Longitudinal analysis of factors related to Helicobacter pylori infection in Chinese adults

Yan Gong#, Yi Luo#, Zhilai Chen, Ying Sui, Yansong Zheng*

Abstract: This research aimed to analyze lifestyle-related factors which influence Helicobacter pylori (Hp) infection and outcomes in Chinese adults. A single-center, retrospective study was performed from January 2012 to December 2020. Self-administered questionnaires were used to collect relevant lifestyle information, and the 13C-urea breath test was used to diagnose active Hp infection. A total of 18,211 subjects were enrolled in the study, of which 5,511 were females (30.26%). Subjects were studied longitudinally for up to five follow-up visits. At baseline, gastric Hp test was negative in 10,670 subjects (58.59%) and positive in 7,541 subjects (41.41%). Males exhibited a significantly higher Hp infection rate than females (38.56% vs 2.65%, respectively; \( \chi^2 = 26.45, P < 0.001 \)). Throughout the course of follow-up, Hp positive rates in the subjects decreased (\( \chi^2_{\text{trend}} = 666.04, P < 0.001 \)). Among the subjects with baseline negative results, 3–6% changed from negative to positive during follow-up. In contrast, among those with baseline positive results, >70% remained positive, and 21–26% changed from positive to negative. However, only 22–27% of Hp-infected subjects received pharmacotherapy. The results indicate the prevalence of Hp infection is high in the Chinese population. That additional effort is required to prevent and control Hp infection.

Keywords: Helicobacter pylori, infection rate, follow-up, health management, opportunistic screening

1 Introduction

Helicobacter pylori (Hp) is a gram-negative spiral bacillus bacterium that attacks the epithelial lining of the stomach, typically remaining there for many years [1–3]. Hp infection is a primary causal factor in numerous gastrointestinal (GI) pathologies including chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer [4,5]. In 1994, the World Health Organization/International Agency for Research on Cancer designated Hp as a class I carcinogen. Epidemiological reports suggest that the world’s Hp-infected population has reached 4.4 billion. Prevalence rates differ significantly by geographical region, with the highest prevalence observed in Africa (70.1%; 95% CI = 62.6–77.7) and lowest in Oceania (24.4%; 95% CI = 18.5–30.4). Among individual countries, Hp infection rates vary from 18.9% (95% CI = 13.1–24.7) in Switzerland to 87.7% (95% CI = 83.1–92.2) in Nigeria [6]. Infection rates are significantly higher in developing countries (80%) than in developed countries (30%), and are higher in rural areas than in urban areas. Hp infection is significantly affected by lifestyle. One report documented that the Hp infection rate in the Chinese population is 40–60%, which places China among the group of highly-infected countries [7]. Indeed, Hp is one of China’s most common chronic bacterial infections [8–10].
Among individuals, the conditions which dictate Hp infection may change due to treatment or re-infection.

Many unanswered questions remain concerning Hp infection, including the likelihood of self-recovery and infection clearance if no treatment is received. Also unknown are the mitigating factors which drive treatment paradigms for infected individuals. There is a critical need for more studies which address these important questions. The 13C-urea breath test (UBT) is a gold-standard clinical method used to diagnose an active Hp infection [11]. Routine health examinations provide an opportunistic screening tool for identifying Hp infection and, to some degree, also can be analyzed to identify disease prevalence in the population [12]. The objective of this study is to investigate the lifestyle factors which influence Hp infection rates in the Chinese adult population, as determined by questionnaires and the 13C-UBT. This study was performed in a cohort of patients undergoing routine health examinations at a single center over 10 years of follow-up.

2 Methods

2.1 Study population

All adults (≥18 years) undergoing routine health examination who received a gastric Hp test at the Institute of Health Management, Chinese PLA General Hospital from January 2012 to December 2020 were included in the study. A total of 105,623 subject-visits were evaluated, initially. Examinees who received no re-examination or had only one health examination result were excluded from the study, as were those who took oral antibiotics or proton-pump inhibitors within 1 month prior to the gastric Hp test and those who underwent a second examination within 6 months. In total, 56,075 subject-visits were excluded, and 49,548 subject-visits were included. Among the included subjects were 18,211 individuals who also were tracked longitudinally for up to five follow-up visits over time. The study protocol was approved by the Chinese People’s Liberation Army General Hospital ethics committee (S2021-636-01). All individuals enrolled were informed that their physical examination data would be de-identified, and signed consent documents.

