Sex differences in the prevalence of *Helicobacter pylori* infection: an individual participant data pooled analysis (StoP Project)

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Background *Helicobacter pylori* (*H. pylori*) infection is more frequent among men, though the magnitude of the association might be inaccurate due to potential misclassification of lifetime infection and publication bias. Moreover, infection is common, and most studies are cross-sectional. Thus, prevalence ratios (PRs) may be easier to interpret than odds ratios (ORs).
Aim The aim of this study was to quantify the association between sex and *H. pylori* infection using controls from 14 studies from the Stomach Cancer Pooling (StoP) Project.
Participants and methods *H. pylori* infection was defined based on IgG serum antibody titers or multiplex serology. Participants were also classified as infected if gastric atrophy was present, based on histological examination or serum pepsinogen (PG) levels (PG I ≤ 70 and PG I/II ratio ≤ 3). Summary ORs and PRs, adjusted for age, social class and smoking, and corresponding 95% confidence intervals (CIs), were estimated through random-effects meta-analysis.
Results Men had significantly higher OR (OR: 1.33, 95% CI: 1.04–1.70) and PR (PR: 1.05, 95% CI: 1.00–1.10) of infection, with stronger associations among hospital-based or older controls. Results were similar when considering the presence of gastric atrophy to define infection status, particularly among participants older than 65 years.
Conclusion This collaborative pooled-analysis supports an independent effect of sex on the prevalence of *H. pylori* infection, while minimizing misclassification of lifetime infection status and publication bias. Eur J Gastroenterol Hepatol 31:593–598

Introduction

Helicobacter pylori (*H. pylori*) infection affects more than half of the adult population worldwide [1] and was estimated to have accounted for more than 75% of all gastric cancer cases in 2012 [2], despite the fact that its prevalence has been declining over the past few decades [3]. Gastric cancer, which is the third leading cause of death by cancer, occurs twice as often among men than women [4], with similar sex differences also in mortality rates [5].

The role of sex as a risk factor for *H. pylori* infection has been reported in two meta-analyses of the published literature. Infection was significantly more frequent among male adults (summary odds ratio (OR): 1.16, 95%

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Keywords: consortium, *Helicobacter pylori*, individual participant data, pooled analysis, sex

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confidence interval (95% CI): 1.11–1.22 [6] and summary OR: 1.12, 95% CI: 1.09–1.15 [7]), but weaker associations were observed in children (summary OR: 1.03, 95% CI: 0.91–1.17 [6] and summary OR: 1.06, 95% CI: 1.01–1.12 [7]), suggesting more pronounced sex differences in the persistence of infection than on their acquisition in early life. However, the previous reviews included only a few studies presenting adjusted measures of association, not always adjusted for the same variables, and there are no meta-analyses taking into account the potential misclassification of infection status among participants with gastric atrophy [8].

Moreover, as *H. pylori* infection is a common condition the summary ORs provided in the meta-analyses based on published data may be interpreted as evidence of a stronger association than when it is estimated using more easily interpretable prevalence ratios (PRs) [9], which are seldom available in original reports.

Therefore, this study aimed to quantify the association between sex and *H. pylori* infection through an individual participant data meta-analysis using controls from 14 case–control studies participating in the Stomach Cancer Pooling (StoP) Project, allowing for the estimation of the independent effect of sex on the prevalence of infection, while overcoming the potential misclassification of lifetime infection status and publication bias.

Participants and methods

The StoP Project is a consortium of epidemiological studies (case–control, including nested case–control within cohort studies) on gastric cancer, which included, at least, 80 cases of incident, histologically confirmed gastric cancer from both cardia and noncardia locations. These studies were gathered through personal contact of participating investigators; other principal investigators were contacted and invited to participate after identification of studies through searches in electronic databases, including Medline and Embase, backward citation tracking, and contact with experts. All investigators who agreed to participate provided the complete original data set of the study or a set of core variables including age, sex, education/social class, smoking habits, family history of gastric cancer, selected dietary variables, and markers of *H. pylori* infection, among others. Data harmonization was conducted at the pooling center, in Milan, using prespecified formats; the whole body of information was divided into several sections (e.g. sociodemographic characteristics, smoking habits, lifetime alcohol use, and physical activity), and for each topic, a project codebook was created reporting variables present in each study, their names, and codes. The data for the core variables were standardized, as well as for the variables for selected topics of interest. Further information on the aims and methods of the StoP Project has been previously described elsewhere [10].

The 2.1 version of the StoP Project, which comprises 31 case–control or nested within cohort studies on gastric cancer, for a total of 14 244 cases and 33 932 controls, was used.

