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ORIGINAL ARTICLE

Predictive value of total cholesterol to high-density lipoprotein cholesterol ratio for chronic kidney disease among adult male and female in Northwest China

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Abstract

Background: Studies have found that the ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) was associated with the development of chronic kidney disease (CKD). However, the relationship in different genders was rarely discussed. The aim of this study was to explore this relationship and assess its predictive power for both males and females.

Methods: Based on a prospective cohort platform in northwest China, 32,351 participants without CKD were collected in the baseline and followed up for approximately 5 years. Cox proportional hazard model and restricted cubic spline regression analysis were performed to investigate the association between TC, HDL-C, TC/HDL-C and CKD in adult female and male. The clinical application value of the indicators in predicting CKD was evaluated by the receiver operator characteristic curve.

Results: During a mean follow-up of 2.2 years, 484 males and 164 females developed CKD. After adjusted for relevant confounders, for every one standard deviation increase in TC, HDL-C and TC/HDL-C, the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for CKD were 1.17 (1.05–1.31), 0.84 (0.71–0.99), and 1.15 (1.06–1.25) for males, 0.94 (0.78–1.13), 0.58 (0.35–0.95), and 1.19 (1.01–1.40) for females, respectively. The results also showed that TC, HDL-C, and TC/HDL-C were associated with CKD in a linear dose–response relationship. The TC/HDL-C had the largest area under the curve (AUC) compared to TC and HDL-C, and the AUC among the females was larger than that among males.

Conclusions: The TC/HDL-C was significantly associated with CKD in adult males and females and has better clinical value in predicting CKD than TC and HDL-C, especially in females.

KEYWORDS

chronic kidney disease, gender, Jinchang Cohort, predictive value, TC/HDL-C

Key points

- One standard deviation increase in the total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) ratio was related to a 14% and 15%

Yanli Liu and Kang Lyu contributed equally to this study.

higher risk of chronic kidney disease (CKD) in males and females, respectively.
- There was a positive linear relationship between TC/HDL-C ratio and CKD, and the TC/HDL-C ratio had the highest predictive value in females.

1 | INTRODUCTION

In 2017, the global prevalence of chronic kidney disease (CKD) reached 11.1% (10.4% for males and 11.8% for females) in the world.[1] With an estimated 843.6 million people suffering from CKD, this has caused a huge disease burden and become a major public health problem.[2] The prevalence of CKD in China was 10.8%, and CKD patients approximately accounted for 19.0% of the global patients,[3] among which the prevalence of CKD in females (12.9%) was higher than that in males (8.7%).[4] Therefore, early detection and targeted control of CKD risk factors for females and males are necessary to prevent CKD.

Usually, patients with CKD often have dyslipidemia. Studies have shown that lipoprotein metabolism disorder could cause kidney damage and accelerate the progression of CKD.[5,6] Several epidemiological studies also have represented significant associations between serum lipid profile and CKD risk. Wen et al. found that for one standard deviation (SD) increase in triglyceride (TG) or high-density lipoprotein (HDL-C), the odds ratios (ORs) and 95% confidence interval (95% CI) for CKD risk were 1.17 (1.10–1.23) or 0.86 (0.79–0.93).[7] In a 6-year retrospective cohort study, the total cholesterol (TC), TG, and low-density lipoprotein cholesterol (LDL-C) were found to be significantly associated with CKD risk, with the ORs (95% CI) of 3.84 (1.90–7.76), 3.08 (1.11–6.69), and 1.40 (1.11–2.48), respectively.[8] A Japanese study found that low level of HDL-C was a major predictor of CKD progression, especially in women under 70 years of age with CKD.[9] The results of these studies show the association between different single lipid indicator and CKD. However, the relationships between these single lipid indicators and CKD were not as close as the composite indicators, and the predicting effect for the CKD risk was not strong.[10]

Existing studies have found that some compound lipid indicators were closely related to the risk of cardiovascular disease and CKD and may have better predictive value. Past research have indicated that the level of TC/HDL-C was related to the risk of cardiovascular diseases,[11–13] while cardiovascular disease and CKD have similar pathogenesis of vascular endothelial damage and common risk factors.[14] In the Dongfeng-Tongji cohort study in China, TC/HDL-C was found to be linked to the risk of CKD with ORs of 2.21 (1.91–2.57) comparing the extreme quartiles.[10] A study of patients with hypertension in Korea showed that the elevated TC/HDL-C was associated with the development of albuminuria in women, OR (95% CI) was 1.21 (1.02–1.45), but no relationship was found in men.[15] In addition, Mathews et al. found that TC/HDL-C might be a hallmark with atherogenic particle burden.[16] A cross-sectional study indicated that TC/HDL-C as a sign of atherogenic lipoprotein burdens might provide potential extra information than LDL-C and non-HDL-C and might be more associated with risk events.[17] However, one study in Guangdong, China, found that the log TC/HDL-C was inversely connected with eGFR, but it was not associated with CKD.[18]

In summary, the research results of the correlation between TC/HDL-C and CKD are still inconsistent and limited. In particular, the results differ between males and females in the same study. Due to the different standards for calculating the risk of CKD among women and men, whether this association between TC/HDL-C and CKD will be different in the two sexes is of great significance for accurate prediction of CKD. Furthermore, most of current researches focus on the economically developed areas, while it is very limited in economically undeveloped areas. Therefore, we conducted a prospective cohort study to analyze the association between TC/HDL-C and CKD and to evaluate the predictive value of TC/HDL-C in CKD among different genders in northwestern China.

2 | METHODS

2.1 | Study population

The study was based on the Jinchang Cohort[19] in northwest China. The Jinchang cohort was established in June 2011, baseline data of 48,001 participants were collected in December 2013, and the first follow-up was completed in December 2015, with a total of 33,355 participants collected. In this study, 33,355 participants matched for the baseline and follow-up data were used in this study. After excluding participants with CKD at the baseline ($n = 569$) and missing data at the baseline or the follow-up ($n = 435$), 32,351 participants were enrolled in the analysis (Supporting Information S1: Figure S1).