2.2 Clinical evaluations

Basic demographic information including subjects’ age, sex, date of birth, and date of health examination was recorded at first examination, and follow-up duration was calculated based on the length of time between the first examination and subsequent re-examinations. Each follow-up visit recorded whether Hp pharmacotherapy was received in the time between the previous and current visit, including standard triple or quadruple pharmacotherapy for Hp. A questionnaire was used to determine subjects’ marital status, education level, smoking and drinking habits, and epigastric symptoms including epigastric pain, abdominal distension, hiccup, nausea, and vomiting. If any of these symptoms were frequently present in a subject, he/she was determined to be positive for epigastric discomforts. Marital status was classified to single or married, with the former including never married, divorced, and widowed and the latter explicitly referring to having partners living together. Other important criteria evaluated at initial examination for each subject included the presence or absence of tooth disorders, particularly dental calculus or loose teeth [13]. Halitosis referred to a foul smell in the mouth that was noticeable by the subjects’ themselves, or others.

2.3 13C-UBT

13C-labeled urea breath test diagnostic reagent (Helikit™, Alta Chem Pharma Ltd, Canada) [4] was used to determine Hp infection during examination. Subjects were counseled to not take any antibiotics within 1 month and not eat for at least 4 h before the examination. The diagnostic test required subjects to slowly exhale through a straw into the collection tube for about 4–5 s, upon which the examiner (or subject) tightened the cap immediately. A small volume of drinking water (75 mL) was then added to the plastic bottle containing the 13C-urea kit. The solution was mixed until reagent completely dissolved and then drunk slowly by the subjects. Subjects then rested for 30 min with no eating or drinking, and then exhaled again into the collection tube as before. The samples in the two tubes were then analyzed using gas chromatography coupled with the isotope ratio mass spectrometer (Pure Co, Ltd, USA). A change in value of ≥4 over baseline (the initial test) was judged as Hp positive, indicating the presence of an active gastric Hp infection.

2.4 Data processing and analysis

A library was constructed with Epidata 3.0, and data were entered using a double-blinded method. Data were
automatically verified and relative errors were checked by trained data entry operators. Statistical analysis was performed using Stata 11.0. Endpoint values were expressed as mean ± standard deviation, and follow-up duration was expressed using median only. Main effect differences in the measurement and numeration data between the groups were calculated by t-test and chi-square test, respectively. One-way analysis of variance, chi-square trend test, univariable and multivariable logistics regression analyses all used P < 0.05 as the cut-off value for statistical difference.

Ethical approval and consent to participate: All procedures in this study complied with the guidelines of the Helsinki Declaration on Human Experimentation. The study protocol was approved by the Ethical Committee of the PLA General Hospital, and written informed consent was obtained from all participants.

3 Results

3.1 Baseline characteristics of the study population

The clinical and demographic data of the 18,211 subjects at baseline which were relevant for this study are shown in Table 1. Subjects’ age at baseline was 48.06 ± 8.44 years. About 12,700 (69.74%) subjects were male and 5,511 (30.26%) were female. Rates of Hp infection were significantly higher in males than in females (44.15% vs 33.10%; $\chi^2 = 170.7609; P < 0.001$). The Hp-negative and positive groups were 10,670 (58.59%) and 7,541 (41.41%) subjects, respectively. There were significant differences between these groups in age, sex ratio, education level, smoking and drinking habits, comorbidity with tooth disorders, or halitosis ($P < 0.001$).

