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Association between *Helicobacter pylori* seropositivity and the hemoglobin A1c/high-density lipoprotein cholesterol ratio in U.S. adults: evidence from NHANES

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Background: *Helicobacter pylori* (*H. pylori*) infection is associated with insulin resistance and metabolic syndrome. This study investigates the association between *H. pylori* seropositivity and the newly proposed hemoglobin A1c/high-density lipoprotein cholesterol ratio (HbA1c/HDL-C ratio) in a nationally representative U.S. population.

Methods: Data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) were analyzed. Multivariable linear regression models assessed the association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio. Subgroup analyses were performed to evaluate the consistency of the association across different demographic and clinical strata. Generalized additive models with smoothing splines and threshold effect analysis was conducted to identify potential nonlinear relationships.

Results: The cross-sectional analysis comprised 2,909 participants, including 1,254 with *H. pylori* seropositivity. After multivariable adjustment, a significant positive association was found between *H. pylori* seropositivity and the HbA1c/HDL-C ratio (β: 0.28, 95% CI: 0.13, 0.42). Subgroup analyses revealed a stronger association among non-diabetic individuals compared to diabetic individuals. A "L"-shaped relationship was observed, with an inflection point at an HbA1c/HDL-C ratio of 4.81. Below this threshold, *H. pylori* seropositivity was positively associated with the HbA1c/HDL-C ratio. Above this threshold, the association was no longer statistically significant.

Conclusion: This study identifies a significant association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio, suggesting that metabolic dysfunction may be linked to *H. pylori* infection. Future longitudinal studies are needed to establish causality and explore underlying mechanisms.

KEYWORDS

***Helicobacter pylori*, hemoglobin A1c/high-density lipoprotein cholesterol ratio, metabolic dysfunction, NHANES, cross-sectional study**

1 Introduction

Helicobacter pylori (*H. pylori*) infection is one of the most prevalent chronic bacterial infections in the world, affecting about half of the global population (1, 2). It is a major cause of several gastrointestinal disorders, including chronic gastritis, peptic ulcer and gastric cancer (3, 4). In addition, many extra-gastric diseases have been shown to be associated with *H. pylori* infection, such as metabolic, cardiovascular and neurological disorders (5–7).

Emerging evidence suggests that *H. pylori* infection may contribute to systemic metabolic disturbances, including insulin resistance (IR) and metabolic syndrome (8–10). This association appears to be bidirectional, with individuals who already exhibit metabolic disturbances being more prone to persistent *H. pylori* infection (11). However, the existing literature presents inconsistent results, underscoring the necessity for novel biomarkers to disentangle this intricate interplay. In recent years, the HbA1c/HDL-C ratio has been introduced as a comprehensive indicator of both glucose and lipid metabolism. Hemoglobin A1c (HbA1c), a marker reflecting average blood glucose levels over the past 2–3 months, provides insight into long-term glycemic control (12, 13). On the other hand, high-density lipoprotein cholesterol (HDL-C), known for its anti-inflammatory and antioxidant properties, plays a key role in lipid metabolism and is generally regarded as a protective factor against cardiovascular diseases (14). Thus, the HbA1c/HDL-C ratio serves as a refined measure of the interplay between glucose regulation and lipid balance, offering valuable information about overall metabolic state. This ratio has gained considerable attention for its potential in assessing the risk of various conditions, including carotid atherosclerosis (15), stroke (16), and metabolic associated fatty liver disease (17). Despite its promising clinical significance, no studies have yet examined the relationship between the HbA1c/HDL-C ratio and *H. pylori* infection.

This study aims to investigate the association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio in a nationally representative sample of U.S. adults. By exploring this relationship, we seek to identify potential metabolic markers for *H. pylori* susceptibility and provide new insights into the interplay between metabolic health and infectious diseases.

2 Methods

2.1 Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, cross-sectional program designed to assess the health and nutritional status of the non-institutionalized civilian population in the U.S. (18, 19). Employing a complex, multi-stage probability sampling design, NHANES collects data through structured interviews, standardized physical examinations, and comprehensive laboratory analyses, providing a robust platform for evaluating a wide range of health indicators (19–21). All study protocols were reviewed and approved by the Ethics Review Board of the National Center for Health Statistics, and written informed consent was obtained from all participants.

This study utilized data from the 1999–2000 NHANES cycle. Initially, 4,480 participants aged 20 years or older were included. After excluding individuals with incomplete data on the HbA1c/HDL-C ratio ($n = 764$) and *H. pylori* serological status ($n = 116$), as well as those with missing covariates such as education level ($n = 13$), marital status ($n = 431$), poverty income ratio (PIR) ($n = 484$), drinking status ($n = 143$), smoking status ($n = 3$), and body mass index (BMI) ($n = 17$), a total of 2,909 participants were included in the final analysis (Figure 1).

