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Prevalence of *Helicobacter pylori* infection in a third-tier Chinese city: relationship with gender, age, birth-year and survey years

W. Hong[1], H.-L. Tang[2], X.-L. Dong[3], S.-K. Hu[4], Y. Yan[5], Z. Basharat[6,7], V. Zimmer[8,9], L. Tzivian[10,11], M. Leja[11], Z.-H. Gao[12], A. Sharma[13], V. Tsukanov[14], W.-J. Geng[15]

[1]Department of Gastroenterology and Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China
[2]Department of Anesthesiology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China
[3]Department of Gastroenterology and Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China
[4]Department of Gastroenterology and Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China
[5]Department of Gastroenterology and Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China
[6]Jamil-ur-Rahman Center for Genome Research, Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan
[7]Laboratoire Génomique, Bioinformatique et Chimie Moléculaire, Conservatoire National des Arts et Métiers, Paris, France
[8]Department of Medicine II, Saarland University Medical Center, Saarland University, 66424 Homburg, Germany
[9]Department of Medicine, Marienhausklinik St. Josef Kohlhof, 66539 Neunkirchen, Germany
[10]Faculty of Medicine, University of Latvia, Riga, Latvia
[11]Institute of Clinical and Preventive Medicine, University of Latvia; Digestive Diseases Centre Gastro, Riga, Latvia
[12]Department of Computer and Information, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China
[13]Department of Anesthesia, Pain Management and Critical Care, Nepal Mediciti Hospital, Sainbu, Bhaisepati, Lalitpur, Nepal
[14]Department of Gastroenterology, Scientific Research Institute of Medical Problems of the North, Partizana Zhelezniaka 3G, Krasnoyarsk, Russia
[15]Department of Anesthesiology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China

Corresponding Authors: Wandong Hong, MD; e-mail: xhnk-hwd@163.com
Wujun Geng, MD; e-mail: gengwujun@126.com

Abstract – *Objective:* This study aims to investigate the prevalence of Helicobacter Pylori *(H.pylori)* infection and its relation with gender, age, birth-year, and survey years.
Patients and Methods: We conducted a cross-sectional study on subjects that had undergone healthy check-ups for *H. pylori* infection in a university hospital in mainland China between January 2013 and December 2017. The relationship between age, birth-year, and survey years and prevalence of *H. pylori* infection was investigated by Joinpoint regression analysis.
Results: A total of 53,260 subjects were enrolled in this study. The overall prevalence of *H. pylori* infection was 48.4%. *H. pylori* infection prevalence was higher in females than in men. In subjects with age younger than 36 years, a greater increase in age was associated with an increased prevalence of *H. pylori* infection, reaching a peak at 36 years of age. In subjects with age older than 36 years, the prevalence of *H. pylori* infection did not change significantly with age. As to birth-year, the prevalence of *H. pylori* in subjects born between 1923 and 1980 did not significantly change with birth-year. It was followed by a rapid decline in those born between 1980 and 2004. Age-standardized *H. pylori* infection prevalence was marginally higher in women than in men (44.5% vs. 43.5%, $p = 0.025$). The observed age-adjusted prevalence of *H. pylori* infection decreased with survey year from 53.0% in 2013 to 39.5% in 2017.
Conclusions: The prevalence of *H. pylori* infection was relatively high in this cohort of patients and decreased from 2013 to 2017, and it changes according to gender, age, and birth-year.

Keywords: Epidemiology, Prevalence, *Helicobacter pylori*, Regression, China, Single-center study.

INTRODUCTION

The prevalence of Helicobacter Pylori (*H. pylori*) infection is thought to be varying across the countries and the ethnicities. The prevalence of *H. pylori* infection is high both in Africa (example: 87.7% in Nigeria) and in the developing countries of Asia, but its prevalence is low in the industrialized areas and in Western countries (example: 18.9% in Switzerland)[1]. A systematic review indicated that the urban populations have much lower rates of *H. pylori* infection than rural populations[2]. China is rapidly undergoing industrialization and urbanization with improvements in socioeconomic conditions and hygiene. Therefore, there is a hypothesis that the prevalence of *H. pylori* could be decreased in China over the past years. However, information about the time trends in the prevalence of *H. pylori* infection in the region of mainland China is limited and controversial[1,2].

In addition, several studies about the prevalence of *H. pylori* infection from mainland China have been conducted and published (mostly from first-tier megacities such as Shanghai, Beijing, and Guangzhou)[3-5]. Little information is available about the prevalence of *H. pylori* infection in third-tier Chinese cities, such as Wenzhou city ("Third-tier cities" in China refer to these fast-growing small and medium-sized cities)[6]. Wenzhou city has a resident population of 9.25 million with a per capita gross domestic product (GDP) of 65,055 Chinese Yuan (approximately 9700 US dollars), according to 2018 statistics[7].

