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REVIEW

Population attributable burden of *Helicobacter pylori*-related gastric cancer, coronary heart disease, and ischemic stroke in China

J. Jiang[1,2] · Y. Chen[1,2] · J. Shi[3] · C. Song[1,2] · J. Zhang[2] · K. Wang[1,2]

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Abstract *Helicobacter pylori*, a risk factor of cancer and chronic diseases, remains highly prevalent in China. This review aims to systematically evaluate the *H. pylori*-attributable burden for gastric cancer (GC), coronary heart disease (CHD), and ischemic stroke (IS) in the Chinese population. *Helicobacter pylori* prevalence was updated by pooling the results reported in studies across China. The population attributable fraction (PAF) was calculated based on the *H. pylori* prevalence 10 years ago and relative risks of specific disease by reviewing the prospective studies published from 2000 through 2015. In China, the nationwide average prevalence of *H. pylori* was estimated to be 42.06 % in the general population during 2009–2013. The fixed effects pooled relative risk (RR) of 1.89 [95 % confidence interval (CI): 1.57–2.26] was obtained for gastric cancer and *H. pylori* infection. *Helicobacter pylori* infection was responsible for around 37.38 % of noncardia GC, corresponding to about 105,536 cases in 2012. As for extra-gastric disorders, *H. pylori* infections had higher risk of CHD (RR = 1.55, 95 % CI: 1.37–1.76) and IS (RR = 1.54, 95 % CI: 1.42–1.66). About 23.15 % of CHD and 22.29 % of IS were attributable to *H. pylori* infection. The estimates of *H. pylori*-attributable burden reveal a great potential of reducing *H. pylori*-related chronic disease burden by *H. pylori* eradication. Large prospective studies are warranted to identify which *H. pylori* strains, which subtypes of the disease, and which subgroups of the population have the greatest risk of relevant diseases and the effect of *H. pylori* eradication on the prevention of *H. pylori*-related diseases.

Introduction

Over the past four decades or so, increasing evidence has indicated that infectious agents play an important role in human cancer and impose a large burden on global health. One of the most principal agents was the bacterium *Helicobacter pylori*, which accounted for 32.5 % of the 2 million new cancer cases attributable to infection worldwide that occurred in 2008 [1].

As reported, a similar situation has been occurring in China. In 2005, *H. pylori*, one of the most highly prevalent infections in China, was responsible for 9.8 % and 9.2 % of infection-related cancer cases and deaths, respectively [2].

In terms of *H. pylori*, it is a Gram-negative spiral bacterium usually colonizing gastric mucosa. The seroprevalence of *H. pylori* infection was about 50 % worldwide and the majority of infected subjects remain asymptomatic. Around 10 % of *H. pylori* infections would develop chronic gastritis or gastroduodenal ulcer. Persistent infection could bring about inflammatory cell infiltration and DNA damage, and result in an imbalance between proliferation and apoptosis of the gastric epithelial cells and even by secreting toxins, including CagA, VacA, lipopolysaccharides, and hemolysin [3]. It is well known that whether an individual develops a specific *H. pylori*-related disease, the incidence, and prevalence of

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✉ K. Wang
kjwang@163.com

[1] Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, No. 100 Science Avenue, Zhengzhou 450001, China

[2] Henan Key Laboratory of Tumor Epidemiology, Zhengzhou, China

[3] College of Basic Medicine, Zhengzhou University, Zhengzhou, China

several *H. pylori*-associated diseases depend on the interaction between mutations and recombination frequently of mixed *H. pylori* strains and the capacity of the host immune response. In 1994, *H. pylori* infection was classified as a class 1 carcinogen by the International Agency for Research on Cancer (IARC) [4]. In addition to the well-known *H. pylori*-associated chronic gastritis, peptic ulcer, and duodenal ulcer, enormous epidemiological studies have demonstrated that *H. pylori* infections have an increased risk of gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and a decreased risk of esophageal adenocarcinoma [5]. Actually, screening and eradication for *H. pylori* have been recommended and accepted as a common clinical practice in the treatment of gastritis and ulcer in China. Additionally, evidence has accumulated that *H. pylori* (especially CagA-positive *H. pylori*) may play an inducing role in some extra-digestive conditions, such as cardiovascular diseases, including coronary heart disease and cerebral infarction [6, 7]. The common pathogenesis of both diseases is atherosclerosis, in the initiation, development, or persistence, of which, sustained infection, systematic inflammatory response, and possibly accompanying dyslipidemia, hyperhomocysteinemia, hypercoagulability, impaired glucose metabolism, or endothelial dysfunction may play an important role [8, 9]. Additionally, *H. pylori* infection may also contribute to the development of various other disorders, such as diabetes mellitus, iron deficiency anemia, chronic obstructive pulmonary disease (COPD), and so on [10–13]. Notably, the relation of *H. pylori* prevalence and diverse spectrum of extragastric diseases seem to be ambiguous, vary among different populations of diverse characteristics, and could be modified by other factors. Khamechian et al. reported an inverse correlation between childhood asthma and *H. pylori* in Kashan [14], whereas no inverse association was observed between *H. pylori* and adult asthma with peptic ulcers by Chang and Hu [15]. As pooled by Vasapolli et al. [16], the effect of *H. pylori* infection on the development of gastroesophageal reflux disease (GERD) may differ among diverse categories of GERD in populations of different characteristics. The potential underlying mechanisms remain to be elucidated, which may help stimulate personalized medicine.

In China, these *H. pylori*-associated diseases add a great burden to public health. The morbidity and mortality of gastric cancer in 2012 was estimated to be about 31.28/100,000 and 22.04/100,000, respectively [17]. Stroke and cardiovascular disease have been the leading cause of death and constituted a severe health and social problem. What's more, the overall prevalence of *H. pylori* was as high as 54.76 % in the general population, which was revealed by a nationwide investigation covering 26,341 participants from 19 provinces and autonomous regions performed from January 2002 to June 2004 [18]. Seeing that a systematic quantitation of the disease burden attributable to *H. pylori* has not been performed in the Chinese population, this study aims to update the population attributable fraction (PAF) estimate of gastric cancer and evaluate the attributable burden of other *H. pylori*-related diseases, including coronary heart disease and ischemic stroke. Because of the lack of sufficient available literature on the Chinese population, this review will not address the possible disease burden of MALT, COPD, diabetes mellitus, and iron deficiency anemia attributable to *H. pylori*.

