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Non-linear association of a novel inflammation-lipid composite marker CRP/HDL with insulin resistance and type 2 diabetes: findings from a comprehensive national cross-sectional study

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Abstract

Background Chronic low-grade inflammation and dyslipidemia are central to the development of insulin resistance (IR) and type 2 diabetes (T2D). The ratio of high-sensitivity C-reactive protein (hs-CRP) to high-density lipoprotein cholesterol (HDL-C) integrates these factors, potentially serving as a novel biomarker for metabolic risk. However, the combined impact of these markers on the risks of IR and T2D has not been thoroughly examined. This study aims to elucidate the relationship between the hs-CRP/HDL-C ratio and the risks of IR and T2D.

Methods The cross-sectional methodology of this investigation is underpinned by data procured from the National Health and Nutrition Examination Survey (NHANES), encompassing a sample of 4,928 individuals from 2015 to 2018. The outcome variables were IR and T2D, as defined by the 2013 guidelines of the American Diabetes Association. To thoroughly investigate the association, a variety of analytical techniques were employed. These included weighted multivariate linear regression, weighted multivariate logistic regression, and restricted cubic spline (RCS) models to capture potential nonlinear associations between the hs-CRP/HDL-C ratio and outcomes. Subgroup analyses were also conducted.

Results After controlling for multiple potential confounders, the ratio correlates with an escalated likelihood of of IR (OR = 2.46, 95% CI: 1.78, 3.40) and T2D (OR = 2.45, 95% CI: 1.48, 4.05). An inverted U-shaped, nonlinear relationship was identified between the ratio and IR, while a nonlinear association was also observed for T2D. However, the non-linear correlation between this ratio and T2D is more pronounced in individuals with hypertension, female, and non-drinkers.

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Conclusions The hs-CRP/HDL-C ratio exhibits a postive correlation with IR and T2D. These findings suggest that hs-CRP/HDL-C ratio has the potential to be used as biomarker for assessing IR and T2D risk in clinical settings. These results highlight the significance of keeping the hs-CRP/HDL-C ratio within optimal ranges to promote metabolic health, particularly among high-risk groups. **Keywords**: hs-CRP/HDL-C ratio, Type 2 diabetes, Insulin resistance, NHANES.

Introduction

Insulin resistance (IR) and type 2 diabetes (T2D) are critical components of the metabolic syndrome, significantly increasing the risk of cardiovascular diseases (CVD) [1]. These metabolic abnormalities often coexist with chronic low-grade inflammation and dyslipidemia, both of which play a role in the development of atherosclerotic cardiovascular disease [2]. High-sensitivity C-reactive protein (hs-CRP) is commonly recognized as an indicator of systemic inflammation, while high-density lipoprotein cholesterol (HDL-C) is acknowledged for its anti-inflammatory properties and its protective role against cardiovascular complications [3, 4]. The ratio of hs-CRP/HDL-C combines these inflammatory and lipid parameters, possibly offering a broader understanding of the metabolic irregularities linked to IR and T2D.

Consistently elevated levels of hs-CRP have been associated with a higher incidence of T2D [5]. Conversely, HDL-C plays a crucial role in reverse cholesterol transport and exhibits anti-inflammatory effects, which are protective against IR and T2D [6]. Thus, the hs-CRP to HDL-C ratio reflects the equilibrium between pro-inflammatory and anti-inflammatory factors, which may make it a significant biomarker for evaluating metabolic health. This dual representation could provide a more comprehensive view of the underlying metabolic dysfunctions that are not captured by traditional markers. Prior studies have predominantly focused on the individual components of this ratio rather than their collective impact [7]. Additionally, the complex dose-response relationships between the ratio and metabolic outcomes remain insufficiently explored, which may impede a more profound understanding of the true connection and clinical significance of this biomarker. In addition, identifying the dose-response relationships can enhance the understanding, diagnosis, and treatment of metabolic diseases by developing more accurate diagnostic tools and treatment strategies.

This study aims to examine the relationship between the ratio and IR as well as T2D, utilizing a nationally representative sample obtained from the National Health and Nutrition Examination Survey (NHANES) database. Through this analysis, we aim to clarify the potential of the ratio as a readily available clinical marker for IR and T2D, thereby aiding in improved risk assessment and management of these disorders.

Methods

Data source and study sample

The NHANES is a thorough evaluation of the non-institutionalized U.S. civilian population, overseen by the National Center for Health Statistics (NCHS). This survey employs a stratified, multi-stage probability sampling technique across various subgroups and is carried out every two years [8]. The survey encompassed multiple facets, including face-to-face household interviews designed to gather demographic, socioeconomic, nutritional, and health-related information [9, 10]. The NCHS Ethical Review Committee routinely evaluates and approves the NHANES protocol, and every participant provides their written informed consent [11].

The information for this cross-sectional research was gathered from the NHANES database, screening two sequential periods (2015–2016 and 2017–2018), totaling 19,225 participants. The rationale for selecting these two datasets lies in the fact that hs-CRP data was obtained through distinct experimental methods and equipment. Individuals excluded from the study were those who did not attend a MEC visit, were under 18 years old, had a BMI of 18.5 kg/m^2 or less, were potential type 1 diabetes patients (under 20 years old relying solely on insulin therapy) [12], or lacked sufficient data on independent or dependent variables [13]. Ultimately, a total of 4,928 participants with fully completed datasets were incorporated into the analysis (Fig. 1).

