Original Paper

Association of the TG/HDL-C and Non-HDL-C/HDL-C Ratios with Chronic Kidney Disease in an Adult Chinese Population

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Key Words

Chronic kidney disease • Dyslipidemia • High-density lipoprotein cholesterol • Non-HDL-c

Abstract

Background/Aims: Evidence indicates a role for dyslipidemia in the development of chronic kidney disease (CKD). However, the association of lipid abnormalities and their ratios with kidney disease using the new CKD Epidemiology Collaboration (CKD-EPI) equation is not well understood. **Methods:** This cross-sectional study included 48,054 adult subjects. CKD was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m² or dipstick-positive proteinuria. Logistic regression models were used to examine the relationship between lipid variables and CKD. **Results:** The prevalence of CKD in this study was 3.7%. When the participants exhibited higher serum triglyceride (TG), a higher TG/high-density lipoprotein cholesterol (TG/HDL-c) ratio or a higher non-HDL-c/HDL-c ratio or HDL-c in a lower quartile, the prevalence of CKD tended to be higher. The multivariate adjusted odds ratios for CKD per 1 standard deviation increase in lipid level were 1.17 (1.10-1.23) for TG, 0.86 (0.79-0.93) for HDL-c, 1.21 (1.13-1.31) for the TG/HDL-c ratio, and 1.14 (1.06-1.22) for the non-HDL-c/HDL-c ratio. No significant association was detected between CKD and total cholesterol (TC), non-HDL-c or the low-density lipoprotein cholesterol/HDL-c (LDL-c/HDL-c) ratio. **Conclusion:** In this relatively healthy adult Chinese population, the CKD-EPI equation determined that the TG/HDL-c and non-HDL-c/HDL-c ratios as well as TG and HDL-c correlate with the prevalence of CKD.

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Introduction

Chronic kidney disease (CKD) is a public health issue worldwide. More than 10% of people have CKD, and its prevalence is more than 50% in high-risk populations [1, 2]. The rates of death, cardiovascular events, and hospitalization caused by CKD increase with progressive decreases in the estimated glomerular filtration rate (eGFR) [3]. Early screening and managing the risk factors associated with CKD are therefore needed to prevent disease incidence.

Dyslipidemia, characterized by high levels of triglyceride (TG), low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) or low levels of high-density lipoprotein cholesterol (HDL-c), is a common risk factor for atherogenic cardiovascular disease (CVD) and CKD [4-6]. Recently, the relationship between the ratios of atherogenic lipoproteins to HDL-c and cardiovascular risk has become an area of great interest. Using the TG/HDL-C ratio in particular is a practical approach for identifying individuals who have insulin resistance [7, 8]. Several studies have also revealed that the TG/HDL-c ratio is more closely correlated with the incidence of hypertension [9], coronary heart disease [10], CVD [11] and albuminuria [12] than individual lipid profiles are. Meanwhile, non-HDL-c is calculated as TC minus HDL-c and includes all the atherogenic lipoproteins [13]. Several prospective studies have shown that non-HDL-c/HDL-c may be a better predictor of CVD than LDL-c, non-HDL-c, apolipoprotein B (apoB) or apolipoprotein A1 (apoA1) [13-15]. However, published data on the association between non-HDL-c/HDL-c and CKD are limited.

Accurate estimation of the eGFR is important for the early detection of CKD. The Modification of Diet in Renal Disease (MDRD) Study equation is widely recommended for determining the eGFR [16]. In addition, the CKD Epidemiology Collaboration (CKD-EPI) recently proposed a new equation, the CKD-EPI equation, which more accurately estimates the eGFR, especially at higher eGFR levels and in participants without CKD [17]. However, to the best of our knowledge, few studies have assessed the relationship between dyslipidemia and CKD using the new CKD-EPI equation.

China has the largest number of CKD patients worldwide (approximately 119.5 million) [18], and the prevalence of dyslipidemia is currently greater than 41.9% among Chinese adults [19]. This high prevalence necessitates additional investigation into dyslipidemia and kidney disease in China. In the present study, we examined the association between several lipid variables, including the non-HDL-c/HDL-c ratio, and the prevalence of CKD using the novel CKD-EPI equation in a large cross-sectional study including 48,031 Chinese adults.

Materials and Methods

Study population

The participants were Chinese urban residents who had undergone annual medical examinations at the Health Management Center of The Third Xiangya Hospital from January 2014 to January 2015. In this study, the inclusion criterion was an age of >18 years. The exclusion criteria included the following: (1) missing vital data on age, gender, waist circumference (WC), body mass index (BMI), blood pressure (BP), fasting plasma glucose (FPG), lipid profiles, serum creatinine (Scr) or urine analysis; and (2) representing a duplicate case. Finally, a total of 48,054 participants (27,814 males and 20,240 females) were included for analysis.