Materials and methods

Population attributable fractions

The PAF is an indicator applied to measure the proportion of the disease burden that would be theoretically avoided if the responsible exposure was eliminated or the individual was no longer susceptible to it. The PAFs of *H. pylori*-attributable diseases can be calculated by using the following formula originally proposed by Levin [19]:

$$PAF = \frac{P(RR-1)}{1 + P(RR-1)}$$

where P is the prevalence of *H. pylori* in the Chinese population and RR is the corresponding relative risk (RR) of *H. pylori* infection and specific disease.

It remains to determine differential natural interval periods between *H. pylori* infection and the occurrence of various outcomes. However, what we may agree is that a long enough time is more practical for us to observe the health consequences of *H. pylori* infection and assess their impact on individuals and the whole population. Therefore, considering the interval suggested by other reports and the accumulation of possible confounding effect associated with the interval, we think that a latency time of 10 years could be reasonable between the exposure of *H. pylori* and the occurrence of gastric cancer and other chronic diseases. In the present study, the prevalence of *H. pylori* over the period 2002–2004 was used to estimate the PAFs of *H. pylori*-related diseases in 2014 or later.

Prevalence of *H. pylori* infection in China

In order to update the prevalence of *H. pylori*, we searched the PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang databases. The search parameters were *Helicobacter pylori*, *H. pylori*, *Campylobacter pylori*, prevalence, and their combinations. Those studies conducted from 2005 to 2014 and reporting the prevalence of *H. pylori* in the Chinese population were included. Studies written in English and Chinese were both included. Moreover, the objective population was restricted to the general population or health

examinees without digestive tract symptoms. Eventually, we pooled 55 qualified studies. *Helicobacter pylori* prevalence could be used subsequently to evaluate the PAFs of relevant diseases 10 years later.

Pooled relative risk of *H. pylori* infection and specific disease in the Chinese population

The association between *H. pylori* infection and specific disease (such as coronary heart disease and cerebral infarction) has long been debated. In order to estimate the PAFs of *H. pylori*-related diseases among the Chinese population, we pooled different articles to calculate the overall combined risk of specific disease from *H. pylori* infection targeting the Chinese population by meta-analysis.

Search strategy and selection criteria

We identified studies involving risk estimates of *H. pylori* and related diseases by researching the PubMed, CNKI, and Wanfang databases. The following keywords and their combinations were searched: *Helicobacter pylori*, *H. pylori*, *Campylobacter pylori*, gastric, stomach, cancer, carcinoma, tumor, neoplasm, infarction, stroke, brain attack, cerebrovascular, cardiovascular, and coronary heart disease. Additional studies were obtained by screening references of studies and reviews.

Inclusion criteria of literatures

Studies should focus on the Chinese population, be written in English or Chinese, and conducted from 2000/01/01 to 2015/03/01.

Studies should contain data on RRs, odds ratios (ORs), or hazard ratio (HRs) with corresponding 95 % confidence intervals (CIs) or relevant information that could be used to estimate the magnitude of the association between *H. pylori* infection and the outcomes. The types of the studies were not limited.

Exclusion criteria of literatures

Duplicate studies or those based on the same or overlapping data sets were excluded. Then, the articles with the largest sample size and the most detailed results were included preferentially.

Studies of patients with *H. pylori*-related diseases as controls were excluded.

Two independent reviewers would check and extract data from a given article. Conflicts on extracted data were resolved by reaching a consensus. The methodological quality of the included studies was assessed mostly based on the Newcastle–Ottawa Scale (NOS) [20]. When conducted, the NOS was revised by adding an extra item of "adjustment of confounding factors or not". The studies awarded more than six points were regarded as high quality. All meta-analyses were performed by using the 'metan' command in Stata version 12.0 (StataCorp, College Station, TX, USA) with a two-sided *p*-value. We adopted a random effects model (if p for heterogeneity <0.05) by using the DerSimonian and Laird method (D&L method) [21] and a fixed effects model (if p for heterogeneity >0.05) to evaluate the pooled RRs and 95 % CIs. Meanwhile, potential publication bias was evaluated using a Begg's test and Egger's funnel plot. Heterogeneity among different studies was assessed by the Chi-squared test and calculated by I-squared (variation in RR attributable to heterogeneity).

H. pylori-associated disease morbidity and mortality data

The latest qualified data on the morbidity and mortality of gastric cancer in 2012 were derived from the National Central Cancer Registry (NCCR) and submitted by 193 cancer registries (74 cities and 119 counties) from 31 provinces, which covered about 198,060,406 population, accounting for approximately 16.43 % of the national population [17]. All cancer cases were classified according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). We use the data from the NCCR to estimate the gastric cancer burden attributable to *H. pylori*.

To date, there are no detailed and validated data on the nationwide morbidity of other chronic *H. pylori*-associated diseases, such as coronary heart disease and stroke.

Results

Of the 3616 publications retrieved from the databases, 48 were eventually included in the meta-analyses of risk estimates. A detailed identification of eligible studies is shown in Fig. 1. The data extracted from the 48 included studies and the NOS score are exhibited in Table 1. In addition, no statistical evidence of publication bias were found among studies by using Begg's test ($p = 0.07$ for gastric cancer, $p = 0.35$ for coronary heart disease, $p = 0.23$ for ischemic stroke).

Helicobacter pylori prevalence in different periods in China are listed in Table 2. A significant declining trend from 58.07 % (1990–2002) to 42.06 % (2009–2013) is found among the average prevalence of *H. pylori* infection in China. The detailed information from 53 eligible studies on *H. pylori* prevalence are presented in Supplementary Table 1.

The forest plots and results of the heterogeneity test of the meta-analysis on gastric cancer, coronary heart disease, and ischemic disease are shown in Figs. 2, 3, and 4, respectively.