2.2 Assessment of *Helicobacter pylori* seropositivity status

Helicobacter pylori seropositivity status was assessed using enzyme-linked immunosorbent assay (ELISA) to quantify anti-*H. pylori* immunoglobulin G (IgG) antibody levels (22). Participants were classified into two groups based on established ELISA cutoff values: *H. pylori-positive* (optical density [OD] value ≥1.1) and *H. pylori*-negative (OD value < 0.9). Ambiguous results within the range of 0.9 to 1.1 were excluded from the analysis to ensure precise statistical outcomes, consistent with previous epidemiological studies (23–25).

2.3 Assessment of the HbA1c/HDL-C ratio

Fasting blood samples were analyzed to measure HbA1c and HDL-C levels. The HbA1c/HDL-C ratio was calculated by dividing HbA1c (%) by HDL-C (mg/dL) (15). Participants were categorized into quartiles (Q1 to Q4) based on their HbA1c/HDL-C ratio values, with quartile thresholds determined by dividing the study population into four equal groups.

2.4 Assessment of covariates

To ensure comprehensive adjustments in the analysis, relevant sociodemographic characteristics, lifestyle behaviors, and comorbid health conditions were included as covariates. Sociodemographic variables encompassed age, sex, race, education level, marital status, and PIR. Lifestyle factors included drinking status (classified as <12 or ≥12 alcoholic drinks per year) and smoking status (categorized as never, former, or current smoker). Health conditions were assessed using a combination of self-reported data and objective clinical measurements. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and classified into normal weight (<25), overweight (≥25 and <30), and obesity (≥30) (26). Hypertension was defined as a self-reported physician diagnosis, use of antihypertensive medications, or elevated blood pressure (systolic ≥130 mmHg or diastolic ≥80 mmHg) (27). Cardiovascular disease, encompassing coronary heart disease, angina, congestive heart failure, myocardial infarction, and stroke, was ascertained through self-reported diagnoses provided by healthcare professionals (28).

2.5 Statistical analysis

All statistical analyses were conducted using appropriate NHANES sampling weights to account for the complex, multi-stage cluster survey design. Baseline characteristics of participants were described using weighted means (95% confidence intervals [CIs]) for continuous variables and weighted percentages (95% CIs) for categorical variables. Differences in baseline characteristics were

