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The association of dietary choline intakes with cognitive function among the older people in underdeveloped regions: findings from the NCDFaC study

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Abstract

Objectives We aimed to investigate the associations between dietary choline, its subtypes, and cognitive function in older adults from underdeveloped regions of China, using data from the Nutrition and Chronic Disease Family Cohort (NCDFaC) study.

Methods This cross-sectional study included 1 522 older adults aged 60 and over. Dietary choline intakes were assessed using a food frequency questionnaire, and cognitive function was evaluated with the Mini-Mental State Examination (MMSE). The associations between choline intake and mild cognitive impairment (MCI) were analyzed using logistic regression models, restricted cubic splines and propensity score matching (PSM).

Result Among the 1 522 participants, 292 (19.2%) were diagnosed with MCI. Compared to those in the lowest quartile of total choline intake, participants in the 2nd quartile (169.0 mg/[1000 kcal*d]) had lower odds of MCI, with an OR (95% CI) of 0.63 (0.42, 0.94). Similarly, participants in the 2nd (116.0 mg/[1000 kcal*d]) and 3rd (148.0 mg/[1000 kcal*d]) quartiles of phosphatidylcholine intake had reduced odds of MCI, with ORs (95% CI) of 0.59 (0.39, 0.88) and 0.60 (0.40, 0.91), respectively. For free choline intake, the highest quartile (74.2 mg/[1000 kcal*d]) was associated with an OR (95% CI) of 0.55 (0.35, 0.86). After PSM, higher intakes of total choline and phosphatidylcholine remained associated with lower odds of MCI.

Conclusion Moderate to high dietary intakes of total choline, phosphatidylcholine, and free choline may be associated with lower odds of MCI among older adults in underdeveloped regions.

Keywords Dietary choline, Cognitive function, Older people, Underdeveloped regions

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Introduction

Dementia is a progressive neurocognitive disorder characterized by insidious cognitive and functional decline until death. At present, the number of people with dementia is expected to grow significantly, reaching an estimated 152.8 million worldwide by 2025 [1]. Mild cognitive impairment (MCI) is a transitional stage between healthy aging and dementia and is considered a window period for intervening and delaying dementia [2]. MCI is a proximal risk factor for dementia, falls, and higher health expenditure, and the risk increases proportionally with the number of impaired cognitive domains and symptom severity [3–5]. Adequate nutrition plays a vital role in maintaining cognitive function during aging, with poor nutrition identified as a risk factor for MCI [6–8].

Nutrition plays a critical role in maintaining normal cognitive function, as evidenced by numerous studies. Furthermore, randomized controlled trials have substantiated the significance of nutritional interventions in mitigating cognitive decline or improving cognitive function in individuals with MCI [9, 10]. Choline is an essential nutrient with various biological functions, and it widely exists in a variety of foods [11]. Researchers found dietary choline has a protective effect on nerves and memory [12]. Some animal experiments and population studies have proved a correlation between dietary choline intake and cognitive function in childhood [12, 13]. Previous studies found that total choline intake was positively correlated with the performance of memory tasks and inversely correlated with dementia [14, 15], while others reported that low choline intake was associated with higher odds of incident dementia and Alzheimer's disease (AD) among middle-aged and elderly people [16]. However, the relationship between choline and predementia or MCI is still unclear among the elderly. Similarly, the subtypes and derivatives, such as free choline and phosphatidylcholine are still to be studied. Furthermore, previous studies have been based on results from populations with moderate to high levels of socioeconomic status [14–17], and few studies focus on low levels of socioeconomic status, especially in undeveloped areas.

To address the limitations within this field, we aim to access the associations of choline and its subtypes with MCI among the elderly population in China through the use of the data from the Nutrition and Chronic Disease Family Cohort (NCDFaC) study.

Methods

Study design and participants

The NCDFaC study was established in the Shanxi Province based on the China National Nutrition and Health Survey (CNNHS) [18]. The six regions in Shanxi that participated in the survey were underdeveloped, characterized by low economic development, inadequate infrastructure, and limited public services. Residents of these regions were invited to join the CNNHS in 2002, and the NCDFaC followed them up in 2015 [19]. This study used cross-sectional data from the 2015 follow-up survey, which was the first to document cognitive function. A total of 1 645 people aged 60 or over participated in the 2015 assessment, 98 participants were excluded due to incomplete cognitive function data, and an additional 25 participants were excluded due to missing dietary information. Ultimately, 1 522 participants were included in this study. The flowchart of inclusion screening process is illustrated in eFigure 1.

