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SERUM CHOLESTEROL LEVELS WITHIN THE HIGH NORMAL RANGE ARE ASSOCIATED WITH BETTER COGNITIVE PERFORMANCE AMONG CHINESE ELDERLY

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Abstract: *Objectives:* The association between cognitive function and cholesterol levels is poorly understood and inconsistent results exist among the elderly. The purpose of this study is to investigate the association of cholesterol level with cognitive performance among Chinese elderly. *Design:* A cross-sectional study was implemented in 2012 and data were analyzed using generalized additive models, linear regression models and logistic regression models. *Setting:* Community-based setting in eight longevity areas in China. *Subjects:* A total of 2000 elderly aged 65 years and over (mean 85.8±12.0 years) participated in this study. *Measurements:* Total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) concentration were determined and cognitive impairment was defined as Mini-Mental State Examination (MMSE) score≤23. *Results:* There was a significant positive linear association between TC, TG, LDL-C, HDL-C and MMSE score in linear regression models. Each 1 mmol/L increase in TC, TG, LDL-C and HDL-C corresponded to a decreased risk of cognitive impairment in logistic regression models. Compared with the lowest tertile, the highest tertile of TC, LDL-C and HDL-C had a lower risk of cognitive impairment. The adjusted odds ratios and 95% CI were 0.73(0.62-0.84) for TC, 0.81(0.70-0.94) for LDL-C and 0.81(0.70-0.94) for HDL-C. There was no gender difference in the protective effects of high TC and LDL-C levels on cognitive impairment. However, for high HDL-C levels the effect was only observed in women. High TC, LDL-C and HDL-C levels were associated with lower risk of cognitive impairment in the oldest old (aged 80 and older), but not in the younger elderly (aged 65 to 79 years). *Conclusions:* These findings suggest that cholesterol levels within the high normal range are associated with better cognitive performance in Chinese elderly, specifically in the oldest old. With further validation, low cholesterol may serve a clinical indicator of risk for cognitive impairment in the elderly.

Introduction

Cognitive impairment is a frequent disorder among the elderly. It affects the individual's ability to function independently. With the aging of Chinese population, dementia and mild cognitive impairment (MCI) become a significant public health problem, the prevalence is increasing, now representing 5.14% for dementia and 20.8% for MCI, indicating that approximately 5.9 million and 23.9 million Chinese aged 65 years and older with dementia and MCI are currently living in China respectively (1, 2). This underlines the importance of risk factors assessment and early intervention of cognitive function in China. However, few modifiable risk factors for cognitive impairment have been identified.

The brain has a very high lipid content, and cholesterol provides structural integrity and modulates fluidity of neuronal cells (3). Recently, the effects of cholesterol, including total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) on cognitive impairment among the elderly have attracted particular attention. However, whether cognitive function is affected by cholesterol levels is poorly understood; results to date have been inconsistent. Previous studies found that cholesterol levels were significantly higher in the elderly with cognitive impairment or dementia, and that cholesterol lowering therapy may be a strategy for cognitive impairment prevention (4-6). In addition, previous research indicated that higher consumption of tea, which is linked to lower cholesterol level, was proved to take a protective effect on cognition (7), and higher cholesterol was linked to faster cognitive decline among patients with Alzheimer's disease (4). In contrast, other studies provide contradictory findings that demonstrated no association between cholesterol concentrations and cognitive impairment or dementia (8, 9), and even that higher concentrations of cholesterol were associated with a decreased risk of cognitive impairment among the elderly (10-15).

Most of the existing studies only focused on the total

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population (4, 5, 8-15); therefore, there is still some ambiguity with respect to potential differences in the relationships of cognition and lipids in men and women. Although the association between cholesterol and cognitive function is strongly age-dependent (16), yet few of previous studies focused on the oldest old (12). In an attempt to better understand the relationship between cholesterol and risk of cognitive impairment, a cross-sectional study was conducted among the 2000 Chinese elderly in 2012. The following questions were addressed: 1) Is the relationship between cholesterol and cognitive impairment positive or negative? 2) Is the relationship maintained between different genders or age sub-groups?

