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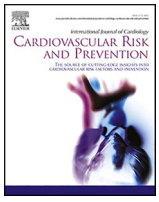

Dyslipidemia and cerebral atrophy among health check-up individuals: A cross-sectional study

Xiaoying He [a,1], Jingyi Xiao [a,1], Yan Wang [a], Christopher Reid [b], Dan Xu [a,b,c,**], Hua Hong [a,*]

[a] The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China
[b] CCRE, Curtin School of Population Health, Faculty of Health Sciences, Curtin University, Australia
[c] Curtin Medical School, Faculty of Health Sciences, Curtin University, Australia

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ABSTRACT

Objective: To examine the association between dyslipidemia and cerebral atrophy in Chinese health check-up population.
Methods: 67,526 participants underwent routine health check-ups at the health management center of the First Affiliated Hospital of Sun Yat-Sen University (FAH-SYSU) in Guangzhou for two years (2022-2023) in this cross-sectional study. Cerebral atrophy was determined by expert physicians based on non-contrast scans of Head Magnetic Resonance Imaging (MRI), Magnetic Resonance Angiography (MRA) and/or Head Computed Tomography (CT). The levels of Total Cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were measured and classified by quartiles into four categories, respectively. The multivariable logistic regression model was used to obtain the odds ratios (ORs) and 95% confidence intervals (CIs).
Results: A total of 1,661 participants were included with ages from 18 to 93 years. Among 1,661 participants, 121 (7.28%) had cerebral atrophy. On multivariate analysis, TC and LDL-C were not associated with cerebral atrophy, although TC and LDL-C were lower in the subgroup with cerebral atrophy.
Conclusions: This cross-sectional study conducted in China is the first to identify that health check-up examinees with cerebral atrophy had lower levels of TC and LDL-C raising the possible association between lower levels of TC and LDL-C with cerebral atrophy, and possible cognitive dysfunction. Future study is planned to overcome the existing limitation and address the lack of statistically significant association between TC and LDL-C levels with cerebral atrophy and possible dementia.

1. Introduction

Dyslipidemia was alarmingly prevalent in adults with America data showing that 39.7% of adults have abnormally high total cholesterol (TC) level worldwide [1,2]. Dyslipidemia is defined as abnormalities in TC and its subcomponents including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG). It is well established that dyslipidemia is a main predictor of cardiovascular disease (CVD) as well as a core metric in CVD risk calculation [3]. Recent studies have shown that high midlife TC may be a risk factor for late-life dementia [4,5].

Despite the mounting evidence exploring the relationship between dyslipidemia (TC, LDL-C, HDL-C, TG) and cognitive dysfunction, the results have been inconsistent and even conflicting. Numerous studies have indicated raised TC or LDL-C was associated with cognitive dysfunction [6,7], higher risks of Alzheimer's dementia (AD) [8], and no significant impacts on cognitive function [9]. However, there were recent studies showing that raised TC and/or LDL-C levels were associated with better cognitive performance [10–12], lower risks of dementia and cognitive deterioration [13,14]. Furthermore, HDL-C has been shown to correlate positively with cognitive functions with raised HDL-C posing a reduced risk of dementia [10,11,13,15], except one

* Corresponding author. Health Management Center, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan Road II, Guangzhou 510080, China.
** Corresponding author. CCRE, Curtin School of Population Health, Faculty of Health Sciences, Curtin University, Australia.
E-mail addresses: daniel.xu@curtin.edu.au (D. Xu), honghua@mail.sysu.edu.cn (H. Hong).
[1] Xiaoying He and Jingyi Xiao contributed equally to this work.

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study presenting the opposite finding [16]. Another more recent study showed that greater HDL-C variability was associated with increased cognitive decline risk [17]. With respect to the relationship between Non-HDL-C and cognitive impairment, numerous recent studies have explored the potential non-linear relationship between dyslipidemia and cognitive functions [18,19,20]. The most recent analysis of the potential nonlinear relationship revealed a U-shaped relationship between non-HDL-C and the risk of cognitive impairment with an inflection point showing that reduced risks of cognitive impairment was associated with increased non-HDL-C before the inflection point while increased risks of cognitive impairment was associated with increased non-HDL-C after inflection point [21]. A retrospective longitudinal study in Taiwan found a non-linear and inverted U-shaped relationships between serum cholesterol and cognitive function among older people including the relationship between LDL-C and cognitive function highlighting the fact the lower LDL-C level was associated with cognitive decline among older people in preclinical stages of dementia [22].