The NCDFaC was approved by the ethics committee of the National Institute for Nutrition and Health of the Chinese Center for Disease Control and Prevention (Grant no. 2015-019), and all participants obtained written informed consent (or their proxies).

Assessment of choline intake

Dietary intake over the prior year was assessed by a 40-item food frequency questionnaire (FFQ), which has been verified for reliability and validity in previous study [20]. In addition, we also compared the nutrient intakes between FFQ and 24-hour dietary recall in this study population (eTable1). Participants were asked to report the consumption frequency and amount of each food item or food group. Consumption frequency was ascertained with the following questions: [1] how many times per day; [2] how many times per week; [3] how many times per month; or [4] how many times per year. Consumption frequency was uniformly converted to average daily frequency based on the above responses. The dietary intake amount of each food item was calculated by multiplying the average daily frequency and amount of consumption per time.

We estimated the total choline and other nutrients for each of the 40 food items according to published data by Zeisel et al. [21]. Total choline refers to a sum intake of free choline, glycerophosphocholine, phosphocholine, phosphatidylcholine, and sphingomyelin. In this study, dietary choline intake was calculated as the amount of choline per 1000 kcal of energy intake. Finally, participants were divided into four groups according to quartile. Furthermore, referring to the USDA classification of food sources [22], we classified food items into eggs, meat and fish, whole grains, breakfast cereal, milk and dairy products, tubers, vegetables and fruits, bean products, and others, then we calculated the main food sources of total dietary choline based on this classification.

Assessment of cognitive function

Cognitive function was measured using the validated Chinese version of the Mini-Mental State Examination (MMSE) [23, 24]. The MMSE includes five main cognitive domains: Orientation to time and place (10 points), Registration (3 points), Attention and calculation (5 points), Recall (3 points), Language and constructional ability (9 scores), with total scores ranging from 0 to 30 [25].

Scores below 24 are defined as MCI, while scores equal to or greater than 24 are defined as normal [26]. The test was executed by the interviewer face to face, and to reduce the investigation bias, interviewers were professionally trained. Additionally, we assessed the five cognitive domains of the MMSE to explore specific cognitive areas potentially affected in participants. Functional impairment was defined as a score below the 75th percentile in each domain [27].

Assessment of covariates

Information on covariates was obtained from the baseline data, including age, sex, dietary energy, education levels, marital status, waist circumference, history of hypertension, diabetes, hyperlipidemia, cardiovascular and cerebrovascular diseases (CVDs), current smoking status, drinking status, active physical activity, dietary intake of saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, protein, carbohydrate and fiber, sleep quality score, and dietary quality score.

Data on waist circumference (cm) was collected by trained surveyor. The intakes of dietary energy and nutrients were estimated based on FFQ through the Chinese food composition table, which offers detailed nutritional data for thousands of foods consumed in China [28]. Education level was divided into three levels, which were no formal education, junior high school and below, or senior high school and above. Marital status was dichotomized as married or non-married, with non-married including those never married, divorced, widowed, or separated. Drinking status was self-reported and defined as if one or more drinks of alcohol were consumed before the last 12 months. Total metabolic equivalents (METs) per week of physical activity were estimated based on the frequency, intensity, and duration of four types of physical activity: occupational activities, transportation, leisure activities, and housework [29]. Physical activity was classified as 'active' if an individual's level of physical activity exceeded the mean METs per week. Blood pressure was measured and fasting blood was collected for each participant. Hypertension was defined as diagnosed hypertension by a doctor, systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication. Diabetes was defined as diagnosed diabetes by a doctor, use of diabetes medication, or fasting glucose levels ≥ 7.0 mmol/L. Hyperlipidemia was defined as fasting triglycerides ≥ 2.26 mmol/L or total cholesterol ≥ 6.22 mmol/L [30]. CVDs were defined as a self-report of a coronary heart disease or stroke diagnosis. Sleep quality score was assessed with the Athens Insomnia Scale (AIS) [31], with a score from 0 to 21, where a higher score reflects worse insomnia. Dietary quality scores were calculated based on the Eastern diet pattern and Chinese dietary guidelines, consisting of 11 indicators [32]. Each indicator was scored as follows: 0 for meeting recommendations, -1 for insufficient intake, and + 1 for excessive intake. The total dietary quality score, ranging from 0 to 11, was calculated as the sum of the absolute values of each indicator, with higher scores reflecting poorer diet quality.

