Original Article

Cognitive function and elderly macronutrient intakes from rural diets in Qingdao, China

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Background and Objectives: Energy provided by macronutrients plays a key role in healthy aging. This study therefore explored the association between macronutrients and cognitive function in elderly populations in rural areas of Qingdao, China. **Methods and Study Design:** This study included 1,504 participants over the age of 65 recruited from Licha Town, Qingdao City, China. Dietary intake was measured using the Food Frequency Questionnaire, and cognitive function was assessed using the Mini-Mental State Examination. Logistic regression models were used to evaluate the association between dietary macronutrient intake and cognitive function. In addition, restricted cubic bars were applied to determine the dose–response relationship between macronutrient ratios and cognitive performance. **Results:** A total of 877 adults over the age of 65 were included. After adjusting the weighted multiple variables, significant positive associations were revealed between protein and moderate carbohydrate intake and cognitive ability, but a negative association between fat intake and cognitive performance was identified. After calculating the daily energy supply ratio, similar associations were revealed between fat and protein intake and cognitive function. Furthermore, the ratio of proteins to carbohydrates had a U-shaped relationship with cognitive function ($p_{nonlinearity}$=0.674), whereas the ratio of proteins to fats was L-shaped with lower cognitive function ($p_{nonlinearity}$<0.001). Compared with the lowest quartile of the ratio of protein to fat intake, the weighted adjusted OR (95% CI) of the highest quartile was 0.509 (0.314, 0.827) for low cognitive performance. **Conclusions:** With an adequate carbohydrate supply, appropriately increasing dietary protein intake and reducing fat intake might benefit the cognitive function of elders in rural areas.

Key Words: macronutrients, cognitive function, older adults, rural area, ratios

INTRODUCTION

Improvements in socioeconomic conditions and medical treatment have resulted in a larger aging population globally, inevitably leading to increased health problems. The aging process is one of physiological decline, including in muscle, bone, and cognitive function. Cognitive function plays a key role in the health and living standards of the elderly population.[1] Mild cognitive impairment (MCI) is a common disease in the senior population. It is characterized by a decline in memory, attention, and cognitive function and is considered a transitional stage of evolutionary dementia with a conversion rate of 10%–15% per year.[2] Alzheimer disease (AD), also a form of dementia, is becoming a global health problem as the elderly population continues to increase.[3] Census data has predicted that by 2050, 13.8 million people in the United States alone will be diagnosed with AD.[4] The progression from cognitive decline to AD is a continuous irreversible process, thus taking steps to reduce or delay the onset of MCI and dementia is crucial. Because no definitive treatment for MCI or dementia currently exists, identifying lifestyle and other risk factors affecting cognitive function is essential for the prevention and treatment of AD.[5]

Dietary patterns and the intake of nutrients are reported to be closely associated with cognitive function. Food nutrients, such as long-chain omega-3 polyunsaturated fatty acids (n3-PUFA) and polyphenols including resveratrol and flavonoids, are likely to be beneficial to cognitive function.[6-9] In addition, a study based on the National Health and Nutrition Examination Survey revealed that dietary and total zinc, copper, and selenium intake were inversely associated with the prevalence of low cognitive performance, suggesting that dietary nutri-

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tion intervention might prevent cognitive decline.[10]

Currently, the focus in nutrition is returning on energy and macronutrients. Carbohydrates, proteins, and fats are the three essential energy-yielding nutrients for physical functions, and they play a key role in many biological processes. As structural and cell surface components, they are involved in essential cell recognition processes and metabolism.[11] Carbohydrates are the main energy source, providing energy for brain activity.[12] Amino acids in proteins are precursors of key neurotransmitters and play a vital role in neuromodulation,[13] and a meta-analysis of randomized controlled trials determined that fatty acids, such as n3-PUFA, could be mildly beneficial for improving memory function in older adults without dementia.[6] By contrast, multiple studies have demonstrated that high fat intake leads to the excessive production of circulating free fatty acids and inflammation throughout the body, which adversely affects cognitive function.[14,15] A study also reported that high protein intake was significantly associated with the increased frequency of MCI.[16]

Carbohydrates, proteins, and fats interact to maintain normal cognitive function; thus, some studies have attempted to analyze their association with cognitive function by calculating the proportion of energy provided by each of them.[16,17] However, epidemiological data on the association between macronutrients and cognitive decline in regions with a relatively low economic level, such as rural areas in China, remain limited. Therefore, we conducted a cross-sectional study to explore the association between macronutrients and cognitive function in the elderly population in a rural area of Qingdao, China. In addition, we estimated the percentage of energy supply in macronutrients, calculated the ratios of pairs of macronutrients based on energy intake, and explored potential dose–response relationships.

METHODS

Research participants

The cross-sectional study was conducted from January to July 2019 in Licha Town, Qingdao City, China. In this survey, researchers underwent uniform training and recruited 1,504 participants through face-to-face interviews. The inclusion criteria were as follows: People aged over 65, lived in the area for at least a year, were capable of self-managing daily life, without self-recognized cognition dysfunction and willing to participate in the study. Exclusion criteria for the participants were as follows: Individuals with severe illnesses (e.g., cancer, severe psychiatric disorders, recent history of heart or respiratory failure, chronic renal or liver failure); individuals with conditions known to influence cognitive function (e.g., alcohol abuse, cerebral apoplexy and infraction); individuals with neurological disease (e.g., AD, Parkinson's disease (PD)) or long-term frequent intake of antidepressants and other medications for neurological diseases; individuals lack of information on cognitive function and dietary intake. The study protocol was approved by the Medical Research Ethics Committee of Qingdao Center for Disease Control and Prevention (ID SPAQ-2016-125), and all participants were provided with written informed consent during the survey period and allowed to terminate their participation any time. Ultimately, 877 participants (395 men and 482 women) were included in this study.

Assessment of dietary intake

Dietary intake was measured by 97-item (such as whole grain, red meat, pork, beef, mutton, chicken, fish, vegetables, milk, eggs, fruit, nuts, cooking oil, soybeans and their products) Food Frequency Questionnaire (FFQ) and the dietary intake data was assessed through face-to-face recall interviews. The frequency (daily, weekly, monthly, or yearly) and how much they ate were studied. Based on the Chinese Food Ingredients Table (6th edition), the nutrient intake was converted using a nutrition calculator. The residual method was used to adjust the energy of each nutrient.