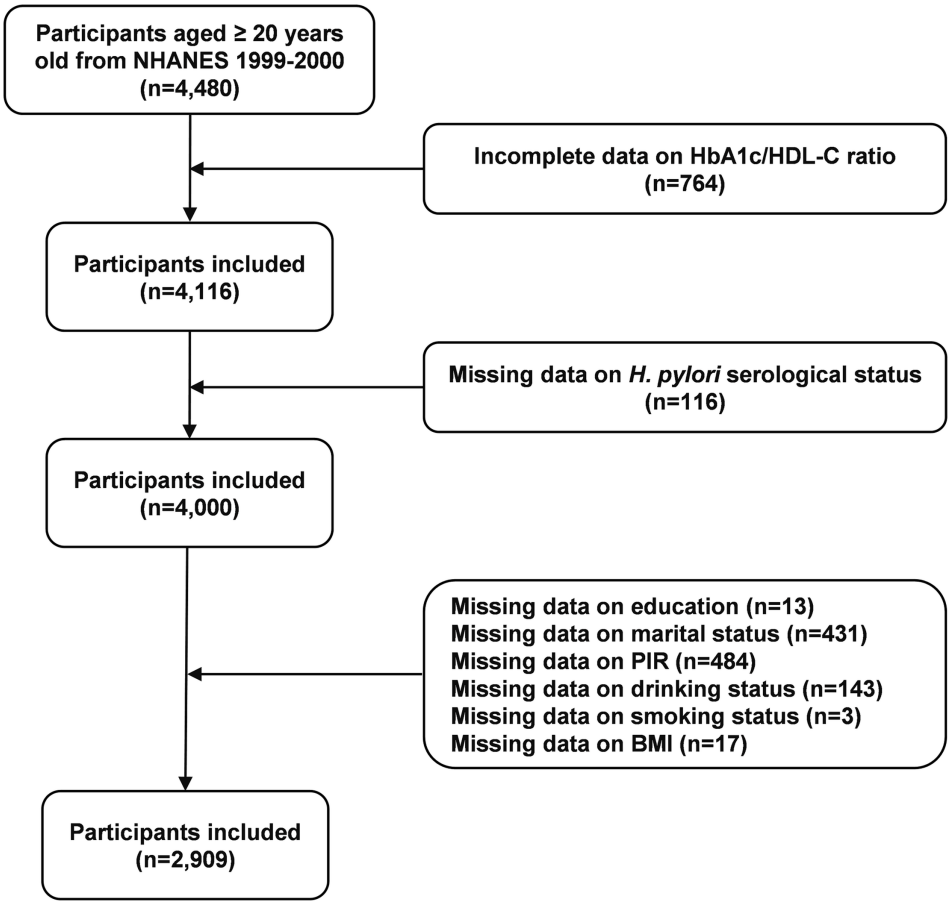

FIGURE 1
Flow chart of participants selection. *H. pylori*, *Helicobacter pylori*; PIR, poverty income ratio; BMI, body mass index; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey.

assessed using weighted linear regression for continuous variables and weighted chi-square test for categorical variables.

The association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio was evaluated using multivariable linear regression models. Crude model was unadjusted, Model 1 adjusted for age, sex, and race, and Model 2 further adjusted for education, marital status, PIR, drinking status, smoking status, BMI, hypertension, diabetes, and cardiovascular disease. Results were reported as beta (β) coefficients with corresponding 95% CIs. Subgroup analyses were conducted to examine the association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio across different age, sex, race, PIR, BMI, and disease histories (hypertension and cardiovascular disease). Interaction tests were used to evaluate the consistency of these associations across subgroups.

As a sensitivity analysis, we performed logistic regression analyses with *H. pylori seropositivity* as the dependent variable and the HbA1c/HDL-C ratio as the independent variable. Both continuous and quartile-based forms of the HbA1c/HDL-C ratio were included in the regression analyses. Results were reported as odds ratios (ORs) with corresponding 95% CIs.

To explore potential non-linear relationships between *H. pylori* seropositivity and the HbA1c/HDL-C ratio, generalized additive models with smoothing splines were employed. Additionally, recursive algorithms and two-stage logistic models were utilized to detect any potential inflection points in the relationship. Likelihood ratio tests were performed to compare the fit of single logistic regression models with that of two-stage logistic models.

All analyses were performed using R (http://www.R-project.org, version 4.3.1) and EmpowerStats (http://www.empowerstats.com, version 4.2). Statistical significance was defined as a two-sided p value < 0.05.

3 Results

3.1 Baseline characteristics

This analysis included 2,909 U.S. adults with a weighted mean age of 44.65 years (95% CI: 43.59, 45.70), of whom 48.22% were male and 43.8% exhibited *H. pylori* seropositive. Table 1 summarizes the comparative analysis of demographic, socioeconomic, and clinical characteristics between *H. pylori* seropositive and seronegative participants. Within the *H. pylori* seropositive group, there was a greater proportion of older individuals and Mexican Americans. They also had lower levels of education, lower PIR, and were more likely to be married or living

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TABLE 1 Basic characteristics of the study population.