Statistical analysis

Participant baseline characteristics between normal and MCI were compared by Wilcoxon test for continuous variables and by chi-square tests for categorical variables, and the characteristics were respectively expressed as mean (Standard Deviation, SD) and percentages for continuous and categorical variables. Missing data (eTable2) were interpolated by multiple imputation method, and 10 databases were created during this process.

Dietary choline intake was divided into four groups according to quartiles, and the lowest quartile was defined as the reference group. Logistic regression models were used to estimate the association of dietary choline intake with MCI, odds ratio (OR) and its 95% confidence intervals (CIs). We also used restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th centiles to flexibly model the association between choline intake and the ORs of MCI. In addition, we used propensity score matching (PSM) to perform 1:1 matching between the case and control groups based on age, sex, education levels, marital status, waist circumference, history of hypertension, diabetes, hyperlipidemia and CVDs, current smoking status, and drinking status, and logistic regression models were used among those who were successfully matched.

Confounders in the analyses were selected based on the established risk factors for dementia, previously published associations with dementia [33], or associations with exposures or outcomes in the current analysis. The multivariable model adjusted for age (continuous, years), sex (male or female), dietary energy (continuous, kcal/d), education levels (no formal education, junior high school and below or senior high school and above), marital status (married or non-married), waist circumference (continuous, cm), history of hypertension(yes or no), diabetes (yes or no), hyperlipidemia(yes or no), and CVDs (yes or no), current smoking status (yes or no), drinking status (yes or no), active physical activity (yes or no), dietary saturated fatty acids (continuous, g/d), dietary monounsaturated fatty acids (continuous, g/d), dietary polyunsaturated fatty acids (continuous, g/d), dietary protein (continuous, g/d), dietary carbohydrate (continuous, g/d), dietary fiber (continuous, g/d), sleep quality score (continuous), and dietary quality score (continuous).

To evaluate the robustness of our results, we conducted three sensitivity analysis: [1] Sensitivity analyses were performed using an alternative cutoff of 18 for MCI to account for the specific characteristics of the NCDFaC study population and validate the stability of our results [34]; [2] Analyses were repeated using the dataset without interpolation; and [3] E-values were calculated to assess the impact of potential unmeasured confounding on the observed associations [35]. Additionally, extended explorations were performed by analyzing the associations between dietary choline intake and five specific cognitive domains to investigate nuanced impairments [36].

All statistical analyses were analyzed with the use of R Studio 4.2.1, and all P values were 2-tailed ($\alpha = 0.05$).

Result

Participants characteristics

Among the 1 522 participants aged 60 or over, there were 292 (19.2%) participants with MCI, and the characteristics of the participants by cognitive status are listed in Table 1. Compared to individuals with normal cognition, those with MCI were more likely to be female, older, unmarried, and non-smokers or non-drinkers. They are also less likely to have a higher level of education, active physical activity, or have higher intake of dietary protein, carbohydrate, fiber, and energy. For the participants, the mean (SD) dietary intakes of total choline, phosphatidylcholine, and free choline were 214.1 (97.65) mg/[1000 kcal*d], 152.4 (80.9) mg/[1000 kcal*d], and 39.2 (27.4) mg/[1000 kcal*d], respectively. And we found that the primary dietary sources of total choline in this population were eggs, vegetables and fruits, whole grains, meat and fish (Fig. 1).

Association of daily dietary choline intake and MCI

The results of the unadjusted and multi-adjusted analyses of associations between daily choline intake and MCI are summarized in Table 2. There were inverse associations between choline with MCI. Compared to those in the lowest quartile of total choline intake (128.0 mg/[1000 kcal*d]), participants in the 2nd quartile (169.0 mg/[1000 kcal*d]) had lower odds of MCI, with an OR (95% CI) of 0.63 (0.42, 0.94). Similarly, participants in the 2nd (116.0 mg/[1000 kcal*d]) and 3rd (148.0 mg/[1000 kcal*d]) quartiles of phosphatidylcholine intake had reduced odds of MCI, with ORs (95% CI) of 0.59 (0.39, 0.88) and 0.60 (0.40, 0.91), respectively. For free choline intake, the highest quartile (74.2 mg/[1000 kcal*d]) was associated with an OR (95% CI) of 0.55 (0.35, 0.86). Dose-response associations of dietary choline intake with MCI are shown in Fig. 2.