Helicobacter pylori infection is known as the most important cause of peptic ulcer disease and gastric cancer[1,8]. A decline in the prevalence of the *H. pylori* infection in most countries has been associated with a parallel decline in peptic ulcer disease and gastric cancer[9,10]. Approximately 90% of non-cardia gastric cancer worldwide is estimated to be explained by this infection[8]. Peptic ulcer and gastric cancer occur more frequently in men[11,12]. Therefore, a particular interest subsists whether there is a specific gender predilection in *H. pylori* infection, since both peptic ulcer disease and gastric cancer have a high male-to-female ratio. However, the relationship between gender and the prevalence of *H. pylori* infection is still controversial[3]. On the other hand, Banatvala et al[13] indicated that the difference in the prevalence of *H. pylori* infection in the same geographic area over time might be due to the birth cohort effect. However, the effect of the birth-year on *H. pylori* prevalence has not been examined by Joinpoint regression analysis in China[14]. The degree of change by single birth year effect has not yet been clarified.

Understanding the epidemiologic patterns of *H. pylori* will aid us in prioritizing and customizing public health efforts to better manage the burden of this disease[1]. Sugano et al[15] claimed that older data on the prevalence of *H. pylori* cannot be used to describe the current situation in Asia.

On the basis of the above-mentioned reasons, this study aims to investigate the time trends in the prevalence of *H. pylori* infection and its relationship with age, gender, and birth-year.

MATERIALS AND METHODS

Study Design and Subject Selection

We conducted a cross-sectional study in the First Affiliated Hospital of Wenzhou Medical University in mainland China. All subjects who did annual healthy routine checkups between January 2013 and December 2017 were eligible for inclusion in this study. *H. pylori* infection was assessed by the ^{13}C-urea breath test after a minimum 6-hour fast[4]. The ^{13}C-urea breath test kit was purchased from Boran Pharmaceutical Company (Beijing, China). Each subject was requested to swallow a pill containing 75 mg ^{13}C-urea when performing the ^{13}C-urea breath test. All subjects were diagnosed with *H. pylori* infection if the ^{13}C-urea breath test was positive. The delta over baseline-value (DOB) of 4.0 was used as a cut-off point for the diagnosis of *H. pylori* infection. We compared the results of the cross-sectional analyses performed in all years of the study to investigate the common time trend for these years.

Inclusion, Exclusion Criteria, and Data Collection

Inclusion criteria were asymptomatic individuals with at least one-time undergoing the ^{13}C-urea breath test between January 2013 and December 2017. Exclusion criteria were: repeated ^{13}C-urea breath tests for the same subject during January 2013 and December 2017 (for which only the first ^{13}C-urea breath test was included in our study), and unavailability of results of ^{13}C-urea breath tests. Gender, birth-year, age, and results of ^{13}C-urea breath tests were recorded.

Statistical Analysis

Categorical variables were presented by counts and proportions and compared by the χ^2-test. A Shapiro-Wilk test was used to evaluate whether the continuous data had a normal distribution. According to the results of the Shapiro-Wilk test, continuous variables were expressed by mean ± standard deviation (SD) or median and interquartile range (IQR) and compared using the independent-samples *t*-test or the Kruskal-Wallis nonparametric test[16].

The overall prevalence of *H. pylori* infection was calculated as: all individuals with positive *H. pylori* test) / (all individuals who performed *H. pylori* test.

Firstly, we performed a stratified analysis of the prevalence of *H. pylori* by age groups and by sex. For this analysis, age was divided into five subgroups as follows: ≤30 years, 31 to 40 years, 41 to 50 years, 51 to 60 years, >61 years.

Secondly, we identified junction points, in which the prevalence of *H. pylori* assessed for all years of the study begun to increase or decrease. For this purpose, we built univariate Joinpoint regression in which relationships between age/birth year/survey year of participants and the prevalence of *H. pylori* was analyzed[17]. The annual percentage change (APC) with corresponding 95% confidence interval (CI) was calculated for each effect estimate[17].

Thirdly, we built a univariate linear regression model for the association between age of participants and the prevalence of *H. pylori*. Crude and age-standardized prevalence of *H. pylori* infection were reported when comparing gender differences and reporting yearly trends. The age-standardized prevalence was calculated using the direct standardization method using the World Population Standard (2000-2025), which was reported by the World Health Organization (WHO)[18,19].

Last, we built a multiple logistic regression analysis to evaluate the relationship between *H. pylori* infection, gender, and survey year. Odds ratio (OR) was calculated with 95% CI. Two-sided *p*-values below 0.05 were considered statistically significant. All analyses were performed using Joinpoint Trend Analysis Software Version 4.7.0.0 and STATA version 12.0.