Table 1: Clinical and demographic data of 18,211 subjects at baseline

| Characteristic                  | Hp-negative group (n = 10,670) | Hp-positive group (n = 7,541) | Statistical parameters and P value |
|--------------------------------|--------------------------------|------------------------------|-----------------------------------|
|                                | Age 47.65 ± 8.41                | 48.58 ± 8.74                 | $\chi^2$ 7.232 $P < 0.001$         |
|                                | Gender                          |                              |                                   |
|                                | Female 3,018 (28.28)            | 1,493 (19.80)                | 170.76 $P < 0.001$                |
|                                | Male 7,652 (71.72)              | 6,048 (81.20)                |                                   |
|                                | Marital status                  |                              |                                   |
|                                | Single 4,652 (43.60)            | 3,236 (42.91)                | 0.849 0.357                       |
|                                | Married 6,018 (56.40)           | 4,305 (57.09)                |                                   |
|                                | Education level                 |                              |                                   |
|                                | Senior high school or below 3,146 (29.48) | 3,846 (51.01) | 868.653 $P < 0.001$              |
|                                | Undergraduate 6,253 (58.61)     | 3,013 (39.95)                |                                   |
|                                | Postgraduate or above 1,271 (11.91) | 682 (9.04)     |                                   |
|                                | Smoking habit                   |                              |                                   |
|                                | Non-smoker 6,084 (57.02)        | 4,056 (53.79)                | 33.959 $P < 0.001$                |
|                                | Ex-smoker 865 (8.11)            | 542 (7.19)                   |                                   |
|                                | Smoker 3,721 (34.87)            | 2,943 (39.02)                |                                   |
|                                | Drinking habit                  |                              |                                   |
|                                | No drinking 4,512 (42.29)       | 3,051 (40.46)                | 68.537 $P < 0.001$                |
|                                | Occasional drinking 2,459 (23.05) | 1,458 (19.33) |                                   |
|                                | Frequent drinking 3,699 (34.66) | 3,032 (40.21)                |                                   |
|                                | Comorbidity with tooth disorders|                              |                                   |
|                                | No tooth disorders 6,879 (64.47) | 3,342 (44.32) | 751.428 $P < 0.001$              |
|                                | Dental calculus 2,713 (25.43)    | 3,199 (42.42)                |                                   |
|                                | Loose teeth 1,078 (10.10)       | 1,000 (13.26)                |                                   |
|                                | Epigastric discomforts          |                              |                                   |
|                                | No 8,945 (83.83)                | 5,465 (72.47)                | 345.404 $P < 0.001$               |
|                                | Yes 1,725 (16.17)               | 2,076 (27.53)                |                                   |
|                                | Halitosis                       |                              | 347.907 $P < 0.001$               |
|                                | No 6,977 (65.39)                | 3,893 (51.62)                |                                   |
|                                | Yes 3,693 (34.61)               | 3,648 (48.38)                |                                   |
3.2 Risk factor analysis associated with *Hp* infection

Risk factors found to be significantly associated with *Hp* infection status shown in Table 1 were analyzed in a stratified manner and presented in Table 2. Education status is clearly associated with *Hp* infection, as high education level had significantly lower OR of *Hp* infection as compared with low education level. Additional risk factors for *Hp* infection included age, male sex, smoking, frequent drinking, dental calculus, loose teeth, epigastric discomforts, and halitosis.

### 3.3 Longitudinal assessment of *Hp* infection rates in follow-up

Basic information pertaining to follow-up completion is shown in Table 3. As expected, a small but significant increase in the mean age of subjects during follow-up was observed ($F = 255.94, P < 0.001$). Subjects who completed all five follow-up visits were more likely to be male than female ($\chi^2_{\text{trend}} = 25.64, P < 0.001$), and there was a significant decrease in rates of *Hp*-positive tests during the follow-up period ($\chi^2_{\text{trend}} = 666.04, P < 0.001$).

### 3.4 Changes in *Hp* infection status during follow-up

A summary of the overall changes in *Hp* infection status of the 18,211 subjects is shown in Table 4. The data suggest that of those subjects who tested negative at baseline, 94–98% remained negative after a median of 1,893 days of follow-up, and 3–6% went on to test positive for *Hp* infection. Conversely, of those who tested positive at baseline, 74–79% remained positive and 21–26% went on to test negative during follow-up. Interestingly, the total percentage of subjects changing from *Hp*-positive to negative during follow-up was significantly greater than that changing from negative to positive ($n = 890, 20.92\%$ vs $n = 2,822, 10.56\%$; $\chi^2 = 1,500, P < 0.001$). This was the case for each follow-up visit, where the percentage of subjects changing from *Hp*-positive to negative was significantly higher than that changing from negative to positive ($P < 0.001$).