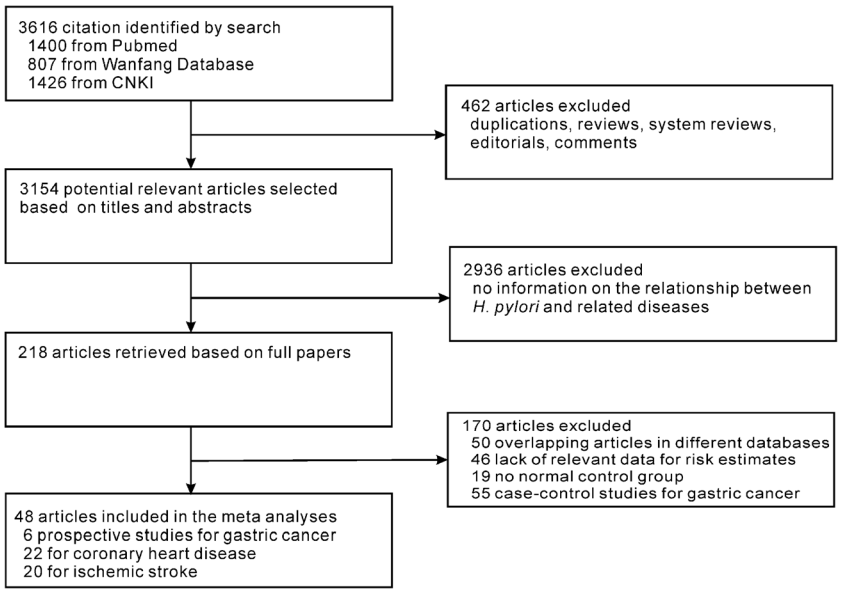

Fig. 1 Flow chart of article selection from different databases

For gastric cancer, the fixed effects pooled relative risk (RR) of 1.92 (95 % CI: 1.60–2.30) with no heterogeneity between studies ($p = 0.09$) was obtained for gastric cancer and *H. pylori* infection. For cardiovascular diseases, similar random effect pooled ORs were discovered, being 2.33 (95 % CI: 1.84–2.94) for coronary heart disease and 2.42 (95 % CI: 1.99–2.94) for ischemic stroke.

In order to investigate the relationship between *H. pylori* infection and the three related diseases more comprehensively, we conducted subgroup meta-analyses stratified by subtypes of disease, adjustment or not, detection of *H. pylori*, follow-up time, and study design separately. The detailed results of subgroup meta-analyses for gastric cancer, coronary heart disease, and ischemic disease are listed in Tables 3, 4, and 5, respectively. For gastric cancer, the subgroup meta-analysis involving six prospective studies with follow-up (8–11 years) adjusting for age, sex, and other factors revealed that *H. pylori* infections have a higher risk (RR: 1.89, 95 % CI: 1.57–2.26) of gastric cancer. Furthermore, similar RR (1.82, 95 % CI: 1.40–2.63) of noncardia cancer from *H. pylori* was obtained in another subgroup meta-analysis of two high-quality prospective studies. We found 19 case–control studies and two high-quality prospective studies assessing the relationship between *H. pylori* infection and coronary heart disease, the pooled OR and RR if which were 2.40 (95 %: 1.78–3.23) and 1.55 (95 %: 1.37–1.76), respectively. Similar risk estimates of *H. pylori* infection for ischemic disease were acquired by subgroup meta-analyses according to the study design. The pooled OR based on 18 case–control studies and the RR based on two high-quality prospective studies were 2.53 (95 %: 2.19–2.93) and 1.54 (95 %: 1.42–1.66), respectively.

The estimated PAFs of the diseases due to *H. pylori* infection or *H. pylori* eradication are shown in Table 6. Assuming that the time interval of *H. pylori* exposure and occurrence of related diseases is around 10 years, the PAFs of *H. pylori*-associated diseases in around 2014 are obtained by applying *H. pylori* prevalence data (54.76 %) during 2002–2004. *Helicobacter pylori* infection was estimated to account for 32.77 % of gastric cancer. When considering the gastric cancer by subsites, the estimated PAF for noncardia gastric cancer due to *H. pylori* infection was 37.38 %. The latest meta-analysis was based on eight cohort studies assessing the association between *H. pylori* eradication and gastric cancer incidence. The direct evidence showed that around 22.82 % of gastric cancer cases could be reduced by *H. pylori* eradication. Among the extragastric diseases in China, 23.15 % of coronary heart disease was attributable to *H. pylori* infection. In addition, *H. pylori* infection was responsible for 22.49 % of ischemic stroke cases. As a whole, with the prevalence of *H. pylori* decreasing from 54.76 % during 2002–2004 to 42.06 % during 2009–2013 across China, the three relevant diseases burden attributable to *H. pylori* would decline by about 5 % by 2024 or later.

Discussion

The present study is the first to systematically estimate the major disease burden attributable to *H. pylori* infection focusing on the Chinese population. In China, the nationwide average prevalence of *H. pylori* has declined steadily from 58.07 % (1990–2002) to 42.06 % (2009–2013) over the past two decades. We mainly pooled the high-quality Chinese prospective studies and validated the magnitude of the risk estimates by comparing with other relevant meta-analyses. We estimated that *H. pylori* infection may explain around 32.77 % of gastric cancer, 23.15 % of coronary heart disease,

