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Correlation of the lipid complex marker hs-CRP/HDL-C ratio with hyperuricaemia: a cross-sectional retrospective study from NHANES 2015–2018

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the high-sensitivity C-reactive protein (hs-CRP) to high-density lipoprotein cholesterol (HDL-C) ratio and hyperuricemia among the population of the United States, the ratio still has predictive value for cardiovascular disease in middle age. Methods 4,780 adult participators from the National Health and Nutrition Examination Survey (NHANES) were involved in this research. Through the NHANES laboratory testing, all biochemical indications were discovered. In order to observe the differences in indications, propensity score methods were used to match age and sex confounders.The relationship between hs-CRP/HDL-C ratio and hyperuricemia was explored using propensity matching and weighted multivariate logistic regression analysis, with the potential nonlinear relationship between hs-CRP/HDL-C ratio and hyperuricemia was investigated using a restricted cubic spline test. Results Sex, age, hypercholesterolaemia, diabetes, fasting glucose, cholesterol, high and low density lipoprotein, did not differ statistically significantly (P > 0.05); however, uric acid, triglycerides, high-density lipoprotein, CRP/HDL ratio, C-reactive protein, ethnicity, and hypertriglyceridemia differed (P < 0.05). In a weighted multifactor model, the relative odds ratio for hyperuricemia increased by 0.383 times at the second quintile (OR = 1.383, 95%CI(1.382–1.385), P < 0.001), 2.001 times at the third quintile (OR = 3.001, 95%CI (2.998–3.005), P < 0.001), and 2.533 times at the fourth quintile (OR = 3.533, 95%CI (3.529–3.538), P < 0.001). In the univariate and multivariate models, the restricted cubic spline test demonstrated a nonlinear correlation between the CRP/HDL ratio and hyperuricaemia, with a growing "log-function" shaped trend (P for overall < 0.001). Conclusion The hs-CRP/HDL-C ratio is significantly positively correlated with hyperuricemia among American adults. Maintaining the ideal hs-CRP/HDL-C ratio may contribute to reducing the burden of hyperuricemia.

Keywords Hyperuricemia, Hs-CRP/HDL-C ratio, Hs-CRP, HDL-C, NHANES, Propensity score matching

As a byproduct of purine metabolism, uric acid is primarily produced by the liver and eliminated by the kidney[1]. It emerges when nucleic acids and other purine-like substances from cellular metabolic catabolism are broken down[2,3]. Furthermore, a blood uric acid content ≥ 7.0 mg/dL in males and ≥ 6.0 mg/dL in females are considered as hyperuricemia[4], which is a risk factor for type 2 diabetes, dyslipidemia, cardiovascular diseases, etc. More importantly, hyperuricemia serves as a prelude to gout[5–8]. Due to changes in lifestyle caused by economic development, hyperuricemia has become more common in recent years. According to epidemiology, 21% of people worldwide had hyperuricemia as of 2016[9]. In America, the prevalence of gout reached 3.9% in 2015–2016 and is still rising annually[10,11], whereas the prevalence of hyperuricemia was 14.6% in the same year.

A novel composite marker to predict CVD is hs-CRP/HDL-C. Prior research has demonstrated that HDL-C has antioxidant properties and protects vascular endothelial cells by impeding the transfer of cholesterol[12,13]. HDL-C levels are inversely correlated with the risk of CVD[14]. Meanwhile, highly sensitive C-reactive protein (hs-CRP) has been shown to have the potential to predict short - or long-term CVD in patients with cardiovascular disease[15,16]. A research on the US population has revealed that the ratios of total cholesterol, triglycerides (TGs),

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low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) closely relate with serum uric acid levels[7]. It is found that Serum HDL-C levels are significantly negatively correlated with serum uric acid. Simultaneously, high sensitive C-reactive protein (hs-CRP) is significantly positively correlated with serum uric acid[17–19].

Currently, no research investigates the correlation between the CRP/HDL index and hyperuricemia. In view of this, our research serves to assess the pertinence through the data from the National Health and Nutrition Examination Survey (NHANES) subject population.

Methods

Data collection

The NHANES is a continuous survey that employs a stratified, multistage sample methodology to produce nationally representative estimations of nutritional and health variables. It publishes U.S. civilian data on a two-year cycle. The Centers for Disease Control and Prevention (CDC) are responsible for administering the NHANES sample. Moreover, the NHANES is a publicly accessible dataset that may be evaluated online (URL: http://www.cdc.gov/nchs/nhanes.htm). Every survey taker underwent a physical checkup at a mobile screening facility in addition to completing an interview at home. There is another publication that contains a thorough explanation of the NHANES approach. The NHANES procedure was authorized by the National Center for Health Statistics Research's Ethics Review Board. Additionally, written informed consent was offered by each participator.