Albeit the inconsistent or even controversial findings regarding the relationship between dyslipidemia and cognitive dysfunction, one well-established piece of evidence declared that cognitive dysfunction and dementias have been well documented to be associated with cerebral atrophy with study showing pathologically distinct dementias exhibit characteristic patterns of regional volume loss on imaging compared with controls and other dementias [23]. A more recent study has uncovered that cerebral atrophy precedes cognitive deterioration by years in dominantly inherited Alzheimer's disease [24]. All these studies have cemented the fact that brain imaging is an important tool for screening, diagnosing and treatment follow-up in cognitive dysfunction and dementia.

There have been a few recent studies that explored the relationship between dyslipidemia and brain structure/function using brain imaging with one of the most consistent findings being the association between raised HDL-C and less cerebral atrophy in middle-aged to older adults. In the study of 183 healthy adults (mean age 58.4 years), HDL-C was found to be positively associated with gray matter volume in bilateral temporal lobes and para-hippocampal region [25]. In another study involving healthy older controls and individuals with mild cognitive impairment (MCI) or AD, low HDL-C was associated with low hippocampal volume [26]. Another recent study with older adults who had subjective memory complaints, HDL-C was positively associated with memory performance and bray matter volume [27]. In another longitudinal cohort study followed-up 11 years found that raised HDL-C was associated with less gray matter volume loss as well as lower risks of developing cognitive dysfunction [28].

In contrary, the association between cerebral atrophy and LDL-C/TC was even more inconsistent. One study revealed in 82 cognitively normal older adults about the same age (77.7–78.9 years old) that total gray matter volume negatively correlated with LDL-C and TC [29], which was confirmed by another study [30]. In another study, raised LDL-C was associated with reduced white matter integrity in regions of brain prone to develop atrophy associated with dementia [31]. Study using resting-state functional MRI (fMRI) techniques found that raised TC was associated with both increased connectivity in the default mode network and reduced connectivity in the salience network, displaying a paradoxical picture [32]. Moreover, several recent studies uncovered the association between raised LDL-C/TC and increased cortical thickness [33], increased gray matter volume [33], and white matter integrity [14], which indicated that raised LDL-C/TC could be potentially beneficial in middle aged to older adults. Taken together, the contrasting outcomes from these studies suggest that the relationship between dyslipidemia and cerebral atrophy/cognitive function warrants further research. This current cross-sectional study aimed to explore the association between LDL-C levels reduction and cerebral atrophy in a group of Chinese health check-up examinees, ultimately pave ways for large scale study to clear the inconsistent findings between dyslipidemia and cerebral atrophy and cognitive dysfunction.

2. Materials and Methods

2.1. Study design and participants

This was a cross-sectional study. The source population for this study comprised 67,526 examinees who underwent brain health check-ups at the tertiary hospital of the University in Guangzhou, southern China between January 1st, 2022, and December 31st, 2023. Of these, 1,751 men and women, aged 18–92 years had brain health check-ups records by Magnetic Resonance (MR), Magnetic Resonance Angiography (MRA), Computed Tomography (CT). Among the 1,751 individuals, we excluded 74 duplicate health check-up records and retained the most recent ones. Subsequently, we further excluded 16 participants without blood lipids test results. Finally, 1,661 individuals were included for the analysis (Figure 1).

2.2. Characteristics collection and Biochemistry measurements

The demographic characteristics and clinical information including age, sex, weight (kg), height (cm), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were collected. Trained nurses used validated automated sphygmomanometer [34] to measure SBP and DBP in the seated position after the participant had rested for 5-10 minutes and recorded as the average of three measurements. Fasting blood samples were collected in the morning of participants who had fasted for a minimum of 8 hours or more last night. In addition, a range of biochemical parameters including the fasting serum lipids concentration (mmol/L) of all participants including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG), as well as fasting blood glucose (FBG) (mmol/L), hemoglobin A1c (HbA1c) (%), lipase A (LipA) (mg/L), homocysteine (HCY) (μmol/L), uric acid (UA) (μmol/L) and high-sensitivity C-reactive protein (hs-CRP) (mg/L) were measured at the clinical laboratory of the FAN-SYSU. Serum TC, LDL-C, HDL-C and TG were measured by enzymatic colorimetry by BECKMAN COULTER Chemistry Analyzer AU5800 and matching reagent.