Study variables and outcome

The variable for exposure in this research was established by calculating the ratio of hs-CRP(mg/L) levels to HDL-C(mg/dL) levels [14]. HDL-C levels were measured through enzymatic assays utilizing the Roche/Hitachi Cobas 6000 Analyzer. hs-CRP concentrations were determined using the highly sensitive Near Infrared Particle Immunoassay rate methodology, employing the Beckman Coulter UniCel DxC 600 Synchron and the Beckman Coulter UniCel DxC 660i Synchron Access chemistry analyzers. Subsequently, all subjects were categorized into four separate groups in accordance with the quartiles of the ratio. The variables for outcomes encompassed IR and T2D, as well as T2D risk markers such as glycosylated hemoglobin (HbA1c, %), fasting plasma glucose (FPG, mmol/L), homeostasis model assessment of insulin resistance (HOMA-IR) and the fasting serum insulin (FSI, pmol/L). HOMA-IR was computed using

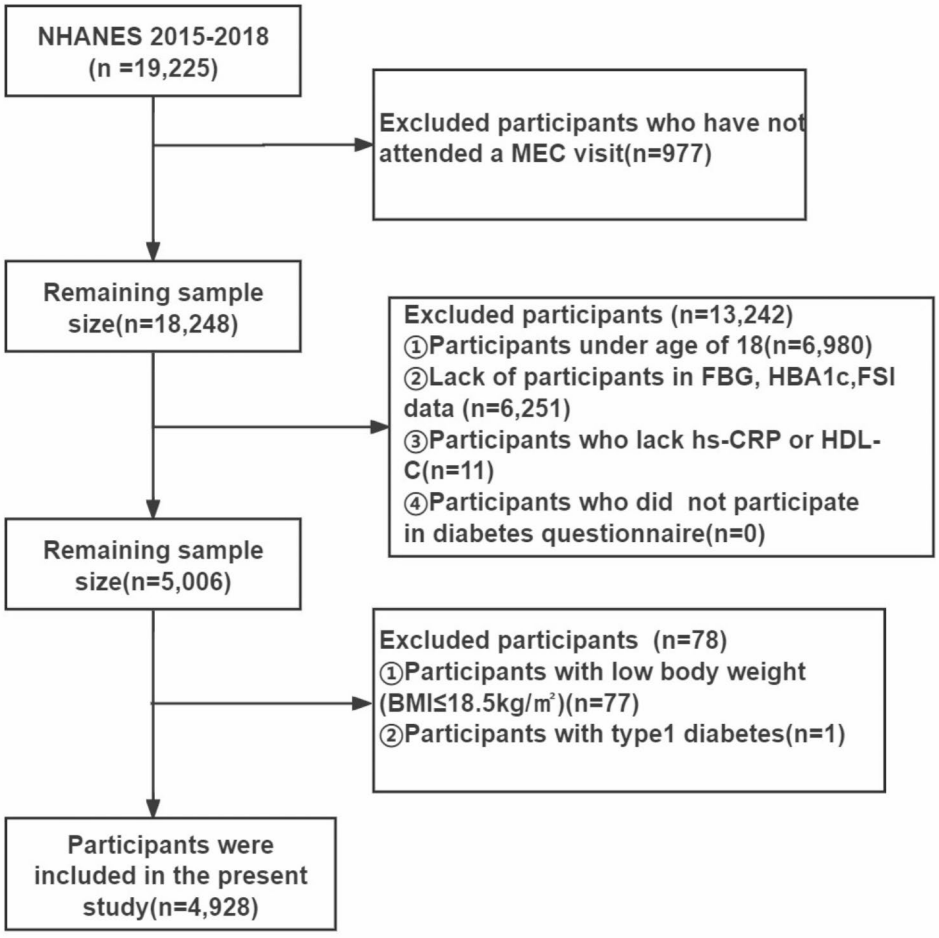

Fig. 1 Flow chart of the sample selection from National Health and Nutrition Examination Survey (NHANES) 2015–2018

the equation: [FPG (mmol/L) * FSI (μU/ml)] / 22.5 [15]. Consistent with previous research, a HOMA-IR value greater than 2.6 was considered indicative of IR in the general U.S. population [16]. In this study, T2D was defined based on relevant questionnaires and laboratory tests, which included an FPG level of 7.0 mmol/L (126 mg/dL) or higher, a 2-hour plasma glucose reading of 11.1 mmol/L (200 mg/dL) or more following an oral glucose tolerance test, an HbA1c level of 6.5% or greater, self-reported T2D status, or active use of hypoglycemic medication [11, 17].

Covariates

Drawing from earlier studies and clinical knowledge, we included the subsequent covariates: age, gender, race/ethnicity, educational attainment, smoking habits, alcohol intake, hypertension, the household income poverty index (PIR), body mass index (BMI), hemoglobin (Hb, g/dL), serum uric acid (SUA, μmol/L), serum creatinine(SCr, μmol/L), gamma-glutamyl transpeptidase (γ-GGT, U/L), alanine aminotransferase (ALT, U/L), and total cholesterol (TC, mmol/L).

The classification of race consisted of five categories: individuals of Mexican American descent, those identifying as Other Hispanic, Non-Hispanic White individuals, Non-Hispanic Black individuals, and those classified as Others, with the others category encompassing all other non-Hispanic racial individuals. Educational levels were segmented into three categories: less than high school, high school or its equivalent, and college or higher. Following the standards set by the World Health Organization, BMI was divided into three categories: normal weight (18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2), overweight (25 $kg/m^2 \leq$ BMI < 30 kg/m^2), and obesity (BMI ≥ 30 kg/m^2) [18]. Participants were classified according to their smoking behaviors into three categories: current smokers, which includes individuals who have smoked more than 100 cigarettes in their lifetime and currently smoking on some days or every day and non-active smokers (including never smokers [fewer than 100 cigarettes in their lifetime] or former smokers[more than 100 cigarettes in their lifetime but not currently smoking]) [19]. Alcohol intake was classified into two groups: drinkers, defined as those who have more than 12 beverages annually, and

non-drinkers, who consume 12 or fewer drinks each year [20]. Hypertension was characterized according to the criteria set forth by the 2017 American Heart Association Blood Pressure Guidelines. Specifically, Specifically, individuals were diagnosed with hypertension if their systolic blood pressure (SBP) was 140 mmHg or above, and/or their diastolic blood pressure (DBP) was 90 mmHg or greater. Additionally, individuals may also be classified as hypertensive if they self-report a history of hypertension and were currently utilizing antihypertensive medications [21].

