

# Association between *Helicobacter pylori* infection and insulin resistance: Data from the US and Chinese cohorts

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## Abstract

**Background:** *Helicobacter pylori* infection has been associated with diverse extraintestinal morbidities, including cardiometabolic diseases. Insulin resistance is a key pathogenic factor involved in the development of various metabolic diseases. This study aimed to investigate the association between *Helicobacter pylori* infection and insulin resistance.

**Methods:** This cross-sectional study analyzed two independent cohorts: 2918 participants from the US National Health and Nutrition Examination Survey (1999–2000) and 912 inpatients from Southern China. *Helicobacter pylori* infection was determined using serum antibodies (National Health and Nutrition Examination Survey), <sup>13</sup>C-urea breath test, or rapid urease test (China cohort).

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Insulin resistance was assessed using the triglyceride–glucose index or homeostasis model assessment of insulin resistance. Multivariate linear regression models were used to analyze the associations.

**Results:** In the National Health and Nutrition Examination Survey cohort, *Helicobacter pylori* positivity was initially associated with a higher triglyceride–glucose index (coefficient = 1.17,  $p = 0.001$ ); however, this association lost statistical significance after full adjustment, and no significant association was observed with the homeostasis model assessment of insulin resistance index (coefficient = 0.03,  $p = 0.900$ ). Similarly, in the Southern China cohort, no significant relationship was found between *Helicobacter pylori* infection status and the triglyceride–glucose index (coefficient = 0.06,  $p = 0.689$ ).

**Conclusions:** *Helicobacter pylori* infection is not consistently associated with insulin resistance. Further studies are needed to clarify its role in metabolic diseases.

### Keywords

Insulin resistance, homeostasis model assessment of insulin resistance, triglyceride–glucose, *Helicobacter pylori*, metabolic diseases

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## Introduction

*Helicobacter pylori*, is one of the most prevalent pathogenic bacteria causing gastrointestinal infections and represents a major global public health concern, with a higher prevalence in developing countries.<sup>1</sup> *H. pylori* infection can cause several gastric diseases, including peptic ulcers, chronic active gastritis, gastric adenocarcinoma, and type B low-grade mucosa-associated lymphoid tissue lymphoma.<sup>2</sup> Recent studies have further demonstrated that *H. pylori* infection is associated with multiple non-gastrointestinal tract morbidities, including metabolic syndrome, diabetes mellitus (DM), cardiovascular diseases, and autoimmune disorders.<sup>3–7</sup>

Insulin resistance (IR) is a condition characterized by reduced responsiveness of insulin-targeted tissues to physiological insulin levels. IR is considered a pathogenic driver of numerous conditions, such as metabolic syndrome, atherosclerosis, DM, and nonalcoholic fatty liver disease.<sup>8–11</sup> The hyperinsulinemic–euglycemic clamp is the

gold standard diagnostic method for diagnosing IR; however, its complexity and cost limit its widespread use in clinical practice.<sup>12</sup> The triglyceride–glucose (TyG) index and the homeostasis model assessment of IR (HOMA-IR) are novel, simple, accessible, and reproducible clinical alternative indices for studying IR.<sup>13,14</sup>

However, the relationship between *H. pylori* infection and IR remains unclear. Some studies suggest that successful *H. pylori* eradication may improve insulin sensitivity and glycemic control, supporting a potential pathophysiological link.<sup>15–17</sup> Conversely, other studies have reported no significant association between *H. pylori* infection and IR.<sup>18–20</sup> This inconsistency may arise from racial differences, varying methodologies for IR assessment, and, crucially, unaccounted confounding. A major confounder is type 2 DM (T2DM), a condition whose pathogenesis is fundamentally driven by IR. The interplay is complex: T2DM is associated with an increased risk of *H. pylori* infection,<sup>21–25</sup> and antidiabetic

medications may differentially influence this risk; for example, metformin use has been associated with a dose-dependent reduction in infection risk,<sup>26</sup> whereas the use of insulin and calcium channel blockers in patients with diabetes has been significantly associated with a higher incidence of *H. pylori* eradication.<sup>27</sup> These observations underscore the necessity of accounting for T2DM status and metabolic pharmacotherapy as potential confounders when examining the relationship between *H. pylori* and IR. Furthermore, to further investigate the downstream effects of IR, it is crucial to examine its key downstream manifestations. IR is a central driver of dyslipidemia, characterized primarily by elevated triglyceride (TG) levels. Therefore, examining the association between *H. pylori* and TG provides a direct link to the atherogenic lipid profile that contributes to the increased cardiovascular risk observed in infected individuals.

