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RESEARCH PAPER

Consumption of dietary nuts in midlife and risk of cognitive impairment in late-life: the Singapore Chinese Health Study

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Abstract

Background: evidence from prospective studies investigating the association between consumption of nuts in midlife and risk of cognitive impairment in late life is limited.
Methods: this study analysed data from 16,737 participants in a population-based cohort, the Singapore Chinese Health Study. Intake of nuts was assessed using a validated food-frequency questionnaire at baseline (1993–1998), when participants were 45–74 years old (mean age = 53.5 years). Cognitive function was tested using the Singapore modified Mini-Mental State Examination during the third follow-up visit (2014–2016), when participants were 61–96 years old (mean age = 73.2 years). Cognitive impairment was defined using education-specific cut-off points. Logistic regression models were used to estimate the odds ratio (OR) and the 95% confidence interval (CI) for the association between intake and risk of cognitive impairment.
Results: cognitive impairment was identified in 2,397 (14.3%) participants. Compared with those who consumed <1 serving/month of nuts, participants who consumed 1–3 servings/month, 1 serving/week and ≥ 2 servings/week had 12% (95% CI 2–20%), 19% (95% CI 4–31%) and 21% (2–36%) lower risk of cognitive impairment, respectively (P-trend = 0.01). Further adjustment for intake of unsaturated fatty acids attenuated the association to non-significance. Mediation analysis showed that the 50.8% of the association between nuts and risk of cognitive impairment was mediated by the intake of total unsaturated fatty acids ($P < 0.001$).
Conclusion: higher intake of nuts in midlife was related to a lower risk of cognitive impairment in late life, which was partly mediated by unsaturated fatty acids.

Keywords: dietary intake, nut, SM-MMSE, cognitive function, cohort study, older people

Key Points

- Higher intake of nuts in midlife was related to a lower risk of cognitive impairment in late life.
- Mediation analysis showed that the 50.8% of the association was mediated by the intake of total unsaturated fatty acids.
- Further studies are needed to explore the relation for different types of nuts and the optimal dose.

Introduction

With the rapid rate of population ageing across the world, age-related diseases, especially dementia has become a major public health problem [1]. Cognitive impairment is one of the main symptoms of dementia. Due to lack of effective therapies to reverse cognitive impairment, identifying modifiable factors to prevent or delay the onset of cognitive impairment is imperative.

Nuts are rich in a variety of nutrients, including unsaturated fatty acids, vitamins, dietary fibre and minerals, as well as a number of phytochemicals [2]. Mechanistic studies from animals and human have suggested that nuts may be beneficial for cognition due to the antioxidant, anti-inflammatory and endothelial vasodilator functions [3–5]. Positive relation between nuts consumption and cognitive function has been reported in some cross-sectional studies [6–10] and prospective cohort studies [11–14]. Among the four existing cohort studies, one was conducted among 15,467 US women over 70 years old [11], one was in 119 Italian adults aged ≥ 65 years [12], one was in 4,822 Chinese adults aged ≥ 55 years [13] and the other one was in 2,613 Dutch adults aged ≥45 years [14]. Clinical trials are limited and have generated controversial results [15,16]. Taken together, clinical trials and some cohort studies were conducted in older adults with mean age > 65 years [11,12,15,16], whereas two cohort studies in middle-aged adults had relatively smaller sample size and shorter follow-up duration [13,14]. Considering the chronic influence of diet on health outcomes, it is unclear if consumption of nuts in midlife may play an important role in cognition.

Therefore, we investigated the relationship of nut consumption in midlife with risk of cognitive impairment in late life in a cohort study of Chinese adults.

Methods

Study population

The Singapore Chinese Health Study is a population-based cohort study that enrolled Singaporean citizens or permanent residents of Chinese ethnicity. Details of the study design have been reported previously [17]. Participants were restricted to two major Chinese dialect groups, the Hokkiens and the Cantonese, who originally came from Fujian and Guangdong provinces in China, respectively.

A total of 63,257 participants aged 45–74 years were recruited at baseline (1993–1998), and were followed up about every 5 years. During the 3rd follow-up visit (2014–2016), cognition testing was planned for survival participants ($n = 45{,}109$). Due to funding restraint, the 3rd follow-up visit was terminated early and a total of 17,107 participants were recruited. Participants were further excluded if they had implausible energy intake (<600 or >3,000 kcal/d for women and <700 or >3,700 kcal/d for men; $n = 211$), missing items in the Singapore modified version of the Mini-Mental State Examination (SM-MMSE) ($n = 55$), or inability to complete SM-MMSE (mute, blind or deaf; $n = 104$), leaving 16,737 participants in the final analysis (Supplemental Figure 1). This study was approved by the Institute Review Board of the National University of Singapore. All participants gave written informed consent forms.