Before the investigation, all subjects signed informed consent after understanding the study purpose and privacy protection terms. The investigation information included face-to-face interview, physical examination, and clinical laboratory test. Then face-to-face interview was conducted by investigators using standardized and uniform questionnaires. All the investigators received uniform training before the investigation. The contents

of the questionnaire included demographic characteristics (gender, age, occupation, education, income), dietary habit (high-salt diet, high-fat diet), lifestyle (smoking, drinking, exercise), disease history (hypertension, coronary heart disease [CHD], diabetes, dyslipidemia), and family history of kidney disease. In addition, the physical examination was carried out by professional clinicians from a tertiary staff hospital. The blood pressure (BP) was measured with the electronic sphygmomanometer (AMPall BP705). Height and weight were measured with an automated measuring machine (SK-X80/TCS-160D-W/H, Sonka). The blood and urine samples after fasting overnight were also collected. Blood samples were tested, including blood lipid, fasting glucose, serum creatinine, and uric acid (UA), by an automatic biochemical analyzer (Hitachi 7600-020). In urine samples, albuminuria was also measured using an automatic analyzer, which was divided into five grades (-, ±, 1+, 2+, and 3+).

2.2 | Variable definitions

Current smoker smoked per day at least one cigarette for more than 6 months. Current drinker drank alcohol on average at least even once a week for over 6 months. Regular exercise was referred to exercise three times a week or more, each time more than 30 min. According to the Dietary Guidelines for Chinese Residents (2011), the high-salt diet was classified as the salt intake over 6 g per day, and high-fat diet was defined as consumption of over 30 g of edible oil each day.[20] Body mass index (BMI) was calculated by weight (kg) divided by height (m) squared and BMI ≥ 28.0 kg/m^2 was deemed to obesity. Hypertension was determined as blood pressure ≥140/90 mmHg in the physical examination or self-reported doctor-diagnosed hypertension. CHD was self-reported by the participants and a physician diagnosis report was provided. Diabetes was determined as fasting glucose ≥7.0 mmol/L in the physical examination or self-reported doctor-diagnosed diabetes. Dyslipidemia was determined as TC ≥ 6.2 mmol/L, TG ≥ 2.3 mmol/L, HDL-C < 1 mmol/L, or self-reported doctor-diagnosed dyslipidemia. Family history of kidney disease included first degree relatives (parents or siblings) with CKD.

2.3 | Study outcomes

Incident CKD was the primary outcome of this study. According to the definition for CKD in the KDIGO Clinical Practice Guideline,[21] incident CKD was considered as eGFR <60 mL/min/1.73 m^2 and/or the occurrence of albuminuria (albuminuria ≥ 1+). The eGFR was calculated from the CKD-EPI creatinine equation using the serum creatine, ethnicity, sex, and age (Supporting Information S1: Table S1).[22]

2.4 | Statistical analyses

Data were displayed as mean ± standard deviation (SD, continuous variable) and frequencies (categorical variable). Student's *t*-test and chi-square test were applied to analyze the intergroup differences of continuous and categorical variables between males and females, respectively. We calculated the incidence of chronic kidney disease using a cumulative incidence rate with a mean follow-up of 2.2 years. Cumulative incidence rate (CI) equals to number of incidences during the observation period/number at the beginning of observation. Cox proportional hazards model was implemented to analyze the relationship of serum lipids (TC, HDL-C, and TC/HDL-C) with the risk of CKD. The proportional hazards hypothesis test of the controlling variable was performed by combining the Schoenfeld residuals chart and the Schoenfeld residuals correlation analysis with the rank of time. Three models were established by adjusting different confounding factors. Model 1 was adjusted only for age. Model 2 was additionally adjusted for demographic characteristics (occupation, education, and income), lifestyle behaviors (smoking, drinking, exercise, high-salt diet, and high-fat diet) and BMI based on model 1. Model 3 was additionally adjusted for disease history (hypertension, CHD, dyslipidemia, and diabetes), family history of kidney disease and baseline eGFR based on model 2. Restricted cubic spline regression (RCS) analysis was applied to test the dose–response relationship. Serum lipids were grouped by quartiles to explore the relationship between different serum lipid levels and the risk of CKD, and the *p* for trend was used to assess the potential dose–response relationship. If there was a nonlinear dose–response relationship (*p* for nonlinear < 0.05), the inflection point was found and the risks on both sides of the inflection point were analyzed separately. Different subgroups might have an impact on the association between serum lipids and CKD risk, so a stratified analysis was used. In addition, receiver operator characteristic (ROC) curve was employed to ascertain the effect of serum lipids in predicting CKD. Meanwhile, the area under the curve (AUC), sensitivity, specificity, and cut-off value were also calculated.

All analyses were performed by R4.0.2 (R Foundation for Statistical Computing) and MedCalc18.2.1 (MedCalc Software). A two-tailed *p*-value below 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Description statistics

In this study, 19,651 males (60.74%) and 12,700 females (39.26%) were included, their average ages were (46.41 ± 13.43) and (45.98 ± 11.34) years, respectively. Differences between male and female were significant for the most characteristics with the exception of family history of kidney

disease. Among both males and females, workers and those in junior high school and below accounted for the largest proportion. The males have higher proportion of smoking, drinking, high-salt diet, high-fat diet, overweight, and comorbidities (hypertension, CHD, dyslipidemia, and diabetes) than females. Females had a higher level of eGFR at the baseline than males. In addition, the higher levels of TG and TC/HDL-C in males were (2.06 ± 1.23) mmol/L and (3.80 ± 1.02), respectively; the higher levels of TC, HDL-C, and HDL-C in females were (4.75 ± 0.90) mmol/L, (1.50 ± 0.35) mmol/L and (3.11 ± 0.76) mmol/L, respectively (Table 1).

The mean time of follow-up was 2.2 years, during which 2.46% of males ($n = 484$) and 1.29% of females ($n = 164$) had CKD. The number of CKD in males was higher than in females. Among the male participants, there were 291 (1.48%) with proteinuria and 211 (1.07%) with eGFR < 60 mL/min/1.73 m^2; while there were 91 (0.72%) with proteinuria and 75 (0.59%) with eGFR < 60 mL/min/1.73 m^2 in female (Supporting Information S1: Table S2).

3.2 | Association between lipids and risk of CKD in male and female

Three models were established to analyze the independent influence of serum lipids on CKD. After adjusted

TABLE 1 Baseline characteristics of the study population.