Hence, this study was designed to examine the association between *H. pylori* infection and IR across different ethnic populations while accounting for potential confounders as well as extend this investigation by assessing the association between *H. pylori* infection and TG levels as a direct marker of IR-related dyslipidemia. We used data from the 1999–2000 cycle of the US

National Health and Nutrition Examination Survey (NHANES) and a cohort from Southern China.

Methods

Study cohorts

Two cross-sectional cohorts—one from the NHANES and the other from Southern China—were used for the analysis. For the NHANES cohort, we derived data from the 1999–2000 cycle, as *H. pylori* status was only assessed during this cycle. A total of 9965 adults were evaluated. Individuals meeting the following criteria were excluded: (a) missing serum *H. pylori* antibody data; (b) ambiguous *H. pylori* antibody results (i.e. *H. pylori* antibody titers between 0.91 and 1.09); and (c) missing fasting blood glucose and fasting triglyceride measurements (see Figure 1 for the sample selection flow diagram). All participants provided written informed consent. The NHANES was approved by the Research Ethics Review Board of the National Center for Health Statistics and the Centers for Disease Control and Prevention. Data on race, age, sex, poverty–income ratio, body mass index (BMI), household size, educational level, smoking

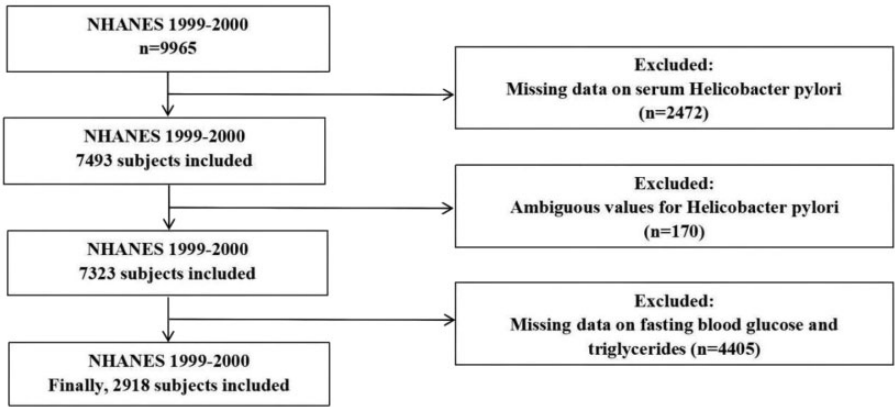


Figure 1. Flow chart of participant selection.

and drinking history, and history of stroke and coronary heart disease (CHD) were obtained through interviews and physical examinations. Serum biochemical variables, including C-reactive protein (CRP), fasting glucose, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and fasting TG levels, were obtained from laboratory records. Information on DM and hypertension (HTN) was obtained through interviews and laboratory records.

For the Southern China cohort, we enrolled patients hospitalized at the Cardiovascular Center of Shunde Hospital, Southern Medical University, between January 2019 and December 2021. This cohort was originally established to investigate the association between *H. pylori* infection and CHD. In summary, we enrolled adults aged  $\geq 18$  years who underwent *H. pylori* testing during hospitalization. Exclusion criteria included use of antibiotics or bismuth within 1 month before hospitalization, use of H2 receptor antagonists or proton pump inhibitors within 1 month before hospitalization, gastrointestinal hemorrhage, history of gastrectomy, hematological disease, severe renal or liver dysfunction, autoimmune disease, acute infection, cachexia, malignancy, or thyroid disease. Data on age, sex, BMI, heart rate, smoking and drinking history, history of DM and HTN, laboratory parameters, and carbon breath test outcomes were collected. Laboratory detection parameters, including TG, TC, and fasting glucose concentrations, were obtained from the medical record system.

### Assessment of *H. pylori* infection status

In the NHANES cohort, *H. pylori* infection was determined by serum *H. pylori* IgG antibody titers measured using enzyme-linked immunosorbent assays. An antibody titer  $< 0.90$  indicated the absence of detectable IgG antibodies (negative), whereas a

titer  $> 1.10$  indicated the presence of IgG antibodies (positive). Titers ranging from 0.91 to 1.09 were considered ambiguous and excluded from the analysis.

