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Association of blood lipid level with cognitive performance in older adults: A cross-sectional study based on NHANES

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Abstract: *This study aimed to explore the relationship between blood lipid levels and cognitive performance in older adults. The information was extracted from the American National Health and Nutrition Examination Survey (2011-2014), encompassing data on blood total cholesterol (TC), high density lipoprotein (HDL-C), cognitive performance, and 11 covariates (including age, gender, race, etc.). Logistics regression analysis shows that when all covariables are corrected, compared with HDL-C of the lowest third array, The OR values and 95%CI of the highest third array are 1.587(1.236-2.039), 1.533(1.195-1.966) and 1.774(1.393-2.258), respectively. When no covariates are corrected, the OR value and 95%CI of the highest When no covariates are corrected, the OR value and 95%CI of the highest tripartite array are 1.587(1.236-2.039), 1.444(1.124-1.855) and 1.774(1.393-2.258), respectively, compared with the TC of the lowest tripartite array. No correlation was found between TC and cognitive ability. There was no statistical significance between the TC:HDL-C ratio and the CERAD test, but in the AF test, compared with the TC of the lowest tripartite. There was no statistical significance between the TC:HDL-C ratio and the CERAD test, but in the AF test, compared with the TC:HDL-C ratio of the lowest third array, The OR values and 95%CI of the middle third array are 0.766(0.599- 0.981), 0.723(0.563-0.929) and 0.750(0.572-0.982) respectively in the three models, and the correlation is not strong in the DSST test.* ***Conclusion*** *HDL-C level was positively correlated with the TC:HDL-C ratio of the lowest third array. TC was positively correlated with cognitive ability in the elderly, and TC: HDL-C ratio was negatively correlated with cognitive level in the elderly. The conclusions of this study need to be validated by further prospective cohort studies.*

Keywords: *cognitive performance; total cholesterol; High-density lipoprotein; Senescence*

1. Introduction

In the context of global aging, cognitive decline is an important public health problem among older adults. Cognitive dysfunction in older adults not only affects patients' quality of life, but also places a serious burden on caregivers and patients' families[1] . Cognitive decline involves many factors[2] . First, an unhealthy lifestyle is a recognized factor in cognitive decline, and controlling smoking, developing a sensible exercise program, and controlling appropriate body weight can reduce cognitive decline[3] .Control of smoking, a sensible exercise program, and control of body weight can reduce cognitive decline. Secondly, diet. A study in China showed that improving the quality of diet and adhering to the Dietary Guidelines for Chinese may improve cognitive performance in Chinese adults aged 55 and older[4] .And studies have pointed to a link between high coffee intake and better cognitive performance[5]. In addition, lipid profile is another important factor in cognitive impairment. There are gender and regional differences in the correlation between the two[6] . Also low cholesterol levels lead to reduced verbal fluency[7] . A two-way Mendelian randomization study found a causal effect of hypertension, any stroke and its subtypes (ischemic and small vessel stroke) on cognitive performance[8] . Correspondingly, One meta-analysis suggested homocysteine (Hcy), C-reactive protein (CRP), total cholesterol (TC), and low density lipoprotein (LDL) as possible biomarkers for patients with post-stroke cognitive impairment[9] . A cross-sectional study conducted in Xi'an, China, showed that high levels of serum TC and LDL-C may be risk factors for cognitive impairment in elderly men

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and women, respectively, while high levels of serum TG may be a protective factor for cognitive impairment in middle-aged men[10] . Cerebral infarction patients from the city of Miaozhou showed that peripheral blood non-HDL-C/HDL-C levels were a risk factor for secondary cognitive impairment after cerebral infarction[11] . Another study indicated that HDL-C may be a reference indicator for screening Alzheimer's disease and vascular dementia[12]. The study also suggests that HDL-C may be a reference for screening for Alzheimer's disease and vascular dementia. Although the above studies suggest that multiple lipid parameters are risk factors for cognitive dysfunction, the results are not consistent. Meanwhile, there are no studies showing whether serum TC:HDL-C ratio can be used as an indicator of cognitive decline. The aim of our study was to determine whether there is an association between TC and HDL-C levels, as well as TC:HDL-C, and cognitive performance in older adults, and to provide a theoretical basis for cognitive disorders in older adults in research and clinical practice.

2. Materials & methods

2.1 Study population

The NHANES is a 2-year-cycle cross-sectional survey conducted by the Centers for Disease Control and Prevention (CDC) of America, which aims to evaluate the health and nutritional status of the U.S. population. Representative samples of the non-institutional U.S. NHANES database is a publicly available dataset used by people worldwide . All participants have provided informed consent both before the interview and examination stages[13] .

