

Associations of LDL-C-to-HDL-C and TG-to-HDL-C Ratios with Type 2 Diabetes Mellitus and Cardiovascular Disease: A Prospective Cohort Study with 6 years' Follow-Up

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Research

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Abstract

Background: Traditional blood lipids play an important role in diabetes and cardiovascular diseases, but the evidences were not enough . The lipoprotein indices of low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratios may be the predictive parameters to diabetes and cardiovascular disease.

Methods: A 6-year follow-up study was performed in 22,649 subjects (were aged 18–95 years old) without a history of cardiovascular disease (CVD) or diabetes. The information about cardiovascular disease and T2DM was extracted from the Disease Surveillance Points (DSP) system in 2019. Biochemical and demographic variables were acquired by laboratory test and the face-to-face interview with structured questionnaire, the response rate was 88.9%. Lipid ratios were stratified by tertile to ascertain the hazard ratio (HR) of diseases by Cox proportional hazard model.

Results: The mean age of subjects was 54.9(14.5) years, 41.9% were males. LDL-C /HDL-C was strongly associated with coronary heart disease (CHD) (second vs. first tertile: HR, 1.86; 95% CI, 1.03-3.37, p =0.04 ; third vs. first tertile: HR, 3.29; 95% CI, 1.91-5.69, p< 0.001), meanwhile the TG/HDL-C was specifically associated with type 2 diabetes mellitus (T2DM) (second vs. first tertile: HR, 1.56; 95% CI, 1.2-2.02, p =0.001; third vs. first tertile: HR, 2.7; 95% CI, 2.13-3.43, p< 0.001). Moreover, the HR, of diseases was increased with LDL-C, TG/HDL-C ratios. The results of sensitivity analysis revealed the associations of LDL-C, TG/HDL-C ratios with CHD and T2DM were independent on confounders.

Conclusion: Our findings suggested that the LDL-C/HDL-C ratio and TG/HDL-C ratio associated with CHD and T2DM , and hazard ratio of disease increased with lipoprotein derived indices.

Introduction

The increasing prevalence of diabetes, coronary heart disease (CHD) and stroke is emerging as the major cause of mortality in China, with cardiovascular diseases (CVD) is a leading cause of death worldwide.[1] In 2016, an estimated 17.9 million people worldwide died of CVD, and about four-fifths of them caused by heart attacks and strokes. By 2015, the number of patients with CVD in China reached 290 million, and the incidence was still rising.[2] Meanwhile, the prevalence of diabetes in Chinese adults (over 18 years old) also increased in recent years. The prevalence in 2002, 2007 and 2010 were 2.7%, 9.7%, and 11.6%, respectively.[3] The number of diabetes in China reached 109.6 million in 2015, of which 1.3 million died of diabetes and complications.[4] It was estimated that the economic loss of China caused by diabetes and complications in the past 10 years before 2015 were about \$577.7 billion.[5] Coronary heart disease (CHD), cerebral stroke and Type 2 Diabetes Mellitus (T2DM) become a public health problem that can't be ignored in China.[6] It is remindful that early identification and treatment of individuals with diabetes and/or cardiovascular disorders is vital to prevent debilitating consequences.

Dyslipidemia plays an important role in the development of T2DM, CHD and stroke. Dyslipidemia is a contributing factor to the formation of arterial plaque and the stimulation of CVD, and will contribute to

the increase of T2DM too.[7–10] The traditional lipids profile (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]) are bound to apolipoproteins in the blood and transported/metabolized in the form of lipoproteins.[11] When the body absorbs more energy than it consumes, it will accumulate those energy in the form of fat, and at same time, free fatty acids may increase.[12] Excessive free fatty acids accumulate in the liver, skeletal muscle, and adipose tissue, producing “lipid toxicity”, which interferes with the normal metabolism of sugar and lipids, such as causing or aggravating insulin resistance or islet endothelial dysfunction.[13] Previously most researches focused on the relationship between traditional blood lipids and adverse cardiovascular events or diabetes, but their contradictions were great contradictions.[14–17] Low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) are well-established as risk factors for cardiovascular disease (CVD). Lowering LDL-C and/or TG has been the cornerstone in the prevention and treatment of atherosclerosis.[18, 19] However, Ding et al[15] found that even higher baseline LDL-TG closely associated with major adverse cardiovascular events (MACEs), it was only a moderate predictive factor for MACEs. In addition, some studies revealed that low levels of TG will generate more serious damage to cardiovascular disease than low levels of LDL-C. And LDL-C can have a greater impact on diabetes independent of TG interference.[20, 21] Inversely, Qin et al[22] didn't explore the association between LDL-C and TG with atherosclerosis in young women, however, they found that the cardiovascular risk still occurs in some patients who were treated to reduce LDL-C. Increasing cardiovascular disease (CVD) risk in these conditions is at least in part related to low plasma levels of high-density lipoprotein cholesterol (HDL-C), in line with the adverse impact of low HDL-C in general population studies.[23, 24]

