

Association between nonalcoholic fatty liver disease and *Helicobacter pylori* infection in Dali City, China

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ABSTRACT

الأهداف: لمعرفة ما إذا كانت عدوى هيليكوباكتر بيلوري (*H. pylori*) مرتبطة بتطور مرض الكبد الدهني غير الكحولي (NAFLD) في مدينة دالي، الصين.

المنهجية: سجلنا 1185 من البالغين الذين زاروا مركز الفحص الصحي. تم تقييم مرض الكبد الدهني غير الكحولي وعدوى هيليكوباكتر بيلوري عن طريق الموجات فوق الصوتية واختبار التنفس اليوريا، على التوالي. قارنا أيضا مؤشرات التمثيل الغذائي للدهون في الدم بين الأشخاص الذين يعانون من NAFLD دون الإصابة بعدوى هيليكوباكتر بيلوري.

النتائج: بلغ معدل انتشار NAFLD لجميع مجتمع الدراسة (العدد=1185) 44.6% (العدد=529)، بما في ذلك 167 امرأة و 362 رجلاً. من بين 529 شخصاً مصاب NAFLD، تم تأكيد عدوى هيليكوباكتر بيلوري كعامل خطر مهم ومستقل عامل الثقة 95% فترة الثقة (1.02-1.79)، $p=0.036$ ، نسبة الاحتمالات=1.35. بالمقارنة مع الأفراد غير المصابين بعدوى هيليكوباكتر بيلوري (العدد=721)، لوحظ أيضاً ارتفاع LDL-C إضافة إلى ارتفاع TC القيمة الإحصائية ($p=0.014$) في المصابين بعدوى هيليكوباكتر بيلوري (العدد=464).

الخلاصة: وجدنا ارتباطاً إيجابياً بين عدوى هيليكوباكتر بيلوري و NAFLD.

Objectives: To investigate whether gastric *Helicobacter pylori* (*H. pylori*) infection is associated with the progress of nonalcoholic fatty liver disease (NAFLD) in Dali city, China.

Methods: One thousand and one hundred eighty-five adults who had visited a health examination center were enrolled. Nonalcoholic fatty liver disease and *H. pylori* infection were assessed by abdominal color ultrasound and ¹³C-urea breath test, respectively. Serum lipid metabolic indices were compared between NAFLD subjects without and with *H. pylori* infection.

Results: The prevalence rate of NAFLD for the entire study population (n=1185) was 44.6% (n=529), including 167 women and 362 men. Among 529 NAFLD subjects, *H. pylori* was confirmed as a significant and independent risk factor for NAFLD (95% CI 1.02-1.79, $p=0.036$, OR =1.35). Compared with *H. pylori* non-infected individuals (n=721), higher contents of

LDL-C ($p=0.012$) along with TC ($p=0.014$) were also observed in *H. pylori*-infected individuals (n=464).

Conclusion: A positive correlation is identified between *H. pylori* infection and NAFLD.

Keywords: *H. pylori* infection, nonalcoholic fatty liver disease, lipid metabolic dysfunction, Dali city

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Nonalcoholic fatty liver disease (NAFLD) is a frequent metabolic condition in humans, creating a global public health concern.¹ An estimated 400 million people have NAFLD in China, and it has been linked to more than 100 thousand deaths.^{2,3} Research evidence shows that NAFLD is strongly related to insulin resistance, metabolic syndrome, as well as obesity.⁴ However, the association of gastrointestinal microbes to the pathogenesis of NAFLD remains unclear.⁵

Helicobacter pylori (*H. pylori*) pose a threat to nearly half of the world's population.^{6,7} Infection of *H. pylori* is commonly responsible for gastritis, gastric cancer, as well as peptic ulcer disease. In particular, novel research findings have opined a strong link between *H. pylori* infection and extra-digestive manifestations, namely, diabetes, obesity, liver tumors, cardiovascular disease, and lipid metabolism disorders.⁸ Notably, in recent years, *H. pylori* infection has been viewed as a

potentially important causative agent associated with the development of NAFLD.