A total of 19,931 individuals participated in the data survey during 2011-2014, and we limited our analysis to 3,632 participants aged 60 years or older. Of these, we excluded participants with incomplete cognitive testing (776) and incomplete lipid data (154). In addition, participants with cancer or malignant tumors (534) were excluded. After exclusion, there were a total of 2,168 participants aged 60 years or older in this study (1,055 men and 1,113 women) .

2.2 Cognitive capacity assessment

A series of assessments for cognitive performance in NHANES were used in 2011–2014 and cognitive testing was performed among participants aged 60 years or older. Cognitive performance was assessed in a household interview or a Mobile Examination Center (MEC) and was evaluated by the Consortium to Establish a Registry for Alzheimer’s disease (CERAD) Word Learning sub-test, the Animal Fluency test and the Digit Symbol Substitution Test (DSST). These tests, which have been used in large screenings, epidemiological and clinical studies[14], evaluated working memory, language, processing speed, and executive functioning in older adults.

Although there was no consensus definition of low cognitive function, previous studies using the NHANES database defined participants who scored the lowest 25th percentile in the cognitive tests as having low cognitive function[15]. Thus, this research adopted <25th percentile as the cutoff of low cognitive performance. Participants who scored CERAD < 5, AF < 13, and DSST < 34 were classified into the low cognitive function group, otherwise categorized into the normal cognitive function group.

2.3 Measurement of Serum Lipids Profiles

TC and HDL-C data were obtained from the "HDL" and "TCHOL" files in the laboratory data. Based on the TC and HDL-C data, the TC:HDL-C ratio was calculated. The TC, HDL-C levels and TC:HDL-C ratios were divided into three groups according to tertiles.T1: (<33rd percentile), T2: (≥33rd to 67th percentile), T3: (≥67th percentile).

2.4 Covariates

In addition to serum levels of TC and HDL-C, we investigated some potential confounding factors, which included: age, gender, race, educational level, marital status, body mass index (BMI), smoking, drinking ,hypertension and diabetes.;The PIR is the ratio of family income to poverty, calculated by dividing family income by the poverty guidelines.

2.5 Statistical Analysis

All statistical analyses were performed using SPSS 27.0. The Kolmogorov–Smirnov normality test was adopted to test the normality of continuous variables, and we described normally distributed variables with mean ± standard deviation (SD) and non-normally distributed variables with median (interquartile range). Student's t-test was used to compare the mean levels between the low cognitive performance group and the normal cognitive performance group if the variable was normally distributed. The Mann–Whitney U test was adopted if the variable was not normally distributed. Chi-square tests were chosen to compare the percentages of categorical variables between the different groups.

The relationship between serum levels of TC and HDL-C and TC: HDL-C and cognitive ability was analyzed using binary logistic regression analysis, where serum levels of TC and HDL-C and TC: HDL-C were categorized on the basis of tertiles, and T1 served as the control group. Model 1 was adjusted for age and sex. Model 2 was also adjusted for age, sex, race, education, marital status, poverty-to-income ratio, body mass index, drinking status, smoking status, diabetes, and hypertension.

3. Results

3.1 Characteristics of the Study Population

Table 1: Characteristics of the study population.