Characteristics	Male ($n = 19651$)	Female ($n = 12,700$)	χ^2/t	p
Age, years	46.41 ± 13.43	45.98 ± 11.34	3.123	<0.01
Occupation, n (%)			265.964	<0.01
Managerial staff	2337 (1.89)	1870 (14.72)		
Worker staff	15,805 (80.43)	9284 (73.10)		
Technical and logistics staff	1509 (7.68)	1546 (12.17)		
Education, n %			48.356	<0.01
Junior middle school or below	7097 (36.12)	5069 (39.91)		
Senior middle school or equivalent	5678 (28.89)	3398 (26.76)		
College or above	6876 (34.99)	4233 (33.33)		
Income (≥¥2000), n (%)	8955 (45.57)	6779 (53.38)	188.251	<0.01
Current smoker, n (%)	11,723 (59.66)	154 (1.21)	1134.640	<0.01
Current drinker, n (%)	6441 (32.78)	301 (2.37)	4323.529	<0.01
Regular exercise, n (%)	8824 (44.90)	6074 (47.83)	26.534	<0.01
High-salt diet, n (%)	5130 (26.10)	2052 (16.16)	442.020	<0.01
High-fat diet, n (%)	4467 (22.73)	1798 (14.16)	363.190	<0.01
Obesity (BMI ≥ 28), n (%)	1961 (9.98)	841 (6.62)	1297.751	<0.01
Hypertension, n (%)	6332 (32.22)	2861 (22.53)	356.442	<0.01
CHD n (%)	571 (2.90)	299 (2.35)	8.962	<0.01
Diabetes, n (%)	1629 (8.29)	622 (4.90)	137.104	<0.01
Dyslipidemia, n (%)	8558 (43.55)	3259 (25.66)	1189.382	<0.01
Family history of kidney disease, n (%)	32 (0.16)	21 (0.16)	0.003	0.956
TC, mmol/L	4.66 ± 0.88	4.75 ± 0.90	−8.962	<0.01
TG, mmol/L	2.06 ± 1.23	1.54 ± 0.93	43.175	<0.01
HDL-C, mmol/L	1.28 ± 0.31	1.50 ± 0.35	−57.533	<0.01
LDL-C, mmol/L	3.02 ± 0.73	3.11 ± 0.76	−9.464	<0.01
TC/HDL-C	3.80 ± 1.02	3.30 ± 0.88	47.287	<0.01
eGFR, mL/min/1.73 m^2	102.99 ± 13.67	104.46 ± 13.33	−9.523	<0.01

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

for age in model 1, for every one SD increase in TC and TC/HDL-C, the risk of CKD increased by 26% and 24% for male, 13% and 28% for female, respectively. For every one SD increase in HDL-C, the risk of CKD decreased by 34% for male, 53% for female, respectively. As more confounding variables were adjusted, the estimates of association between serum lipids and CKD decreased. In model 3, for every one SD increase in TC, HDL-C and TC/HDL-C, the hazard ratios (HRs) and 95% CI for CKD were 1.17 (1.05–1.31), 0.84 (0.71–0.99), and 1.15 (1.06–1.25) for male, 0.94 (0.78–1.13), 0.58 (0.35–0.95), and 1.19 (1.01–1.40) for female, respectively (Table 2).

Figure 1 shows the relationship between lipids and CKD in model 3, including the dose–response relationship (A) and the risk of different lipid levels (B). There was a linear dose–response relationship between levels of serum lipids and CKD. TC and TC/HDL-C were positively linked to CKD, while HDL-C was negatively linked. The trends of HDL-C and TC/HDL-C were similar in males and females, but TC was not consistent. TC mainly increased linearly in males, while the association between TC and CKD in females was not statistically significant. Compared to the lowest quartile level, the highest quartile of TC and TC/HDL-C had significant effect in males, and the *P* for trend for them was also significant; HDL-C and TC/HDL-C had significant effect in females, but no dose–response relationship was found (Figure 2).

3.3 | Stratified analysis

As shown in Figure 3, TC, HDL-C, and TC/HDL-C were not consistently correlated with changes in the risk of CKD, and the results were different between males and females. Generally, the performance of TC/HDL-C in each subgroup was more stable than that of TC and HDL-C. For males, the significant association between TC/HDL-C and CKD was observed in participants with age ≥65 years old, overweight, smoking, exercise, high-salt diet, high-fat diet, hypertension, and dyslipidemia. No significant relationship was detected between HDL-C levels and CKD in the subgroups. For females, the significant relationship between TC/HDL-C and CKD was found in participants with overweight, exercise, high-salt diet, high-fat diet, and dyslipidemia. No significant relationship was found between TC levels and CKD in the subgroups.

3.4 | ROC analysis

Figure 3 shows the ROC curve of TC, HDL-C, and TC/HDL-C in forecasting the risk of CKD. The AUC for TC, HDL-C, and TC/HDL-C were 0.542, 0.550, and 0.581 in males (Figure 3A), 0.550, 0.583, and 0.634 in females (Figure 3B), respectively. The corresponding cut-off values were >4.96 mmol/L, ≤1.17 mmol/L, and >3.87 in males, >5.26 mmol/L, ≤1.21 mmol/L, and >3.59 in females, respectively (Table 3).

4 | DISCUSSION

In this study, the incidence of CKD was 2.46% in males and 1.29% in females after 2 years' follow-up. The results showed that the high TC, low HDL-C, and high TC/HDL-C were significantly associated to the risk of CKD in both males and females, even after adjusted for related confounders, except for TC in females. It also found a dose–response relationship of TC, HDL-C, and TC/HDL-C on CKD. In the stratified analysis, the associations between TC/HDL-C and CKD were also consistent. Besides, the TC/HDL-C was a better index than TC and HDL-C for predicting CKD and had a higher predictive value in females.

TABLE 2 HRs and 95% CI for CKD per SD increase in serum lipids.

