

High normal plasma triglycerides are associated with preserved cognitive function in Chinese oldest-old

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Abstract

Objective: to explore the relationship between blood lipids/lipoproteins and cognitive function in the Chinese oldest-old.

Design: multivariate statistical analysis using cross-sectional data.

Setting: community-based setting in longevity areas in China.

Subjects: eight hundred and thirty-six subjects aged 80 and older were included in the sample.

Methods: plasma total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure and fasting plasma glucose were measured and information about demographics and lifestyle was collected. Cognitive status was assessed using the Mini-Mental State Examination (MMSE).

Results: cumulative logit model analysis showed that triglyceride was significantly negatively associated with cognitive impairment. By general linear modelling, there was a significant linear trend of MMSE scores with the level of triglyceride, but not with levels of cholesterol after adjustment. The odds ratio (OR) of cognitive impairment (MMSE score < 18) was significantly reduced for the highest quartile of plasma triglyceride concentration (OR: 0.52, 95% CI: 0.33–0.84), but not for the second or third quartile, compared with the lowest quartile (adjusted models). There were no significant associations between cognitive impairment and cholesterol.

Conclusion: we concluded that high normal plasma triglyceride was associated with preservation of cognitive function while lower concentrations were not in the Chinese oldest-old.

Keywords: *triglycerides, cognitive function, lipids, oldest-old, elderly*

Introduction

About 10% of people aged over 65 have cognitive impairment, including mild deficits and dementia [1]; prevalence of cognitive impairment among a sample of Chinese older

adults aged 90 years and over was 57.8% overall and up to 67.2% among women [2]. Cognitive impairment contributes to decreased quality of life, increased neuropsychiatric symptoms and healthcare costs [3–5]. Cognitive health in old age is likely related to cardiovascular risk factors [6], but there is

a need to clarify the impact of these factors and the mechanisms through which they influence cognitive function [7].

Prospective and cross-sectional observational studies have investigated the relationship between cognitive impairment and the level of serum lipids/lipoproteins, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL), but these studies have yielded inconsistent and conflicting results. Some studies found no relationship between cognitive impairment and lipids/lipoproteins [2, 7]. Some studies show a relationship between cognitive impairment and the low HDL level [8, 9–11], while some did not [12]. High levels of TC or LDL have been thought to be associated with an increased risk of cognitive impairment or Alzheimer's disease (AD) [13]; and in some studies, the effect of TC on cognition occurred in midlife but not late life [14, 15, 16, 17]. In contrast, the Framingham Heart Study found high cholesterol levels were associated with improved cognitive function [18]. Limited studies have considered the relationship of TG to cognition, and the findings are inconsistent. Among them, two studies concluded that the level of TG was lower in patients with dementia [9] or AD [19] compared with control groups, while several found no relationship between TG and cognition [2, 10, 20], and others found that high levels of TG were inversely related with performance on various cognitive measures [21, 22].

Except for one study focused on mild cognitive impairment [7], few studies have taken into consideration the degree of cognitive impairment in its relationship with lipids. Although the risk of cognitive impairment increases with age, literature concerning the oldest-old, is rare, especially for developing countries, and results are mixed and confusing. For these reasons, the goal of our study was to address these knowledge gaps through analyses of the relationships between levels of all four types of blood lipids/lipoproteins (TC, TG, HDL and LDL) and cognitive function among a group of the oldest-old in China.

Materials and methods

Subjects and setting

Participants in this study represent a subset of individuals who live in seven longevity areas in China and were interviewed in 2008–09 during the fifth wave of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). The study design was community-based, and has been described elsewhere [23], (more information can be found in the Supplementary data available in *Age and Ageing* online, Appendix 1).

Questionnaire survey and health examination

The nationwide CLHLS collected home-based interview data about sociodemographics, smoking, alcohol use and leisure activities; questions were answered by one of the participant's adult relatives if the participant was unable to answer. For this subsample, in-home physical examinations

were also conducted by medical personnel and biological specimens were collected.

Assessment of cognitive function

Cognitive function was measured using the Mini-Mental State Examination (MMSE) [24], which is widely used for assessing cognitive mental status [25, 26]. MMSE scores ranged from 0 to 30, with higher scores indicating better cognition. Cognitive function was classified into four groups based on the standard classification system [27–29]: no cognitive impairment (scores 24–30); mild cognitive impairment (scores 18–23); moderate cognitive impairment (scores 10–17) and severe cognitive impairment (scores 0–9). When logistic regression was conducted, a dichotomous variable, as some studies used [2, 30], was created using a cut-off of <18 as indicating cognitive impairment.