Table 1 Characteristics of studies included in the meta-analyses

First author (year)	Disease	Design	Sample size	Effect size (95 % CI)	Detection of *H. pylori*	Matched or adjusted variables	NOS score
Kamangar F (2007) [22]	CGC	PS	1574	1.64 (1.26, 2.41)	Anti-Hp IgG	Adjusted by age, age-squared, and sex	8
Kamangar F (2007) [22]	NCGC	PS	1335	1.60 (1.15, 2.21)	Anti-Hp IgG	Adjusted by age, age-squared, and sex	8
Epplein M (2012) [23]	NCGC	PS	677	2.30 (1.47, 3.58)	Anti-Hp IgG	Matched by age, date, and time of sample collection, time interval since last meal, and antibiotic use in the past week	8
Ma JL (2005) [24]	GC	PS	2469	1.87 (1.01, 3.46)	Anti-Hp IgG	Adjusted by age and sex	8
Zhang XH (2012) [25]	GC	PS	1501	3.90 (1.18, 12.92)	Anti-Hp IgG	NA	7
Wang RT (2002) [26]	GC	PS	2719	1.99 (1.00, 3.93)	Biopsy	Adjusted by age and sex	8
Hsu WY (2014) [27]	GC	PS	30,110	5.21 (2.46, 11.05)	Biopsy	Adjusted by age, sex, hypertension, diabetes, peptic ulcer, hyperlipidemia, CAD, stroke, COPD, chronic hepatitis, CKD, and liver cirrhosis	8
Liu XH (2005) [28]	CHD	CCS	200	2.82 (1.58, 5.02)	Anti-Hp IgG	NA	7
Lu SY (2003) [29]	CHD	CCS	295	2.29 (1.42, 3.70)	Anti-Hp IgG	NA	6
Qiao ZF (2010) [30]	CHD	CCS	386	3.86 (2.36, 6.32)	Anti-Hp IgG	NA	6
Wang C (2014) [31]	CHD	CCS	150	3.82 (1.93, 7.55)	Anti-Hp IgG	NA	7
Wang SQ (2008) [32]	CHD	CCS	154	2.12 (1.04, 4.33)	Anti-Hp IgG	NA	6
Lai YQ (2005) [33]	CHD	CCS	400	1.84 (1.21, 2.80)	Anti-Hp IgG	NA	7
Wang YP (2008) [34]	CHD	CCS	142	2.90 (1.44, 5.82)	Anti-Hp IgG and UBT	NA	6
Cao PL (2011) [35]	CHD	CCS	120	2.85 (1.35, 6.04)	Biopsy	NA	7
Chuai YC (2012) [36]	CHD	CCS	263	1.53 (0.89, 2.63)	Biopsy	NA	6
Dian Q (2014) [37]	CHD	CCS	144	3.82 (1.87, 7.81)	Anti-Hp IgG and UBT	NA	7
Zhang J (2008) [38]	CHD	CCS	405	1.77 (1.17, 2.68)	UBT	NA	7
Wang WY (2013) [39]	CHD	CCS	213	2.25 (1.26, 4.03)	UBT	NA	7
Guan XR (2010) [40]	MI	CCS	252	1.90 (0.90, 3.80)	Anti-Hp IgG	NA	7
Liu MY (2011) [41]	CHD	CCS	124	3.67 (1.65, 8.17)	UBT	NA	7
Deng X (2005) [42]	CHD	CCS	106	2.36 (1.03, 5.40)	Anti-Hp IgG	Matched by gender, age(±5 years), and smoking	7
Qu W (2012) [43]	CHD	CCS	240	2.09 (1.48, 3.00)	Anti-Hp IgG	Adjusted by age, gender, BMI, disease history, smoking, alcohol	7
Tian F (2004) [44]	CHD	CCS	142	3.94 (1.53, 10.18)	Anti-Hp IgG	Adjusted by cytomegalovirus antibody (CMVIgM), chlamydia pneumonia antibodies (CPIgG, CPIgM)	8
Zeng Z (2000) [45]	CHD	CCS	137	1.03 (1.00, 1.07)	Anti-Hp IgG	Adjusted by age	7
Huang WS (2014) [10]	CHD	PS	85,375	1.48 (1.30, 1.69)	Biopsy	4-fold frequency-matched by age, sex, and diagnosis year; adjusted for age, sex, and comorbidities of hypertension diabetes, hyperlipidemia, stroke, COPD, and heart failure	8
Liu DN (2003) [46]	MI	CCS	82	3.26 (1.02, 10.49)	Anti-Hp IgG	Adjusted by age, sex, smoking, hypertension, obesity, diabetes, hyperlipidemia	8

Table 1 (continued)

First author (year)	Disease	Design	Sample size	Effect size (95 % CI)	Detection of *H. pylori*	Matched or adjusted variables	NOS score
Lu YL (2015) [47]	MI	PS	2084	3.26 (1.41, 3.99)	UBT	Adjusted by SBP, LDL-C, HDL-C, TG, Fib, hs-CRP, Hcy, white cell number	8
Hao R (2013) [48]	CI	CCS	166	3.50 (1.85, 6.65)	UBT	NA	6
Yu Z (2011) [49]	CI	CCS	240	2.12 (1.26, 3.57)	UBT	NA	7
Shu AM (2006) [50]	CI	CCS	162	3.75 (1.42, 9.92)	UBT	NA	7
Zhang A (2009) [51]	CI	CCS	300	3.75 (2.30, 6.12)	UBT	NA	7
Wang Y (2006) [52]	CI	CCS	150	2.66 (1.32, 5.36)	Anti-Hp IgG	NA	6
Wei ZH (2014) [53]	CI	CCS	104	3.56 (1.58, 7.98)	Anti-Hp IgG	NA	7
Wu HQ (2012) [54]	CI	CCS	125	2.67 (1.10, 6.47)	Anti-Hp IgG	NA	6
Wu XX (2003) [55]	CI	CCS	138	2.06 (1.03, 4.11)	Anti-Hp IgG	NA	7
Zhang X (2007) [56]	CI	CCS	118	3.99 (1.83, 8.74)	Anti-Hp IgG	NA	6
Zhang Q (2008) [57]	CI	CCS	140	2.12 (1.07, 4.21)	Anti-Hp IgG	NA	7
Lu YL (2015) [47]	CI	PS	2084	1.85 (1.26, 2.53)	UBT	Adjusted by SBP, LDL-C, HDL-C, TG,Fib, hs-CRP, Hcy, white cell number	8
Zhao M (2012) [58]	CI	CCS	360	3.29 (1.60, 6.77)	UBT	Adjusted by smoking, diabetes, hypertension, total cholesterol	8
Dou YC (2008) [59]	CI	CCS	466	2.08 (1.46, 3.01)	Anti-Hp IgG	Adjusted by age, gender, BMI, living conditions, disease history, lifestyle	7
Duan HL (2005) [60]	CI	CCS	320	2.24 (1.39, 3.61)	Anti-Hp IgG	Adjusted by age, gender, hypertension, smoking	8
Su ZJ (2007) [61]	CI	CCS	182	4.20 (2.23, 7.92)	Anti-Hp IgG	Adjusted by gender, age, nationality, occupation, smoking history, drinking history, and hypertension	7
Zhou GA (2013) [62]	CI	CCS	140	1.61 (0.81, 3.20)	Anti-Hp IgG	Matched by age and gender	6
Li XH (2007) [63]	CI	CCS	100	3.46 (1.17, 10.24)	Anti-Hp IgG	Matched by age and sex	8
Xu F (2013) [64]	IS	CCS	140	3.05 (1.53, 6.08)	UBT	Matched by age and sex	7
Lai CY (2015) [11]	IS	PS	86,660	1.52 (1.40, 1.65)	Biopsy	Matched by age (5 years), gender, and index year; adjusted by age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, CHF, CAD, AF, COPD, and asthma	8
Yang X (2011) [65]	IS	CCS	281	1.22 (0.69, 2.17)	Anti-Hp IgG	Sex, hypertension, diabetes mellitus, familial history of stroke, BMI, smoking, education, peptic ulcer history, social status	8