	Model 1		Model 2		Model 3	
Serum lipids	**HRs (95% CI)**	***p***	**HRs (95% CI)**	***p***	**HRs (95% CI)**	***p***
Male						
TC	1.26 (1.13–1.41)	<0.01	1.22 (1.09–1.36)	<0.01	1.17 (1.05–1.31)	<0.01
HDL-C	0.66 (0.49–0.88)	<0.01	0.79 (0.65–0.96)	<0.05	0.84 (0.71–0.99)	<0.05
TC/HDL-C	1.24 (1.16–1.32)	<0.01	1.19 (1.10–1.29)	<0.01	1.15 (1.06–1.25)	<0.01
Female						
TC	1.13 (0.97–1.33)	0.118	1.00 (0.83–1.22)	0.975	0.94 (0.78–1.13)	0.499
HDL-C	0.47 (0.29–0.75)	<0.01	0.55 (0.34–0.90)	<0.05	0.58 (0.35–0.95)	<0.05
TC/HDL-C	1.28 (1.11–1.48)	<0.01	1.23 (1.05–1.43)	<0.05	1.19 (1.01–1.40)	<0.05

Note: Model 1 adjusted for age. Model 2 additionally adjusted for occupation, education, income, smoking, drinking, exercise, high-salt diet, high-fat diet, and BMI. Model 3 additionally adjusted for hypertension, coronary heart disease, diabetes, dyslipidemia, family history of kidney disease, and baseline eGFR.
Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HRs, hazard ratios; TC, total cholesterol.

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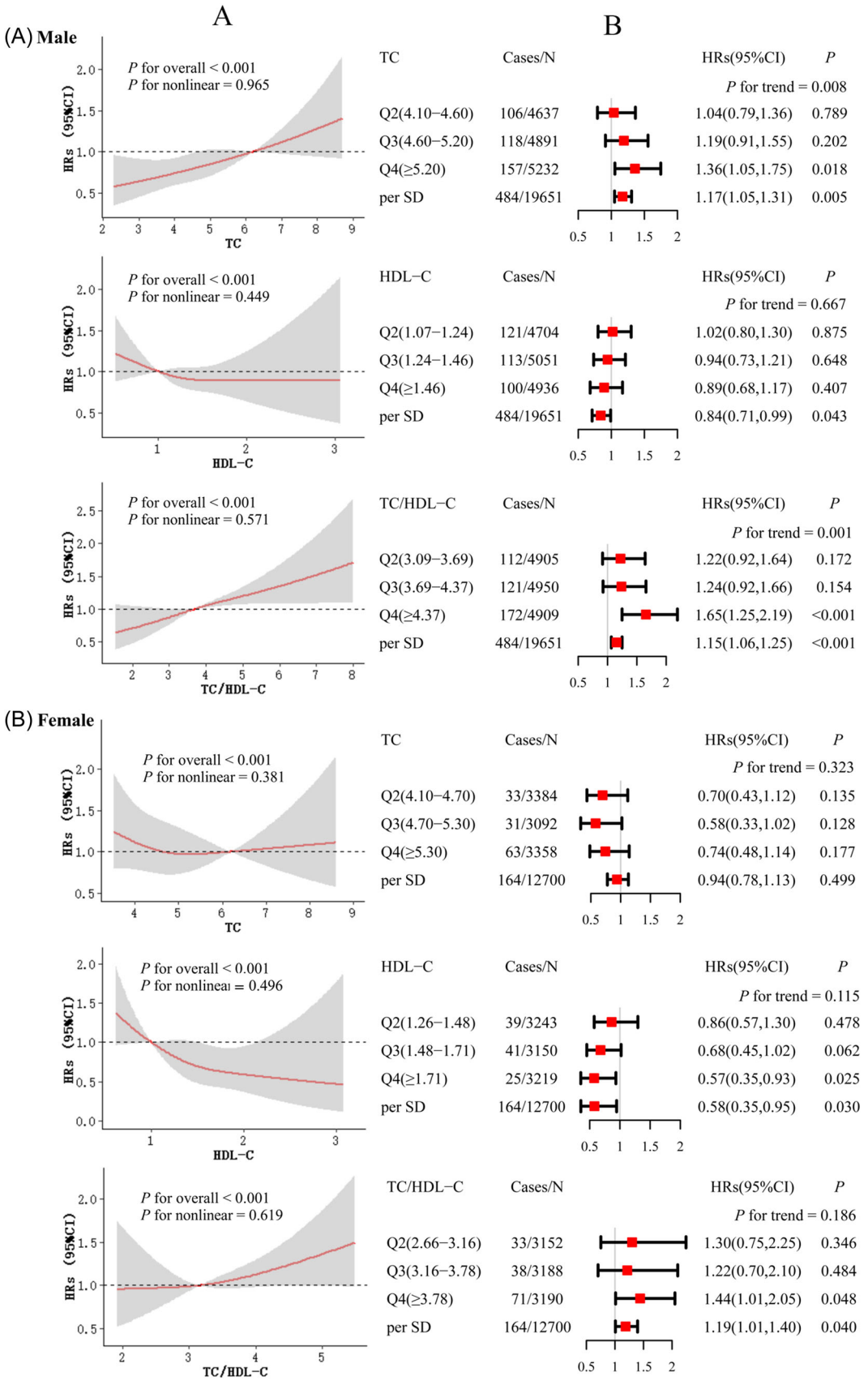

FIGURE 1 (See caption on next page).