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of The Third Xiangya Hospital at Central South University in Changsha, China (Text S1: 2017-S207).

Data collection

Baseline information on demographics, medical history, and health-related habits was collected using

a standardized questionnaire. Smoking or drinking status was classified as 'current' (smoking or drinking in the past 6 months or quit smoking or drinking within the past 6 months), 'former' (cessation of smoking or drinking for more than 6 months), or 'never' [20]. Exercise habits were grouped as frequency per week (that is, ≤ 2 times/week or ≥ 3 times/week, with the latter indicating that the individual was physically active) [21]. Any personal history of hypertension, diabetes mellitus, stroke or heart disease (defined as self-reported myocardial infarction, angina, or coronary artery bypass graft) [5], as well as medication use for hypertension, dyslipidemia or diabetes was recorded. Body height and body weight were recorded while participants were wearing light indoor clothing without shoes. WC was measured at the middle point between the costal margin and the iliac crest. BP was measured according to the Joint National Committee (JNC) 7 report [22]: that is, three readings were taken at 5-min intervals, and a mean was calculated, but if the difference between any two readings was greater than 10 mmHg, the 2 closest of the 3 measurements were used. Blood samples were collected in the morning after an overnight fast of at least 8 h. FPG, TG, TC, HDL-c, and Scr levels were measured using standard laboratory methods. LDL-c was calculated according to the Friedewald formula, and non-HDL-c was calculated as TC minus HDL-c. Qualitative analysis of urinary protein was performed on an early-morning spot urine sample using the sulfosalicylic acid method. The levels of proteinuria were assessed using the following criteria: negative, <15 mg/dl; trace, 15-30 mg/dl; 1+, 30-100 mg/dl; 2+, 100-300 mg/dl; and 3+, ≥ 300 mg/dl.

Definitions of CKD, diabetes mellitus, hypertension and obesity

The eGFR was calculated using the equation from the CKD-EPI [17]. For women with Scr (in mg/dl) ≤ 0.7 , $eGFR = 144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age}$, and for women with Scr > 0.7 , $eGFR = 144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age}$.

For men with Scr ≤ 0.9 , $eGFR = 141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$, and for men with Scr > 0.9 , $eGFR = 141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age}$. Proteinuria was defined by a dipstick urinalysis score of 1 or more. CKD was defined as eGFR < 60 ml/min/1.73 m² (low eGFR) or dipstick proteinuria (≥ 1). Diabetes was defined as a self-reported history of a prior diagnosis of diabetes or FPG ≥ 7.0 mmol/l (126 mg/dl) [23]. Hypertension was defined as systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg or current use of antihypertensive medication [22]. Finally, obesity was defined as a BMI of 30 kg/m² or greater [24].

Statistical analyses

Baseline characteristics are expressed as the mean $\pm$ standard deviation (SD) (interquartile range) or proportion (%). Skewed distributions (for the TG/HDL-c ratio and TG) were log transformed to improve normality prior to analysis. Comparisons of baseline characteristics by CKD status (present/absent) were performed using t-tests or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. The multivariable logistic regression model was utilized to evaluate the independent association between lipid profiles and the prevalence of CKD; the odds ratios (ORs) for continuous variables were computed for 1-SD increases. The ability to discriminate CKD cases based on the lipid profiles was compared using the area under the receiver operating curve (AUC). Subjects were then categorized into quartiles based on their baseline lipid profiles, which were associated with the prevalence of CKD, and we compared the prevalence of CKD among the lipids or lipid ratio quartiles by multivariable logistic regression analysis. We also compared the prevalence of CKD among lipids or lipid ratio quartiles using a linear regression model. The variance inflation factor was used to detect the collinearity, and a variance inflation factor ≥ 10 indicated a collinearity problem. All statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL) and MedCalc 17.8 (<http://www.medcalc.org>). We corrected for multiple comparisons by adjusting for the number of independent tests using the Li and Ji method [25]. Thus, a *P* value less than 0.0125 (0.05/4) was considered to be statistically significant.

Results

Demographic and clinical characteristics of the study population

In the current study 26, 061 participants were excluded because of missing data, so ultimately, the analytical sample included 48, 054 participants. The mean age of the study population was 44.3 years, and 57.8% of the subjects were male. CKD was common, with a

prevalence of 3.7%.

The general characteristics of the participants by CKD status are described in Table 1. Participants with CKD were more likely to be male and older; were more likely to be using antihypertensive, oral hypoglycemic and lipid-lowering agents; and had a higher rate of CVD. These patients also had higher BP, BMI, WC, FPG, TG, TC and non-HDL-c values but a lower level of serum HDL-c. In contrast, there was no significant difference in serum LDL between groups. The baseline characteristics of the total 74,115 and eligible 48,054 subjects are shown in Table 2.

Associations between lipid profiles with CKD, low eGFR, and proteinuria.

