proportion of poor cognition category (cognition score<7) increased. Among participants in all rounds of the survey, the mean cognition score decreased from 13.0 (SD 6.7) in 1997 to 12.9 (SD 6.4) in 2001, to 11.6 (SD 6.4) in 2004, and to 10.2 (SD 6.2) in 2006 and the decrease was 0.25 (95% CI 0.22-0.28) of one-year aging. The decrease was 0.10 (0.07-0.13) by survey year.

Poor cognition was significantly more likely in older and female participants. Participants from highly urbanized areas or having higher education or household income were less likely to have poor cognition function. When age and sex were adjusted, previous smoking increased the likelihood of poor cognition by 51%. Alcohol drinking, physical activity level, hypertension, and self-reported diabetes were not associated with declined cognition, while BMI>=25 kg/m^2 was inversely associated with poor cognition (OR: 0.66, 95% CI 0.57-0.77) (Supplement Table).

Nut consumption was significantly lower among those having cognitive function<7 (1.4 g/d vs 2.7g/d among those scored >=7) suggesting one-gram higher nut consumption was associated with decreased likelihood of poor function by 2% (OR 0.98, 95% CI 0.97-0.99), while the proportion of poor cognitive function was lower among consumers of over 10g/d (4.3% vs 8.3% among those scored >=7) by 43% (95% CI 0.33-0.57) (Supplement Table). After adjusting for age and sex in Model 1, the protective association remained significant (OR 0.49, 95% CI 0.47-0.76), and further adjustment for socioeconomic status, lifestyle factors, nutrients intake, and health factor did not change the association substantially (OR 0.60, 9% CI 0.43-0.84) (Table 2).

Using cognition score as the continuous outcome, the age and sex adjusted results showed high consumption was associated with increased score by 1.27 points (95% CI 0.80-

1.73); further adjustment for a series of covariate attenuated the association to a slope of 0.63 (95% CI 0.15-1.12) and it remained significant (Table 2).

The fully adjusted sensitivity analysis model including 795 participants of all the surveys showed consistently that high nut consumption was significantly associated with increased cognition score (beta or slop 0.99, 95% CI 0.05-1.93) or 46% less likely of poor cognition function (cognition score <7) (95% CI 0.30-0.97) (Table 2).

The association of nut consumption and global cognition score was not different among strata by age group, or socioeconomic, or BMI categories (data not show).

Discussion

This is the first report on the prospective association between cognition with nut intake in adults aged 55+ years participating in CHNS during 1991-2006.

We found in this population that 17% reported consuming nuts during the study period. The most consumed nut was peanuts. The peanut production increased steadily in China from 14.4 million tonnes in 2000 to 17.29 million tonnes in 2016 (21). The estimated annual per capita consumption slightly decreased from 13.7 kg in 2012 to 13.5 kg in 2016, though it was nearly doubled the consumption in American (22). Compared to the national consumption, mixed nuts consumption of 5.53-20 g/d in this population was far less. It may be due to the fact that a high proportion of peanut was used to produce peanut oil and peanut is a major oil-bearing crop in China (21).

Our results showed that a long-term high consumption of nuts (mostly peanuts) was associated with an increased global cognition score or less likelihood to have poor cognitive function after adjusted for potential confounders including demographic, lifestyle, and health factors. The strength of the association was equivalent to the natural two-year cognition decline, consistent with the report using American Nurses' Health Study in women aged above 70 years having nut 20g/d for 15-20 years (9). Stronger association was reported in a 5-y follow up of middle-aged Dutch men and women in the Doetinchem Cohort Study, in which the difference in cognition function between the lowest and the highest quintile of nut consumption was equivalence to 5-8 years' difference (10). Despite the differences in nut consumption, population profile, study design, diet and cognition function measurement in these cohort studies, results of the current and other prospective studies in general middle- or older aged populations were consistent showing a favourable association of nut intake with cognition.

Peanuts have similar nutrient profile to other tree nuts and are rich in unsaturated fat, folate, vitamin E, magnesium, potassium and arginine, and contain fibre and polyphenols (23). The benefits of peanut include their anti-inflammatory, antioxidant, or lipid-lowering effects (24-26), which improve vascular endothelial function (8, 27), and neurocognition, neuronal synchronization indicated by electroencephalography (28). In addition, a 12-week randomized crossover trial among overweight Australians aged 50-75 years suggested that consuming 56-84g/d of peanuts increased middle cerebral artery, elasticity of small artery and cognitive function (29).

Key strengths of our study include the longitudinal study design, multiple measurements of dietary intake and cognition function, relatively large sample size, and a 15 year follow up period. The use of cumulative intake from the repeated measure of 3-day dietary intake in combination with household food inventory provides a robust estimate of long-term nut intake. Diet intake was collected in the earlier rounds before cognitive impairment is present, therefore, it did not alter as a result of cognitive function. A series of confounding factors including sociodemographic, behavioural factors, nutrient intake, health factors were adjusted, but residual confounding is possible. For example, biochemical markers for inflammation were not available at any wave of the surveys for a comprehensive understanding the pathways between nut and cognitive function. Among the participants, only 16.9% reported nuts consumption, mostly peanut of an IQR was 5.53-20 g/d. The sample size, the amount and type of nut consumption were not sufficient or varied for dose response association and nut specific assessment. The global cognition in this study was relied on auditory and verbal processing skills. We did not have other cognition measures such as speed of processing or visual processing.

In summary, the current study showed that long-term high nut consumption was associated with better cognitive function and lower likelihood of cognition decline in Chinese adults aged 55+. Further studies are warranted to evaluate the effect size of nut consumption on cognitive function and to investigate if other nuts such as walnut, another native nut (30), confirm these findings.

Conflicts of interest: The authors have no conflict of interest to declare.

Ethical standard: The survey was approved by the institutional review committees of the University of North Carolina (USA) and the National Institute of Nutrition and Food Safety (China).

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