variant	(grand) total	CERAD		*P*	AF		*P*	DSST		*P*
	2168	Low Cognitive Performance (n=498)	Normal Cognitive Performance (n=1,670)		Low Cognitive Performance (n=497)	Normal Cognitive Performance (n=1,671)		Low Cognitive Performance (n=554)	Normal Cognitive Performance (n=1,614)	
Age , *n* (%)				<0.001			<0.001			<0.001
60~69	1 279 (59.0)	201 (40.4)	1 078 (64.6)		232 (46.7)	1 047 (62.7)		250 (45.1)	1 029 (63.8)	
70~79	593 (27.4)	158 (31.7)	435 (26.0)		165 (33.2)	428 (25.6)		186 (33.6)	407 (25.2)	
≥80	296 (13.7)	139 (27.9)	157 (9.4)		100 (20.1)	196 (11.7)		118 (21.3)	178 (11.0)	
Gender, *n* (%)				<0.001			0.550			0.001
male	1 055 (48.7)	300 (60.2)	755 (45.2)		236 (47.5)	819 (49.0)		302 (54.5)	753 (46.7)	
women	1 113 (51.3)	198 (39.8)	915 (54.8)		261 (52.5)	852 (51.0)		252 (45.5)	861 (53.3)	
Educational level, *n* (%)				<0.001			<0.001			<0.001
Up to grade 9	247 (11.4)	101 (20.3)	146 (8.7)		106 (21.3)	141 (8.4)		185 (33.4)	62 (3.8)	
Grades 9-11	328 (15.1)	90 (18.1)	238 (14.3)		106 (21.3)	222 (13.3)		136 (24.5)	192 (11.9)	
High school	529 (24.4)	133 (25.1)	396 (23.7)		141 (28.4)	388 (23.2)		128 (23.1)	401(24.8)	
Some universities	593 (27.4)	96 (19.3)	497 (29.8)		97 (19.5)	496 (29.7)		79 (14.3)	514 (31.8)	
College or above	471 (21.7)	78 (15.7)	393 (23.5)		47 (9.5)	424 (25.4)		26 (4.7)	445 (27.6)	
Marital status, *n* (%)				<0.001			<0.001			<0.001
married	1 186 (54.7)	250 (50.2)	936 (56.0)		253 (50.9)	835 (56.1)		247 (44.6)	939 (58.2)	
Widowed	401(18.5)	128 (25.7)	273 (16.3)		125 (25.2)	242 (16.3)		150 (27.1)	251 (15.6)	
Divorced	326 (15.0)	61 (12.2)	263 (15.9)		61 (12.3)	239 (16.1)		74 (13.4)	252 (15.6)	
Separated/	61 (2.8)	16 (3.2)	45 (2.7)		21 (4.2)	38 (2.6)		32 (5.8)	29 (1.8)	
Never married.	134 (6.2)	28 (5.6)	106 (6.3)		28 (5.6)	93 (6.3)		35 (6.3)	99 (6.1)	
Living with partner	60 (2.8)	15 (3.0)	45 (2.7)		9 (1.8)	41 (2.8)		16 (2.9)	44 (2.7)	
Body mass index , *n* (%)				0.030			0.489			0.733
18.5 to <25	565 (26.1)	134 (26.9)	431 (25.8)		138 (27.8)	427 (25.6)		141 (25.5)	424 (26.3)	
25 to <30	780 (36.0)	199 (40.0)	581 (34.8)		169 (34.0)	611 (36.6)		207 (37.4)	573 (35.5)	
≥ 30	823 (38.0)	165 (33.1)	658 (39.4)		190 (38.2)	633 (37.9)		206 (37.2)	617 (38.2)	
TC (mmol/L) $[M(P_{25},P_{75})]$	2168	4.71 (3.970, 5.450)	4.94 (4.200, 5.680)	<0.001	4.71 (4.010, 5.410)	4.97 (4.220, 5.720)	<0.001	4.76 (4.050,5.470)	4.94 (4.190, 5.690)	0.002
HDL-C (mmol/L) $[M(P_{25},P_{75})]$	2168	1.29 (1.045, 1.535)	1.34 (1.065,1.615)	<0.001	1.27 (1.040, 1.500)	1.34 (1.065,1.615)	<0.001	1.27 (1.025,1.515)	1.34 (1.080,1.600)	<0.001
TC:HDL-C ratio	2168	3.59 (2.785, 4.395)	3.57 (2.795, 4.345)	0.758	3.61 (2.930,4.290)	3.57 (2.780, 4.360)	0.626	3.64 (2.855,4.425)	3.54 (2.765,4.315)	0.025

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Table 1 summarizes and compares the baseline characteristics of the study participants. Of the 2,168 participants, 48.7% were male and 51.3% were female. The study population consisted primarily of non-Hispanic whites (43.8%). There were more overweight (38.0%) than normal weight (26.1%) and obese (36.0%) individuals. There were significant differences in the distribution of age, race, education, and TC and HDL-C levels between those with low cognitive ability and those with normal cognitive ability on the CERAD test, the AF test, and the DSST test, with the older the person, the lower the cognitive ability on all three tests. Compared to those with normal cognitive ability, those with low cognitive ability tended to have lower education, and higher serum TC and HDL-C levels. Individuals with low cognitive ability on the CERAD and DSST tests were more likely to be male. Individuals with low cognitive ability on the DSST test tended to have lower TC and HDL-C levels.