Statistical analysis

In order to achieve results that were representative of the entire national population, suitable weighting methods were employed to address the intricate sampling design, as suggested by NHANES Guidelines [22]. The participants of the study were categorized into four distinct groups with reference to the quartiles of the ratio, labeled as Q1 through Q4, to identify varying levels of IR and T2D risk and inform tailored clinical interventions. The fundamental attributes of categorical variables were displayed as frequencies and proportions (%), whereas continuous variables were depicted using means and standard deviations (SD). Group comparisons were carried out utilizing the rank-sum test and the chi-squared test. In order to investigate the association between the ratio and the probability of IR as well as T2D, multivariable logistic regression was executed through three separate models. Model 1 employed a univariate logistic regression approach to analyze the data; Model 2 adjusted for age, race, gender, PIR, and education level; and Model 3 included hypertension, BMI, smoking, drinking, TC, ALT, γ-GGT, Cr, UA and Hb additional adjustments. To explore the dose-response association, a restricted cubic spline (RCS) analysis with four knots was employed. The four knots were placed at the 5th, 35th, 65th, and 95th percentiles of the data distribution.

Three weighted multiple linear regression models were developed to examine the relationship between the ratio of hs-CRP/HDL-C and T2D risk markers (HbA1c, FPG, FSI, HOMA-IR). Furthermore, analyses of subgroups and interactions were conducted, categorized by sex(male/female), BMI classification (normal, overweight, obese), alcohol intake (no/yes), smoking history(never/former/current), and race (White, Black, Hispanic, Mexican, or Others) and hypertension status (no/yes) through the application of weighted multivariable logistic regression models. The stratified variables were also taken into account as possible effect modifiers. For the primary analysis, we utilized multiple imputation through "MICE" package in R software to address the issue of missing covariate data. On average, under 20% of the data was missing. To address the missing baseline data, we employed multiple imputation using five imputed datasets. These datasets were then averaged to create a final imputed dataset for analysis. We conducted a series of sensitivity analyses to confirm the robustness of our results. Weighted non-imputed data were used to reevaluate the association between the ratio and both IR and T2D. Furthermore, following the exclusion of patients with diabetes, the connection between the ratio and markers indicative of T2D risk was analyzed again. A *P*-value of less than 0.05, derived from a two-tailed test, was deemed to represent statistical significance for our research. All analyses were conducted using R version 4.3.2 (http://www.R-project.org).

Results

Weighted baseline characteristics of the study population

The detailed baseline characteristics were demonstrated in Table 1. The research involved 4,928 participants with an average age of 48.00 ± 17.54 years old, of whom 51.46% were female and 48.54% were male. In contrast to those in the lower ratio group(Q1), individuals within the highest quartile (Q4) were more frequently female, Non-Hispanic White, and non-smokers, along with having a higher occurrence of hypertension. Interestingly, individuals exhibiting elevated hs-CRP/HDL-C ratio showed a higher occurrence of T2D and IR, with all *P* values being less than 0.05.

Association between ratio of hs-CRP/HDL-C and risk markers of T2D

In fully adjusted comprehensive multivariate linear regression models, a significant positive correlation was found between the ratio and FPG (β = 2.6, 95% CI: 1.8, 3.4), HbA1c (β = 0.09, 95% CI: 0.06, 0.11), FSI (β = 1.5, 95% CI: 0.77, 2.3), as well as HOMA-IR (β = 0.51, 95% CI: 0.24, 0.78, all $p < 0.05$). This trend continued to be statistically significant throughout the quartiles of the ratio, as those in the Q2, Q3, and Q4 exhibited increasingly elevated levels of FPG, FSI, HbA1c, and HOMA-IR in comparison to the Q1 (all p for trend < 0.0001, Table 2).

Relationship between ratio of hs-CRP/HDL-C and IR

In multivariate logistic regression analyses, an elevated ratio of hs-CRP/HDL-C consistently showed a significant association with increased IR risk (OR = 2.46, 95% CI: 1.78, 3.40, $p < 0.001$). It is important to note that higher levels of the ratio corresponded with an increasing risk of IR when compared to the Q1 in all analyzed models (P for trend < 0.001). Detailed findings are presented in Table 3.

Association of the hs-CRP/HDL-C ratio withT2D

In the multivariate logistic regression analyses, the positive association between the ratio and the prevalence of