Characteristics	Overall (*n* = 2,909)	*H. pylori* seronegative (*n* = 1,655)	*H. pylori* seropositive (*n* = 1,254)	*p* value
Age (years)	44.65 (43.59, 45.70)	42.85 (41.55, 44.15)	48.95 (47.30, 50.60)	<0.001
Sex (%)				0.390
Male	48.22 (46.20, 50.25)	47.79 (45.47, 50.12)	49.26 (46.06, 52.47)	
Female	51.78 (49.75, 53.80)	52.21 (49.88, 54.53)	50.74 (47.53, 53.94)	
Race (%)				<0.001
Mexican American	5.91 (3.41, 10.05)	3.23 (1.86, 5.57)	12.33 (6.71, 21.56)	
Other Hispanic	8.02 (3.51, 17.29)	4.87 (2.13, 10.77)	15.58 (6.90, 31.46)	
Non-Hispanic White	72.86 (66.28, 78.58)	82.04 (77.07, 86.13)	50.83 (41.85, 59.76)	
Non-Hispanic Black	8.76 (5.62, 13.42)	6.32 (4.07, 9.69)	14.61 (8.85, 23.17)	
Other Race	4.45 (2.39, 8.15)	3.53 (1.70, 7.18)	6.65 (3.79, 11.41)	
Education (%)				<0.001
Less than high school	22.08 (19.30, 25.14)	14.42 (11.94, 17.31)	40.47 (37.08, 43.96)	
High school	25.97 (21.49, 31.03)	25.91 (20.16, 32.63)	26.13 (23.54, 28.90)	
More than high school	51.95 (46.20, 57.64)	59.67 (51.97, 66.92)	33.40 (30.05, 36.93)	
Marital status (%)				0.011
Never married	17.86 (15.23, 20.83)	19.54 (15.84, 23.85)	13.83 (10.66, 17.75)	
Widowed/divorced/separated	17.77 (15.01, 20.93)	16.58 (13.74, 19.88)	20.64 (17.43, 24.27)	
Married/living with partner	64.36 (59.71, 68.76)	63.88 (58.08, 69.30)	65.53 (60.86, 69.92)	
PIR (%)				<0.001
<1.3	23.24 (17.69, 29.89)	18.33 (12.58, 25.94)	35.00 (29.15, 41.35)	
1.3 to <3.5	34.72 (30.75, 38.92)	32.93 (28.32, 37.89)	39.03 (34.78, 43.45)	
≥3.5	42.04 (34.73, 49.72)	48.74 (39.81, 57.75)	25.97 (21.66, 30.79)	
Drinking (%)				0.045
<12 alcoholic drinks per year	27.14 (23.60, 30.98)	25.73 (22.40, 29.37)	30.52 (24.65, 37.10)	
≥12 alcoholic drinks per year	72.86 (69.02, 76.40)	74.27 (70.63, 77.60)	69.48 (62.90, 75.35)	
Smoking (%)				0.005
Never smoker	50.71 (46.38, 55.04)	53.20 (48.36, 57.97)	44.75 (39.09, 50.55)	
Former smoker	24.63 (22.06, 27.39)	24.29 (20.81, 28.14)	25.45 (21.53, 29.81)	
Current smoker	24.66 (21.23, 28.43)	22.52 (19.08, 26.38)	29.79 (24.75, 35.38)	
BMI (%)				0.764
<25	35.60 (31.76, 39.63)	35.84 (31.41, 40.53)	35.01 (30.24, 40.11)	
25–30	33.72 (30.55, 37.04)	33.93 (30.84, 37.15)	33.22 (28.26, 38.57)	
≥30	30.68 (27.81, 33.72)	30.23 (26.67, 34.05)	31.77 (29.41, 34.22)	
Hypertension (%)				0.001
No	50.37 (47.06, 53.68)	53.39 (49.13, 57.60)	43.11 (38.42, 47.93)	
Yes	49.63 (46.32, 52.94)	46.61 (42.40, 50.87)	56.89 (52.07, 61.58)	
Diabetes (%)				<0.001
No	92.10 (90.31, 93.58)	93.70 (92.24, 94.91)	88.25 (83.71, 91.65)	
Yes	7.90 (6.42, 9.69)	6.30 (5.09, 7.76)	11.75 (8.35, 16.29)	
Cardiovascular disease (%)				0.001
No	91.79 (90.29, 93.08)	92.90 (91.20, 94.29)	89.12 (86.50, 91.29)	
Yes	8.21 (6.92, 9.71)	7.10 (5.71, 8.80)	10.88 (8.71, 13.50)	
FBG (mg/dL)	100.38 (98.48, 102.29)	98.63 (96.30, 100.95)	105.01 (101.11, 108.91)	0.015
HbA1c (%)	5.40 (5.31, 5.48)	5.30 (5.22, 5.39)	5.62 (5.50, 5.74)	<0.001
TC (mg/dL)	202.58 (199.71, 205.44)	202.36 (199.08, 205.65)	203.09 (198.53, 207.64)	0.788
TG (mg/dL)	143.21 (134.63, 151.79)	139.42 (127.86, 150.98)	153.16 (138.68, 167.64)	0.204
HDL-C (mg/dL)	50.29 (48.95, 51.63)	51.10 (49.59, 52.60)	48.36 (46.54, 50.18)	0.018
LDL-C (mg/dL)	125.47 (122.28, 128.65)	125.26 (121.63, 128.88)	126.04 (122.37, 129.70)	0.700
Uric acid (mg/dL)	5.30 (5.21, 5.39)	5.27 (5.17, 5.37)	5.36 (5.21, 5.51)	0.313
HbA1c/HDL-C ratio	4.57 (4.39, 4.74)	4.42 (4.23, 4.61)	4.93 (4.71, 5.15)	<0.001

Data were presented as weighted means or percentages (95% CIs). *H. pylori*, *Helicobacter pylori*; PIR, poverty income ratio; BMI, body mass index; FBG, fasting blood glucose, HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

with a partner. Additionally, *H. pylori* seropositive participants were more likely to be smokers and less likely to consume alcohol. Furthermore, individuals with *H. pylori* seropositive exhibited higher prevalence rates of hypertension, diabetes, and cardiovascular disease. However, traditional metabolic markers, such as TC, TG, LDL-C, and uric acid, did not differ significantly between the two groups. Notably, the HbA1c/HDL-C ratio was significantly higher among *H. pylori* seropositive participants.