Inclusion and exclusion of research objects are shown in Fig. 1. American adults at the age of 18 to 80 years old who partook in NHANES from 2015 to 2018 ($n = 4780$) were included in our study. The following criteria were used to exclude participants: (1) Participants under 18 years old or over 80 years old $n = 7377$; (2) Participants with deficient uric acid values $n = 1312$; (3) Participants with missing total cholesterol values $n = 6$; (4) Participants with missing triglyceride values $n = 5690$; (5) Participants with a low density lipoprotein deletion $n = 49$; (6) Participants with deletion of C-reactive protein values $n = 11$.

Socio-demographic characteristics, laboratory tests and definitions

Age, gender, and race (Mexican American, Hispanic, white, black, and other mixed) were all reported by the participants. Uricase oxidized uric acid to hydrogen peroxide and allantoin through a Synchron LX20 or UniCel R DxC800 Synchron (Beckman Coulter, Inc., USA), and serum uric acid levels were adopted to quantify blood uric acid values. Serum uric acid levels ≥ 7.0 mg/dL in males and ≥ 6.0 mg/dL in females were considered hyperuricemia[20]. Using known venipuncture protocols and methods, the NHANES constitutors took 3 ml or 5 mL of K3 EDTA anticoagulant whole blood from the total participators aged 18 and over. Enzymatic methods were used to determine the values of total cholesterol, HDL, LDL, and triglycerides. Hypercholesterolemia is defined as a fasting total cholesterol levels over 200 mg/dL. Hypertriglyceridemia is defined as a fasting triglyceride levels over 150 mg/dL. High LDL is defined as an LDL levels over 130 mg/dL[21]. The glucose oxidase

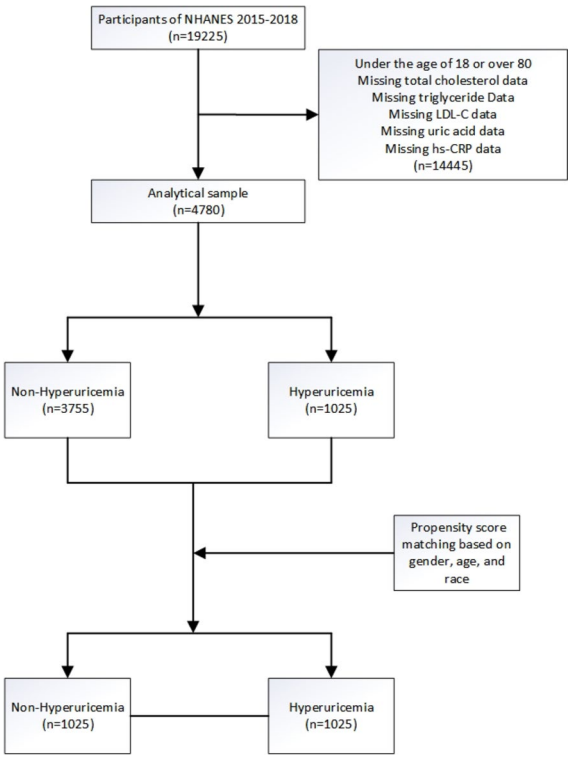

Fig. 1. Inclusion and exclusion of study subjects.

approach was employed to test the levels of blood glucose after a fast. Diabetes was regarded as fasting blood glucose levels of 140 mg/dL or higher[22]. The NHANES lab method was used to determine the C-reactive protein values in serum sample. The hs-CRP level (mg/L) was divided by the HDL-C level (mg/dL/1000) to obtain the CRP/HDL ratio, which was a marker of the inflammation-lipid complex[23]. The quartiles of the CRP/HDL ratio were used to divide the participants into four groups: groups 1, 2, 3 had hs-CRP/HDL-C ratios less than 14.32, 37.00, and 91.33, respectively, while group 4 had hs-CRP/HDL-C ratios greater than 91.33. Three age groups were established: 18–44, 45–59, and 60–80.