Table 1 Weighted baseline characteristics of the study population

Characteristic	Overall, *N* = 4928 (100%)	Q1, *N* = 1145 (25%)	Q2, *N* = 1200 (25%)	Q3, *N* = 1245 (25%)	Q4, *N* = 1338 (25%)	*P* Value
Age, (years)	48.00 ±(17.54)	44.00 ±(18.10)	50.00 ±(17.74)	49.00 ±(17.36)	48.00 ±(16.58)	< 0.001
Gender, n (%)						**< 0.001**
female	2,536.00 (51.46%)	574.00 (50.13%)	579.00 (48.25%)	614.00 (49.32%)	769.00 (57.47%)	
male	2,392.00 (48.54%)	571.00 (49.87%)	621.00 (51.75%)	631.00 (50.68%)	569.00 (42.53%)	
Race, n (%)						**< 0.001**
Mexican American	789.00 (16.01%)	128.00 (11.18%)	211.00 (17.58%)	218.00 (17.51%)	232.00 (17.34%)	
Other Hispanic	569.00 (11.55%)	97.00 (8.47%)	127.00 (10.58%)	164.00 (13.17%)	181.00 (13.53%)	
Non-Hispanic White	1,657.00 (33.62%)	368.00 (32.14%)	423.00 (35.25%)	433.00 (34.78%)	433.00 (32.36%)	
Non-Hispanic Black	1,073.00 (21.77%)	255.00 (22.27%)	225.00 (18.75%)	237.00 (19.04%)	356.00 (26.61%)	
Others	840.00 (17.05%)	297.00 (25.94%)	214.00 (17.83%)	193.00 (15.50%)	136.00 (10.16%)	
PIR	2.88 ±(1.61)	3.45 ±(1.60)	3.13 ±(1.60)	2.68 ±(1.59)	2.42 ±(1.57)	**< 0.001**
Education levels, n(%)						**0.002**
Less than high school	1,083.00 (21.98%)	200.00 (17.47%)	266.00 (22.17%)	293.00 (23.53%)	324.00 (24.22%)	
High school or equivalent	1,117.00 (22.67%)	239.00 (20.87%)	262.00 (21.83%)	284.00 (22.81%)	332.00 (24.81%)	
College or more	2,728.00 (55.36%)	706.00 (61.66%)	672.00 (56.00%)	668.00 (53.65%)	682.00 (50.97%)	
Alcohol consumption, n (%),						0.2
Drinker	3,629.00 (73.64%)	857.00 (74.85%)	877.00 (73.08%)	929.00 (74.62%)	966.00 (72.20%)	
Non-drinker	1,299.00 (26.36%)	288.00 (25.15%)	323.00 (26.92%)	316.00 (25.38%)	372.00 (27.80%)	
BMI(kg/m2)	28.30 ±(7.01)	24.20 ±(4.14)	27.40 ±(5.08)	29.69 ±(6.15)	33.85 ±(8.11)	**< 0.001**
Diabetes, n %	1,184.00 (24.03%)	158.00 (13.80%)	228.00 (19.00%)	338.00 (27.15%)	460.00 (34.38%)	**< 0.001**
Hypertension, n %	4,708.00 (95.54%)	1,058.00 (92.40%)	1,156.00 (96.33%)	1,195.00 (95.98%)	1,299.00 (97.09%)	**0.003**
Smoking status, n %						**0.001**
current smoking	900.00 (18.26%)	182.00 (15.90%)	187.00 (15.58%)	227.00 (18.23%)	304.00 (22.72%)	
former smoking	1,169.00 (23.72%)	235.00 (20.52%)	279.00 (23.25%)	311.00 (24.98%)	344.00 (25.71%)	
never smoking	2,859.00 (58.02%)	728.00 (63.58%)	734.00 (61.17%)	707.00 (56.79%)	690.00 (51.57%)	
IR						**< 0.001**
No	2,560.00 (51.95%)	872.00 (76.16%)	717.00 (59.75%)	573.00 (46.02%)	398.00 (29.75%)	
Yes	2,368.00 (48.05%)	273.00 (23.84%)	483.00 (40.25%)	672.00 (53.98%)	940.00 (70.25%)	
SCr (umol/L)	74.26 ±(29.16)	74.26 ±(22.44)	76.02 ±(19.90)	74.26 ±(31.54)	71.60 ±(38.81)	**0.001**
ALT (U/L)	20.00 ±(16.92)	18.00 ±(16.48)	20.00 ±(14.32)	20.00 ±(15.62)	21.00 ±(20.30)	**0.001**
γ-GGT (U/L)	19.00 ±(34.77)	15.00 ±(26.44)	19.00 ±(39.35)	21.00 ±(29.39)	23.00 ±(40.51)	**< 0.001**
SUA (umol/L)	321.20 ±(83.29)	291.50 ±(74.38)	315.20 ±(77.65)	333.10 ±(82.62)	339.00 ±(90.19)	**< 0.001**
Hb (g/dL)	14.30 ±(1.47)	14.30 ±(1.34)	14.50 ±(1.53)	14.50 ±(1.49)	14.00 ±(1.50)	**< 0.001**
TC (mmol/L)	186.00 ±(41.30)	180.00 ±(39.34)	187.00 ±(42.28)	187.00 ±(41.12)	186.00 ±(42.26)	0.2
HBA1C (%)	5.50 ±(0.96)	5.30 ±(0.59)	5.40 ±(0.75)	5.50 ±(1.03)	5.70 ±(1.25)	**< 0.001**
FPG (mg/dL)	102.00 ±(32.15)	99.00 ±(16.68)	102.00 ±(25.50)	104.00 ±(36.15)	106.52 ±(41.82)	**< 0.001**

Mean ± SD was for continuous variables. n% was for categorical variables. IR Insulin resistance, BMI body mass index, PIR family income to poverty, FPG fasting plasma glucose, HbA1c glycosylated hemoglobin, FSI fasting serum insulin, HOMA-IR homeostasis model assessment of insulin resistance, TC total cholesterol, ALT alanine aminotransferase, γ-GGT gamma-glutamyl transpeptidase, SCr serum creatinine, SUA serum uric acid, Hb Hemoglobin

T2D persisted (OR = 2.45, 95% CI: 1.48, 4.05, $p < 0.05$). Higher quartiles of the ratio demonstrated a progressively elevated risk of T2D when compared to Q1 across all models analyzed, with a significant trend ($P < 0.001$). Comprehensive results can be found in Table 4.