The associations between lipid profiles with CKD, low eGFR, and proteinuria are shown in Table 3, Table 4 and Table 5, respectively. No collinearity was found between variables. After adjusting for age, gender, smoking and drinking status, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia, the ORs for CKD with a 1-SD increase in lipid profiles were 1.17 (95% CI, 1.10-1.23) for TG, 0.86 (95% CI, 0.79-0.93) for HDL-c, 1.21 (95% CI, 1.13-1.31) for TG/HDL-c and 1.14 (95% CI, 1.06-1.22) for non-HDL-c/HDL-c. No significant association was detected between CKD and TC, non-HDL-c or LDL-c/HDL-c. The receiver operating characteristic (ROC) curve analysis also showed that the AUC values of TG, HDL-c, TG/HDL-c and non-HDL-c/HDL-c for predicting CKD were higher than those of other lipid profiles. Similarly, there were significant associations between TG, HDL-c, TG/HDL-c and non-HDL-c/HDL-c with low eGFR, whereas HDL-c was not associated with proteinuria. Furthermore, these results remained significant after excluding patients with diabetes (Table 6) or obesity (Table 7). Whereas this was not the case for participants without hypertension (Table 8).

Table 1. Characteristics of study subjects with and without chronic kidney disease. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; and eGFR, estimated glomerular filtration rate

Characteristic	Total (n=48,054)	Non-CKD (n=46,255)	CKD (n=1,799)	P value
Age, years	44.3±13.9	43.9±13.5	56.3±17.8	<0.001
Men, %	57.9	57.1	78.9	<0.001
Current smoking, %	32.8	32.5	39.4	<0.001
Current drinking, %	55.0	55.2	50.5	0.001
Physical activity, %	53.0	52.7	60.2	<0.001
SBP, mmHg	121.5±15.4	120.9±14.9	135.1±19.6	<0.001
DBP, mmHg	74.6±10.8	74.3±10.6	81.0±13.3	<0.001
BMI, kg/m ²	23.9±3.3	23.8±3.3	25.2±3.7	<0.001
WC, cm	81.6±10.1	81.4±10.0	86.9±10.3	<0.001
FPG, mmol/l	5.4±1.2	5.3±1.1	6.4±2.5	<0.001
TG, mmol/l	1.2(0.9-1.9)	1.2(0.8-1.9)	1.6(1.1-2.4)	<0.001
TC, mmol/l	5.1±1.0	5.1±1.0	5.2±1.3	<0.001
LDL-c, mmol/l	2.8±0.8	2.8±0.8	2.8±0.9	0.644
HDL-c, mmol/l	1.6±0.4	1.6±0.4	1.4±0.4	<0.001
Non-HDL-c, mmol/l	3.5±1.0	3.5±1.0	3.8±1.3	<0.001
TG/HDL-c ratio	0.79(0.47-1.36)	0.78(0.47-1.34)	1.14(0.67-1.94)	<0.001
Non-HDL-c/HDL-c ratio	2.3±1.0	2.3±1.0	2.7±1.1	<0.001
LDL-c/HDL-c ratio	1.8±0.7	1.8±0.7	2.0±0.8	<0.001
eGFR, ml/min/1.73 m ²	105.1±16.2	105.9±14.9	82.4±28.3	<0.001
History of stroke, %	0.2	0.1	1.4	<0.001
History of heart disease, %	1.6	1.4	6.7	<0.001
Medication for hypertension, %	8.9	7.9	35.2	<0.001
Medication for diabetes, %	2.2	1.9	9.5	<0.001
Medication for dyslipidemia, %	1.2	1.1	4.1	<0.001

Table 2. Characteristics of all subjects and the eligible participants in this study. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; and eGFR, estimated glomerular filtration rate

Characteristic	All participants (n=74,115)	Eligible participants (n=48,054)	P value
Age, years	43.9±13.5	44.3±13.9	<0.001
Men, %	55.4	57.9	<0.001
Current smoking, %	32.9	32.8	0.630
Current drinking, %	49.7	55.0	<0.001
Physical activity, %	36.4	53.0	<0.001
SBP, mmHg	121.7±15.4	121.5±15.4	0.021
DBP, mmHg	74.9±10.9	74.6±10.8	0.302
BMI, kg/m ²	23.9±3.3	23.9±3.3	0.396
WC, cm	81.6±10.1	81.6±10.1	0.037
FPG, mmol/l	5.3±1.2	5.4±1.2	0.749
TG, mmol/l	1.2(0.8-1.9)	1.2(0.9-1.9)	<0.001
TC, mmol/l	5.1±1.0	5.1±1.0	0.309
LDL-c, mmol/l	2.8±0.8	2.8±0.8	0.138
HDL-c, mmol/l	1.6±0.4	1.6±0.4	0.002
Non-HDL-c, mmol/l	3.5±1.0	3.5±1.0	0.028
TG/HDL-c ratio	0.77(0.46-1.34)	0.79(0.47-1.36)	<0.001
Non-HDL-c/HDL-c ratio	2.3±1.0	2.3±1.0	0.021
LDL-c/HDL-c ratio	1.8±0.7	1.8±0.7	0.033
eGFR, ml/min/1.73 m ²	106.1±16.1	105.1±16.2	<0.001
Proteinuria, %	2.7	2.9	0.062
History of stroke, %	0.2	0.2	0.154
History of heart disease, %	1.2	1.6	<0.001
Medication for hypertension, %	8.1	8.9	<0.001
Medication for diabetes, %	2.2	2.2	0.625
Medication for dyslipidemia, %	1.2	1.2	0.741

