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RESEARCH ARTICLE

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Relationship between remnant cholesterol and risk of kidney stones in U.S. Adults: a 2007–2016 NHANES analysis

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ABSTRACT

Purpose: Remnant cholesterol (RC) is the cholesterol content of triglyceride-rich lipoproteins. This study aimed to investigate the association between RC levels and kidney stones in U.S. adults.

Methods: Data were obtained from the 2007 to 2016 National Health and Nutrition Examination Survey (NHANES). A total of 10,551 participants with complete data were included and analyzed in this study. Univariate and multivariate logistic regression analysis, restricted cubic spline function, subgroup analysis and mediation analysis were preformed to estimate the independent relationship between RC levels and kidney stones.

Results: Participants with stone formation had higher levels of RC than those with without stone formation (25.78 ± 13.83 vs 23.27 ± 13.04, $p < 0.001$). The results of logistic regression analysis and dose-response risk curves revealed a positive nonlinear association between RC levels and risk of kidney stones [univariate: adjusted odds ratio (aOR) =2.388, 95% CI: 1.797–3.173, $p < 0.001$; multivariate: aOR = 1.424, 95% CI: 1.050–1.929, $p = 0.023$]. Compared with the discordantly low RC group, the discordantly high RC group was associated with increased risk of kidney stones (aOR = 1.185, 95% CI: 1.013–1.386, $p = 0.034$). Similar results were demonstrated according to the discordance of different clinical cut points. And metabolic syndrome parameters and vitamin D levels parallelly mediated the association between RC and kidney stone risk.

Conclusions: Higher RC levels were independently associated with an increased risk of kidney stone incidence.

KEY MESSAGES

Higher remnant cholesterol levels were independently associated with an increased risk of kidney stone incidence.

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Kidney stone; remnant cholesterol; national health and nutrition examination survey; prevalence; cross-sectional study

Introduction

Nephrolithiasis is one of the most common diseases of the urinary system and result from an imbalance in the dissolution and precipitation of crystalline material in the kidney. The main types include stones that occur in the calyces, pelvis and pelvic ureteral junction [1]. It was estimated that the global prevalence of nephrolithiasis is 7.2%–7.7% and increasing year by year [2]. The prevalence is 1%–19% in Asia, 4% in South America, and 5%–10% in Europe [3,4]. The incidence of kidney stones was associated with a variety of factors, such as gender, age, race, diet, underlying disease, and smoking [5]. Kidney stones can cause pain, hematuria, infection, severe cases with kidney dysfunction, and their recurrence rate is relatively high, which affects the survival quality of patients to a certain extent, so it is very crucial to explore the factors of kidney stones and their prevention [6].

Remnant cholesterol (RC) is the cholesterol content of triglyceride-rich lipoproteins (TRLs) and consists of very low-density lipoproteins cholesterol (VLDL-C) and intermediate-density lipoproteins cholesterol (IDL-C) in the fasting state as well as chylomicron cholesterol in the non-fasting state [7]. It was demonstrated that elevated residual cholesterol is associated with an increased risk of ischemic stroke, and that the mechanism may be atherosclerosis-induced inflammation,

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foam cell formation, and cholesterol deposition in atherosclerotic plaques [8,9]. In recent years, RC concentrations have also been identified to be significantly associated with chronic kidney disease (CKD) [10]. Moreover, it has been demonstrated that metabolic syndrome, an independent risk factor for kidney stones, increases the risk of developing stones [11, 12]. Dyslipidemia is a component of the metabolic syndrome and RC can be used as a very accurate lipid parameter to identify the metabolic syndrome, but it is unknown whether RC concentrations increases the risk of kidney stones [13].

In this study, we used various analysis methods to assess the relationship between RC level and the risk of kidney stones based on data from National Health and Nutrition Examination Survey (NHANES). We hypothesized that higher RC levels are associated with an increased risk of kidney stones.

Participants and methods

Study population

NHANES is a nationally and cross-sectional representative survey conducted by National Center for Health Statistics (NCHS) at the U.S. Centers for Disease Control and Prevention (CDC). NHANES collects information from diverse populations using a complex probability sampling design that includes standardized interviews, physical examinations, and sample tests to assess the health and nutritional status of the U.S. population. The data have been released every two years since 1999. The NHANES research protocol was approved by the NCHS Institutional Review Board. Moreover, all participants have signed an informed consent form following the Declaration of Helsinki. All data in this study are accessible on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

In the present observational study, we obtained and combined publicly available data for five cycles of NHANES 2007–2008, 2009–2010, 2011–2011, 2013–2014, and 2015–2016. To account for the complex sampling design and to obtain appropriate weights, we used sampling weights for the interviews (WTSA2YR) and study design variables (SDMVPSU and SDMVSTRA) in our data analysis and performed a weighted analysis. A total of 50,588 participants were enrolled in our study between 2007 and 2016. Exclusion criteria were as follows [1]: Participants with missing data on kidney stones (21,476) [2]; Participants with missing data on blood lipid ($n = 16,753$), metabolic syndrome (MstS) ($n = 1,750$) and serum uric acid ($n = 67$). After excluding the above participants, a total of 1,0551 participants were included in our final analysis.

Study variables and outcome

We summarized potential variables that could confound the association between RC and kidney stones in the multivariate-adjusted model. Variables in the present study included age, gender, race, education level, marital status, body mass index (BMI), hypertension, diabetes, apolipoprotein B (apoB), total cholesterol, high-density lipoprotein cholesterol (HDL-C), waist circumference, glycated hemoglobin (HbA1c), vitamin D, plasma fasting glucose, triglycerides, low-density lipoprotein cholesterol (LDL-C), physical activity, blood urea nitrogen, serum uric acid and serum creatinine. Race was categorized as Mexican American, non-Hispanic White, non-Hispanic Black, other Hispanic and other race. We divided the participants into two groups according to whether they graduated from high school or not. Marital status was grade from married and unmarried and others. Overweight was considered to be BMI greater than or equal to 25. RC levels were calculated as total cholesterol (TC) minus HDL-C and LDL-C. Although there is no standard method for estimating RC, it can be obtained from a standard lipid profile, and previous studies have often used this method to calculate [14–17]. Levels of non-HDL-C was calculated as TC minus HDL-C. As recommended in the guidelines, the Friedewald equation was applied to calculate LDL-C when serum triglycerides were less than 400 mg/dL [18]. Due to the limitations of the above equation, LDL-C values for participants with serum triglycerides exceeding 400 mg/dL were not available in NHANES laboratory data. Detailed instructions on specimen collection and processing can be found on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

Using a self-administered questionnaire, NHANES collected information on hypertension and diabetes. Participants without a history of hypertension were defined as having responded to the 'Ever told you had high blood pressure?' question, answering 'No'. Participants without a history of diabetes were defined as having responded to the 'Doctor told you have diabetes?' question, answering 'No'. The outcome variable of the study, the history of kidney stones, was extracted from the questionnaire data file. Participants without a history of kidney stones were defined as having responded to the 'Have you ever had kidney stones?' question, answering 'No'. The NHANES CAPI system is programmed with built-in consistency checks to reduce data entry errors and ensure the quality and

effectiveness of this question. For more details on the QA/QC process for this component, please refer to the NHANES Interviewer Procedure Manuals and the MEC Interviewer Exam Manual on the NHANES website.