CGC cardia gastric cancer, *NCGC* noncardia gastric cancer, *GC* gastric cancer, *CHD* coronary heart disease, *MI* myocardial infarction, *CI* cerebral infarction, *IS* ischemic infarction, *CCS* case–control study, *PS* prospective study, *Hp Helicobacter pylori*, *UBT* urea breath test

Table 2 Prevalence of *H. pylori* in different periods in China

Period covered	No. of provinces or regions covered	Population size	Average prevalence rate (%)	Data sources
1990–2002	21	25,209	58.07	Previous review [66]
2002–2004	19	26,341	54.76	Previous review [18]
2004–2008	12	41,955	45.47 Men: 44.53, women: 46.47	Present review of 19 articles*
2009–2013	18	149,391	42.06 Men: 40.05, women: 43.77	Present review of 34 articles*

*The references cited in the reviews are presented in the Supplementary Table 2

and 22.29 % of ischemic stroke during 2012–2014. With the decreasing prevalence of *H. pylori*, the overall attributable burden of the three *H. pylori*-related diseases may decline by about 5 % 10 years later.

In terms of *H. pylori* prevalence in the general Chinese population, the prevalence of *H. pylori* during 2009–2013, compared with that which occurred 10 years ago, seemed to become weaker according to our estimates (58.07 % vs. 42.06 %, $p < 0.01$). Furthermore, the trend was consistently observed in several specific regions. As reported by Chen et al., the decreasing prevalence of *H. pylori* infection was observed during 1993–2003 in Guangzhou, Southern China (62.5 % vs. 49.3 %, $p < 0.001$) [72]. Another two regions, Muping County in Shandong [73.78 % vs. 50.95 %, $p < 0.001$) and Yanqing County in Beijing (55.35 % vs. 41.35 %, $p < 0.01$], both exhibited a significant decline in *H. pylori* prevalence during 1990–2006 [73]. In addition to the whole decreasing trend, the prevalence of *H. pylori* infection (42.06 %) during 2009–2013, which we estimated based on the data from 34 articles covering 149,391 individuals of 18 provinces or regions, was highly consistent with the *H. pylori* prevalence (42.39 %) demonstrated by the baseline data of a large community-based intervention trial involving 183,970 participants launched in Linqu County in 2011, a high-risk area of gastric cancer in China [74]. All these evidences suggested that our estimate of *H. pylori* prevalence was stable and convincing. The positive decline may be partly explained by *H. pylori* eradication, which is widely accepted as a common clinical practice in the treatment of chronic gastritis and peptic ulcers across China as recommended by the Fourth Chinese National Consensus Report on the management of *H. pylori* infection [75]. It may be more closely associated with the significant improvement of the economic level, living conditions, hygiene practices, education status, and people's health awareness in China [76, 77]. All these advances have hugely benefitted the public health of China. With the declining prevalence of *H. pylori* in

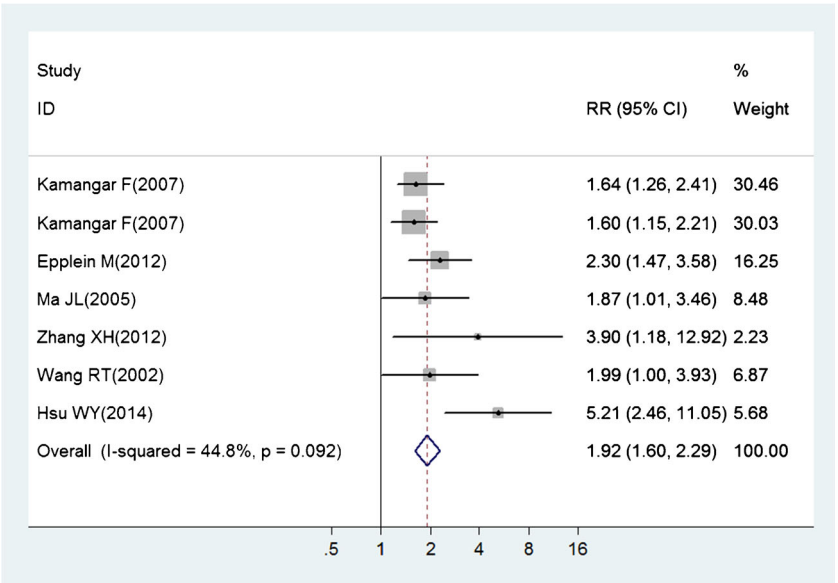

Fig. 2 Fixed effects meta-analysis evaluating *H. pylori* infection and gastric cancer risk

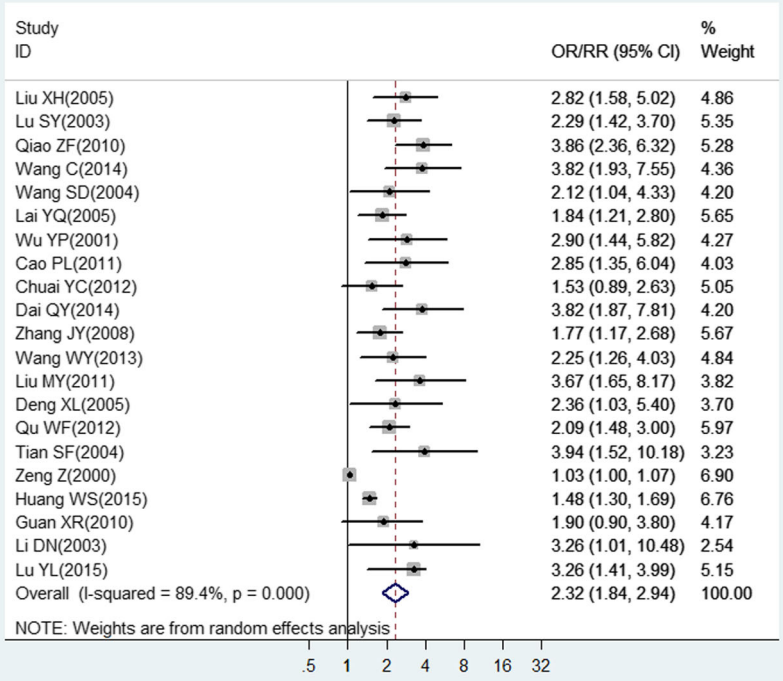

Fig. 3 Random effects meta-analysis evaluating *H. pylori* infection and coronary heart disease risk

the recent 5–10 years, the proportion of corresponding diseases attributable to *H. pylori* infection may decrease in the future. Besides, it should be mentioned that further investigation on gender-, age-, and setting-specific (urban and rural) *H. pylori* prevalence would aid in more accurately estimating the attributable burden of *H. pylori* infection. However, the interpretation of the decreasing *H. pylori* prevalence and its impact remains to be further clarified.