Prevalence of CKD according to lipids or lipid ratio quartiles

Fig. 1 presents the prevalence of CKD according to TG and HDL-c as well as the TG/HDL-c and non-HDL-c/HDL-c ratios. The prevalence of CKD approximately tripled in the highest TG quartile group compared to that in the lowest group. Similar trends in the prevalence of CKD were observed in the TG/HDL-c and non-HDL-c/HDL-c quartiles. There was an inverse relationship between the prevalence of CKD and the HDL-c level.

Association between lipids or lipid ratio quartiles and CKD

Table 9 shows the association between categorized lipid or lipid ratio levels and CKD. After adjusting for all the confounding factors, the prevalence of CKD increased as the TG and TG/HDL-c ratio quartiles increased, whereas the prevalence of CKD decreased with increasing HDL-c quartile. In addition, the prevalence of CKD increased as the non-HDL-c/HDL-c ratio quartile increased relative to the lowest quartile.

Table 3. Odds ratios with 95% confidence intervals for CKD for a 1-SD increase in baseline lipid or lipid ratio variables. CKD, chronic kidney disease; SD, standard deviation; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; WC, waist circumference; FPG, fasting plasma glucose; and SBP, systolic blood pressure. Model 1: adjusted for age and gender. Model 2: adjusted for current smoking, current drinking, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia in addition to Model 1 adjustment. TG and TG/HDL-c were log transformed. ^a Indicates a significant difference compared to TG. ^b Indicates a significant difference compared to TC. ^c Indicates a significant difference compared to LDL-c. ^d Indicates a significant difference compared to HDL-c. ^e Indicates a significant difference compared to non-HDL-c. ^f Indicates a significant difference compared to TG/HDL-c. ^g Indicates a significant difference compared to non-HDL-c/HDL-c

	AUC (95% CI)	Odds ratio (95% CI)					
		Unadjusted	P value	Model 1	P value	Model 2	P value
TG	0.622 (0.618-0.627)	1.49 (1.43-1.55)	<0.001	1.38 (1.32-1.45)	<0.001	1.17 (1.10-1.23)	<0.001
TC	0.530 (0.526-0.535) ^a	1.15 (1.10-1.20)	<0.001	1.07 (1.02-1.12)	0.005	1.00 (0.94-1.06)	0.990
LDL-c	0.502 (0.498-0.507) ^{a,b}	1.02 (0.97-1.06)	0.540	0.92 (0.88-0.97)	0.001	0.94 (0.88-1.00)	0.055
HDL-c	0.603 (0.599-0.607) ^{a,b,c}	0.68 (0.65-0.72)	<0.001	0.76 (0.72-0.81)	<0.001	0.86 (0.79-0.93)	<0.001
Non-HDL-c	0.569 (0.565-0.573) ^{a,b,c,d}	1.28 (1.23-1.33)	<0.001	1.16 (1.11-1.21)	<0.001	1.04 (0.98-1.11)	0.210
TG/HDL-c	0.630 (0.625-0.634) ^{a,b,c,d,e}	1.54 (1.47-1.61)	<0.001	1.43 (1.36-1.50)	<0.001	1.21 (1.13-1.31)	<0.001
Non-HDL/HDL-c	0.607 (0.603-0.611) ^{a,b,c,e,f}	1.42 (1.36-1.48)	<0.001	1.30 (1.24-1.37)	<0.001	1.14 (1.06-1.22)	<0.001
LDL/HDL-c	0.563 (0.558-0.567) ^{a,b,c,d,f,g}	1.23 (1.18-1.28)	<0.001	1.08 (1.03-1.13)	0.002	1.03 (0.96-1.10)	0.457

Table 4. Odds ratios with 95% confidence intervals for low eGFR for a 1-SD increase in baseline lipid or lipid ratio variables. CKD, chronic kidney disease; SD, standard deviation; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; WC, waist circumference; FPG, fasting plasma glucose; and SBP, systolic blood pressure. Model 1: adjusted for age and gender. Model 2: adjusted for current smoking, current drinking, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia, presence of proteinuria in addition to Model 1 adjustment. TG and TG/HDL-c were log transformed