However, connection linking *H. pylori* infection to NAFLD remains debated. Positive associations of NAFLD with *H. pylori* infection have been investigated in numerous studies,⁹⁻¹¹ whereas some studies have reported conflicting results.¹²⁻¹⁵ Under these circumstance, more clinical data are needed to address the connection of NAFLD with *H. pylori* infection. Locally, no studies regarding NAFLD and *H. pylori* association are available. Therefore, herein, we primarily purposed to explore the association of NAFLD with *H. pylori* infection in medical check-ups in Dali city, a Bai ethnic minority area in western Yunnan province of China.

Methods. We conducted this retrospective research using electronic medical data from participants (age, >18 years) who underwent comprehensive health check-ups at a tertiary hospital in Dali city between January 2017 and June 2019 (Figure 1). We included data from participants consisting of anthropometric parameters and results of ¹³C-urea breath test (UBT), serum biochemistry, ultrasound color imaging of the abdomen, and ultrasound color imaging of neck. We excluded subjects who had (i) a history of significant alcohol intake: females (≥ 140 g/week), and males (≥ 210 g/week); (ii) a treatment history with amiodarone, methotrexate, glucocorticoid and tamoxifen; (iii) individuals with celiac disease, Wilson's disease, viral hepatitis, lack of beta lipoprotein, autoimmune hepatitis, total parenteral nutrition, and congenital lipid atrophy; (iv) those under treatment with proton pump inhibitors (PPI) for 2 weeks or under treatment with bismuth salts and antibiotics for 4 weeks prior to the ¹³C-UBT; (v) individuals with upper gastrointestinal disorders' history; (vi) participants with cancer or mental conditions; and (vii) previously underwent gastric surgery. The ethical committee of Dali University Hospital granted the study protocol and ethical approval (No: 20200118).

Physical examinations and serum biochemical examinations. Anthropometric parameters (weight along with height) were also assessed. And body mass index (BMI) was determined as kg/m². We recorded the systolic, as well as diastolic blood pressure during the

physical examination. A fully automatic biochemical system (Hitachi 7600, Tokyo, Japan) was used to test the serum biochemical indices: alanine aminotransferase (ALT), total cholesterol (TC), aspartate aminotransferase (AST), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), urea, albumin (ALB), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), creatinine, and uric acid.

Assessment of NAFLD. Each of the participant was subjected to Color Doppler ultrasound imaging of the abdomen by an independent radiologist with a Logiq E8 radiology ultrasound equipment (GE Corp., Chicago, IL, USA). We diagnosed NAFLD on the basis of the results of the ultrasound photographs and the current diagnostic reference criteria.¹⁶

Establishment of *H. pylori* infection. Each subject was assessed for *H. pylori* infection using ¹³C-UBT kit (Headway, Zhonghe, Shenzhen, China). After ≥ 8 hours of fasting overnight, we orally administered a 75 mg ¹³C-urea capsule to all subjects and collected 2 samples of exhaled breath at baseline, as well as 30 mins after the capsule was consumed. We analyzed the samples using a HCBT-01 ¹³C detection system (Headway, Shenzhen, China). If the results of 2 samples differed by >4 /thousand ($\delta\%$) meant a participant was positive for *H. pylori* infection, as previously described.¹⁷

Statistical statistics. The characteristics of the subjects are presented as mean \pm SD for normally distributed continuous variables and as percentages for categorical data. We compared the characteristics of subjects across the NAFLD status with the Chi-square test or t-test. Then logistic regression was employed to investigate the effect of various parameters on NAFLD and *H. pylori* infection association by adjusted odds ratios (ORs). We also constructed 4 different models. Model 1 included only *H. pylori* infection. Age and carotid plaque status were added to Model 2. Model 3 was Model 2 with further adjustment for ALT, AST, and UA levels. Finally, more potential indicators and confounders, including FPG, TC, TG, SBP, DBP, LDL-C, and BMI were added to Model 4. Point-biserial correlation was employed to evaluate the correlation between *H. pylori* infection and TC, as well as LDL-C.