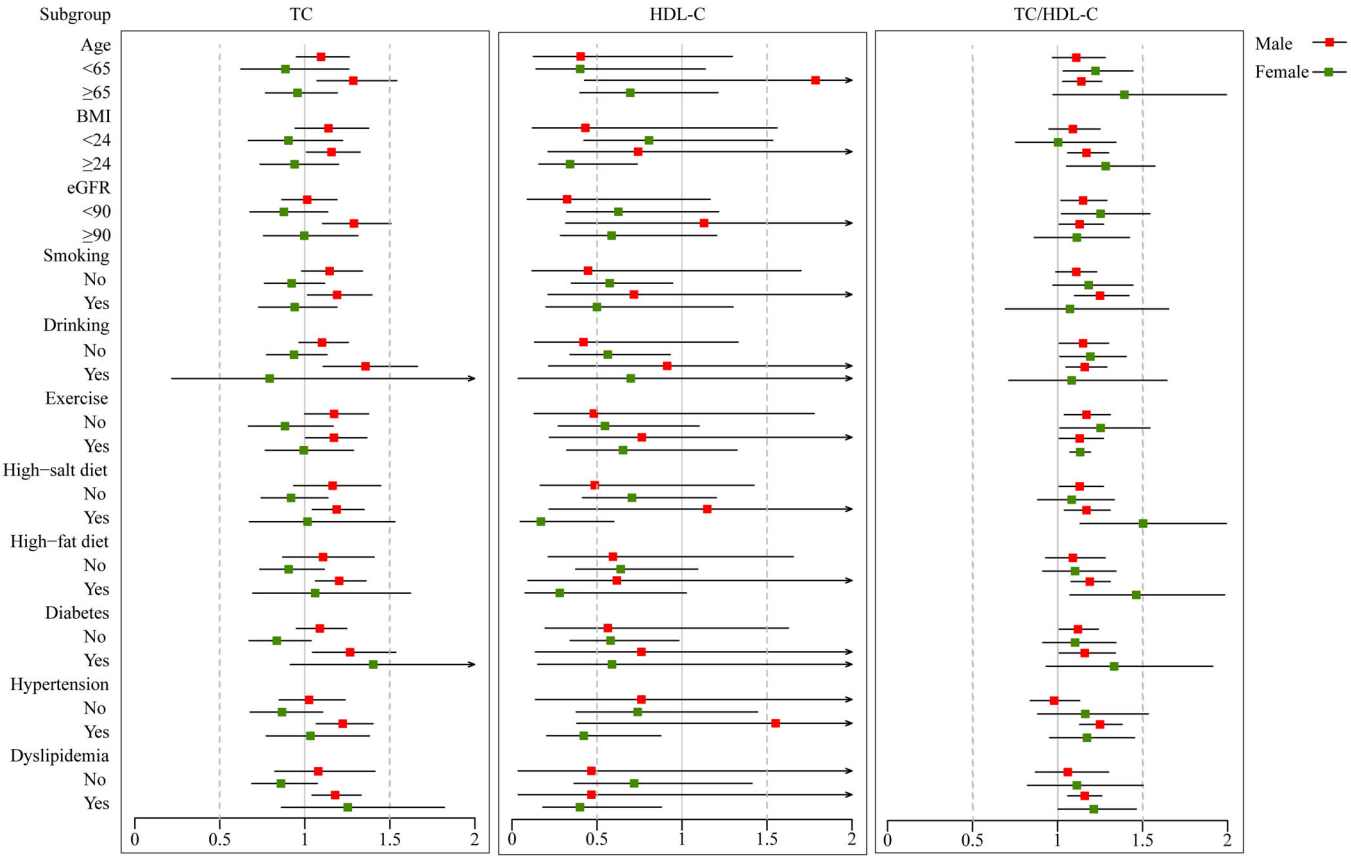

FIGURE 2 Relationship between serum lipids and risk of chronic kidney disease (CKD) in different subgroups. The *x*-axes showed the hazard ratios for CKD, and the *y*-axes showed the different subgroups. Model was adjusted for age, occupation, education, income, smoking, drinking, exercise, high-salt diet, high-fat diet, body mass index (BMI), hypertension, coronary heart disease, diabetes, dyslipidemia, family history of kidney disease, and baseline eGFR (model 3). HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

Previous studies suggested that both TC and HDL-C were the significant predictors of CKD.[8,9] Lanktree et al.[23] showed that genetically high HDL-C was causally connected to superior renal function, and the latest study further confirmed that TC also was causally associated with the risk of CKD.[24] Some studies[8,25,26] showed that the onset and progress of CKD were strongly, positively linked to TC and negatively linked to HDL-C, so the use of combined indicators (TC/HDL-C) may better represent the relationships between serum lipids and CKD. Our findings were consistent with this inference. A study demonstrated that high TC/HDL-C was observed to be connected with a higher risk of CKD.[10] In our study, the TC/HDL-C was significantly linked to CKD risk among different models. After gradually adding confounding factors to the model, the TC/HDL-C was still independently related to CKD. Moreover, the study found that TC/HDL-C had a positive linear relation with CKD.

In several agreement with our findings, some studies[15,18,27] have shown that existed gender disparities in the associations between CKD and dyslipidemia. In our study, there were associations between TC/HDL-C and CKD for both males and females, and the risk was greater in females. A study of hypertensive patients[15] showed that TC/HDL-C was related to an elevated prevalence of albuminuria in females, but not in males. Zhang et al.[18] found that the logTC/HDL-C was inversely connected with eGFR only in female. Both our and other studies[28] showed that females had higher lipid levels than males,

FIGURE 1 The relationship between serum lipids and risk of chronic kidney disease (CKD) in male and female. (A) The dose–response relationship between lipid levels and CKD, and (B) shows the hazard ratios of CKD associated with different levels of serum lipids. In (A) the solid lines indicated the adjusted hazard ratios (HRs), and the shaded areas represented 95% confidence interval (95% CI) for HRs; the *x*-axes showed the level of blood lipid, and the *y*-axes showed the hazard ratios for CKD where the reference values are the clinical cutoff of TC and HDL-C (6.2 mmol/L for TC, 1 mmol/L for HDL-C) or the median of TC/HDL-C (3.69 in male, 3.16 in female). In (B) the lowest quartile as a reference to which the remaining quartiles are compared; the median level per quartile group in serum lipids was used to detect the *P* for trend. Model was adjusted for age, occupation, education, income, smoking, drinking, exercise, high-salt diet, high-fat diet, body mass index (BMI), hypertension, coronary heart disease, diabetes, dyslipidemia, family history of kidney disease, and baseline eGFR (model 3).