	Odds ratio (95% CI)					
	Unadjusted	P value	Model 1	P value	Model 2	P value
TG	1.28 (1.18-1.38)	<0.001	1.43 (1.30-1.57)	<0.001	1.31 (1.13-1.52)	<0.001
TC	1.07 (0.99-1.16)	0.082	1.08 (0.99-1.17)	0.080	1.12 (1.00-1.26)	0.051
LDL-c	1.10 (1.02-1.19)	0.018	1.06 (0.98-1.16)	0.153	1.11 (0.99-1.25)	0.088
HDL-c	0.77 (0.70-0.84)	<0.001	0.73 (0.67-0.81)	<0.001	0.82 (0.71-0.95)	0.006
Non-HDL-c	1.17 (1.08-1.26)	<0.001	1.21 (1.11-1.32)	<0.001	1.21 (1.07-1.37)	0.002
TG/HDL-c	1.32 (1.22-1.42)	<0.001	1.49 (1.35-1.64)	<0.001	1.34 (1.15-1.56)	<0.001
Non-HDL/HDL-c	1.24 (1.15-1.33)	<0.001	1.38 (1.26-1.51)	<0.001	1.30 (1.13-1.49)	<0.001
LDL/HDL-c	1.22 (1.13-1.31)	<0.001	1.25 (1.15-1.36)	<0.001	1.21 (1.06-1.37)	0.004

Table 5. Odds ratios with 95% confidence intervals for proteinuria for a 1-SD increase in baseline lipid or lipid ratio variables. CKD, chronic kidney disease; SD, standard deviation; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; WC, waist circumference; FPG, fasting plasma glucose; and SBP, systolic blood pressure. Model 1: adjusted for age and gender. Model 2: adjusted for current smoking, current drinking, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia, eGFR in addition to Model 1 adjustment. TG and TG/HDL-c were log transformed

	Odds ratio (95% CI)					
	Unadjusted	P value	Model 1	P value	Model 2	P value
TG	1.58 (1.51-1.66)	<0.001	1.43 (1.36-1.51)	<0.001	1.16 (1.08-1.26)	<0.001
TC	1.20 (1.14-1.25)	<0.001	1.13 (1.07-1.18)	<0.004	1.00 (0.94-1.08)	0.900
LDL-c	1.00 (0.95-1.06)	0.877	0.92 (0.88-0.98)	0.004	0.92 (0.85-0.99)	0.020
HDL-c	0.65 (0.61-0.69)	<0.001	0.76 (0.72-0.82)	<0.001	0.90 (0.82-0.99)	0.023
Non-HDL-c	1.34 (1.28-1.40)	<0.001	1.21 (1.16-1.27)	<0.001	1.03 (0.96-1.11)	0.389
TG/HDL-c	1.64 (1.56-1.72)	<0.001	1.47 (1.39-1.55)	<0.001	1.19 (1.09-1.29)	<0.001
Non-HDL/HDL-c	1.50 (1.43-1.57)	<0.001	1.34 (1.27-1.41)	<0.001	1.11 (1.02-1.20)	0.012
LDL/HDL-c	1.25 (1.19-1.31)	<0.001	1.08 (1.02-1.14)	0.008	0.98 (0.91-1.06)	0.669

Table 6. Odds ratios with 95% confidence intervals of CKD for a 1-SD increase in baseline lipid or lipid ratio variables in the subpopulation without hypertension (n=39247). CKD, chronic kidney disease; SD, standard deviation; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; WC, waist circumference; FPG, fasting plasma glucose; and SBP, systolic blood pressure. Model 1: adjusted for age and gender. Model 2: adjusted for current smoking, current drinking, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia in addition to Model 1. ^a Values were log transformed

	Odds ratios (95% CI)					
	Unadjusted	P value	Model 1	P value	Model 2	P value
TG ^a	1.36 (1.28-1.45)	<0.001	1.19 (1.10-1.27)	<0.001	1.09 (0.99-1.22)	0.093
TC	1.09 (1.02-1.17)	0.017	0.98 (0.91-1.06)	0.605	0.95 (0.86-1.05)	0.331
LDL-c	0.99 (0.92-1.06)	0.740	0.88 (0.82-0.94)	<0.001	0.93 (0.84-1.02)	0.129
HDL-c	0.73 (0.67-0.79)	<0.001	0.84 (0.77-0.92)	<0.001	0.87 (0.77-0.98)	0.020
Non-HDL-c	1.21 (1.13-1.29)	<0.001	1.04 (0.97-1.12)	0.306	0.99 (0.89-1.10)	0.886
TG/HDL-c ^a	1.41 (1.32-1.50)	<0.001	1.22 (1.13-1.31)	<0.001	1.13 (1.01-1.26)	0.029
Non-HDL-c/HDL-c	1.33 (1.25-1.42)	<0.001	1.15 (1.07-1.23)	<0.001	1.08 (0.97-1.20)	0.182
LDL-c/HDL-c	1.18 (1.10-1.26)	<0.001	0.99 (0.92-1.07)	0.871	1.00 (0.91-1.11)	0.956