Materials and methods

Study design and participants

A total of 2437 participants between the ages of 65 and 112 were enrolled in 8 longevity areas during the sixth wave of the Chinese Longitudinal Healthy Longevity Survey (CLHLS) in 2012. A detailed description of the study design and sampling method of CLHLS has been published elsewhere (17, 18). The longevity areas meed the following three criteria : (1) the percentage of centenarians must be > 7 per 100,000 population; (2) the life expectancy of local residents must be 3 years higher than the national average; and (3) the percentage of the elderly aged 80 and over must be >1.4% among the total population. This study was approved by the Ethics Committee of Peking University and the Ethics Committee of the National University of Singapore. All participants signed written consent. Four hundred and thirty seven participants with missing data on key variables including cognitive function and cholesterol level so were excluded from the data analysis. Finally, 2000 participants were eligible for data analysis.

Questionnaire survey and health examination

Structured interviews were carried out with all participants face-to-face. Some information was collected from proxies (relatives) who knew participants best, for those participants who were unable to answer the questions by themselves. A variety of potential risk factors for cognitive function, such as sociodemographic characteristics, and life style were included in the questionnaire. In addition, medical personnel determined physical measurements including waist circumference, systolic blood pressure and diastolic blood pressure.

Laboratory testing

Five milliliters of venous blood and 15 milliliters of urine were collected in the morning after an overnight fast for at least 12 hours. Blood plasma analyses included TC, TG, HDL-C, creatinine, fasting plasma glucose, and hemoglobin, were determined by an Automatic Biochemistry Analyzer (Hitachi 7180, Japan) using commercially available diagnostic kits (Roche Diagnostic, Mannheim, Germany) at Capital Medical University in Beijing. Urine was tested for microalbumin and creatinine using Siemens Microalbustix (Siemen Healthcare Diagnostic, USA). LDL-C was calculated using the formula of Friedewald et al: (LDL-C) =TC-(HDL-C)-TG/5 (19).

Assessment of cognitive function

Cognitive function was assessed using the Mini-Mental Status Examination (MMSE) and scores ranged from 0 to 30. The MMSE is the most widely used tool for screening cognitive impairment (20). Cognitive function was classified into a dichotomous variable according to the MMSE score: normal cognition (score: 24-30) and cognitive impairment (score: 0-23) (21).

Covariates

Marital status was categorized as "currently married" if the subject was currently married, and 'not married' if divorced, widowed, or never married. Education was treated as continuous a variable in the linear regression model, and categorized dichotomously in the logistic model and coded «yes» if the subject reported at least one or more years of any formal education in response to the question, 'How many years of formal education have you received?'. Hypertension was defined as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg, and/or being treated with antihypertensive medicine. Central obesity was defined as waist circumference ≥85cm in men or waist circumference ≥80cm in women. Type 2 diabetes mellitus was designated as fasting plasma glucose ≥7.0 mmol/L or self-report of using hypoglycemic drugs. Anemia was classified as hemoglobin <130g/L in men or hemoglobin <120g/L in women. Sleep quality was assessed by the question "How about the quality of your sleep?". Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m2 and/or albuminuria (22), eGFR was calculated with the modification of diet in renal disease (MDRD) equations for as follows : $eGFR=175\times(\text{serum creatinine})^{-1.234}\times age^{-0.179}\times 0.79$ (if female) (23). Albuminuria was defined by the albumin/creatinine ratio (ACR) ≥30 mg/g. TC, TG, LDL-C and HDL-C were treated as continuous as well as categorical, by tertiles (see cut-points in Table 1). Table 1 shows the tertile cut-point values of serum TC, TG, LDL-C and HDL-C.

