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Nonlinear association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and hyperuricemia in cancer patients: evidence from NHANES 2007–2018

Ran He[1†], Qilei Zhu[2†], Youjun Ye[2†], Shuaihang Chen[3] and Changsheng Xie[4*]

Abstract

Background Evidence shows that cancer patients are more likely to have hyperuricemia (HUA) compared to the general population, with lipid metabolism playing a significant role. However, it is still unclear whether there is a non-linear relationship between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and HUA in these patients. This study aims to explore the association between NHHR and HUA in cancer patients.

Methods This study included participants from the NHANES database from 2007 to 2018. We used multivariable logistic regression, restricted cubic splines (RCS) analysis, and subgroup analysis to examine the association between NHHR and HUA and gout in cancer patients, as well as to investigate differences in this association among specific subgroups.

Results A total of 2826 participants were included, with a HUA prevalence of 24.30%. Weighted multivariable logistic regression showed that for each unit increase in NHHR, the odds of HUA in cancer patients increased by 16% (95% confidence interval [CI]: 1.06, 1.29, $P=0.002$). When NHHR was divided into tertiles, those in the highest tertile (Q3) had a 1.84 times higher odds of developing HUA compared to those in the lowest tertile (Q1) (95% CI: 1.32, 2.58, $P<0.001$). However, there was no significant association with gout. RCS analysis further revealed a significant non-linear positive association, particularly among males. Subgroup analysis and interaction tests indicated a stronger association in cancer patients who did not have a history of stroke.

Conclusion There is a non-linear association between NHHR and HUA in cancer patients.

Keywords NHHR, Cancer, Hyperuricemia, Cross-sectional study, NHANES

†Ran He, Qilei Zhu and Youjun Ye contributed equally to this work and share first authorship.

*Correspondence:
Changsheng Xie
19913030@zcmu.edu.cn
Full list of author information is available at the end of the article

Introduction

Hyperuricemia (HUA) is a frequently encountered metabolic disorder in clinical settings, caused by either an overproduction or insufficient excretion of uric acid due to purine nucleotide metabolism. It is the primary cause of gout and is closely associated with an increased risk of cardiovascular diseases, kidney diseases, and metabolic syndrome [1]. Globally, approximately 20% of the population suffers from HUA [2], with about 5% affected by gout [3]. Despite regional differences in prevalence, the frequency of these conditions is notably increasing year by year [4].

Among cancer patients, abnormalities in uric acid metabolism are even more common, with growing evidence showing a significant association between cancer and HUA [5, 6]. Chronic inflammation in the tumor microenvironment can raise uric acid levels, while high uric acid promotes the recruitment of C-reactive protein and adiponectin, which further exacerbates inflammatory infiltration [7]. Additionally, the breakdown of tumor cells releases intracellular substances like nucleic acids and cytokines, whose catabolism contributes to HUA [8]. At normal levels, uric acid serves as a powerful antioxidant. However, at elevated intracellular levels, it acts as a pro-oxidant, activating inflammatory and metabolic pathways, disrupting metabolism, inhibiting autophagy, and fostering cancer progression [9, 10]. Moreover, HUA and gout adversely affect cancer outcomes, associating with increased cancer mortality. Thus, identifying markers that can indicate the likelihood of HUA in cancer patients from a new perspective is essential for clinical prevention and treatment.

The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) is a new lipid metabolism marker that reflects lipid metabolism status, particularly that involving high-density lipoprotein cholesterol (HDL-C). Recent findings highlight its superior diagnostic value over other lipid markers for assessing cardiovascular diseases, metabolic syndrome, fatty liver, and certain kidney diseases [11]. NHHR provides an effective measure of atherosclerosis severity, and there is a strong association between HUA and the development of atherosclerosis [12]. Individuals with HUA face significantly heightened risks of atherosclerotic events and mortality from coronary heart disease [13]. Recent research has shown that higher HDL-C levels are associated with a decreased likelihood of cancer, while higher levels of non-HDL-C cholesterol are associated with a increased likelihood of cancer [14, 15]. This suggests that NHHR could have valuable applications in the management of cancer patients. Therefore, using NHHR to evaluate cancer patients may have promising prospects.

There is a significant association between abnormal lipid levels and HUA. Research has confirmed the association between traditional lipid markers and HUA [16, 2]. Many studies have also highlighted that decreased HDL-C is an indicator for HUA [17], underscoring the clinical connection between lipid metabolism and HUA. Furthermore, studies focusing on cancer have employed the uric acid to HDL-C as a model to evaluate hepatic steatosis and predict the progression and intrahepatic recurrence of colorectal cancer liver metastasis [18]. Additional research indicates a positive association between lipid metabolism disorders and HUA in patients with clear cell renal cell carcinoma [19].

However, traditional lipid indicators often only reveal linear relationships and fail to account for the varying impacts on specific populations, leading to limitations and inconsistencies, therefore, NHHR may serve as a more accurate and comprehensive lipid metabolism marker for evaluating the association between cancer patients and HUA. Recent research has identified an association between higher NHHR and HUA [20]. However, there remains a gap in studying the relationship between lipid metabolism and HUA or gout in cancer patients. No studies have thoroughly investigated potential factors in these patients from a lipid metabolism perspective. Hence, developing new lipid metabolism assessment indicators and performing comprehensive and detailed evaluations is crucial. This study included data from the National Health and Nutrition Examination Survey (NHANES) database from 2007 to 2018, comprehensively exploring the potential relationship between NHHR and HUA in cancer patients through a large-scale cross-sectional study.