Table 7. Odds ratios with 95% confidence intervals of CKD for a 1-SD increase in baseline lipid or lipid ratio variables in the subpopulation without diabetes (n=45,531). Abbreviations: CKD, chronic kidney disease; SD, standard deviation; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; WC, waist circumference; FPG, fasting plasma glucose; and SBP, systolic blood pressure. Model 1: adjusted for age and gender. Model 2: adjusted for current smoking, current drinking, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia in addition to Model 1. ^a Values were log transformed

	Odds ratios (95% CI)		Model 1	P value	Model 2	P value
	Unadjusted	P value				
TG ^a	1.38 (1.32-1.45)	<0.001	1.24 (1.17-1.31)	<0.001	1.15 (1.06-1.25)	0.001
TC	1.07 (1.02-1.13)	0.012	0.97 (0.92-1.03)	0.341	0.98 (0.91-1.06)	0.578
LDL-c	1.03 (0.98-1.09)	0.295	0.92 (0.87-0.97)	0.004	0.95 (0.88-1.02)	0.139
HDL-c	0.73 (0.69-0.77)	<0.001	0.81 (0.76-0.86)	<0.001	0.87 (0.79-0.95)	0.003
Non-HDL-c	1.20 (1.14-1.26)	<0.001	1.05 (0.99-1.11)	0.118	1.02 (0.94-1.11)	0.601
TG/HDL-c ^a	1.42 (1.35-1.50)	<0.001	1.28 (1.21-1.35)	<0.001	1.18 (1.08-1.28)	<0.001
Non-HDL-c/HDL-c	1.31 (1.25-1.38)	<0.001	1.17 (1.11-1.24)	<0.001	1.10 (1.02-1.20)	0.018
LDL-c/HDL-c	1.20 (1.14-1.26)	<0.001	1.05 (0.99-1.11)	0.102	1.02 (0.95-1.11)	0.560

Table 8. Odds ratios with 95% confidence intervals of CKD for a 1-SD increase in baseline lipid or lipid ratio variables in the subpopulation without obesity (n=46,145). CKD, chronic kidney disease; SD, standard deviation; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; WC, waist circumference; FPG, fasting plasma glucose; and SBP, systolic blood pressure. Model 1: adjusted for age and gender. Model 2: adjusted for current smoking, current drinking, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia in addition to Model 1. ^a Values were log transformed

	Odds ratios (95% CI)		Model 1	P value	Model 2	P value
	Unadjusted	P value				
TG ^a	1.45 (1.39-1.52)	<0.001	1.33 (1.26-1.40)	<0.001	1.17 (1.09-1.27)	<0.001
TC	1.12 (1.07-1.18)	<0.001	1.04 (0.99-1.09)	0.125	0.99 (0.93-1.06)	0.823
LDL-c	1.01 (0.96-1.06)	0.671	0.91 (0.87-0.96)	<0.001	0.94 (0.88-1.01)	0.090
HDL-c	0.70 (0.66-0.74)	<0.001	0.78 (0.74-0.83)	<0.001	0.84 (0.78-0.92)	<0.001
Non-HDL-c	1.25 (1.20-1.31)	<0.001	1.12 (1.07-1.18)	<0.001	1.04 (0.97-1.11)	0.263
TG/HDL-c ^a	1.50 (1.44-1.58)	<0.001	1.37 (1.30-1.44)	<0.001	1.22 (1.13-1.32)	<0.001
Non-HDL-c/HDL-c	1.39 (1.33-1.46)	<0.001	1.26 (1.20-1.32)	<0.001	1.15 (1.07-1.24)	<0.001
LDL-c /HDL-c	1.22 (1.17-1.28)	<0.001	1.06 (1.01-1.12)	0.021	1.04 (0.97-1.12)	0.262

Discussion

The cross-sectional analysis of this large Chinese study population documents a significant association of higher TG and lower HDL-c with CKD; a similar association was also found between CKD and a higher TG/HDL-c or non-HDL-c/HDL-c ratio. In addition, a direct comparison of lipid parameters indicated better discrimination capacity for TG, HDL-c, TG/HDL-c and non-HDL-c/HDL-c in predicting CKD than for other lipid profiles.