2.3. Imaging measurements

Cerebral atrophy was determined by expert imaging physicians based on the imaging result of Head Magnetic Resonance Imaging (MRI) without contrast, and/or Magnetic Resonance Angiography (MRA) without contrast, and/or Head Computed Tomography (CT) scan without contrast. The Head MRI, MRA and Head CT scans were performed using the Siemens Magnetom Trio Tim 3.0 Tesla Magnetic Resonance Imaging System and Toshiba Aquilion 16-slice Spiral Computed Tomography Scanner. In the clinical practice, cerebral atrophy image interpretation was visually evaluated by two expert imaging physicians, and any disagreement is decided by deliberation. The two expert imaging physicians do not have access to medical history information and can only objectively assess the images they obtain. Cerebral atrophy was defined as a lower brain volume that is not related to a specific macroscopic focal injury such as trauma or infarction. Tissue loss is assumed from the enlargement of peripheral (sulcal) and central (ventricular) cerebrospinal fluid spaces in relation to intracranial volume and other measures. The imaging features may include the following: widening of cortical sulci, enlargement of ventricles, thinning of cortex, shrinking of hippocampus.

2.4. Statistical analysis

Continuous variables were reported as means ± standard deviations (SD) (normal distribution) or medians with interquartile range (IQR) (non-normal distribution Categorical variables were reported as a percentage. We classified participants into two groups based on cerebral atrophy status. To examine differences between these two groups, we

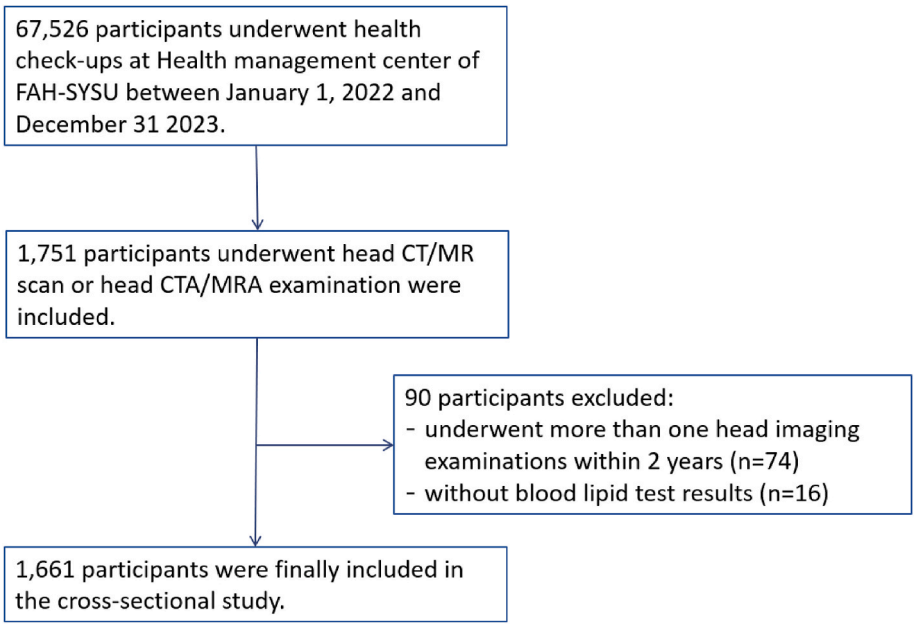

Fig. 1. Diagram for inclusion and exclusion of research participants.

used one-way analysis of variance (normal distribution) or the Kruskal-Wallis test (non-normal distribution) for continuous variables, and used the chi-squared test for categorical variables. The level of lipids including TC, LDL-C, HDL-C and TG were classified by quartiles into four categories. Multivariable logistic regression model was used to assess the associations between lipids level with cerebral atrophy giving the odds ratios (ORs) and 95% confidence intervals (CIs) taking the 1st quartiles as the reference group. Model 1 was adjusted by age and sex. Model 2 was additionally adjusted by potential confounders with statistical differences in univariate analysis. When calculating P values for trend, quartile categories of TC, LDL-C, HDL-C, and TG were performed as continuous variables in the logistic regression models. All data analysis was performed using Stata/MP 17.0 (Stata Corp. LP, College Station, TX, USA). All statistical analysis were 2-side, and the P-value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of study participants