Discordance definition

We used different methods to define the discordance between different lipids or lipoproteins due to there is no physiological discordance between their cut points. First, RC percentile minus LDL-C percentile differences greater than 10 were defined as discordance. Then, we divided the participants into three cohorts according to previous studies [14]. Discordantly low RC was defined as RC percentile < LDL-C percentile by greater than 10 percentile units. Participants with RC percentile > LDL-C percentile by greater than 10 percentile units were classified in the discordantly high RC group. Concordant RC and LDL-C was defined as being within ± 10 percentile units. Previous studies have used median as cutpoint [19–21], but we focused more on the clinically relevant LDL-C cutpoints (70, 100 and 130 mg/dL) recommended in the global guidelines [18, 22, 23]. Clinical cutpoints were used to define discordances to assess the stability of our study results. The equivalent population percentile in the cohort corresponding to these LDL-C values were used to determine the respective RC cut points.

Statistical analysis

In the present study, means with standard deviations were used to represent continuous variables and percentages were used to represent categorical variables. Student's *t*-test for continuous variables and chi-square test for categorical variables were performed to assess the clinical characteristics of all participants. We constructed univariate and multivariate logistic regression models to assess the adjusted odds ratios (aORs) and 95% confidence interval (CI) of the independent relationship between factors and kidney stones. Three different logical regression models were performed to investigate the independent relationship between continuous log-transformed RC levels and kidney stones. Model 1 adjusts for basic information about the participants, including age, gender, race, marital status, and education. Subsequently, we further adjusted for lifestyle factors in Model 2, including moderate recreational activity and BMI. Model 3 was additionally adjusted for high risk factors for kidney stone formation, including hypertension, diabetes, lipoprotein B, blood urea nitrogen, serum uric acid, and serum creatinine. In the same models, differences in percentile units, LDL-C clinical cut points were used to assess the association of RC and LDL-C concordant/discordant groups with kidney stone occurrence. Constrained cubic spline curve functions are frequently applied to describe the dose-response relationships between continuous variables and outcomes [24]. We applied restricted cubic spline function to describe the dose-response relationship between RC levels and kidney stone risk and adjusting for model variables. Subsequently, we estimated the potential mediating effects of metabolic syndrome parameters and vitamin D levels with kidney stone risk by parallel mediation. Individual indicators were used as mediators in the parallel mediation models. The direct effect (DE) represented the effects of metabolic syndrome parameters and vitamin D levels on kidney stone without a mediator. The indirect effect (IE) represented the effects of metabolic syndrome parameters and vitamin D levels on kidney stone through the mediator. The IE was divided by the TE (total effect) to calculate the proportion of mediation.

All date were analyzed by *R* (version 3.5.3) and SPSS software (version 24.0). Differences were considered statistically significant at $p < 0.05$ for double-sided.

Results

Characteristics of participants

As shown in Figure 1 for inclusion and exclusion criteria, 10,551 qualified participants from NHANES 2007–2016 were included in this retrospective study. Of these, 9566 participants were without stone formers and 985 participants were stone formers. Table 1 indicated the clinical characteristics of the participants with or without kidney stones. The mean age at baseline of all participants was 49.28 ± 17.46, 51.2% was female, 42.8% was non-Hispanic white, and 70.3% had BMI values greater than or equal to 25 (Table 1). The stone formers and without stone formers groups were compared by chi-square test and significant differences were found between several variables, including age ($p < 0.001$), gender ($p < 0.001$), race ($p < 0.001$), marital status ($p < 0.001$), BMI ($p < 0.001$), moderate recreational activities ($p = 0.006$), hypertension ($p < 0.001$), diabetes ($p < 0.001$), blood urea nitrogen ($p < 0.001$), serum creatinine ($p = 0.008$), RC ($p = 0.008$), triglycerides ($p = 0.005$), waist circumference ($p < 0.001$), HbA1c ($p < 0.001$), plasma fasting glucose ($p < 0.001$) and serum uric acid ($p < 0.001$). Participants with history of kidney stones were more frequently ≥ 50 years (63.6%), male (54.6%), non-Hispanic white (54.6%), married (60.5%),

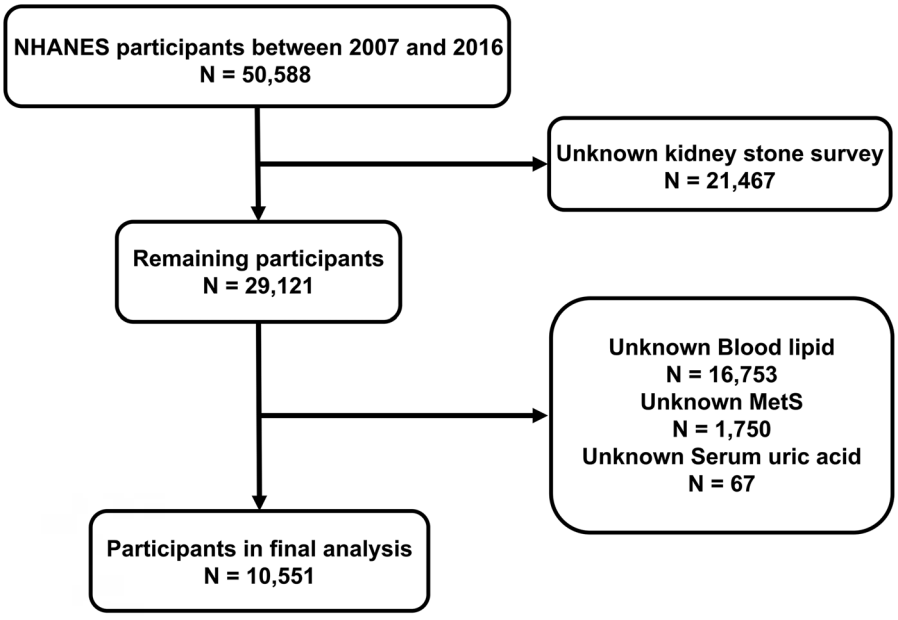

Figure 1. Flow diagram of the inclusion and exclusion criteria from National Health and Nutrition Examination Survey (NHANES) 2007–2016.