3.2 Binary logistic regression analysis between TC and HDL-C and CERAD

Table 2 shows the relationship between serum TC and HDL-C levels, TC:HDL-C ratio and CERAD. Three logistic regression models were used in this study. In the logistic regression analysis, T1, the first tertiary subgroup of serum TC levels (<4.45 mmol/L) was set as the reference group. T2 (4.45-5.40 mmol/L) and T3 (≥5.40 mmol/L) were compared with T1 for the risk of low cognitive performance, and the same was done for the HDL-C level and TC:HDL-C ratio subgroups. In the unadjusted model, the ORs and 95% *CIs* for the highest tertile compared with the lowest tertile of TC and HDL-C in serum were 1.542 (1.207 to 1.970) and 1.587 (1.236 to 2.039), respectively. After adjusting for age and gender, HDL-C levels remained proportional to CERAD. In model 2, the OR and 95% *CI* for the highest tertile compared with the lowest tertile of HDL-C in serum were 1.393 (1.032 to 1.881), respectively.There was no statistically significant relationship between the TC: HDL-C ratio and CERAD.

Table 2: Binary logistic regression analysis of TC, HDL-C, and TC:HDL-C with CERAD.

Variables	Crude	*P*	Model 1	*P*	Model 2	*P*
	OR (95% *CI*)		OR (95% *CI*)		OR (95% *CI*)	
TC (mmol/L)						
T1 (<4.45)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (4.45 to <5.40)	1.291 (1.014-1.645)	0.038	1.069 (0.827-1.381)	0.611	1.020 (0.777-1.339)	0.886
T3 (≥5.40)	1.542 (1.207-1.970)	<0.001	1.045 (0.802-1.363)	0.744	1.021 (0.770~1.355)	0.884
HDL-C (mmol/L)						
T1 (<1.19)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (1.19 to <1.52)	1.216 (0.958-1.543)	0.108	1.124 (0.872-1.449)	0.368	1.080 (0.828-1.407)	0.571
T3 (≥1.52)	1.587 (1.236-2.039)	<0.001	1.450 (1.101-1.909)	0.008	1.393 (1.032-1.881)	0.030
TC:HDL-C						
T1 (<3.11)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (3.11 to <4.05)	1.041 (0.814-1.332)	0.490	0.943 (0.728-1.222)	0.658	0.966 (0.736~1.268)	0.805
T3 (≥4.05)	1.016 (0.795~1.298)	0.806	0.875 (0.674-1.137)	0.318	0.914 (0.692-1.207)	0.527

3.3 Binary logistic regression analysis between TC and HDL-C and AF

Table 3: Binary logistic regression analysis of TC, HDL-C, and TC:HDL-C with AF.

Variables	Crude	*P*	Model 1	*P*	Model 2	*P*
	OR (95% *CI*)		OR (95% *CI*)		OR (95% *CI*)	
TC (mmol/L)						
T1 (<4.45)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (4.45 to <5.40)	1.100 (0.865-1.398)	0.436	1.082 (0.846-1.384)	0.529	1.000 (0.764~1.308)	0.998
T3 (≥5.40)	1.533 (1.195~1.966)	<0.001	1.429 (1.102-1.853)	0.007	1.300 (0.979-1.728)	0.070
HDL-C (mmol/L)						
T1 (<1.19)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (1.19 to <1.52)	1.121 (0.883-1.424)	0.349	1.195 (0.933-1.531)	0.158	1.174 (0.900-1.531)	0.236
T3 (≥1.52)	1.444 (1.124-1.855)	0.004	1.636 (1.252-2.139)	<0.001	1.515 (1.122-2.044)	0.007
TC:HDL-C						
T1 (<3.11)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (3.11 to <4.05)	0.766 (0.599~0.981)	0.034	0.723 (0.563~0.929)	0.011	0.750 (0.572~0.982)	0.037
T3 (≥4.05)	0.904 (0.703-1.161)	0.429	0.788 (0.609~1.021)	0.071	0.811 (0.612-1.074)	0.144

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The relationships between serum levels of TC and HDL-C, TC:HDL-C ratios and AF are presented in Table 3. In the unadjusted model, the OR and 95% *CI* for the highest tertile compared with the lowest tertile of TC and HDL-C in serum were 1.533 (1.195 to 1.966) and 1.444 (1.124 to 1.855), respectively. After adjustment for age and sex, TC and HDL-C levels remained proportional to AF. In model 2, the OR and 95% *CI* for the highest tertile compared with the lowest tertile of HDL-C in serum was 1.515 (1.122 to 2.044). In the unadjusted model, the OR and 95% *CI* for the middle tertile compared with the lowest tertile of the TC:HDL-C ratio in serum was 0.766 (0.599 to 0.981). The TC:HDL-C ratio remained inversely associated with AF, both after adjustment for age and sex and in Model II. A correlation between the TC:HDL-C ratio and AF can be seen.