### 3.5 Comparison of treatment

Of the 7,541 subjects who were *Hp*-positive at baseline, the infection status outcomes in subjects who received standard triple or quadruple therapy are shown in Table 5. At each follow-up visit, the percentage of *Hp*-infected subjects receiving pharmacotherapy was 22–27%, and those not receiving pharmacotherapy was 73–78% ($P < 0.001$). Of the subjects receiving pharmacotherapy, the percentage of subjects changing from *Hp*-positive to negative remained 93–96% throughout follow-up ($\chi^2 = 1.09, P = 0.895$). Of those who did not receive pharmacotherapy, the percentage of subjects changing from positive to negative was 0–0.05%.

### 3.6 Analysis of influencing factors of receiving treatment

Of the 7,541 subjects who were positive at baseline, 2,006 subjects received pharmacotherapy and 5,535
Table 3: Follow-up results of *Hp* infection status in the subjects

| Follow-up visit | Baseline test | The first follow-up | The second follow-up | The third follow-up | The fourth follow-up | The fifth follow-up |
|-----------------|---------------|---------------------|----------------------|---------------------|----------------------|---------------------|
| Sample size (n) | 18,211        | 18,211              | 7,719                | 3,587               | 1,436                | 384                 |
| Age (years)     | 48.06 ± 8.43  | 48.06 ± 8.43        | 51.22 ± 8.19*        | 52.68 ± 8.22*       | 54.14 ± 8.28*        | 55.68 ± 8.66*       |
| Follow-up duration (day) |             |                     |                      |                     |                      |                     |
| Median          | 485           | 841                 | 1,150                | 1,488.5             | 1,893                |                     |
| (P5–P95) interval | 279, 1,480   | 572, 1,819          | 824, 2,330           | 1,056, 2,301        | 1,063, 2,568         |                     |
| Min. and Max.   | 181, 44,555   | 370, 42,702         | 545, 42,667          | 736, 43,006         | 920, 2,779           |                     |
| Gender          |               |                     |                      |                     |                      |                     |
| Male (%)        | 12,700 (69.74) | 5,523 (71.55)*     | 2,598 (72.43)*       | 1,039 (72.35)*      | 301 (78.39)*         |                     |
| Female (%)      | 5,511 (30.26) | 2,196 (28.45)       | 989 (27.57)          | 397 (27.65)         | 83 (21.61)           |                     |
| *Hp* infection  |               |                     |                      |                     |                      |                     |
| Negative (%)    | 10,670 (58.59) | 5,478 (70.97)       | 2,678 (74.66)        | 1,106 (77.02)       | 289 (75.26)          |                     |
| Positive (%)    | 7,541 (41.11) | 2,241 (29.03)*      | 909 (25.34)*         | 330 (22.98)*        | 95 (24.74)*          |                     |

*When compared with the baseline or the first follow-up results, *P* < 0.05.

Table 4: Changes in *Hp* infection status at each follow-up visit from baseline

| Follow-up visit | Number of subjects | *Hp*-negative at baseline (10,670 subjects) | *Hp*-positive at baseline (7,541 subjects) | Statistical parameters and *P* value |
|-----------------|--------------------|---------------------------------------------|---------------------------------------------|-----------------------------------|
|                 |                    | Keeping negative (%) | Changing to positive (%) | Keeping positive (%) | Changing to negative (%) | *χ*² | *P* |
| First           | 7,541              | 10,121 (94.85)       | 549 (5.15)                        | 5,623 (74.57)       | 1,918 (25.43)          | 1,600 | <0.001* |
| Second          | 2,583              | 4,921 (95.81)        | 215 (4.19)                        | 2,026 (78.44)       | 557 (21.56)           | 575.20 | <0.001* |
| Third           | 1,063              | 2,443 (96.79)        | 81 (3.21)                         | 828 (77.89)         | 235 (22.11)           | 332.52 | <0.001* |
| Fourth          | 377                | 1,021 (96.41)        | 38 (3.59)                         | 292 (77.45)         | 85 (22.55)            | 127.59 | <0.001* |
| Fifth           | 115                | 262 (97.40)          | 7 (2.60)                          | 88 (76.52)          | 27 (23.48)            | 43.50  | <0.001* |

*Comparison of percentage of subjects changing from negative to positive versus that from positive to negative at each follow-up visit, *P* < 0.05.

