International Urology and Nephrology (2019) 51:2005–2014
https://doi.org/10.1007/s11255-019-02287-y

NEPHROLOGY - ORIGINAL PAPER

Nonlinear relationship between triglyceride/high-density lipoprotein cholesterol ratio and chronic kidney disease in US adults: a National Health and Nutrition Examination Survey investigation

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Received: 13 May 2019 / Accepted: 15 September 2019 / Published online: 19 September 2019

Abstract

Purpose Published data on the association between triglycerides/high-density lipoprotein cholesterol (TG/HDL-C) ratio and chronic kidney disease (CKD) in US populations are limited. We examined the association between TG/HDL-C ratio and the prevalence of CKD using US National Health and Nutrition Examination Survey (NHANES) database.

Methods This cross-sectional study included 13,780 US adults from NHANES (1999–2006). CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or albuminuria. Multivariable logistic regression models were used to examine the relationship between TG/HDL-C ratio and CKD. A generalized additive model (GAM) and smooth curve fitting (penalized spline method) and a two-piecewise logistic regression models were also conducted to address for nonlinearity between TG/HDL-C ratio and CKD.

Results The prevalence of CKD was 15.8%. Multiple logistic analyses showed that showed that TG/HDL-C ratio was associated with 5% increased prevalence of CKD. Analyses using restricted cubic spline showed a saturation and nonlinear association between TG/HDL-C ratio and CKD. The inflection point for the curve was found at a TG/HDL-C ratio level of 6.68. The ORs (95% CIs) for CKD were 1.08 (1.04, 1.13) and 0.97 (0.89, 1.05) to the left and right of the inflection point, respectively. None of all stratified variables showed significant effect modification on the association between TG/HDL-C ratio and CKD (*P*-interaction > 0.05).

Conclusions Our study suggested saturated effects of TG/HDL-C ratio on the prevalence of CKD among US adults. TG/HDL-C ratio less than 6.68 was positively and independently associated with CKD.

Keywords Triglycerides to high-density lipoprotein cholesterol · Chronic kidney disease · Nonlinearity · US adults · National Health and Nutrition Examination Survey

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Abbreviations

TG/HDL-C	Triglycerides/high-density lipoprotein cholesterol
CKD	Chronic kidney disease
NHANES	National Health and Nutrition Examination Survey
CVD	Cardiovascular disease
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TMFA	Total monounsaturated fatty acids
TPFA	Total polyunsaturated fatty acids
TSFA	Total saturated fatty acids
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ACR	Albumin–creatinine ratio
eGFR	Estimated glomerular filtration rate

FBG	Fasting blood glucose
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol

Introduction

Dyslipidemia, defined as high levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG), or low levels of high-density lipoprotein cholesterol (HDL-C), is a well-known risk factor for cardiovascular disease (CVD) [1–3]. Recently, the relationship between TG/HDL-C ratio and CVD has become an area of great interest. TG/HDL-C ratio is an acknowledged marker of insulin resistance and may be a better predictor of cardiovascular events than other lipid parameters [4–6]. In addition, Boizel et al. [7] included 60 patients with type 2 diabetes and found that TG/HDL-C ratio might be related to the processes involved in LDL size pathophysiology and relevant with regard to the risk of clinical vascular disease. Chizuko Maruyama et al. [8] used data from 39 healthy subjects and found that TG/HDL-C ratio was a potentially convenient biochemical parameter for assessing LDL particle size. These findings suggest that TG/HDL-C ratio may be suitable for the selection of patients needing an earlier and aggressive treatment of lipid abnormalities.

Chronic kidney disease (CKD) is one of the major public health issues worldwide [9]. The rates of mortality and cardiovascular events caused by CKD increase with progressive decreases in the estimated glomerular filtration rate (eGFR) [9]. Early screening and appropriate managing the influencing factors associated with CKD are therefore needed in order to prevent disease incidence. Elevated TG and decreased HDL-C were implicated as a cause or consequence of CKD [11, 12]. Several studies have shown the association between TG/HDL-C ratio and CKD [13–15]. Kang et al. [13] performed a cross-sectional study which included 5,503 subjects (≥ 19 years of age) who participated in the 2005 Korean National Health and Nutrition Examination Survey. The results showed that TG/HDL-C ratio was independently associated with increased prevalence of CKD. Zoppini et al. [14] conducted a prospective cohort study of 979 type 2 diabetes mellitus and found that TG/HDL-C ratio was positively associated with an increased risk of incident retinopathy and/or CKD. Wen et al. [15] used data from 48,054 Chinese adult subjects and found that TG/HDL-C ratio was correlated with the prevalence of CKD. However, published data on the association between TG/HDL-C ratio and CKD in US populations are limited. Moreover, to the best of our knowledge, 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 [16]. Few studies have assessed the relationship between TG/HDL-C ratio and CKD using the new CKD-EPI equation [15]. Additionally, previous studies only investigated the linear relationship between TG/HDL-C ratio and CKD, but not discuss the nonlinearity [13–15].

Therefore, in the present study, we examined the association between TG/HDL-C ratio and the prevalence of CKD using the novel CKD-EPI equation in a large representative sample of US adults from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2006.

Methods

Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey to investigate the health and nutritional status of the civilian noninstitutionalized US population using highly stratified multistage probability designs. The survey which was conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) consists of interviews conducted in participants' homes and standardized physical examinations conducted in mobile examination centers. The design and methods for the survey are available at http://www.cdc.gov/nchs/nhanes.htm. The NCHS Ethics Review Board approved collection of the NHANES data and posting of the files for public use (http://www.cdc.gov/nchs/nhanes/irba98.htm). Written informed consent was acquired from each NHANES participant. The NHANES datasets are available at https://doi.org/10.5061/dryad.d5h62.