Method

Data source and study population

This study conducted a cross-sectional analysis of data from six cycles of the NHANES database covering the years 2007–2018. The NHANES database employs a complex probabilistic sampling method to collect nutritional and health information from the United States. All NHANES surveys are approved by the National Center for Health Statistics ethics review board, and participants provide informed consent. This study utilized publicly available data from the NHANES website. A total of 59,842 participants in the NHANES database from 2007–2018, we excluded 25,651 participants who were 20 years old or younger. Among the remaining participants, 3,368 had malignant tumors. The pathological mechanisms and metabolic pathways of hematologic malignancies differ significantly from those of solid tumors. During rapid progression or treatment, hematologic malignancies

often develop tumor lysis syndrome, which leads to elevated uric acid levels. Tumor lysis syndrome is likely to be accompanied by hypocalcemia and hyperkalemia, resulting in serious adverse outcomes such as arrhythmias and renal failure in a short period. Including patients with hematologic malignancies could introduce heterogeneity and increase data variability. To minimize these confounding factors, this study excluded 96 patients with hematologic malignancies, resulting in 3,272 solid tumor patients. After further excluding those missing data on uric acid, total cholesterol (TC), HDL-C, and gout status, 2,826 eligible participants were included in the final analysis. Details are shown in Fig. 1.

Definition of NHHR

Serum samples were collected from the subjects, and TC and HDL-C were measured using a series of enzymatic reactions. According to relevant studies, NHHR is calculated as the ratio of non-HDL-C to HDL-C, where non-HDL-C is determined by subtracting HDL-C from TC and includes LDL-C as well as residual cholesterol.

Definitions of HUA and gout

NHANES measured serum uric acid concentrations using the timed endpoint method on the DxC800 system. HUA was defined as serum uric acid levels $\geq$ 416 μmol/L (7.0 mg/dl) in men and $\geq$ 357 μmol/L (6.0 mg/dl) in women. Gout status was determined based on responses to the question "Have you ever been told by a doctor

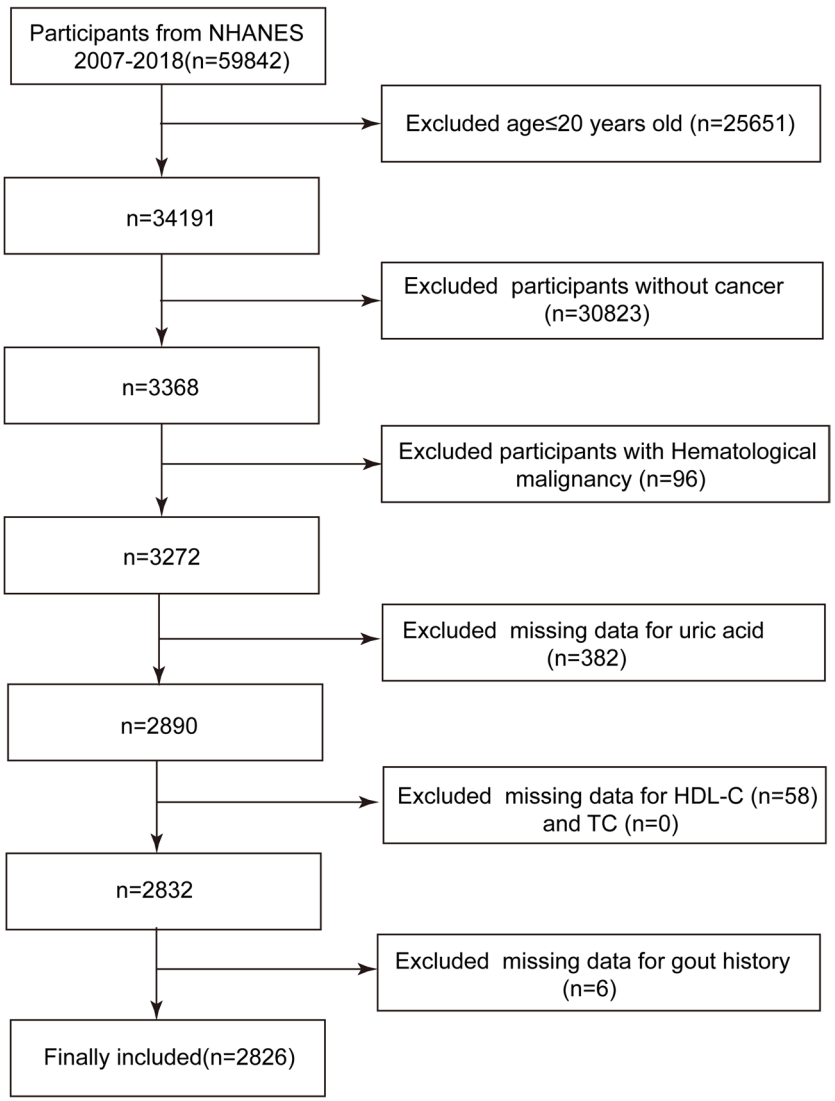

Fig. 1 Study flowchart

or other health professional that you had gout?" in the MCQ160N questionnaire.