Statistical analysis was implemented in the SPSS Statistics 23.0 software (for windows, IBM, Armonk, NY, USA). P-value of <0.05 signified statistical significance.

Results. Overall, 1185 participants (407 women and 778 men) were enrolled. The prevalence rate of NAFLD for the entire study population (n=1185) was 44.6% (n=529), including 167 women and 362 men.

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Participants with NAFLD were significantly older, with lower levels of HDL-C and higher weight, SBP, and DBP, as well as elevated contents of TC, AST, TG, FPG, LDL-C, and ALT (all $p < 0.05$). Differences in ALB contents and height between the NAFLD and non-NAFLD subjects were not significant ($p > 0.05$). A higher prevalence rate of *H. pylori* infection was reported in the individuals with NAFLD (43.5%) relative to that of in the individuals without NAFLD (35.7%, $p = 0.007$) (Table 1).

Table 2 summarizes several risk factors related to NAFLD after logistic regression analysis. The levels of ALT (OR = 1.02, 95% CI 1.01-1.03), BMI (OR = 4.38, 95% CI 3.29-5.84), FPG (OR = 2.29, 95% CI 1.31-3.40), TG (OR = 2.33, 95% CI 1.73-3.14), and DBP (OR = 1.73, 95% CI 1.17-2.56) were independent risk factor of NAFLD (all $p < 0.05$). Notably, *H. pylori* was similarly a strong independent risk factor for NAFLD (95% CI 1.02-1.79, OR = 1.35, $p = 0.036$). These findings illustrate that *H. pylori* functions as a mediator of NAFLD.

Furthermore, to clarify the link between NAFLD and *H. pylori* infection, we constructed 4 different

models. Consequently, *H. pylori* infection (unadjusted OR = 1.38; for 95% CI 1.09-1.75, $p = 0.007$) was remarkably linked to NAFLD as indicated in Table 3. Additional adjustment for carotid plaque and age attenuated the result was 95% CI 1.05-1.68, OR = 1.33, $p = 0.020$. However, after adjusting the model for AST, UA, and ALT, the OR for NAFLD was escalated (95% CI 1.10-1.83, OR = 1.42, $p = 0.008$). In the fully adjusted model (Model 4), infection of *H. pylori* correlated with an elevated risk of NAFLD (95% CI 1.02-1.79, OR 1.35, $p = 0.036$). To elucidate the potential underlying mechanisms of *H. pylori* infection in NAFLD, we conducted an analysis to determine the correlation of *H. pylori* infection with several metabolic syndrome constituents. Compared to the *H. pylori* (-) individuals, the *H. pylori* (+) individuals had elevated TC and LDL-C contents (all $p < 0.05$, Table 4). However, the differences in FPG ($p = 0.492$), TG ($p = 0.409$), DBP ($p = 0.614$), BMI ($p = 0.142$), SBP ($p = 0.776$), and HDL-C ($p = 0.087$) between these 2 groups were not significant. Furthermore, point-biserial correlation was employed to evaluate the correlation between *H. pylori* infection and TC, as well as LDL-C.

Table 1 - Comparison of study participants demographics and biochemical profiles between cgroup and non-NAFLD group.