BMI ≥ 25.0 kg/m^2 (79.7%) and less moderate recreational activities (63.7%). Moreover, participants with history of kidney stones had higher levels of blood urea nitrogen, serum creatinine, serum uric acid, serum uric acid, non-HDL-C, ApoB, waist circumference, HbA1c, vitamin D, plasma fasting glucose and triglycerides than those without a history of kidney stones. Importantly, participants with history of kidney stones had significantly higher RC values relative to healthy controls (25.78 ± 13.83 vs 23.27 ± 13.04, $p < 0.001$).

We further analyzed the baseline characteristics of all participants by concordant/discordant categories between LDL-C and RC (Table 2). Individuals with inconsistent high RC were older, male, non-Hispanic white, married, less moderate recreational activities, and had higher BMI, blood urea nitrogen, serum creatinine, serum uric acid, triglyceride, waist circumference, HbA1c, vitamin D, plasma fasting glucose levels and RC than those with consistent and inconsistent low RC. In addition, compared to those with discordantly low RC, participants with discordantly high RC had lower levels of TC, HDL-C, non-HDL-C, LDL-C, and ApoB.

Association between remnant cholesterol and kidney stones prevalence

To further determine the relationship between various cholesterol indicators and the prevalence of kidney stones, we performed univariate and multivariate logistic regression analysis (Table S1 and Table 3). In our analysis, we found a positive association between log-transformed RC levels and risk of kidney stones after adjusting all factors. Univariate analysis revealed that log-transformed RC levels were significantly and positively correlated with the prevalence of kidney stones (aOR = 2.388, 95% CI: 1.797–3.173, $p < 0.001$). In the model 3, each unit of increased log-transformed RC levels was associated with a 42.4% increase in the risk of kidney stones (aOR = 1.424, 95% CI: 1.050–1.929, $p = 0.023$). As shown in Figure 2, nonlinear dose-response risk curves indicated that the risk of kidney stones increases with increasing levels of log-transformed RC. And the trends for other cholesterol indicators were the similar as in the logistic regression analysis.

Subsequently, we stratified RC by discordance definitions and performed univariate and multivariate logistic regression analysis to investigate the relationship between RC and kidney stones incidence (Table S2 and Figure 3). In both univariate and multivariate analysis, the results indicated significantly increased incidence of kidney stones in the discordantly high RC group compared with the discordantly low RC group (aOR = 1.495, 95% CI: 1.287–1.737, $p < 0.001$; aOR = 1.185, 95% CI: 1.013–1.386, $p = 0.034$, respectively). However, the difference between the concordant group relative to the discordantly low RC group was not statistically significant (aOR = 1. 046, 95% CI: 0.875–1.249, $p = 0.624$; aOR = 0.986, 95% CI: 0.824–1.181, $p = 0.880$, respectively).

Table 1. Baseline characteristics of NHANES participants between 2007 and 2016 ($n = 12117$).[a]

	All patients	Without stone formers No. (%)	Stone formers No. (%)	
Characteristic	$N = 10551$	$N = 9566$ (90.7)	$N = 985$ (9.3)	*P value*
Age				<0.001
Mean (SD)	49.28 (17.46)	48.66 (17.46)	55.32 (16.25)	<0.001
<50 years	6060 (50.0)	5012 (52.4)	359 (36.4)	
≥50 years	6057 (50.0)	4554 (47.6)	626 (63.6)	
Gender				<0.001
Male	5149 (48.8)	4611 (48.2)	538 (54.6)	
Female	5402 (51.2)	4955 (51.8)	447 (45.4)	
Race				<0.001
Mexican American	1626 (15.4)	1492 (15.6)	134 (13.6)	
Non-Hispanic white	4518 (42.8)	3980 (41.6)	538 (54.6)	
Non-Hispanic black	2038 (19.3)	1924 (20.1)	114 (11.6)	
Other Hispanic	1207 (11.4)	1084 (11.3)	123 (12.5)	
Other race	1162 (11.0)	1086 (11.4)	76 (7.7)	
Education				0.454
≤High school	5022 (47.6)	4542 (47.5)	480 (48.7)	
>High school	5529 (52.4)	5024 (52.5)	505 (51.3)	
Marital status				<0.001
Married	5528 (52.4)	4932 (51.6)	596 (60.5)	
Unmarried and others	5023 (47.6)	4634 (48.4)	389 (39.5)	
BMI (kg/m^2)				<0.001
Mean (SD)	28.92 (6.68)	28.82 (6.82)	30.42 (6.94)	<0.001
<25.0	3135 (29.7)	2935 (30.7)	200 (20.3)	
≥25.0	7416 (70.3)	6631 (69.3)	785 (79.7)	
Moderate recreational activities				0.004
Yes	4287 (40.6)	3929 (41.1)	358 (36.3)	
No	6264 (59.4)	5637 (58.9)	627 (63.7)	
Hypertension				<0.001
Yes	3761 (35.6)	3274 (34.2)	487 (49.4)	
No	6790 (64.4)	6292 (65.8)	498 (50.6)	
Diabetes				<0.001
Yes	1263 (12.0)	1063 (11.1)	200 (20.3)	
No	9288 (88)	8503 (88.9)	785 (79.7)	
Blood urea nitrogen (mg/dL)	13.34 (5.69)	13.24 (5.69)	14.34 (5.65)	<0.001
Serum creatinine (mg/dL)	0.88 (0.43)	0.88 (0.43)	0.91 (0.41)	0.008
Serum uric acid (mg/dL)	5.48 (1.41)	5.46 (1.41)	5.62 (1.42)	0.260
TC (mg/dL)	191.63 (40.49)	191.87 (40.61)	189.37 (39.32)	0.998
RC (mg/dL)	23.51 (13.14)	23.27 (13.04)	25.78 (13.83)	0.008
HDL-C (mg/dL)	54.19 (15.88)	54.50 (15.92)	51.15 (15.15)	<0.001
Non-HDL-C (mg/dL)	137.44 (39.96)	137.36 (40.17)	138.21 (37.89)	0.728
LDL-C (mg/dL)	113.93 (35.42)	114.09 (35.54)	112.43 (34.25)	0.961
ApoB (mg/dL)	91.40 (24.56)	91.29 (24.67)	92.47 (23.43)	0.837
Triglycerides (mg/dL)	117.52 (65.64)	116.35 (65.17)	128.94 (69.08)	0.005
Waist circumference	99.02 (16.13)	98.48 (16.00)	104.20 (16.44)	<0.001
HbA1c	5.75 (1.06)	5.73 (1.04)	5.96 (1.17)	<0.001
Vitamin D	64.53 (27.17)	64.23 (27.18)	67.53 (26.86)	0.655
Plasma fasting glucose	108.23 (33.62)	107.55 (33.01)	114.89 (38.39)	<0.001