Covariables

To investigate the independent association between NHHR and HUA in cancer patients, we accounted for a range of potential confounders that could influence this relationship. Demographic factors included age, sex, race, marital status, education level, and poverty-to-income ratio (PIR). A PIR less than 1 indicated relative poverty. Lifestyle factors included smoking and alcohol consumption. A drinking habit was defined as consuming at least 12 alcoholic drinks in the past year, and a smoking habit was defined as having smoked more than 100 cigarettes in the past. Physical measurements included Body mass index (BMI). Previous research has demonstrated that HUA can significantly impair kidney function and disrupt normal liver metabolism [21, 22], therefore, laboratory tests included estimated glomerular filtration rate (eGFR) and total bilirubin. The eGFR calculated using the CKD-EPI 2009 equation [23], which considers serum creatinine levels, sex, age, and race to determine GFR. Research has indicated that HUA is significantly associated with hypertension, diabetes, rheumatoid arthritis, and cardiovascular and cerebrovascular diseases [24–26], therefore, health conditions included hypertension, diabetes, coronary heart disease, heart failure, stroke, and arthritis. The criteria for including covariables in the regression equation are: 1. Statistically, covariables with a P-value < 0.1 in univariable screening are included. 2. If adding the covariables changes the effect size of NHHR and HUA in cancer patients by more than 10%, it is included. 3. Covariables identified by previous research as influencing the relationship between lipid metabolism and HUA are included.

Statistical analysis

Given that the NHANES database employs a multi-stage, complex sampling design, we included sample weights in this study to accurately reflect the United States population. Weight calculations were performed using the survey package in R. The mean and standard deviation describe continuous variables that follow a normal distribution, while the median and interquartile range describe those that do not. Percentages are used for categorical variables. For continuous variables, BMI, eGFR, total bilirubin, HDL-C, TC, and UA approximately follow a normal distribution and are analyzed using the weighted Student's t-test. Age does not follow a normal distribution and is analyzed using the weighted rank-sum test. Categorical variables are analyzed using the weighted chi-square test for statistical differences. To better understand the distribution of NHHR and compare differences across levels, NHHR was divided into three tertiles: Q1 (0.45–2.11), Q2 (2.11–3.11), and Q3 (3.11–15.03). For covariables with minor missing data, multiple imputation was carried out using the mice package in R. Sensitivity analysis on five iteratively generated datasets ensured the robustness of our results, with one dataset randomly selected to fill in missing values for subsequent analysis.

We employed multivariable logistic regression to examine the relationship between NHHR and HUA and gout in cancer patients. Weighted multivariable logistic regression analysis provided odds ratios (OR) and 95% confidence intervals (CI). Our analysis included three models: an unadjusted model (no covariable adjustment), adjusted Model 1 (adjusted for age, sex, race, education level, marital status, PIR, and BMI), and adjusted Model 2 (fully adjusted, including all variables in Model 1 plus smoking, drinking, eGFR, total bilirubin, hypertension, diabetes, coronary heart disease, heart failure, stroke, and arthritis). To evaluate potential non-linear relationships between NHHR and HUA in cancer patients, we used weighted restricted cubic splines (RCS) analysis in adjusted Model 2 and conducted further analysis on different subgroups. To ensure representative results, we included NHHR values within the 2.5–97.5% range. Using the Akaike information criterion, we determined that the optimal number of nodes, which minimized the Akaike information criterion value, was 3. At this point, the RCS model fit the best. The first node was at the 10th percentile, with an NHHR value of 1.408. The second node was at the 50th percentile, with an NHHR value of 2.586. The third node was at the 90th percentile, with an NHHR value of 4.488. To further explore the potential factors influencing NHHR and HUA in cancer patients, we included some s that might have an impact in the subgroup analysis. We conducted weighted regression analysis on Adjusted Model 2 to observe whether there were significant interactions between subgroups. All statistical analyses were conducted using R version 4.2.3, with a P-value < 0.05 considered statistically significant.

Results

Baseline characteristics of the study population

Based on the inclusion and exclusion criteria, 2,826 participants with cancer were included in the final analysis. The prevalence of HUA was 24.30%, and the prevalence of gout was 10.08%. The median age was 65 years, with men making up 47.10% of the participants. Stratification by NHHR tertiles revealed that, compared to the Q1 group, those in the Q3 group were more likely to be male, younger, have higher BMI, higher eGFR levels, more likely to consume alcohol, and more likely to have a history of stroke, all of which were statistically significant differences (P < 0.05). Additionally, the Q3 group had

significantly higher uric acid levels and a higher prevalence of HUA ($P<0.05$), but no significant difference in the prevalence of gout ($P=0.327$). These details are presented in Table 1. The total weighted sample size of this study was 20,901,106. We performed intergroup comparisons based on the presence or absence of HUA as a stratification factor and presented the weighted number of participants in each group (Supplementary Table 1). We also illustrated the distribution of various cancers in the study using pie charts, with non-melanoma skin cancer, prostate cancer, and breast cancer being the most common, as shown in Supplementary Fig. 1A. Among the more prevalent cancers, kidney cancer, lung cancer, and bladder cancer were associated with a higher likelihood of HUA, as depicted in Supplementary Fig. 1B.