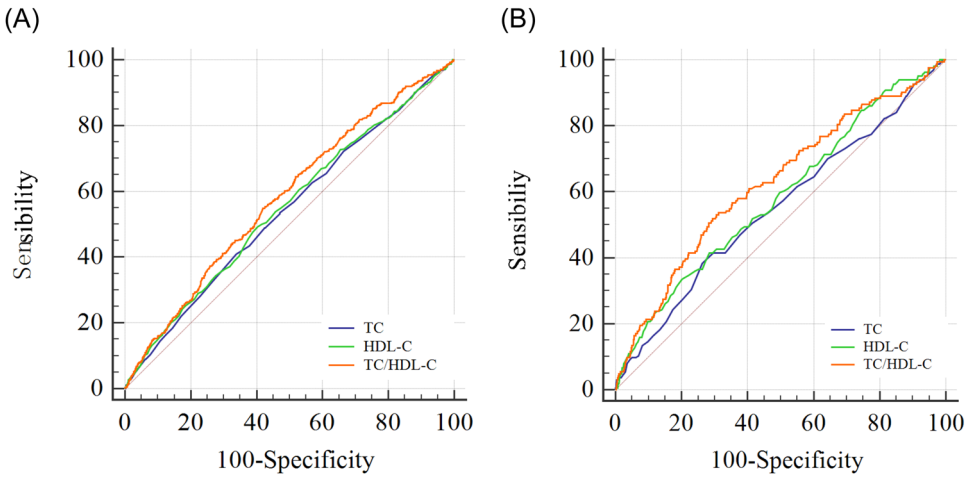

FIGURE 3 The receiver operator characteristic curves between serum lipids and CKD (A) male and (B) female. CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

TABLE 3 The AUC, cut-off value, sensitivity, and specificity of serum lipids for CKD in male and female.

Items	AUC (95% CI)	*p*	Cut-off according to Youden's index	Sensitivity (%)	Specificity (%)
Male					
TC	0.542 (0.535–0.549)	<0.01	>4.96 mmol/L	40.91	66.12
HDL-C	0.550 (0.543–0.557)	<0.01	≤1.17 mmol/L	49.17	59.72
TC/HDL-C	0.581 (0.574–0.588)	<0.01	>3.87	54.96	58.02
Female					
TC	0.550 (0.542–0.559)	<0.05	>5.26 mmol/L	38.41	73.72
HDL-C	0.583 (0.575–0.592)	<0.01	≤1.21 mmol/L	33.54	79.79
TC/HDL-C	0.634 (0.626–0.643)	<0.01	>3.59	45.43	75.61

Abbreviations: AUC, area under the curve; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

and a study measuring lipoprotein subclasses indicated that females generally had a favorable lipoprotein profile,[29] which may contribute to explain the gender differences. Compared with the males, other factors, such as visceral fat and testosterone levels are less important in females, and dyslipidemia caused by hormone or metabolic changes may have a greater impact on proteinuria and eGFR in females than in males.[30,31]

In the present study, overweight was an important risk factor for CKD. Consistent with previous studies, the risk of CKD was higher in the presence of obesity and overweight.[32,33] Obesity was found to be significantly associated with adverse renal outcomes in a prospective cohort study from Korea, and the HRs (95% CI) was 1.41 (1.08–1.83).[33] Obesity disrupts renal autophagy by increasing lipid accumulation and oxidation, inflammation, and insulin resistance,[34] and one of the consequences of obesity was increased GFR leading to glomerular enlargement.[35] In addition, our study found that exercise reduced the risk of CKD, and high-salt and high-fat diet increased this risk. As we all know, exercise could increase the body's immunity and prevent the occurrence of diseases. A meta-analysis of 41 trials found that exercise improved the health status of CKD.[36] High-salt diet implies a higher intake of sodium. High-sodium diet was thought to be related to the CKD risk, and increased disability-adjusted life years in CKD was reported in a prediction study between high-sodium diet and chronic disease.[37] High-fat diet causes damage to the proximal renal tubules, which then develops into CKD.[38] This study also found that participants with dyslipidemia had a higher risk of CKD, and this result was consistent to some existing studies. One study in the northeastern China[39] found that dyslipidemia was significantly related with decreased eGFR. Another elderly based study found the ORs (95% CI) of hypertriglyceridemia and CKD was 1.279 (1.165–1.404).[32] In conclusion, regular exercise, low-salt and low-fat diet, and the use of lipid-lowering drugs may help reduce the risk of CKD.

The result of ROC analysis showed that TC/HDL-C had more power to forecast the CKD risk than TC and

HDL-C. Notably, TC/HDL-C has been included as a secondary therapeutic goal in the 2006 Lipid Guidelines of Canada.[40] And TC/HDL-C has created a new paradigm that reflected the concentration and size of lipoprotein particles.[17] In clinical practice, the cutoff value in this study may be used to diagnose the CKD for different gender. Meanwhile, it is important to be aware of the TC/HDL-C, even in participants with normal serum lipids level. There was no significant difference between the critical and clinical values of ROC in this study.[41]

Since the glomerulosclerosis and atherosclerosis have similar pathogenesis,[14] it is reasonable to assume high level of TC/HDL-C was related to increased incidence of CKD. Despite the mechanisms of TC/HDL-C on the pathogenesis of CKD was incompletely clear, it could be based on previous studies to give some explanation. First, the reabsorption of tubular epithelial cells on cholesterol and phospholipids could cause tubular interstitial inflammation, foam cells formation, and tissue damage.[42] Second, cellular cholesterol accumulation due to elevated synthesis and decreased outflow might change in the structure and function of podocytes and proximal tubule cells to promote fibrosis and the development of CKD.[43,44] Finally, the decline of kidney function could enhance lipid permeation and excretion, dyslipidemia further aggravated in a vicious cycle.[45]

In this study, we analyzed the relationships between TC/HDL-C and CKD in different genders and evaluate the value of TC/HDL-C on predicting CKD. The findings of this study may have important clinical and public health significance, which suggested that people with high TC/HDL-C need to pay attention to their renal function, especially in female populations.

There were also some limitations. First, the insufficient length of follow-up may have limited the incidence of CKD to a certain extent. Second, we used one-time eGFR and albuminuria to define CKD, without considering the level of eGFR and proteinuria after 3 months, or other biomarkers of renal injuries, and thus have the potential misclassification bias. However, prior research has discovered that when using a single or a combination of other indicators to define the CKD, the association of serum lipid with CKD was consistent.[46,47] Third, we did not compare other nontraditional lipid parameters and medication information was lacking in the study. In the meantime, due to space constraints, the definition of CKD is not stratified, among the included and excluded subjects; there were differences in the occupation of men and the income of women. However, the excluded subjects were not many and the results were consistent, so the influence of this bias on the results was relatively limited. Finally, since all the participants were from the northwestern China, whether these observations could be generalized to other regions and ethnicities remain to be determined. Multi-center prospective studies will be needed in future.