Assessment of cognitive function

Cognitive function was evaluated by the Chinese version of the Mini Mental State Examination (MMSE), which possessed good validity and reliability in cognitive screening and was applicable to the preferred scale for dementia screening.[18] As a cognitive screening test, MMSE is easy to operate and widely used. The scale includes the following 7 aspects: time orientation (5 points), location orientation (5 points), immediate memory (3 points), attention and calculation ability (5 points), delayed memory (3 points), language (8 points) and visual space (1 point). In this study, time and place orientation assessment required participants to tell the year, month, day, season and day of the week on the test day as accurately as possible, and to tell their city, district or county, street or township, community or village, and several floors as far as possible. The scores for each section were expressed in exact quantities that can be answered, ranging from 0 to 5. The immediate memory assessment required participants to repeat all three items after the questioner had said their names, with scores ranging from 0 to 3 on the correct number of items they could answer. The attention and calculation ability assessments asked participants to subtract 7 from 100 and say what was the result of each calculation, with scores on a scale of 0 to 5 expressed as the correct number of answers. The delayed memory assessment asked participants to repeat three of the things you have said before, with scores ranging from 0 to 3. For language assessment, participants were asked to performed as the instructions they heard, identify the items and name them correctly, with scores ranging from 0 to 8. The visual space assessment required participants to imitate the example diagram for drawing, and the score was based on the degree of characteristic fit of the simulated picture, and the score was 1. With a total score between 0 and 30, the higher the scores suggested the better the cognitive function. As is known, the MMSE is strongly influenced by educational background and varying cut-offs stratified by educational level are recommended for the purpose of improving the effectiveness of the screening. Consequently, the assessment criteria for cognitive impairment were: ≤17 for illiteracy individuals, ≤20 for individuals with 1-6 years of education, and ≤24 for individuals with 7 or more years of education. Meanwhile, a neurologist participated in our survey and assisted our cognitive evaluation with his clinical experience.

Covariates

We selected covariables based on the literature, MMSE scores and potential risk factors for cognitive function. This research included the self-reported questionnaire research of individuals' age, sex, educational level, income, smoking, drinking, history of chronic disease (diabetes, hypertension, dyslipidemia, heart problems and gout), Body mass index (BMI) and physical activities. BMI was calculated as the weight (kg) / height (m^2). Mini Nutritional Assessment Short Form (MNA-SF) was used to measure nutritional status, with score ranging from 0 to 14 and a higher score indicating better nutritional status.

Statistical analysis

If the continuous variables were normally distributed, the data was presented by mean and standard deviation (SD), otherwise by median and quartile range (IQR). According to the distribution of continuous variables, factorial design ANOVA analyses or Wilcoxon rank sum test were used to compare the average of continuous variables between the MCI group and the normal group. Pearson's Chi-square test or Fisher's Exact test were used to compare the distribution of category variables between the cognitively underperforming group and the cognitively normal group. Proteins, fats, carbohydrates, protein to fat ratio, protein to carbohydrate ratio, and fat to carbohydrate ratio were classified as quartiles and the higher the quartile, the higher the intake. Logistic regression analysis was used to study the relationship between macronutrients and cognitive function, and the intake of the lowest quartile was used as a reference. Rough models did not adjust any confounding factors, multivariate adjustment model for age (years), sex, marital status, smoking, drinking, chronic disease, BMI, physical activities and energy.

We used restricted cubic plot to further investigate the dose-response relationship between the ratios of macronutrient intake and low cognitive function after adjusting for the confounders. A multivariate linear regression model was established to analyze the MCI with multivariate adjusted ORs as the dependent variable and the ratios between macronutrients as the independent variable. All statistical analyses were performed using SPSS software (version 26.0) and Stata 15.0 (Stata Corporation, College Station, TX, USA). All the statistical analyses were performed at the conventional two-tailed alpha level of 0.05.

RESULTS

Dietary patterns and characteristics of the population by cognitive performance status

The dietary patterns of the elderly population in the rural area studied are presented in Supplementary Table 1. The consumption of grains, vegetables, red meat and poultry, eggs, beans, and nuts met dietary guideline recommendations, the consumption of plant oils was considerably higher than that recommended, but the consumption of whole grains, potatoes, and fruit was positively associated with cognitive function at Q2 and higher quantiles (Q3, Q4), respectively. slightly less than that recommended. The local elderly population seldom ate aquatic products.

Sample characteristics in relation to various measures of low cognitive performance are summarized in Table 1. Differences in sex, age, marital status, MNA, calf-circumference, and activity time between those with MCI and those with normal cognitive function were significant (p<0.001). Men (p=0.041), those of older age (p<0.001), and people who were unmarried or widowed were more likely to have poor cognitive performance. Compared with people with normal cognitive function, people with lower cognitive ability were more likely to have smaller calf and hip circumferences, higher rates of poor nutrition, and less daily activity.

Association between intake of macronutrients and the risk of MCI

Elderly people with normal cognitive performance consumed significantly more energy and macronutrients than those with MCI (Table 1). A higher percentage of fat energy supply was observed in elderly people with MCI, but this result was nonsignificant (p=0.116). The dietary intake of macronutrients was divided into four quartiles (Q1–Q4). Table 2 summarized the association between macronutrients and cognitive function. The OR with a 95% CI for cognitive function demonstrated that dietary protein intake was significantly positively associated with cognitive function. However, dietary fat intake was not significantly associated with cognitive function, but a higher intake of dietary carbohydrates (Q3, Q4) was significantly positively associated with cognitive function. After adjusting for potential confounders (age, sex, marriage, smoking, alcohol consumption, hypertension, diabetes, coronary heart disease, gout, dyslipidemia, daily activity time, and BMI), the same associations with cognitive function were identified for proteins, fats, and carbohydrates. After adjusting for energy, dietary protein intake was significantly positively associated with cognitive function. For dietary fat intake, the OR (95%CI) of Q2 was 1.614 (1.010–2.579), and the OR (95%CI) of Q3 was 1.823 (1.093–3.041). The OR (95%CI) of Q3 for carbohydrate intake was 0.528 (0.290–0.963).