After using PSM to match participants, a total of 532 participants completed the match and the characteristics of the participants after matching are listed in eTable3. The results of the logistic regression models from PSM are shown in Table 3. We found that the association between higher total dietary choline or phosphatidylcholine intakes and lower odds of MCI persisted.

Association of daily dietary choline intake and specific cognitive domains

Moreover, we explored the association of dietary choline intake with 5 cognitive domains. The results suggested that higher intakes of total choline and phosphatidylcholine are associated with lower odds of functional impairment in the dimension of recall, while a higher intake of free choline was associated with lower odds of functional impairment in the dimension of registration (eTable7).

Sensitivity analyses

To assess the robustness of our result, we redefined MCI using an 18-point cut-off, 421 (27.7%) out of 1 522 were considered MCI patients. The association between total choline or free choline intake and low odds of MCI still remained, but the significance of phosphatidylcholine disappeared (eTable4). We also used the same statistical method to analyze the data without interpolation, and the results obtained are shown in eTable5. The results showed that the association between choline intake and MCI exhibited only slight variations from the primary results following adjustment for multiple variables. Furthermore, E-values were 2.6 (1.3), 2.7 (1.4), and 3.0 (1.6) for total choline, phosphatidylcholine, and free choline intakes (eTable6).

Discussion

In this cross-sectional study involving older adults residing in undeveloped regions of China, we found that the main dietary choline of the participants was eggs, vegetables and fruits, whole grains, meat and fish. The moderate to high total choline intake, phosphatidylcholine, and free choline were associated with lower odds of MCI. For specific cognitive domains, higher intakes of total choline and phosphatidylcholine are associated with lower odds of functional impairment in recall, and higher intake of free choline was associated with lower odds of registration. Our findings provide valuable insights into the dietary choline intake levels among the elderly population in underdeveloped regions of China. These findings can assist health institutions understand choline intake patterns and provide evidence to support the nutritionists in developing specific choline intake recommendations to prevent MCI in this population.

Prior studies have identified an association between choline and cognitive function [14–17]. A study from

Table 1 Basic characteristics of participants

Characteristic	Normal	MCI	*P* -value
Participants, **n (%)**	1230 (80.8)	292 (19.2)	
Sex, **n (%)**			< 0.001
Male	637 (53.6)	112 (40.1)	
Female	552 (46.4)	167 (59.9)	
Age, **mean (SD)**, **(years)**	67.7 (6.8)	72.7 (7.9)	< 0.001
Waist circumference, **mean (SD)**, **(cm)**	81.7 (11.4)	80.3 (10.6)	0.09
Education levels, **n (%)**			< 0.001
No formal education	66 (5.4)	85 (29.5)	
Junior high school and blow	1003 (82.6)	188 (65.3)	
Senior high school and above	146 (12.0)	15 (5.2)	
Marital status, **n (%)**			< 0.001
Married	1054 (86.7)	221 (76.5)	
Non-married	161 (13.3)	68 (23.5)	
Diseases history, **n (%)**			
Hypertension	417 (34.2)	101 (35.3)	0.78
Diabetes	102 (8.5)	31 (10.9)	0.25
Hyperlipidemia	156 (12.9)	14 (4.9)	< 0.001
CVDs	214 (17.4)	56 (19.2)	0.53
Current smoking, **n (%)**			< 0.001
Yes	303 (24.7)	38 (13.1)	
No	923 (75.3)	253 (86.9)	
Drinking status, **n (%)**			
Yes	312 (25.5)	45 (15.5)	< 0.001
No	911 (74.5)	246 (84.5)	
Active physical activity, **n (%)**			0.004
Yes	285 (23.4)	45 (15.4)	
No	933 (76.6)	247 (84.6)	
Sleep quality score, **mean (SD)**	1.5 (3.0)	1.8 (3.6)	0.15
Dietary quality score, **mean (SD)**	5.9 (1.3)	5.9 (1.3)	0.59
Dietary intake, **mean (SD)**,			
Energy, kcal/d	1243.7 (790.3)	1034.2 (613.0)	< 0.001
Protein, g/d	42.7 (28.3)	35.0 (20.8)	< 0.001
Saturated fatty acid, g/d	1.8 (4.1)	1.9 (4.9)	0.61
Monounsaturated fatty acid, g/d	2.1 (5.8)	2.3 (6.3)	0.59
Polyunsaturated fatty acid, g/d	2.1 (3.8)	1.8 (2.9)	0.26
Carbohydrate, g/d	226.7 (140.5)	186.6 (114.0)	< 0.001
Fiber, g/d	8.4 (7.6)	6.4 (4.5)	< 0.001
Total choline, mg/(1000 kcal*d)	214.0 (96.3)	214.4 (103.3)	0.95
Phosphatidylcholine, mg/(1000 kcal*d)	152.4 (79.6)	152.0 (86.2)	0.94
Free choline, mg/(1000 kcal*d)	39.3 (26.4)	38.8 (31.3)	0.78