Table 5: Effects of pharmacotherapy on subjects who were *Hp*-positive

| Follow-up visit | Subjects (n) | Receiving no pharmacotherapy | Receiving pharmacotherapy |
|-----------------|--------------|-------------------------------|----------------------------|
|                 |              | Keeping positive (%) | Changing to negative (%) | Total (%) | Keeping positive (%) | Changing to negative (%) | Total (%) |
| First           | 7,541        | 5,532 (99.95)              | 3 (0.05)                   | 5,535 (73.40) | 51 (4.54)           | 1,915 (95.46)           | 2,006 (26.60)* |
| Second          | 2,583        | 1,997 (99.95)              | 1 (0.05)                   | 1,998 (77.35) | 29 (4.96)           | 556 (95.04)            | 585 (22.65)*  |
| Third           | 1,063        | 814 (100.00)               | 0                          | 814 (76.58)       | 14 (5.62)           | 235 (94.38)            | 249 (23.42)*  |
| Fourth          | 377          | 287 (100.00)               | 0                          | 287 (76.13)       | 5 (5.56)            | 85 (94.44)             | 90 (23.87)*   |
| Fifth           | 115          | 86 (100.00)                | 0                          | 86 (74.78)        | 2 (6.90)            | 27 (93.10)             | 29 (25.22)*   |

*P < 0.001 for the percentage of subjects receiving treatment versus that receiving no treatment.

received no pharmacotherapy between the initial examination and first follow-up. Factors influencing the subjects’ decision to receive pharmacotherapy were epigastric discomforts (OR = 1.488, *P* < 0.001, 95% CI: 1.262–1.756) and halitosis (OR = 1.343, *P* < 0.001, 95% CI: 1.215–1.485), as determined by the stepwise multivariable logistics regression analysis of the questionnaire.
4 Discussion

A number of studies have been performed on *Hp* infection rates in China, the consensus of which have reported a *Hp* prevalence rate of 40–60% [7], meaning that almost one out of every two individuals is infected. However, most of these studies are cross-sectional in nature, and cohort studies have been rare [14–18]. Prior research has confirmed that chronic gastritis, peptic ulcer [19], and gastric cancer [20] are closely associated with *Hp* infection, and ~1% of infected individuals eventually progress to have gastric cancer [21,22]. In contrast with the numerous probiotic microbeota that colonize the GI system, *Hp* are pathogenic microbes, and *Hp* eradication is an important step in preventing gastric cancer. Eradication at the superficial gastritis or asymptomatic stage has been shown to have the most significant benefit. Health benefits of *Hp* eradication outweigh the risks, as there is no evidence of an association between *Hp* eradication and disease risk [23].

The optimal time for *Hp* eradication appears to be prior to the onset of gastric mucosal atrophy and intestinal metaplasia [24]. Professor Correa, an American pathologist, believes that *Hp* eradication prior to onset of gastric mucosal atrophy and intestinal metaplasia can prevent the development of intestinal gastric cancer by nearly 100% [25]. Even after the onset of intestinal metaplasia, *Hp* eradication still contributes to the repair of gastric mucosa by helping to maintain the intestinal status quo and prevent progression to gastric cancer [26].

One thing which remains clear is that *Hp* pathogenicity in humans is influenced by both the duration of infection combined with individual susceptibility. Factors associated with high *Hp* prevalence rate observed in many countries worldwide include hygiene, dietary hygiene, living habits, and even housing conditions.

This study found that the *Hp* infection rate was 41.41% in Chinese adult subjects at our institution and was significantly higher in males than that in females. We used the non-invasive 13C-UBT which remains the gold-standard test to confirm *Hp* infection, having sensitivity and specificity greater than 95% [11,27]. The population of this study is unique, having a higher overall income and health awareness, which probably explains why the *Hp* infection rate was on the lowest end of those previously reported. However, the infection rate in this cohort was higher in males than in females, consistent with previous studies [28].

A large-scale prospective case–cohort study in the Chinese population recently reported that the *Hp* infection rate was significantly higher in urban populations, or those with higher education levels, but no significant differences were observed between sexes or across the age spectrum [29]. In contrast, in the present study, education level was determined to be associated with a lower *Hp* infection rate, and age, male sex, smoking, frequent drinking, dental calculus, loose teeth, epigastric discomforts, and halitosis were additional risk factors in *Hp* infection.