Table 1
Tertile cut-points of serum levels of TC, TG, LDL-C and HDL-C among 2,000 Chinese elderly

Variable	Lower tertile	Middle tertile	Upper tertile
TC (mmol/L)	<3.82	3.82-4.66	≥4.66
TG (mmol/L)	<0.68	0.68-1.05	≥1.05
LDL-C (mmol/L)	<2.16	2.16-2.84	≥2.84
HDL-C (mmol/L)	<1.10	1.10-1.41	≥1.41

TC =Total cholesterol; TG=triglycerides, LDL-C =low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol;

Statistical analysis

Differences in characteristics were assessed by Student's t or Cochran-Cox test for continuous variables, and by Chi-square tests for categorical variables between the participants with cognitive impairment and without.

Generalized additive models were performed to explore the shape of the association between cholesterol and cognitive impairment, and found that it was a linear rather than a curvilinear relationships between TC, TG, LDL-C and cognitive impairment. The relationship between TC, TG, LDL-C, HDL-C (mmol/L) and the MMSE score was evaluated using the simple and multiple linear model controlling for age (year), sex, education (year). Then the logistic regression model was run to evaluate the risk of cognitive impairment; the cholesterol was examined as 1 mmol/L increments and in tertiles using the lowest tertile as the reference. We adjusted for demographic variables including age, gender, marital status, residence and education level in the basic model. Further adjustment were included in the final models for current cigarette smoking, current alcohol drinking, central obesity, sleep quality, anemia, hypertension, type 2 diabetes mellitus, and CKD were included in the final model. All the analyses were repeated, stratified by gender and age group (65-79 years, and 80 years and older) including the adjustments described for the final model. Results of logistic regression analyses were presented as odds ratios (ORs) with 95% confidence intervals (CIs).

All statistical analyses were performed with SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA). P value <0.05 was considered statistically significant, and all p-values were two-sided.

Results

Characteristics of study participants

A total of 2000 participants aged 65 and over were included in this study, including 934 were men and 1066 were women.

Table 2

Characteristics of participants by cognitive function among 2,000 Chinese elderly

Variable	Normal cognition (n=1370)	Cognitive impairment (n=630)	Total	P value
Age (year) ‡	81.7 (11.2)	94.6 (9.2)	85.8 (12.0)	<0.01
Gender†	<0.01			
Male	767 (56.0)	167 (26.5)	1066 (53.3)	
Female	603 (44.0)	463 (73.5)	934 (46.7)	
Marital status†	<0.01			
Currently married	727 (58.1)	106 (17.0)	833 (41.9)	
Not married	817 (40.9)	519 (83.0)	1154 (58.8)	
Education†	<0.01			
Illiteracy	656 (47.9)	527 (16.4)	1183 (59.2)	
Literacy	714 (52.1)	103 (83.7)	817 (40.9)	
Current cigarette smoking†	290 (21.2)	48 (7.6)	338 (16.9)	<0.01
Current alcohol drinking†	245 (18.0)	46 (7.3)	291 (14.6)	<0.01
Bad sleep quality†	499 (36.5)	275 (43.7)	774 (38.7)	<0.01
Central obesity†	568 (41.5)	194 (30.8)	762 (38.1)	<0.01
Anemia †	686 (50.1)	369 (58.6)	1055 (52.8)	<0.01
Type 2 diabetes †	201 (14.7)	102 (16.2)	303 (15.2)	0.38
Hypertension†	745 (54.4)	323 (51.3)	1068 (53.4)	0.20
CKD†	367 (26.8)	240 (38.1)	607 (30.4)	<0.01
TC(mmol/L) ‡	4.37 (0.98)	4.13 (0.98)	4.30 (0.98)	<0.01
TG (mmol/L) ‡	1.04 (0.70)	0.90 (0.49)	1.00 (0.65)	<0.01
LDL-C (mmol/L) ‡	2.59 (0.82)	2.45 (0.82)	2.55 (0.82)	<0.01
HDL-C (mmol/L) ‡	1.29 (0.37)	1.26 (0.35)	1.28 (0.36)	0.21
MMSE (point) ‡	28.5 (1.7)	14.8 (7.1)	24.2 (7.6)	<0.01

TC =Total cholesterol; TG=triglycerides, LDL-C =low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; CKD=chronic kidney disease; MMSE=Mini-Mental Status Examination; † Dichotomous variables (n, %) were tested using chi-square tests; ‡ Continuous variables (mean, SD) were tested for differences between the two groups using Student's t or Cochran-Cox tests.