With regard to percentages of energy supply (Supplementary Table 2), high protein energy supply ratios were positively associated with cognitive function, but the association was not linear. A high fat (Q4) energy supply ratio was negatively associated with cognitive function. No significant association between carbohydrate energy supply and cognitive function was identified.

Association between ratios of macronutrient intake and the risk of MCI

To further analyze the association between macronutrients and cognitive function, we calculated the ratio of pairs of macronutrients based on energy intake, as presented in Table 3. The OR of the 95% CI for cognitive function indicated that the highest ratio (Q4) of fats to carbohydrates exhibited a negative association with cognitive function. The ratios of proteins to carbohydrates and proteins to fats were significantly positively associated with cognitive function at Q2 and higher quantiles (Q3, Q4), respectively.

Table 1. Characteristics of the population by cognitive performance status

	Normal cognitive performance	MCI	*p*
Number	671	206	
Gender, Male, n (%)	315 (46.9)	80 (38.8)	0.041
Age (years)	71.54 (5.59)	74.78 (6.69)	<0.001
Education, n (%)			<0.001
Illiteracy	252 (37.6)	129 (62.6)	
Primary school	253 (37.7)	57 (27.7)	
Secondary school and above	166 (24.7)	20 (2.3)	
Marital status, n (%)			<0.001
Spinsterhood	4 (0.5)	4 9(1.9)	
Married	529 (78.8)	130 (63.1)	
Widowed	138 (20.6)	72 (35.0)	
Smoking, n (%)	176 (26.2)	45 (21.8)	0.205
Alcohol drinking, n (%)	184 (27.4)	45 (21.8)	0.111
MNA, n (%)			<0.001
Good nutritional status	553 (82.4)	148 (71.8)	
Underlying malnutrition	117 (17.4)	52 (25.2)	
Malnutrition	1 (0.1)	6 (2.9)	
BMI, kg/m^2	24.6 (3.84)	24.5 (3.50)	0.177
Calf circumference, cm	34.2 (3.64)	32.6(3.09)	<0.001
Waist circumference, cm	91.5 (36.8)	89.8 (9.13)	0.511
Hip circumference, cm	97.6 (8.47)	96.1 (±8.55)	0.031
Chronic disease history, n (%)			0.199
0	295 (44.4)	81 (41.1)	
1	255 (38.4)	69 (35.0)	
2	81 (12.2)	37 (18.8)	
3	20 (3.0)	5 (2.5)	
>3	13 (2.0)	5 (2.5)	
Physical activity, h/d	2.54(1.97)	2.00(1.77)	0.001
Energy intake, kcal/d	2088 (812)	1760 (769)	<0.001
Protein intake, g/d	81.0 (38.3)	62.44 (31.9)	<0.001
Animal sources, g/d	21.6 (16.6)	15.3 (11.7)	<0.001
Plant sources, g/d	59.8 (36.6)	48.3 (32.2)	0.056
Fat intake, g/d	73.3 (40.6)	65.3 (38.1)	0.002
Animal sources, g/d	21.8 (20.9)	14.35 (14.6)	<0.001
Plant sources, g/d	51.6 (30.4)	46.8 (26.8)	0.002
Carbohydrate intake, g/d	277 (129)	231 (127)	<0.001
Fiber intake, g/d	20.3 (9.75)	16.2 (9.34)	<0.001
Protein/energy, %	15.5 (3.9)	14.3 (4.4)	<0.001
Fat/energy, %	31.9 (12.5)	34.4 (14.9)	0.006
Carbohydrate/energy, %	52.7 (11.8)	51.4 (13.9)	0.116

After adjusting for potential confounding factors (age, sex, marriage, smoking, alcohol consumption, hypertension, diabetes, coronary heart disease, gout, dyslipidemia, daily activity time, and BMI), similar results were observed. After adjusting for energy, the ratio of proteins to fats was positively associated with cognitive function, and the ratio of proteins to carbohydrates exhibited a positive association with cognitive function at Q2 and Q3 quantiles. No significant association was identified in the fats to carbohydrates ratio.

To further and clearly reflect the dose–response relationships, a restricted cubic spline analysis was used, as depicted in Figure 1. The relationship between the ratio of fat to carbohydrate energy intake and cognitive function was not significant. For low cognitive function, we identified an L-shaped association with the ratio of proteins to fats and a U-shaped association with the ratio of proteins to carbohydrates. The prevalence of low cognitive function decreased with an increase in the protein to fat energy intake ratio in a linear dose-dependent manner ($p_{nonlinearity}$<0.001), and with an increase in the protein to carbohydrates ratio, a nonlinear dose-dependent relationship ($p_{nonlinearity}$=0.674) was observed. The MCI OR values exhibited a decreasing and then increasing trend.

DISCUSSION

Summary of the main findings

In this population-based cross-sectional study of older adults, we analyzed the association between three macronutrients (carbohydrates, proteins, and fats) and cognitive function. After adjusting for influencing confounders, these macronutrients were significantly associated with cognitive ability. Moreover, the ratio of proteins to fats, based on energy intake, exhibited a significant dose–response association with the cognitive performance of the elderly population.