RESULTS

Baseline Characteristics of Participants

A total of 53,260 subjects (62.0% males) were enrolled in this study (Figure 1). There were 1094, 1844, 2704, 10897, and 9222 individuals taken ^{13}C-urea breath test in 2013, 2014, 2015, 2016, and 2017, respectively. The overall prevalence of *H. pylori* infection was 48.4% irrespectively from the survey year. Subjects with *H. pylori* infection were more likely to be older (mean age: 46.5 ± 11.5 *vs.* 45.8 ± 12.1, $p < 0.001$) than those without *H. pylori* infection, and had a higher proportion of women (38.6% *vs.* 37.4%, $p = 0.002$). Distribution of sex and age-groups among 53,260 subjects is shown in Figure 2. The proportion of males and every age group did not significantly change during all study years, though the overall number of individuals who underwent ^{13}C-urea breath test increased rapidly with survey years (Figure 3).

Sex, Age, and Birth-Year

For all age categories combined, crude *H. pylori* infection prevalence was higher in females than in men (49.2% *vs.* 47.9%, $p = 0.002$). Age-standardized *H. pylori* infection prevalence was marginally higher in women than in men (44.5% *vs.* 43.5%, $p = 0.025$). The overall prevalence of *H. pylori* infection was 38.8%, 49.1%, 49.7%, 49.6%, and 48.1% in age groups ≤30, 31-40, 41-50, 51-60, and >60 years, respectively.

Based on the Joinpoint regression model, a non-linear association between ages and prevalence of *H. pylori* infection was observed (Figure 4). There were 11321 individuals with age ≤ 36 (mean age: 30.8 ± 4.1 years; male 61.1%). In subjects younger than 36 years, there was an association between older age and high prevalence of *H. pylori* (APC 2.81%; 95% CI 2.19 to 3.44; $p < 0.001$), reaching a peak at 36 years of age with an observed crude rate of 49.3% (modeled crude rate: 50.4%) (Figure 4). In subjects older than 36 years, the prevalence of *H. pylori* infection did not significantly change with age (Figure 4) (APC -0.10%; 95% CI -0.21 to 0.004; $p = 0.059$). Further linear regression analysis indicated that there were strong positive linear relationships between prevalence of *H. pylori* infection and age ≤ 36 years ($r = 0.91$, $p < 0.001$) (Figure 5).

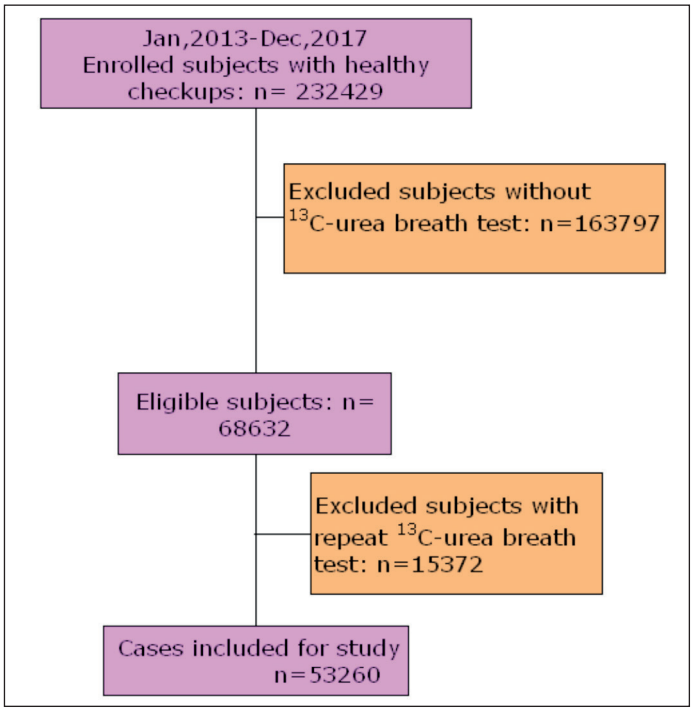

Figure 1. Flow diagram of patients included in the study.