Table 2 displayed the characteristics of participants by cognitive function. The mean age of the participants was 85.8±12.0 years. A majority of participants had at least one chronic condition, e.g., 38.1% had central obesity, 52.8% anemia, 15.2% type 2 diabetes, 53.4% hypertension, and 30.4% CKD.

With the exception of type 2 diabetes, hypertension and HDL-C, characteristics among the participants with cognitive impairment and without were significantly different. Compared to counterparts with normal cognitive, participants with cognitive impairment were more likely to be female, not in marriage, illiterate, have poor sleep quality as well as anemia and CKD. Participants with normal cognition were more likely to be current cigarette smokers, current alcohol drinkers, centrally obese, and with higher TC, TG and LDL-C concentrations than their counterparts with cognitive impairment.

Association between serum cholesterol and cognitive impairment

By linear regression, there was a significant positive linear association between TC, TG, LDL-C, HDL-C and MMSE score. Each 1mmol/L increase in TC, TG, LDL-C and HDL-C corresponded, after adjustment, to a statistically significant enhancement of 0.67, 0.56, 0.52 and 1.25 points in MMSE scores respectively.

When the cholesterol measures were taken as continuous variables, the crude odds ratios of each 1mmol/L increment in TC, TG and LDL-C for the risk of cognitive impairment was 0.78 (0.71-0.86), 0.67 (0.56-0.80) and 0.80 (0.72-0.89) respectively; with further adjustments using the basic and final models the odds ratios remained substantially the same (Table 3). When exploring the differences in gender and age group, there was a significant decreased risk of cognitive impairment with increasing TC and LDL-C in men, with increasing TC

Table 3

Association between cholesterol levels and cognitive impairment among 2,000 Chinese elderly

Variable	Crude OR (95% CI)	Basic model † (aOR, 95% CI)	Final model ‡ (aOR, 95% CI)
TC			
Each1mmol/L increment in TC	0.78(0.71-0.86)**	0.75 (0.67-0.85)**	0.75 (0.66-0.85)**
Tertiles of TC			
Low	1.00 reference	1.00 reference	1.00 reference
Middle	0.73(0.58-0.92)**	0.73 (0.56-0.97)*	0.74 (0.56-0.98)*
High	0.73(0.65-0.83)**	0.73 (0.63-0.84)**	0.73 (0.62-0.84)**
Triglycerides			
Each1mmol/L increment	0.67 (0.56-0.80)**	0.80 (0.65-0.98)*	0.80 (0.65-1.00)*
Tertiles of TG			
Low	1.00 reference	1.00 reference	1.00 reference
Middle	0.94 (0.75-1.18)	0.88 (0.67-1.15)	0.89 (0.67-1.17)
High	0.80 (0.71-0.90)**	0.86 (0.74-1.00)*	0.88 (0.76-1.03)
LDL-C			
Each1mmol/L increment	0.80 (0.72-0.89)**	0.75 (0.65-0.87)**	0.75 (0.65-0.87)**
Tertiles of LDL-C			
Low	1.00 reference	1.00 reference	1.00 reference
Middle	0.83 (0.64-1.08)	0.69 (0.51-0.94)*	0.70 (0.51-0.96)*
High	0.87 (0.76-0.99)*	0.81 (0.70-0.95)**	0.82 (0.70-0.96)*
HDL-C			
Each1mmol/L increment	0.82 (0.63-1.07)	0.72 (0.52-0.99)*	0.73 (0.53-1.01)
Tertiles of HDL-C			
Low	1.00 reference	1.00 reference	1.00 reference
Middle	0.89 (0.71-1.12)	0.91 (0.69-1.19)	0.91 (0.68-1.20)
High	0.90 (0.80-1.00)*	0.82 (0.71-0.94)**	0.81 (0.70-0.94)**

TC =Total cholesterol; TG=triglycerides, LDL-C =low density lipoprotein; HDL-C=high density lipoprotein; OR=odds ratio; aOR=adjusted odds ratio; CI=confidence interval; *p<0.05; **p<0.0; †Adjusted for potential confounders included age, gender, marital status, residence and education level; ‡ Adjusted for potential confounders including age, gender, marital status, residence, education level, and current cigarette smoking, current alcohol drinking, central obesity, sleep quality, anemia, hypertension, type 2 diabetes mellitus and CKD.