In the Southern China cohort, *H. pylori* infection was assessed using the  $^{13}\text{C}$  urea breath test or rapid urease testing during painless electrogastroscopy. The  $^{13}\text{C}$  urea breath test was performed as follows: an initial breath sample was collected after fasting, a  $^{13}\text{C}$ -labeled capsule was administered, a second respiratory sample was collected after 30 min, and both samples were assayed. During upper gastrointestinal endoscopy, antral biopsy specimens were obtained for rapid urease testing. *H. pylori* infection was considered present if the biopsy tissue caused the test strip dip to change from yellow to red within 1 min (strongly positive) or within 3 min (weakly positive). If no color change was observed, the rapid urease test was considered negative, and the patient was classified as negative for *H. pylori* infection.

### Assessment of IR

We used two metrics, the TyG index and HOMA-IR index, to assess the IR status among participants in the NHANES cohort. The TyG index was calculated using the following formula:  $\text{TyG} = \ln(\text{fasting triglyceride concentration (mg/dL)} \times \text{fasting glucose concentration (mg/dL)}) / 2$ .<sup>28</sup> The HOMA-IR index was calculated using the following formula:  $\text{HOMA-IR} = (\text{fasting glucose concentration (mmol/L)} \times \text{fasting insulin concentration (}\mu\text{U/mL)}) / 22.5$ .<sup>29</sup> In the Southern China cohort, only the TyG index was calculated because fasting insulin concentrations were not detected.

### Statistical analysis

First, to evaluate potential selection bias resulting from the high rate of exclusions,

we compared the baseline characteristics between participants included in the final analysis and those who were excluded. Subsequently, we described the baseline characteristics of the study participants from the NHANES database and the Southern China cohort, respectively. Participants were categorized into two groups based on *H. pylori* infection status (positive vs. negative). To account for the complex survey design and unanswered questions in the NHANES, appropriate sample weights were used in the current analysis. In the NHANES, continuous variables were summarized as means and SD, and categorical variables were classified as counts and proportions. We employed multivariable linear regression models to assess the associations between *H. pylori* infection and the outcome variables. The primary analysis aimed to examine the relationship between *H. pylori* infection and surrogate indices of IR, including the TyG index and HOMA-IR. As a complementary analysis, we further evaluated the association between *H. pylori* infection and TG levels to preliminarily investigate a key downstream manifestation of IR. For all regression analyses, we applied an identical sequential modeling strategy to ensure comparability using three models: (a) Model 1: unadjusted; (b) Model 2: adjusted for key clinical characteristics (age, sex, race, and BMI); and (c) Model 3: further adjusted for lifestyle and clinical covariates (smoking status, drinking status, CRP, TC, and history of DM, HTN, stroke, and CHD). TG levels were adjusted for only in the models where TyG or HOMA-IR served as the outcome, but not in the models where TG itself served as the outcome variable. Furthermore, due to substantial missing data precluding direct adjustment for antidiabetic and antihypertensive medications, we addressed potential confounding by these agents through stratified analyses based on T2DM status.

All statistical analyses were performed using R software version 4.3.1 (<http://www.R-project.org>). Statistical significance was defined as a two-tailed p-value <0.05.

## Results

### *Comparison of baseline characteristics between included and excluded US participants*

To assess potential selection bias resulting from the exclusion of a substantial number of participants due to data unavailability, we compared the baseline characteristics between included and excluded populations from the original NHANES cohort (Table S1). The results indicated that, compared to the excluded group, the included participants were older and had better socioeconomic status and higher educational levels. Critically, the included population exhibited a greater cardiometabolic disease burden. The prevalence rates of DM, HTN, stroke, and CHD were all markedly higher in the included group. Consistently, the use of insulin, oral hypoglycemic agents, and antihypertensive drugs was substantially higher in the included population. Regarding biochemical markers, the included group exhibited higher TyG index values and HDL-C concentrations. In summary, the final analytical sample represents an older population with more complex health profiles and a higher cardiometabolic risk burden.

### *Baseline characteristics of US participants*

The final sample of the NHANES cohort included 2918 participants, representing a weighted population of 216,872,581 individuals. The mean age of all participants was 38 years, and 49% were male. The prevalence of *H. pylori* infection differed significantly across racial groups. Participants with positive *H. pylori* serology

were older and had higher TG concentrations, CRP levels, TyG indices, and HOMA-IR indices as well as lower levels of education, income, and HDL-C concentrations than those with negative *H. pylori* serology. Moreover, positive serology was significantly associated with a greater

burden of comorbidities, specifically higher prevalence of DM, HTN, stroke, and CHD (all  $p < 0.001$ ). There were no significant differences between the two groups with regard to sex, BMI, household size, smoking and drinking history, or fasting LDL-C and TC levels (Table 1).