Given the divergences among multiple studies on the association between individual blood lipid with diabetes and cardiovascular disease, the effects of HDL-C on disease are not considered. The lipoprotein indices provide methodologies on predicting the risk of diabetes and cardiovascular disease and the lipoprotein derived indices could be better indicators of the interactions between lipid fractions.[25, 26]

The LDL-C/HDL-C ratio and TG/HDL-C ratio provide a new perspective and could be better indicators of the interactions between lipid fractions. In the present study, we explored clinical utility of LDL-C/HDL-C ratio and TG/HDL-C ratio to identify the effects of lipid ratios on T2DM and CVD in Chinese elder adults.

Material And Methods

Study population

Zhejiang metabolic syndrome cohort is an ongoing community-based prospective cohort study initiated in Zhejiang Province from 2009 to 2012, with the purpose of tracking T2DM, CVD and evaluating related determinants. A total of 22,649 participants (9527 men and 13122 women, mean age was 54.86 ± 14.2 years) were recruited. The follow-up contents were consistent with baseline derived from 2014 to 2019 years and mean years of follow up were 6 years. Exclusion criteria: (1) severe infective diseases and malignancies in baseline; (2) patients with T2DM, CVD and Stroke in baseline; (3) less than 18 years old; (4) without biochemical and anthropometric data. Finally, a total of 21061 patients met these criteria.

Additionally, inclusion criteria and selection flowchart for all samples are shown in Fig. 1. This study was approved by the Human Research Ethics Committee of the Zhejiang University, Zhejiang, China. All participants provided written informed consent before participation.

Measurements

Height (cm), body weight (kg), waist circumference (WC; cm), hip circumference (HC; cm), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained assistants using same equipment. Height and weight were measured with the subjects wearing light clothing and no shoes. Height was recorded to the nearest 0.1 cm and body weight to the nearest 0.1 kg. Body mass index (BMI) was computed as weight (kg) divided by height squared (m^2). Girth of the midpoint between the lowest point of the rib and the upper edge of the iliac crest were calculated as waist circumference (WC). The length of the horizontal position of the hip protrusion was calculated as the hip circumference (HC) with a soft tape.[27] The measurements of WC and HC were taken to the nearest 0.1 cm. Waist-to-hip ratio (WHR) was calculated by dividing WC by HC. Sitting blood pressure was measured 2 times after at least 20 minutes of rest using the standardized desktop sphygmomanometer.[28] The average blood pressure derived from two measurement readings was used.

After an overnight fast of at least 12 hours, blood samples of each participant were collected by venipuncture. EDTA blood was collected in pre-cooled tubes on ice, centrifuged at 4000 rpm for 15 min at 4°C. EDTA plasma and serum aliquots were stored at - 80°C until use. Fasting plasma glucose (FPG) was measured by the hexokinase method, and lipid profile containing total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured by the enzymatic method using an Abbott Aeroset autoanalyzer. TG to HDL-C ratio (TG/HDL-C) and LDL-C to HDL-C ratio (LDL-C/HDL-C) were separately calculated.

Outcome Measures

The vital endpoint of each participant was extracted from the Disease Surveillance Points (DSP) system of the China CDC and were checked annually against local health insurance and were confirmed with street committees or village administrators. Furthermore, information about major diseases and hospitalization was collected through linkages with disease registries (for cancer, cardiovascular disease, and diabetes). The International Classification of Diseases, 10th Revision (ICD-10) was used in medical records. The main outcome measures that were examined were Type 2 Diabetes (ICD-10 codes E11) and the incidence of major coronary events (coronary heart disease [codes I20 to I25]), hemorrhagic stroke (code I61), and ischemic stroke (code I63). Other cerebrovascular diseases (ICD-10 codes F01, G45, G46, I60-64, I690, I691, I692, I694, I698, I699) were analyzed. For analyses of incident disease, only the first cardiovascular event was counted. All the subjects were Han ethnicity and living in the communities for more than ten years.

Covariates

Data on demographic characteristics, meditation use, personal behaviors and family histories of disease were collected by standardized questionnaires. Smoking and drinking were categorized as current, former and never. Current smokers and drinkers were defined as those who were still smoking or drinking during the investigation. Former smokers or drinkers were those who had a history of smoking or drinking and stopped for at least one year. The physical activities were defined as mild labor, moderate labor, and heavy labor. The data from all prior participants was obtained by face-to-face questionnaires.