In conclusion, among the three indexes of TC, HDL-C, and TC/HDL-C, TC/HDL-C has better predictive efficacy for CKD. From the current conclusion, it does not have a very definite application value, but it provides a reference for judging the risk of CKD in male and female populations.

AUTHOR CONTRIBUTIONS

Yanli Liu: Conceptualization; software; formal analysis; writing—original draft. **Kang Lyu**: Formal analysis; writing—review and editing. **Shaodong Liu**: Formal analysis. **Jinlong You**: Formal analysis. **Xue Wang**: Formal analysis; investigation. **Minzhen Wang**: Resources; data curation. **Desheng Zhang**: Data curation; resources. **Yana Bai**: Data curation; project administration. **Chun Yin**: Data curation; resources. **Min Jiang**: Validation; supervision. **Shan Zheng**: Conceptualization; methodology; validation, writing—review and editing; supervision. All authors have read and approved the submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted in accordance with the principles of the Declaration of Helsinki. All study participants provided written informed consent, and the study protocol was approved by the Ethics Committees of the Public Health School of Lanzhou University.

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REFERENCES

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Kidney Int.* 2019;96(5):1048-1050. doi:10.1016/j.kint.2019.07.012

2. Fraser SDS, Roderick PJ. Kidney disease in the Global Burden of Disease Study 2017. *Nat Rev Nephrol*. 2019;15(4):193-194. doi:10.1038/s41581-019-0120-0
3. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395(10225):709-733. doi:10.1016/s0140-6736(20)30045-3
4. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*. 2012;379(9818):815-822. doi:10.1016/S0140-6736(12)60033-6
5. Opazo-Ríos L, Mas S, Marín-Royo G, et al. Lipotoxicity and diabetic nephropathy: novel mechanistic insights and therapeutic opportunities. *Int J Mol Sci*. 2020;21(7):2632. doi:10.3390/ijms21072632
6. Su H, Wan C, Lei C-T, et al. Lipid deposition in kidney diseases: interplay among redox, lipid mediators, and renal impairment. *Antioxid Redox Signal*. 2018;28(10):1027-1043. doi:10.1089/ars.2017.7066
7. Wen J, Chen Y, Huang Y, et al. Association of the TG/HDL-C and non-HDL-C/HDL-C ratios with chronic kidney disease in an adult Chinese population. *Kidney Blood Press Res*. 2017;42(6):1141-1154. doi:10.1159/000485861
8. Liang X, Ye M, Tao M, et al. The association between dyslipidemia and the incidence of chronic kidney disease in the general Zhejiang population: a retrospective study. *BMC Nephrol*. 2020;21(1):252. doi:10.1186/s12882-020-01907-5
9. Kawachi K, Kataoka H, Manabe S, Mochizuki T, Nitta K. Low HDL cholesterol as a predictor of chronic kidney disease progression: a cross-classification approach and matched cohort analysis. *Heart Vessels*. 2019;34(9):1440-1455. doi:10.1007/s00380-019-01375-4
10. Zhang YB, Sheng LT, Wei W, et al. Association of blood lipid profile with incident chronic kidney disease: a Mendelian randomization study. *Atherosclerosis*. 2020;300:19-25. doi:10.1016/j.atherosclerosis.2020.03.020
11. McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;372(9634):224-233. doi:10.1016/s0140-6736(08)61076-4
12. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B-100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005;294(3):326-333. doi:10.1001/jama.294.3.326
13. Agirbasli M, Tanrikulu A, Acar Sevim B, Azizy M, Bekiroglu N. Total cholesterol-to-high-density lipoprotein cholesterol ratio predicts high-sensitivity C-reactive protein levels in Turkish children. *J Clin Lipidol*. 2015;9(2):195-200. doi:10.1016/j.jacl.2014.12.010
14. Chabowski DS, Cohen KE, Abu-Hatoum O, Gutterman DD, Freed JK. Crossing signals: bioactive lipids in the microvasculature. *Am J Physiol Heart Circul Physiol*. 2020;318(5):H1185-H1197. doi:10.1152/ajpheart.00706.2019
15. Lee S-H, Kim DH, Kim Y-H, et al. Relationship between dyslipidemia and albuminuria in hypertensive adults a nationwide population-based study. *Medicine*. 2016;95(16):e3224. doi:10.1097/md.0000000000003224
16. Mathews SC, Mallidi J, Kulkarni K, Toth PP, Jones SR. Achieving secondary prevention low-density lipoprotein particle concentration goals using lipoprotein cholesterol-based data. *PLoS One*. 2012;7(3):e33692. doi:10.1371/journal.pone.0033692
17. Elshazly MB, Quispe R, Michos ED, et al. Patient-level discordance in population percentiles of the total cholesterol to high-density lipoprotein cholesterol ratio in comparison with low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol: the very large database of lipids study (VLDL-2B). *Circulation*. 2015;132(8):667-676. doi:10.1161/CIRCULATIONAHA.115.016163
18. Zhang L, Yuan Z, Chen W, et al. Serum lipid profiles, lipid ratios and chronic kidney disease in a Chinese population. *Int J Environ Res Public Health*. 2014;11(8):7622-7635. doi:10.3390/ijerph110807622
19. Bai Y, Yang A, Pu H, et al. Cohort profile: the China metal-exposed workers cohort study (Jinchang Cohort). *Int J Epidemiol*. 2016;46(4):dyw223. doi:10.1093/ije/dyw223
20. Zheng S, Zhu W, Shi Q, et al. Effects of cold and hot temperature on metabolic indicators in adults from a prospective cohort study. *Sci Total Environ*. 2021;772:145046. doi:10.1016/j.scitotenv.2021.145046
21. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825. doi:10.7326/0003-4819-158-11-201306040-00007
22. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006
23. Lanktree MB, Thériault S, Walsh M, Paré G. HDL cholesterol, LDL cholesterol, and triglycerides as risk factors for CKD: a mendelian randomization study. *Am J Kidney Dis*. 2018;71(2):166-172. doi:10.1053/j.ajkd.2017.06.011
24. Miao L, Min Y, Qi B, et al. Causal effect between total cholesterol and HDL cholesterol as risk factors for chronic kidney disease: a Mendelian randomization study. *BMC Nephrol*. 2021;22(1):35. doi:10.1186/s12882-020-02228-3
25. Tsai CW, Huang HC, Chiang HY, et al. Longitudinal lipid trends and adverse outcomes in patients with CKD: a 13-year observational cohort study. *J Lipid Res*. 2019;60(3):648-660. doi:10.1194/jlr.P084590
26. Navaneethan SD, Schold JD, Walther CP, et al. High-density lipoprotein cholesterol and causes of death in chronic kidney disease. *J Clin Lipidol*. 2018;12(4):1061-1071. doi:10.1016/j.jacl.2018.03.085
27. Swartling O, Rydell H, Stendahl M, Segelmark M, Trolle Lagerros Y, Evans M. CKD progression and mortality among men and women: a nationwide study in Sweden. *Am J Kidney Dis*. 2021;78:190-199. doi:10.1053/j.ajkd.2020.11.026
28. Xue J, Wang Y, Li B, et al. Triglycerides to high-density lipoprotein cholesterol ratio is superior to triglycerides and other lipid ratios as an indicator of increased urinary albumin-to-creatinine ratio in the general population of China: a cross-sectional study. *Lipids Health Dis*. 2021;20(1):13. doi:10.1186/s12944-021-01442-8
29. Freedman DS, Otvos JD, Jeyarajah EJ, et al. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. *Clin Chem*. 2004;50(7):1189-1200. doi:10.1373/clinchem.2004.032763
30. Seong JM, Lee JH, Gi MY, et al. Gender difference in the association of chronic kidney disease with visceral adiposity index and lipid accumulation product index in Korean adults: Korean National Health and Nutrition Examination Survey. *Int Urol Nephrol*. 2021;53:1417-1425. doi:10.1007/s11255-020-02735-0
31. de Boer IH, Astor BC, Kramer H, et al. Mild elevations of urine albumin excretion are associated with atherogenic lipoprotein abnormalities in the multi-ethnic study of atheroslcerosis (MESA). *Atherosclerosis*. 2008;197(1):407-414. doi:10.1016/j.atherosclerosis.2007.06.018
32. Ji A, Pan C, Wang H, et al. Prevalence and associated risk factors of chronic kidney disease in an elderly population from eastern China. *Int J Environ Res Public Health*. 2019;16(22):4383. doi:10.3390/ijerph16224383
33. Yun HR, Kim H, Park JT, et al. Obesity, metabolic abnormality, and progression of CKD. *Am J Kidney Dis*. 2018;72(3):400-410. doi:10.1053/j.ajkd.2018.02.362
34. Ghandriz R, Lerman LO. Renal cellular autophagy in obesity: boon or bane. *Sem Nephrol*. 2021;41(4):349-357. doi:10.1016/j.semnephrol.2021.06.006