Energy is essential for living things to maintain their basic functions. The total amount of macronutrients and the proportion of energy supply are closely related to a variety of physical functions, such as cardiovascular function, cognitive function, exercise ability, and basic metabolism.[19,20] As one of the three productive nutrients,

Table 2. Population odds ratios (95% confidence intervals) of cognitive performance status by quartiles of macronutrient intakes

Variables (g/d)	Normal	MCI	Model†	Model‡	Model§
Protein					
Q1 (lowest-52.4)	135	85	1 (reference)	1 (reference)	1 (reference)
Q2 (52.4-72.3)	174	45	0.411 (0.268, 0.629)	0.406 (0.259, 0.635)	0.437 (0.266, 0.719)
Q3 (72.3-97.7)	175	45	0.408 (0.267, 0.625)	0.430 (0.275, 0.670)	0.485 (0.275, 0.856)
Q4 (97.7-highest)	187	31	0.263 (0.165, 0.420)	0.285 (0.174, 0.465)	0.354 (0.160, 0.784)
Fat					
Q1 (lowest-42.2)	164	56	1 (reference)	1 (reference)	1 (reference)
Q2 (42.2-62.0)	161	59	1.073 (0.701, 1.642)	1.165 (0.747, 1.817)	1.614 (1.010, 2.579)
Q3 (62.0-95.0)	167	51	0.894 (0.578, 1.384)	1.043 (0.659, 1.651)	1.823 (1.093, 3.041)
Q4 (95.0-highest)	179	40	0.654 (0.414, 1.034)	0.786 (0.486, 1.273)	1.799 (0.995, 3.251)
Carbohydrate					
Q1 (lowest-173)	144	75	1 (reference)	1 (reference)	1 (reference)
Q2 (173-252)	161	59	0.704 (0.468, 1.059)	0.723 (0.472, 1.108)	0.868 (0.538, 1.402)
Q3 (252-339)	183	36	0.378 (0.240, 0.594)	0.386 (0.241, 0.617)	0.528 (0.290, 0.963)
Q4 (339-highest)	183	36	0.378 (0.240, 0.594)	0.401 (0.249, 0.646)	0.695 (0.310, 1.561)

†Crude model did not adjust any confounders.
‡Adjusted for age (years), gender, marital status, smoking status, alcohol drinking, chronic diseases, BMI and the activity time.
§Adjusted for age (years), gender, marital status, smoking status, alcohol drinking, chronic diseases, BMI, the activity time and the total energy.

Table 3. Population odds ratios (95% confidence intervals) of cognitive performance status by quartiles of macronutrient intakes' ratio

Variables (g/d)	Normal	MCI	Model†	Model‡	Model§
Protein					
Q1 (lowest-0.24)	151	68	1 (reference)	1 (reference)	1 (reference)
Q2 (0.24-0.29)	182	37	0.451 (0.286, 0.711)	0.436 (0.271, 0.701)	0.403 (0.249, 0.653)
Q3 (0.29-0.37)	169	50	0.657 (0.429, 1.006)	0.647 (0.414, 1.010)	0.605 (0.384, 0.952)
Q4 (0.37-highest)	169	51	0.670 (0.438, 1.024)	0.764 (0.490, 1.190)	0.690 (0.439, 1.085)
Fat					
Q1 (lowest-0.36)	178	43	1 (reference)	1 (reference)	1 (reference)
Q2 (0.36-0.56)	169	47	1.151 (0.724, 1.831)	1.167 (0.721, 1.887)	1.045 (0.641, 1.703)
Q3 (0.56-0.93)	167	53	1.314 (0.834, 2.069)	1.351 (0.843, 2.166)	1.256 (0.777, 2.030)
Q4 (0.93-highest)	157	63	1.661 (1.066, 2.587)	1.755 (1.108, 2.780)	1.542 (0.964, 2.466)
Carbohydrate					
Q1 (lowest-0.35)	151	68	1 (reference)	1 (reference)	1 (reference)
Q2 (0.35-0.52)	168	52	0.687 (0.450, 1.049)	0.657 (0.420, 1.027)	0.620 (0.393, 0.978)
Q3 (0.52-0.76)	171	48	0.623 (0.406, 0.958)	0.592 (0.377, 0.929)	0.566 (0.358, 0.896)
Q4 (0.76-highest)	181	38	0.466 (0.297, 0.733)	0.457 (0.285, 0.734)	0.496 (0.307, 0.801)

†Crude model did not adjust any confounders.
‡Adjusted for age (years), gender, marital status, smoking status, alcohol drinking, chronic diseases, BMI and the activity time.
§Adjusted for age (years), gender, marital status, smoking status, alcohol drinking, chronic diseases, BMI, the activity time and the total energy.