3.4 Logistic regression between TC and HDL-C levels in serum and DSST

Table 4 shows the relationship between serum TC and HDL-C levels, TC:HDL-C ratio and DSST. In the unadjusted model, the OR and 95% *CI* for the highest tertile of TC and HDL-C levels were 1.402 (1.108-1.774) and 1.774 (1.393-2.258), respectively. After adjusting for age and sex, HDL-C levels remained positively associated with DSST, whereas the TC:HDL-C ratio was inversely associated with DSST. In model 2, the OR and 95% *CI* for the highest tertile of serum HDL-C levels was 1.555 (1.112-2.175), whereas there was no correlation for the TC:HDL-C ratio.There was a correlation between the TC:HDL-C ratio and DSST.

Table 4: Binary logistic regression analysis of TC, HDL-C and TC:HDL-C in serum versus DSST

Variables	Crude	*P*	Model 1	*P*	Model 2	*P*
	OR (95% *CI*)		OR (95% *CI*)		OR (95% *CI*)	
TC (mmol/L)						
T1 (<4.45)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (4.45 to <5.40)	1.237 (0.978~1.564)	0.076	1.108 (0.869~1.413)	0.409	0.963 (0.708-1.308)	0.807
T3 (≥5.40)	1.402 (1.108-1.774)	0.005	1.110 (0.865-1.424)	0.411	0.964 (0.703-1.322)	0.821
HDL-C (mmol/L)						
T1 (<1.19)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (1.19 to <1.52)	1.341 (1.066-1.687)	0.012	1.333 (1.049-1.694)	0.019	1.226 (0.911-1.649)	0.179
T3 (≥1.52)	1.774 (1.393-2.258)	<0.001	1.798 (1.386-2.333)	<0.001	1.555 (1.112-2.175)	0.010
TC:HDL-C						
T1 (<3.11)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
T2 (3.11 to <4.05)	0.825 (0.649-1.050)	0.118	0.762 (0.595~0.976)	0.031	0.825 (0.606-1.124)	0.224
T3 (≥4.05)	0.792 (0.624-1.006)	0.056	0.691 (0.538~0.887)	0.004	0.749 (0.548-1.025)	0.071

4. Discussion

This study examined the relationship between serum TC, HDL-C, and TC:HDL-C ratio and cognitive performance in a population of older adults aged 60 years and older in the United States. We found that older adults with higher serum HDL-C concentrations had good performance on the CERAD, AF, and DSST. In binary logistic regression analyses, there was a strong correlation in both Model 1 (adjusted for age and sex) and Model 2 (adjusted for race, education, marital status, poverty-to-income ratio, body mass index, drinking status, smoking status, diabetes, and hypertension). In addition, our findings suggest that the low level HDL-C group was more likely to exhibit lower scores on cognitive tests compared to the high level HDL-C group. TC:HDL-C was not correlated with the CERAD and AF, but was strongly correlated with the DSST. In particular, the TC:HDL-C ratio was inversely related to DSST, with higher TC:HDL-C reducing cognitive test scores. Thus, high levels of HDL-C may be protective against cognitive impairment, and lower TC:HDL-C may be protective against declines in cognitive ability and responsiveness.

Consistent with existing findings, data in the United Kingdom suggest that in women, most lipids are associated with risk of dementia, and that TC, LDL-C, non-HDL-C, TC/HDL-C, and LDL-C/HDL-C are higher in dementia cases in middle age and then gradually decline[16]. And a study in Singapore showed that an increase in visceral adiposity index and a decrease in HDL-C led to a decrease in cognitive performance[17]. In addition, a study in Western Australia reported that HDL slows the onset of Alzheimer's disease and dementia and is important for its beneficial effects on memory for verbal fragments[18]. Although the above findings are consistent with ours. However, the underlying mechanisms by which lipids affect any ability remain unclear, and their association with vascular

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disease may help to explain their link: one study has shown that in patients with AD, the composition of HDL is altered, and that this change is associated with alterations in regional brain volume data[19]. Although the effect of lipids on cognitive impairment depends on many circumstances, our findings suggests that the study of the link between lipids and cognition needs more attention.

5. Conclusions

The present study showed that HDL-C level was positively correlated with cognitive performance and TC:HDL-C ratio was negatively correlated with cognitive level in older adults. Therefore, Lifestyle changes and a balanced and healthy diet to maintain high HDL-C levels and low TC:HDL-C ratios have some effect on improving cognitive function in older adults. The findings need to be validated in further prospective cohort studies.

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