Association between NHHR and HUA and gout in *cancer* patients

This study identified a significant association between NHHR and HUA in cancer patients, but no significant association with gout. Weighted multivariable logistic regression analysis revealed that in adjusted Model 2, each one-unit increase in NHHR was associated with a 16% increase in the likelihood of HUA (95% CI: 1.06, 1.29, $P=0.002$). However, there was no significant association with gout (OR = 1.07, 95% CI: 0.91, 1.25, $P=0.402$). We further analyzed the association between NHHR levels (Q1, Q2, Q3) and HUA in cancer patients. The results showed that in adjusted Model 2, patients in the Q3 group with the highest NHHR had 1.84 times higher odds of having HUA compared to the Q1 group with the lowest NHHR (95% CI: 1.32, 2.58, $P<0.001$). This association was significant in both adjusted Model 1 and the unadjusted Model, with trend tests for all three models also showing statistical significance. Detailed results are presented in Table 2. Furthermore, we conducted subgroup analyses on several cancers with larger sample sizes. The results showed that NHHR was significantly associated with HUA only in uterine and cervical cancer (OR = 1.33, 95%, 95% CI: 1.08, 1.63, $P=0.009$).

Nonlinear association between NHHR and HUA in cancer patients and specific subgroups

Using adjusted Model 2, we employed weighted RCS analysis to explore the potential nonlinear association between NHHR and HUA in cancer patients(Fig. 2). The results revealed a significant nonlinear association between NHHR and HUA (P for non-linearity = 0.004). When NHHR was below 2.59, a lower NHHR corresponded to a reduced likelihood of HUA (Fig. 2A). Considering the substantial impact of sex on the likelihood of HUA, we performed a weighted RCS analysis stratified by sex. For female cancer patients, the analysis showed a linear association between NHHR and HUA (P for non-linearity = 0.157), as shown in Fig. 2B. However, in male cancer patients, a nonlinear association was evident (P for non-linearity = 0.034). In this group, a lower NHHR was associated with a lower likelihood of HUA when NHHR was below 2.70 (Fig. 2C).

Subgroup analysis

To investigate whether the association between NHHR and HUA in cancer patients differs across various subgroups, we performed weighted interaction tests and subgroup analyses. The stratification factors included sex, age, education level, BMI, alcohol consumption, smoking status, history of stroke, coronary heart disease, heart failure, hypertension, and diabetes. The interaction tests revealed that significant statistical significance was found only in the history of stroke, particularly in patients without a history of stroke (OR = 1.21, 95% CI: 1.08, 1.34, P for interaction <0.001). This is detailed in Table 3. RCS analysis, stratified by stroke status, showed a negative association between NHHR and HUA in cancer patients with a history of stroke (Supplementary Fig. 2A). Conversely, in patients without a history of stroke, there was a significant nonlinear association between NHHR and HUA (Supplementary Fig. 2B).

Discussion

This large cross-sectional study, based on the NHANES database from 2007 to 2018, includes 2,826 cancer patients. Our findings reveal a significant positive association between NHHR levels and HUA in cancer patients, which persists and shows a trend when NHHR is divided into tertiles. However, there is no significant link between NHHR levels and gout. RCS analysis further highlights a notable nonlinear positive association, particularly evident in males. Subgroup analysis and interaction tests show that this association is more pronounced and demonstrates a nonlinear positive association in cancer patients without a history of stroke.

Previous epidemiological studies have reported that HUA, or gout, raises the likelihood of cancer [27], or have documented the likelihood of HUA in specific types of malignancies [28]. However, there is a lack of systematic reviews on the epidemiology of cancer complicated by HUA or gout. Research has indicated that patients with genitourinary cancers, including prostate cancer, bladder cancer, and kidney cancer, are more likely to have elevated uric acid levels [29]. In our study of 2,826 cancer patients, we found that those with kidney cancer, lung cancer, bladder cancer, breast cancer, colorectal cancer, and melanoma had a higher prevalence of HUA. This suggests that these cancers may have a greater propensity for developing HUA, underscoring the need for targeted