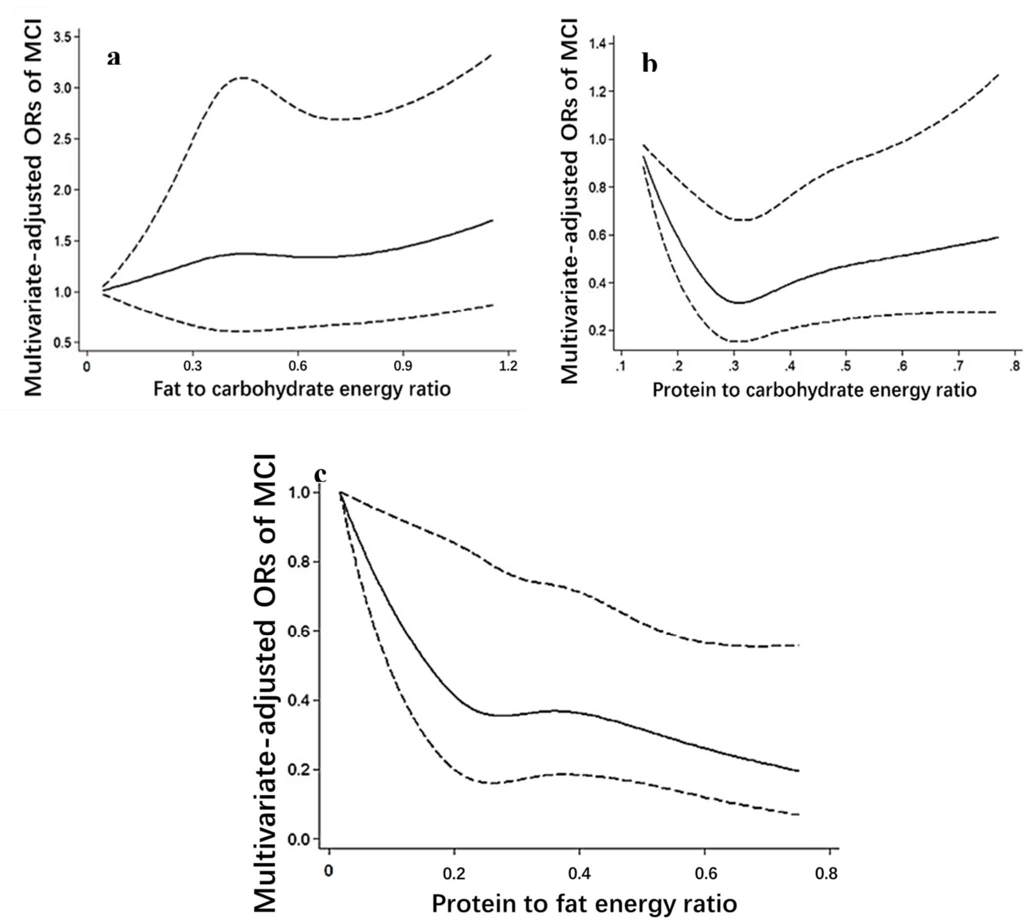

Figure 1. Restricted cubic spline model of the ORs of low cognitive performance (MCI) with ratios of nutrient intake for productivity, adjusted for age (years), gender (male, or female), BMI, smoking status, alcohol drinking, occupation, marriage, total daily energy intake (kcal/d). The solid lines represent the ORs, and dashed lines represent the 95% CIs. b) $p_{nonlinearity} = 0.674$; c) $p_{nonlinearity} < 0.001$.

proteins, such as those in lean meat and milk, play a key role in the maintenance of the human body's functions and health, and numerous studies have reported an association between dietary protein intake and cognitive function. Data on the US population aged 60 and older demonstrated positive associations between dietary protein intake and performance in a variety of cognitive domains. In addition, Roberts et al observed a significant association between dietary protein intake amounting to 16% to 20% of total energy intake and a reduced risk of MCI or dementia.[21] Our study also demonstrated that higher dietary protein intake was associated with improved cognitive function.[22] Tryptophan and tyrosine are precursors of key neurotransmitters that regulate cognitive function by influencing the synthesis and release of serotonin (5-hydroxytryptophan) and catecholamine neurotransmitters (dopamine, norepinephrine, and epinephrine).[23] Animal and human studies have demonstrated that tryptophan deficiency reduces signaling to serotonin receptors and tyrosine weakens dopamine function, leading to impairment in some areas of cognition.[24,25] Providing tryptophan and tyrosine supplements might have beneficial effects on emotional functioning and cognitive tasks in older adults.[26] In addition, several amino acids, such as arginine (nitric oxide and polyamines), histidine (histamine), and serine (phosphatidylserine), act as neuromodulators that affect cognitive function.[27] Moreover, malnutrition and weakness could lead to cognitive decline, and proteins could improve and prevent these conditions.[28] Therefore, we hypothesized that dietary proteins might prevent cognitive decline by improving nutritional status and vulnerability.[29] Studies have also demonstrated that the overconsumption of protein might be harmful to cognition, which is not consistent with our results.[16] However, our results demonstrated that Q3 of the protein energy supply ratio performed the best cognitive function, indicating that not the higher the protein intake is, the better cognitive performance is. The elderly population in the rural areas surveyed was still largely reliant on the crops they grew for their diet, and with their proteins derived primarily from grains, they required a higher protein intake to maintain cognitive function. But that did not mean that more protein was better. Overconsumption should also be avoided.

Fats are another major source of energy for the body and produce heat to protect the body from the cold. Many studies have verified the relationship between dietary fat intake and total intake with cognition function. Prospective population studies have demonstrated that the intake of total fat, high saturated fat, and cholesterol increase the risk of dementia. Total fat is particularly associated with vascular dementia because of its impact on cardiovascular structure and function, and thus, it is associated with AD. A randomized controlled clinical trial revealed that attention, speed, and mood were impaired in a group of young men (age: 22±1 years) who received a high-fat, low-carbohydrate diet for five days, suggesting that a high-fat diet might be harmful to the brains of healthy individuals.[30] In animal studies, rats on a long-term high-fat diet developed hippocampal microvascular insulin resistance and significantly reduced cognitive function.[31] As human and animal studies have demonstrated, this mechanism might be responsible for the increased risk of MCI caused by high fat intake. These studies are consistent with our findings that a high-fat diet is significantly negatively associated with cognitive function; the intake of unsaturated fat is also reported to be negatively associated with such function. Eating fish or foods containing polyunsaturated fatty acids could reduce this risk, such as in the "Mediterranean diet." N-3 fatty acids are known to be beneficial for neuroprotection,[32] but the intake of these fatty acids by the rural elderly population we surveyed was relatively low because of the low intake of aquatic products. We therefore hypothesized that the overconsumption of oils might be responsible for the increased risk of MCI.[33]

Carbohydrates are the largest productive nutrient and play a key role in the body's energy supply, making them essential for the prevention and treatment of cognitive diseases -they provide the nervous system with glucose, which is required continuously for normal function. A study of nutritional strategies for optimizing the cognitive function of the aging brain noted that adequate carbohydrate intake is critical to brain function because glucose is the main energy source for the brain. The brain requires about 25% of the total glucose energy consumed despite only comprising 2% of total body weight.[34] By contrast, a chronic excess of glucose consumption could lead to reduced synaptic plasticity and high levels of inflammation, which might contribute to cognitive deficits.[35] Notably, cognitive fatigue is common in older adults, which might be due to a decline in neuronal glucose utilization with age, possibly as the result of reduced brain sensitivity to insulin.[36]