SD: standard deviation; BMI: body mass index; TC: total cholesterol; RC: remnant cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol; ApoB: apolipoprotein B; HbA1c: glycated hemoglobin.
The HDL-C, LDL-C, RC, TC and non-HDL-C in mg/dL was converted to mmol/L (LBDTCSI) by multiplying by 0.02586.
[a]For categorical variables, *P* values were analyzed by chi-square tests. For continuous variables, the *t*-test for slope was used in generalized linear models.

Participants were further classified into different groups for analysis according to clinical LDL-C cut-points (70, 100, and 130 mg/dL) and percentile equivalents for RC (10, 17, and 27 mg/dL). As indicated in Table 4, compared with LDL-C < cutpoint and RC < cut-point group, the risk of kidney stones was significantly elevated in the remaining groups. In particular, the risk was highest in the LDL-C < cutpoint and RC > cutpoint group (aOR = 2.570, 95% CI: 1.097–6.019, $p = 0.030$; aOR = 1.419, 95% CI: 1.118–1.802, $p = 0.004$; aOR = 1.272, 95% CI: 1.060–1.526, $p = 0.010$, respectively). In addition, we performed a restricted cubic spline function by LDL-C clinical cutpoint to assess the dose-response relationship between kidney stone risk and log-transformed RC levels. After adjusting for numerous potential confounding factors, nonlinear dose-response risk curves indicated that the risk of kidney stones increased with increasing log-transformed RC levels in all groups except for the LDL-C greater than or equal to 130 mg/dL group (Figure S1).

Table 2. Characteristics of the study population in concordant and discordant groups–remnant cholesterol vs. low-density lipoprotein cholesterol.[a]

Characteristic	RC < LDL-C (discordantly low RC) N = 4242	RC ~ LDL-C (concordant) N = 2956	RC > LDL-C (discordantly high RC) N = 4290	p value
Age				<0.001
Mean (SD)	48.00 (16.26)	48.01 (17.67)	51.63 (18.38)	<0.001
<50 years	2310 (54.5)	1385 (53.5)	1676 (45.0)	
≥50 years	1932 (45.5)	1202 (46.5)	2046 (55.0)	
Gender				<0.001
Male	1921 (45.3)	1224 (47.3)	2004 (53.8)	
Female	2321 (54.7)	1363 (52.7)	1718 (46.2)	
Race				<0.001
Mexican American	543 (12.8)	415 (16.0)	668 (17.9)	
Non-Hispanic white	1670 (39.4)	1741 (46.8)	1741 (46.8)	
Non-Hispanic black	1090 (25.7)	472 (12.7)	472 (12.7)	
Other Hispanic	467 (11.0)	436 (11.7)	436 (11.7)	
Other race	472 (11.1)	405 (10.9)	405 (10.9)	
Education				<0.001
≤High school	1877 (44.2)	1208 (46.7)	1937 (52.0)	
>High school	2365 (55.8)	1379 (53.3)	1785 (48.0)	
Marital status				0.053
Married	2240 (52.8)	1303 (50.4)	1985 (53.3)	
Unmarried and others	2002 (47.2)	1284 (49.6)	1737 (46.7)	
BMI (kg/m^2)				<0.001
Mean (SD)	28.17 (6.60)	28.56 (6.60)	30.02 (6.70)	<0.001
<25.0	1459 (34.4)	842 (32.5)	834 (22.4)	
≥25.0	2783 (65.6)	1745 (67.5)	2888 (77.6)	
Moderate recreational activities				<0.001
Yes	1860 (43.8)	1041 (40.2)	1386 (37.2)	
No	2382 (56.2)	1546 (59.8)	2336 (62.8)	
Hypertension				<0.001
Yes	1238 (29.2)	852 (32.9)	1671 (44.9)	
No	3004 (70.8)	1735 (67.1)	2051 (55.1)	
Diabetes				<0.001
Yes	249 (5.90)	265 (10.2)	749 (20.1)	
No	3993 (94.1)	2322 (89.8)	2973 (79.9)	
Blood urea nitrogen (mg/dL)	12.98 (4.73)	13.13 (5.44)	13.89 (6.74)	<0.001
Serum creatinine (mg/dL)	0.85 (0.30)	0.88 (0.53)	0.92 (0.47)	<0.001
Serum uric acid (mg/dL)	5.26 (1.33)	5.42 (1.39)	5.78 (1.46)	<0.001
TC (mg/dL)	209.07 (36.89)	189.75 (44.82)	173.07 (31.75)	<0.001
RC (mg/dL)	16.31 (6.53)	22.78 (12.36)	32.21 (14.12)	<0.001
HDL-C (mg/dL)	59.29 (15.58)	54.52 (15.77)	48.16 (14.10)	<0.001
Non-HDL-C (mg/dL)	149.79 (36.77)	135.23 (48.04)	124.91 (32.38)	<0.001
LDL-C (mg/dL)	133.48 (31.92)	112.44 (36.46)	92.70 (24.16)	<0.001
ApoB (mg/dL)	98.56 (22.55)	90.19 (29.15)	84.08 (20.68)	<0.001
Triglycerides (mg/dL)	81.60 (32.63)	113.92 (61.74)	160.98 (70.60)	<0.001
Waist circumference	96.30 (15.41)	98.15 (16.22)	102.71 (16.17)	<0.001
HbA1c	5.63 (0.94)	5.69 (1.03)	5.93 (1.17)	<0.001
Vitamin D	64.46 (27.99)	63.88 (26.96)	65.08 (26.36)	0.349
Plasma fasting glucose	103.33 (27.59)	106.33 (32.73)	115.14 (38.92)	<0.001

SD: standard deviation; BMI: body mass index; TC: total cholesterol; RC: remnant cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol; ApoB: apolipoprotein B; HbA1c: glycated hemoglobin.
The HDL-C, LDL-C, RC, TC and non-HDL-C in mg/dL was converted to mmol/L (LBDTCSI) by multiplying by 0.02586.
[a]For categorical variables, *P* values were analyzed by chi-square tests. For continuous variables, the *t*-test for slope was used in generalized linear models.