Table 1 Baseline study population characteristics

Characteristic	Total ($n=2826$)	Q1 (0.45–2.11, $n=942$)	Q2 (2.11–3.11, $n=942$)	Q3 (3.11–15.03, $n=942$)	*P*-value
Gender (%)					< 0.001
Male	1331 (47.10%)	390 (41.40%)	445 (47.24%)	496 (52.65%)	
Female	1495 (52.90%)	552 (58.60%)	497 (52.76%)	446 (47.35%)	
Age (year)	65 [54, 75]	68 [56, 77]	66 [56, 77]	62 [53, 72]	< 0.001
< 65	1114 (39.42%)	315 (33.44%)	345 (36.62%)	454 (48.20%)	< 0.001
≥ 65	1712 (60.58%)	627 (66.56%)	397 (63.38%)	488 (51.80%)	
Race(%)					0.210
Mexican American	198 (7.01%)	47 (4.99%)	71 (7.54%)	80 (8.49%)	
Other Hispanic	179 (6.33%)	45 (4.78%)	60 (6.37%)	74 (7.86%)	
Non-Hispanic White	1910 (67.59%)	636 (67.52%)	639 (67.83%)	635 (67.41%)	
Non-Hispanic Black	385 (13.62%)	160 (16.99%)	124 (13.16%)	101 (10.72%)	
Other Race	154 (5.45%)	54 (5.73%)	48 (5.10%)	52 (5.52%)	
Educational attainment (%)					0.010
Below high school	592 (20.95%)	178 (18.90%)	201 (21.34%)	213 (22.61%)	
High school	628 (22.22%)	186 (19.75%)	219 (23.25%)	223 (23.67%)	
Above high school	1606 (56.83%)	578 (61.36%)	522 (55.41%)	506 (53.72%)	
Marital status (%)					0.115
Married or Living with Partner	1688 (59.73%)	540 (57.32%)	572 (60.72%)	576 (61.15%)	
Divorced or Living without Partner	1138 (40.27%)	402 (42.68%)	370 (39.28%)	366 (38.85%)	
PIR (%)					0.659
< 1	440 (15.57%)	137 (14.54%)	133 (14.12%)	170 (18.05%)	
≥ 1	2386 (84.43%)	805 (85.46%)	809 (85.88%)	772 (81.95%)	
Body mass index (%)	29.27 ± 6.56	27.46 ± 6.48	29.48 ± 6.28	30.88 ± 6.48	< 0.001
< 25	751 (26.57%)	367 (38.96%)	233 (24.73%)	151 (16.03%)	< 0.001
≥ 25, ≤ 30	979 (34.64%)	310 (32.91%)	331 (35.14%)	338 (35.88%)	
> 30	1096 (38.78%)	265 (28.13%)	378 (40.13%)	453 (48.09%)	
Alcohol habit (%)					0.012
Yes	496 (17.55%)	161 (17.09%)	148 (15.71%)	187 (19.85%)	
No	2330 (82.45%)	781 (82.91%)	794 (84.29%)	755 (80.15%)	
Smoking habit (%)					0.091
Yes	779 (27.57%)	248 (26.33%)	241 (25.58%)	290 (30.79%)	
NO	2047 (72.43%)	694 (73.67%)	701 (74.42%)	652 (69.21%)	
Total bilirubin (μmol/L)	11.14 ± 5.22	11.28 ± 5.36	11.24 ± 5.32	10.89 ± 4.98	0.261
eGFR (mL/min/1.73 m^2)	78.96 ± 21.20	79.15 ± 21.36	77.50 ± 21.12	80.15 ± 21.07	0.124
Heart Failure (%)					0.576
Yes	205 (7.25%)	72 (7.64%)	66 (7.01%)	67 (7.11%)	
No	2621 (92.75%)	870 (92.36%)	876 (92.99%)	875 (92.89%)	
Coronary heart diease (%)					0.116
Yes	276 (9.77%)	109 (11.57%)	79 (8.39%)	88 (9.34%)	
No	2550 (90.23%)	833 (88.43%)	863 (91.61%)	854 (90.66%)	
Stroke (%)					0.022
Yes	251 (8.88%)	97 (10.30%)	77 (8.17%)	77 (8.17%)	
No	2575 (91.12%)	845 (89.7%)	865 (91.83%)	865 (91.83%)	
Arthritis (%)					0.604
Yes	1500 (53.08%)	506 (53.72%)	486 (51.59%)	508 (53.93%)	
No	1326 (46.92%)	436 (46.28%)	456 (48.41%)	434 (46.07%)	
Hypertension (%)					0.134
Yes	1638 (57.96%)	543 (57.64%)	535 (56.79%)	560 (59.45%)	
No	1188 (42.04%)	399 (42.36%)	407 (43.21%)	382 (40.55%)	

Table 1 (continued)

Characteristic	Total ($n=2826$)	Q1 (0.45–2.11, $n=942$)	Q2 (2.11–3.11, $n=942$)	Q3 (3.11–15.03, $n=942$)	*P*-value
Diabetes (%)					0.100
Yes	695 (24.59%)	214 (22.72%)	223 (23.67%)	258 (27.39%)	
No	2131 (75.41%)	728 (77.28%)	719 (76.33%)	684 (72.61%)	
HDL-C (mg/dl)	53.97 ± 17.04	68.17 ± 17.77	52.31 ± 11.07	41.43 ± 8.46	< 0.001
TC (mg/dl)	191.06 ± 43.35	173.20 ± 37.94	186.31 ± 37.39	213.66 ± 44.17	< 0.001
Uric acid (μmol/L)	334.03 ± 87.77	313.73 ± 85.05	335.42 ± 87.20	352.96 ± 86.68	< 0.001
Uric acid (mg/dl)	3.67 ± 0.98	3.43 ± 0.94	3.69 ± 0.97	3.91 ± 0.94	< 0.001
Gout (%)					0.327
Yes	285 (10.08%)	74 (7.86%)	104 (11.04%)	107 (11.36%)	
No	2541 (89.92%)	868 (92.14%)	838 (88.96%)	835 (88.64%)	
Hyperuricemia (%)					< 0.001
Yes	687 (24.31%)	170 (18.05%)	244 (25.90%)	273 (28.98%)	
No	2139 (75.69%)	772 (81.95%)	698 (74.10%)	669 (71.02%)	