Statistical analysis

Due to the complex sampling design of NHANES, researchers used weights obtained from the official NHANES website to correct the sampling bias for the representativeness and reliability of the results. The Weight calculation formula of the sampling weight is: Fasting Subsample 2 Year MEC Weight (WTSAF2YR) /2. Categorical data were denoted by percentages. Besides, continuous data was denoted by means ± standard deviation. Normally distributed data was processed through one-way ANOVA, or abnormal distributed data was treated through the Kruskal-Wallis H test. In addition, the rank sum test was employed to assess the differences in continuous data, whilst the chi-square test was adopted to assess the differences in categorical data. Based on the quartile distribution of continuous data, weighted binary logistic regression of the hs-CRP/HDL-C ratios (< 14.32, 14.32–37.00, 37.00–91.33, ≥ 91.33) with uric acid was carried out. The CRP/HDL ratio with hyperuricemia was subjected to a restricted triple spline analysis to look into possible non-linear connections.The restricted cubic spline (RCS) test, is an approach to fitting and modeling continuous variables. A smooth curve was created by splitting the data into several intervals and using a cubic polynomial to fit within each interval. A linear model was established to observe whether there was a linear relationship between variables[24]. Firstly, the hs-CRP/HDL-C ratio was divided into quadricle categories according to inclusion and exclusion criteria, and then propensity score matching (PSM) was used according to sex, age, and race to optimize the subjects meeting the screening requirements with a caliper value of 0.02 without reset 1: 1 Matching. Further, weighted binary logistic regression was used for univariate analysis to estimate the correlation between hyperuricemia and the hs-CRP/HDL-C ratio; After that, the covariate was added to their variables, which included diabetes mellitus (yes, no), hypertriglyceridemia (yes, no), and LDL abnormality (high, normal). Then, weighted multifactorial analyses were performed to measure the relationship between the two variables. Such relationship was examined through a restricted cubic spline analysis curve (node = 4) to search for possible nonlinear relationships. The software R studio 4.3.0 was used to statistically analyze all of the data. Statistics were deemed significant if $P < 0.05$. Every test had two tails.

Results

A total of 2,050 adults were included in our research, involving 1,140 males and 910 females, as indicated in Table 1. Among them, the number of subjects with hyperuricemia was 1025 (50%), with 564 male patients occupying 49.5% of male participants and 461 female patients occupying 50.7% of female participants. Before PSM, only TC had no statistical significance, while HDL, TG, LDL, FBG, CRP, HDL/CRP, SUA, gender, age, diabetes, ethnicity, hypercholesterolemia, hypertriglyceridemia, elevated low-density lipoprotein, and HDL/CRP were statistically significant. After PSM, TC, LDL, FBG, elevated low-density lipoprotein, diabetes, hypercholesterolemia, age group and sex group were not statistically significant, while HDL, TG, CRP, SUA, HDL/CRP, HDL/CRP group, ethnicity group and hypertriglyceridemia group were statistically significant.

Table 2 displays the binary logistic regression results.In this study, both univariate and multivariate logistic regression results showed that the hs-CRP/HDL-C ratio was positively correlated with hyperuricemia. In a univariate model, the relative odds ratio for hyperuricemia was 0.471 times higher at the second quintile ($OR = 1.471$, 95%CI(1.469–1.473), $P < 0.001$), 2.363 times higher at the third quintile ($OR = 3.363$, 95%CI (1.469–1.473), $P < 0.001$) compared with the first quartile 95%CI(3.359–3.367), $P < 0.001$), and 3.034 times higher at the fourth quartile ($OR = 4.034$, 95%CI(4.030–4.039), $P < 0.001$). In the multivariate model with total cholesterol, triglyceride, low-density lipoprotein, and fasting blood glucose, the relative odds ratio of hyperuricemia increased by 0.383 times in the second quarter compared with the first quartile ($OR = 1.383$, 95%CI(1.382–1.385), $P < 0.001$). It was increased 2.001 times in the third quartile ($OR = 3.001$, 95%CI (2.998–3.005), $P < 0.001$) and 2.533 times in the fourth quartile ($OR = 3.533$, 95%CI (3.529–3.538), $P < 0.001$).

The restricted cubic spline test showed that there was a nonlinear relationship between hs-CRP/HDL-C ratio and hyperuricemia in both univariate and multivariate models, and the image showed a "log function" trend as the hs-CRP/HDL-C ratio increased. (P for overall < 0.001, P for nonlinear < 0.001)., as depicted in Fig. 2.

Discussion

In accordance with a U.S. population, this cross-sectional investigation revealed a significant pertinence between the CRP/HDL ratio and hyperuricemia. If the CRP/HDL ratio was higher, hyperuricemia would be also higher.