Table 3. Logistic models (95% confidence intervals) of kidney stone events for log-transformed RS levels in NHANES participants between 2007 and 2016.[a]

		Model 1		Model 2		Model 3	
	Mean (SD)	aOR (95% CI)	*P*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Log RC	1.31 (0.23)	1.823 (1.357–1.245)	< 0.001	1.553 (1.147–2.102)	0.004	1.424 (1.050–1.929)	0.023

SD: standard deviation; RC: remnant cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol; CI: confidence interval; aOR: adjusted odds ratio.
[a]Model 1: adjusted basic information for age, gender, race, marital status and education.
Model 2: model 1 further adjusted lifestyle factors for moderate recreational activities and BMI.
Model 3: model 2 further adjusted high risk factors for kidney stone formation for hypertension, diabetes, apolipoprotein B, blood urea nitrogen, serum uric acid and serum creatinine.

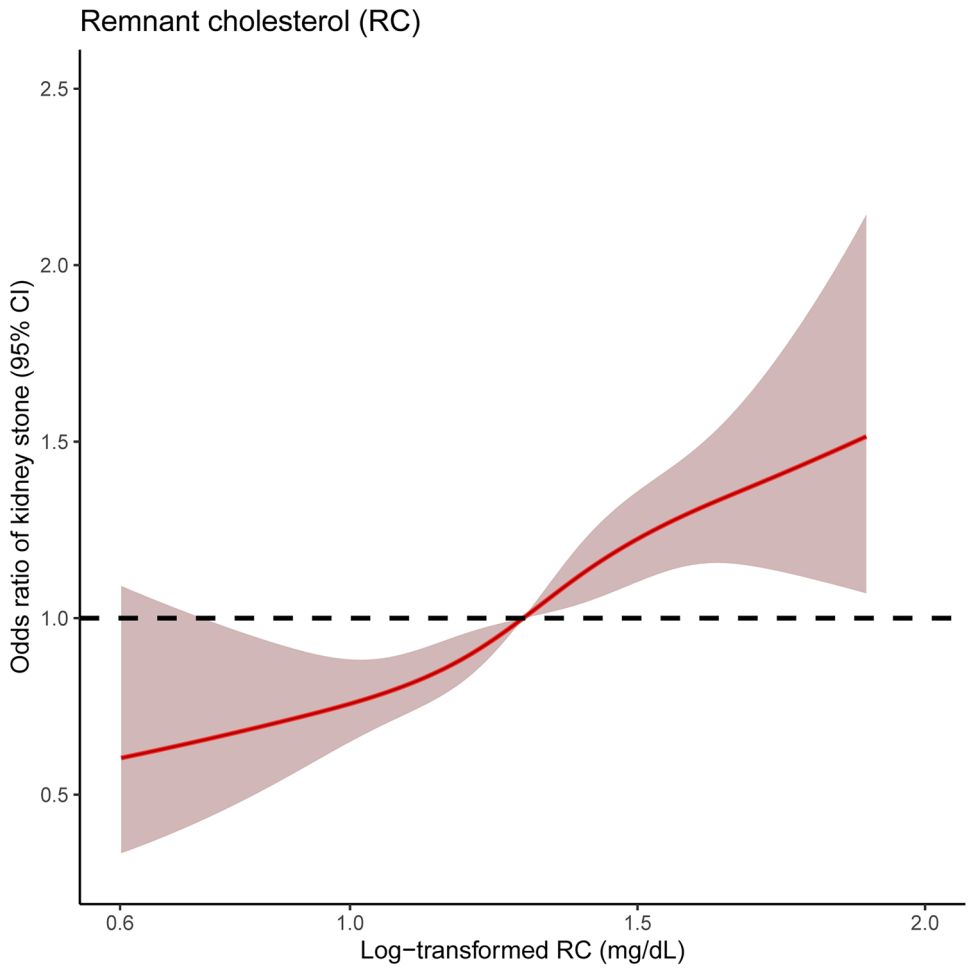

Figure 2. The dose–response analysis between log-transformed remnant cholesterol (RC) levels and risk of kidney stone in the weighted population. The upper and lower limits of the 95% CI are shaded.

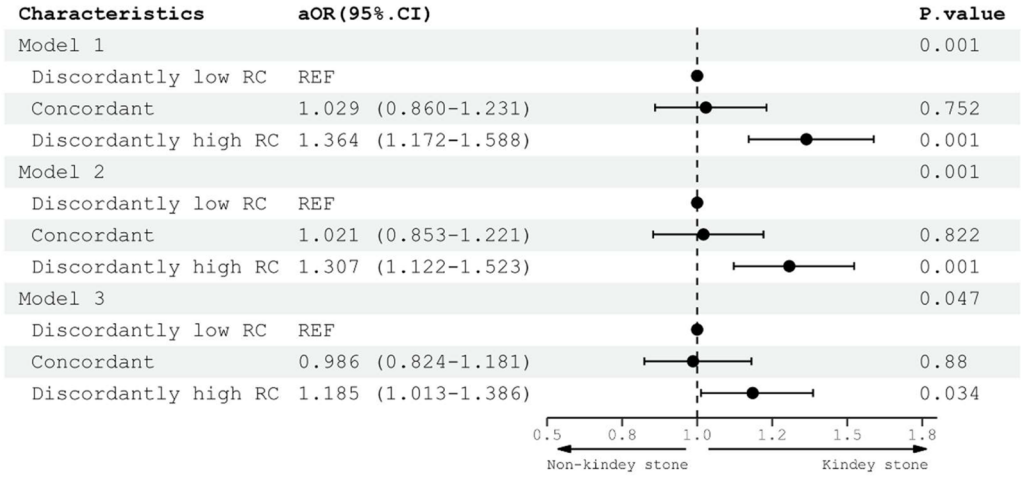

Figure 3. Association of different categories of remnant cholesterol (RC) with kidney stones. Model 1: adjusted basic information for age, gender, race, marital status and education. Model 2: model 1 further adjusted lifestyle factors for moderate recreational activities and BMI. Model 3: model 2 further adjusted high risk factors for kidney stone formation for hypertension, diabetes, apolipoprotein B, blood urea nitrogen, serum uric acid and serum creatinine.