Table 2 The association between NHHR, HUA and gout in patients with cancer

	Unadjusted Model	Adjusted Model 1	Adjusted Model 2
Outcome variables	OR (95%CI), *P*-value		
Gout	1.08 (0.96, 1.20), 0.195	1.06 (0.92, 1.22), 0.400	1.07 (0.91, 1.25), 0.402
HUA	1.14 (1.04, 1.25), 0.006	1.15 (1.04, 1.27), 0.005	1.16 (1.06, 1.29), 0.002
NHHR (Tertiles)			
Q1	Reference	Reference	Reference
Q2	1.69 (1.24, 2.28), 0.001	1.67 (1.20, 2.32), 0.003	1.64 (1.18, 2.29), 0.004
Q3	1.93 (1.45, 2.57), < 0.001	1.91 (1.38, 2.64), < 0.001	1.84 (1.32, 2.58), < 0.001
P for trend	< 0.001	< 0.001	< 0.001
Cancer subgroups			
Non-melanoma skin cancer	1.17 (0.96, 1.43), 0.124	1.10 (0.93, 1.31), 0.267	1.10 (0.92, 1.31), 0.280
Prostate cancer	1.10 (0.89, 1.35), 0.384	1.10 (0.89, 1.35), 0.379	1.11 (0.91, 1.36), 0.292
Breast cancer	1.05 (0.85, 1.29), 0.645	1.07 (0.83, 1.39), 0.593	1.17 (0.87, 1.56), 0.298
Uterine and cervical cancers	1.21 (1.03, 1.43), 0.024	1.26 (1.06, 1.50), 0.011	1.33 (1.08, 1.63), 0.009
Colorectal cancer	1.00 (0.74, 1.37), 0.983	1.06 (0.73, 1.54), 0.739	1.04 (0.61, 1.75), 0.885

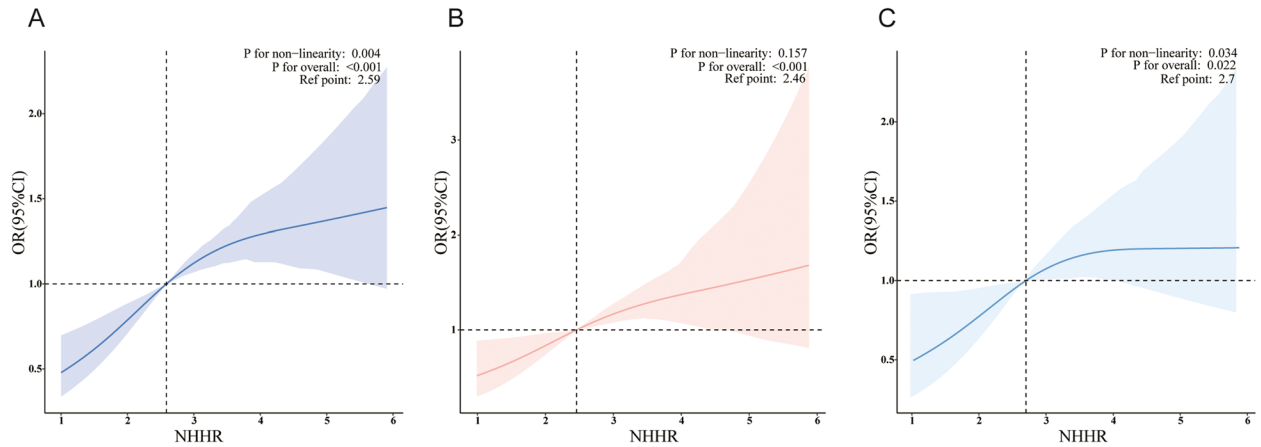

Fig. 2 **A** There is a nonlinear association between NHHR and HUA in cancer patients. **B** There is a linear association between NHHR and HUA in female cancer patients. **C** There is a nonlinear association between NHHR and HUA in male cancer patients

Table 3 Association between NHHR and HUA in subgroups

NHHR	HUA		
Subgroup	**OR (95% CI)**	***P*-value**	***P* for interaction**
Gender			0.639
Male	1.10 (0.97, 1.26)	0.130	
Female	1.22 (1.07, 1.39)	0.004	
Age			0.429
< 65	1.21 (1.05, 1.39)	0.008	
≥ 65	1.13 (0.99, 1.28)	0.065	
Educational attainment			0.326
Below high school	1.45 (1.16, 1.81)	< 0.001	
High school	1.15 (0.96, 1.38)	0.114	
Above high school	1.16 (1.02, 1.32)	0.025	
Body mass index			0.133
< 25	1.29 (1.01, 1.66)	0.044	
≥ 25, ≤ 30	1.00 (0.87, 1.15)	0.992	
> 30	1.26 (1.09, 1.44)	0.002	
Alcohol habit			0.604
Yes	1.11 (0.95, 1.29)	0.170	
No	1.19 (1.06, 1.34)	0.003	
Smoking habit			0.783
Yes	1.18 (1.02, 1.37)	0.024	
No	1.18 (1.04, 1.33)	0.011	
Stroke			< 0.001
Yes	0.82 (0.64, 1.04)	0.096	
No	1.21 (1.08, 1.34)	< 0.001	
Heart Failure (%)			0.092
Yes	0.92 (0.62, 1.38)	0.680	
No	1.18 (1.07, 1.31)	0.002	
Coronary heart diease			0.327
Yes	1.04 (0.71, 1.54)	0.821	
No	1.19 (1.07, 1.33)	0.001	
Hypertension			0.603
Yes	1.19 (1.06, 1.35)	0.004	
No	1.12 (0.96, 1.30)	0.138	
Diabetes			0.198
Yes	1.07 (0.91, 1.27)	0.384	
No	1.18 (1.04, 1.34)	0.003	