Statistical analysis

The continuous variables were presented as means and standard deviations (SD), categorical variables as percentages. The one-way analysis of variance and the chi-squared test were used to compare the baseline characteristics of participants stratified by tertiles of LDL-C/HDL-C and TG/HDL-C ratio. The person-years of follow-up were the product of the duration (yearly) between the baseline survey year and the year of follow-up survey or the year of follow-up data was obtained and the number of new cases in specific disease (Type 2 Diabetes Mellitus, Coronary Heart Disease, Stroke). The incidence density of specific disease was the number of newly diagnosed type 2 diabetes mellitus, coronary heart disease and stroke during the follow-up period divided by the number of follow-up years. A multivariable Cox proportional regression analysis was used to study the independent association of the categorical LDL-C/HDL-C and TG/HDL-C with type 2 diabetes mellitus and cardiovascular diseases after adjustment for several potential confounders. Meanwhile, sensitivity analysis was performed in different subgroups. BMI < 18.5 kg/m² and BMI ≥ 24 kg/m² were defined as normal weight and overweight/obesity. WC ≥ 90 cm for men and WC ≥ 80 cm for women, WHR ≥ 0.9 for men and WHR ≥ 0.8 for women were divided to abnormal. Smoking and drinking were classified as “yes” or “no”. The physical activities were defined as mild, moderate and heavy labor. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Statistical analyses were performed by SPSS 22.0 software. All analyses were two-sided, and the difference was statistically significant at $p < 0.05$.

Results

Baseline participant characteristics stratified by tertile of LDL-C/HDL-C and TG/HDL-C ratios were presented in Table 1. In general, participants in the lowest tertile for LDL-C/HDL-C and TG/HDL-C ratios were younger. 41.9% (n = 8,865) of 21,061 subjects were males, mean age was 54.9 (14.5) years. As compared the lowest tertile with those in uppermost tertile of LDL-C/HDL-C and TG/HDL-C ratios, they were more likely to be smoker, elder and heavier ($p < 0.001$) in lowest tertile group. Meanwhile, there were higher levels of SBP, DBP, FPG and TC in uppermost tertile of LDL-C/HDL-C and TG/HDL-C ratios ($p < 0.001$). During a mean follow-up of 6 years, there were 491 (2.3%) participants with T2DM, 122 (0.5%) with CHD and 674 (3%) of whom from Stroke.

Table 1
Basic characteristics of study subjects in different levels of lipid ratios

Variables	N	LDL-C/HDL-C ratio			TG/HDL-C ratio				
		0 < 1.58	1.58– 2.28	> 2.28	p_value	< 0.67	0.67– 1.21	> 1.21	p_value
Gender, n (%)					< 0.001				< 0.001
Males	8865	2693 (39.2)	2870 (41.7)	2997 (43.6)		2946 (40.8)	2932 (40.6)	3188 (44.2)	
Females	12196	4182 (60.8)	4007 (58.3)	3877 (56.4)		4268 (59.2)	4285 (59.4)	4023 (55.8)	
Age (y)	21061	53.9 (14.8)	55.3 (14.3)	56.8 (13.6)	< 0.001	53.7 (15.0)	55.4 (14.1)	55.7 (13.2)	< 0.001
BMI (kg/m ²)	20669	22.1 (3.0)	23.0 (3.2)	24.2 (3.2)	< 0.001	21.8 (3.0)	23.2 (3.2)	24.6 (3.1)	< 0.001
WC (cm)	20772	77.0 (9.1)	79.4 (9.4)	83.1 (9.1)	< 0.001	75.8 (8.7)	80.0 (9.2)	84.4 (8.8)	< 0.001
WHR	19780	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	< 0.001	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	< 0.001
Current smoker, n (%)	4544	1061 (16)	1467 (22.7)	1630 (25.5)	< 0.001	1409 (20.5)	1448 (21.2)	1637 (24.1)	< 0.001
Alcohol use, n (%)	5133	1986 (34.7)	1619 (26.7)	1312 (20.9)	< 0.001	1871 (29.7)	1620 (25.6)	1620 (25.2)	< 0.001
Physical activity, n (%)	19532				< 0.001				< 0.001
Mild	12553	2717 (47.1)	4091 (65)	4937 (74.8)		3918 (60.6)	4240 (65)	4578 (68.4)	
Moderate	3535	1810 (31.4)	1059 (16.8)	647 (9.8)		1264 (19.6)	1206 (18.5)	1064 (15.9)	
Heavy	3444	1241 (21.5)	1143 (18.2)	1014 (15.4)		1281 (19.8)	1073 (16.5)	1049 (15.7)	
SBP (mmHg)	20638	125.5 (21.1)	130 (21.2)	134.9 (22.3)	< 0.001	125.5 (21.4)	129.7 (21.2)	134.5 (21.3)	< 0.001

WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; LDL-C, LDL-cholesterol; HDL-C, HDL cholesterol; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease.

All values are expressed as means (standard deviation) or percentages (%).