Of the 1,661 participants, 121 (7.28%) had cerebral atrophy. Table 1 showed that, compared to participants without cerebral atrophy, those who had cerebral atrophy were older (68.01 ± 10.13 vs. 50.07 ± 10.42 years, $P < 0.001$), had a higher proportion of men (71.90% vs. 55.39%, $P < 0.001$), had higher blood pressure (SBP 140.83 ± 19.95 vs. 126.33 ± 17.63 mmHg, $P < 0.001$; DBP 81.81 ± 13.60 vs. 77.45 ± 11.73 mmHg, $P < 0.001$), had higher blood glucose (FBG 5.66 ± 1.48 vs. 5.18 ± 1.28 mmol/L, $P < 0.001$; HbA1c 5.94 ± 0.71 vs. 5.68 ± 0.85 %, $P = 0.001$), and had higher HCY (median 12.30 vs. 10.95 mmol/L, $P < 0.001$). Moreover, the levels of TC and LDL-C were significantly lower in the cerebral atrophy group than in the non-cerebral atrophy group (5.32 ± 1.38 vs. 5.58 ± 1.14 mmol/L, $P = 0.018$; 3.30 ± 1.01 vs. 3.50 ± 0.82 mmol/L, $P = 0.010$; respectively). However, there was no significant difference in BMI, LipA, UA, hs-CRP, TG and HDL-C levels between the cerebral atrophy group and the non-cerebral atrophy group.

Table 1
Characteristics by brain atrophy of participants (n=1,661)

Characteristics	Non-brain atrophy	Brain atrophy	F/χ2	P
	n=1540	n=121		
Age (year), mean (SD)	50.07±10.42	68.01±10.13	333.63	**<0.001**
Sex			12.45	**<0.001**
Men, n (%)	853 (55.39)	87 (71.90)		
Women, n (%)	687 (44.61)	34 (28.10)		
BMI (kg/m2), mean ±SD	24.58±3.23	25.07±3.91	1.92	0.167
SBP (mmHg), mean ±SD	126.33±17.63	140.83±19.95	66.66	**<0.001**
DBP (mmHg), mean ±SD	77.45±11.74	81.81±13.60	13.49	**<0.001**
TC (mmol/L), mean ±SD	5.58±1.14	5.32±1.38	5.61	**0.018**
TG (mmol/L), median (IQR)	1.27 (0.90, 1.90)	1.19 (0.93, 1.67)	0.59	0.441
LDL-C (mmol/L), mean±SD	3.50±0.82	3.30±1.01	6.70	**0.010**
HDL-C (mmol/L), mean±SD	1.38±0.31	1.35±0.32	1.18	0.278
FBG (mmol/L), mean ±SD	5.18±1.28	5.66±1.48	15.63	**<0.001**
HbA1c (%), mean±SD	5.68±0.85	5.94±0.72	10.67	**0.001**
LipA (mg/L), median (IQR)	113.50 (56.00, 277.00)	128.00 (64.00, 418.00)	1.15	0.284
HCY (μmol/L), median (IQR)	10.95 (9.70, 12.60)	12.30 (11.20, 14.80)	28.61	**<0.001**
UA (μmol/L), mean ±SD	381.13±95.52	394.12±94.77	2.06	0.152
hs-CRP (mg/L), median (IQR)	0.99 (0.49, 2.00)	1.11 (0.55, 2.08)	2.67	0.103

Data were mean±SD or median (IQR) for continuous variables or numbers (percentage) for categorical variables.
P value for one-way analysis of variance or chi-square test.

3.2. The association between lipids and cerebral atrophy

Table 2 showed that participants in the 2nd, 3rd and 4th LDL-C quartiles of LDL-C had significantly lower prevalence of cerebral atrophy compared to those in the 1st LDL-C quartile (<2.91 mmol/L) with the OR (95%CI) of 0.430 (0.255, 0.727), 0.431 (0.255, 0.729) and 0.566 (0.349, 0.916), respectively (P for trend =0.015). A similar association was found for TC in related to cerebral atrophy risk (P for trend =0.013). However, neither TC, TG, LDL-C nor HDL-C were significantly associated with cerebral atrophy risk in the multivariate-adjusted

Table 2
Odds ratios (OR) and 95% confidence intervals (CI) for lipids level by brain atrophy in 1,661 participants