Lab testing

Blood samples were collected after an overnight fast from all willing participants ($n = 1,932$). Plasma lipids/lipoproteins (TC, TG, HDL and LDL) and fasting plasma glucose (FPG) were measured by an Automatic Biochemistry Analyzer (Hitachi 7180, Japan) using commercially available diagnostic kits (Roche Diagnostic, Mannheim, Germany). All laboratory analyses were conducted by the central clinical lab at Capital Medical University in Beijing.

Description of covariates

Covariates included sociodemographic information (age, sex, ethnicity and education), lifestyle (smoking and drinking), leisure activities, biological factors [systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG], and prevalence of hypertension and diabetes. Education was defined as 'no' if the subject had no education whatsoever, and as 'yes' if the subject ever received any formal education. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. For this study, diabetes was defined as FPG ≥ 7.0 mmol/l. Leisure activities included: outdoor activities, growing flowers, reading, raising pets, playing cards, watching TV, listening to the radio, and participating in social activities. A positive response to any leisure activity was coded as a positive value for the leisure activity variable.

Statistical analysis

Subject characteristics were compared by analysis of variance for continuous variables and by Chi-square tests (or trend tests if applicable) for dichotomous variables across the four groups of cognitive status. Two methods of statistical analysis were employed, cumulative logit models and logistic regression.

Cumulative logit models were used to analyse the association between lipid/lipoproteins (coded as continuous variables) and degree of cognitive impairment (none, mild, moderate, severe), as the dependent variable. ORs and

95% confidence intervals (95% CIs) were calculated. Models were run without adjusting for any covariates, then adjusted for demographic variables (model 1), and also for smoking, drinking, leisure activities and SBP (model 2).

Lipids/lipoproteins were divided into four groups (lowest, second, third, highest) according to quartile values of plasma concentrations. Analysis of variance was used to compare unadjusted and adjusted MMSE scores among the quartiles of change in lipids/lipoproteins. Linear trends of MMSE scores across strata of lipids/lipoproteins were tested to analyse the relationship between lipid/lipoproteins and the MMSE score using the linear estimate from a general linear model. To elucidate the level of lipids/lipoproteins associated with cognitive impairment, logistic regression was used to evaluate the odds of cognitive impairment (MMSE cut-off score of <18) as a function of lipid/lipoprotein quartiles, using the lowest quartile as the reference group.

All statistical analyses were performed with SAS, version 9.1.3 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant, and all P -values were two-sided.

Results

Characteristics of study participants

Among the 2,029 CLHLS participants, 1,128 were aged 80 years and over and included in this substudy. We excluded subjects with missing data on key variables and the final sample size was 836 participants. The characteristics of the subjects by category of cognitive status are listed in Table 1.

The majority were female. The percentage with any cognitive impairment was 65.31%, most of which was severe impairment. With increasing degree of cognitive impairment, the percentage of subjects who had no education also increased ($P < 0.001$), and the percentage who practiced leisure activities decreased ($P < 0.001$). SBP, DBP, FPG, and prevalence of hypertension and diabetes were not significantly different by cognitive status ($P > 0.05$).

Cumulative logit modelling analysis of relationship between lipid/lipoproteins and cognitive status

Table 2 shows the results of cumulative logit modelling. When the model for TC and HDL was adjusted, the relationships became insignificant ($P > 0.05$), though it is significant in the unadjusted model. There was no association between LDL and cognitive status in univariate or multivariate analyses ($P > 0.05$).

Although TG was not associated with cognitive status in unadjusted models, the association of TG and cognition was significant upon adjustment for demographic characteristics in model 1 ($P < 0.01$), with odds ratio (OR) 0.67 (95% CI: 0.52–0.86). A significant association was maintained even after adjustment for leisure activities, smoking, drinking and SBP in model 2 ($P < 0.01$), with OR 0.65 (95% CI: 0.50–0.84). In addition, the standardised β (regression coefficient) of age was higher than that of TG (0.49 versus -0.11). A higher level of TG was associated with a decreased risk of cognitive impairment independent of cognitive function.