Table 4. Logistic models (95% confidence intervals) of kidney stone events for remnant cholesterol in NHANES participants between 2007 and 2016.[a]

		Model 1		Model 2		Model 3	
Lipid groups	RC	aOR (95% CI)	*P*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Cutpoints: LDL-C 70 mg/dL; RC 10 mg/dL							
LDL-*C* < 70 mg/dL	RC < 10 mg/dL	REF		REF		REF	
N = 1085	RC ≥ 10 mg/dL	2.997 (1.286–6.987)	0.011	2.717 (1.164–6.345)	0.021	2.570 (1.097–6.019)	0.030
LDL-*C* ≥ 70 mg/dL	RC < 10 mg/dL	1.931 (0.804–4.637)	0.141	1.908 (0.794–4.586)	0.149	2.051 (0.848–4.962)	0.111
N = 11032	RC ≥ 10 mg/dL	2.295 (1.009–5.220)	0.074	2.061 (0.905–4.695)	0.085	2.169 (0.940–5.008)	0.070
Cutpoints: LDL-C 100 mg/dL; RC 20 mg/dL							
LDL-*C* < 100 mg/dL	RC < 17 mg/dL	REF		REF		REF	
N = 4439	RC ≥ 17 mg/dL	1.658 (1.312–2.095)	< 0.001	1.518 (1.198–1.924)	0.001	1.419 (1.118–1.802)	0.004
LDL-*C* ≥ 100 mg/dL	RC < 17 mg/dL	1.297 (1.011–1.663)	0.041	1.256 (0.979–1.612)	0.073	1.340 (1.043–1.722)	0.022
N = 7678	RC ≥ 17 mg/dL	1.328 (1.072–1.645)	0.009	1.217 (0.980–1.511)	0.076	1.264 (1.017–1.571)	0.035
Cutpoints: LDL-C 130 mg/dL; RC 27 mg/dL							
LDL-*C* < 130 mg/dL	RC < 27 mg/dL	REF		REF		REF	
N = 8448	RC ≥ 27 mg/dL	1.398 (1.181–1.654)	< 0.001	1.303 (1.099–1.544)	0.002	1.272 (1.060–1.526)	0.010
LDL-*C* ≥ 130 mg/dL	RC < 27 mg/dL	0.978 (0.808–1.184)	0.821	0.954 (0.788–1.155)	0.629	1.039 (0.819–1.318)	0.755
N = 3669	RC ≥ 27 mg/dL	1.072 (0.873–1.317)	0.505	1.001 (0.814-1.232)	0.989	1.089 (0.814–1.457)	0.567

SD: standard deviation; RC: remnant cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol; CI: confidence interval; aOR: adjusted odds ratio.
[a]Model 1: adjusted basic information for age, gender, race, marital status and education.
Model 2: model 1 further adjusted lifestyle factors for moderate recreational activities and BMI.
Model 3: model 2 further adjusted high risk factors for kidney stone formation for hypertension, diabetes, apolipoprotein B, blood urea nitrogen, serum uric acid and serum creatinine.

Subgroup analysis

We assessed the robustness of the association of different discordantly/concordant RC with kidney stones using subgroup analysis (Table 5). The results revealed that the risk of kidney stones was higher in the concordant and discordantly high RC groups when the discordantly low RC group served as a reference in most subgroups. After being adjusted for confounding factors including age, gender, race, BMI, blood urea nitrogen, education, marital status, apolipoprotein B, moderate recreational activities, serum uric acid, hypertension, diabetes and serum creatinine, the association between discordantly high RC and kidney stones was still significant in younger participants, non-Hispanic white, high school graduates, unmarried and others, BMI ≥ 25.0 and no diabetes participants (all $p < 0.05$).

Mediation analyses

In addition, we performed parallel mediation analyses to assess the potential mediation of metabolic syndrome parameters and vitamin D levels on the risk of kidney stone (Figure 4). The results revealed that metabolic syndrome parameters including waist circumference, HbA1c, fasting glucose, HDL and hypertension and vitamin D levels parallelly mediated the association between RC and kidney stone risk with 15.46%, 9.0%, 9.7%, 36.0%, 10.8% and 2.6% proportion of mediation respectively (all $p < 0.01$).

Discussion

In this retrospective study that included 10,551 participants, we found a positive association between RC and the risk of kidney stone using the nationally representative NHANES database. The results of this study revealed for the first time that participants with history of kidney stones had significantly higher levels of RC than those without history of kidney stones. After adjusting for age, gender, race, BMI, blood urea nitrogen, education, marital status, apolipoprotein B, moderate recreational activities, serum uric acid, hypertension, diabetes and serum creatinine, the discordantly high RC group had an 18.5% increased risk of kidney stones compared with the discordantly low RC group. This positive association was consistent across subgroups stratified by age, race, education level, marital status, BMI and history of diabetes. And metabolic syndrome parameters including waist circumference, HbA1c, fasting glucose, HDL and hypertension and vitamin D levels parallelly mediated the association between RC and kidney stone risk.

RC was a novel indicator of lipoproteins, defined as the cholesterol content of triglycerides, including non-HDL-C and non-low-density lipoprotein cholesterol (non-LDL-C) [25]. In recent years, more and more studies have concerned the role of RC in various diseases. RC was an independent factor associated with metabolic dysfunction–associated fatty liver disease risk and was able to predict all-cause, cardiovascular

Table 5. Subgroup analysis of kidney stone events for standardized remnant cholesterol concordant and discordant groups in NHANES participants between 2007 and 2016.[a]