The present study includes data from NHANES participants surveyed in NHANES (1999–2006). In total, 41,474 respondents were enrolled. We excluded individuals aged < 18 years. In total, 22,624 adults were included. Next, we excluded participants with missing CKD ($n = 1991$), using lipid-lowering drugs ($n = 976$), and missing TG/HDL-C ratio ($n = 5644$). Given the TG/HDL-C ratio > mean + 3SD defined as outliers statistically, we further excluded individuals with TG/HDL-C ratio > mean + 3SD ($n = 233$).

Measurement methods

Exposure variable and outcomes

The exposure variable was TG/HDL-C ratio, and the outcome variable was CKD. Serum creatinine (Scr) was measured by the Jaffe reaction and standardized by methods described previously [17]. Estimated glomerular filtration rate (eGFR, mL/min per 1.73 m^2) was calculated via the newly developed CKD-EPI

equation [16]: $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black], κ is 0.7 for females and 0.9 for males, α is − 0.329 for females and − 0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. A random urine specimen was collected and urinary creatinine was measured by the Jaffé rate reaction; urinary albumin was measured by solid-phase fluorescent immunoassay [18]. Albuminuria was measured by urinary albumin–creatinine ratio (ACR). CKD was defined as eGFR < 60 mL/min/1.73 m^2 or albuminuria as urine ACR ≥ 30 mg/g [19]. More detailed information about lipoprotein measurement process is available at http://cdc.gov/nchs/nhanes.

Covariates and definition of terms

We selected the appropriate covariates based on previous studies examining risk factors for CKD as well as adjusting for covariates that, when added to this model, changed the matched odds ratio by at least 10% [20]. Therefore, the following variables were used to construct the fully adjusted model. Continuous variables included age (years), body mass index (BMI, kg/m^2), poverty-to-income ratio (a ratio of family income to poverty threshold), dietary data [alcohol (gm), cholesterol (mg), energy (kcal), total monounsaturated fatty acids (TMFA, gm), total polyunsaturated fatty acids (TPFA, gm), total saturated fatty acids (TSFA, gm), total fat (gm)] and laboratory data [total protein (g/dL), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), total bilirubin (mg/dL), serum uric acid (mg/dL), total cholesterol (mg/dL), homocysteine (umol/L), serum folate (ng/mL)]. Categorical variables consisted of sex (male, female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican-American, other Hispanic or other), education (less than high school, high school/equivalent, or greater than high school), smoking (never smoker, former smoker or current smoker), physical activity (sedentary, low, moderate, or high), marital status (married, single, or living with partner), any diabetes, any hypertension, antihypertensive drugs and glucose-lowering drugs.

Definition of hypertension and diabetes

Hypertension was defined by ≥ 1 of the following criteria: systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg or use of medications to treat hypertension. We defined diabetes using 1 of the following 5 criteria [21]: previous diagnosis of diabetes, intake of glucose-lowering drugs, glycated hemoglobin level of ≥ 6.5%, fasting blood glucose (FBG) level of ≥ 126 mg/dL, or a 2-h glucose level of ≥ 200 mg/dL after an oral glucose tolerance test (OGTT).

Statistical analysis

Continuous variables were reported as mean ± SD, while categorical variables were reported as frequency and percentage. Baseline characteristics of study population were described by TG/HDL-C ratio tertiles. The ranges of TG/HDL-C ratio tertiles 1–3 were < 1.4, 1.4- < 2.7, and ≥ 2.7, respectively. Comparisons of baseline characteristics by different TG/HDL-C ratio groups (tertiles) were performed using one-way ANOVA test (normal distributions) or Kruskal–Wallis test (skewed distributions) for continuous variables and Chi-square test for categorical variables. To investigate the association between TG/HDL-C ratio and CKD, our statistical analyses consisted of three main steps. Step 1: univariate and multivariate binary logistic regression models were employed. We constructed three models: model 1, adjusted for no covariates; model 2, adjusted for sociodemographic data; model 3, model 2 + other covariates presented in Table 1. We used a generalized additive model (GAM) to adjust for age (smooth) in all models to account for potential nonlinearity in the association between age and CKD. Step 2: to address the nonlinearity of TG/HDL-C ratio and CKD, a GAM and smooth curve fitting (penalized spline method) were conducted. If nonlinearity was detected, we first calculated the inflection point using a recursive algorithm, and then constructed a two-piecewise binary logistic regression model on both sides of the inflection point. The threshold level was determined by choosing the inflection point which provided the maximum model likelihood, using the trial-and-error method, along with a log-likelihood ratio test comparing the one-line logistic regression model with a two-piecewise logistic model to examine the statistical significance [22]. Step 3: subgroup analyses were performed. Potential effect modifications of the association between TG/HDL-C ratio and CKD were performed for the following variables: sex (male, female), age (< 60, ≥ 60 years), race (non-Hispanic White, non-Hispanic Black, Mexican-American, other Hispanic, other), education (< high school, high school, > high school), smoking (never smoker, former smoker, current smoker), physical activity (sedentary, low, moderate, high), marital status (married, single, living with partner), BMI (< 25, 25–< 30, ≥ 30 kg/m^2), hypertension (no, yes) and diabetes (no, yes). Heterogeneity across subgroups was assessed by fitting simultaneous conditional logistic regressions and presented in forest plots, and interactions between subgroups and TG/HDL-C ratio were examined by likelihood ratio testing. All analyses adjusted for sex, age (smooth), BMI, ethnicity, education status, smoking, alcohol consumption, physical activity, marital status, poverty-to-income ratio, comorbidities (hypertension and diabetes), medication use (antihypertensive drugs and glucose-lowering drugs), cholesterol intake, energy intake, TMFA, TPFA, TSFA, total fat intake, total protein, ALT, AST, total