Table 1. Characteristics of study subjects by level of cognitive status ($n = 836$)^{a,b}

	No impairment	Mild impairment	Moderate impairment	Severe impairment	F/Z	P -value
n	290 (34.69)	118 (14.11)	114 (13.64)	314 (37.56)		
MMSE	27.72 \pm 1.90	20.47 \pm 1.74	13.68 \pm 2.29	2.00 \pm 0.99	6014.87	<0.001
Age	91.24 \pm 7.81	94.63 \pm 7.70	95.23 \pm 6.65	98.86 \pm 5.76	60.99	<0.001
Sex						
Male	129 (44.48)	28 (23.73)	20 (17.54)	60 (19.11)	-6.91	<0.001
Female	161 (55.52)	90 (76.27)	94 (82.46)	254 (80.89)		
Ethnicity						
Minority	87 (30)	9 (7.63)	6 (5.26)	7 (2.23)	-9.94	<0.001
Han	203 (70)	109 (92.37)	108 (94.74)	307 (97.77)		
Education						
No	214 (74.31)	101 (85.59)	106 (92.98)	292 (93.29)	6.76	<0.001
Yes	74 (25.69)	17 (14.41)	8 (7.02)	21 (6.71)		
Leisure activities	262 (90.34)	94 (79.66)	84 (73.68)	183 (58.28)	9.08	<0.001
Smoking	61 (21.03)	17 (14.41)	21 (18.42)	38 (12.10)	2.73	0.006
Drinking	49 (16.90)	16 (13.56)	16 (14.04)	45 (14.33)	0.83	0.41
SBP	144.44 \pm 26.91	140.12 \pm 26.55	139.26 \pm 24.18	140.31 \pm 25.86	1.83	0.14
DBP	78.98 \pm 14.99	79.76 \pm 17.42	79.45 \pm 11.98	77.45 \pm 14.90	1.04	0.37
FPG	5.43 \pm 2.20	5.19 \pm 1.07	5.37 \pm 1.23	5.41 \pm 1.39	0.60	0.62
Diabetes	29 (10.00)	12 (10.17)	12 (10.53)	27 (8.60)	0.56	0.57
Hypertension	174 (60.00)	69 (58.47)	64 (56.14)	190 (60.51)	-0.07	0.94

^aData listed as n (%) for dichotomous variables, including sex, ethnicity, education, leisure activities, smoking, drinking, diabetes and hypertension, were tested for trend among the four groups using the Chi-square test, with χ^2 values were showed. Data listed as mean \pm SD for continuous variables, including age, MMSE, SBP, DBP, FPG, were tested for differences among the four groups using analysis of variance, with F values were showed.

^bCognitive status was classified into four groups based on the standard classification system.

MMSE scores across strata of lipid/lipoprotein levels

Mean ± SD levels of the highest quartile of TG, TC, HDL and LDL were 1.85 ± 0.64, 5.17 ± 0.62, 1.62 ± 0.19 and 3.05 ± 0.51 mmol/l, respectively. Notably, the upper 95th percentile levels of the four lipids/lipoproteins were 2.15, 5.54, 1.79, 3.38 mmol/l, and in particular, the upper 95th percentile of TG for this cohort was still within the normal range (hypertriglyceridaemia is defined as >200 mg/dl or >2.26 mmol/l [31, 32]). In other words, almost all subjects' TG levels were within a normal range, so the highest TG

quartile represented a high normal level. Analysis showed that the trends across TC, HDL and LDL strata were not significant after adjustment for covariates ($P > 0.05$), while that across TG quartiles strata was ($P < 0.01$) (the Supplementary data are available in *Age and Ageing* online, Appendix Table).

Odds ratios of cognitive impairment over strata of lipids/lipoproteins

To determine the range of lipid/lipoprotein concentrations associated with cognitive impairment, we conducted logistic regression analysis using the lowest quartile of lipid/lipoprotein concentrations as the reference group. TC and HDL were positively associated with cognitive impairment before adjustment for covariates, but the associations were attenuated after adjustment (Table 3).

A high normal level of TG (the highest quartile) was associated with a decreased OR (0.52, 95% CI: 0.326–0.839) of cognitive impairment after adjustment ($P < 0.01$). When subjects in the second or third quartile of TG were contrasted with the lowest quartile group, no significant association between TG and cognitive impairment was observed.

Discussion

Positive relationship between the high normal level of TG and preserved cognitive function

This study revealed a significant and beneficial effect of high normal TG on cognitive function after adjustment for covariates. Cumulative models showed age significantly increased the odds of cognitive impairment, while higher TG levels decreased the odds of cognitive impairment. Age was associated with the higher TG level but lower

Table 2. Cumulative logit model analysis of cognitive status and lipids/lipoproteins^a