		Crude model		Model 1		Model 2	
	Quartiles (mmol/L)	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
TC	**1st (<4.80)**	**1.000 (ref)**	-	**1.000 (ref)**	-	**1.000 (ref)**	-
	2nd (4.80≤TC<5.50)	0.444 (0.260, 0.756)	0.003	0.875 (0.457, 1.674)	0.686	0.800 (0.333, 1.902)	0.609
	3rd (5.50≤TC<6.30)	0.432 (0.258, 0.724)	0.001	0.767 (0.411, 1.431)	0.404	0.553 (0.195, 1.570)	0.266
	4th (≥6.30)	0.543 (0.335, 0.880)	0.013	0.890 (0.491, 1.613)	0.700	0.600 (0.144, 2.509)	0.484
		P for trend=0.009		**P for trend**=0.607		**P for trend**=0.382	
TG	**1st (<0.90)**	**1.000 (ref)**	-	**1.000 (ref)**	-	**1.000 (ref)**	-
	2nd (0.90≤TG<1.27)	1.711 (1.022, 20,864)	0.041	1.069 (0.567, 2.017)	0.837	0.917 (0.447, 1.881)	0.813
	3rd (1.27≤TG<1.88)	1.139 (0.655, 1.981)	0.644	0.823 (0.423, 1.598)	0.564	0.805 (0.379, 1.711)	0.573
	4th (≥1.88)	0.980 (0.553, 1.736)	0.944	0.823 (0.418, 1.621)	0.574	0.803 (0.366, 1.762)	0.585
		P for trend=0.530		**P for trend**=0.400		**P for trend**=0.531	
LDL-C	**1st (<2.91)**	**1.000 (ref)**	-	**1.000 (ref)**	-	**1.000 (ref)**	-
	2nd (2.91≤LDL-C<3.47)	0.430 (0.255, 0.727)	0.002	0.852 (0.452, 1.608)	0.621	0.744 (0.331, 1.671)	0.474
	3rd (3.47≤LDL-C<4.04)	0.431 (0.255, 0.729)	0.002	0.684 (0.365, 1.282)	0.236	0.425 (0.159, 1.133)	0.087
	4th (≥4.04)	0.566 (0.349, 0.916)	0.021	0.887 (0.489, 1.607)	0.691	0.385 (0.101, 1.470)	0.162
		P for trend=0.015		**P for trend**=0.530		**P for trend**=0.103	
HDL-C	**1st <1.16**	**1.000 (ref)**	-	**1.000 (ref)**	-	**1.000 (ref)**	-
	2nd (1.16≤HDL-C<1.36)	0.894 (0.531, 1.508)	0.676	1.273 (0.664, 2.440)	0.467	1.169 (0.557, 2.456)	0.680
	3rd (1.36≤HDL-C<1.57)	0.918 (0.547, 1.541)	0.747	1.226 (0.651, 2.309)	0.528	1.185 (0.531, 2.646)	0.679
	4th (≥1.57)	0.921 (0.548, 1.545)	0.754	2.218 (1.148, 4.284)	0.018	2.518 (1.000, 6.314)	0.049
		P for trend=0.787		**P for trend**=0.033		**P for trend**=0.075	

Model 1: Adjusting for age and sex.
Model 2: Additionally adjusting for other variables with statistical differences in univariate analysis, including age, sex, body mass index, systolic blood pressure, lipids, hemoglobin A1c and homocysteine.

model. (Detailed results in Supplementary Table 1, 2, 3)