Our study confirms the association of serum TG and HDL-c with CKD, as shown by previous studies [4-6]. Although non-HDL-c/HDL-c is a well-studied risk factor for CVD [13-15], this study is one of the first reporting its association with kidney disease [26]. Our study is also one of the first to relate varying lipid parameters to kidney disease using the novel CKD-EPI equation, which is as accurate as the MDRD Study equation at GFR<60 ml/

Fig. 1. The prevalence of CKD among participants based on the categorized lipid or lipid ratio levels. (a) TG, (b) HDL-C, (c) TG/HDL-C ratio, (d) non-HDL-C/HDL-C ratio. CKD, chronic kidney disease; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

Table 9. Odds ratios with 95% confidence intervals for CKD based on the categorized lipid or lipid ratio levels. CKD, chronic kidney disease; TG, triglyceride; and HDL-C, high-density lipoprotein cholesterol. Model 1: adjusted for age and gender. Model 2: adjusted for current smoking, current drinking, physical activity, WC, obesity, FPG, SBP, medication for diabetes, medication for hypertension, history of stroke and heart disease, and medication for dyslipidemia in addition to Model 1 adjustment

	Odds ratio (95% CI)		Model 1	P value	Model 2	P value
	Unadjusted	P value				
TG quartiles						
≤0.85	1		1		1	
0.86~1.24	1.69(1.43-2.00)	<0.001	1.18(1.00-1.40)	0.058	1.10(0.87-1.39)	0.416
1.25~1.87	2.24(1.91-2.62)	<0.001	1.39(1.18-1.64)	<0.001	1.25(1.00-1.57)	0.053
≥1.88	3.20(2.75-3.72)	<0.001	2.04(1.75-2.39)	<0.001	1.44(1.15-1.82)	0.002
HDL-c quartiles						
≤1.31	1		1		1	
1.32~1.56	0.66(0.59-0.75)	<0.001	0.71(0.63-0.81)	<0.001	0.79(0.67-0.93)	0.005
1.57~1.86	0.49(0.43-0.56)	<0.001	0.59(0.51-0.67)	<0.001	0.73(0.61-0.89)	0.001
≥1.87	0.43(0.37-0.49)	<0.001	0.58(0.50-0.67)	<0.001	0.77(0.62-0.96)	0.021
TG/HDL-c quartiles						
≤0.47	1		1		1	
0.48~0.79	1.65(1.39-1.96)	<0.001	1.22(1.02-1.45)	0.029	1.10(0.87-1.41)	0.426
0.80~1.36	2.38(2.03-2.81)	<0.001	1.49(1.27-1.77)	<0.001	1.29(1.02-1.63)	0.037
≥1.37	3.48(2.99-4.06)	<0.001	2.27(1.93-2.67)	<0.001	1.63(1.28-2.07)	<0.001
Non-HDL-c/HDL-c quartiles						
≤1.58	1		1		1	
1.59~2.21	1.19(1.01-1.39)	0.035	0.88(0.75-1.04)	0.134	0.81(0.65-1.01)	0.064
2.22~2.95	1.67(1.44-1.94)	<0.001	1.08(0.92-1.26)	0.357	0.91(0.73-1.13)	0.403
≥2.96	2.51(2.18-2.88)	<0.001	1.61(1.39-1.87)	<0.001	1.16(0.93-1.44)	0.186

min/1.73 m² but is more accurate at higher GFRs [17]. Moreover, a recent multicenter study of 977 Chinese participants, including healthy adults and CKD patients, indicated that the CKD-EPI equation performed better than the MDRD Study equation, with less bias, improved precision and greater accuracy [27]. The prevalence of CKD in our study was 3.7%, and our previous study indicated the prevalence of CKD was 9.0% in hypertensive subjects [28], which is lower than that in participants from Beijing [29], partly because of the younger age and better socioeconomic status of our present patient cohort.

High TG and low HDL-c are most commonly seen in patients with CKD. TG-rich lipoproteins (very-low-density lipoprotein (VLDL), chylomicrons, and chylomicron remnants) increase at the early stage of CKD due to depressed lipoprotein lipase (LPL) and an excess level of the LPL inhibitor apolipoprotein C-III [30, 31]; these remnant lipoproteins can penetrate the vascular endothelium and lead to atherosclerosis [30]. Circulating HDL-c protects against atherosclerosis via reverse cholesterol transport (RCT), and it also has antioxidant, anti-inflammatory and antithrombotic properties [32]. Patients with kidney dysfunction frequently exhibit a diminished plasma concentration of apoA-I and lecithin cholesterol acyltransferase deficiency [30, 31], which results in lower plasma HDL-c. The biological functions of HDL-C are also impaired in CKD [30, 32]. In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study [33], higher HDL-c was associated with reduced mortality risk and coronary artery disease severity in participants with normal kidney function but not in patients with reduced kidney function. A recent study indicated the function of HDL-c, not its circulating levels, are associated with subclinical atherosclerosis [34]. HDL-c cholesterol efflux capacity (CEC) plays a central role in RCT and is regarded as a key metric of HDL-c functionality. However, CEC did not predict the incidence of cardiovascular events in patients with CKD in the German Diabetes Dialysis Study (4D Study) [35] and the CARE FOR HOME study [36]. Further studies are needed to test whether other potential atheroprotective activities of HDL-c (e.g., antioxidant and anti-inflammatory properties, increased endothelial nitric oxide production) predict cardiovascular events in CKD patients [37]. Nonetheless, in the Very Large Database of Lipids-4 study of 1, 350, 908 individuals [38], higher TG/HDL-c was associated with a more atherogenic lipid phenotype, which is characterized by higher levels of remnant lipoprotein particle cholesterol. Previous investigations have shown that higher TG/HDL-c is independently correlated with coronary heart disease [10, 39] and all-cause mortality [40]. Several cross-sectional [41] and longitudinal studies [42, 43] have also shown a relationship between TG/HDL-c and CKD. In the present analysis, we were able to reproduce this finding utilizing the new CKD-EPI equation.