Assessment of diet and covariates

At enrolment, participants were interviewed face-to-face at home using structured questionnaires to collect their information on demographics, lifestyles and medical histories. History of cancer was collected through linkage with the Singapore Cancer Registry database.

Dietary intake was assessed using a 165-item semi-quantitative food-frequency questionnaire (FFQ) at baseline. The nutrients and energy intakes were subsequently calculated with the Singapore Food Composition Table. The validation of the FFQ has been described previously [17]. In this study, dietary intakes of nuts included combination of peanuts and tree nuts as a single item from 16 mixed food dishes in the FFQ, and did not distinguish by types of nuts. Because a standard serving size of 28 g (1 ounce) is commonly used in Western populations and included in the United States Department of Agriculture database, we transformed the intake level to servings per month (or per week) in the analysis as well.

Assessment of cognitive function

During the 3rd follow-up visit, cognitive function was evaluated with SM-MMSE by trained interviewers at the participants' home [18]. All the interviews were audio-recorded and 20% of the interview records were randomly checked for quality control.

The SM-MMSE covers 30 items (range 0–30 scores) with higher score indicating better cognitive performance. Because cognitive function could be heavily affected by education level, we adopted education-specific cut-off points to definite cognitive impairment: less than 18, 21 and 25 for individuals with no formal education, with 1–6 years' education, and with 7 or more years' education, respectively. These cut-off points were derived from the Shanghai Dementia Survey, whose participants had comparable education levels as our study population [19].

Statistical analysis

The characteristics of the participants across different groups of nut consumption were compared with Kruskal–Wallis rank test (for continuous variables) and Cochran–Mantel–Haenszel test (for categorical variables).

Logistic regression models were used to evaluate odds ratios (ORs) and 95% confidence intervals (CIs). In model 1, we adjusted for age at cognition assessment (years), sex, dialect groups (Cantonese, Hokkiens), education level (no formal education, primary school, secondary school, high school or above) and marital status (married, widowed, separated/divorced, never married). In model 2, we additionally adjusted for smoking status (never, former and current), alcohol consumption (never/monthly, weekly and daily), moderate or vigorous physical activity level (<0.5, 0.5–3.9, ≥4.0 h/week), body mass index (BMI; <18.5, 18.5–22.9, 23–27.4, ≥27.5 kg/m^2), sleep duration (≤5, 6, 7, 8, ≥9 h/day), energy intake (kcal/d), tea drinking (never, monthly, weekly and daily) and the alternative Healthy Eating Index-2010 score (AHEI-2010; quartiles). In model 3, we further adjusted for baseline comorbidities, including diabetes, hypertension, cardiovascular disease (CVD) and cancer. Median values of nut intake across groups were treated as a continuous variable to calculate *P* for linear trend. In order to explore possible mediators underlying the relationship, we further adjusted for total intakes of fibre, vitamins (riboflavin, vitamin B6, folate and vitamin E), and unsaturated fatty acids based on Model 3. Mediation analysis was performed using Stata's *paramed* command [20]. Generalised linear models were performed to calculate mean SM-MMSE scores and differences across intake groups with adjustment for the covariates mentioned above.

Multiplicative interaction was tested by including a cross-product term between the ordinal value of nut intake and the potential effect modifier in the model: age at interview (<75, ≥75), sex, education level (≤6 or >6 years' education) and BMI (<23, ≥23 kg/m^2). To test the robustness of the results, we repeated our analyses by excluding participants with cancer or CVD at baseline, or using <24 as cut-off points to define cognitive impairment, which is commonly seen in studies among Western population. To account for the potential influence of selection bias due to loss-to-follow-up, we used inverse probability weighted model to estimate the effect size in a pseudo-population [21]. The expected lifespan in Singapore is 83 years in 2016 [22]. A recent study among older persons without dementia found a more than 7-fold increase in rate of global cognitive decline beginning 3–4 years before death [23]. Hence, we restricted to participants aged < 79 years at the 3rd follow-up visit to minimise the bias from terminal decline before death.

The mediation analysis was performed using STATA/MP version 13, and all other analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Cary, NC), with two-tailed *P* values <0.05 considered as statistically significant.

Results

The participants aged 53.5 ± 6.22 years at recruitment and 73.2 years ±6.41 at the 3rd follow-up interview. Women accounted for 59.2% of the participants. Participants with higher intake of nuts were younger, more likely to be men and current smokers, to have higher education levels, physical activity levels, alcohol intake levels and dietary energy intake (Table 1).