RCS analysis

We utilized RCS to investigate potential nonlinear relationships between the ratio and the risk of IR. In our fully adjusted model, we observed a nonlinear inverted U-shaped correlation between the ratio and the risk of IR (Fig. 2A), with an inflection point at 0.23. Below this threshold, the risk of IR increased until the hs-CRP/HDL-C ratio reached 0.23, beyond which the association plateaued, suggesting adaptive responses may mitigate further metabolic damage. Moreover, our investigation uncovered a relationship between the ratio and the risk of T2D, with the non-linearity test yielding a *p* value significantly below 0.001 (Fig. 2B).

Subgroup analyses

Subgroup analyses and interaction tests were conducted to investigate how consistently the ratio is related to the probability of IR and T2D among various population subgroups. The subgroups comprised gender, race, BMI, smoking status, hypertension, and alcohol intake.

Table 2 The associations between hs-CRP/HDL-C ratio and risk markers of T2D

Outcomes	β (95% CI) (hs-CRP/HDL-C)*10	Q1	Q2	Q3	Q4	*P* for trend
FPG						
Model1	2.6(1.7, 3.5)	Reference	4.9(3.0, 6.9)	11.0(7.3,14.0)	16.0(14.0, 19.0)	**< 0.001**
Model2	2.5(1.7, 3.3)	Reference	2.0(0.33, 3.7)	8.1(5.1,11.0)	15.0(12.0,17.0)	**< 0.001**
Model3	2.6(1.8, 3.4)	Reference	0.26(-1.6, 2.2)	5.2(2.0, 8.5)	9.6(5.8, 13.0)	**< 0.001**
HBA1C						
Model1	0.10(0.07, 0.13)	Reference	0.15(0.09,0.21)	0.33(0.24, 0.43)	0.56(0.48, 0.65)	**< 0.001**
Model2	0.09(0.06, 0.11)	Reference	0.05(0.00, 0.10)	0.24(0.15, 0.32)	0.47(0.40, 0.54)	**< 0.001**
Model3	0.09(0.06, 0.11)	Reference	0.00(-0.06, 0.06)	0.15(0.06, 0.24)	0.31(0.21, 0.41)	**< 0.001**
FSI						
Model1	1.9(1.1, 2.6)	Reference	2.3(1.3, 3.4)	6.4(5.0, 7.9)	13.0(11.0, 14.0)	**< 0.001**
Model2	1.8(1.1, 2.6)	Reference	1.9(0.85, 2.9)	6.0(4.5, 7.5)	12.0(11.0, 14.0)	**< 0.001**
Model3	1.5(0.77, 2.3)	Reference	-0.62(-1.7, 0.47)	1.5(-0.26, 3.2)	4.3(2.8, 5.9)	**< 0.001**
HOMA-IR						
Model1	0.61(0.35, 0.88)	Reference	0.59(0.29, 0.89)	1.9(1.4, 2.3)	3.8(3.3, 4.3)	**< 0.001**
Model2	0.59(0.33, 0.85)	Reference	0.38(0.09, 0.68)	1.7(1.2, 2.1)	3.6(3.1, 4.1)	**< 0.001**
Model3	0.51(0.24, 0.78)	Reference	-0.3(-0.62, 0.01)	0.44(-0.10, 0.97)	1.5(0.79, 2.1)	**< 0.001**

Model1: Non-adjusted

Model2: adjusted for age, gender, race, education level, and PIR ratio

Model3: included additional adjustments for hypertension, BMI, smoking status, alcohol consumption, TC, ALT, γ-GGT, SCr, SUA, and Hb

Abbreviations: OR: Odds Ratio; CI: confidence interval; T2D type 2 diabetes, BMI body mass index, PIR family income to poverty, FPG fasting plasma glucose, HbA1c glycosylated hemoglobin, FSI fasting serum insulin, HOMA-IR homeostasis model assessment of insulin resistance, TC total cholesterol, ALT alanine aminotransferase, γ-GGT gamma-glutamyl transpeptidase, SCr serum creatinine, SUA serum uric acid, Hb Hemoglobin

Table 3 The associations between hs-CRP/HDL-C ratio and IR

Variable	Model 1			Model 2			Model 3		
	OR[1]	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
(hs-CRP/HDL-C)*10	1.65	1.37, 1.99	**< 0.001**	1.64	1.35, 1.99	**< 0.001**	1.10	1.02, 1.18	**0.022**
Quartile									
Q1	1.00	Reference		1.00	Reference		1.00	Reference	
Q2	2.25	1.53, 3.33	**< 0.001**	2.08	1.42, 3.05	**< 0.001**	1.27	0.80, 1.99	0.261
Q3	4.19	2.98, 5.88	**< 0.001**	3.94	2.78, 5.59	**< 0.001**	1.70	1.17, 2.48	**0.013**
Q4	9.13	6.82, 12.2	**< 0.001**	8.91	6.68, 11.9	**< 0.001**	2.46	1.78, 3.40	**< 0.001**
P for trend		**< 0.001**			**< 0.001**			**< 0.001**	

Model1: Non-adjusted

Model2: adjusted for age, gender, race, education level, and PIR ratio

Model3: included additional adjustments for hypertension, BMI, smoking status, alcohol consumption, TC, ALT, γ-GGT, SCr, SUA, and Hb

Abbreviations: OR: Odds Ratio; CI: confidence interval; IR Insulin resistance, BMI body mass index, PIR family income to poverty, FPG fasting plasma glucose, HbA1c glycosylated hemoglobin, FSI fasting serum insulin, HOMA-IR homeostasis model assessment of insulin resistance, TC total cholesterol, ALT alanine aminotransferase, γ-GGT gamma-glutamyl transpeptidase, SCr serum creatinine, SUA serum uric acid, Hb Hemoglobin

The likelihood of IR was notably higher among females, obese individuals, non-smokers, alcohol consumers, and participants with hypertension (Fig. 3A). Interaction terms were utilized to evaluate the heterogeneities within these subgroups, indicating notable differences particularly regarding alcohol intake and hypertension (P for interaction < 0.05). The implication was that alcohol intake and hypertension affect the positive relationship observed. Similarly, a positive correlation was observed in the risk of T2D. Interaction tests indicated significant differences particularly in alcohol consumption, gender, and hypertension (all P for interaction < 0.05) (Fig. 3B). It's important to highlight that the risk of both IR and T2D is higher in women, potentially linked to studies on how estrogen influences inflammation and blood lipid regulation.