Although all three macronutrients are associated with cognitive function, their proportions might be of more importance to cognitive function with respect to meeting energy requirements. Ding et al revealed a high percentage of energy intake from fats and proteins with low-energy intake from carbohydrates might be associated with cognitive decline.[16] We also analyzed the association between the energy supply ratio of macronutrients and cognitive function. Because the effect of the relationship among the three nutrients on cognition is not well understood, we calculated the ratio of pairs of productive nutrients based on energy intake and evaluated the dose–response relationship between cognitive function and these ratios. We determined that the energy ratio of fats to carbohydrates had no significant effect on cognitive function. This result indicates that neither high-carbohydrate and low-fat nor high-fat and low-carbohydrate diets are strongly associated with cognitive function. However, the energy ratios of proteins to carbohydrates and proteins to fats were revealed to have a significant effect on cognitive function, indicating that proteins might play a key role in cognitive function in the elderly population. As for the ratio of proteins to carbohydrates, we observed that the OR value decreased gradually with the increase in the ratio of proteins to carbohydrates within a certain range. When the ratio continued to increase, the OR value began to rise. We speculated that though proteins are beneficial for cognitive function, a high level of protein with a low-carbohydrate diet was not superior to the ratio at a moderate level. Notably, the energy ratio of proteins to fats exhibited a linear dose–response relationship with cognitive performance, suggesting that a higher amount of proteins relative to fats is more conducive to the maintenance of cognitive function with the same energy supply. As discussed previously, the fat intake of the elderly population in rural areas is mainly saturated fatty acids and n-6 polyunsaturated fatty acids (vegetable oil), and the intake of n-3 PUFA is low. However, the elderly population in rural areas might consume a certain amount of plant protein. The phytochemicals in plant-based food might help protect cognitive function; hence, a higher energy ratio of proteins to fats would benefit cognitive function. When this ratio increases, however, the OR value for MCI flattens, suggesting that too high a protein to fat ratio might not result in improved cognitive performance. In addition, the ratio of proteins to carbohydrates indicates that a diet too low in carbohydrates would also not improve cognitive performance; thus, the carbohydrate energy supply is essential for maintaining cognitive function. This is somewhat consistent with the macronutrient composition of healthy dietary patterns we reported previously, which was based on the consumption of rice and flour, red meat, poultry, vegetables, aquatic products, and fruits, which protect against cognitive dysfunction.[37] Therefore, we speculated that to maintain a sufficient carbohydrate energy supply, increasing the ratio of proteins to fats might be beneficial to the maintenance of cognitive function in the elderly population in rural areas.

In addition to the intake of macronutrients, we identified other potential risk factors for MCI in this study. Because of differences in socioeconomic status, physiological status, and access to health services, women have a significant cognitive disadvantage over men.[38] Moreover, studies have revealed that aerobic exercise could increase the volume of the hippocampus in later life and have a positive effect on memory performance, which is consistent with our findings.[39]

Advantages and limitations

Our study has several advantages. A major advantage is that we evaluated the association between macronutrients and cognitive function in a rural elderly population and also explored the association between their macronutrient ratios and cognitive function. The inverse relationship between "ratio of protein to fat intake" and low cognitive performance remained significant after adjustments for major confounders. In addition, we used restricted cube splines to investigate the dose–response relationship between each ratio and cognitive performance. Finally, combined with the results of our previous studies, we determined that lower consumption of coarse cereals, potatoes, fruits, red meat and poultry, eggs, and nuts was

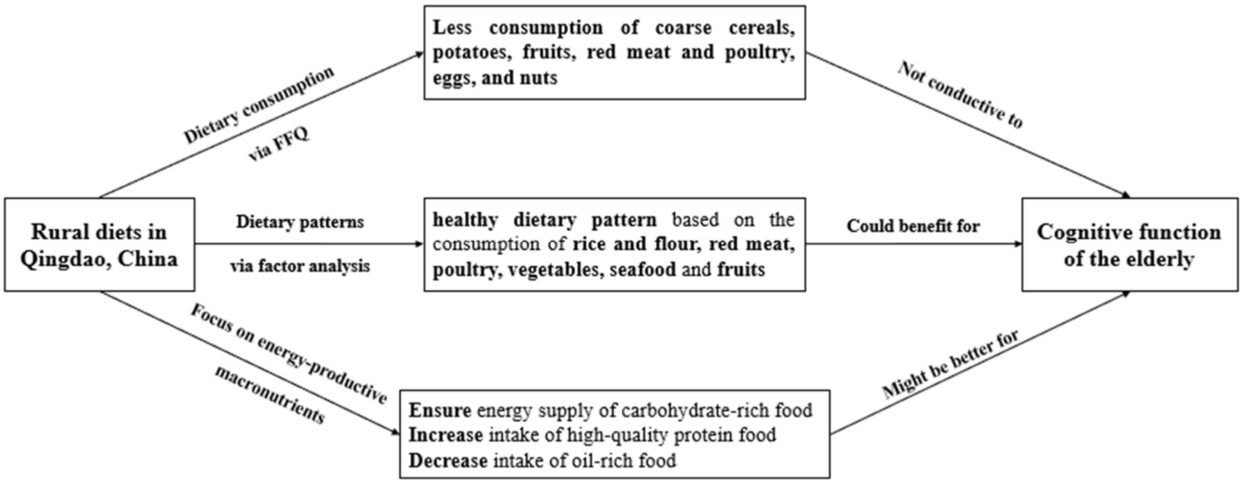

Figure 2. The association between rural diets and cognitive function in the elderly in Qingdao, combining with our previous work.

not conducive to cognitive function in the elderly population in rural areas in Qingdao. We also analyzed dietary patterns through a factor analysis and determined that healthy dietary patterns based on the consumption of rice and flour, red meat, poultry, vegetables, aquatic products, and fruits could benefit cognitive performance. In this study, we focused on energy-productive macronutrients and further analyzed the macronutrient intake characteristics of the diet of elderly people in rural areas, providing appropriate recommendations; we have clarified the association between diet and the cognitive function of the elderly population in the rural areas of Qingdao (Figure 2).

The potential limitations of our research should be acknowledged. First, this was a cross-sectional study, and the risk of unmeasured confounders from a large number of dietary, environmental, and lifestyle factors was high; we were thus unable to determine a causal relationship between dietary intake and poor cognitive performance. Further prospective cohort studies are necessary to confirm temporal relationships because individuals with the lowest cognitive performance might make poor decisions about their metabolic or activity status, and therefore, they might have lower levels of nutrient intake. Second, our dietary data were collected using the FFQ. Although this instrument is considered to have high validity, recall bias might exist in the self-reported dietary intake. Third, hypertension and diabetes were self-reported, which may lead to information bias. Moreover, this study only analyzed and discussed the energy supply ratio between macronutrients without further distinguishing the sources of the nutrients. To better understand the underlying mechanisms, macronutrients from different food sources should be analyzed separately. Finally, because the participants were recruited only from the rural area of Qingdao, any generalizations from the results of this study to other places and ethnic groups should be treated with caution.