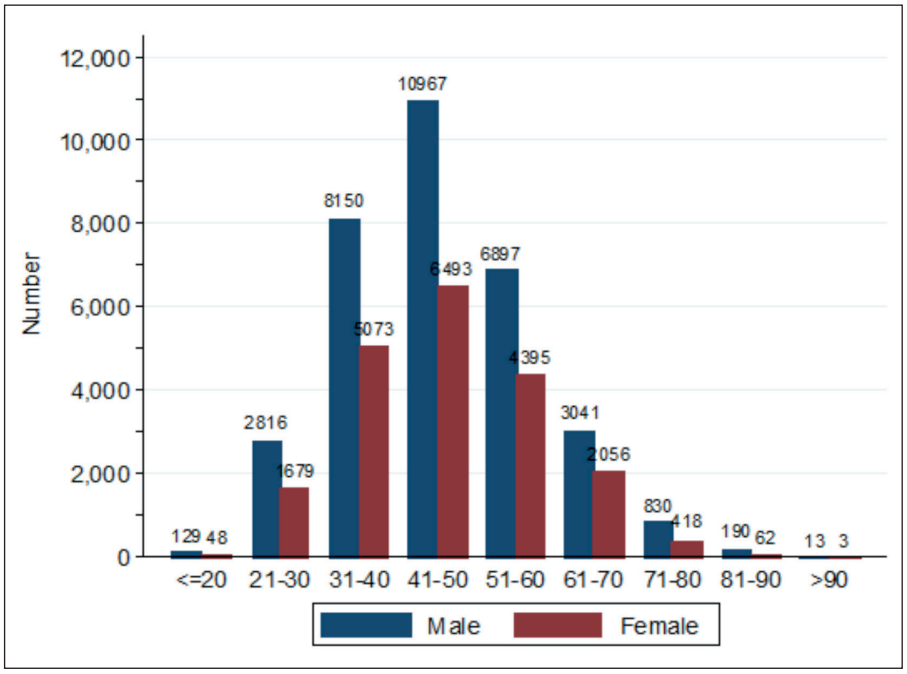

Figure 2. Distribution of sex and age-groups among 53,260 subjects irrespective of survey year.

As to birth-year, there was one significant joinpoint in the prevalence of *H. pylori* till 1980 (Figure 6). The prevalence of *H. pylori* in subjects was stable between participants that were born between 1923 and 1980 (APC = 0.08%; 95% CI -0.03 to 0.18; $p = 0.162$). It was followed by a rapid decline in those born between 1980 and 2004 with APC of -2.88% (95% CI -3.46 to -2.30; $p < 0.001$).

Multivariate logistic regression analysis indicated that male gender (OR = 0.94; 95% CI 0.90 to 0.97; $p < 0.001$) and age in groups of five years (OR = 1.03; 95% CI 1.02 to 1.03; $p < 0.001$) were associated with prevalence of *H. pylori* infection after adjustment by the year of survey.

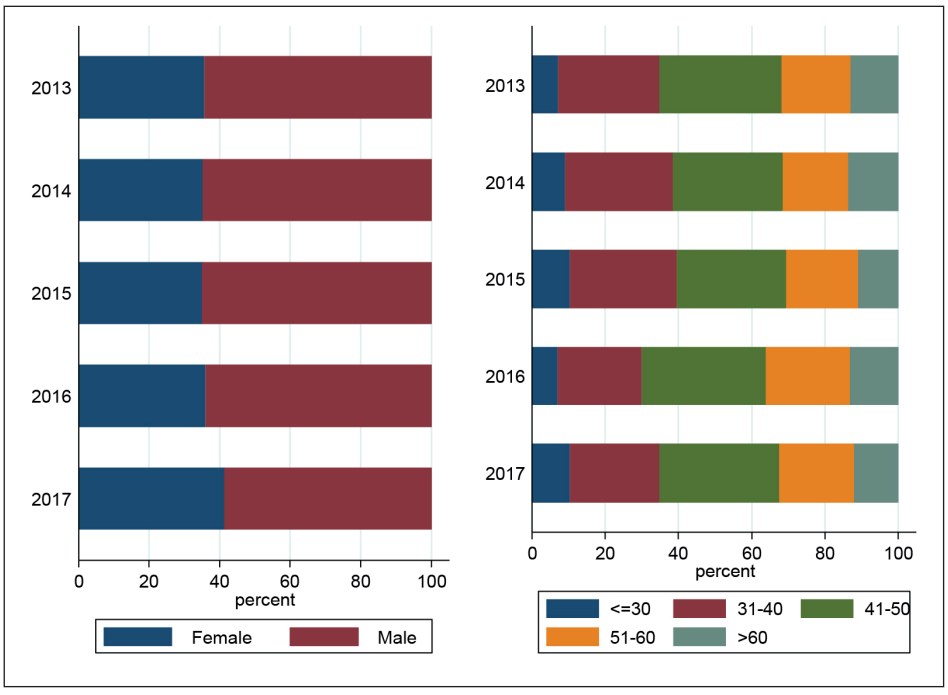

Figure 3. Distribution of sex and age groups among 53,260 subjects by survey year.