Sensitivity analysis

In sensitivity analysis, the results were still robust when non imputed data were used and additional confounding factors such as neutrophil-lymphocyte ratio (NLR), triglycerides (TG), low-density lipoprotein (LDL), and white blood cells (WBC) were adjusted (refer to Additional file: Table S1-S2). Additionally, after excluding patients with diabetes, we reaffirmed the positive association between the ratio and T2D risk markers in the fully adjusted model (see Additional file: Table S3). These analyses confirm the reliability and robustness of our findings.

Table 4 The associations between hs-CRP/HDL-C ratio and T2D

Variable	Model 1			Model 2			Model 3		
	OR[1]	95% CI	*p*-value	OR[1]	95% CI	*p*-value	OR	95% CI[1]	*p*-value
(hs-CRP/HDL-C)*10	1.24	1.15, 1.34	**< 0.001**	1.27	1.15, 1.40	**< 0.001**	1.15	1.05, 1.27	**0.008**
Quartile									
Q1	1.00	Reference		1.00	Reference		1.00	Reference	
Q2	1.80	1.20, 2.69	**0.006**	1.46	0.97, 2.19	0.069	1.23	0.76, 1.99	0.337
Q3	3.31	2.27, 4.84	**< 0.001**	3.02	2.04, 4.46	**< 0.001**	2.24	1.34, 3.73	**0.007**
Q4	4.18	2.93, 5.96	**< 0.001**	4.32	3.06, 6.09	**< 0.001**	2.45	1.48, 4.05	**0.004**
P for trend		**< 0.001**			**< 0.001**			**< 0.001**	

Model1: Non-adjusted

Model2: adjusted for age, gender, race, education level, and PIR ratio

Model3: included additional adjustments for hypertension, BMI, smoking status, alcohol consumption, TC, ALT, γ-GGT, SCr, SUA, and Hb

Abbreviations: OR: Odds Ratio; CI: confidence interval; T2D type 2 diabetes, BMI body mass index, PIR family income to poverty, FPG fasting plasma glucose, HbA1c glycosylated hemoglobin, FSI fasting serum insulin, HOMA-IR homeostasis model assessment of insulin resistance, TC total cholesterol, ALT alanine aminotransferase, γ-GGT gamma-glutamyl transpeptidase, SCr serum creatinine, SUA serum uric acid, Hb Hemoglobin

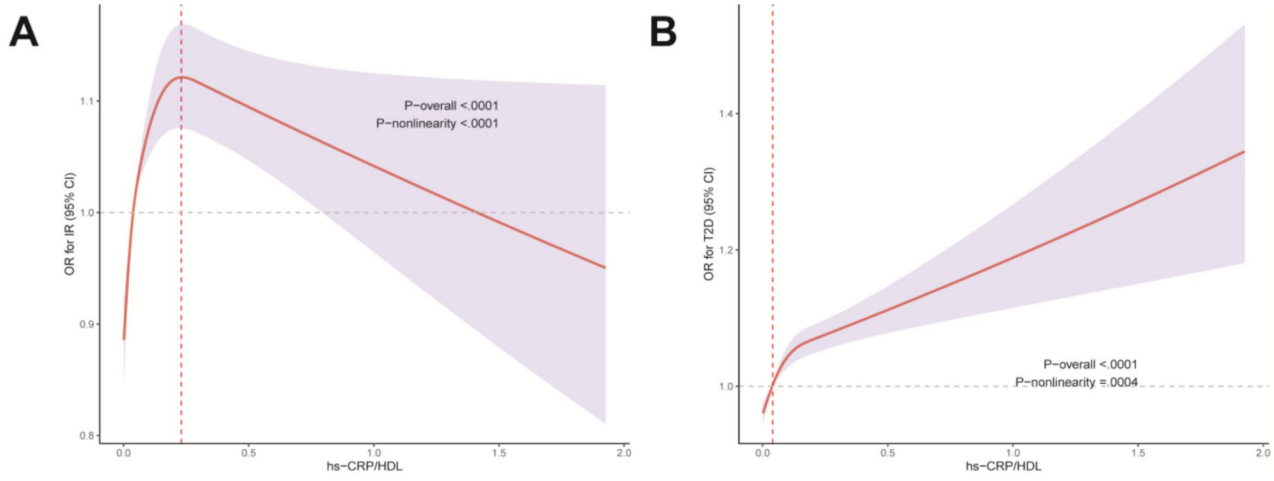

Fig. 2 The RCS analysis between the hs-CRP/HDL-C ratio and the risk of IR and T2D. **A** RCS analysis between the hs-CRP/HDL-C ratio and the risk of IR. **B** RCS analysis between the hs-CRP/HDL-C ratio and the risk of T2D. The area between blue represents a 95% confidence interval. The red solid dashed line indicates a nonlinear relationship between the ratio and IR. IR, Insulin resistance; T2D, Type 2 diabetes; HDL-C, High-Density Lipoprotein Cholesterol; hs-CRP, High-sensitivity C-reactive protein; RCS, restricted cubic spline; OR, odds ratio; CI, confidence interval

Discussion

In our examination of adults in the United States, we found noteworthy positive associations between the ratio of hs-CRP/HDL-C and both IR and T2D, even when controlling for various confounding variables. Our results indicate that the ratio could be a valuable biomarker for detecting individuals at heightened risk for IR and T2D. The hs-CRP/HDL-C ratio likely reflects a balance between systemic inflammation and lipid transport. Elevated inflammation may overwhelm HDL's protective effects, leading to higher metabolic risk. Furthermore, we observed a non-linear, inverted U-shaped relationship between the ratio and IR, as well as a non-linear relationship with T2D.