MCI = mild cognitive impairment; CVDs = cardiovascular and cerebrovascular diseases; SD = Standard Deviation;

Continuous variables were expressed as mean and Standard Deviation (SD), and P -values were calculated by Wilcoxon test;

Categorical variables were expressed as number and percentage (n%), and P -values were calculated by chi-square test

Finland showed that higher dietary phosphatidylcholine intake significantly reduced the odds of dementia in men [15]. Furthermore, a survey conducted among patients with stroke also showed that for those with higher plasma choline, the odds of cognitive impairment are lower [37]. Results from two studies from the Framingham cohort showed that there was a U-shaped association between dietary choline intake and incident dementia [14, 16, 17]. Results from the UK biobank showed that there was no association between dietary choline intake and incident MCI [17]. Different from the Framingham study and the UK biobank, we found that higher intakes of total choline, free choline, and phosphatidylcholine were linearly associated with reduced odds of MCI in participants aged over 60 years residing in underdeveloped areas. Perhaps attributed to the special background of our sample, where the intake of choline-rich foods was comparatively limited.

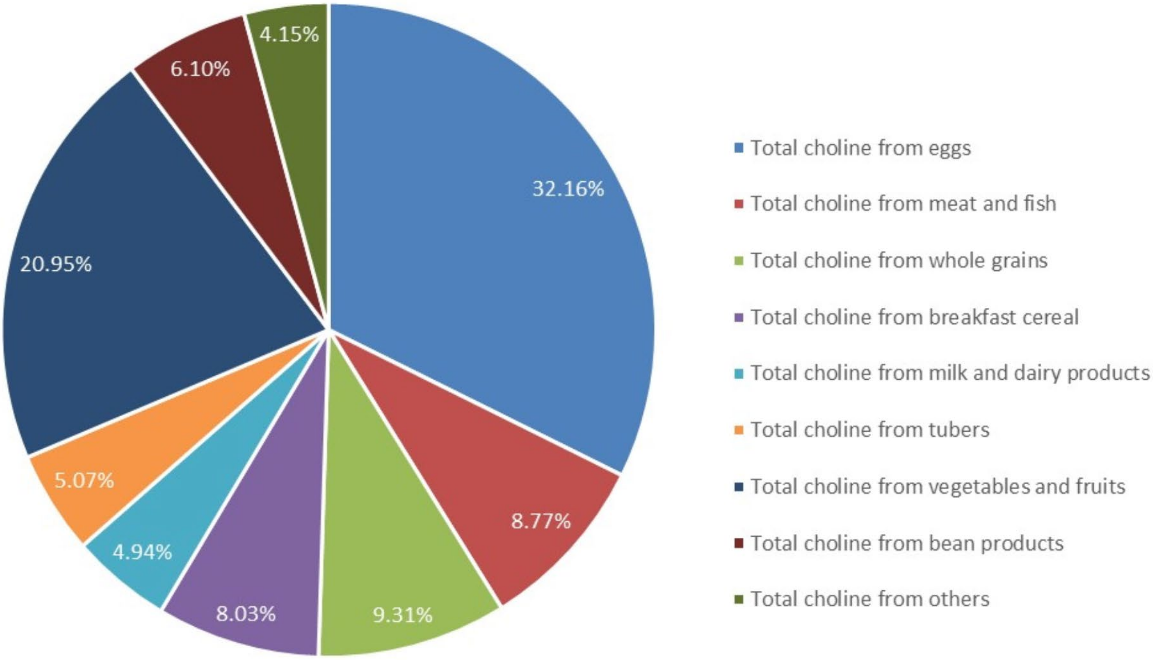

Fig. 1 Percentage of dietary total choline sources from 9 food classifications

Table 2 Association of dietary choline intake and MCI ($n = 1\ 522$)