As shown in previous studies, Hs-CRP is the most sensitive biomarker of inflammation and correlated with uric acid[25–27]. For example, in a study about a Chinese population, hs-CRP as a risk predictor of asymptomatic hyperuricemia, was found to be elevated among patients with hyperuricemia[27]. Meanwhile, hs-CRP in hypertensive subjects was significantly higher in hyperuricemia patients than in normal subjects[26]. The possible mechanism is that the formation of monosodium urate crystals (MSU) due to elevated uric acid levels causes inflammation of joints and surrounding tissues[28,29]. Monosodium urate crystals are involved in the Caspase-1-activated NALP3 inflammasomes, resulting in the production of active IL-1β and IL-18[30,31], along with the elevated hs-CRP in patients with hyperuricemia. Significantly, our research further confirmed that inflammation played a key role in the pathogenesis of hyperuricemia.

Variable	Before PSM				After PSM			
	Non-HUA ($n=3755$)	HUA ($n=1025$)	Z/t/χ^2	*P*	Non-HUA ($n=1025$)	HUA ($n=1025$)	Z/t/χ^2	*P*
TC (mg/dL)	185.85 ± 40.82	188.54 ± 42.52	−1.808	0.071	188.90 ± 42.11	188.54 ± 42.52	0.196	0.845
TG (mg/dL)	84.00 (58.00, 126.00)	113.00 (79.00, 160.00)	−13.943	< 0.001*	89.00 (61.00, 128.00)	113.00 (79.00, 160.00)	−9.828	< 0.001*
LDL-C (mg/dL)	107.00 (85.00, 131.00)	110.00 (86.00, 135.00)	−2.289	0.022*	111.92 ± 36.73	112.80 ± 37.27	−0.615	0.538
HDL-C (mg/dL)	53.00 (44.00, 65.00)	47.00 (40.00, 57.00)	−11.692	< 0.001*	53.00 (44.00, 67.00)	47.00 (40.00, 57.00)	−9.209	< 0.001*
FBG (mg/dL)	102.00 (95.00, 112.00)	108.00 (99.00, 121.00)	−9.742	< 0.001*	103.00 (96.00, 114.00)	108.00 (99.00, 121.00)	−5.630	< 0.001*
UA (mg/dL)	5.00 (4.20, 5.70)	7.30 (6.80, 8.00)	−46.536	< 0.001*	5.00 (4.30, 5.80)	7.30 (6.80, 8.00)	−36.861	< 0.001*
hs-CRP (mg/L)	1.67(0.70,4.00)	2.94 (1.38,6.00)	−12.134	< 0.001*	1.70 (0.70, 4.10)	2.94 (1.38,6.00)	−9.944	< 0.001*
hs-CRP/HDL-C	31.11 (12.50,81.07)	62.69(26.90,130.88)	−13.762	< 0.001*	31.11 (12.00, 81.97)	62.69 (26.90, 130.88)	−11.282	< 0.001*
Race, n (%)			15.595	0.004			15.795	0.003
Mexican	617 (16.43)	134 (13.07)			139 (13.56)	134 (13.07)		
Hispanic	449 (11.96)	102 (9.95)			152 (14.83)	102 (9.95)		
White	1252 (33.34)	355 (34.63)			353(34.44)	355 (34.63)		
Black	783 (20.85)	257 (25.07)			205(20.00)	257 (25.07)		
Other Multiracial	654 (17.42)	177 (17.27)			176 (17.17)	177 (17.27)		
Ages, n (%)			78.301	< 0.001			4.607	0.100
18–44 years	1652 (43.99)	314 (30.63)			308 (30.05)	314 (30.63)		
45–59 years	903 (24.05)	243 (23.71)			284 (27.71)	243 (23.71)		
60–80 years	1200 (31.96)	468 (45.66)			433 (42.24)	468 (45.66)		
Gender, n (%)			24.034	< 0.001			0.285	0.594
Male	1742 (46.39)	564 (55.02)			576 (56.20)	564 (55.02)		
Female	2013 (53.61)	461 (44.98)			449 (43.80)	461 (44.98)		

Table 1. Baseline characteristics of participants. * is the rank sum test p-value.