3.2 Association between *Helicobacter pylori* seropositivity and the HbA1c/HDL-C ratio

Table 2 presents the associations between *H. pylori* seropositivity and HbA1c/HDL-C ratio. The results indicated that *H. pylori* seropositivity was positively associated with the HbA1c/HDL-C ratio in the unadjusted model (β: 0.55, 95% CI: 0.41, 0.69), the partially adjusted model (β: 0.36, 95% CI: 0.22, 0.51), and the fully adjusted model (β: 0.28, 95% CI: 0.13, 0.42).

3.3 Subgroup analysis

Subgroup analyses and interaction tests were conducted to evaluate the consistency of the association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio across various demographic and clinical subgroups, including age, sex, race, PIR, BMI, hypertension, diabetes, and cardiovascular disease (Figure 2). The positive association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio was generally consistent across most subgroups (*P* for interaction >0.05). However, a significant interaction was identified for diabetes status (*P* for interaction = 0.038). Specifically, the association was stronger in individuals without diabetes (β: 0.31, 95% CI: 0.19, 0.43) compared to those with diabetes (β: 0.21, 95% CI: −0.03, 0.45).

3.4 Sensitivity analysis

To further validate the robustness of our findings, we conducted additional sensitivity analyses. In the fully adjusted model, participants in the highest quartile (Q4) of the HbA1c/HDL-C ratio exhibited an 84% increased probability of *H. pylori* seropositivity (OR: 1.75, 95% CI: 1.38, 2.44) compared to those in the lowest quartile (Q1). Notably, trend tests confirmed the statistical significance of the overall positive association between the HbA1c/HDL-C ratio and *H. pylori* seropositivity (all *P* for trend <0.05) (Supplementary Table 1).

3.5 Dose–response relationship between *Helicobacter pylori* seropositivity and the HbA1c/HDL-C ratio

Generalized additive models with smoothing splines revealed a nonlinear, L-shaped association between the HbA1c/HDL-C ratio and *H. pylori* seropositivity (Figure 3). Threshold effect analysis identified an inflection point at an HbA1c/HDL-C ratio of 4.81. Below this threshold, a significant positive association was observed between the HbA1c/HDL-C ratio and *H. pylori* seropositivity (OR: 1.29, 95% CI: 1.14, 1.46), whereas no significant association was observed above the threshold (OR: 1.02, 95% CI: 0.96, 1.09). The log-likelihood ratio test confirmed the superiority of the two-piecewise linear regression model over the one-line linear model ($p = 0.003$) (Supplementary Table 2). We constructed stratified curves for the association between the HbA1c/HDL-C ratio and *H. pylori* seropositivity by diabetes status (Supplementary Figure 1). In non-diabetic individuals, the HbA1c/HDL-C ratio exhibited a linear association with *H. pylori* seropositivity (OR: 1.19, 95% CI: 1.10, 1.28), and the log-likelihood ratio test ($p = 0.205$) supported the adequacy of the linear model. Among diabetic individuals, no significant association between the HbA1c/HDL-C ratio and *H. pylori seropositivity* was found (Supplementary Table 3).

4 Discussion

In this cross-sectional study conducted among U.S. population, we identified a significant positive association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio. Notably, we observed a "L"-shaped relationship between *H. pylori* seropositivity and the HbA1c/HDL-C ratio, with an inflection point at 4.81. Below this threshold, *H. pylori* seropositivity was positively associated with the HbA1c/HDL-C ratio. However, above this value, no significant association was detected.

H. pylori infection may increase the risk of metabolic dysfunction. A systematic review has reported a positive correlation between *H. pylori* infection and metabolic syndrome, with infected individuals exhibiting elevated levels of TG, fasting blood glucose (FBG), BMI, and reduced HDL-C (29). Several studies have also demonstrated that *H. pylori* infection is linked to abnormal glucose metabolism and an increased risk of diabetes (30–32). Specifically, individuals with *H. pylori* infection exhibit significantly higher HbA1c levels compared to uninfected individuals, and a positive correlation has been observed between *H. pylori* infection and elevated HbA1c levels in diabetic patients (33). These findings suggest that *H. pylori* infection may be closely associated with IR-related disorders. However, the relationship between *H. pylori* infection and markers such as HbA1c and IR remains controversial. For instance, a large cross-sectional study

TABLE 2 Association of *H. pylori* seropositivity with the HbA1c/HDL-C ratio.