**Table 1.** Demographic and clinical data of *H. pylori*-positive and -negative groups (NHANES 1999–2000).

| Characteristic               | Overall<br>(n = 2918) | Negative<br>(n = 1817) | Positive<br>(n = 1101) | p-value |
|------------------------------|-----------------------|------------------------|------------------------|---------|
| Age (years)                  | 38.0 (18.3)           | 37.0 (17.9)            | 44.0 (18.1)            | <0.001  |
| Male, n (%)                  | 1418 (49)             | 854 (48)               | 564 (50)               | 0.325   |
| Race, n (%)                  |                       |                        |                        | <0.001  |
| Non-Hispanic White           | 1083.0 (37.1)         | 877.0 (48.3)           | 206.0 (18.7)           |         |
| Mexican American             | 954.0 (32.7)          | 453.0 (24.9)           | 501.0 (45.5)           |         |
| Non-Hispanic Black           | 620.0 (21.2)          | 349.0 (19.2)           | 271.0 (24.6)           |         |
| Other Hispanic               | 174.0 (6.0)           | 84.0 (4.6)             | 90.0 (8.2)             |         |
| Other Race                   | 87.0 (3.0)            | 54.0 (2.9)             | 33.0 (2.9)             |         |
| Poverty-income ratio         | 2.93 (1.57)           | 3.18 (1.56)            | 2.21 (1.51)            | <0.001  |
| BMI (kg/m <sup>2</sup> )     | 26 (5.13)             | 26 (5.93)              | 26 (5.19)              | 0.039   |
| Household, n (%)             |                       |                        |                        | 0.527   |
| Large (four or more members) | 1399 (37)             | 866 (37)               | 533 (38)               |         |
| Small (1–3 members)          | 1519 (63)             | 951 (63)               | 568 (62)               |         |
| Educational level, n (%)     |                       |                        |                        | <0.001  |
| Less than high school        | 1572 (32)             | 867 (27)               | 705 (45)               |         |
| High school diploma          | 521 (24)              | 350 (25)               | 171 (21)               |         |
| More than high school        | 825 (44)              | 600 (48)               | 225 (34)               |         |
| Smoke, n (%)                 | 1186 (48)             | 701 (47)               | 485 (53)               | 0.110   |
| Drink, n (%)                 | 1981 (72)             | 1263 (73)              | 718 (69)               | 0.110   |
| CRP (mg/dL)                  | 0.19 (0.67)           | 0.18 (0.68)            | 0.21 (0.63)            | 0.023   |
| Fasting glucose (mg/dL)      | 93 (28)               | 93 (20)                | 95 (41)                | 0.005   |
| TG (mg/dL)                   | 112 (96)              | 108 (95)               | 121 (100)              | 0.005   |
| TC (mg/dL)                   | 194 (42)              | 192 (41)               | 198 (43)               | 0.181   |
| HDL-C (mg/dL)                | 47 (14)               | 48 (14)                | 45 (14)                | 0.026   |
| LDL-C (mg/dL)                | 117 (36)              | 116 (36)               | 120 (37)               | 0.106   |
| DM, n (%)                    | 463 (15.8)            | 235 (12.9)             | 228 (20.7)             | <0.001  |
| HTN, n (%)                   | 1287 (44.1)           | 650 (35.8)             | 637 (57.8)             | <0.001  |
| Stroke, n (%)                | 112 (3.8)             | 45 (2.5)               | 67 (6.1)               | <0.001  |
| CHD, n (%)                   | 184 (6.3)             | 75 (4.1)               | 109 (9.9)              | <0.001  |
| TyG index                    | 8.57 (0.64)           | 8.53 (0.62)            | 8.66 (0.67)            | 0.002   |
| HOMA-IR index                | 2.28 (2.90)           | 2.23 (2.88)            | 2.45 (2.94)            | 0.029   |

Values are the mean (SD) and count (proportion) for continuous and categorical variables, respectively, Wilcoxon rank-sum test for complex survey samples, and chi-square test with Rao and Scott's second-order correction.

BMI: body mass index; CHD: coronary heart disease; CRP: C-reactive protein; DM: diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; HTN: hypertension; LDL-C: low-density lipoprotein cholesterol; NHANES: National Health and Nutrition Examination Survey; TC: total cholesterol; TG: triglycerides; TyG: triglyceride-glucose.

# Association between *H. pylori* infection and TyG/HOMA-IR in US participants

The association between *H. pylori* infection status and the TyG index was evaluated in the NHANES 1999–2000 cohort (Table 2). The results indicated that *H. pylori* seropositivity was associated with a higher TyG index ( $\beta = 1.17$ , 95% confidence interval (CI): 1.07–1.27). After adjustment for age, sex, race, and BMI (Model 2) and additional adjustment for smoking and drinking history, CRP, TC concentration, TG concentration, and cardiometabolic comorbidities including DM, HTN, stroke, and CHD (Model 3), the association was substantially attenuated and was no longer statistically significant ( $\beta = 0.02$ , 95% CI: 0.00–0.05).