4. Discussion

Our result was the first to document that Chinese health check-up examinees with cerebral atrophy had lower levels of LDL-C, suggesting the possible association between low levels of LDL-C and cognitive dysfunction. Several recent studies have demonstrated the non-linear (inverted U-shaped) association between TC and cognitive dysfunction [1,17–20]. The Baltimore Longitudinal Study of Aging identified two opposite non-linear associations between total cholesterol levels and performance on several neuropsychological tests in healthy older adults aged between 54 and 83 years [35]. Another study including 190 participants aged 54-83 found that participants had high and low levels of total cholesterol performed better than those at midrange TC (U-shaped) in 70+ years old group, however, the inverted U shape association between TC and cognitive performance was found in <70 years old group [18]. A Chinese cohort study with age between 50 and 65 years identified an inverted U-shape association between TC/LDL-C and neuropsychological test scores in men versus a U-shaped relationship between HDL-C and neuropsychological test scores in women [19]. Another relevant large cohort study revealed older adults aged between 60 and 80 with low (120 mg/dl) and high (210 mg/dl) non−HDL-C levels had modestly higher risk of AD than those with intermediate (160 mg/dl) level [20]. The most recent analysis of the potential nonlinear relationship by smoothed curve fitting and saturation threshold effects revealed a U-shaped relationship between non-HDL-C and the risk of cognitive impairment with an inflection point of 4.83mmol. When non-HDL-C level is below 4.83mmol, increased non-HDL-C levels were associated with a significantly decreased risk of cognitive impairment. However, when non-HDL-C level is above 4.83mmol, increased non-HDL-C levels were associated with significantly increased risk of cognitive impairment. The retrospective longitudinal study in Taiwan again confirmed the non-linear and inverted U-shaped relationships between LDL-C and cognitive function among older people in preclinical stages of dementia [23]. A recent study suggested that longitudinal increases in non-HDL-c may be associated with reduced risks of cognitive dysfunction among females or individuals without cardiovascular disease [36]. Another similar report concluded the risk of global cognitive and memory decline was significantly lower among older people with long-term increased level of non-HDL-c in comparison to the consistently low-level group [37].

Taking all these studies together, evidence is trending towards the non-linear associations between cholesterol levels and cognitive performance in an inverted U-shaped relationship. All these studies were undertaken to explore the relationship by applying only neuropsychological testing without imaging investigation to strengthen and support the conclusion.

To lend support to the conclusions of these studies, our study showed the non-linear associations between LDL-C levels and brain imaging with either MRI or CT scans. Although our study does not have any data of neuropsychological testing, it is evidently well established that cognitive dysfunction and dementias are associated with cerebral atrophy showing pathologically distinct and characteristic patterns of regional volume loss on imaging compared with controls and other dementias [23]. A more recent study has uncovered that cerebral atrophy precedes cognitive deterioration by years in dominantly inherited Alzheimer's disease [24]. All these studies have cemented the fact that brain imaging is an important tool for screening, diagnosing and treatment follow-up in cognitive dysfunction and dementia, which has been well reflected in our study.

As our study being a cross-sectional study was conducted in a relatively healthy population with only blood investigation and imaging data, a few limitations do exist. Firstly, the causal association between lipid levels and cerebral atrophy could not be conclusively determined due to the lack of neuropsychological and cognitive testing to draw the direct association of TC and LDL-C with cognitive dysfunction. Secondly, the assessment of cerebral atrophy applied three modality including MRI brain, MRA brain and head CT scans. MRI is the preferred method of screening for cerebral atrophy and is particularly sensitive in identifying early or mild cerebral atrophy [38]. Middle-aged and elderly populations usually especially with higher risks for cardiovascular and cerebrovascular diseases may be more inclined to choose cerebrovascular MRA brain to focus on vascular abnormalities. CT is suitable for screening for severe or widespread cerebral atrophy [38]. Our study population included predominantly middle-aged and elderly undertaking MRA brain rather than MRI brain and CT of the head (MRA No=1499, MRI No=63, CT head No=105), with the reported prevalence of cerebral atrophy being 2.86%, 6.14% and 39.68%, respectively. Higher rates of MRA in this study target population may underestimate

the association between TC and LDL-C with cerebral atrophy. Thirdly, the small sample size and the difficulty of matching controls of similar age limited the use of the case-matching analysis, which is the better method of analysis with our study setting. Finally, our priority will be the need to expand our study target population size to overcome the lack of statistically significant correlation between the LDL-C and cerebral atrophy after adjustment of the confounding factors.

5. Conclusion and Future Perspectives

This cross-sectional study conducted in China is the first to identify that health check-up examinees with cerebral atrophy had lower levels of TC and LDL-C suggesting the possible association between lower levels of TC and LDL-C with cognitive dysfunction and dementias. To further elucidate the association between lipid levels, cerebral atrophy, and dementia, future studies need more large sample size and need to obtain comprehensive data, especially neuropsychological testing, and conduct prospective cohort studies based on prospective, regular follow-up data from participants.

CRediT authorship contribution statement

Xiaoying He: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jingyi Xiao:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Yan Wang:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Christopher Reid:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Dan Xu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Hua Hong:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare no conflicts of interest in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2025.200394.

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