Variables	N	LDL-C/HDL-C ratio			TG/HDL-C ratio				
		0 < 1.58	1.58– 2.28	> 2.28	p_value	< 0.67	0.67– 1.21	> 1.21	p_value
DBP (mmHg)	20550	75.9 (11.4)	77.3 (11.9)	79.3 (12.2)	< 0.001	75.3 (11.6)	77.7 (11.6)	80.3 (11.8)	< 0.001
FPG (mmol/L)	20722	4.9 (1.1)	5.1 (1.2)	5.3 (1.6)	< 0.001	5.0 (1.1)	5.1 (1.2)	5.3 (1.5)	< 0.001
TC (mmol/L)	20722	4.4 (1.0)	4.6 (1.0)	5.0 (1.2)	< 0.001	4.5 (1.0)	4.7 (1.0)	4.8 (1.2)	< 0.001
TG (mmol/L)	20719	1.4 (1.3)	1.5 (1.1)	1.9 (1.4)	< 0.001	0.8 (0.2)	1.3 (0.3)	2.7 (1.7)	< 0.001
HDL-C (mmol/L)	20525	1.8 (0.4)	1.4 (0.3)	1.2 (0.2)	< 0.001	1.7 (0.4)	1.4 (0.3)	1.2 (0.3)	< 0.001
LDL-C (mmol/L)	19724	2.1 (0.5)	2.7 (0.5)	3.4 (0.7)	< 0.001	2.5 (0.7)	2.8 (0.8)	2.8 (0.9)	< 0.001
T2DM, n (%)	491	137 (2.1)	123 (1.9)	190 (2.9)	< 0.001	95 (1.3)	145 (2.1)	244 (3.6)	< 0.001
CHD, n (%)	122	18 (0.3)	39 (0.6)	58 (0.9)	0.002	37 (0.5)	41 (0.6)	39 (0.5)	0.312
Stroke, n (%)	674	207 (3)	199 (2.9)	243 (3.6)	0.055	188 (2.6)	211 (3)	257 (3.6)	0.001
WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; LDL-C, LDL-cholesterol; HDL-C, HDL cholesterol; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease.									
All values are expressed as means (standard deviation) or percentages (%).									

Table 2 shows the result of LDL-C/HDL-C and TG/HDL-C ratios in adjusted/or unadjusted Cox proportional regression. During 136,717 person-years of follow-up, 421 patients with T2DM, 103 patients with CHD and 564 patients with major stroke were recorded in researching the association of LDL-C/HDL-C ratio with interested diseases. It indicates that LDL-C/HDL-C was associated with T2DM (third vs. first tertile: HR, 1.45; 95% CI, 1.16–1.81, $p = 0.01$) (Model 1). Meanwhile, LDL-C/HDL-C ratio was strongly associated with coronary heart disease (CHD) (second vs. first tertile: HR, 1.86; 95% CI, 1.03–3.37, $p = 0.04$; third vs. first tertile: HR, 3.29; 95% CI, 1.91–5.69, $p < 0.001$). In addition, the HRs of T2DM and CHD were increased with LDL-C/HDL-C ratios.

Table 2

Associations of LDL-C-to-HDL-C and TG-to-HDL-C ratios with type 2 diabetes and cardiovascular diseases

Outcomes	N	PYs	incidence case n (%)	ID	Model 1	Model 2	Model 3	
					HR(95%CI)	HR(95%CI)	HR(95%CI)	
LDL-C/HDL-C								
T2DM ^a	0-	6665	45813	137(2.1)	2.99	Ref	Ref	Ref
	1.580-	6608	45331	123(1.9)	2.71	0.92 (0.72–1.17)	0.88 (0.69–1.13)	0.8 (0.60–1.05)
	2.275-	6517	45573	190(2.9)	4.17	1.45 (1.16–1.81) *	1.35 (1.08–1.68) *	0.97 (0.74–1.27)
CHD ^b	0-	6724	45813	18(0.3)	0.39	Ref	Ref	Ref
	1.580-	6805	45331	39(0.6)	0.86	1.86 (1.03–3.37) *	1.75 (0.97–3.17)	1.67 (0.86–3.25)
	2.275-	6793	45573	58(0.9)	1.27	3.29 (1.91–5.69) **	2.98 (1.73–5.16) **	2.41 (1.25–4.64) *
Stroke ^b	0-	6810	45813	207(3.0)	4.52	Ref	Ref	Ref
	1.580-	6826	45331	199(2.9)	4.39	0.96 (0.79–1.17)	0.9 (0.74–1.1)	0.83 (0.67–1.04)
	2.275-	6812	45573	243(3.6)	5.33	1.19 (0.99–1.43)	1.05 (0.87–1.26)	0.82 (0.65–1.03)
TG/HDL-C								

T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; PYs, person-years of follow-up; ID, incidence density (/1000 person-years); HR (95%CI), hazard ratio and 95% confidence interval; Ref, reference group;

Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, ^aadjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides; ^badjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, fasting plasma glucose; ^cadjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL-cholesterol; ^dadjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL-cholesterol, fasting plasma glucose.