	Model 1		Model 2		Model 3	
Subgroups	aOR (95% CI)	*P*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Age (years)						
<50		0.012		0.028		0.030
Discordantly low RC	REF		REF		REF	
Concordant	1.244 (0.946–1.635)	0.118	1.244 (0.946–1.636)	0.118	1.256 (0.949–1.662)	0.111
Discordantly high RC	1.460 (1.137–1.876)	0.003	1.403 (1.091–1.804)	0.008	1.431 (1.095–1.871)	0.009
≥50		0.001		0.005		0.087
Discordantly low RC	REF		REF		REF	
Concordant	0.902 (0.712–1.144)	0.396	0.889 (0.700–1.127)	0.330	0.858 (0.674–1.092)	0.212
Discordantly high RC	1.317 (1.088–1.594)	0.005	1.254 (1.034–1.521)	0.021	1.117 (0.902–1.385)	0.311
Gender						
Male		0.003		0.014		0.072
Discordantly low RC	REF		REF		REF	
Concordant	0.939 (0.728–1.212)	0.629	0.928 (0.719–1.198)	0.568	0.919 (0.709–1.190)	0.521
Discordantly high RC	1.333 (1.085–1.637)	0.006	1.271 (1.033–1.564)	0.024	1.206 (0.961–1.512)	0.106
Female		0.009		0.048		0.137
Discordantly low RC	REF		REF		REF	
Concordant	1.148 (0.893–1.477)	0.282	1.120 (0.870–1.441)	0.381	1.117 (0.864–1.445)	0.398
Discordantly high RC	1.420 (1.135–1.777)	0.002	1.328 (1.059–1.666)	0.014	1.288 (1.004–1.651)	0.046
Race						
Non-Hispanic white		<0.001		0.001		0.017
Discordantly low RC	REF		REF		REF	
Concordant	0.943 (0.730–1.218)	0.653	0.917 (0.709–1.185)	0.506	0.887 (0.686–1.147)	0.361
Discordantly high RC	1.467 (1.191–1.807)	<0.001	1.363 (1.105–1.682)	0.004	1.239 (0.997–1.541)	0.054
Others		0.430		0.594		0.857
Discordantly low RC	REF		REF		REF	
Concordant	1.087 (0.845–1.398)	0.515	1.080 (0.840–1.390)	0.549	1.065 (0.824–1.376)	0.631
Discordantly high RC	1.161 (0.926–1.456)	0.195	1.124 (0.895–1.410)	0.315	1.061 (0.829–1.358)	0.638
Education						
≤High school		0.120		0.212		0.517
Discordantly low RC	REF		REF		REF	
Concordant	1.016 (0.784–1.317)	0.903	1.012 (0.781–1.312)	0.927	1.007 (0.775–1.310)	0.955
Discordantly high RC	1.231 (0.989–1.533)	0.062	1.195 (0.959–1.489)	0.112	1.134 (0.893–1.442)	0.302
>High school		<0.001		0.001		0.015
Discordantly low RC	REF		REF		REF	
Concordant	1.054 (0.822–1.351)	0.678	1.031 (0.804–1.323)	0.808	0.999 (0.778–1.283)	0.992
Discordantly high RC	1.562 (1.266–1.927)	<0.001	1.452 (1.174–1.796)	0.001	1.332 (1.071–1.657)	0.010
Marital status						
Married		0.003		0.015		0.086
Discordantly low RC	REF		REF		REF	
Concordant	0.902 (0.711–1.143)	0.392	0.887 (0.699–1.125)	0.323	0.855 (0.672–1.088)	0.203
Discordantly high RC	1.289 (1.061–1.565)	0.010	1.223 (1.006–1.488)	0.044	1.121 (0.904–1.389)	0.299
Unmarried and others		0.005		0.004		0.031
Discordantly low RC	REF		REF		REF	
Concordant	1.247 (0.946–1.643)	0.117	1.279 (0.971–1.685)	0.080	1.261 (0.952–1.671)	0.106
Discordantly high RC	1.501 (1.175–1.918)	0.001	1.508 (1.182–1.925)	0.001	1.427 (1.093–1.863)	0.009
BMI						
<25.0		0.224		0.223		0.420
Discordantly low RC	REF		REF		REF	
Concordant	0.942 (0.653–1.359)	0.750	0.939 (0.651–1.355)	0.738	0.899 (0.614–1.317)	0.584
Discordantly high RC	1.284 (0.916–1.800)	0.147	1.283 (0.915–1.798)	0.149	1.170 (0.810–1.692)	0.402
≥25.0		0.002		0.002		0.042
Discordantly low RC	REF		REF		REF	
Concordant	1.059 (0.862–1.301)	0.585	1.059 (0.862–1.301)	0.585	1.027 (0.834–1.264)	0.804
Discordantly high RC	1.339 (1.127–1.590)	0.001	1.339 (1.127–1.590)	0.001	1.247 (1.034–1.505)	0.021
Moderate recreational activities						
Yes		0.012		0.034		0.171
Discordantly low RC	REF		REF		REF	
Concordant	1.127 (0.844–1.504)	0.419	1.117 (0.836–1.492)	0.454	1.078 (0.802–1.448)	0.621
Discordantly high RC	1.453 (1.131–1.867)	0.003	1.391 (1.081–1.789)	0.010	1.293 (0.982–1.702)	0.067
No		0.005		0.014		0.106
Discordantly low RC	REF		REF		REF	
Concordant	0.968 (0.770–1.216)	0.778	0.965 (0.768–1.212)	0.758	0.946 (0.751–1.193)	0.641
Discordantly high RC	1.307 (1.080–1.582)	0.006	1.268 (1.047–1.536)	0.015	1.186 (0.961–1.463)	0.111
Hypertension						
Yes		0.106		0.153		0.210
Discordantly low RC	REF		REF		REF	
Concordant	0.927 (0.705–1.220)	0.591	0.920 (0.699–1.211)	0.551	0.917 (0.694–1.211)	0.540
Discordantly high RC	1.188 (0.950–1.486)	0.132	1.161 (0.927–1.454)	0.194	1.147 (0.900–1.462)	0.267

(*Continued*)

Table 5. Continued.

Subgroups	Model 1		Model 2		Model 3	
	aOR (95% CI)	*P*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
No		0.006		0.015		0.075
Discordantly low RC	REF		REF		REF	
Concordant	1.079 (0.851–1.369)	0.529	1.081 (0.852–1.371)	0.523	1.062 (0.834–1.352)	0.624
Discordantly high RC	1.399 (1.131–1.730)	0.002	1.361 (1.100–1.684)	0.005	1.298 (1.030–1.635)	0.027
Diabetes						
Yes		0.908		0.942		0.546
Discordantly low RC	REF		REF		REF	
Concordant	1.009 (0.617–1.650)	0.970	1.020 (0.624–1.670)	0.936	1.085 (0.660–1.783)	0.747
Discordantly high RC	1.079 (0.716–1.626)	0.717	1.067 (0.707–1.611)	0.756	1.256 (0.811–1.945)	0.307
No		0.001		0.005		0.036
Discordantly low RC	REF		REF		REF	
Concordant	0.991 (0.816–1.204)	0.931	0.995 (0.819–1.209)	0.961	0.970 (0.797–1.182)	0.765
Discordantly high RC	1.322 (1.117–1.565)	0.001	1.290 (1.089–1.527)	0.003	1.221 (1.018–1.463)	0.031

SD: standard deviation; RC: remnant cholesterol; CI: confidence interval; aOR: adjusted odds ratio.
[a]Model 1: adjusted basic information for age, gender, race, marital status and education.
Model 2: model 1 further adjusted lifestyle factors for moderate recreational activities and BMI.
Model 3: model 2 further adjusted high risk factors for kidney stone formation for hypertension, diabetes, apolipoprotein B, blood urea nitrogen, serum uric acid and serum creatinine.