Table 1 Characteristics of study population

Characteristics	Total	TG/HDL-C ratio tertiles			*P* value
		T1 (< 1.4)	T2 (1.4–< 2.7)	T3 (≥ 2.7)	
N	13,780	3928	4618	5234	
Age, years	45.4 ± 20.3	41.2 ± 20.1	45.5 ± 20.7	48.5 ± 19.5	< 0.001
Male, %	6480 (47.0)	1498 (38.1)	2046 (44.3)	2936 (56.1)	< 0.001
Race, %					
Non-Hispanic White	6480 (47.0)	1758 (44.8)	2142 (46.4)	2580 (49.3)	< 0.001
Non-Hispanic Black	2777 (20.2)	1170 (29.8)	976 (21.1)	631 (12.1)	
Mexican-American	3389 (24.6)	745 (19.0)	1103 (23.9)	1541 (29.4)	
Other Hispanic	629 (4.6)	128 (3.3)	222 (4.8)	279 (5.3)	
Other race	505 (3.7)	127 (3.2)	175 (3.8)	203 (3.9)	
Education, %					
< High school	4597 (33.4)	1145 (29.2)	1519 (33.0)	1933 (37.0)	< 0.001
High school	3322 (24.2)	898 (22.9)	1155 (25.1)	1269 (24.3)	
> High school	5835 (42.4)	1880 (47.9)	1930 (41.9)	2025 (38.7)	
Smoking, %					
Never	6378 (52.1)	1911 (58.5)	2134 (52.2)	2333 (47.8)	< 0.001
Former	3158 (25.8)	708 (21.7)	1054 (25.8)	1396 (28.6)	
Current	2703 (22.1)	645 (19.8)	903 (22.1)	1155 (23.6)	
Physical activity, %[a]					
Sedentary	3366 (26.3)	802 (22.3)	1149 (26.8)	1415 (28.9)	< 0.001
Low	3506 (27.4)	948 (26.4)	1158 (27.0)	1400 (28.6)	
Moderate	2194 (17.2)	655 (18.2)	738 (17.2)	801 (16.4)	
High	3715 (29.1)	1192 (33.1)	1244 (29.0)	1279 (26.1)	
Marital status, %					
Married	6687 (50.1)	1634 (42.7)	2185 (49.1)	2868 (56.7)	< 0.001
Single	5880 (44.1)	1976 (51.6)	2000 (44.9)	1904 (37.7)	
Living with partner	770 (5.8)	220 (5.7)	265 (6.0)	285 (5.6)	
Poverty-to-income ratio	2.5 ± 1.6	2.6 ± 1.7	2.5 ± 1.6	2.5 ± 1.6	< 0.001
Comorbidities, %					
Any hypertension	3828 (27.8)	810 (20.7)	1242 (26.9)	1776 (34.0)	< 0.001
Any diabetes	1519 (11.1)	160 (4.1)	415 (9.0)	944 (18.2)	< 0.001
Medication use, %					
Antihypertensive drugs	1200 (8.7)	233 (5.9)	381 (8.3)	586 (11.2)	< 0.001
Glucose-lowering drugs	551 (4.0)	60 (1.5)	135 (2.9)	356 (6.8)	< 0.001
Physical examination data					
BMI, kg/m^{2}[b]	27.9 ± 6.3	25.2 ± 5.5	28.0 ± 6.4	29.9 ± 6.0	< 0.001
Mean SBP, mm Hg	117.8 ± 14.8	115.1 ± 14.2	117.5 ± 15.0	120.2 ± 14.9	< 0.001
Mean DBP, mm Hg	69.1 ± 13.0	68.3 ± 11.7	68.6 ± 13.1	70.2 ± 13.7	< 0.001
Dietary					
Alcohol, g	9.0 ± 30.4	11.2 ± 33.3	8.6 ± 29.3	7.7 ± 29.0	< 0.001
Cholesterol, mg	289.9 ± 229.0	283.8 ± 217.9	285.1 ± 226.2	298.6 ± 239.0	0.003
Energy, kcal	2142.6 ± 1006.3	2153.1 ± 987.7	2110.6 ± 1023.2	2162.8 ± 1004.5	0.032
TMFA, g	29.7 ± 17.8	30.3 ± 17.9	29.2 ± 18.2	29.7 ± 17.5	0.017
TPFA, g	16.4 ± 10.8	17.1 ± 10.9	16.2 ± 11.2	16.1 ± 10.2	< 0.001
TSFA, g	25.9 ± 16.2	26.2 ± 15.8	25.4 ± 16.2	26.2 ± 16.4	0.034
Total fat, g	79.1 ± 44.8	80.7 ± 44.4	77.8 ± 45.9	79.1 ± 44.2	0.015
Laboratory data					
Total protein, g/dL	7.4 ± 0.5	7.4 ± 0.5	7.4 ± 0.5	7.4 ± 0.5	0.146
ALT, U/L	25.1 ± 32.2	21.7 ± 36.7	23.8 ± 17.8	28.8 ± 37.7	< 0.001

Table 1 (continued)