The association between *H. pylori* infection status and the HOMA-IR index was also examined. Nevertheless, no significant

association was observed between *H. pylori* infection and HOMA-IR index in any of the statistical models (Table 3).

# Association between *H. pylori* infection and TyG in Southern China

Overall, 912 inpatients who underwent *H. pylori* testing were enrolled in the Southern China cohort. The average age was 58.4 years, and 51.6% of the participants were male. A total of 603 participants were *H. pylori*-positive (66.1%). Individuals in the *H. pylori*-positive group were more likely to be female and had higher BMI, TG concentrations, and fasting glucose concentrations. There were no statistically significant differences between the two groups in terms of heart rate, TC concentrations, history of DM, and HTN (Table 4). In the unadjusted model, *H. pylori* positivity

**Table 2.** Association between *H. pylori* infection and TyG in US participants

| Characteristic              | Model 1 |                     |         | Model 2 |                     |         | Model 3 |                     |         |
|-----------------------------|---------|---------------------|---------|---------|---------------------|---------|---------|---------------------|---------|
|                             | Beta    | 95% CI <sup>1</sup> | p-value | Beta    | 95% CI <sup>1</sup> | p-value | Beta    | 95% CI <sup>1</sup> | p-value |
| <i>H. pylori</i> = positive | 1.17    | 1.07, 1.27          | 0.001   | 0.09    | 0.01, 0.17          | 0.031   | 0.02    | 0.00, 0.05          | 0.101   |
| Race                        |         |                     |         |         |                     |         |         |                     |         |
| Other Hispanic              |         |                     |         | −0.09   | −0.22, 0.05         | 0.200   | −0.02   | −0.07, 0.03         | 0.401   |
| Non-Hispanic White          |         |                     |         | −0.03   | −0.18, 0.11         | 0.600   | −0.03   | −0.06, 0.00         | 0.021   |
| Non-Hispanic Black          |         |                     |         | −0.41   | −0.51, −0.31        | <0.001  | −0.13   | −0.16, −0.10        | <0.001  |
| Other race                  |         |                     |         | −0.11   | −0.29, 0.07         | 0.200   | −0.03   | −0.09, 0.04         | 0.400   |
| Age                         |         |                     |         | 0.01    | 0.01, 0.01          | <0.001  | 0.01    | 0.00, 0.01          | <0.001  |
| Sex = male                  |         |                     |         | 0.13    | 0.04, 0.22          | 0.012   | 0.04    | 0.02, 0.07          | <0.001  |
| BMI                         |         |                     |         | 0.03    | 0.03, 0.04          | <0.001  | 0.01    | 0.01, 0.01          | <0.001  |
| Smoke = yes                 |         |                     |         |         |                     |         | 0.04    | 0.02, 0.06          | <0.001  |
| Drink = yes                 |         |                     |         |         |                     |         | −0.03   | −0.06, −0.01        | 0.010   |
| CRP                         |         |                     |         |         |                     |         | 0.02    | 0.00, 0.03          | 0.036   |
| TC                          |         |                     |         |         |                     |         | 0.01    | 0.00, 0.00          | <0.001  |
| TG                          |         |                     |         |         |                     |         | 0.01    | 0.00, 0.01          | <0.001  |
| DM = yes                    |         |                     |         |         |                     |         | 0.01    | −0.03, 0.03         | 0.802   |
| HTN = yes                   |         |                     |         |         |                     |         | 0.03    | 0.00, 0.05          | 0.029   |
| Stroke = yes                |         |                     |         |         |                     |         | −0.02   | −0.08, 0.03         | 0.403   |
| CHD = yes                   |         |                     |         |         |                     |         | −0.01   | −0.06, 0.03         | 0.600   |

Model 1: Unadjusted; Model 2: Adjusted for age, sex, race, and BMI; Model 3: Adjusted for model 2 + smoke and drink history, CRP level, TC level, triglyceride level, DM, hypertension, stroke, and CHD.

95% CI<sup>1</sup>: confidence Interval.

BMI: body mass index; CHD: coronary heart disease; CRP: C-reactive protein; DM: diabetes mellitus; HTN: hypertension; TC: total cholesterol; TyG: triglyceride–glucose.