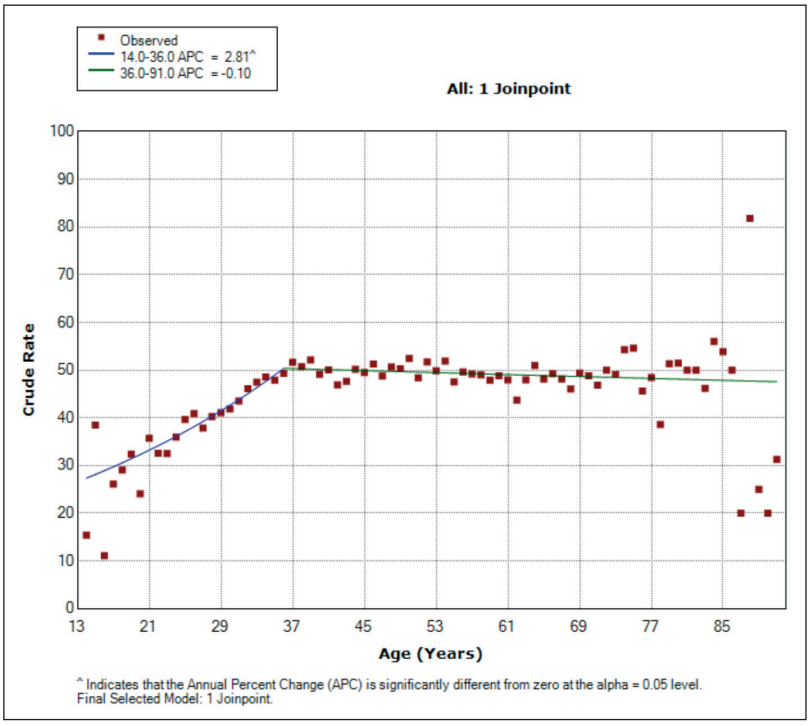

Figure 4. Relationship between age and prevalence of *Helicobacter pylori* infection among 53,260 subjects.

Yearly Trends

The crude prevalence of *H. pylori* infection gradually and significantly decreased with survey year from 55.2% in 2013 to 43.7% in 2017 irrespective of gender (Figure 7). The trend of decreasing crude prevalence of *H. pylori* infection over survey year remained stable when the analysis was stratified by gender (Figure 7) and age groups (Figure 8). The observed age-adjusted prevalence of *H. pylori* infection gradually and significantly decreased with survey year from 53.0% in 2013 to 39.5% in 2017 (APC=-8.52%; 95% CI-12.45 to -4.41; $p = 0.008$) (Figure 9). Multiple logistic regression adjusted for gender and age revealed that the survey year was associated with prevalence of *H. pylori* infection (OR = 0.87; 95% CI 0.86 to 0.89; $p < 0.001$).

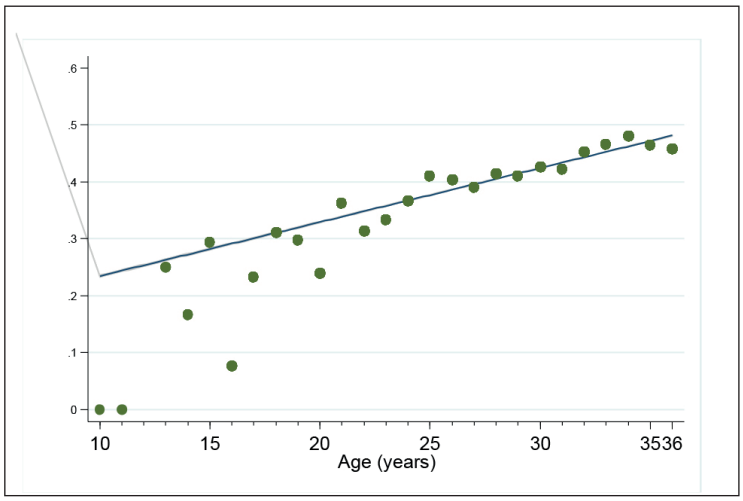

Figure 5. Relationship between age and prevalence of *H. pylori* infection for participants ≤36 years of age.

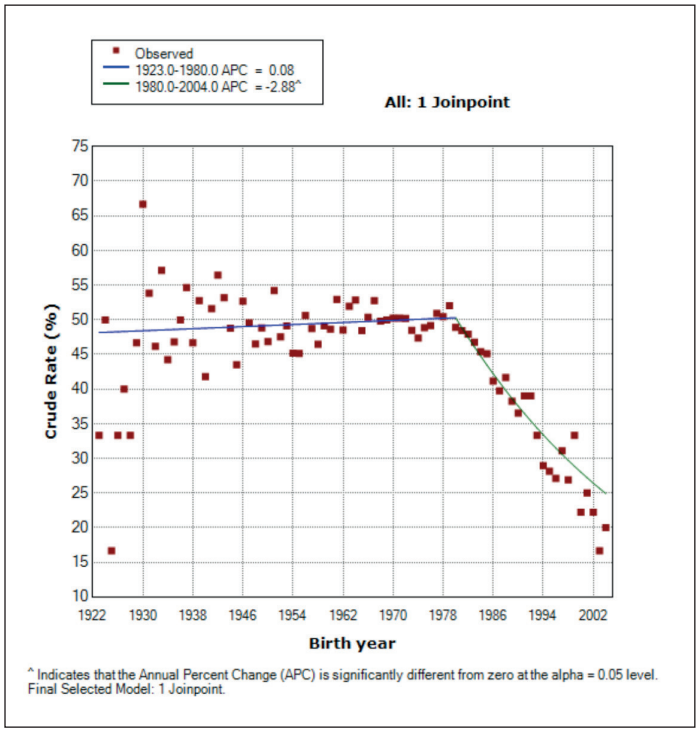

Figure 6. Relationship between birth-year and prevalence of *Helicobacter pylori* infection among 53,260 subjects.