Characteristics	Total	TG/HDL-C ratio tertiles			*P* value
		T1 (< 1.4)	T2 (1.4–< 2.7)	T3 (≥ 2.7)	
AST, U/L	24.9 ± 22.4	24.5 ± 29.9	24.4 ± 17.7	25.6 ± 19.5	0.012
Total bilirubin, mg/dL	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	< 0.001
ACR, mg/g	42.7 ± 375.1	23.2 ± 226.7	33.0 ± 269.1	65.8 ± 517.1	< 0.001
eGFR, mL/min per 1.73 m^2	102.2 ± 27.2	107.3 ± 25.6	102.8 ± 27.5	97.9 ± 27.3	< 0.001
Serum uric acid, mg/dL	5.3 ± 1.5	4.8 ± 1.3	5.2 ± 1.4	5.7 ± 1.5	< 0.001
FBG, mg/dL	95.4 ± 32.1	88.9 ± 18.5	93.1 ± 24.8	102.2 ± 42.9	< 0.001
Glycated hemoglobin	5.5 ± 1.0	5.3 ± 0.6	5.4 ± 0.8	5.7 ± 1.2	< 0.001
Total cholesterol, mg/dL	199.6 ± 42.3	185.6 ± 38.1	197.7 ± 41.2	211.6 ± 42.8	< 0.001
TG, mg/dL	129.6 ± 79.4	62.4 ± 18.2	104.2 ± 26.6	202.5 ± 80.2	< 0.001
HDL-C, mg/dL	53.1 ± 15.6	66.0 ± 15.7	53.7 ± 12.1	42.9 ± 9.9	< 0.001
Homocysteine, μmol/L	8.6 ± 4.5	8.2 ± 4.0	8.6 ± 4.6	8.9 ± 4.6	< 0.001
Serum folate, ng/mL	14.2 ± 10.9	13.7 ± 8.1	14.1 ± 9.6	14.5 ± 13.5	0.002
CKD, %	2176 (15.8)	440 (11.2)	694 (15.0)	1042 (19.9)	< 0.001

TG/HDL-C triglycerides/high-density lipoprotein cholesterol, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TMFA* total monounsaturated fatty acids, *TPFA* total polyunsaturated fatty acids, *TSFA* total saturated fatty acids, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ACR* albumin–creatinine ratio, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *CKD* chronic kidney disease

[a]The physical activity categories were based on the distribution of MET-minute levels for the present NHANES sample

[b]BMI was calculated as the body weight in kilograms divided by the square of the height in meters

bilirubin, serum uric acid, total cholesterol, homocysteine and serum folate, except for the variable that was stratified.

To ensure the robustness of our data analysis, we conducted the following sensitivity analyses: (1) we converted the TG/HDL-C ratio into a categorical variable, and calculated the *P* for trend. The purpose was to verify the results of TG/HDL-C ratio as the continuous variable and to observe the possibility of nonlinearity; (2) we used the GAM model to adjust the continuous variables in the model 3; (3) we also performed stratified analyses to explore potential effect modifications of the association between TG/HDL-C ratio and CKD.

All the analyses were performed using the statistical package R (http://www.R-project.org, The R Foundation) and Empower (R) (http://www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). A *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics of selected participants

Based on the inclusion and exclusion criteria, a total of 13,780 participants were included in the final analysis (Fig. 1). The average age of the participants was 45.4 ± 20.3 (18–85) years old, and about 47.0% of them were males. The prevalence of CKD was 15.8% (2176/13780). The

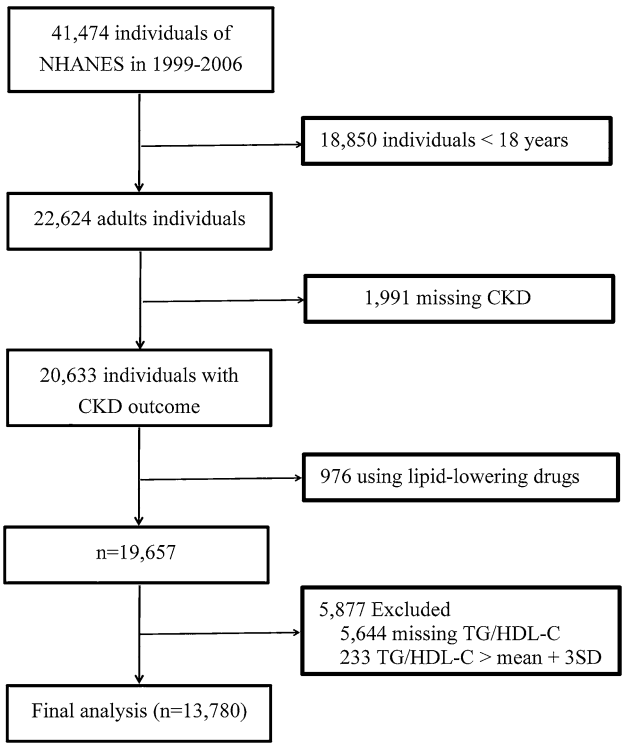

Fig. 1 Flowchart of study participants. *NHANES* National Health and Nutrition Examination Survey, *TG/HDL-C* triglycerides/high-density lipoprotein cholesterol, *CKD* chronic kidney disease

distribution of selective participants sociodemographic characteristics and other covariates according to TG/HDL-C ratio tertiles is shown in Table 1. There were significant differences between TG/HDL-C ratio tertiles for all included characteristics, except for serum total protein. Compared with T1 and T2 of TG/HDL-C ratio, participants in T3 (≥ 2.7) were more likely to: be males, have a high educational level, be a current smoker, have a higher sedentary physical activity, as well as a greater number of comorbidities, and higher age, BMI, SBP, DBP, cholesterol intake, energy intake, TSFA intake, ALT, AST, total bilirubin, ACR, serum uric acid, FBG, glycated hemoglobin, total cholesterol, TG, HDL-C, homocysteine and serum folate (all $P < 0.001$).