hs-CRP/HDL-C ratio	Model 1					Model 2				
	β	S.E	Wald	*P*	OR (95% CI)	β	S.E	Wald	*P*	OR (95% CI)
Q1	-	-	-	-	1.00 (Reference)	-	-	-	-	1.00 (Reference)
Q2	0.386	0.001	377751.877	< 0.001	1.471(1.469–1.473)	0.352	0.001	260889.786	< 0.001	1.383 (1.382–1.385)
Q3	1.213	0.001	4113052.239	< 0.001	3.363 (3.359–3.367)	1.099	0.001	3229583.576	< 0.001	3.001 (2.998–3.005)
Q4	1.395	0.001	5245415.411	< 0.001	4.034(4.030–4.039)	1.262	0.001	4059027.216	< 0.001	3.533 (3.529–3.538)
P for trend	-	-	-	-	< 0.001	-	-	-	-	< 0.001

Table 2. Multivariate-adjusted correlations between hs-CRP/HDL-C ratio and HUA. Model 1: no cofounder. Model 2: adjusted for total cholesterol, triglycerides, low-density lipoprotein cholesterol, fasting blood glucose. OR, odds ratio; CI, confidence interval. In Model 1, compared with Q1, the incidence ratio of Q2-Q4 increased by 1.934, 3.364, and 3.692 times for each unit increase in *OR* value; In Model 2, when the OR value of Q2-Q4 increased by one unit, the incidence ratio increased by 1.868, 3.152, and 3.411 times, respectively, compared with Q1.

The association between high density lipoprotein (HDL) and hyperuricemia involves multiple molecular mechanisms. Studies have shown that the anti-inflammatory and antioxidant properties of HDL may be affected by hyperuricemia. Hyperuricemia may impair the function of HDL while reducing its anti-inflammatory and antioxidant abilities by increasing oxidative stress and inflammatory responses[30]. The formation of urate crystals is considered as an inflammatory stimulator that can activate the immune system, especially through the myeloid differentiation major reactive protein 88 (MyD88) pathway, which promotes the production of interleukin-1β (IL-1β) by inflammatory cells, thereby activating pro-inflammatory mechanisms triggering increased production of hs-CRP[32]. In addition, hyperuricemia is associated with multiple chronic inflammatory diseases, including cardiovascular disease, hypertension, metabolic syndrome, and chronic kidney disease, all of which are associated with the activation of inflammatory pathways (38). These molecular mechanisms reveal the complex interaction between HDL and hyperuricemia and may provide targets for future therapeutic strategies. Previous research has demonstrated a high correlation between dyslipidemia and hyperuricemia[7], and lipid levels may be a useful predictor of hyperuricemia. Retrospective research on a sizable American population reveal that HDL is inversely correlated with blood uric acid[7], while the total cholesterol, triglycerides, and LDL are all risk factors for hyperuricemia. Once more, the Chinese population showed this finding[33].

Meanwhile, another retrospective study about a large sample of the United States population showed a significant association between the serum uric acid to creatinine ratio and metabolic syndrome, particularly