Demographics and biochemical profiles	NAFLD group (n=529)	Non-NAFLD group (n=656)	t/ χ^2	P-value
Gender, male, N (%)	362 (68.4)	416 (63.4)	3.268	0.071
<i>Helicobacter pylori</i> (+), N (%)	230 (43.5)	234 (35.7)	7.285	0.007
Carotid plaque (+), N (%)	104 (19.7)	63 (9.6)	24.461	0.000
Age (years)	43.50±9.94	40.90±11.28	-4.211	0.000
Body mass index (kg/m ²)	26.83±3.48	23.02±3.12	-19.594	0.000
Systolic blood pressure (mm Hg)	125.42±16.81	117.34±15.56	-8.573	0.000
Diastolic blood pressure (mm Hg)	81.75±11.98	76.12±10.76	-8.421	0.000
Total cholesterol (mmol/L)	5.36±1.34	4.98±0.94	-6.276	0.000
Triglyceride (mmol/L)	2.43±1.57	1.31±0.82	-11.562	0.000
HDL-C (mmol/L)	1.22±0.34	1.44±0.42	9.866	0.000
LDL-C (mmol/L)	3.15±0.89	2.92±0.78	-4.490	0.000
Fasting plasma glucose (mmol/L)	5.19±1.62	4.69±1.20	-6.016	0.000
Alanine aminotransferase (U/L)	32.50±9.12	20.82±10.91	-11.810	0.000
Aspartate aminotransferase (U/L)	26.15±6.28	20.40±4.14	-5.107	0.000
Albumin (g/L)	47.58±3.11	47.26±3.61	-1.573	0.116

LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol

Table 2 - Univariate regression analysis for risk factors associated with nonalcoholic fatty liver disease (NAFLD).

Risk Factors	β	S.E.	Wald	P-value	Odds ratio	95% Confidence intervals
<i>Helicobacter pylori</i>	0.30	0.14	4.38	0.036	1.35	1.02-1.79
Age	0.01	0.01	3.03	0.043	1.01	0.99-1.03
Carotid plaque	0.37	0.21	2.30	0.014	1.45	0.95-2.21
Alanine aminotransferase (U/L)	0.02	0.01	17.81	0.000	1.02	1.01-1.03
Aspartate aminotransferase (U/L)	0.03	0.01	9.31	0.002	1.95	1.90-2.00
Uric acid	0.00	0.00	2.46	0.001	1.03	1.02-1.04
Body mass index (kg/m ²)	1.48	0.15	102.19	0.000	4.38	3.29-5.84
Fasting plasma glucose (mmol/L)	0.83	0.28	8.53	0.003	2.29	1.31-3.40
Total cholesterol (mmol/L)	-0.14	0.19	0.52	0.040	2.78	2.54-3.72
Triglyceride (mmol/L)	0.85	0.15	30.83	0.000	2.33	1.73-3.14
HDL-C	-0.27	0.20	1.90	0.168	0.76	0.52-1.12
LDL-C	0.32	0.20	2.56	0.000	2.83	2.35-3.34
Systolic blood pressure (mm Hg)	0.06	0.23	0.06	0.800	1.06	0.68-1.66
Diastolic blood pressure (mm Hg)	0.55	0.20	7.56	0.006	1.73	1.17-2.56

S. E.: standard error, B: unstandardized coefficient

Table 3 - Multivariate logistic regression analysis for nonalcoholic fatty liver disease (NAFLD) after adjusting effects of confounders.

Multivariate logistic regression analysis	β	S. E.	Wald test	P-value	Odds ratio	95% Confidence intervals
Model 1	0.32	0.12	7.27	0.007	1.38	1.09-1.75
Model 2	0.28	0.12	5.40	0.020	1.33	1.05-1.68
Model 3	0.35	0.13	7.14	0.008	1.42	1.10-1.83
Model 4	0.30	0.14	4.38	0.036	1.35	1.02-1.79

Model 1 included only *Helicobacter pylori* infection. Age and carotid plaque status were added to Model 2. Model 3 was Model 2 with further adjustment for alanine aminotransferase, aspartate aminotransferase, and uric acid levels. Finally, more potential indicators and confounders, including fasting plasma glucose, total cholesterol, triglyceride, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, and body mass index were added to Model 4.