Table 4
Association between cholesterol level and cognitive impairment and cholesterol in 2,000 Chinese elderly, by gender and age group

Variable	Gender†		Age group†	
	Men (n=934)	Women (n=1066)	Young elderly (age≤79(n=703)	Oldest old (age≥80, n=1297)
TC				
Each1mmol/L increment	0.74(0.60-0.93)**	0.76(0.65-0.88)**	0.77(0.55-1.10)	0.75(0.66-0.86)**
Tertiles of TC				
Low	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Middle	0.88(0.57-1.36)	0.65(0.45-0.95)**	0.66(0.31-1.41)	0.77(0.57-1.07)
High	0.71(0.55-0.94)*	0.71(0.59-0.86) **	0.78(0.53-1.16)	0.71(0.61-0.84)**
TG				
Each1mmol/L increment	0.84(0.6-1.26)	0.79(0.61-1.02)	1.14(0.77-1.67)	0.72(0.55-0.92)*
Tertiles of LDL-C				
Low	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Middle	1.08(0.67-1.69)	0.82(0.57-1.19)	0.62(0.27-1.41)	0.92(0.68-1.24)
High	0.93(0.71-1.21)	0.85(0.70-1.03)	0.87(0.59-1.26)	0.87(0.74-1.03)
LDL-C				
Each1mmol/L increment	0.69(0.53-0.91)**	0.77(0.65-0.92)**	0.66(0.44-0.99)*	0.76(0.65-0.89)**
Tertiles of LDL-C				
Low	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Middle	0.62(0.39-0.97)*	0.76(0.52-1.10)	0.78(0.38-1.62)	0.70(0.51-0.96)*
High	0.84(0.65-1.07)	0.77(0.64-0.93)**	0.72(0.49-1.08)	0.82(0.70-0.96)*
HDL-C				
Each1mmol/L increment	0.84(0.47-1.48)	0.67(0.45-1.00)*	1.04(0.45-2.40)	0.69(0.49-0.99)*
Tertiles of HDL-C				
Low	1.00 reference	1.00 reference	1.00 reference	1.00 reference
Middle	0.68(0.43-1.07)	1.08(0.75-1.56)	0.85(0.41-1.80)	0.92(0.68-1.25)
High	0.82(0.64-1.05)	0.80(0.67-0.96)*	0.85(0.57-1.29)	0.81(0.70-0.95)**

TC =Total cholesterol; TG=triglycerides, LDL-C =low density lipoprotein; HDL-C=high density lipoprotein; *p<0.05; **p<0.01; Data in the table are adjusted odds ratio (OR) and 95% confidence intervals (CI, in parentheses); † Adjusted for potential confounders including age, gender, marital status, residence education level, current cigarette smoking practices, current alcohol drinking habits, central obesity, sleep quality, anemia, hypertension, type 2 diabetes mellitus and CKD.

and LDL-C in women, and with increasing TC, TG, LDL-C and HDL-C in the oldest old after full adjustment (Table 4). There was no significant association between cholesterol and cognitive impairment among young elderly (under age 79).

To explore the range of cholesterol in relation to cognitive impairment, a multivariable logistic model was conducted with the lowest tertile as the reference. Compared with the lowest tertile of TC and LDL-C, the risk of cognitive impairment was significantly decreased for the middle and highest tertile after adjustment, the odds ratio and 95% CI were 0.74(0.56-0.98) and 0.73(0.62-0.84) for TC, 0.70(0.51-0.96) and 0.82(0.70-0.96) for LDL-C. These associations remained significant after adjustment in basic and final models (Table 3). In addition, the decreased risk of cognitive impairment was also found in the highest tertile of HDL-C compared with lowest tertile of HDL-C, with an adjusted OR of 0.81(0.70-0.94) (Table 3).