Our previous study reported that males are more susceptible to *Hp* infection, and that efforts to maintain proper oral hygiene and prevent oral disorders, particularly dental calculus and loose teeth, are essential for avoiding or eradicating *Hp* [13]. Moreover, we and others have consistently shown that *Hp* prevalence increases with age [30,31]. One surprising outcome of the present study is that, despite the subjects’ age and male percentage increasing over time during follow-up, the *Hp* infection rate decreased ($\chi^2_{\text{end}} = 666.04, P < 0.001$). This contrasts with what is expected based on previous reports. Additionally, the percentage of subjects changing from *Hp*-positive to negative during follow-up was significantly higher than that from negative to positive ($\chi^2 = 1,500, P < 0.001$). We believe that a principal reason for this could be due to the increase in individual awareness of the dangers of *Hp* infection, thus leading to more individuals seeking pharmacotherapy. From a healthcare perspective this could be viewed as a positive development because it indicates that *Hp* testing during routine health examination is having a beneficial impact on public health.

At each follow-up visit, the percentage of subjects receiving no pharmacotherapy (73–78%) remained significantly greater than that of subjects receiving treatment (22–27%, $P < 0.001$). Among the untreated subjects, vanishingly few (0–0.05%) reverted from *Hp*-positive to negative, and the vast majority remained positive. Also of interest was the percentage of *Hp*-negative subjects (~3–6%) who subsequently tested positive upon follow-up after 485 days (1.33 years) or 1,893 days (5.19 years). This suggests that *Hp*-negative people may become infected, or previously treated patients may become re-infected if they do not take precautions. Clearly there is much to be learned regarding mechanisms of *Hp* infection and the means to prevent its occurrence.

The results of the present study suggest that pharmacotherapy is highly effective in *Hp*-positive patients, with an eradication rate >90%. Indeed, pharmacotherapy may be the principal reason for the decline in *Hp* infection rate observed in the subjects over time. Throughout the course of follow-up, 70% of individuals who were *Hp*-positive at baseline remained positive, even up to 2,779 days of follow-up. At the same time, a subset of *Hp*-negative people has the potential to become infected. Based on
this evidence we conclude that health examination plays an important role in the screening, prevention, and control of Hp infection, especially for Hp-negative adults. Furthermore, it is of great practical importance to take active measures to prevent and control Hp infection. For the Hp-positive population, the presence of frequent epigastric discomforts (OR = 1.488, P < 0.001, 95% CI: 1.262–1.756) and halitosis (OR = 1.343, P < 0.001, 95% CI: 1.215–1.485) were significant factors which influenced their decision to seek pharmacotherapy. The low percentage of subjects receiving pharmacotherapy suggests that efforts to re-enforce health education are vital for encouraging asymptomatic populations to seek therapy.

Our study was strengthened by the large size of the cohort examined (18,211), combined with the duration of follow-up in this cohort. Intervals of at least 6 months between each follow-up visit prevented the potential for error caused by re-examination within a short period after pharmacotherapy. Hp test results were dynamically monitored over time in each subject that received a follow-up examination, which allowed us to discern the duration and outcomes of Hp infection in this population. These results will inform healthcare practitioners and provide guidance for screening and managing Hp infection in the population.

A notable limitation to this study is that a substantial number of subjects were lost to follow-up after the second visit, such that only ~2.11% of the original 18,211 completed all five follow-up visits, because physical examinations concerned were opportunistic and optional, the loss of follow-up was more severe in this retrospective study. Given this limitation, this study can only confirm that >70% of the Hp-positive population remained positive in a median follow-up duration of 1,893 days. While this finding does not necessarily suggest that Hp infection will last forever in the absence of therapy, it does suggest that the possibility of self-recovery after Hp infection is relatively low. As such, individuals should be counseled on the long-term benefits and advantages of Hp eradication.

In conclusion, we demonstrated that the prevalence of Hp infection is high in the Chinese adult population. Aggressive pharmacotherapy consistently eradicates Hp at a high clearance rate, but this outcome is limited by the fact that <30% of all Hp-positive patients receive therapy. Rates of Hp-positivity remain high in the absence of pharmacotherapy. Thus, it is clear from this study that additional effort is required on the part of healthcare providers and their patients, to prevent and control Hp infection in the long term.