DISCUSSION

The overall prevalence of *H. pylori* infection in our study was 48.4%, comparable to the result (47%) reported by Chen et al[3] from Guangzhou Province of China one decade ago. However, it was significantly lower than that (57.6%) in Linqu city, an underdeveloped rural region in Shandong Province in China[20]. It was also lower than that (71.7%) of Shanghai city in China[5]. These differences in *H. pylori* prevalence likely reflect the level of urbanization, sanitation, access to clean water, varied socioeconomic status, and different genetic background because there was an association between toll-like receptor 1 and *H. pylori* seroprevalence[21]. In ad-

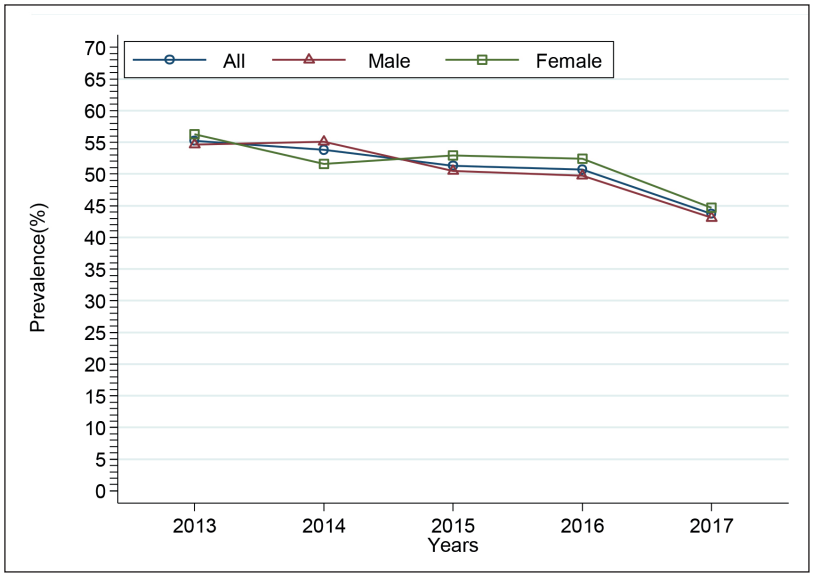

Figure 7. Prevalence of *H. pylori* infection in different survey years stratified by gender.

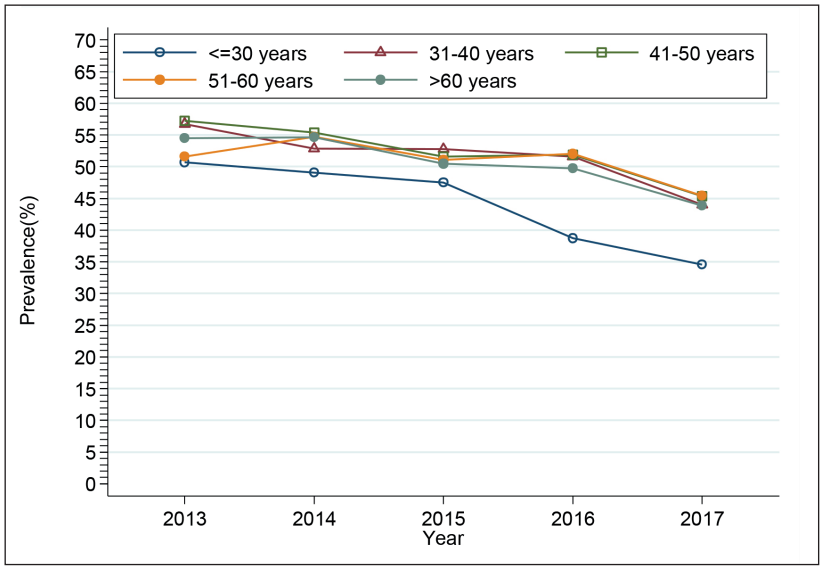

Figure 8. Prevalence of *Helicobacter pylori* infection in different survey years stratified by age groups.

dition, the differences in the technique used to detect *H. pylori* infection (^{13}C breath test or serology) may contribute to the variation in reported prevalence[5].

Data on the association between gender and the prevalence of *H. pylori* infection is somewhat conflicting. Indeed, most studies reported no significant difference of *H. pylori* infection between men and women, both in adults and in children[9,22]. Shi et al[22] showed that there was no association between the *H. pylori* infection and sex. This may have been because of reduced statistical power associated with the small sample size of these studies.