The mean SM-MMSE score was 24.81 ± 3.89 and a total of 2,397 (14.3%) participants were considered to have cognitive impairment in the 3rd follow-up visit. Intake of nuts was inversely related to risk of cognitive impairment: the ORs (95% CIs) for participants consuming 1–3 servings/month (median = 2.03 g/d), 1 serving/week (median = 5.5 g/d) and ≥2 servings/week (median = 11.87 g/d) of nuts were 0.88 (0.80–0.98), 0.81 (0.69–0.96) and 0.79 (0.64–0.98), respectively, compared with those who consumed <1 serving/month (median = 0.25 g/d; *P*-trend = 0.01 in the model 3). Each 1 serving/week increment of nut consumption was related to 6% (1–11%) lower risk of cognitive impairment (Table 2).

Further adjustment for dietary intake of fibre, B vitamins (riboflavin, vitamin B6 and folate) or vitamin E individually did not substantially change the results (all *P*-trend <0.05). Adjustment for intake of total unsaturated fatty acids attenuated the association to nonsignificance and the OR (95% CI) comparing ≥2 servings/week versus <1 serving/month was 0.88 (0.71–1.09; *P*-trend = 0.15), indicating a 50.8% of mediation effect (Table 3).

Compared with participants who consumed <1 serving/month of nuts, the mean adjusted SM-MMSE scores were significantly higher by 0.16, 0.25 and 0.37 points for those who consumed 1–3 servings/month, 1 serving/week and ≥2 servings/week (all *P* value <0.01; Table 4), which were equivalent to 0.85, 1.35 and 2.04 years' difference in age in the final model, respectively.

We did not find significant interactions between intake of nuts and age at baseline, sex, education level and BMI (all *P* for interaction values >0.05; data not shown). The associations remained unchanged in all sensitivity analyses (Supplemental Tables 1–4). The ORs and 95% CIs for cognitive impairment with other variables in the final model are shown in the Supplemental Table 5.

Discussion

In this large-scale cohort study among Chinese adults living in Singapore, we found that higher intake of nuts in midlife was related to a lower risk of cognitive impairment in late life. The association was robust in sensitivity analyses and was partly mediated by dietary intake of unsaturated fatty acids.

Our results are consistent with the previous cohort studies on this topic. The Nurses' Health Study conducted 5–6 repeated FFQ surveys and 4 repeated complex cognition tests among 15,476 US women (mean age = 74 years), and reported that higher long-term consumption of total nuts was associated with better overall cognition at older ages [11]. The InCHIANTI study among 119 Italian adults aged ≥65 years also showed that higher consumption of nuts was associated with higher MMSE score and lower risk of cognitive decline during 3 years' follow-up [12]. The Doetinchem Cohort Study with 2,613 Dutch participants (mean age = 55 years) also reported a positive association between

Table 1. Characteristics of participants according to intake of nuts: the Singapore Chinese Health Study