As presented in **Figure 1**, there was a positive correlation between *H. pylori* infection and TC ($p=0.015$, $r=0.071$, **Figure 2A**). And *H. pylori* infection was also positively correlated with LDL-C ($p=0.013$, $r=0.072$, **Figure 2B**). Collectively, our results provide evidence that infection of *H. pylori* may be involved in the pathogenesis of NAFLD by influencing the metabolism of cholesterol.

Discussion. Nonalcoholic fatty liver disease is a frequent metabolic affecting nearly one-third of the world's population, but the underlying mechanism remains poorly understood. Many factors, namely, metabolic, behavioral, genetic, and environmental, may be responsible for NAFLD pathogenesis.¹⁸

Findings over recent years have established possible associations of *H. pylori* infection with NAFLD.¹⁹ Herein, a positive influence of *H. pylori* infection on NAFLD was demonstrated. Remarkably, after ruling out additional confounders, consisting of age, blood lipids, carotid plaque, blood glucose, liver enzymes, and blood pressure, *H. pylori* infection (95% CI 1.02-1.79, OR 1.35, $p=0.036$) remained the only independent factor for NAFLD. This finding is in accordance with that of a previous report which documented a positive correlation between NAFLD and *H. pylori* infection.²⁰

The initial view of NAFLD is a hepatic indication of the metabolic disorder has been changing, and it is currently regarded that the occurrence of NAFLD may

Table 4 - Effect of *Helicobacter pylori* (*H. pylori*) infection on metabolic syndrome indicators in nonalcoholic fatty liver disease (NAFLD) individuals.

Biochemical profiles	<i>H. pylori</i> (+) (n=230)	<i>H. pylori</i> (-) (n=299)	t / U	P-value
Total cholesterol (mmol/L)	5.24±1.10	5.09±1.02	-2.47	0.014
Triglyceride (mmol/L)	1.71±1.24	1.69±1.34	-0.659	0.411
HDL-C	1.31±0.37	1.35±0.42	1.71	0.087
LDL-C	3.10±0.86	2.98±0.82	-2.51	0.012
Systolic blood pressure (mm Hg)	121.14±16.29	120.86±16.79	-0.29	0.776
Diastolic blood pressure (mm Hg)	78.85±11.74	78.50±11.61	-0.50	0.614
Fasting plasma glucose (mmol/L)	4.95±1.34	4.89±1.48	-0.69	0.492
Body mass index (kg/m ²)	24.92±3.64	24.59±3.89	-1.47	0.142

HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

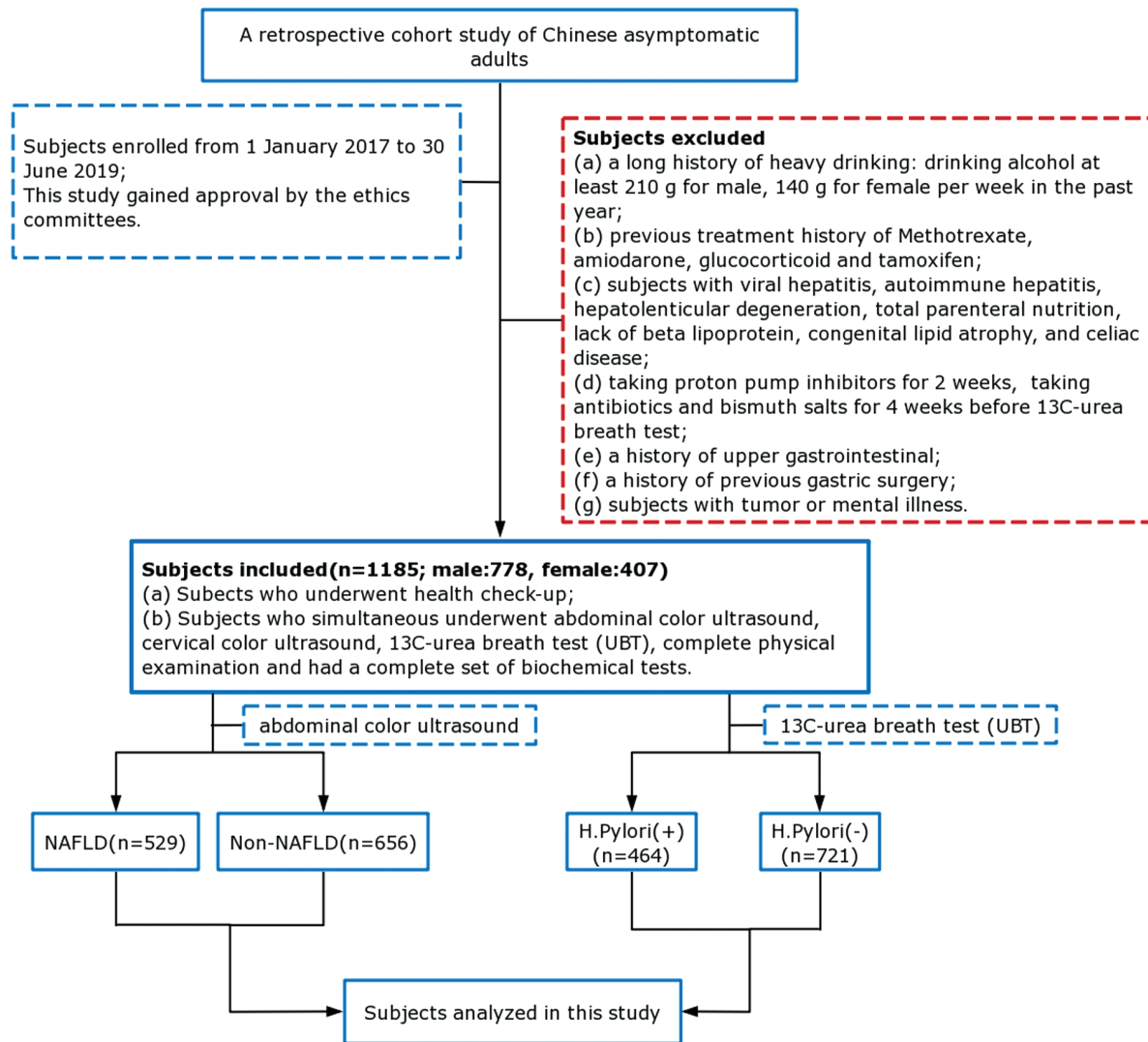


Figure 1 - Flowchart of study population selection flowchart. NAFLD: nonalcoholic fatty liver disease, *H. pylori*: *Helicobacter pylori*