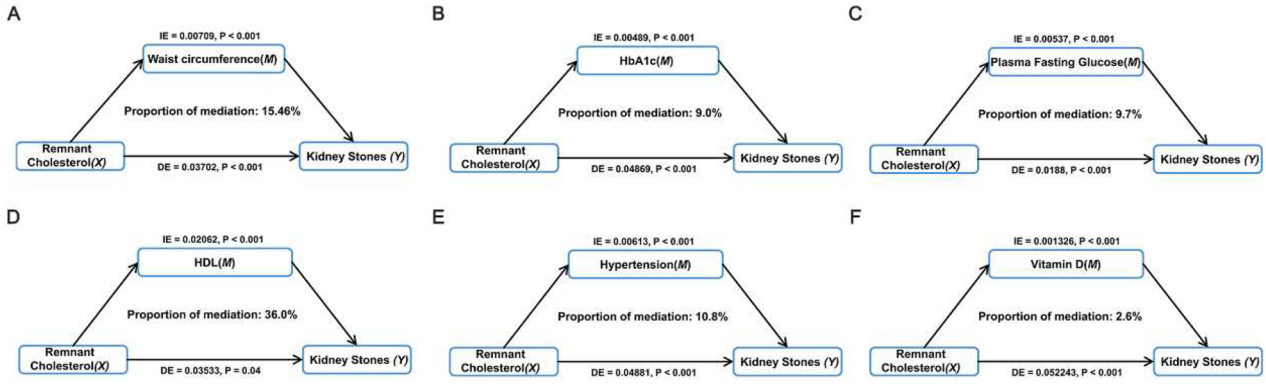

Figure 4. Mediation analysis of metabolic syndrome parameters and vitamin D levels on the interaction between RC and kidney stone risk.

and cancer-related mortality in patients [26]. In the general Chinese middle-aged and elderly population, higher RC was independently associated with an increased risk of prevalent chronic kidney diseases, including subjects with normal HDL-C, appropriate and high LDL-C, and no cardiovascular diseases events [10]. Several studies have identified the predictive role of RC in patients at high cardiovascular risk and in patients with angiographically confirmed cardiovascular disease in terms of poor outcomes [27, 28]. Elshazly et al. revealed that RC was associated with coronary atherosclerosis progression in patients treated with statins, independent of LDL-C and HDL-C [27]. In addition, high levels of RC were associated with increased all-cause mortality in patients with ischemic heart disease [17].

The pathophysiology of kidney stone formation is multifactorial and complicated and related to age, genetics, gender, race, diet and geographic location [29–31]. Association between serum vitamin D concentration and risk of kidney stone disease has been demonstrated [32]. In two randomized placebo-controlled clinical trials of concomitant vitamin D and calcium supplementation, kidney stone episodes were described as adverse events [33, 34]. It has been observed that in both uric acid and CaOx stone matrices contain high levels of cholesterol, cholesteryl esters, phospholipids and glycolipids. This indicated that lipids regulate the nucleation and aggregation involved in the crystal process of kidney stones [35]. Schmiedl et al. found by constructing an animal model that high fat diets induced acidic urine, which resulted in the formation of uric acid crystals and calcium-containing crystals [36]. In fact, epidemiological studies have demonstrated that metabolic syndrome is associated with kidney stones, and dyslipidemia has been widely recognized as an independent risk factor for kidney stone formation and recurrence [37–40]. A prospective cohort study with 7-year follow-up of patients revealed that hypertriglyceridemia increased the risk of

kidney stones [41]. In a study that included 655 stone formers and 1965 healthy controls, Kang et al. found that HDL-C and LDL-C levels were significantly lower in the stone formers group than in the control group [42]. In a study of a Chinese population, dyslipidemia was found to be associated with the risk of kidney stones, particularly in patients with CaOx stones [43].

Currently, an increasing number of studies have confirmed the involvement of oxidative stress and inflammation in the formation of kidney stones [2, 44, 45]. Low-grade inflammatory markers, including interleukins 6 and 8, tumour necrosis factor alpha, and C-reactive protein, have been demonstrated to be associated with RC [46, 47]. Considering the role of inflammation in the mechanism of kidney stone formation, we speculate that it may be partly responsible for the risk of kidney stones caused by high RC levels. And our findings provide a potential basis for studying the relationship between RC and the prevalence of kidney stones.

To the best of our knowledge, this was the first study to assess the relationship between RC levels and the risk of kidney stones in U.S. population. We found that RC levels have good performance as predictors of kidney stone occurrence through various analyses, which can inform individualized treatment and clinical decision making. Nevertheless, it should be considered that the current study includes several limitations as follows. First, this study was a retrospective study based on the NHANES database, and further prospective studies are required to explore the relationship between RC levels and kidney stones. Second, all data in this study pertain only to the U.S. population, and results may differ between regions and races. Third, although we incorporated potential confounders of stone formation wherever possible, there may still be unavailable confounders and thus potential selection bias and outcome bias. In addition, we were unable to obtain data on the type of kidney stones from the NHANES database. Finally, the results of the kidney stone history were based on data obtained from the participants' self-report, and recall bias could not be avoided. And we were unable to determine the temporal relationship between the measurement of remnant cholesterol and the eventual development of kidney stones.

Conclusion

Higher RC levels were associated with an increased risk of kidney stone incidence. The causal relationship between RC and kidney stone needs to be verified in more prospective studies.

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Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study used previously collected deidentified data, which was deemed exempt from review by the Ethics Committee of the People's Hospital of Yingshang.

Author contributions

LY and PY gathered the data for statistical purposes, performed the statistical analyses, checked the statistical accuracy, performed the literature search and wrote the first draft of the manuscript, revised and edited the final version of the manuscript and mentorship on every part of the research. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Disclosure statement

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Data availability statement

The datasets generated for this study are available on request to the corresponding author.

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