H. pylori seropositivity	Crude model		Model 1		Model 2	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
Seropositive vs. Seronegative	0.55 (0.41, 0.69)	<0.001	0.36 (0.22, 0.51)	<0.001	0.28 (0.13, 0.42)	<0.001

H. pylori, *Helicobacter pylori*; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol.
Model 1: Adjusted for age, sex, and race.
Model 2: Adjusted for age, sex, race, education, marital status, PIR, drinking status, smoking status, BMI, hypertension, and cardiovascular disease.

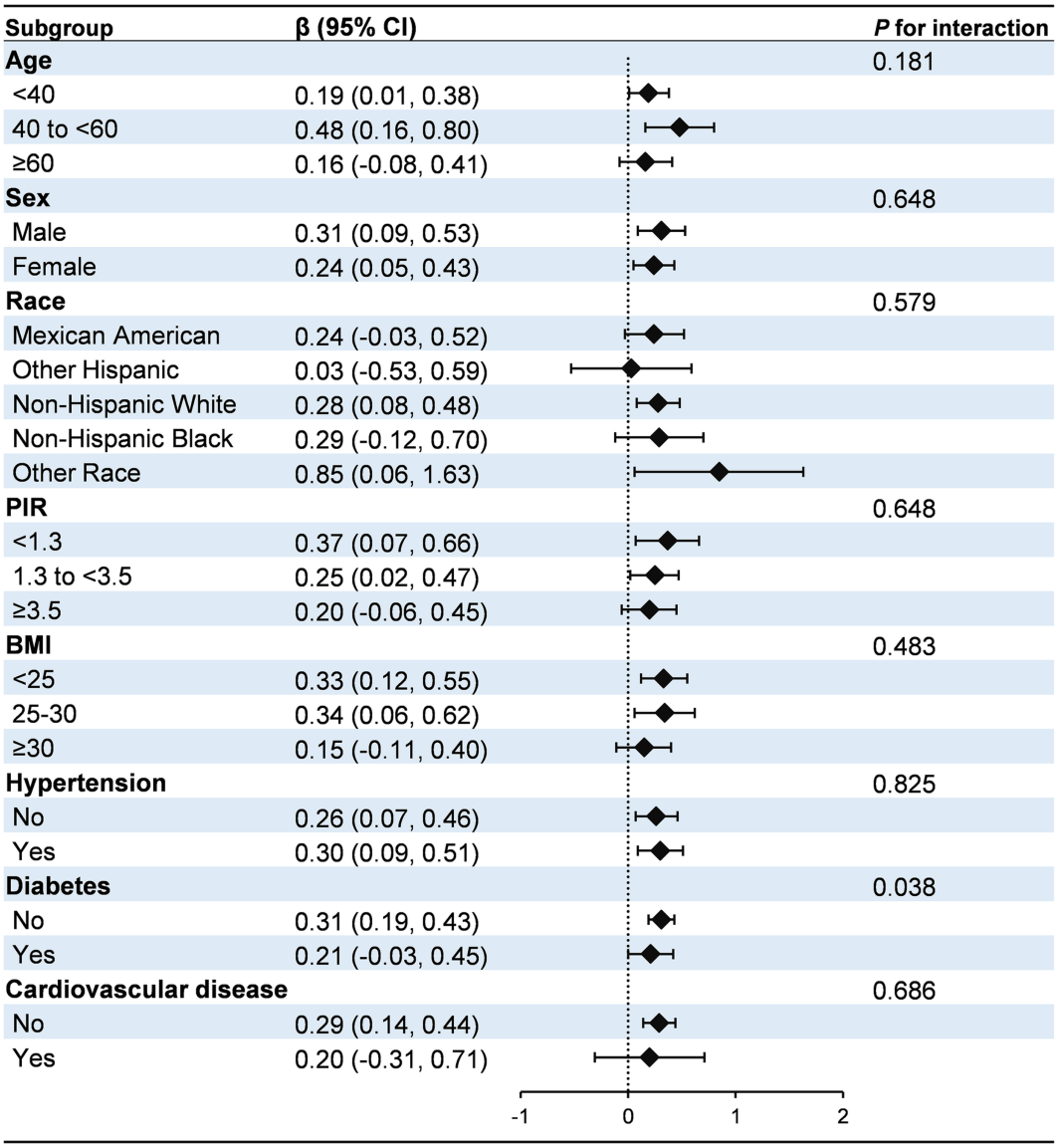

FIGURE 2
Subgroup analysis for the association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio. The model was adjusted for age, sex, race, education, marital status, PIR, drinking, smoking, BMI, hypertension, diabetes, and cardiovascular disease. Diabetes was identified based on self-reported physician diagnosis, use of insulin or glucose-lowering medications, fasting blood glucose levels ≥126 mg/dL, or glycated hemoglobin levels ≥6.5%. PIR, poverty income ratio; BMI, body mass index.