prognostic management and early intervention for these specific cancer types.

While previous research based on NHANES data has shown that higher NHHR is associated with an increased likelihood of HUA [20], our study is the first to specifically examine the nonlinear positive relationship between NHHR and HUA in cancer patients, indicating that NHHR might play a crucial role in the development of HUA among these patients.

Previous research on middle-aged and elderly populations in China identified that triglycerides and non-HDL-C are the most strongly associated lipid indicators with HUA [30]. Other studies have shown a significant independent association between dyslipidemia, especially elevated TC levels, and HUA [31]. Additionally, research on other lipid metabolism indicators, such as the triglyceride-glucose index, the triglyceride to HDL-C ratio, and residual cholesterol, has revealed linear positive associations with HUA [2, 16]. However, prior research on lipid indicators often focuses on single components, which are highly susceptible to fluctuations due to nutritional status, or primarily considers triglycerides without adequately accounting for the impact of cholesterol level fluctuations on HUA. NHHR, as a novel and comprehensive lipid metabolism indicator, shows a unique nonlinear positive relationship with HUA. This may provide greater value in the monitoring and prevention of HUA.

Cancer patients are often more susceptible to lipid metabolism disorders. Malignant cells consume more cholesterol to support their growth and proliferation, which leads to a decrease in HDL-C levels [32]. Additionally, studies have shown that the composition and functional properties of HDL-C in cancer patients are altered [33]. When cellular cholesterol levels drop, the *SREBP2* protein is cleaved and upregulates low-density lipoprotein receptor expression in the nucleus, promoting low-density lipoprotein absorption and increasing low-density lipoprotein cholesterol (LDL-C) levels [34].

Lipid metabolism disorders significantly affect uric acid levels. HDL-C is a key component of NHHR, and its reduction may impair glomerular filtration and insulin sensitivity, leading to an imbalance in uric acid metabolism [35, 36]. HDL-C also has strong anti-inflammatory properties, inhibiting endothelial inflammatory factors and downregulating xanthine oxidase gene expression, thus reducing uric acid production [37, 38]. Non-HDL-C, another major component of NHHR, includes LDL-C and residual cholesterol, which also affect uric acid metabolism. Elevated residual cholesterol increases free fatty acid production and utilization, enhancing ATP catabolism and increasing uric acid levels [39]. It can also induce insulin resistance, increasing uric acid reabsorption in the proximal renal tubules [40]. The imbalance between free radicals and antioxidants is a shared factor for lipid metabolism disorders and HUA in cancer patients [41], with LDL-C oxidation and lipid peroxidation leading to purine metabolism disorders and higher uric acid levels [42].

Notably, lipophilic statins like atorvastatin and simvastatin can lower serum uric acid levels [43] and promote cancer cell death through the mevalonate pathway, autophagy regulation, and ferroptosis induction [44]. However, there is limited literature on their shared

pathways. Uric acid-lowering drugs such as febuxostat and allopurinol can have anti-cancer effects by reducing oxidative stress and inflammation [45, 46], and can decrease the expression of lipid synthesis genes and their upstream regulators, addressing mitochondrial dysfunction caused by high uric acid, thereby lowering serum TC and LDL-C levels [47]. Both lipid disorders and uric acid metabolism imbalances are key features of metabolic syndrome, and their effects on cancer warrant further investigation.

Analyzing specific cancers with larger sample sizes among the 2,826 study participants, we found a significant association between NHHR and HUA in uterine and cervical cancers. Previous studies have shown that patients with uterine and cervical cancers have abnormal plasma lipid profiles, characterized by increased triglycerides, TC, and LDL-C, and decreased HDL-C [48, 49]. To support their rapid growth, tumor cells exhibit abnormal expression of lipid metabolism-related genes. Bioinformatics analyses have identified significant enrichment of lipid metabolism pathways in cervical cancer compared to normal cervical tissue, including glycerophosphate metabolism, arachidonic acid metabolism, and fatty acid metabolism [50]. Endometrial cancer also shows severe lipid metabolism disorders and changes in amino acids, inositol, and glutathione compared to healthy endometrial tissue, with characteristic increases in phosphocholine levels, activation of the insulin signaling pathway, upregulation of sterol regulatory element-binding protein-1, and changes in sphingolipid metabolism marked by increased ceramide levels [51]. These metabolic alterations directly or indirectly lead to HUA [52].