Conclusions

Our study indicated that a dietary pattern with a high ratio of proteins to fats was negatively associated with the risk of MCI in older adults, and an L-type dose–response relationship was detected. Moreover, the relationship between moderate carbohydrate intake and the maintenance of cognitive function should not be disregarded. This result suggests that elderly people should increase their intake of high-quality protein-rich foods and decrease their intake of oil-rich foods by enriching their food sources and dietary structure while also ensuring an energy supply of carbohydrate-rich food such as grains, which might be of significance for the maintenance of cognitive function. However, because this was a cross-sectional study, further prospective cohort studies and research into the mechanisms involved are required to verify these findings. These findings could be valuable for guiding the elderly population in selecting an appropriate diet with balanced nutrition and benefits for their cognitive function.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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REFERENCES

1. Ashley S, Bradburn S, Murgatroyd C. A meta-analysis of peripheral tocopherol levels in age-related cognitive decline and Alzheimer's disease. Nutr Neurosci. 2021;24:795-809. doi: 10.1080/1028415X.2019.1681066.
2. Eshkoor SA, Hamid TA, Mun CY, Ng CK. Mild cognitive impairment and its management in older people. Clin Interv Aging. 2015;10:687-93. doi:10.2147/CIA.S73922.
3. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol.2018;25:59-70. doi: 10.1111/ene.13439
4. Hebert L, Weuve J, Scherr P, Evans D. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013;80:1778-83. doi:10.1212/WNL.0b013e31828726f5.

5. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's disease: past, present, and future. J Int Neuropsychol Soc. 2017;23: 818-31. doi: 10.1017/S135561771700100X.
6. Alex A, Abbott K, McEvoy M, Schofield P, Garg M. Long-chain omega-3 polyunsaturated fatty acids and cognitive decline in non-demented adults: a systematic review and meta-analysis. Nutr Rev. 2020;78:563-78. doi: 10.1093/nutrit/nuz073.
7. Kennedy D. Phytochemicals for improving aspects of cognitive function and psychological state potentially relevant to sports performance. Sports Med. 2019;49:39-58. doi: 10.1007/s40279-018-1007-0.
8. Howes M, Perry N, Vásquez-Londoño C, Perry E. Role of phytochemicals as nutraceuticals for cognitive functions affected in ageing. Br J Pharmacol. 2020;177:1294-315. doi: 10.1111/bph.14898.
9. Cicero A, Fogacci F, Banach M. Botanicals and phytochemicals active on cognitive decline: The clinical evidence. Pharmacol Res. 2018;130:204-12. doi: 10.1016/j.phrs.2017.12.029.
10. Li S, Sun W, Zhang D. Association of zinc, iron, copper, and selenium intakes with low cognitive performance in older adults: a cross-sectional study from National Health and Nutrition Examination Survey (NHANES). J Alzheimers Dis. 2019;72:1145-57. doi: 10.3233/JAD-190263.
11. Ernst B, Magnani J. From carbohydrate leads to glycomimetic drugs. Nat Rev Drug Discov. 2009;8:661-77. doi:10.1038/nrd2852.
12. Wang C, Szabo J, Dykman R. Effects of a carbohydrate supplement upon resting brain activity. Integr Physiol Behav Sci. 2004;39:126-38. doi: 10.1007/BF02734278.
13. Ruxton CHS, Derbyshire E. Which nutrients may contribute to healthy aging? A systematic review. Proceeding of the Nutrition Society. 2016;75:E164. doi: 10.1017/S0029665116001798
14. Tan BL, Norhaizan ME. Effect of high-fat diets on oxidative stress, cellular inflammatory response and cognitive function. Nutrients. 2019;11:2579. doi: 10.3390/nu11112579.
15. Netto Candido TL, Bressan J, Alfenas RCG. Dysbiosis and metabolic endotoxemia induced by high-fat diet. Nutr Hosp. 2018;35:1432-40. doi: 10.20960/nh.1792.
16. Ding BJ, Xiao R, Ma WW, Zhao L, Bi YX, Zhang Y. The association between macronutrient intake and cognition in individuals aged under 65 in China: a cross-sectional study. BMJ Open. 2018;8:e018573. doi: 10.1136/bmjopen-2017-018573.
17. Ugartemendia L, Bravo R, Castaño M, Cubero J, Zamoscik V, Kirsch P, Rodríguez A, Reuter M. Influence of diet on mood and social cognition: a pilot study. Food Funct. 2020;11:8320-30. doi: 10.1039/d0fo00620c.
18. Trivedi D. Cochrane Review Summary: Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Prim Health Care Res Dev. 2017;18:527-8. doi: 10.1017/S1463423617000202.
19. Casas R, Castro-Barquero S, Estruch R, Sacanella E. Nutrition and cardiovascular health. Int J Mol Sci. 2018;19: 3988. doi: 10.3390/ijms19123988.
20. Meeusen R, Decroix L. Nutritional supplements and the brain. Int J Sport Nutr Exerc Metab. 2018;28:200-11. doi: 10.1123/ijsnem.2017-0314.
21. Roberts R, Roberts L, Geda Y, Cha R, Pankratz V, O'Connor H, Knopman D, Petersen R. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. J Alzheimers Dis. 2012;32:329-39. doi: 10.3233/JAD-2012-120862.
22. Wu G. Dietary protein intake and human health. Food Funct. 2016;7:1251-65. doi: 10.1039/c5fo01530h.
23. Fernstrom J. Large neutral amino acids: dietary effects on brain neurochemistry and function. Amino Acids. 2013;45: 419-30. doi: 10.1007/s00726-012-1330-y.
24. Uchida S, Umeeda H, Kitamoto A, Masushige S, Kida S. Chronic reduction in dietary tryptophan leads to a selective impairment of contextual fear memory in mice. Brain Res. 2007;1149:149-56. doi: 10.1016/j.brainres.2007.02.049.
25. Harmer C, McTavish S, Clark L, Goodwin G, Cowen P. Tyrosine depletion attenuates dopamine function in healthy volunteers. Psychopharmacology. 2001;154:105-11. doi: 10.1007/s002130000613.
26. Hensel C, Becker M, Düzel S, Demuth I, Norman K, Steinhagen-Thiessen E, Gallinat J, Lindenberger U, Kühn S. Influence of nutritional tyrosine on cognition and functional connectivity in healthy old humans. NeuroImage. 2019;193: 139-45. doi: 10.1016/j.neuroimage.2019.03.005.
27. Rajagopal S, Sangam S, Singh S, Joginapally V. Modulatory effects of dietary amino acids on neurodegenerative diseases. Adv Neurobiol. 2016;12:401-14. doi: 10.1007/978-3-319-28383-8_22.
28. Mantzorou M, Vadikolias K, Pavlidou E, Serdari A, Vasios G, Tryfonos C, Giaginis C. Nutritional status is associated with the degree of cognitive impairment and depressive symptoms in a Greek elderly population. Nut Neurosci. 2020;23:201-9. doi: 10.1080/1028415X.2018.1486940.
29. Crichton G, Murphy K, Bryan J. Dairy intake and cognitive health in middle-aged South Australians. Asia Pac J Clin Nutr. 2010;19:161-71.
30. Holloway CJ, Cochlin LE, Emmanuel Y, Murray A, Codreanu I, Edwards LM et al. A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. Am J Clin Nutr. 2011;93:748-55. doi: 10.3945/ajcn.110.002758.
31. Kothari V, Luo Y W, Tornabene T, O'Neill A M, Greene M W, Geetha T, Babu J R. High fat diet induces brain insulin resistance and cognitive impairment in mice. Bba-Mol Basis Dis. 2017;1863:499-508. doi: 10.1016/j.bbadis.2016.10.006.
32. Ooi C P, Loke S C, Yassin Z, Hamid T A. Carbohydrates for improving the cognitive performance of independent-living older adults with normal cognition or mild cognitive impairment. Cochrane Database Syst Rev. 2011;2011: CD007220. doi: 10.1002/14651858.CD007220.pub2.
33. Hill M, Takechi R, Chaliha D, Albrecht M, Wright J, James A, Clark K, Dhaliwal S, Lam V, Mamo J. Dietary saturated fats and apolipoprotein B48 levels are similarly associated with cognitive decline in healthy older aged Australians. Asia Pac J Clin Nutr. 2020;29:537-44. doi: 10.6133/apjcn.202009_29(3).0012.
34. Sokoloff L. Energetics of functional activation in neural tissues. Neurochem Res. 1999;24:321-9. doi: 10.1022534709672.
35. Stefanidis A, Watt MJ. Does too much sugar make for lost memories? J Physiol. 2012;590:3633-4. doi: 10.1113/jphysiol.2012.235028.
36. Galeffi F, Shetty PK, Sadgrove P, Turner DA. Age-related metabolic fatigue during low glucose conditions in rat hippocampus. Neurobiol Aging. 2015;36:982-92. doi: 10.1016/j.neurobiolaging.2014.09.016.
37. Ding K, Zhou H, Gao T, Xu R, Chen L, Cai J, Zhang H, Zhong F, Ma A. Dietary patterns and cognitive function in older adults residing in rural China. Asia Pac J Clin Nutr. 2021;30:253-62. doi: 10.6133/apjcn.202106_30(2).0010.
38. Zhang Q, Wu Y, Han T, Liu E. Changes in cognitive function and risk factors for cognitive impairment of the elderly in