P* value < 0.05; *P* value < 0.001.

Outcomes		N	PYs	incidence case n (%)	ID	Model 1	Model 2	Model 3
						HR(95%CI)	HR(95%CI)	HR(95%CI)
T2DM ^c	0-	7049	45936	95(1.3)	2.07	Ref	Ref	Ref
	0.669-	6940	45577	145(2.1)	3.18	1.56 (1.2–2.02) *	1.5 (1.16–1.95) *	1.21 (0.91–1.62)
	1.214-	6789	45270	244(3.6)	5.39	2.7 (2.13–3.43) **	2.62 (2.07–3.32) **	1.68 (1.28–2.21) **
CHD ^d	0-	7114	45936	37(0.5)	0.81	Ref	Ref	Ref
	0.669-	7123	45577	41(0.6)	0.90	1.24 (0.76–2.00)	1.22 (0.75–1.98)	1.12 (0.66–1.91)
	1.214-	7092	45270	39(0.5)	0.86	1.25 (0.77–2.02)	1.28 (0.79–2.07)	1.09 (0.63–1.89)
Stroke ^d	0-	7162	45936	188(2.6)	4.09	Ref	Ref	Ref
	0.669-	7152	45577	211(3.0)	4.63	1.13 (0.93–1.37)	1.07 (0.88–1.31)	0.99 (0.8–1.24)
	1.214-	7144	45270	257(3.6)	5.68	1.38 (1.15–1.67) *	1.39 (1.15–1.68) *	1.17 (0.94–1.46)
T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; PYs, person-years of follow-up; ID, incidence density (/1000 person-years); HR (95%CI), hazard ratio and 95% confidence interval; Ref, reference group;								
Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, ^a adjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides; ^b adjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, fasting plasma glucose; ^c adjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL-cholesterol; ^d adjusted as in Model 2 and also for BMI, smoking, drinking, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL-cholesterol, fasting plasma glucose.								
* <i>P</i> value < 0.05; ** <i>P</i> value < 0.001.								

Moreover, during 136,782 person-years of follow-up, there were patients with 455 T2DM, 105 patients with CHD and 571 patients with major stroke were recorded in researching the association of TG/HDL-C ratio with interested diseases. The risks of T2DM were strongly and positively associated with the level of TG/HDL-C ratio (second vs. first tertile: HR, 1.56; 95% CI, 1.2–2.02, *p* = 0.001; third vs. first tertile: HR, 2.7;

95% CI, 2.13–3.43, $p < 0.001$) (Model 1). The association of TG/HDL-C with Stroke (third vs. first tertile: HR, 1.38; 95% CI, 1.15–1.67, $p = 0.01$) were also obtained (Model 1). In addition, the HRs of T2DM and Stroke were increased with TG/HDL-C ratios.

Figure 2 presents the results of sensitivity analysis in multiple stratification of potential confounders. The hazard ratio of CHD with LDL-C/HDL-C ratio in female (HR, 1.85; 95% CI, 1.24–2.76, $p = 0.003$) was higher than in male (HR, 1.72; 95% CI, 1.23–2.44, $p = 0.002$). Meanwhile, the association between LDL-C/HDL-C ratio and CHD in normal group was more significant ($p < 0.05$), compared with abnormal group. The association of LDL-C/HDL-C ratio with CHD may be interacted by gender, WHR, smoking, drinking and physical activity. However, the significant association between TG/HDL-C ratio and T2DM was found in any group of covariates ($p < 0.05$), while the association was independent on confounders.

Discussion

In this prospective study, we aimed to identify the relationships between LDL-C/HDL-C ratio, TG/HDL-C ratio with Type 2 Diabetes Mellitus (T2DM), coronary heart disease (CHD) and stroke in Chinese elder adults. Our results indicated a significant association between LDL-C/HDL-C ratio with CHD. However, the association may be interacted by gender, WHR, smoking, drinking and physical activity. Inversely, the association between TG/HDL-C ratio and T2DM was independent on confounders. In addition, the hazard ratios of T2DM, CHD and Stroke were increased with LDL-C, TG/HDL-C ratios.