	β	SE	Wald χ^2	OR (95% CI)
TG				
Unadjusted	-0.11	0.11	0.82	0.9 (0.72–1.13)
Model 1	-0.41	0.13	9.91	0.67 (0.52–0.86)**
Model 2	-0.43	0.13	10.62	0.65 (0.50–0.84)**
TC				
Unadjusted	0.19	0.06	8.76	1.21 (1.07–1.37)*
Model 1	-0.09	0.07	1.72	0.91 (0.79–1.05)
Model 2	-0.08	0.07	1.11	0.93 (0.80–1.07)
HDL				
Unadjusted	0.97	0.21	21.22	2.65 (1.75–4.01)**
Model 1	0.12	0.23	0.25	1.12 (0.71–1.77)
Model 2	0.19	0.24	0.62	1.21 (0.76–1.92)
LDL				
Unadjusted	0.12	0.08	1.83	1.12 (0.95–1.33)
Model 1	-0.04	0.09	0.16	0.96 (0.81–1.15)
Model 2	-0.02	0.09	0.04	0.98 (0.82–1.18)

^aCognitive status was separated into four groups (none, mild, moderate or severe impairment), and β indicate the coefficient derived from the cumulative logit model, SE is the standard error of β . Model 1 adjusted for age, sex, ethnicity and education; Model 2 adjusted for age, sex, ethnicity, education, smoking, drinking, leisure activities and systolic blood pressure.

* $P < 0.05$.

** $P < 0.01$.

Table 3. Odds ratios of cognitive impairment over strata of lipid/lipoprotein for all subjects^a

	Lowest quartile	Second quartile (odds ratio and 95% CI)	Third quartile (odds ratio and 95% CI)	Highest quartile (odds ratio and 95% CI)
TG				
Unadjusted	1	1.44 (0.98–2.11)	1.35 (0.92–1.99)	0.92 (0.62–1.36)
Adjusted	1	1.25 (0.79–1.98)	1.07 (0.66–1.72)	0.52 (0.33–0.84)**
TC				
Unadjusted	1	1.42 (0.96–2.09)	1.60 (1.09–2.36)*	1.84 (1.25–2.71)**
Adjusted	1	1.04 (0.65–1.66)	1.09 (0.69–1.75)	0.94 (0.58–1.51)
HDL				
Unadjusted	1	1.53 (1.03–2.26)*	2.00 (1.35–2.96)**	2.20 (1.49–3.24)**
Adjusted	1	1.11 (0.69–1.77)	1.25 (0.78–2.01)	1.18 (0.74–1.90)
LDL				
Unadjusted	1	1.21 (0.83–1.78)	1.37 (0.93–2.01)	1.30 (0.89–1.91)
Adjusted	1	0.81 (0.51–1.29)	0.90 (0.56–1.45)	0.71 (0.44–1.14)

^aCognitive impairment was defined as a score of less than 18 on the MMSE. Adjusted represents model 2 adjusted for age, sex, ethnicity, education, leisure activity, smoking, drinking and systolic blood pressure. The lowest quartile was the reference group for the other lipid/lipoprotein quartiles.

* $P < 0.05$.

** $P < 0.01$.

cognition, which obscured the positive effect of TG on cognitive function that was revealed upon adjustment for age effects, and standardised β of age in model 2 was far higher than that of TG (0.49 versus -0.11). This was consistent with another study, which proposed that age-related decline in cognitive function may have attenuated the effect of other risk factors, such as lipids/lipoproteins [2]. This effect represents an example of suppression, age being the variable which increased the predictive validity of another variable (TG) by its inclusion in the regression.

Currently, there are very few studies on the direct association between cognitive function and TG. Two epidemiology studies observed that subjects with probable AD or dementia had significantly lower serum TG compared with the control group, but the authors did not provide explanation or potential causes [9, 19]. The results are consistent with our current findings. However, some other studies have concluded that hypertriglyceridaemia would produce cognitive impairment [21, 22, 33]. Taken together, these studies suggest that both extreme low and high levels of TG might promote cognitive impairment. The mean level of TG in this subsample was less than 1.2 mmol/l, and the 95th percentile of TG was 2.15 mmol/l, while hypertriglyceridaemia is defined by a TG level equal to or greater than 2.26 mmol/l [31, 32]. This suggests that higher normal concentrations of TG are beneficial for cognitive function, while a pathological concentration of TG may outweigh any protective effects. This conclusion is supported by some related studies and theories.

Firstly, our results are consistent with recent molecular biology studies showing that TGs can increase the blood-brain barrier transport of ghrelin and insulin [34, 35], which are peripherally derived peptides that have positive effects on cognition. Raising serum TG levels could also affect the expression of orexigenic hypothalamic peptides [36], many of which have effects on cognition [37]. In this way, TG could play an important role in improving cognition.