Irrespective of gastric cancer subsites, the adjusted RR of gastric cancer associated with *H. pylori* was estimated to be 1.89 (95 % CI: 1.57–2.26) based on Chinese prospective

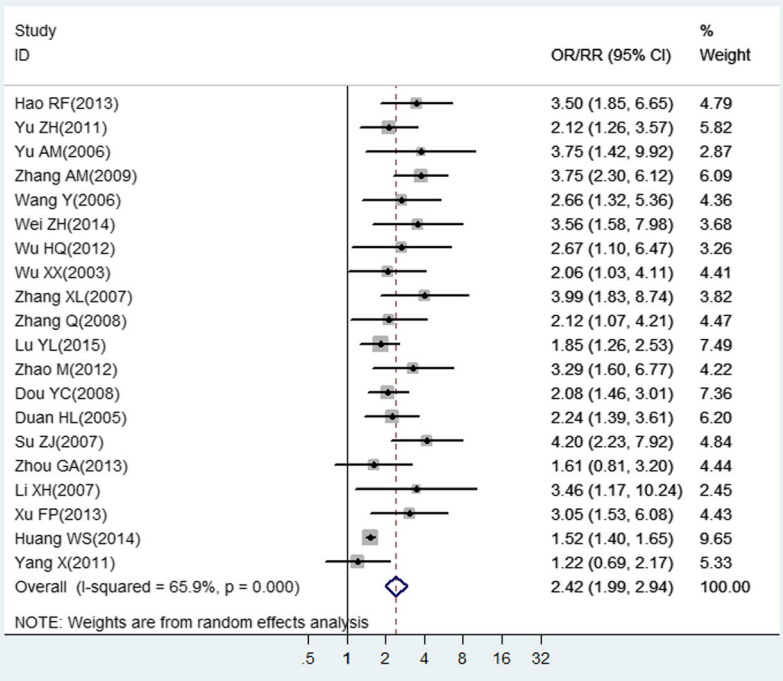

Fig. 4 Random effects meta-analysis evaluating *H. pylori* infection and ischemic stroke risk

Table 3 Results of subgroup meta-analysis on gastric cancer

Subgroup	No. of studies	RR (95 % CI)[a]	*p*-Value[b]
Subtypes of disease			
Cardia cancer	1	1.64 (1.19, 2.27)	
Noncardia cancer	2	1.82 (1.40, 2.63)	0.20
Gastric cancer	4	2.62 (1.81, 3.80)	0.14
Adjustment or not			
No adjustment	1	3.90 (1.18, 12.92)	
Adjustment	6	1.89 (1.57, 2.26)[c]	0.09
Detection of *H. pylori*			
Anti-Hp IgG	5	1.79 (1.48, 2.17)	0.46
Biopsy	2	3.07 (1.85, 5.09)	0.06
Follow-up time (years)			
8–11	6	1.89 (1.57, 2.26)[c]	0.09
14	1	3.90 (1.18, 12.92)	
Overall	7	1.92 (1.60, 2.30)	0.09

RR relative risk, *CI* confidence interval

[a] If $p > 0.05$, the fixed effects model was used. If not, the random effects model was used

[b] *p*-Value for heterogeneity

[c] The RR was used in subsequently evaluating the PAF of gastric cancer due to *H. pylori*

Table 4 Results of subgroup meta-analysis on coronary heart disease

Subgroup	No. of studies	RR/OR (95 % CI)[a]	*p*-Value[b]
Subtypes of disease			
Coronary heart disease	18	2.27 (1.78, 2.90)	<0.01
Myocardial infarction	3	2.33 (1.84, 2.94)	0.47
Study design			
Case–control study	19	2.40 (1.78, 3.23)	<0.01
Prospective study	2	1.55 (1.37, 1.76)[c]	<0.01
Adjustment or not			
No adjustment	14	2.39 (2.05, 2.78)	0.27
Adjustment	7	1.93 (1.38, 2.69)	<0.01
Detection of *H. pylori*			
Anti-Hp IgG	12	2.35 (1.60, 3.46)	<0.01
Anti-Hp IgG and UBT	2	3.32 (2.01, 5.47)	0.59
Biopsy	3	1.48 (1.30, 1.69)	0.24
UBT	4	2.37 (1.82, 3.10)	0.21
Overall	21	2.33 (1.84, 2.94)	<0.01

RR relative risk, *OR* odds ratio, *CI* confidence interval, *UBT* urea breath test

[a] If $p > 0.05$, the fixed effects model was used. If not, the random effects model was used

[b] *p*-Value for heterogeneity

[c] The RR was used in subsequently evaluating the PAF of coronary heart disease due to *H. pylori*

Table 5 Results of subgroup meta-analysis on ischemic stroke

Subgroup	No. of studies	RR/OR (95 % CI)[a]	*p*-Value[b]
Subtypes of disease			
Ischemic stroke	3	1.53 (1.41, 1.66)	0.11
Cerebral infarction	17	2.49 (2.16, 2.87)	0.41
Study design			
Case–control study	18	2.53 (2.19, 2.93)	0.28
Prospective study	2	1.54 (1.42, 1.66)[c]	0.28
Adjustment or not			
No adjustment	11	2.89 (2.36, 3.54)	0.83
Adjustment	9	2.01 (1.59, 2.54)	<0.01
Detection of *H. pylori*			
Anti-Hp IgG	12	2.30 (1.92, 2.75)	0.26
Biopsy	1	1.52 (1.40, 1.65)	
UBT	7	2.59 (2.11, 3.18)	0.21
Overall	20	2.42 (1.99, 2.94)	<0.01