Dyslipidemia can cause a series of metabolic disorders, which are closely related to abnormal insulin levels, metabolic syndrome and cardiovascular disease.[29, 30] Laboratory investigation found that lipids abnormality was one of the causes of glucose metabolism disorders.[31] Additionally, as a hydrolysate of triglyceride (TG), the free fatty acid is easily reactivated into TG by activation of a non-oxidative metabolic pathway, and then the apoptotic pathway is activated to cause cell death and to decrease the function of islet cells.[14, 32] Besides, the accumulation of free fatty acids in the plasma will enter the cells to hinder the oxidation and utilization of glucose, promote structural changes in the insulin receptor substrate in the liver and muscle, and inhibit insulin signaling, thereby causing insulin resistance.[32, 33] Increased dyslipidemia and glucose metabolism, metabolic syndrome, and elevated risk of an atherosclerotic cardiovascular disease characterized by elevated LDL cholesterol, elevated triglycerides and decreased high-density lipoprotein cholesterol.[14, 15] For a long time, the metabolism of blood lipids has been judged by the traditional indicators LDL-C, TG, HDL-C, and recently found that the ratio of LDL-C/HDL-C had the same effects on the predictability cardiovascular disease.[16, 34, 35]

The lipid ratio is a simple and effective index to identify apparently healthy individuals who are at increased diabetes and cardiometabolic risk. The reaction to blood lipids triggers a more serious disorder of lipid metabolism.[20] Therefore, abnormal blood lipids accelerate evolution and gradually develop into cardiovascular diseases or diabetes.[14] Most people will take measures after they are overweight or after the disease occurs, but people with normal body weight or without T2DM and CVD may also have dyslipidemia and develop lesions.[36] Therefore, we want to use the blood lipid index to screen out high-

risk groups early, control the occurrence of cardiovascular diseases and diabetes, and reduce the harm. The result of MY Hong et al[37] revealed the LDL-C/HDL-C ratio and TG were independently associated with diabetes. After the interaction variable was included, the LDL-C/HDL-C ratio remained an independently associated with diabetes, but TG was replaced by TG*LDL-C/HDL-C. However, the significant association was obtained in LDL-C/HDL-C with CHD, the association with T2DM was eliminated in upper LDL-C/HDL-C ratio when included covariates. The result alerted that the association of LDL-C/HDL-C with T2DM may be faint. LDL-C/HDL-C ratio is an independent risk factor for coronary heart disease and it is positively correlated with the severity of coronary artery lesions.[38] In addition, TG/HDL-C ratio was associated with T2DM, and the relationship with stroke also was observed in upper. Increases in plasma triglyceride and decreases in HDL-C have been identified, as risk factors for CHD.[39] Several studies have shown that levels of the triglyceride/HDL-C ratio are closely associated with parameters of cardiovascular risk, and that it can predict the development of CHD and cardiovascular mortality.[40, 41] Meanwhile, high TG/HDL-C ratio in adolescence was associated with hypertension in early adulthood.[37] Contradictorily, the association of high TG/HDL-C ratio with CHD wasn't observed in our result that informed us this association with CVD may be caused by diabetes.

From the results of the demographic characteristics, the mean age, systolic blood pressure, diastolic blood pressure, BMI, and waist circumference increased with the TG/HDL-C and LDL-C/HDL-C levels. However, with the increasing of LDL-C/HDL-C levels, the proportion of males is increasing gradually, the proportion of females is decreasing, and the proportion of smokers and light manual workers is increasing, while proportion of the drinkers, moderate and heavy physical activists is decreasing. This suggests that males have more dyslipidemia than females and dyslipidemia is more common in smokers in Chinese elder adults, which is consistent with previous study.[29] However, workers with moderate physical activities have lower dyslipidemia than mild manual workers, the reason may be that the fat accumulates hardly and the decomposition products are less in workers with moderate physical activities than obesity. The blood lipids of drinkers are more normal than those who do not drink, which is contrary to the conclusion that alcohol may be a risk factor for dyslipidemia.[20] In order to unify the data collected by on-site questionnaires in different regions, the alcohol-related data only retains the "yes/no drinking", and the difference in the amount of alcohol consumed by drinkers may trigger the bias in results, which can be further explored.

The present study, was performed with qualified Chinese elder adults and the sample size is large enough for stratification. However, several limitations warrant mentioning. Firstly, we were unable to avoid the potential effects of medication and the presence of other diseases on the concentration of lipid proteins due to inadequate information. Additionally, this is a single-center study and the subjects were periodic health check-ups population could lead to selection bias. Most subjects of the study were recruited from similar regions, where people had similar lifestyles, and the study population was Chinese and findings did not be replicated in other racial groups. Nevertheless, it was helpless that we assessed the prospective risk of cardio-metabolic disease and related organ damage according to those lipoprotein ratios that are needed to fully elucidate the reported relationships.

Conclusion

In conclusion, the LDL-C/HDL-C ratio and TG/HDL-C ratio are strongly associated with CHD and T2DM, respectively. Moreover, the associations are independent on confounders and the risk of disease increased with the lipoprotein derived indices, the lipid ratios are likely to be the better clinical marker to discriminate individuals with/or without CHD and T2DM. In short, although our study is primary, the results are somehow interesting. Thereby, further study is needed to confirm our findings in the future. Moreover, more clinical trials are needed to determine whether it is protective for subclinical atherosclerotic population to control the level of LDL-C/HDL-C and TG/HDL-C ratios.