The analyses were repeated, stratified by gender and age groups. Notably, compared with individuals in the lowest tertile of TC, both men and women with the highest tertiles of TC had a lower risk of cognitive impairment. However, a decreased risk of cognitive impairment was only revealed in women but not in men in those with the highest tertiles of LDL-C and HDL-C. In the oldest-old (age≥80 years) groups, the highest tertiles of TC, LDL-C and HDL-C were associated with a better cognitive performance compared to those with the lowest tertile. However, there was no significant association between

cholesterol except LDL-C and cognitive impairment among young elderly (age≤79 years) (Table 4).

Discussion

This study revealed that there was a significant positive relationship between the serum cholesterol level and preserved cognitive function among Chinese elderly. This association was also revealed in men and women sub-samples, and in the oldest old, even though some of the associations were attenuated.

Currently, the role of cholesterol in the pathogenesis of cognitive impairment in the elderly remains unclear. Previous studies, which were inconsistent with ours, argued that higher levels of TC, TG, and LDL-C increase the risk of cognitive impairment (4, 5). A suggested explanation for a negative association was that TC, TG, and LDL-C might increase the β-amyloid production and deposition in the brain, and promote the formation of neurotoxicity fibrils and neuritis, thereby accelerating the progression of cognitive impairment or dementia. However, reports have revealed that it is not higher TC, TG, or LDL-C but lower HDL-C in plasma that is associated with the increased numbers of neurotic plaques and neurofibrillary tangles (24) and that plasma cholesterol levels had no effect on brain HMG-CoA reductase activity (25).

Notably, our findings are consistent with several previous studies (10-15, 26-28). One cross-sectional population based study found that higher levels of TC were associated with a decreased risk of incident Alzheimer's disease after adjustment for many confounding factors among the Finnish elderly aged 69 to 78 (13). Prospective longitudinal studies also revealed that hypercholesterolaemia was associated with a protective effect for development of dementia and cognitive decline in the Australian elderly aged 75 years and over (14). Lower naturally occurring TC levels are associated with poorer performance on cognitive measures among elderly aged 55 to 88 years in the Framingham Heart Study (15). Further, in a 26 year follow-up study of elderly, serum cholesterol levels decreased in elderly who developed mild cognitive impairment, while increased in those who maintained normal cognition in Asian elderly (11). Moreover, our previous study found a significant association between high normal plasma TG and preserved cognitive function in the Chinese oldest old (12), which was also confirmed in this study. There was also emerging evidence that cholesterol-lowering therapy was associated with some adverse effects on cognitive function in rodents (26) and human (27). In 2012, the US Food and Drug Administration (FDA) updated information associated with statin prescriptions to include possible adverse cognitive effects, including memory problems and confusion (28).

The present results may be explained by several related theories and empirical studies. It may be conjectured that high levels of cholesterol suggest a better general health status or socioeconomic status in the elderly. Lower cholesterol has been correlated with a higher risk of mortality in the elderly (29, 30), and may accompany chronic diseases, cancer, and poor intake or absorption of nutrients (31, 32), which in turn may be associated with cognitive impairment (33). Central obesity, which may indicate a better nutritional status, was associated with better cognitive function in our study ($p<0.01$). And higher consumption of dairy products, which may also means a better nutrition intake and a higher level of cholesterol, has been proved to decrease risk of cognitive decline among female elderly (34). Specifically, higher cholesterol concentration may indicate a better liver functioning, as low cholesterol levels may be a symptom of liver disease, which has been linked to poorer cognitive function (35).