RR relative risk, *OR* odds ratio, *CI* confidence interval, *UBT* urea breath test

[a] If $p > 0.05$, the fixed effects model was used. If not, the random effects model was used

[b] *p*-Value for heterogeneity

[c] The RR was used in subsequently evaluating the PAF of ischemic stroke due to *H. pylori*

studies. Actually, several risk estimates of gastric cancer from *H. pylori*-positive serology were yielded in previous meta-analyses conducted by the Helicobacter and Cancer Collaborative Group (OR: 3.12, 95 % CI: 2.23–4.35) [67], Xue et al. (OR: 2.56, 95 % CI: 1.85–3.55) [78], and Huang et al. (OR: 2.28, 95 % CI: 1.71–3.05) [79]. The pooled RRs were usually lower than the pooled ORs, which may be due to the difference in the interval between sample collection and cancer diagnosis [67]. Considering that the previous meta-analyses were mostly based on case–control studies and missed many literatures on the Chinese population, our present pooled RR was supposed to be more reliable to some extent in assessing the PAF of gastric cancer due to *H. pylori* in China.

Though the relationship between *H. pylori* and cardia cancer was conflicting, the association of noncardia cancer with *H. pylori* is widely recognized. Moreover, the magnitude of the risk of developing noncardia cancer associated with *H. pylori* infection has proven to be positively related with the interval between *H. pylori* detection and gastric cancer diagnosis. That may be because *H. pylori* tends not to colonize such areas as atrophy, intestinal metaplasia, or cancer [80]. Therefore, we further calculate the PAF of noncardia cancer due to *H. pylori* based on the relative risk (2.09, 95 % CI: 1.33–3.29) pooled by the meta-analysis of case–control studies nested within prospective cohorts when blood samples for *H. pylori* serology were collected 5–9.9 years before cancer

Table 6 Estimated PAFs of diseases attributable to *H. pylori* infection or *H. pylori* eradication in China

Disease	RR/OR (95 % CI)	Data resource	PAF[a] (%)	PAF[b] (%)	PAF[a,b](%)
Gastric cancer	1.89 (1.57, 2.26)*	Present subgroup meta-analysis	32.77	27.24	−5.53
Noncardia cancer	2.09 (1.33, 3.29)*	Previous subgroup meta-analysis[c] [67]	37.38	31.43	−5.95
Gastric cancer	0.46 (0.32, 0.66)*	Previous meta-analysis[d] [68]	22.82	18.51	−4.31
Coronary heart disease	1.55 (1.37, 1.76)*	Present subgroup meta-analysis	23.15	18.79	−4.36
Coronary heart disease	1.15 (1.00, 1.32)*	Previous subgroup meta-analysis [6]	7.59	5.93	−1.66
Myocardial infarction	2.33 (1.84, 2.94)#	Present subgroup meta-analysis	42.14	35.87	−6.27
Myocardial infarction	1.75 (1.12, 2.73)*	Previous subgroup meta-analysis [69]	29.11	23.98	−5.13
Ischemic stroke	1.53 (1.41, 1.66)*	Present subgroup meta-analysis	22.29	18.23	−4.06
Ischemic stroke	1.60 (1.21, 2.11)#	Previous subgroup meta-analysis [70]	24.73	20.15	−4.58
Cerebral infarction	2.49 (2.16, 2.87)#	Present subgroup meta-analysis	44.93	38.53	−6.40
Cerebral infarction	2.60 (1.93, 3.49)#	Previous subgroup meta-analysis[e] [71]	46.70	40.23	−6.47

*Denotes RR (95 % CI)

# Denotes OR (95 % CI)

PAF population attributable fraction, *RR* relative risk, *OR* odds ratio, *CI* confidence interval

[a] The PAFs were calculated based on the corresponding RRs and average *H. pylori* prevalence of 54.76 % during 2002–2004

[b] The PAFs were calculated based on the corresponding RRs and average *H. pylori* prevalence of 42.06 % during 2009–2013

[c] The meta-analysis was based on case–control studies nested within prospective cohorts when blood samples for *H. pylori* serology were collected 5–9.9 years before cancer diagnosis

[d] The latest meta-analysis was based on eight cohort studies assessing the association between *H. pylori* eradication and gastric cancer incidence

[e] The meta-analysis was based on six retrospective case–control studies investigating the relationship between the cytotoxin-associated gene A (CagA) status of *H. pylori* strains and cerebral infarction among Chinese Han

diagnosis [67]. According to the global patterns of two major subsites of gastric cancer incidence in 2012, the average ratio of noncardia to cardia gastric cancer cases was 2:1 [81]. As suggested in the annual report by Chen et al., the year of 2012 witnessed around 420,489 cases due to gastric cancer in China [82], which indicated that approximately 105,536 noncardia gastric cancer cases may be attributable to *H. pylori* infection in China in 2012. The results demonstrated that taking the noncardia and cardia cancer as a whole may underestimate the burden of gastric cancer due to *H. pylori* infection. So the best choice was to estimate the attributable burden of gastric cancer by subsites.

Notably, compelling evidence suggested that *H. pylori* treatment had a positive effect on the morbidity and mortality of gastric cancer in China. The latest meta-analysis of cohort studies determined that *H. pylori* eradication was associated with a reduced risk of gastric cancer (RR: 0.46, 95 % CI: 0.32–0.66) [68]. A previous meta-analysis of randomized controlled trials also reinforced the eradication therapy of *H. pylori* as an effective strategy of preventing gastric cancer incidence (RR: 0.66, 95 % CI: 0.46–0.95) [83]. Another meta-analysis by Lee et al. also suggested that, after adjustment for baseline gastric cancer incidence, individuals with eradication of *H. pylori* infection had a lower incidence of gastric cancer (pooled incidence rate ratio = 0.53, 95 % CI: 0.44–0.64) [84]. By applying the relative risk of 0.46 (95 % CI: 0.32–0.66) to the calculation of PAF of gastric cancer due to *H. pylori* eradication, around 22.82 % of gastric cancer cases could be prevented by *H. pylori* eradication. Furthermore, by using an empirically calibrated natural history model, Yeh et al. [85] found that screening young adults for *H. pylori* and treating *H. pylori* infection could prevent 1 in every 4 to 6 cases of gastric cancer in China and would be considered cost-effective using the GDP per capita threshold in reducing the attributable burden due to *H. pylori* [86]. In China, the early screening and diagnosis of gastric cancer urgently remains to be improved. So a screen-and-treat strategy for *H. pylori* should be given priority to promote the prevention of gastric cancer.