involving 37,263 participants found that *H. pylori* infection was associated only with dyslipidemia, showing no significant correlation with FBG or HbA1c levels (34). In addition to its potential impact on glucose metabolism, *H. pylori* infection has been shown to significantly influence lipid profiles. Studies indicate that individuals with *H. pylori* infection tend to exhibit elevated levels of TC, TG and LDL-C, alongside reduced HDL-C levels (35–37). Notably, the prevalence of dyslipidemia is significantly lower in individuals who have undergone *H. pylori* eradication compared to those with active infection (38). Eradication of *H. pylori* has been associated with improved lipid profiles, including increased HDL-C levels and decreased TG and LDL-C levels (39, 40). These findings demonstrate the complexity of the relationship between *H. pylori* infection and metabolic disorders and suggest that more research is needed to focus on the association between *H. pylori* infection and abnormal glucose and lipid metabolism.

Glucose and lipid metabolism interact through complex physiological and pathological processes (41, 42). The triglyceride-glucose (TyG) index, derived from FPG and TG levels, has emerged as a reliable marker of IR and metabolic dysfunction (43, 44). Previous studies have shown that an elevated TyG index is associated with an increased risk of *H. pylori* infection (24, 45). Compared to the short-term glucose indicators used in the TyG index, HbA1c reflects long-term glucose control and provides a more stable measure than fasting glucose (46). Our findings are consistent with studies using the TyG index, revealing the close association between *H. pylori* seropositivity and glycolipid metabolism. The HbA1c/HDL-C ratio may offer more stable and clinically meaningful insights into the relationship between *H. pylori* infection and metabolic dysfunction.

In this study, we identified a saturation effect in the relationship between *H. pylori* seropositivity and the HbA1c/HDL-C ratio using

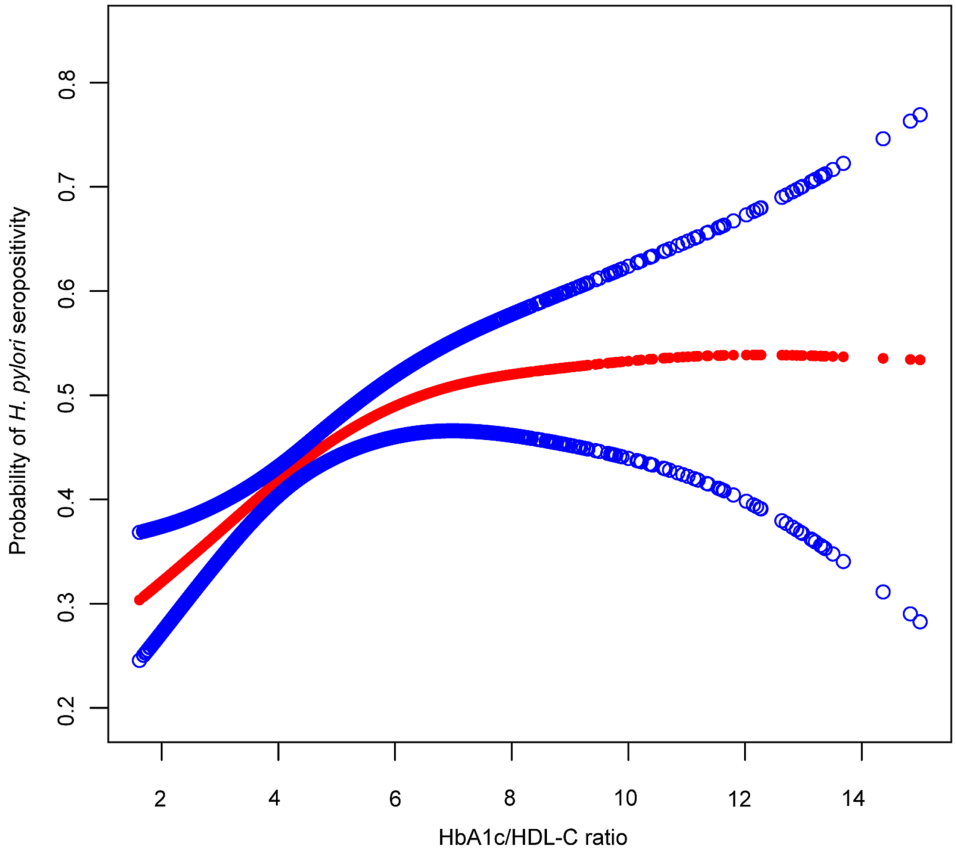

FIGURE 3
The association between the HbA1c/HDL-C ratio and *H. pylori* seropositivity. The red line represents the smooth curve fit between variables, with blue bands representing the 95% CI of the fit. The model was adjusted for age, sex, race, education, marital status, PIR, drinking, smoking, BMI, hypertension, and cardiovascular disease. *H. pylori*, *Helicobacter pylori*; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol.