This study found a significant association between NHHR and HUA in cancer patients, but no direct significant association with gout. On one hand, asymptomatic HUA is more prevalent in the population, and the eventual development of gout is often influenced by factors such as age and physical condition [53]. On the other hand, gout is often accompanied by acute inflammatory infiltration and activation of innate immunity [54], and this reactive manifestation may obscure the potential intervention effects of NHHR. Regardless of whether HUA leads to gout, it significantly increases the risk of cardiovascular and kidney diseases [55]. Therefore, using NHHR to explore the association of HUA in cancer patients has clinical value for preventing complications.

Sex is a significant factor affecting the occurrence of HUA, with notably higher odds for males than females [56]. Therefore, we conducted a stratified RCS analysis by sex and found that NHHR and HUA exhibited a significant nonlinear positive association in male cancer patients, whereas a significant linear association was observed in females. This indicates that within a certain range, NHHR can more effectively reflect the likelihood of HUA in male cancer patients. Subgroup analysis and interaction tests revealed that NHHR was more sensitive to HUA in non-stroke cancer patients. This result suggests that, although both this study and previous studies indicate that HUA is a potential factor for stroke [57], NHHR has a stronger association with HUA in non-stroke cancer patients. This might be due to the disease changes in stroke itself masking the influence of NHHR, making it harder to observe this effect in the subgroup. Alternatively, it could be due to the relatively small sample size of stroke patients, potentially leading to insufficient statistical power.

Strengths and limitations

This study, using a large-scale cross-sectional design, is the first to report a nonlinear positive association between NHHR and HUA in cancer patients. By incorporating weights, considering multiple confounding variables, and employing multivariable regression equations, RCS analysis, and subgroup analysis, a comprehensive statistical analysis was conducted. It not only further confirmed the nonlinear positive association between NHHR and HUA in male cancer patients but also found that males and non-stroke populations might be more sensitive to this indicator. Furthermore, our subgroup analysis across various cancer types highlights that NHHR has a more pronounced association with HUA specifically in patients with uterine and cervical cancers.

However, this study has several limitations. As a cross-sectional study, it cannot clarify the causal relationship between NHHR and HUA in cancer patients. Additionally, since the NHANES database does not provide specific information about cancer patients, such as pathological type, clinical staging, or whether they are undergoing radiotherapy or chemotherapy, and it is not clear whether HUA occurred before or after the onset of cancer, further subgroup analysis is hindered. Moreover, advanced cancer patients frequently experience poor nutrition or cancer cachexia, leading to reduced NHHR levels. The absence of clinical staging data prevents us from performing a detailed subgroup analysis for these scenarios. Finally, other potential factors affecting HUA, such as a diet rich in purines, history of hyperthyroidism, and medication history, are not recorded in the NHANES database. Therefore, the conclusions of this study need to be further verified by prospective studies with more comprehensive clinical information and individual patient data.

Conclusion

This study identified a nonlinear association between NHHR and HUA in cancer patients, with no significant association found with gout. This association is particularly pronounced in patients with uterine and cervical cancer, male cancer patients, and cancer patients without a history of stroke. Therefore, prevention of HUA in cancer patients, especially those without symptomatic gout, may benefit from maintaining NHHR levels within a reasonable range.

Abbreviations

BMI	Body mass index
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
HUA	Hyperuricemia
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
NHANES	National Health and Nutrition Examination Survey
NHHR	Non-HDL-C and HDL-C ratio
OR	Odds ratio
PIR	Poverty-to-income ratio
RCS	Restricted cubic splines
TC	Total Cholesterol

Supplementary Information

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Supplementary Material 1. Supplementary Fig. 1 (A) Distribution of cancer types among study participants. (B) Prevalence of HUA among different cancer types.

Supplementary Material 2. Supplementary Fig. 2 (A) There is a relationship between NHHR and HUA in stroke cancer patients. (B) There is a nonlinear relationship between NHHR and the presence of HUA in non-stroke cancer patients.

Supplementary Material 3. Supplementary Table 1 Baseline study population characteristics (weighted).

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Authors' contributions

Ran He created the study subject and handled data analysis, Youjun Ye and Qilei Zhu advanced the article's conceptualization and writing, Shuaihang Chen contributed to literature checks and data visualization. Changsheng Xie directed the article's writing direction. The submission of the manuscript was reviewed and approved by all authors.

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Availability of data and materials

All data used in this study were sourced from NHANES, www.cdc.gov/nchs/NHANEs/.

Declarations

Ethics approval and consent to participate

The NHANES protocol was approved by the Ethics Review Board of the National Center for Health Statistics. Each participant provided written informed consent during the survey. The NHANES study protocol complies with the ethical principles of the Helsinki Declaration of 1975 and obtained informed consent from all participants. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cross-sectional studies and is a secondary analysis of the NHANES database.

Competing interests

The authors declare no competing interests.

Author details

[1]The First School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, China. [2]The Third Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, China. [3]The Second Clinical Medical College of Zhejiang, Chinese Medical University, Hangzhou, China. [4]Department of Medical Oncology, Zhejiang Provincial Hospital of Traditional Chinese Medicine), The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China.

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