**Table 3.** Association between *H. pylori* infection and HOMA-IR in US participants.

| Characteristic              | Model 1 |                     |         | Model 2 |                     |         | Model 3 |                     |         |
|-----------------------------|---------|---------------------|---------|---------|---------------------|---------|---------|---------------------|---------|
|                             | Beta    | 95% CI <sup>†</sup> | p-value | Beta    | 95% CI <sup>†</sup> | p-value | Beta    | 95% CI <sup>†</sup> | p-value |
| <i>H. pylori</i> = positive | 1.27    | 0.86, 1.87          | 0.200   | 0.03    | −0.37, 0.42         | 0.900   | 0.03    | −0.33, 0.39         | 0.900   |
| Race                        |         |                     |         |         |                     |         |         |                     |         |
| Other Hispanic              |         |                     |         | 0.17    | −0.93, 1.3          | 0.700   | −0.10   | −0.80, 0.59         | 0.803   |
| Non-Hispanic White          |         |                     |         | −0.14   | −0.70, 0.42         | 0.600   | −0.46   | −0.88, −0.05        | 0.028   |
| Non-Hispanic Black          |         |                     |         | −0.22   | −0.62, 0.18         | 0.200   | 0.42    | −0.02, 0.87         | 0.061   |
| Other Race                  |         |                     |         | −0.18   | −0.66, 0.30         | 0.400   | 0.42    | −0.52, 1.4          | 0.400   |
| Age                         |         |                     |         | 0.00    | −0.01, 0.02         | 0.400   | 0.01    | 0.00, 0.02          | 0.006   |
| Sex = male                  |         |                     |         | 0.39    | 0.09, 0.69          | 0.020   | 0.31    | −0.04, 0.65         | 0.085   |
| BMI                         |         |                     |         | 0.23    | 0.17, 0.29          | <0.001  | 0.20    | 0.17, 0.22          | <0.001  |
| Smoke = yes                 |         |                     |         |         |                     |         | 0.08    | −0.26, 0.43         | 0.602   |
| Drink = yes                 |         |                     |         |         |                     |         | −0.49   | −0.87, −0.12        | 0.010   |
| CRP                         |         |                     |         |         |                     |         | 0.19    | −0.05, 0.42         | 0.121   |
| TC                          |         |                     |         |         |                     |         | −0.01   | −0.02, −0.01        | <0.001  |
| TG                          |         |                     |         |         |                     |         | 0.01    | 0.01, 0.01          | <0.001  |
| DM = yes                    |         |                     |         |         |                     |         | 0.32    | −0.13, 0.77         | 0.201   |
| HTN = yes                   |         |                     |         |         |                     |         | 0.01    | −0.32, 0.34         | >0.9    |
| Stroke = yes                |         |                     |         |         |                     |         | −0.02   | −0.85, 0.81         | >0.9    |
| CHD = yes                   |         |                     |         |         |                     |         | −0.76   | −1.4, −0.10         | 0.054   |

Model 1: Unadjusted; Model 2: Adjusted for age, sex, race, and BMI; Model 3: Adjusted for model 2 + smoke and drink history, CRP level, TC level, triglyceride level, DM, hypertension, stroke, and CHD. 95% CI<sup>†</sup>: confidence Interval. BMI: body mass index; CHD: coronary heart disease; CRP: C-reactive protein; DM: diabetes mellitus; HOMA-IR: homeostasis model assessment of insulin resistance; HTN: hypertension; TC: total cholesterol.

**Table 4.** Demographic and clinical data of *H. pylori*-positive and -negative groups in Southern China.

| Characteristic           | Overall<br>(n = 912) | Negative<br>(n = 309) | Positive<br>(n = 603) | p-value |
|--------------------------|----------------------|-----------------------|-----------------------|---------|
| Age (years)              | 58.44 (10.87)        | 57.93 (11.16)         | 58.70 (10.72)         | 0.315   |
| Male, n (%)              | 471.0 (51.6%)        | 142.0 (46.0%)         | 329.0 (54.6%)         | 0.017   |
| BMI (kg/m <sup>2</sup> ) | 24.48 (3.40)         | 24.14 (3.17)          | 24.65 (3.50)          | 0.028   |
| Smoke, n (%)             | 187.0 (20.5%)        | 55.0 (17.8%)          | 132.0 (21.9%)         | 0.173   |
| Drink, n (%)             | 31.0 (3.4%)          | 10.0 (3.2%)           | 21.0 (3.5%)           | 0.999   |
| Heart rate (bpm)         | 74.71 (11.31)        | 74.26 (10.62)         | 74.95 (11.65)         | 0.374   |
| HTN, n (%)               | 463.0 (50.8%)        | 151.0 (48.9%)         | 312.0 (51.7%)         | 0.452   |
| DM, n (%)                | 153.0 (16.8%)        | 50.0 (16.2%)          | 103.0 (17.1%)         | 0.802   |
| TC (mmol/L)              | 4.98 (1.23)          | 4.89 (1.14)           | 5.02 (1.27)           | 0.112   |
| TG (mmol/L)              | 1.56 (1.02)          | 1.47 (0.97)           | 1.61 (1.05)           | 0.047   |
| Fasting glucose (mmol/L) | 5.80 (1.75)          | 5.64 (1.42)           | 5.88 (1.89)           | 0.030   |
| TyG index                | 4.66 (4.14)          | 4.29 (4.11)           | 4.84 (4.14)           | 0.055   |