Low cholesterol may be related to poorer cognitive performance because plasma cholesterol promotes the structural integrity and modulates fluidity of neuronal cells (3). Interestingly, a deficiency in cellular cholesterol or a deficiency in cholesterol supply to neurons was shown to inhibit dendrite outgrowth (36) and synaptogenesis (37), and to induce neurodegeneration (25, 38). Cholesterol may also be a limiting factor for synaptogenesis in the central nervous system (39). Cholesterol is an essential molecule for many other physiologic processes as well. Cholesterol plays an important role in the transformation or transportation of steroid hormones (estrogens, androgens) and lipid-soluble vitamin and delivery of lipid-soluble vitamin to cells, which are essential for basic synaptic integrity and neurotransmission (40-42). The observed positive association between cholesterol level and cognitive function is also consistent with recent studies showing that cholesterol depletion may increase the risk of blood-brain barrier breakdown, with resulting progressive synaptic and neuronal dysfunction and cognitive impairment (43).

It has also been found lower cholesterol was specifically associated with poorer immune level and decreased defense against bacteria and viruses (44, 45), which were also associated with poorer cognitive function (46). Serotonergic activity may also partly account for the negative cognitive effects of low cholesterol (33), membrane cholesterol stabilizes the serotonin receptor (47), and certain serotonin receptor ligands have the ability to modify or improve memory or cognition (48). In addition, it is known that the membrane cholesterol/phospholipid ratio increases with age, with consequent increases in membrane rigidity (49); such an accumulation may actually serve to protect neuronal tissue from oxidative damage in animals (50). And in vitro study has suggested that cholesterol acts as an antioxidant and therefore has a protective role in the pathogenesis of dementia (51).

Some studies showed that the association of cholesterol with cognitive function could differ between elderly women and men. The gender differences may be related to the faster transport of lipids in the bloodstream of women compared with men in the blood stream, earlier age-graded serum cholesterol changes in women, and higher concentrations of cholesterol in elderly women than men (52-54). However,

our results underscored the importance of keeping cholesterol concentration within the high normal range, although a longitudinal follow-up is needed to determine whether higher cholesterol prevents later life cognitive impairment in both men and women.

In addition, our results suggested that the protective impact of a high normal level of serum cholesterol concentration on cognitive function is more prominent after age 80. It is important to note that lipid concentration decrease with aging and may not play the same role they have played in middle age or in younger elderly. The successful aging of the elderly depends on their successful responses to all kinds of risk factors in middle age or in young elderly. Elderly who survive to oldest-old age with a high cholesterol level may be relatively invulnerable to the potential adverse effects of high cholesterol, including cognitive impairment. Many studies have suggested that high cholesterol levels in mid-life (55), but not late life (56) is associated with an increased risk of cardiovascular disease. It is possible that a similar age-dependent phenomenon exists in the association of cholesterol with cognitive impairment (16).

Strengths and limitations

A strength of this study is the large sample size of community-based elderly (n = 2000) that permits us to focus not only on the association of cholesterol with cognitive impairment, but also to explore the effect of gender and age group differences. With 1297 oldest old allowed us to identify statistically significant and meaningful associations for this increasingly important group.

This study has several limitations. First, the cross-sectional sample does not allow us to examine causation, and numerous comparisons are conducted, which could raise the possibility of type 1 error in our significant findings. Moreover, we did not adjust for some confounding factors that are related to cognitive decline and cognitive function, such as specific biologic (e.g., APOE genotype), psychological (e.g., depression), dietary and/or behavioral factors. Furthermore, we did not investigate treatment with lipid-lowering drugs. Because only 6.6% participants in the self-report questionnaire were diagnosed as having dyslipidemic by a doctor, it was unlikely that use of lipid-lowering drugs would affect the association. In addition, our study focused on Chinese elderly in longevity areas, so it may not be generalizable to other ethnic or age groups.

Conclusions

In conclusion, our findings suggested that there is a significant relationship between the high normal level of cholesterol and preserved cognitive function in Chinese elderly, specifically in the oldest-old. Low levels of cholesterol may serve as an indicator for potential cognitive impairment in elderly in the medical practice. Additional prospective cohort studies researches are needed to confirm the noted age difference in the association of cholesterol with cognitive impairment in the elderly in present study.

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Conflict of interest: The authors declare that there are no conflicts of interests.

Ethical standards: The authors declare that all the experiments of this study complied with the current laws of China in which they were performed.

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