Characteristics	Intake of nuts				*P* value
	<1 Serving/month	1–3 Servings/month	1 Serving/week	≥2 Servings/week	
Median intake, g/d	0.25 (0.03–0.57)	2.03 (1.39–2.71)	5.50 (4.62–6.45)	11.87 (9.94–16.27)	
Age at recruitment, y	53.50 (48.81–58.51)	52.23 (48.12–57.23)	51.15 (47.65–56.59)	51.40 (47.94–56.73)	<0.001
Age at interview, y	73.43 (68.73–78.40)	71.92 (67.87–76.96)	70.78 (67.08–76.15)	70.95 (67.13–75.85)	<0.001
BMI, kg/m^2	23.11 (21.10–24.80)	23.03 (21.09–24.80)	23.03 (20.90–24.75)	22.89 (20.96–24.97)	0.27
Energy intake, kcal/d	1,320.69 (1,083.37–1,626.14)	1,528.09 (1257.87–1,861.30)	1,822.96 (1,495.54–2,227.35)	2,010.82 (1,646.55–2,471.31)	<0.001
AHEI-2010 score	45.66 (42.10–49.46)	45.10 (41.47–48.78)	44.17 (40.22–48.61)	45.01 (40.10–49.48)	<0.001
Sex (male%)	2,186 (35.24)	2,935 (40.13)	1,030 (49.45)	683 (60.02)	<0.001
Dialect group (%)					
Cantonese	2,848 (45.91)	3,711 (50.75)	1,129 (54.2)	653 (57.38)	<0.001
Hokkien	3,355 (54.09)	3,602 (49.25)	954 (45.8)	485 (42.62)	
Marriage (married%)	5,403 (87.1)	6,526 (89.24)	1,877 (90.11)	1,038 (91.21)	<0.001
Educational levels (%)					
No formal	1,475 (23.78)	1,303 (17.82)	258 (12.39)	101 (8.88)	<0.001
Primary	2,902 (46.78)	3,315 (45.33)	839 (40.28)	448 (39.37)	
Secondary	1,487 (23.97)	2,130 (29.13)	760 (36.49)	474 (41.65)	
Higher	339 (5.47)	565 (7.73)	226 (10.85)	115 (10.11)	
Current smokers (%)	745 (12.01)	932 (12.74)	283 (13.59)	222 (19.51)	<0.001
Non-drinkers (%)	5,669 (91.39)	6,484 (88.66)	1,796 (86.22)	886 (77.86)	<0.001
Daily tea drinkers (%)	1,227 (19.78)	1,748 (23.9)	596 (28.61)	340 (29.88)	<0.001
Physical activity (%)					
<0.5 h/week	4,191 (67.56)	4,582 (62.66)	1,204 (57.8)	616 (54.13)	<0.001
0.5–3.9 h/week	1,276 (20.57)	1,718 (23.49)	576 (27.65)	328 (28.82)	
≥4.0 h/week	736 (11.87)	1,013 (13.85)	303 (14.55)	194 (17.05)	
Hypertension (%)	1,271 (20.49)	1,380 (18.87)	372 (17.86)	221 (19.42)	0.03
Diabetes (%)	329 (5.30)	320 (4.38)	109 (5.23)	59 (5.18)	0.07
CVD (%)	153 (2.47)	184 (2.52)	53 (2.54)	30 (2.64)	0.99
Cancer (%)	137 (2.21)	124 (1.7)	35 (1.68)	22 (1.93)	0.15

Data are shown as median (interquartile range) for continuous variables and *n* (%) for categorical variables.

Table 2. Relationships between intake of nuts and risk of cognitive impairment in the Singapore Chinese Health Study

	Intake of nuts				*P*-trend	OR (95% CI) per 1 serving/week
	<1 Serving/month	1–3 Servings/month	1 Serving/week	≥2 Servings/week		
Cases/*N*	1,013/6,203	992/7,313	252/2,083	140/1,138		
Model 1[a]	1.00	0.88 (0.80–0.98)	0.84 (0.72–0.98)	0.84 (0.69–1.02)	0.03	0.95 (0.91–1.00)
Model 2[b]	1.00	0.88 (0.80–0.98)	0.82 (0.70–0.96)	0.79 (0.64–0.98)	0.01	0.94 (0.89–0.99)
Model 3[c]	1.00	0.88 (0.80–0.98)	0.81 (0.69–0.96)	0.79 (0.64–0.98)	0.01	0.94 (0.89–0.99)

Linear trend was calculated by treating median values across groups as a continuous variable in the model. [a]Model 1 was adjusted for age at cognition assessment, sex, dialect groups, educational level and marital status. [b]Model 2 was further adjusted for physical activities, BMI, smoking status, alcohol consumption, sleep duration, total daily energy intake, tea drinking and AHEI-2010 score (excluding the item for nuts and legumes). [c]Model 3 was further adjusted for physician-diagnosed history of diabetes, hypertension, CVD and cancer.

total intake of nuts and cognitive function at baseline and a suggestive inverse association with cognitive decline in 5 years' follow-up [14]. To our knowledge, the only available cohort study in Chinese population was from the China Health Nutrition Survey (CHNS) with 4,822 participants (mean age = 62 years) [13]. This study used 3-day 24-h recalls to measure intake of nuts, and found that higher intake was associated with lower risk of poor cognitive function [13]. However, nuts were not commonly consumed in Chinese (e.g. ≥90.5% of the participants reported zero consumption in the 3-day 24-h recalls in the 1997 CHNS survey cycle), thus the 24-h recalls might not be able to capture the low consumption levels well. Furthermore, the authors used the mixed effect regression models that were useful in handling repeated measures but less useful in determining the temporal relation. In addition, the CHNS used a subset of items from the modified Telephone Interview for Cognitive Status to assess cognitive function, which mainly relied on auditory and verbal processing skills [13]. Unlike CHNS, our study used the 30-item modified MMSE to evaluate global cognitive function, which included comprehensive aspects of cognition including orientation, registration, attention and calculation, recall, and language abilities [18].