Acknowledgements: The authors would like to acknowledge the wholehearted support from the faculty of the Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital.

Funding information: This work was supported by grants from the Applied Basic Research Project of Logistics Support Department of CMC (No. 19BJZ24).

Author contributions: All listed authors meet the requirements for authorship. Y.S. Zheng designed this study, wrote the review, and prepared the tables. Y. Gong and Y. Luo wrote the original drafts, reviewed, and edited the manuscript. Z.L. Chen and Y. Sui acquired and analyzed the data. All authors read and approved the final manuscript.

Conflict of interest: Authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

[1] Lee YC, Dore MP, Graham DY. Diagnosis and treatment of Helicobacter pylori infection. Annu Rev Med. 2022;73:183–95. doi: 10.1146/annurev-med-042220-020814.

[2] Zeng M, Mao XH, Li JX, Tong WD, Wang B, Zhang YJ, et al. Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386(10002):1457–64. doi: 10.1016/S0140-6736(15)60310-5.

[3] Yuan C, Adeloye D, Luk TT, Huang L, He Y, Xu Y, et al. The global prevalence of and factors associated with Helicobacter pylori infection in children: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2022;6(3):185–94. doi: 10.1016/S2352-4642(21)00400-4.

[4] Aumpan N, Vilaichone RK, Nunanpan P, Chonprasertserk S, Siramolpiwat S, Bhanthumkomol P, et al. Predictors for development of complete and incomplete intestinal metaplasia (IM) associated with H. pylori infection: a large-scale study from low prevalence area of gastric cancer (IM-HP trial). PLoS One. 2020;15(10):e0239434. doi: 10.1371/journal.pone.0239434.

[5] Collatuzzo G, Pelucchi C, Negri E, López-Carrillo L, Tugane S, Hidaka A, et al. Exploring the interactions between Helicobacter pylori (Hp) infection and other risk factors of gastric cancer: a pooled analysis in the Stomach cancer Pooling (StoP) Project. Int J Cancer. 2021;149(6):1228–38. doi: 10.1002/ijc.33678.
Factors related to *Helicobacter pylori* infection

[6] Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. Gastroenterology. 2017;153(2):420–9. doi: 10.1053/j.gastro.2017.04.022.

[7] Ren S, Cai P, Liu Y, Wang T, Zhang Y, Li Q, et al. Prevalence of *Helicobacter pylori* infection in China: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2022;37(3):644–70. doi: 10.1111/jgh.15751.

[8] Chen L, Xu W, Lee A, He J, Huang B, Zheng W, et al. The impact of *Helicobacter pylori* infection, eradication therapy and probiotic supplementation on gut microenvironment homeostasis: an open-label, randomized clinical trial. EBioMedicine. 2018;35:87–96. doi: 10.1016/j.ebiom.2018.08.028.

[9] Liu Y, Li D, Liu Y, Shuai P. Association between *Helicobacter pylori* infection and non-alcoholic fatty liver disease, hepatic adipose deposition and stiffness in southwest China. Front Med (Lausanne). 2021;8:764472. doi: 10.3389/fmed.2021.764472.

[10] Ding SZ, Du YQ, Lu H, Wang WH, Cheng H, Chen SY, et al. Chinese consensus report on family-based *Helicobacter pylori* infection control and management (2021 Edition). Gut. 2022;71(2):238–53. doi: 10.1136/gutjnl-2021-325630.

[11] Best LM, Takwoingi Y, Siddique S, Selladurai A, Gandhi A, Low B, et al. Non-invasive diagnostic tests for *Helicobacter pylori* infection. Cochrane Database Syst Rev. 2018;3(3):CD012080. doi: 10.1002/14651858.CD012080.

[12] Hsairi M, Medhi F, Bellaaj R, Kassim M. Health screening strategies in Maghreb countries: situation analysis and perspectives. Tunis Med. 2018;96(10–11):688–95.

[13] Zheng Y, Liu M, Shu H, Chen Z, Liu G, Zhang Y. Relationship between oral problems and *Helicobacter pylori* infection. Arch Oral Biol. 2014;59(9):938–43. doi: 10.1016/j.archoralbio.2014.05.020.