A meta-analysis suggested that male sex was associated with a greater prevalence of *H. pylori* infection, both in children (OR=1.06) and adults (OR=1.12)[23]. However, the reliability of the meta-analysis might have been impaired by a significant heterogeneity across the studies[23,24]. Malcolm et al[25] reported that the *H. pylori* infection was associated with age, sex, and socioeconomic conditions. Our study indicated that crude *H. pylori* infection prevalence was higher in females than in men (49.2% *vs.* 47.9%, $p = 0.002$). Age-standardized *H. pylori* infection prevalence was marginally higher in women than in men (44.5% *vs.* 43.5%, $p = 0.0246$).

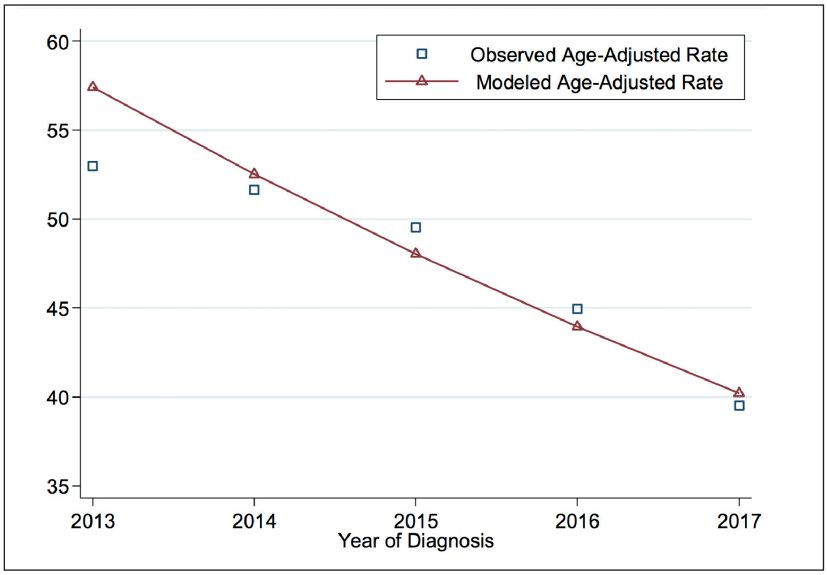

Figure 9. Annual age-standardized prevalence for *Helicobacter pylori* infection from 2013 to 2016.

The way in which the gender contributes to the different prevalence of *H. pylori* infection is unclear, though it is now becoming widely recognized that there are important sex differences in many diseases[18,26]. Women had higher IL-35 levels than men among *H. pylori*-infected peptic ulcer patients, *H. pylori*-infected asymptomatic subjects, and non-infected healthy subjects[27]. Female gender affects *Helicobacter pylori* eradication failure in chronic gastritis[28]. Therefore, there may be other co-factors in addition to *H. pylori* that are important for the development of gastric cancer.

There is controversy about the relationship between age and prevalence of *H. pylori*. Several studies[3,29] showed that the prevalence of *H. pylori* infection increased with age, and the prevalence was lower in subjects younger than 20 years old. Shi et al[22] showed that the prevalence at this age was similar to that in adults. Chen et al[3] noted that the prevalence rate steadily increased in children aged 1-5 years with a prevalence rate of 19.4%, reaching a plateau of 55% after the age of 50 years. *H. pylori* infection significantly varied with age (ranging from 5 to 32% for those aged <40 and >70 years, respectively) and was higher among those born overseas, as well as in the lowest socioeconomic areas[30]. Prevalence of *H. pylori* infection increased with age but reached a plateau by age 30, consistent with the notion that the disease is primarily acquired in childhood[31]. By contrast, Zou et al[5] indicated that the prevalence of *H. pylori* infection was similar in men and women and showed no clear trend with age. A similarly high prevalence was found in all age groups studied (72.7% for individuals aged 18-29 years, 71.7% for individuals with all age groups)[5].

Our study suggested that the overall prevalence of *H. pylori* infection in the age group ≤30 years (38.8%) was lower than that of the age group with 31-40 years (49.1%). When stratified by survey year, the individuals with age group ≤30 had the lowest prevalence of *H. pylori* infection compared to other age groups (Figure 8). In subjects with age younger than 36 years, there was an association between older age and high prevalence of *H. pylori* (APC 2.81%; 95% CI 2.19 to 3.44; $p < 0.001$) (Figure 4). Further Pearson correlation and linear regression analysis indicated that there was a strong positive linear correlation between the prevalence of *H. pylori* infection and age ≤36 years (r=0.91, $p < 0.001$) (Figure 5). In subjects with age older than 36 years, the prevalence of *H. pylori* infection did not significantly change with age (Figure 4) (APC -0.10%; 95% CI -0.21 to 0.004; $p = 0.059$). These results indicated that *H. pylori* infection is believed to be acquired mainly during childhood, remaining for the lifetime of the individual unless eradicated[2].