Continuous variables were presented as mean ± SD or median and interquartile range, and categorical variables were expressed as numbers and percentages. BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; TC: total cholesterol; TG: triglycerides; TyG: triglyceride-glucose.

showed a borderline association with the TyG index ( $\beta = 0.55$ ,  $p = 0.056$ ). This association became nonsignificant after sequential adjustment for covariates (Table 5).

### Association between *H. pylori* infection and TG

Analysis of the NHANES cohort revealed that *H. pylori* positivity was associated with significantly higher TG levels in the unadjusted model. However, after sequential adjustment for demographic, clinical, and lifestyle factors in Models 2 and 3, the association was substantially attenuated and no longer statistically significant (Table S2). In Chinese participants, *H. pylori* positivity showed a borderline association with TG levels ( $\beta = 0.14$ ,  $p = 0.053$ ), which was attenuated to nonsignificance after covariate adjustment ( $\beta = 0.04$ ,  $p = 0.518$ ) (Table S3).

### Association between *H. pylori* infection and TyG/HOMA-IR in participants with T2DM

In stratified analyses conducted to address potential confounding by antidiabetic and antihypertensive medications, associations between *H. pylori* infection and IR indices were examined among participants with T2DM. Within the US T2DM subgroup,

*H. pylori* positivity was initially associated with a higher HOMA-IR index in the unadjusted model ( $\beta = 1.2$ , 95% CI: 0.21–2.2,  $p = 0.018$ ); however, this association was substantially attenuated and no longer statistically significant after multivariable adjustment (Model 3:  $\beta = 0.32$ , 95% CI: –0.75 to 1.4,  $p = 0.601$ ). A similar pattern was observed for the TyG index (Tables S4 and S5). In the Chinese T2DM cohort, a similar trend was observed for the TyG index (Table S6).

## Discussion

In an analysis of a representative sample of US adults with data collected between 1999 and 2000, *H. pylori* infection showed a tendency toward an association with the TyG index. However, this association became nonsignificant ( $p = 0.101$ ) after full adjustment for confounders. We strongly suspect that this association may be coincidental and requires further confirmation. We also found no association between *H. pylori* infection and HOMA-IR and TG levels. Furthermore, we did not find a significant correlation between *H. pylori* infection and TyG levels in the southern Chinese population. In the subgroup of US participants with T2DM, the associations between

**Table 5.** Association between *H. pylori* infection and TyG in Chinese participants

| Characteristic              | Model 1 |                     |         | Model 2 |                     |         | Model 3 |                     |         |
|-----------------------------|---------|---------------------|---------|---------|---------------------|---------|---------|---------------------|---------|
|                             | Beta    | 95% CI <sup>1</sup> | p-value | Beta    | 95% CI <sup>1</sup> | p-value | Beta    | 95% CI <sup>1</sup> | p-value |
| <i>H. pylori</i> = positive | 0.55    | –0.01, 1.12         | 0.056   | 0.50    | –0.07, 1.07         | 0.086   | 0.06    | –0.23, 0.35         | 0.689   |
| Age                         |         |                     |         | –0.01   | –0.04, 0.01         | 0.399   | 0.01    | –0.00, 0.02         | 0.071   |
| Sex = male                  |         |                     |         | 0.76    | 0.21, 1.30          | 0.006   | –0.03   | –0.36, 0.29         | 0.851   |
| BMI                         |         |                     |         |         |                     |         | 0.02    | –0.02, 0.07         | 0.259   |
| Smoke = yes                 |         |                     |         |         |                     |         | –0.14   | –0.53, 0.26         | 0.492   |
| Drink = yes                 |         |                     |         |         |                     |         | 1.02    | 0.23, 1.80          | 0.011   |
| TC                          |         |                     |         |         |                     |         | 0.01    | –0.11, 0.13         | 0.827   |
| TG                          |         |                     |         |         |                     |         | 3.45    | 3.30, 3.60          | <0.001  |

Model 1: Unadjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for model 2 + smoke and drink history, BMI, TC, triglyceride. 95% CI<sup>1</sup>: confidence interval.