Association between TG/HDL-C ratio and CKD

In this study, we constructed different models for analyzing the independent effects of TG/HDL-C ratio on CKD after adjusting for other potential confounders. The effect sizes (ORs) and 95% CIs are listed in Table 2. In the unadjusted model (model 1), for every 1 increase in TG/HDL-C ratio, the prevalence of CKD increased by 11% (1.11, 95% CI 1.09–1.13). In the minimally adjusted model (model 2), for every 1 increase in TG/HDL-C ratio, the prevalence of CKD increased by 10% (1.10, 95% CI 1.07–1.13). In the fully adjusted model (model 3), for every 1 increase in TG/HDL-C ratio, the prevalence of CKD increased by 5% (1.05, 95% CI 1.02–1.08). We also converted TG/HDL-C ratio from a continuous variable to a categorical variable (tertiles). Compared to participants in T1 of TG/HDL-C ratio, there was a significant increased prevalence of CKD for the participants in both T2 and T3. *P* for trend in the all models was significant. We also used GAM to adjust continuous variables in covariates. Despite these transformations (fitting continuous variables as smooth), the results did not change significantly (Model 4).

Nonlinearity between TG/HDL-C ratio and CKD

To address the nonlinearity of the relationship between TG/HDL-C ratio and CKD, a GAM model and penalized spline method were conducted (Fig. 2). The fully adjusted smooth curve showed that the relationship between TG/HDL-C ratio and CKD was nonlinear. We fitted the association between TG/HDL-C ratio and CKD using the standard binary logistic regression model and the two-piecewise binary logistic regression model, respectively (Table 3). The *P* for log-likelihood ratio test was less than 0.05, indicating that the two-piecewise binary logistic regression model was more suitable for analyzing the association between TG/HDL-C ratio and CKD. The inflection point that we identified for TG/HDL-C ratio was 6.68. When TG/HDL-C ratio was ≤ 6.68, the OR (95% CI) was 1.08 (1.04–1.13). When TG/HDL-C ratio was > 6.68, the OR (95% CI) was 0.97 (0.89–1.05). The results suggest saturation effects of TG/HDL-C ratio on the prevalence of CKD.

Subgroup analysis

To further confirm that the results in Table 2 are robust to potential confounders, we also performed stratified analyses. Figure 3 reveals a highly consistent pattern: regardless of subgroup, TG/HDL-C ratio was positively associated with

Table 2 Relationship between TG/HDL-C ratio and CKD in different models

TG/HDL-C ratio	Events (%)	CKD OR (95% CI), *P* value			GAM model
		Model 1	Model 2	Model 3	
Continuous	2176 (15.8)	1.11 (1.09, 1.13), < 0.001	1.10 (1.07, 1.13), < 0.001	1.05 (1.02, 1.08), 0.003	1.06 (1.03, 1.09), < 0.001
Tertiles					
T1 (< 1.4)	440 (11.2)	Reference	Reference	Reference	Reference
T2 (1.4–< 2.7)	694 (15.0)	1.40 (1.23, 1.59), < 0.001	1.24 (1.04, 1.48), 0.018	1.10 (0.92, 1.33), 0.300	1.13 (0.94, 1.36), 0.200
T3 (≥ 2.7)	1042 (19.9)	1.97 (1.75, 2.22), < 0.001	1.84 (1.54, 2.19), < 0.001	1.36 (1.13, 1.65), 0.002	1.44 (1.19, 1.75), < 0.001
P for trend		< 0.001	< 0.001	< 0.001	< 0.001

Model 1: crude model

Model 2: adjusted for sex, age (smooth), body mass index, ethnicity, education status, smoking, alcohol consumption, physical activity, marital status and poverty-to-income ratio

Model 3: adjusted for all covariables in model 2 plus adjusted for comorbidities (hypertension and diabetes), medication use (antihypertensive drugs and glucose-lowering drugs), cholesterol intake, energy intake, total monounsaturated fatty acids intake, total polyunsaturated fatty acids intake, total saturated fatty acids intake, total fat intake, total protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, serum uric acid, total cholesterol, homocysteine and serum folate

GAM models: all continuous variables in model 3 were adjusted as smooth

TG/HDL-C triglycerides/high-density lipoprotein cholesterol, *CKD* chronic kidney disease, *OR* odds ratio, *CI* confidence interval, *GAM* generalized additive model