segmented regression analysis. Within the lower range of the HbA1c/HDL-C ratio, mild disturbances in glucose and lipid metabolism were associated with a higher probability of *H. pylori* seropositivity. However, beyond a certain threshold, this association was no longer significant. This saturation effect aligns with previous observations of nonlinear relationships between metabolic indicators and health outcomes (16, 47), suggesting that the association between metabolic status and *H. pylori* infection may vary depending on the severity of metabolic disturbances.

Subgroup analyses revealed that the association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio was more pronounced in individuals without diabetes than in those with diabetes. This discrepancy may be attributed to the complex metabolic disturbances in individuals with diabetes, characterized by hyperglycemia and dyslipidemia, which could obscure the relationship between *H. pylori* seropositivity and the HbA1c/HDL-C ratio (48, 49). Unfortunately, our study lacked detailed data on disease duration, treatment regimens, and the presence of complications, limiting our ability to explore these potential influences. Additionally, glycemic and lipid-lowering therapies, which are common in diabetes management, may alter the measurement of the HbA1c/HDL-C ratio and impact *H. pylori* colonization or eradication, thereby attenuating the observed association (50, 51). Our findings suggest that *H. pylori* seropositivity is positively associated with the HbA1c/HDL-C ratio, especially in non-diabetic populations. Future research should explore the mechanisms underlying this association and develop personalized strategies for metabolic management.

The potential mechanisms underlying the association between the HbA1c/HDL-C ratio and *H. pylori* infection are multifaceted. *H. pylori* infection induces systemic inflammation through the release of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, which disrupt insulin signaling pathways and exacerbate insulin resistance (52, 53). Moreover, *H. pylori* infection may alter the gastric environment, influencing gut microbiota composition and contributing to systemic inflammation and metabolic dysregulation (54, 55). The relationship between metabolic disorders and *H. pylori* infection appears to be bidirectional. Metabolic dysfunction, characterized by IR, hyperglycemia, and dyslipidemia, promotes oxidative stress and impairs gastric mucosal defenses, thereby creating a favorable environment for *H. pylori* colonization and persistence (10, 56, 57). Additionally, IR-related autonomic dysfunction may slow gastrointestinal motility and reduce gastric acid secretion, further facilitating *H. pylori* survival (58–60). These interconnected mechanisms highlight the complex interplay between metabolic health and *H. pylori* infection, with the exact mechanisms warranting further investigation.

This study is the first to investigate the association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio. A key strength of this study is its use of a large, nationally representative sample of

U.S. adults, which enhances the generalizability of the findings to broader populations. However, several limitations should be noted. First, as a cross-sectional study, it cannot establish a causal relationship between *H. pylori* seropositivity and the HbA1c/HDL-C ratio. Further longitudinal studies are needed to clarify the directionality of this association. Second, the NHANES database provides only serological data on *H. pylori* infection status, which precludes differentiation between past and current infections among seropositive participants. Although serology is a widely used and reliable method for assessing *H. pylori* status in large epidemiological studies (25, 28), it does not capture the activity of infection, thereby limiting our ability to assess the relationship between chronic versus acute infection and metabolic disturbances. Third, there may be unmeasured confounding factors, such as genetic predisposition, unaccounted medication use, and environmental influences, which could affect the observed association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio. Finally, the study focused exclusively on a U.S. population, which may limit the generalizability of the findings to other ethnic or geographic groups.

5 Conclusion

This study identifies a positive association between *H. pylori* seropositivity and the HbA1c/HDL-C ratio in a nationally representative sample. The findings suggest that this metabolic marker may serve as a potential indicator of *H. pylori* infection in clinical settings. Future longitudinal studies are needed to establish causality and explore underlying mechanisms.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics Research Ethics Review Board provided ethics approval (Protocol #98-12). 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.

Author contributions

CX: Conceptualization, Formal analysis, Methodology, Writing – original draft. X-yJ: Data curation, Software, Visualization, Writing – original draft. J-mL: Data curation, Visualization, Writing – original draft. Y-fZ: Investigation, Validation, Writing – original draft. J-yH: Supervision, Writing – review & editing. C-CL: Funding acquisition, Writing – review & editing. HS: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2025.1589510/full#supplementary-material

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