The findings of our research indicate that the ratio shows a positive correlation with FPG, HbA1c, FSI, and HOMA-IR, suggesting that it serves as a standalone influencing factor in the progression of IR and T2D. The hs-CRP/HDL-C ratio amalgamates two critical dimensions of metabolic health: inflammation and lipid metabolism. Elevated hs-CRP levels signify systemic inflammation, which is a known contributor to the pathogenesis of IR and T2D [23, 24]. HDL-C is involved in the process of reverse cholesterol transport and has anti-inflammatory characteristics [25]. In a similar vein, cellular experiments have shown that HDL can inhibit inflammation by promoting cholesterol efflux [26]. The integration of these two markers into a single ratio offers a more comprehensive assessment of metabolic risk than either marker alone.

IR and T2D can be influenced by a variety of factors such as gender, race, BMI, hypertension, smoking, and alcohol consumption. Previous studies have explored gender differences in metabolic risk factors and the impact of lifestyle factors like smoking and alcohol consumption on metabolic health [27, 28]. One study found

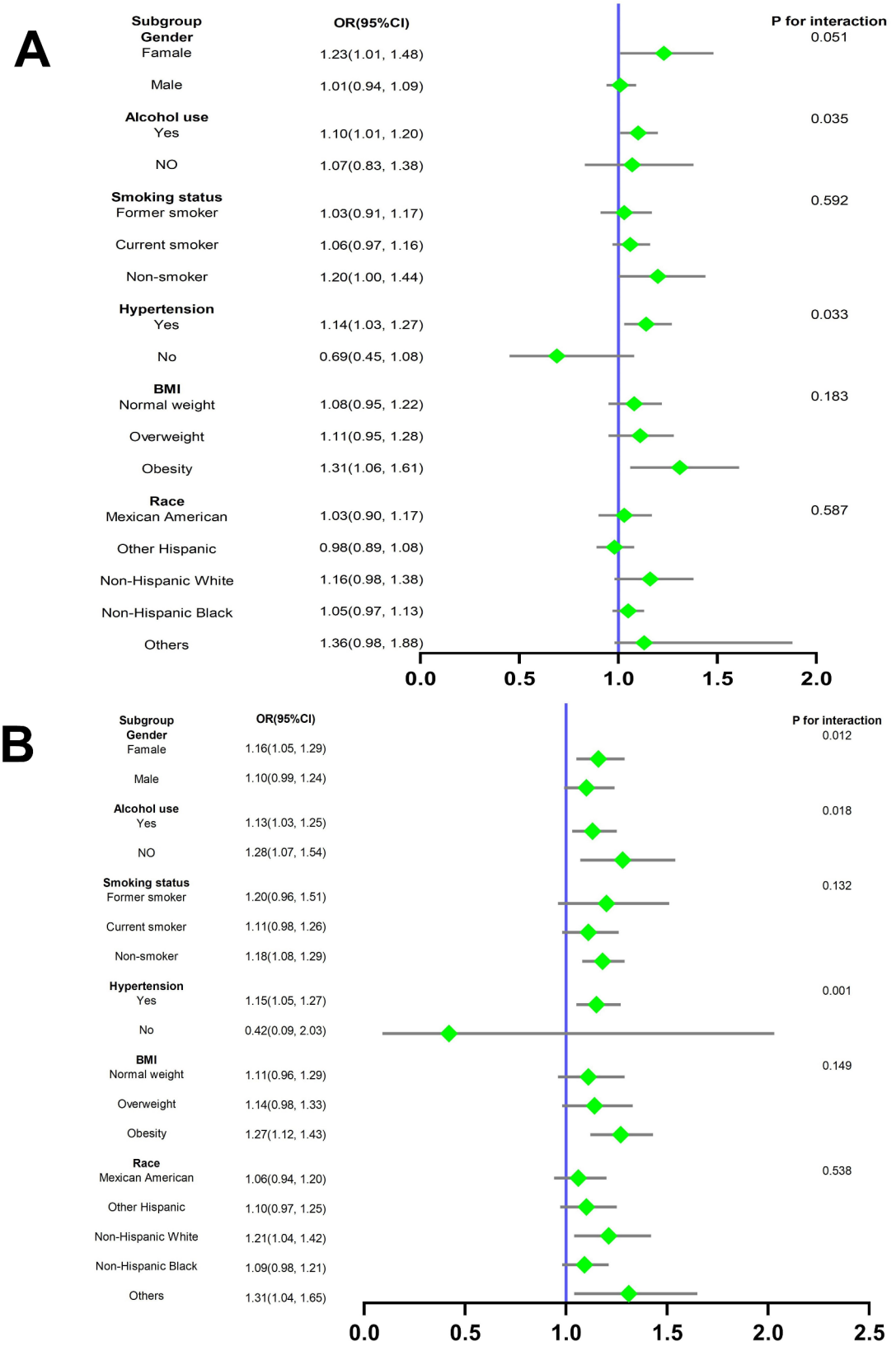

Fig. 3 Subgroup analysis for the association between the hs-CRP/HDL-C ratio and the risk of IR and T2D. **A** Subgroup analysis for the association between the hs-CRP/HDL-C ratio and the risk of IR. **B** Subgroup analysis for the association between the hs-CRP/HDL-C ratio and the risk of T2D. IR, Insulin resistance; T2D, Type 2 diabetes; HDL-C, High-Density Lipoprotein Cholesterol; hs-CRP, High-sensitivity C-reactive protein; BMI, Body mass index; OR, odds ratio; CI, confidence interval