Abbreviations

LDL-C, low-density lipoprotein cholesterol;

HDL-C, high-density lipoprotein cholesterol;

CHD, coronary heart disease;

T2DM, Type II Diabetes Mellitus;

CVD, Cardiovascular diseases

PYs, Person-years of follow-up;

ID, Incidence density (/1000 person-years);

HR (95%CI), hazard ratio and 95% confidence interval;

Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YMZ and XHZ conceived of the study, participated in the design, and drafted the manuscript. JJX carried out the study searches and performed the statistical analyses, YYH, QW and QHW collected the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

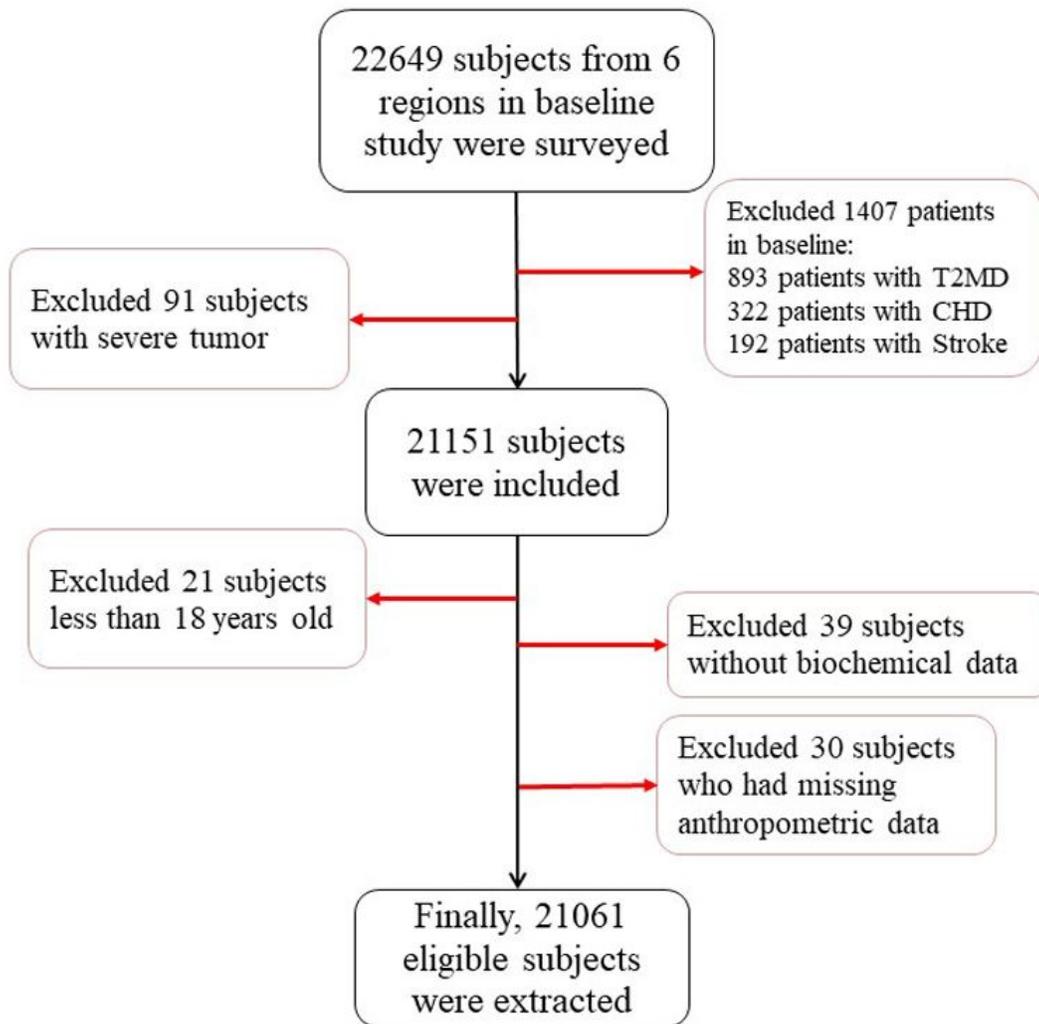
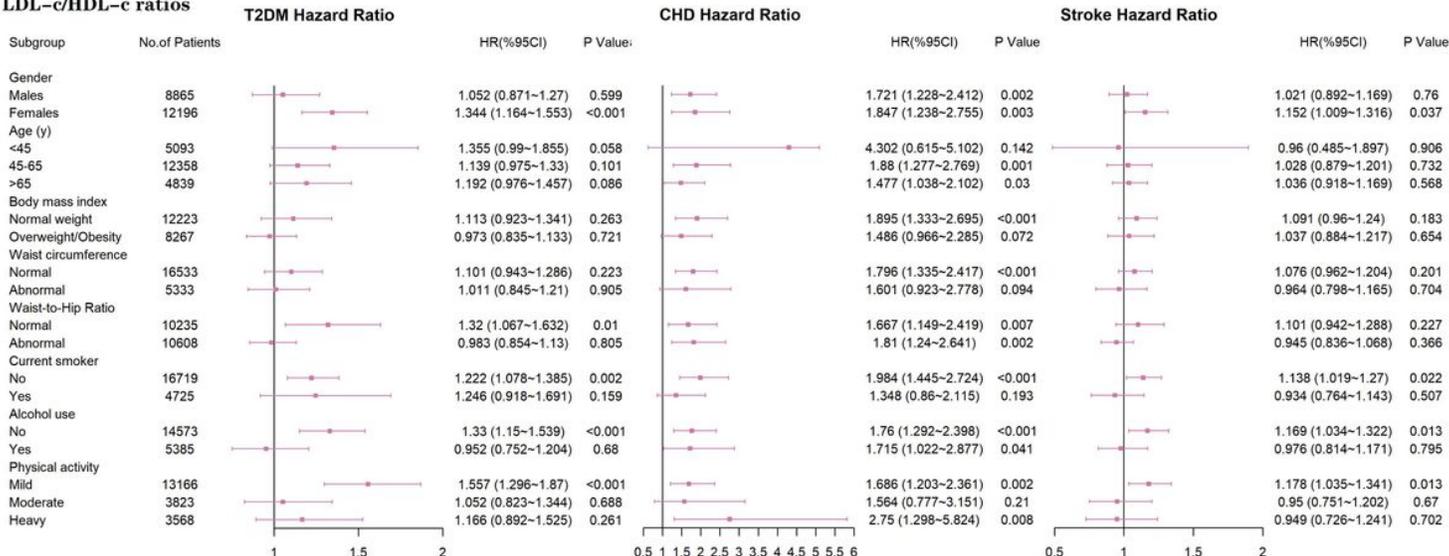