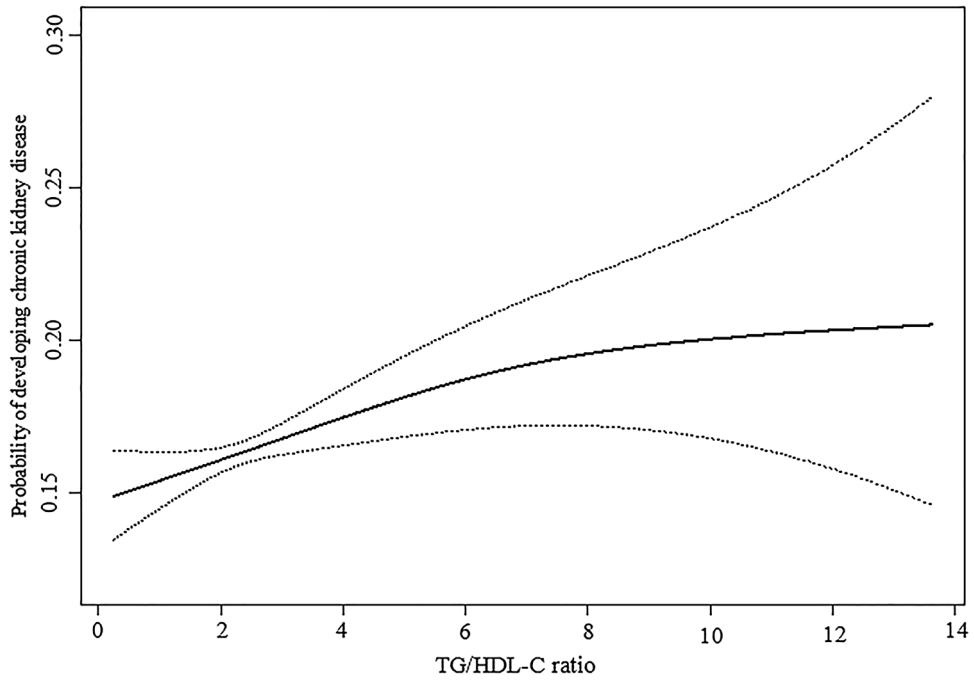

Fig. 2 Association between TG/HDL-C ratio and the prevalence of CKD. A saturation, nonlinear association between TG/HDL-C ratio and CKD was found ($P < 0.001$) in a generalized additive model (GAM). The solid line and dashed line represent the estimated values and their corresponding 95% confidence intervals. Adjustment factors included sex, age (smooth), body mass index, ethnicity, education status, smoking, alcohol consumption, physical activity, marital status, poverty-to-income ratio, comorbidities (hypertension and diabetes), medication use (antihypertensive drugs and glucose-lowering drugs), cholesterol intake, energy intake, total monounsaturated fatty acids intake, total polyunsaturated fatty acids intake, total saturated fatty acids intake, total fat intake, total protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, serum uric acid, total cholesterol, homocysteine and serum folate. *TG/HDL-C* triglycerides/high-density lipoprotein cholesterol, *CKD* chronic kidney disease

Table 3 Threshold and saturation effect analysis of TG/HDL-C ratio on CKD

TG/HDL-C ratio	Events (%)	CKD OR (95% CI), *P* value		
		Model 1	Model 2	Model 3
Standard logistic regression model	2176 (15.8)	1.11 (1.09, 1.13), < 0.001	1.10 (1.07, 1.13), < 0.001	1.05 (1.02, 1.08), 0.003
Two-piecewise logistic regression models				
Inflection point of TG/HDL-C ratio				
≤ 6.68	1947 (15.2)	1.17 (1.14, 1.20), < 0.001	1.15 (1.11, 1.20), < 0.001	1.08 (1.04, 1.13), < 0.001
> 6.68	229 (24.3)	0.99 (0.93, 1.05), 0.638	0.99 (0.92, 1.07), 0.847	0.97 (0.89, 1.05), 0.429
P for log-likelihood ratio test		< 0.001	0.003	0.041

Model 1: crude model

Model 2: adjusted for sex, age (smooth), body mass index, ethnicity, education status, smoking, alcohol consumption, physical activity, marital status and poverty-to-income ratio

Model 3: adjusted for all covariables in model 2 plus adjusted for comorbidities (hypertension and diabetes), medication use (antihypertensive drugs and glucose-lowering drugs), cholesterol intake, energy intake, total monounsaturated fatty acids intake, total polyunsaturated fatty acids intake, total saturated fatty acids intake, total fat intake, total protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, serum uric acid, total cholesterol, homocysteine and serum folate

TG/HDL-C triglycerides/high-density lipoprotein cholesterol, *CKD* chronic kidney disease, *OR* odds ratio, *CI* confidence interval