Choline	**Intake quartile, ORs (95% CI)**			
	Q1	**Q2**	**Q3**	**Q4**
Total choline				
Mean (SD), mg/(1000 kcal*d)	128.0 (20.5)	169.0 (10.5)	216.0 (18.2)	343.0 (106.0)
Cases No, /total No.	89/380	61/381	64/381	78/380
Model 1[†]	1(reference)	0.66 (0.45, 0.97)	0.69 (0.47, 1.00)	0.72 (0.49, 1.04)
Model 2[††]	1(reference)	0.63 (0.42, 0.94)	0.66 (0.44, 1.00)	0.65 (0.41, 1.02)
Phosphatidylcholine				
Mean (SD), mg/(1000 kcal*d)	89.3 (13.9)	116.0 (7.0)	148.0 (12.3)	257.0 (97.4)
Cases No, /total No.	92/381	59/380	65/381	76/380
Model 1[†]	1(reference)	0.63 (0.43, 0.92)	0.65 (0.45, 0.95)	0.73 (0.50, 1.05)
Model 2[††]	1(reference)	0.59 (0.39, 0.88)	0.60 (0.40, 0.91)	0.72 (0.46, 1.11)
Free choline				
Mean (SD), mg/(1000 kcal*d)	16.9 (3.7)	26.3 (2.8)	39.2 (4.9)	74.2 (32.7)
Cases No, /total No.	86/380	71/381	68/380	67/381
Model 1[†]	1(reference)	0.78 (0.53, 1.13)	0.76 (0.52, 1.10)	0.63 (0.43, 0.92)
Model 2[††]	1(reference)	0.77 (0.52, 1.14)	0.72 (0.48, 1.09)	0.55 (0.35, 0.86)

[†] Model 1 adjusted for age (continuous, years), sex (male or female), and dietary energy (continuous, kcal/d)

[††] Model 2 adjusted for age (continuous, years), sex (male or female), dietary energy (continuous, kcal/d), education levels (no formal education, junior high school and below or senior high school and above), marital status (married or non-married), waist circumference (continuous, cm), history of hypertension (yes or no), history of diabetes (yes or no), history of hyperlipidemia (yes or no), history of CVDs (yes or no), current smoking status (yes or no), drinking status (yes or no), active physical activity (yes or no), dietary saturated fatty acids (continuous, g/d), dietary monounsaturated fatty acids (continuous, g/d), dietary polyunsaturated fatty acids (continuous, g/d), dietary protein (continuous, g/d), dietary carbohydrate (continuous, g/d), dietary fiber (continuous, g/d), sleep quality score (continuous), and dietary quality score (continuous)