In our study, participants with higher non-HDL-c/HDL-c were associated with a prevalence of CKD after adjustment for confounders; however, higher non-HDL-c alone was not. Non-HDL-c is calculated as TC minus HDL-c and includes all of the atherogenic lipoproteins [13], such as TG-rich lipoproteins, intermediate-density lipoprotein cholesterol (IDL-c), LDL-c, and lipoprotein(a) (Lp(a)). Data from the Third National Health and Nutrition Examination Survey [14], the Swedish National Diabetes Register [15], and the Atherosclerosis Risk in Communities study [13] confirmed that the predictive value of non-HDL-c/HDL-c for cardiovascular risk is as good as, if not better than, that of non-HDL-c, implying that non-HDL-c/HDL-c more closely reflects the complex interactions of lipoprotein metabolism and can better predict plasma atherogenicity than isolated lipid values. However, few studies have demonstrated whether non-HDL-c/HDL-c can predict renal dysfunction. Tolonen et al [44]. observed varying non-HDL-c concentrations at different stages of albuminuria in type 1 diabetes and found that non-HDL-c was predictive of progression to end-stage renal disease (ESRD). Bae et al [45]. showed that higher non-HDL-c/HDL-c, but not non-HDL-c, was associated with a higher risk of incident CKD in a large and apparently healthy cohort. Our findings are largely consistent with those of other studies.

Screening for dyslipidemia in patients with CKD is supported by clinical guidelines. The evaluation of TC, LDL-c, HDL-c, TG, and non-HDL-c is recommended [46-48]. Additional lipid analyses that may be considered are Lp(a), apoB/apoA1 and non-HDL-c/HDL-c analyses

[46] TC and LDL-c are specifically recommended as primary targets [46-48], non-HDL-c and apoB are considered to be secondary targets [46, 48], and non-HDL-c/HDL-c has been identified as a potentially important marker for risk estimation [46]. Recent studies have suggested that statin treatment might not exert beneficial effects on the progression of CKD. In the Heart and Renal Protection (SHARP) [49] study, decreasing LDL-c with simvastatin plus ezetimibe for nearly 5 years did not affect the progression from kidney disease to ESRD in 6, 247 patients who were not on dialysis. A meta-analysis by Hou et al [50], involving 48, 429 patients also suggested that statin therapy had no clear effect on kidney failure events. Nonetheless, health behavior interventions, including a Mediterranean diet, body weight reduction, regular physical exercise, and smoking cessation, have positive effects on plasma lipid profiles [46].

Our study has certain limitations. First, the cohort was voluntary, and those already under treatment for CVD or CKD might not have participated. Therefore, the study may be biased by the healthy worker effect [51]. However, we believe that our conclusion would remain unchanged in the general population, as the associations between lipid parameters and CKD were robust regardless of the presence of diabetes or obesity (Tables 7-8). Second, further selection bias may have occurred because those participants without complete data were excluded. However, we compared the baseline characteristics of the total 74, 115 and eligible 48, 054 subjects and found that nearly all variables (except physical activity) were nearly the same. Significant differences did exist in several variables, but this type of discrepancy commonly occurs when evaluating big data (Table 2). Third, our study cohort mostly comprised urban participants who underwent an annual check-up; this population was therefore not nationally representative or geographically diverse. Finally, due to the cross-sectional study design, it is difficult to infer causality between dyslipidemia and CKD based on our study.

Conclusion

Our study demonstrates that TG/HDL-c, non-HDL-c/HDL-c and TG, HDL-c were associated with CKD prevalence in a large Chinese population. Long-term studies to examine the relationship between non-HDL-c/HDL-c and the development or progression of kidney disease are thus warranted.

Disclosure Statement

The authors declare that they have no conflict of interest.

Abbreviations

SBP (systolic blood pressure); DBP (diastolic blood pressure); BMI (body mass index); WC (waist circumference); FPG (fasting plasma glucose); TG (triglyceride); TC (total cholesterol); LDL-c (low-density lipoprotein cholesterol); HDL-c (high-density lipoprotein cholesterol); eGF (estimated glomerular filtration rate); CKD (chronic kidney disease); SD (standard deviation); CI (confidence interval).

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