China: 2005-2014. Int J Environ Res Public Health. 2019;16:2847. doi: 10.3390/ijerph16162847.
39. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011;108:3017-22. doi: 10.1073/pnas.101595010.

Supplementary table 1. Dietary patterns of the elderly in rural area of Qingdao

Food groups, g/d	Local senior citizens	Dietary Guidelines for Chinese residents (2016)
Grains and potatoes	357 (150, 664)	250-400
Whole grains and legumes	42.9 (0, 157)	50-150
potatoes	14.3 (0, 57.1)	50-100
vegetables	446 (297)	300-500
fruits	140 (0, 200)	200-350
Red meat and poultry	46.4 (8.57, 95.7)	40-75
aquatic products	1.61 (0, 15.0)	40-75
eggs	42.0 (14.3, 50.0)	40-50
Milk and milk products	17.0 (0, 104)	300
Beans and nuts	26.5 (0, 43.9)	25-35
oils	65.5 (38.5)	25-30

Supplementary table 2. Population odds ratios (95% confidence intervals) of cognitive performance status by quartiles of macronutrients energy supply ratios

Variables (g/d)	Normal	MCI	Model†	Model‡
Protein				
Q1 (lowest-12.5)	135	74	1 (reference)	1 (reference)
Q2 (12.5-14.9)	168	56	0.610 (0.427, 0.873)	0.581 (0.402, 0.839)
Q3 (14.9-17.4)	184	36	0.363 (0.245, 0.538)	0.357 (0.239, 0.533)
Q4 (17.4-highest)	175	45	0.475 (0.327, 0.690)	0.475 (0.324, 0.697)
Fat				
Q1 (lowest-22.9)	172	43	1 (reference)	1 (reference)
Q2 (22.9-31.1)	166	53	1.273 (0.860, 1.885)	1.227 (0.822, 1.831)
Q3 (31.1-41.1)	165	54	1.321 (0.894, 1.952)	1.312 (0.880, 1.956)
Q4 (41.1-highest)	158	61	1.547 (1.053, 2.271)	1.549 (1.045, 2.298)
Carbohydrate				
Q1 (lowest-44.3)	157	60	1 (reference)	1 (reference)
Q2 (44.3-53.2)	170	47	0.731 (0.502, 1.067)	0.703 (0.478, 1.036)
Q3 (53.2-61.5)	170	49	0.766 (0.527, 1.113)	0.770 (0.525, 1.130)
Q4 (61.5- highest)	165	53	0.849 (0.587, 1.228)	0.823 (0.563, 1.202)

†Crude model did not adjust any confounders.
‡Adjusted for age (years), gender, marital status, smoking status, alcohol drinking, chronic diseases, BMI and the activity time.