BMI: body mass index; TC: total cholesterol; TG: triglycerides; TyG: triglyceride–glucose.

*H. pylori* infection and both the TyG index and HOMA-IR were similarly attenuated and lost significance after multivariable adjustment.

The most plausible explanation for these findings is the potent confounding effect of sociodemographic and cardiometabolic factors. As demonstrated by the baseline characteristics, *H. pylori*-positive individuals exhibited a markedly different risk profile, including lower socioeconomic status and a heavier burden of traditional cardiometabolic comorbidities. These factors are independently associated with both an increased risk of *H. pylori* acquisition in early life and the development of IR and dyslipidemia later in life. When such confounders are inadequately accounted for, they may generate spurious associations. Our use of sequential modeling and stratified analyses demonstrates how this apparent association dissolves after rigorous adjustment. This underscores the methodological imperative in observational studies of *H. pylori* to thoroughly adjust for this complex web of confounders, a step that may have been insufficiently addressed in prior studies reporting positive associations.

Our results provide a compelling framework for reconciling inconsistencies in the existing literature. The positive associations reported in some earlier studies, often based on smaller sample sizes, may reflect residual confounding rather than a direct pathophysiological link.<sup>30–34</sup> Conversely, our large, well-characterized cohorts with comprehensive adjustment lend greater weight to the null findings reported in other large-scale studies. Furthermore, the absence of an association even within the T2DM subgroup—where confounding by medication use and disease severity is most pronounced—strengthens the conclusion that a clinically relevant independent association is unlikely. The controversial evidence regarding eradication therapy further supports this interpretation.<sup>17,18,33</sup> If the association were

causal and robust, more consistent benefits from eradication would be expected.

These results have several important clinical implications. First, they provide robust evidence against diverting clinical attention toward *H. pylori* as a significant modifiable risk factor for IR. The consistency of findings across populations argues against routine screening for or treatment of *H. pylori* for the specific purpose of improving insulin sensitivity. Furthermore, this evidence supports the avoidance of unnecessary antibiotic use, thereby mitigating public health threats of antibiotic resistance and potential treatment-related side effects. Thus, clinicians should continue to prioritize lifestyle interventions and evidence-based pharmacotherapy targeting conventional risk factors, as these remain the most effective strategies for mitigating IR and its associated cardiometabolic consequences.

Several limitations should be acknowledged when analyzing our results. First, the cross-sectional design precludes the establishment of causal or temporal relationships. Second, substantial missing data on specific antidiabetic and antihypertensive medications in the NHANES database prevented direct adjustment for these potential confounders; this limitation was addressed as methodologically feasible through stratified analyses by T2DM status. Third, the interpretability and generalizability of the findings are further constrained by potential selection biases. These include the high exclusion rate in the NHANES cohort, which resulted in an analytical sample with a different risk profile, and the hospital-based setting of the Southern China cohort, which limits the extrapolation of results to the general population. Finally, the absence of data on specific bacterial virulence factors (e.g. cytotoxin-associated gene A (CagA) and vacuolating cytotoxin gene A (VacA)) and systemic inflammatory mediators precluded investigation into the underlying biological mechanisms.

## Conclusions

In summary, our findings indicate that *H. pylori* infection is not associated with IR. Further research is needed to better identify the relationship between *H. pylori* infection and IR, which may provide novel insights into the prevention and treatment of cardiometabolic diseases.

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## Author contributions

SH, YZ, LL, XC, and YH contributed to the study conception and design. YC, JL, YL, ZC, XH, LM, and LZ interpreted, analyzed, and acquired the data. Manuscript drafting was performed by SH, whereas critical revisions were performed by XC and YH. All authors agree to be accountable for the study aspects to guarantee accuracy and integrity.

## Availability of data

Data supporting the study outcomes would be provided by corresponding author on reasonable demand.

## Consent for publication

Not applicable.

## Declaration of conflicting interests

The authors declare no competing interests.

## Ethics approval and consent to participate

The NHANES was accredited by the Research Ethics Review Board of the National Center for Health Statistics, Center of Disease Control. The cohort from South China was registered at the China Clinical Trial Registration Center (NO: 202100912).

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## Supplemental material

Supplemental material for this article is available online.

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