Figure 1

Flowchart of inclusion criteria for participants in this study

LDL-c/HDL-c ratios



TG/HDL-c ratios

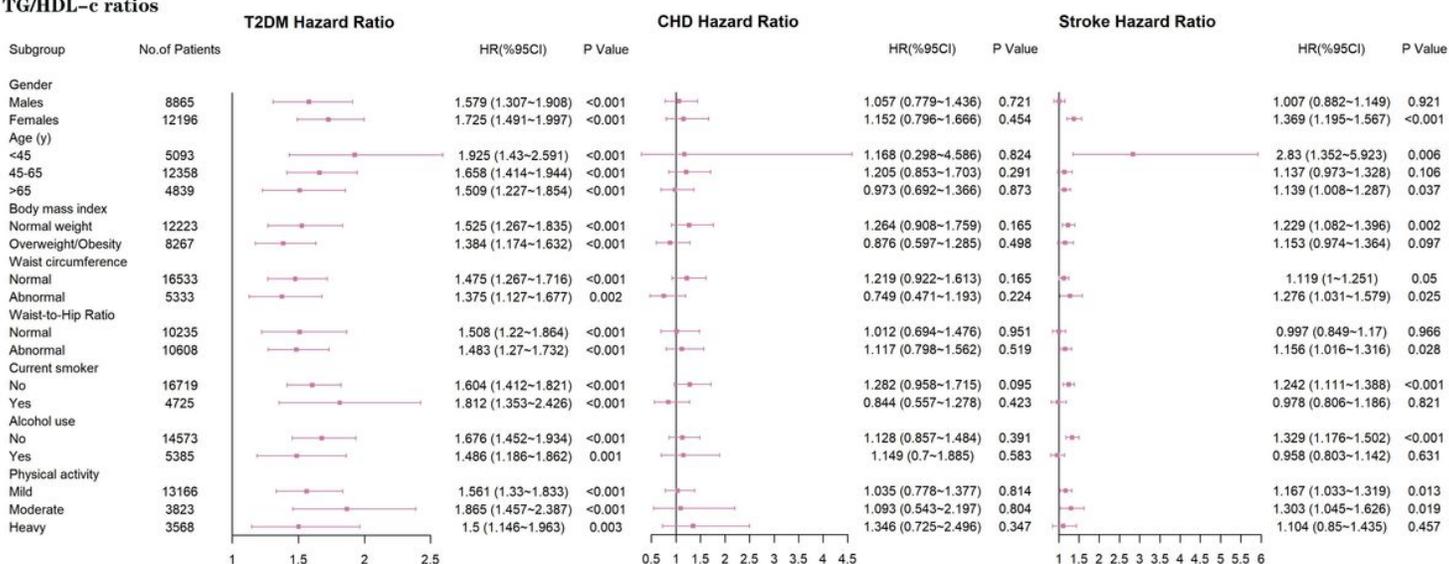


Figure 2

Sensitivity analysis of LDL-C-to-HDL-C and TG-to-HDL-C ratios with type 2 diabetes and cardiovascular diseases