35. Sharma I, Liao Y, Zheng X, Kanwar YS. New pandemic: obesity and associated nephropathy. *Front Med*. 2021;8:8673556. doi:10.3389/fmed.2021.673556
36. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. *Am J Kidney Dis*. 2014;64(3):383-393. doi:10.1053/j.ajkd.2014.03.020
37. Nomura S, Yoneoka D, Tanaka S, et al. Forecasting disability-adjusted life years for chronic diseases: reference and alternative scenarios of salt intake for 2017-2040 in Japan. *BMC Public Health*. 2020;20(1):1475. doi:10.1186/s12889-020-09596-3
38. Chen S, Chen J, Li S, et al. High-fat diet-induced renal proximal tubular inflammatory injury: emerging risk factor of chronic kidney disease. *Front Physiol*. 2021;12:12786599. doi:10.3389/fphys.2021.786599
39. Wang X, Wang H, Li J, et al. Combined effects of dyslipidemia and high adiposity on the estimated glomerular filtration rate in a middle-aged Chinese population. *Diab Metab Syndr Obes*. 2021;14:4513-4522. doi:10.2147/dmso.S337190
40. McPherson R, Frohlich J, Fodor G, Genest J. Canadian cardiovascular society position statement—recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol*. 2006;22(11):913-927. doi:10.1016/s0828-282x(06)70310-5
41. Zhu JR, Gao RL, Zhao SP, Lu GP, Zhao D, Li JJ. 2016 Chinese guidelines for the management of dyslipidemia in adults joint committee for guideline revision. *J Geriatr Cardiol*. 2018;15(1):1-29. doi:10.11909/j.issn.1671-5411.2018.01.011
42. Wu Y, Chen Y, Chen D, Zeng C, Li L, Liu Z. Presence of foam cells in kidney interstitium is associated with progression of renal injury in patients with glomerular diseases. *Nephron Clin Pract*. 2009;113(3):c155-c161. doi:10.1159/000232596
43. Gai Z, Wang T, Visentin M, Kullak-Ublick G, Fu X, Wang Z. Lipid accumulation and chronic kidney disease. *Nutrients*. 2019;11(4):722. doi:10.3390/nu11040722
44. Merscher S, Pedigo CE, Mendez AJ. Metabolism, energetics, and lipid biology in the podocyte—cellular cholesterol-mediated glomerular injury. *Front Endocrinol*. 2014;5:169. doi:10.3389/fendo.2014.00169
45. Kang H-T, Shim J-Y, Lee Y-J, et al. Association between the ratio of triglycerides to high-density lipoprotein cholesterol and chronic kidney disease in Korean adults: the 2005 Korean National Health and Nutrition Examination Survey. *Kidney Blood Press Res*. 2011;34(3):173-179. doi:10.1159/000323895
46. Bowe B, Xie Y, Xian H, Balasubramanian S, Al-Aly Z. Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression. *Kidney Int*. 2016;89(4):886-896. doi:10.1016/j.kint.2015.12.034
47. Tsuruya K, Yoshida H, Nagata M, et al. Impact of the triglycerides to high-density lipoprotein cholesterol ratio on the incidence and progression of CKD: a longitudinal study in a large Japanese population. *Am J Kidney Dis*. 2015;66(6):972-983. doi:10.1053/j.ajkd.2015.05.011

SUPPORTING INFORMATION

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