Secondly, circulating TG during fasting is in the form of very-low-density lipoprotein, which is synthesised in the liver using fatty acids. Therefore, higher normal levels of TG indicate an abundance of circulating fatty acids, which are crucial molecular components that determine the brain's integrity and performance [38], and maintaining an abundant level of fatty acids is essential for maintaining good brain function. In addition, unsaturated fatty acids could decrease production of inflammatory cytokines or decrease tissue responsiveness [39]. Studies have shown that high intake of unsaturated fatty acids could protect cognitive function or decrease the risk of dementia [40].

Thirdly, we also think plasma TG may be a meaningful indicator of nutrition status [41–43], so high normal levels of TG may demonstrate adequate but not excessive intake of nutrients and energy. Lee *et al.* showed that good nutritional status, maintaining through intake of sufficient amounts and variety of foods, is important for maintaining cognitive function [44]. In this study, the co-existence of important

nutrients with fatty acids, including anti-oxidants and vitamins, may have formed the basis of good nutritional status, which promoted maintenance of cognitive function.

No association with cholesterol at oldest-old ages

Our study and several other studies [7, 15] failed to substantiate such a relationship, while some others concluded that abnormal levels of lipoprotein impaired cognitive function [8, 9, 10, 11]. In addition to ethnic difference of subjects, another explanation for inconsistent results may be different age ranges of subjects in different studies. The subjects from many studies were younger, while the association between lipoprotein and cognitive function may differ by age, as some studies showed [16]. The effect of cholesterol on cognition may be non-linear with age, for instance, being significantly associated at younger ages but not among the oldest-old. Furthermore, the pattern of cholesterol change may be more relevant for late-life cognition than cholesterol levels after midlife [15]. In addition, 'survivor bias' may have also influenced the results.

Strengths and limitations of this study

This is one of few studies which investigated the blood lipid/lipoprotein profiles related to cognitive impairment in the oldest-old in a developing country, and to the best of our knowledge, this is the first study in which various degrees of cognitive impairment were considered in analyses of the association with lipids/lipoproteins. Notably, this is the first study that investigated the level of lipids/lipoproteins associated with cognitive function, and adjusted for various important confounders including leisure activities [45], which was not considered in many other studies that evaluated the association of cognitive impairment and lipids/lipoproteins. This might help explain the difference in conclusions among studies, because leisure activities are not only different from general physical activities, but also more achievable than general physical activities among the oldest-old.

There were two limitations in our study. Firstly, cognitive function had been assessed 2–5 months before the blood samples were taken, so the data we not precisely contemporaneous; however, we do not think that dietary habits or plasma lipid/lipoprotein levels would change in such a short time. For this reason, our analyses considered all data as cross-sectional. Secondly, our subjects were Chinese oldest-old, so these results may not be generalised to other populations of different nationalities or ages.

In conclusion, we found that high normal levels of TG were significantly related to lower odds of cognitive impairment while there were no significant associations between cognitive impairment and cholesterol (TC, HDL and LDL). These results suggest that TG supplementation to high normal levels is worthy of study in clinical trials to determine whether it may improve cognitive function in older adults.

Key points

- TG was negatively associated with cognitive impairment among oldest-old Chinese adults, those with the high normal level of TG have good performance in cognitive function.
- Cholesterol (including TC, LDL and HDL cholesterol) was not associated with preserved cognitive function, after adjustment for confounding factors.
- TG supplementation to high normal levels maybe beneficial to improve cognitive function in older adults.

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Conflict of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

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Owing to space constraints, only the most important references are listed here and represented by bold type through the text. The full list of references is available on the Supplementary data are available in *Age and Ageing* online.

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Depressive symptoms in addition to visual impairment, reduced strength and poor balance predict falls in older Taiwanese people

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Abstract

Objective: to determine whether depression is an important and independent predictor of falls in community-dwelling older people living in Taiwan.

Design: longitudinal study.

Setting: five randomly selected villages from Tainan city, Taiwan.

Participants and methods: in total, 280 community-dwelling people not taking anti-depressant medication aged 65–91 years (mean age 74.9). Participants completed the Geriatric Depression Scale and underwent a range of sensorimotor, balance and mobility tasks and were then followed up for 2 years with monthly telephone calls to determine falls incidence.

Results: of the 260 participants with complete follow-up data, 174 (66.9%) experienced no falls, 51 (19.6%) fell once and 35 (13.5%) fell two or more times. Depressive symptoms were significantly more prevalent in recurrent fallers (40.0%) and once-only fallers (27.5%) compared with non-fallers (16.1%). Negative binomial regression analysis identified depression, poor depth perception, reduced lower limb strength and increased sway as independent and significant predictors of falls.