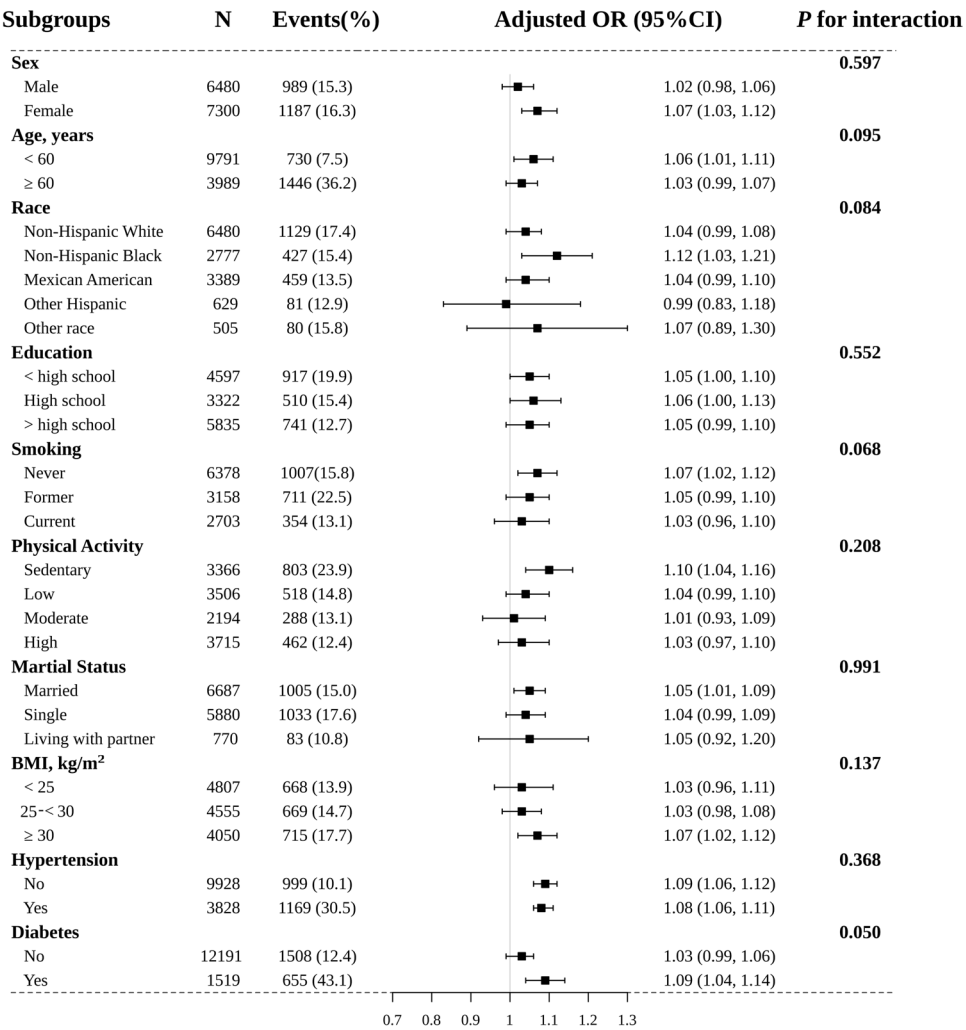

Fig. 3 Subgroup analyses of the effect of TG/HDL-C ratio on CKD. *Adjusted for sex, age (smooth), body mass index, ethnicity, education status, smoking, alcohol consumption, physical activity, marital status, poverty-to-income ratio, comorbidities (hypertension and diabetes), medication use (antihypertensive drugs and glucose-lowering drugs), cholesterol intake, energy intake, total monounsaturated fatty acids intake, total polyunsaturated fatty acids intake, total saturated fatty acids intake, total fat intake, total protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, serum uric acid, total cholesterol, homocysteine and serum folate, if not be stratified. *TG/HDL-C* triglycerides/high-density lipoprotein cholesterol, *CKD* chronic kidney disease, *BMI* body mass index, *OR* odds ratio, *CI* confidence interval

CKD. None of the variables showed significant effect modification on the association between TG/HDL-C ratio and CKD (*P*-interaction > 0.05 for all these stratified variables).

Discussion

The cross-sectional analysis of the large selected sample of US adults showed that TG/HDL-C ratio was independently and positively associated with CKD after adjusting other covariates. Besides, we also found the nonlinear relationship between TG/HDL-C ratio and CKD. The positive correlation between TG/HDL-C ratio and CKD was saturated when the TG/HDL-C ratio reached 6.68.

Several observational studies have reported the association between TG/HDL-C ratio and CKD. After 9 years follow-up in the atherosclerosis risk in communities study, hypertriglyceridemia and low HDL-C were associated with the incidence of CKD among nondiabetic adults [23]. Similarly, Tsuruya et al. [24] used data from 216,007 Japanese adults and found that an elevated TG/HDL-C ratio was associated with the risk of CKD. Ho et al. [25] conducted a cross-sectional study of 46,255 subjects aged ≥ 18 years in Taiwan and found that TG/HDL-C ratio was an independent risk factor for CKD in adults aged 18–50 years. Kang et al. [13] found that TG/HDL-C ratio was independently associated with increased prevalence of CKD in a sample of Korean adults. Zhang et al. [26] and Wen et al. [15] also reported the consistent results in Chinese population. However, after adjusting the covariates, these studies did not adjust the blood biochemistry and nutrient intake in the diet which had been confirmed to be associated with TG/HDL-C ratio or CKD. Moreover, these studies only investigated the linear relationship between TG/HDL-C ratio and the prevalence of CKD and did not discuss a nonlinear relationship. In our present study, we found that higher TG/HDL-C ratio was associated with increased prevalence of CKD after adjustment for other potential confounders. In addition, the nonlinear relationship between TG/HDL-C ratio and the prevalence of CKD using the new CKD-EPI equation was

observed. The positive correlation between TG/HDL-C ratio and CKD was saturated when the TG/HDL-C ratio reached 6.68. Long-term studies to examine the relationship between TG/HDL-C ratio and the development or progression of CKD are thus warranted. According to STROBE statement [27], we also conducted subgroup analysis. The results yield stable conclusion in different subgroups in this study. The findings of this study will help to build future research on predictive models of the incident of CKD.

Although the mechanism of TG/HDL-C ratio accelerating the CKD development is not clearly understood, there are some explanations as to why higher TG/HDL-C ratio was associated with the increased prevalence of CKD. Above all, participants with TG/HDL-C ratio seems to have poor profiles (high metabolic syndrome risk, unhealthy life style, low education), which may increase risk of CKD. Although these risk factors were adjusted, residual confounding remained. Our findings suggest that high TG/HDL-C ratio had higher baseline risk of CKD due to underlying metabolic disease anyway [28]. Besides, TG/HDL-C ratio could also be regarded as an atherogenic index and a powerful marker of CVD incidence [29]. Firstly, as the similar pathogenesis of glomerulosclerosis with atherosclerosis, it is reasonable to suggest that high TG/HDL-C ratio is associated with increased prevalence of CKD. Secondly, reabsorption of phospholipids and cholesterol by tubular epithelial cells could stimulate tubulointerstitial inflammation, foam cell formation, and tissue injury [30]. Thirdly, lipoproteins may stimulate mesangium to promote the generation of pro-inflammatory cytokines and to induce glomerulosclerosis [31]. Furthermore, declined renal function may exacerbate lipid permeability and excretion in glomerulus, resulting in further acceleration of dyslipidemia in a vicious cycle [13].

The clinical significance of this study is as follows. First, we found that TG/HDL-C ratio was positively associated with the prevalence of CKD. It suggests that we should pay attention to the TG/HDL-C ratio even in participants with normal blood lipids. Second, our findings may provide a clinical and public health recommendation for reducing the burden of CKD. Third, the present findings may contribute to the construction of a prediction model for CKD in the future.

Our study has some strengths: (1) this study was the first to report the association between TG/HDL-C ratio and the prevalence of CKD among US adults. (2) In the study, we also addressed the nonlinearity between TG/HDL-C ratio and CKD. Saturation effect was observed. (3) This study was an observational study and therefore susceptible to potential confounding. We used strict statistical adjustment to minimize residual confounders. (4) We handled target independent variable as both continuous variable and categorical variable. Such an approach can reduce the contingency in the data analysis and enhance the robustness of results. (5) The effect modifier factor analysis made the use of data better and yield stable conclusion in different subgroups in this study. (6) We conducted sensitivity analyses to enhance the robustness of results.