that women with a high C-reactive exhibited favorable metabolic and anthropometric profiles [29]. Our study confirms these results, indicating that the positive relationship between the ratio and both IR and T2D is stronger in women compared to men. This could be attributed to differences in sex chromosomes and the reduction in estrogen levels post-menopause, which may exacerbate glucose and lipid metabolism disorders, thereby increasing the risk of T2D in women [30, 31]. Furthermore, earlier research demonstrated that adipocytes secrete tumor necrosis factor alpha and interleukin-6 into the bloodstream of patients with metabolic syndrome. This stimulates the liver to produce plasma CRP and induces insulin resistance, aligning with our findings [23]. Additionally, a study conducted among a large cohort of African Americans found that hs-CRP levels might play a significant role in the development of diabetes within this population [32]. Overall, our findings suggest that a higher ratio of hs-CRP/HDL-C could serve as a pivotal factor in predicting the risk of IR and T2D.

Our study also reveals nonlinear, inverted U-shaped associations between the ratio and IR, as well as nonlinear relationships with T2D. These nonlinearities indicate that the interplay between inflammation, lipid metabolism, and metabolic health is complex and may involve threshold effects or interactions with other risk factors. Many previous studies had also demonstrated the complexity of associations. A large cross-sectional study in Europe has shown a strong positive correlation between circulating CRP and BMI [33]. Another study showed that the CRP of type 2 diabetes patients and healthy groups was analyzed, and LDL and BMI were strongly positively correlated with CRP [34]. Nonlinear relationships highlight thresholds where metabolic compensatory mechanisms may fail, necessitating further investigation into causality.

A key advantage of our research is the robustness conferred by its large-scale sampling. By tapping into the NHANES database spanning 2015 to 2018 and leveraging its intricate weighted structure, our results offer a more accurate reflection of the US demographic landscape. Furthermore, our criteria for defining T2D, aimed at minimizing the risk of overlooked diagnoses, encompass not only self-reported medical histories and FPG levels but also the outcomes of a 2-hour oral glucose tolerance test and measurements of HbA1c. In addition, we also conducted a stratified analysis considering factors such as race, gender, BMI, smoking habits, hypertension status, and alcohol consumption to investigate the influence of possible confounders and bolster statistical robustness. Furthermore, we employed RCS for a detailed examination of nonlinear associations. Finally, hs-CRP and HDL-C involved in our study are routinely measured in clinical practice, making this ratio an easily obtainable indicator without the need for additional expensive testing. The use of the hs CRP/HDL-C ratio can simplify the risk assessment process and enable healthcare providers to effectively identify individuals at higher risk of metabolic diseases. This method may be particularly beneficial in environments with limited medical resources, as comprehensive metabolic analysis may not be feasible.

However, some limitations should be acknowledged. Initially, due to the nature of this observational study, establishing causality is not possible. Therefore, our results must be viewed with caution, taking into account both direct causal and reverse causal interpretations. Consequently, additional prospective research or longitudinal would be essential to clarify the precise connection between them. Secondly, even after accounting for various covariates, there could still be unmeasured confounding factors, such as thyroid dysfunction, liver or kidney disease, and chronic or acute infections that may affect the observed outcomes. Moreover, dietary habits and a family history of T2D could serve as potential confounding factors. Therefore, additional studies are necessary to assess the influence of diet on the research outcomes. Finally, while acknowledging the limitations of our cross-sectional design, it is important to consider how temporality might bias our findings. For instance, the temporal relationship between hs-CRP levels and the onset of T2D could influence our results. Therefore, longitudinal studies are needed to clarify the directionality of this relationship and to better understand the causal pathways involved.

Conclusion

In summary, our research demonstrates a significant association between the hs-CRP/HDL-C ratio and the risk of IR and T2D. In clinical practice, the hs-CRP/HDL-C ratio stands out as a practical and integrative marker for early metabolic risk assessment, offering a valuable tool for healthcare providers, especially in resource-limited settings. By incorporating this ratio into routine screenings, clinicians can enhance early detection and intervention strategies, ultimately improving patient outcomes. While our findings are compelling, further prospective studies are encouraged to expand on these results and explore additional applications.

Abbreviations

γ-GGT	Gamma-glutamyl transpeptidase
ALT	Alanine aminotransferase
BMI	Body mass index
CVD	Cardiovascular disease
FPG	Fasting plasma glucose
FSI	Fasting serum insulin
Hb	Hemoglobi
HbA1c	Glycosylated hemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
hs-CRP	High-sensitivity C-reactive protein
IR	Insulin resistance

NHANES	National Health and Nutrition Examination Survey
PIR	Family income to poverty
SCr	Serum creatinine
SUA	Serum uric
T2D	Type 2 diabetes
TC	Total cholesterol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01690-z.

Supplementary Material 1

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Author contributions
KX: Writing– original draft, Formal analysis, Resources, Software, Validation. MJS: Writing– original draft, Formal analysis, Resources, Software. CZ: Writing– original draft. SSX: Writing– review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. HX: Writing– review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval
The studies involving humans were approved by Institutional Review Board of the NCHS.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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