The potential mechanism underlying the association may be mainly due to some biological active compounds of nuts, which may have benefits on cognition [3–5]. We found

Table 3. Relationships between intake of nuts and risk of cognitive impairment, adjusted for possible mediator nutrients, in the Singapore Chinese Health Study

	Intake of nuts		*P*-trend across 4 levels	OR (95% CI) per 1 serving/week	Indirect effect mediated via nutrient
	<1 Serving/month	≥2 Servings/week			
Model plus dietary fibre	1.00	0.80 (0.65–0.98)	0.01	0.94 (0.89–1.00)	−2.4% ($P = 0.63$)
Model plus vitamin B2, B6, B9	1.00	0.80 (0.65–0.99)	0.02	0.95 (0.89–1.00)	4.2% ($P = 0.52$)
Model plus vitamin E	1.00	0.82 (0.66–1.01)	0.03	0.95 (0.90–1.01)	20.2% ($P = 0.10$)
Model plus MUFAs and PUFAs	1.00	0.88 (0.71–1.09)	0.15	0.97 (0.92–1.03)	50.8% ($P < 0.001$)

Linear trend was calculated by treating median values across groups as a continuous variable in the model. Covariates in the Model included age at cognition assessment, sex, dialect groups, educational level, and marital status, physical activities, BMI, smoking status, alcohol consumption, sleep duration, total daily energy intake, tea drinking, AHEI-2010 score (excluding the item for nuts and legumes), physician-diagnosed history of diabetes, hypertension, CVD and cancer.

Table 4. Least-squares means (95% CI) of SM-MMSE score according to frequency of nut consumption in the Singapore Chinese Health Study

Intake of nuts	Least-squares means (95% CI)			Beta-coefficient (*P* value) for Model 3[c]
	Model 1[a]	Model 2[b]	Model 3[c]	
<1 Serving/month	24.84 (24.70–24.99)	24.69 (24.49–24.88)	24.27 (23.82–24.71)	
1–3 Servings/month	24.99 (24.85–25.13)	24.84 (24.65–25.03)	24.42 (23.98–24.87)	0.16 (0.004)
1 Serving/week	25.03 (24.86–25.21)	24.93 (24.71–25.15)	24.52 (24.06–24.97)	0.25 (0.003)
≥2 Servings/week	25.13 (24.91–25.34)	25.06 (24.80–25.31)	24.64 (24.17–25.12)	0.37 (<0.001)

[a] Model 1 was adjusted for age at cognition assessment, sex, dialect groups, educational level and marital status. [b] Model 2 was further adjusted for physical activities, BMI, smoking status, alcohol consumption, sleep duration, total daily energy intake, tea drinking and AHEI-2010 score (excluding the item of nuts and legumes). [c] Model 3 was further adjusted for physician-diagnosed history of diabetes, hypertension, CVD and cancer.

that the association was partially mediated through dietary intakes of unsaturated fatty acids but not fibre, vitamins B2, B6, B9 or E. Unsaturated fatty acids have important roles in constituting neuron membrane and regulating brain function [24]. Several prospective cohort studies have also found significantly better cognitive function and less cognitive decline with higher consumption of monounsaturated fatty acids (MUFAs) [25–28] and polyunsaturated fatty acids (PUFAs) [25,26,29]. In our previous publication of Singapore Chinese Health Study, we also found significantly inverse relations of MUFAs and PUFAs with risk of cognitive impairment [30]. However, we acknowledge that nuts were not the major food sources of unsaturated fatty acids in this cohort, and adjusting for total intakes of unsaturated fatty acids in the model could not fully demonstrate the mediation estimates.

The strengths of our study include a large sample size, a longitudinal study design, long duration of follow-up and high-quality measurement of cognitive function using SM-MMSE that was designed specifically for this population. Our study has some limitations. First, selection bias was possible. However, the loss to follow-up was mainly caused by limited funding and we did not select participants deliberately. We also used inverse probability weighting models to explore the potential influence of selection bias and the results remained robust in this sensitivity analysis. Second, the consumption of nuts was only assessed once at baseline and time-varying changes during the follow-up could not be measured. In addition, we could not assess the associations with different types of nuts. Third, SM-MMSE was only measured once during the 3rd follow-up visit, hence we could not adjust for cognitive function at baseline and could not examine cognitive decline. However, considering that the participants were relatively young (mean age: 53.5 years) and could finish a set of complex questionnaires, including the 165-item FFQ at baseline, it was likely that they were in robust cognitive state at recruitment. Finally, residual confounding was inevitable in observational studies although we have controlled for a number of potential confounding factors including lifestyle and dietary pattern.

In conclusion, we found that higher nut consumption in midlife was related to lower risk of cognitive impairment in late life in Chinese adults. Further studies are needed to investigate the relation between different types of nuts and cognition, and the optimal dose for cognitive preservation.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

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