[14] Wang X, Shu X, Li Q, Li Y, Chen Z, Wang Y, et al. Prevalence and risk factors of *Helicobacter pylori* infection in Wuwei, a high-risk area for gastric cancer in northwest China: an all-ages population-based cross-sectional study. Helicobacter. 2021;26(4):e12810. doi: 10.1111/hel.12810.

[15] Sun Y, Zhang L. *Helicobacter pylori* recrudescence and its influencing factors. J Cell Mol Med. 2019;23(12):7919–25. doi: 10.1111/jcmm.14682.

[16] Xie Y, Song C, Cheng H, Xu C, Zhang Z, Wang J, et al. Long-term follow-up of *Helicobacter pylori* infection and its risk factors after initial eradication: a large-scale multicentre, prospective open cohort, observational study. Emerg Microbes Infect. 2020;9(1):548–57. doi: 10.1080/22221751.2020.1737579.

[17] Xue Y, Zhou LY, Lu HP, Liu JZ. Recurrence of *Helicobacter pylori* infection: incidence and influential factors. Chin J Med (Engl). 2019;132(7):765–71. doi: 10.1097/CMA.0000000000000146.

[18] Pan KF, Zhang L, Gerhard M, Ma JL, Liu WD, Ulm K, et al. A large randomised controlled intervention trial to prevent gastric cancer by eradication of *Helicobacter pylori* in Linqu County, China: baseline results and factors affecting the eradication. Gut. 2016;65(1):9–18. doi: 10.1136/gutjnl-2015-309197.

[19] Zhu W, Li J, Shen H. Banxia Xieixin Decoction in the treatment of Hp-associated peptic ulcer: a protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021;100(2):e24105. doi: 10.1097/MD.00000000000024105.

[20] Alipour M. Molecular mechanism of *Helicobacter pylori*-induced gastric cancer. J Gastrointest Cancer. 2021;52(1):23–30. doi: 10.1007/s12029-020-00518-5.

[21] Sukri A, Hanafiiah A, Mohamad Z, Kosai NR. Epidemiology and role of *Helicobacter pylori* virulence factors in gastric cancer carcinogenesis. APMIS. 2020;128(2):150–61. doi: 10.1111/apm.13034.

[22] Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut. 2020;69(12):2113–21. doi: 10.1136/gutjnl-2020-320839.

[23] Leung WK, Wu MS, Kagawaga Y, Kim JJ, Yehg KG, Koh KL, et al. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol. 2008;9(3):279–87. doi: 10.1016/S1470-2118(08)70072-X.

[24] Liu JM, Malfertheiner P, Lee YC, Sheu BS, Sugano K, Cheng HC, et al. Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: the Taipei global consensus. Gut. 2020;69:2093–112.

[25] Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. Lancet. 1975;2(7924):58–60. doi: 10.1016/s0140-6736(75)90498-5.

[26] Watari J, Chen N, Amenta PS, Fukui H, Oshima T, Tomita T, et al. *Helicobacter pylori* associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. World J Gastroenterol. 2014;20(18):5461–73. doi: 10.3748/wjg.v20.i18.5461.

[27] Gisbert JP, Esteban C, Jimenez I, Moreno-Otero R. 13C-urea breath test during hospitalization for the diagnosis of *Helicobacter pylori* infection in peptic ulcer bleeding. Helicobacter. 2007;12(3):231–7. doi: 10.1111/j.1523-5738.2007.00492.x.

[28] Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. Aliment Pharmacol Ther. 2018;47(7):868–76. doi: 10.1111/apt.14561.

[29] Yang L, Kartsonaki C, Yao P, de Martel C, Plummer M, Chapman D, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with *Helicobacter pylori* infection in China: a case–cohort study. Lancet Public Health. 2021;6(12):e888–96. doi: 10.1016/S2546-2667(21)00164-X.

[30] Ding Z, Zhao S, Song G, Li Z, Mao M, Xu X, et al. Prevalence and risk factors of *Helicobacter pylori* infection in asymptomatic Chinese children: a prospective, cross-sectional, population-based study. Aliment Pharmacol Ther. 2015;42(8):1019–26. doi: 10.1111/apt.13364.

[31] Chen ZL, Sai XY. A cross sectional survey of infection rate of *Helicobacter pylori* in the health physical examination population. Chin J Clinicians (Electron Ed). 2013;7(22):10044–7.