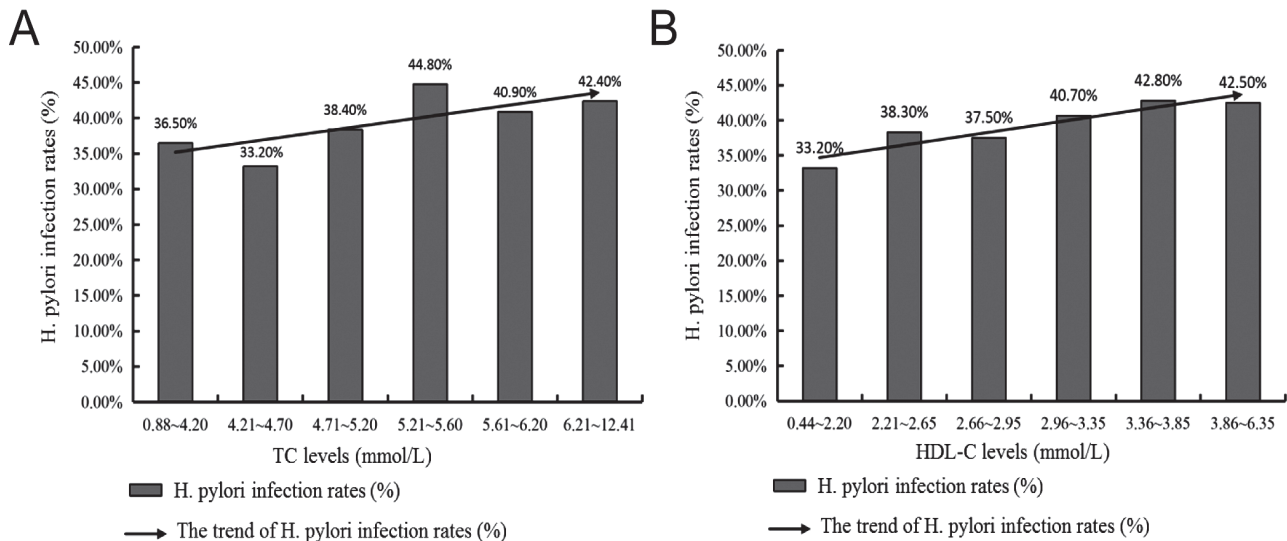


Figure 2 - *Helicobacter pylori* (*H. pylori*) infection rates in nonalcoholic fatty liver disease (NAFLD) individuals categorized by A) total cholesterol (TC) and B) low-density lipoprotein cholesterol (LDL-C).

precede metabolic syndrome.²¹ Thus, when combined with the analysis of several metabolic indices, we obtained higher weight, DBP, and SBP and elevated contents of TG, FPG, TC, BMI, and LDL-C (all $p < 0.05$) in individuals with NAFLD in contrast with those without NAFLD. We also identified DBP, BMI, FPG, and TG, as remarkable risk factors of NAFLD. Therefore, we speculated that a potential interaction exists between the NAFLD and metabolic syndrome constituents. As noted in another study, metabolic syndrome itself may contribute to the onset and progress of NAFLD, and vice versa.²²

Abundant published research has demonstrated that infection of *H. pylori* is strongly associated with NAFLD, as well as metabolic syndrome.²³⁻²⁶ Herein, we also evaluated whether *H. pylori* infection affected various metabolic syndrome indicators (namely, HDL-C, SBP, FPG, TC, DBP, BMI, TG, and LDL-C). Notably, both LDL-C and TC contents were elevated in the *H. pylori* (+) group ($p < 0.05$). Consequently, *H. pylori* infection may contribute to an escalation in LDL-C and TC contents. This finding is in accordance with a previous meta-analyses report that confirmed the influence of *H. pylori* infection on the lipid profile in serum.²⁷ However, herein, the effects of *H. pylori* infection on other metabolic indicators were not verified. Here, we enumerate some possible reasons for our results. First, some guidelines before blood collection were provided to the participants. Some biochemical and physiological indicators of the participants in their original living

environment (namely, kidney function, blood lipid, liver function, blood pressure, and blood glucose,) may have been underestimated. Second, the study included only subjects with higher education level working in government-affiliated institutions in Dali City. They are likely to have a higher level of health awareness than rural populations. Therefore, these study findings may be biased toward participants with better living standards, better dietary profiles, as well as good health awareness.

Study limitations. Our findings merit consideration, along with several potential limitations. First, this was a retrospective, single-center research. Another limitation of this study is the possible sample bias. Only subjects who underwent health check-ups were enrolled in the analysis. Thus, generalizing the findings to other populations is a challenge. Our present results require further verification using larger samples with different socioeconomic backgrounds. Third, no follow-up of the participants was performed. Fourth, we only confirmed that the infection of *H. pylori* was an independent risk factor for NAFLD in present study. The underlying mechanism of *H. pylori* infection evoking NAFLD was mere speculation. More in-depth prospective studies are required for the precise mechanistic association between *H. pylori* infection and NAFLD.

In summary, *H. pylori* infection may be a potential important contributor of NAFLD. However, further studies are needed to elucidate the precise mechanism of the relationship between *H. pylori* infection and NAFLD.

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