As to birth-year, by using Joinpoint regression analysis, Watanabe et al[32] found that there were two significant joinpoints in the prevalence of *H. pylori* infection in subjects born in 1949 and 1961 in a Japanese population. Our study indicated that there was only one significant joinpoint in the prevalence of *H. pylori* in 1980 (Figure 6). The prevalence of *H. pylori* in subjects born was stable between 1923 and 1980 (APC=0.08%; 95% CI -0.03 to 0.18; $p = 0.162$; Figure 6). It was followed by a rapid decline in those born between 1980 and 2004 with APC of -2.88% (95% CI -3.46 to -2.30; $p < 0.001$).

The prevalence of *H. pylori* infection was associated with family size, education level, and low socioeconomic status, including limited education, crowded homes, and difficult access to sanitized water[22]. Socioeconomic status also measured as a low family income, lower educational levels, living in a rural area, in crowded homes, and having contaminated sources of drinking water were risk factors for *H. pylori* infection[9]. China carried out the reform and opening-up policy since 1978, which has resulted in China's rapid economic development and passage to industrialization and urbanization. This has been a forerunner to the improvement in hygiene. As the second largest global economy, China is rapidly progressing and the implementation of the one-child policy since 1982 caused a decrease of family size. Therefore, joinpoint in the prevalence of *H. pylori* in 1980 in our study may be explained by these two policies.

With the improvement of socioeconomic conditions and hygiene, *H. pylori* infection rates present decreasing trends in many regions all over the world[3]. Two reviews indicated a decrease trend of prevalence of *H. pylori* infection over time in China[2] and Japan[8]. Chen et al[3] in China revealed that it was found a statistically significant decrease of *H. pylori* infection rate ranged from 11.4 to 18.0% in different age groups by comparing the prevalence rate of *H. pylori* infection in 2003 with data obtained in 1993. Kamada et al[31] in Japan reported that the overall prevalence of *H. pylori* infection was significantly lower among those studied in the 2010s (35.1%) compared to those evaluated in the 1990s (53%).

The crude prevalence of *H. pylori* infection gradually and significantly decreased with survey year from 55.2% in 2013 to 43.7% in 2017 independently from gender (Figure 7). The trend of decreasing crude prevalence of *H. pylori* infection over survey year remained stable when the analysis was stratified by gender (Figure 7) and age groups (Figure 8). The observed age-adjusted prevalence of *H. pylori* infection gradually and significantly decreased with survey year from 53.0% in 2013 to 39.5% in 2017 (APC=-8.52%; 95% CI-12.45 to -4.41; $p = 0.008$; Figure 9). Economic development with urbanization and reduced horizontal transmission of *H. pylori* due to improved sanitation may contribute to a decline in the prevalence of *H. pylori* infection[2]. Improved living standards associated with urbanization may reduce the prevalence of *H. pylori* infection, which could influence the observed trend. It is likely that the prevalence of *H. pylori* infection in China is decreasing too due to the improvements in living standards associated with recent rapid industrialization and urbanization.

The strength points of this study include a large sample size that gives the study enough statistical power. To our best knowledge, this is the first study investigating the relationship between prevalence of *H. pylori* infection and age, birth-year, and yearly trends in a Chinese population by Joinpoint regression analysis. Stratified analyses of age, gender, and survey year were also performed, which make our conclusion rigorous. All subjects had healthy checkups and all *H. pylori* infections were diagnosed by urea breath test which may make our study more homogeneous. The predominant tool used in most studies was serology; only in few studies urea breath tests or stool antigen tests were used[33]. The use of serology, that could give false positive results due to a past infection, may result in an over estimation of the prevalence of *H. pylori* infection[34]. Given that the detection methods for *H. pylori* infection vary in terms of their sensitivity and specificity, this factor could influence the observed trend in prevalence estimates over time. However, there are some limitations in the present study as well. Because our institution is an adult's hospital, the number of teenager is small.

CONCLUSIONS

The prevalence of *H. pylori* infection was relatively high in this cohort of patients and decreased from 2013 to 2017. *H. pylori* infection prevalence was higher in female than in men. In subjects with age younger than 36 years, a greater increase in age was associated with increased prevalence of *H. pylori* infection, reaching a peak at 36 years of age. In subjects with age older than 36 years, the prevalence of *H. pylori* infection did not significantly change with age. As to birth-year, the prevalence of *H. pylori* in subjects born did not change significantly between 1923 and 1980. It was followed by a rapid decline in those born between 1980 and 2004.

Availability of Data and Materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions:

All authors contributed toward data analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work. All the authors read and approve the manuscript.

Ethics Approval and Consent to Participate:

This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. This study was performed according to the principles expressed in the Declaration of Helsinki and informed consent was obtained from all the subjects.

Conflict of Interests:

The authors declare that they have no conflict of interests.

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