Our study has certain limitations. First, the main limitations of this study were its observational nature. Second, further selection bias may have occurred because those participants without complete data were excluded. Third, single measurements of TG, HDL-C, serum creatinine, and urinary protein might have resulted in the misclassification of some comorbidities. Fourth, due to the cross-sectional study design, it is difficult to infer causality between TG/HDL-C ratio and CKD based on our study. Another limitation was related to old data; it could be expected to have different trends and patterns if the study will be conducted nowadays.

Conclusion

Our study suggested saturated effects of TG/HDL-C ratio on the prevalence of CKD among US adults. TG/HDL-C ratio less than 6.68 was positively and independently associated with CKD. The findings may provide clinical guideline on the primary prevention of CKD. Further researches are needed to elucidate actual role of TG/HDL-C ratio in CKD and potential underlying mechanisms.

Acknowledgements A special thanks to all of the NHANES participants who freely gave their time to make this and other studies possible. Moreover, we gratefully thank Empower U team of the Department of Epidemiology and Biostatistics, X&Y solutions Inc. in Boston for their contribution to the statistical support.

Author contributions LY and LZ (substantial contributions to conception and design, drafting the article); DZ and GH (acquisition of data, or analysis and interpretation of data); GH (revising it critically for important intellectual content); LY, LZ, DZ and GH (final approval of the version to be published and agreed to be accountable for all aspects of the work).

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials Data are available on DataDryad (https://doi.org/10.5061/dryad.d5h62).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (NCHS Research Ethics Review Board) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG (2008) Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA 300:2142–2152
2. Cooney MT, Dudina A, De Bacquer D et al (2009) HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. Atherosclerosis 206:611–616
3. Pikula A, Beiser AS, Wang J et al (2015) Lipid and lipoprotein measurements and the risk of ischemic vascular events: Framingham study. Neurology 84:472–479
4. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F (1998) Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. Circulation 97:1029–1036
5. Vega GL, Barlow CE, Grundy SM, Leonard D, DeFina LF (2014) Triglyceride-to-high-density-lipoprotein-cholesterol ratio is an index of heart disease mortality and of incidence of type 2 diabetes mellitus in men. J Investig Med 62:345–349
6. McLaughlin T, Reaven G, Abbasi F et al (2005) Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? Am J Cardiol 96:399–404
7. Boizel R, Benhamou PY, Lardy B, Laporte F, Foulon T, Halimi S (2000) Ratio of triglycerides to HDL cholesterol is an indicator of LDL particle size in patients with type 2 diabetes and normal HDL cholesterol levels. Diabetes Care 23:1679–1685
8. Maruyama C, Imamura K, Teramoto T (2003) Assessment of LDL particle size by triglyceride/HDL-cholesterol ratio in non-diabetic, healthy subjects without prominent hyperlipidemia. J Atheroscler Thromb 10:186–191
9. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351:1296–1305
10. Stenvinkel P (2010) Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. J Intern Med 268:456–467
11. Saland JM, Ginsberg HN (2007) Lipoprotein metabolism in chronic renal insufficiency. Pediatr Nephrol 22:1095–1112
12. Shlipak MG, Fried LF, Cushman M et al (2005) Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 293:1737–1745
13. Kang HT, Shim JY, Lee YJ et al (2011) 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 34:173–179
14. Zoppini G, Negri C, Stoico V, Casati S, Pichiri I, Bonora E (2012) Triglyceride-high-density lipoprotein cholesterol is associated with microvascular complications in type 2 diabetes mellitus. Metabolism 61:22–29
15. Wen J, Chen Y, Huang Y et al (2017) 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 42:1141–1154
16. Levey AS, Stevens LA, Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
17. Selvin E, Manzi J, Stevens LA et al (2007) Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988–1994, 1999–2004. Am J Kidney Dis 50:918–926
18. Chavers BM, Simonson J, Michael AF (1984) A solid phase fluorescent immunoassay for the measurement of human urinary albumin. Kidney Int 25:576–578
19. Levey AS, de Jong PE, Coresh J et al (2011) The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 80:17–28
20. Kernan WN, Viscoli CM, Brass LM et al (2000) Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 343:1826–1832
21. Association AD (2014) Standards of medical care in diabetes–2014. Diabetes Care 37(Suppl 1):S14–S80
22. Yu X, Cao L, Yu X (2013) Elevated cord serum manganese level is associated with a neonatal high ponderal index. Environ Res 121:79–83
23. Kurella M, Lo JC, Chertow GM (2005) Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 16:2134–2140
24. Tsuruya K, Yoshida H, Nagata M et al (2014) Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. Atherosclerosis 233:260–267
25. Ho CI, Chen JY, Chen SY et al (2015) Relationship between TG/HDL-C ratio and metabolic syndrome risk factors with chronic kidney disease in healthy adult population. Clin Nutr 34:874–880
26. Zhang L, Yuan Z, Chen W et al (2014) Serum lipid profiles, lipid ratios and chronic kidney disease in a Chinese population. Int J Environ Res Public Health 11:7622–7635
27. Vandenbroucke JP, von Elm E, Altman DG et al (2007) Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. PLoS Med 4:e297
28. Miller M, Stone NJ, Ballantyne C et al (2011) Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 123:2292–2333
29. Dobiasova M, Frohlich J (2001) The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). Clin Biochem 34:583–588
30. Magil AB (1999) Interstitial foam cells and oxidized lipoprotein in human glomerular disease. Mod Pathol 12:33–40
31. Wheeler DC, Chana RS (1993) Interactions between lipoproteins, glomerular cells and matrix. Miner Electrolyte Metab 19:149–164