When we compared the pooled RR/OR of coronary heart disease with that of ischemic stroke among *H. pylori* infections in the same subgroup, amazingly, a highly similar magnitude of risk estimates was found in each subgroup of prospective study, case–control study, adjustment, and anti-Hp IgG separately. The phenomenon could be partly explained by the common pathogenesis of atherosclerosis largely shared by CHD and IS. At the same time, we found that the RRs by pooling high-quality prospective studies were consistently lower than pooled ORs based on case–control studies for both CHD and IS. A similar finding was present in another meta-analysis of myocardial infarction (a subtype of CHD) due to *H. pylori* by Liu et al., in that the pooled RR (1.20,

95 % CI: 1.04–1.38) based on seven prospective studies was lower than the OR (1.95, 95 % CI: 1.46–2.60) based on 19 cross-sectional studies [69]. Moreover, as reported by Sun et al., *H. pylori* infection had a higher risk of CHD events revealed by pooling prospective studies that had less than 5 years of follow-up time (RR = 1.15, 95 % CI: 1.00–1.32) than those that had a follow-up time ≥10 years (RR = 1.04, 95 % CI: 0.87–1.24) [6]. The findings above reminded us that the magnitude of the risk estimates of CHD in *H. pylori* infections were negatively associated with the interval time between *H. pylori* detection and CHD diagnosis. We speculated that the true effect *H. pylori* infection had on CHD may be weakened or masked by the accumulation of age and other risk factors or comorbidity in long-term follow-ups, because previous meta-analyses have revealed that the association of *H. pylori* with myocardial infarction were likely age-dependent [69]. Just as suggested by the stratified analysis of a large prospective study involving 85,375 Chinese people, the effect of *H. pylori* infection on CHD tends to decrease with age, ranging from 1.67 (95 % CI: 1.07–2.61) for the ≤49 years age group to 1.32 (95 % CI: 1.07–1.63) for the >75 years age group [11]. As for other *H. pylori*-related diseases, these findings remain to be validated. Therefore, we should calculate the PAF of *H. pylori* infection with caution. We would be better off estimating CHD burden attributable to *H. pylori* based on high-quality prospective studies adjusting for other confounding factors. If not, we may overestimate the attributable burden. To date, there are insufficient direct evidences from the prospective studies and randomized controlled trials that *H. pylori* eradication can reduce the incidence of CHD and IS.

When it comes to ischemic stroke, we found that *H. pylori* infections conferred higher risk of ischemic stroke (RR = 1.53, 95 % CI: 1.41–1.66) in the Chinese population. The present subgroup meta-analysis also suggested that positive anti-*H. pylori* IgG (OR = 2.30, 95 % CI: 1.92–2.75) and ^{13}C-urea breath test (OR = 2.59, 95 % CI: 2.22 –3.18) both have higher risk of IS. Apparently, the magnitude of relative risk based on prospective studies with longer latency periods between *H. pylori* detection and IS diagnosis appeared to be higher than that of ORs based on case–control studies. However, a previous meta-analysis of ten prospective studies determined that there was no association between cytotoxin-associated gene-A-positive/-negative/combined *H. pylori* infection and stroke [85]. This may be due to the heterogeneity across the relationship between *H. pylori* infection and subtypes of stroke. Notably, another meta-analysis including 13 case–control studies indicated that CagA-positive strains of *H. pylori* seemed to be associated with a higher risk of IS than *H. pylori* infections detected by anti-*H. pylori* IgG or ^{13}C-urea breath test [70]. No CagA serology data are available for the present analysis and large prospective studies in the Chinese population are needed to address the relationship between IS/CHD and different strains of *H. pylori*, including CagA-positive strains. All these efforts might benefit the personalized prevention of *H. pylori*-related diseases.

To our knowledge, this is the first systematic assessment of the burden of *H. pylori*-associated diseases focusing on the Chinese population. The bias caused by genetic and geographical factors was reduced to some extent. Furthermore, our study comprehensively identified all relevant articles from the last 15 years or so. Equally important was the quality of the publications, which was ensured through strict inclusion and exclusion criteria of the studies and evaluating them using the NOS. The risk estimates of *H. pylori*-related diseases used to calculate the PAFs were based on subgroup meta-analyses of prospective studies, which might avoid the potential limitations of "reverse causality" and "recall bias", and made the calculation of PAFs more persuasive. In addition, the prevalence of *H. pylori* in the last decade was estimated more accurately than ever due to large general populations and representative areas that the studies covered, and the wide acceptance of standard detection of *H. pylori* infection in clinical practice. However, several limitations should be acknowledged. First, although we managed to validate the risk estimates by deeply comparing them with the reported results from previous meta-analyses, more prospective studies among the Chinese population are needed to confirm it. Second, the overall prevalence of *H. pylori* across the country was estimated based on mainly three measures of *H. pylori* infection. The consistency among the different detections remains to be determined. Furthermore, the relationships between some other diseases (such as diabetes mellitus, iron deficiency anemia, and so on) and *H. pylori* infection are not sufficiently studied in China, so the overall burden of diseases due to *H. pylori* infection remains to be further estimated comprehensively and systematically.

To conclude, in the past 20 years, China has witnessed a steady decline in the prevalence of *H. pylori*. The risk estimates of *H. pylori*-related diseases reinforce *H. pylori* as a common risk factor of various chronic diseases. The PAFs of these diseases above due to *H. pylori* infection remind us that *H. pylori* treatment might be helpful in reducing the burden of these diseases and provide potential opportunities for prevention and treatment. Large high-quality prospective studies are warranted to identify which *H. pylori* strains, which subtypes of the disease, and which subgroups of the population are at greatest risk of relevant diseases (especially cardiovascular diseases and diabetes mellitus) and the effect of *H. pylori* eradication on the prevention of *H. pylori*-related diseases. Randomized controlled trials integrating the best biologic, epidemiologic and economic data, and mathematical simulation models are urgently needed to assess the cost-effectiveness ratios of *H. pylori* screening and treatment.

Compliance with ethical standards

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