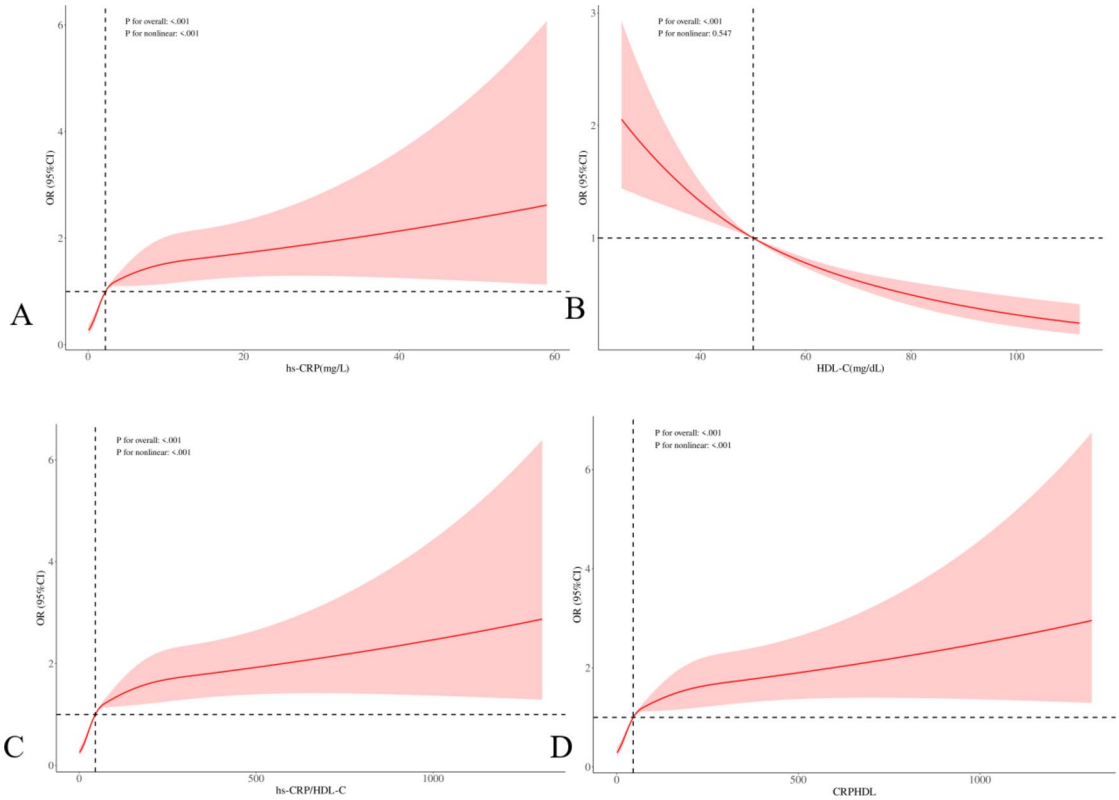

Fig. 2. Correlation of hs-CRP, HDL-C and ratios with hyperuricaemia. Figure A shows the dosage-response relationship between hs-CRP and hyperuricemia; Figure B shows the dose-response relationship with hyperuricemia; and Figure C (univariate) and Figure D (multivariate) show the dosage-response correlation between the CRP/HDL ratio and hyperuricemia.

with elevated triglyceride and low-density lipoprotein levels.The levels of serum triglycerides may be connected to this. Increased amounts of free fatty acids originate from catabolism and adenosine triphosphate, which is highly necessary for esterification or entry into other body tissues. This is, actually, caused by elevated serum triglyceride levels, which in turn promotes the synthesis of uric acid. Uric acid synthesis rises significantly in response to an increase in adenosine triphosphate. Disorders of lipid metabolism result from the production of a significant number of free radicals during the conversion of purines into uric acid, which in turn promotes LDL oxidation and lipid peroxidation in the body[34,35]. Insulin's suppression of plasma free fatty acid concentration falls when the elevated uric acid levels are caused by inhibition of NO synthesis, etc. This leads to an increase in LDL cholesterol formation and the hepatic synthesis of triglycerides. Insulin resistance also results in a decrease in lipoproteinase activity, a slowdown in the breakdown of LDL cholesterol, which raises its content even more, limits the conversion of LDL cholesterol to HDL cholesterol, reduces the HDL cholesterol concentration, and increase the lipid levels that culminates in hyperlipidemia[36,37].

It is worth noting that our research has several advantages. Firstly, it reduces biases and errors caused by sex, age, and race by using propensity score matching to match the subject population 1:1. Secondly, this is the first research to show a significant relationship ($n = 2050$) between the CRP/HDL ratio and hyperuricemia. Thirdly, the effectiveness and accuracy of the data were improved by using qualified staff to evaluate important data about the study respondents and conduct interviews in accordance with established protocols. But there are also drawbacks and imperfections in this research. The cross-sectional design restricted the causal relationship between the CRP/HDL ratio and hyperuricemia. Additionally, blood samples were collected only once in this experiment, which could only reflect the blood level during the collection period, but could not well reflect the long-term changes of blood. Further prospective longitudinal studies are needed to support these conclusions.

Conclusion

In summary, this study reveals that the hs-CRP/HDL-C ratio is a risk factor for hyperuricemia, with above variables positively correlated. RCS test shows a nonlinear relationship between hs-CRP/HDL-C ratio and hyperuricemia. These results suggest that the hs-CRP/HDL-C ratio may have predictive value for hyperuricemia, and that maintaining an ideal level of hs-CRP/HDL-C ratio may reduce the risk of hyperuricemia.

Data availability

Publicly available datasets were analyzed in this study.This data can be found here: [https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx? Component=Laboratory&CycleBeginYear=2017].

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Author contributions

Wei Jinfeng and Guo Jinhao drafted the manuscript, Yin Xianglin, Zheng Jiarui and Qiu Hongbin revised the manuscript. Wei Jinfeng and Guo Jinhao drew Figs. 1 and 2; Table 1, and 2.All authors reviewed and approved the final manuscript.

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Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Ethics statement

All data came from NHANES, which was approved by National Centre for Health Statistics Institutional Ethics Review Board, and all the subjects agreed on the survey and signed written consent. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Additional information

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