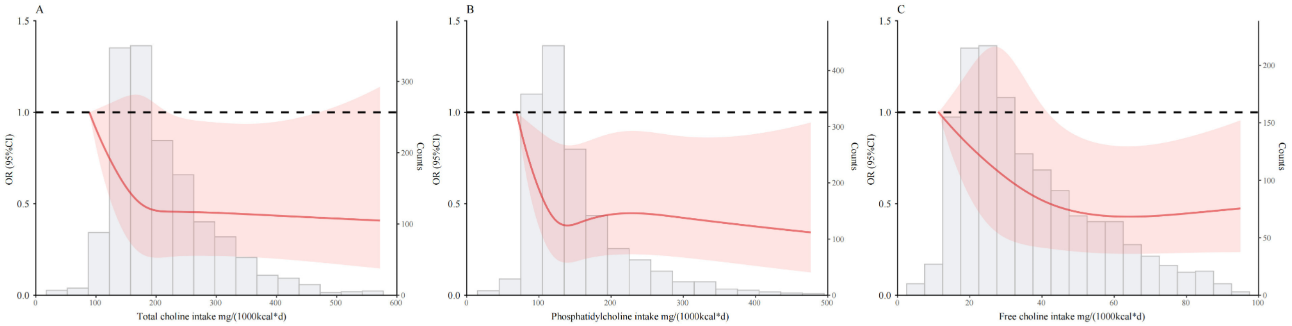

Fig. 2 Dose–response associations of dietary choline intake with MCI
The odds ratios of 95% CI taking into account MCI risk were adjusted for age (continuous, years), sex (male or female), dietary energy (continuous, kcal/d), education levels (no formal education, junior high school and below or senior high school and above), marital status (married or non-married), waist circumference (continuous, cm), history of hypertension (yes or no), history of diabetes (yes or no), history of hyperlipidemia (yes or no), history of CVDs (yes or no), current smoking status (yes or no), drinking status (yes or no), active physical activity (yes or no), dietary saturated fatty acids (continuous, g/d), dietary monounsaturated fatty acids (continuous, g/d), dietary polyunsaturated fatty acids (continuous, g/d), dietary protein (continuous, g/d), dietary carbohydrate (continuous, g/d), dietary fiber (continuous, g/d), sleep quality score (continuous), and dietary quality score (continuous)

Table 3 Association of dietary choline intake and MCI after propensity score matching (*n* = 558)

Choline	**Intake quartile, ORs (95% CI)**			
	Q1	**Q2**	**Q3**	**Q4**
Total choline				
Mean (SD), mg/(1000 kcal*d)	122.9 (25.8)	166.7 (11.5)	220.7 (21.9)	378.1 (124.5)
Cases No, /total No.	82/140	69/139	71/140	70/139
Model 1†	1 (reference)	0.67 (0.41, 1.08)	0.70 (0.43, 1.13)	0.60 (0.37, 0.98)
Model 2††	1 (reference)	0.57 (0.33, 0.98)	0.53 (0.30, 0.93)	0.48 (0.25, 0.91)
Phosphatidylcholine				
Mean (SD), mg/(1000 kcal*d)	85.3 (17.2)	114.9 (8.5)	151.6 (14.0)	288.4 (117.3)
Cases No, /total No.	84/140	72/139	70/140	66/139
Model 1†	1 (reference)	0.72 (0.44, 1.17)	0.67 (0.41, 1.07)	0.54 (0.33, 0.88)
Model 2††	1 (reference)	0.61(0.35, 1.05)	0.54 (0.30, 0.94)	0.49 (0.27, 0.89)
Free choline				
Mean (SD), mg/(1000 kcal*d)	15.8 (3.9)	24.6 (2.4)	36.3 (4.6)	77.6 (41.1)
Cases No, /total No.	76/139	68/140	73/140	75/139
Model 1†	1 (reference)	0.73 (0.45, 1.18)	0.83 (0.51, 1.34)	0.87 (0.54, 1.41)
Model 2††	1 (reference)	0.70 (0.40, 1.20)	0.94 (0.53, 1.65)	0.72 (0.39, 1.32)

† Model 1 adjusted for age (continuous, years), sex (male or female), and dietary energy (continuous, kcal/d)

†† Model 2 adjusted for age (continuous, years), sex (male or female), dietary energy (continuous, kcal/d), education levels (no formal education, junior high school and below or senior high school and above), marital status (married or non-married), waist circumference (continuous, cm), history of hypertension (yes or no), history of diabetes (yes or no), history of hyperlipidemia (yes or no), history of CVDs (yes or no), current smoking status (yes or no), drinking status (yes or no), active physical activity (yes or no), dietary saturated fatty acids (continuous, g/d), dietary monounsaturated fatty acids (continuous, g/d), dietary polyunsaturated fatty acids (continuous, g/d), dietary protein (continuous, g/d), dietary carbohydrate (continuous, g/d), dietary fiber (continuous, g/d), sleep quality score (continuous), and dietary quality score (continuous)

Compared to other studies, choline intake in our participants was significantly lower than in developed countries. The average choline intake was 431 ± 88 mg/d in the Finnish cohort, 324.5 ± 88.5 mg/d in the Framingham study, and 244.8 ± 162.6 mg/d in our study, which was far below the Adequate Intake for choline [38]. Compared to the adequate intake of 450 mg/d for men and 380 mg/d for women [39], the daily dietary intake of choline in our participants, as well as in populations from more developed areas such as Shanghai and Guangdong, was far from adequate, their average choline intakes were 296.8 mg/day and 202.7 mg/day, respectively [40, 41]. These differences may also be attributed to the method used to evaluate choline intake. To enhance the accuracy of choline intake assessments, future studies should incorporate biomarkers such as urinary choline and its metabolites to validate dietary intake data and update food composition databases with the most recent choline content values for various foods.

Several human studies have identified drinking and smoking were associated with increased odds of cognitive impairment [42–48]. However, an intriguing finding in our study was that participants with MCI were more likely to be non-current smokers or non-drinkers. This discrepancy may be attributed to the unique characteristics of our study population. In undeveloped regions of China, where the economic level is generally low, individuals who abstain from smoking and drinking may represent a subgroup with even lower economic status. Nonetheless, it is important to note that low income has been linked to lower health-related quality of life [49, 50]. So the distinct economic circumstances of our sample population may have contributed to differences in baseline characteristics compared to other studies.

Experimental studies indicated that choline exhibited multiple neuroprotective effects [12, 51, 52], providing physiological evidence for our results. Some researchers have explored possible reasons for the reduction of choline in lowering the incidence of cognitive impairment [12, 53, 54]. Firstly, choline is the precursor for several membrane phospholipids, and these phospholipids can maintain the structural and functional integrity of cellular membranes (including neurons and glial cells) [55, 56]. Therefore, the supplement of choline may contribute to strengthening the integrity of membrane [57]. Secondly, with age increasing, the uptake of choline from circulation to the brain significantly decreases, and choline supplementation in the elderly may aid in increasing the choline uptake by the aging brain, thereby elevating choline levels for acetylcholine synthesis and enhancing cholinergic signaling in the brain [53, 58]. Moreover, hypomethylation of the amyloid precursor protein (APP) gene leads to increased expression of APP and deposition of beta-amyloid plaques in the brain [59]. As methyl donors, choline and its metabolites can participate in the synthesis of universal methyl donors, thereby regulating methylation pathways to modulate neuronal gene expression and delay cognitive decline [53, 60]. Therefore, dietary choline may influence the expression of genes associated with learning and memory processing through DNA methylation [61–63]. Supplementing choline can also reduce the activation level of microglia markers, inhibit microglia activation, and mitigate cognitive impairment [51, 53].

Strengths and limitations

Our study has several strengths. Firstly, we have filled the gap in the association between dietary choline and cognitive function in underdeveloped regions. Secondly, our study used different definition methods to analyze the results to ensure the stability of the results. Furthermore, we adjusted for several confounding factors that might influence the analysis outcomes and used E-values to account for unmeasured errors in this observational study. Considering the calculated E-values, it seems unlikely that there are unmeasured confounders with effects that exceed choline.

There are also several limitations. Firstly, as our study was cross-sectional, we were unable to establish a causal relationship between exposure and outcome. Secondly, dietary data were gathered using FFQs, potentially introducing recall bias. Nonetheless, FFQ-derived data can offer insights into participants' dietary habits over an extended timeframe compared to 24-hour dietary recalls. Thirdly, due to the lack of genetic data, we were unable to adjust for factors known to influence cognitive function, such as Apolipoprotein E (APOE) ε4 [64]. Nonetheless, it is worth noting that a separate study has suggested that a healthy lifestyle may confer cognitive benefits to the elderly, irrespective of their genetic phenotype [65]. Fourthly, the participants in our study are all elderly people in underdeveloped areas of China. Due to this inherent characteristic, the results of this study may not apply to people in other countries or regions, but it still complements the lack of relevant studies in China and has certain reference significance. Finally, we used the MMSE to measure cognition function, which is not a clinical diagnostic tool for cognitive impairment [66, 67]. It has been observed to exhibit floor and ceiling effects in various studies and populations [68, 69], which might potentially influence the outcomes when examining the association between choline intake and MCI. It is noteworthy that we employed two different methods to define MCI, and both approaches yielded consistent results, bolstering the reliability of our analysis.

Conclusions

In conclusion, our findings suggest that moderate to high dietary intake of total choline, phosphatidylcholine, and free choline may be associated with lower odds of MCI among older adults in underdeveloped regions of China.

Supplementary Information

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Supplementary Material 1

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Author contributions
D.L. and Y.N. wrote the main manuscript text, H.Y., C.L. and L.C. prepared figure 2 and tables. C.L., K.D., Z.L., J.Z., W.Z., P.S., M.Z., S.P., S.M., X.L. and S.S. interpreted the results. Z.Y. and W.Z. provided the data. All authors reviewed the manuscript.

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Data availability

Data comes from the Nutrition and Chronic Disease Family Cohort (NCDFaC) study, which was based on the China National Nutrition and Health Survey (CNNHS).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have agreed to submit the manuscript to the Nutrition Journal. The authors have declared no competing interests.

Competing interests

The authors declare no competing interests.

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