The present analysis is based on individual participant data from 7247 controls (3207 women and 4040 men) included in the 14 studies providing data on *H. pylori* infection status: Brazil (two studies) [11,12], China [13], Iran (three studies) [14–16], Japan [17], Latvia [18], Mexico (two studies) [19,20], Portugal [21], Russia [22], Spain [23], and Sweden [24]. In each study, the controls were recruited among hospital patients with diseases other than gastric cancer [11,12,16–18,20,22] or among residents of the area/city where the study took place [13–15,19,21,23,24]. *H. pylori* infection status was determined by serological tests, namely enzyme-linked immunosorbent assay tests (12 studies) [11–14,16–22,24] or western blot (one study) [15], to assess immunoglobulin G antibody titers in serum, and in one study through multiplex serology [23], using the same criteria applied in the original studies. When anti-*H. pylori* serum immunoglobulin G titers were determined using an enzyme-linked immunosorbent assay-based method, participants with borderline results were classified as testing positive for *H. pylori* infection.

To estimate the association between sex (men vs. women) and *H. pylori* infection, we used a two-stage modeling approach [25]. In the first stage, we assessed the association between sex and *H. pylori* infection for each study by estimating the ORs and PRs, and the corresponding 95% CIs, using multivariable unconditional logistic regression and Poisson regression with robust SEs, respectively. The models included terms for age (<40, 5-year age-groups from 40–44 to 70–74 and ≥ 75 years), social class (low, intermediate, or high, as defined in each original study, based on education, income, or occupation), and smoking (never and ever).

In the second stage, summary (pooled) effect estimates were computed using a random-effect model, as a weighted average of the study-specific log(ORs) and log(PRs) obtained in the first stage, using as weights the inverse of the sum of the study-specific log(OR) or log(PR) variances, as applicable, and the corresponding between-study variance components [26]. Heterogeneity between studies was quantified using the I^2 (%) statistic [27]. Visual inspection of funnel plots and Egger's regression asymmetry test were used for assessment of selection bias [28].

To investigate whether the effect of sex was heterogeneous across strata of selected covariates, we carried out analyses stratified by type of controls (hospital-based or population-based), age (≤ 55, 56–65, and >65 years), and geographical region (Europe, Asia and Americas).

Misclassification of infection status may occur due to methodological limitations in detecting past infection leading to an underestimation of the prevalence of infection [8,29,30]. In this study, this was minimized by considering data on the presence of gastric atrophy, as the latter is likely to contribute for false-negative results in serological assessment of infection status. Participants testing negative for *H. pylori* infection were classified as infected when atrophy was considered present, as assessed through histological examination or measured by serum pepsinogen (PG) levels (PG I ≤ 70 and PG I/II ratio ≤ 3); this analysis included 1987 controls from six studies (Fig. 1).

The statistical analysis was performed with STATA (StataCorp. 2009 Stata Statistical Software: Release 11; StataCorp LP, College Station, Texas, USA).

The StoP Project received ethical approval from the University of Milan Review Board (reference 19/15, 01/04/2015).

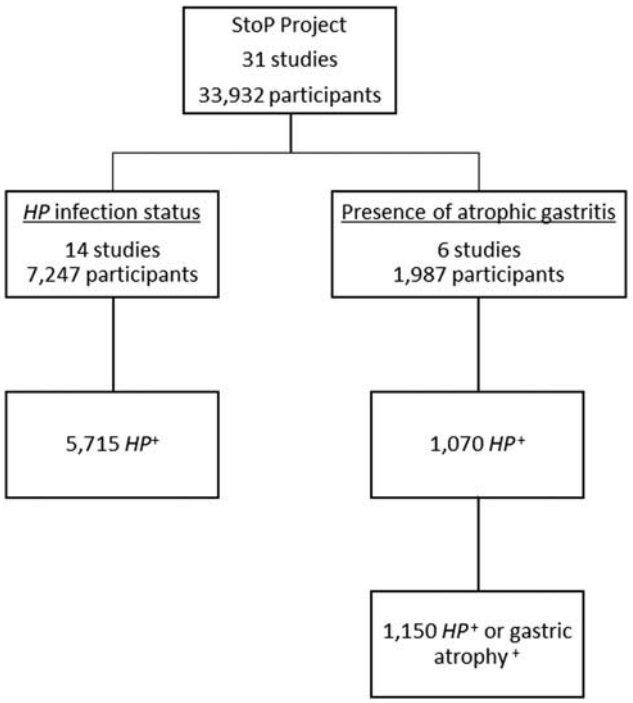

Fig. 1. Data availability for the assessment of the relation between sex and *Helicobacter pylori* infection in the StoP Project under different criteria to define infection status. HP, *Helicobacter pylori*, HP+ infected with *Helicobacter pylori*, gastric atrophy+ positive as evaluated by histological examination or measured by serum pepsinogen (PG) levels (PG I ≤ 70 and PG I/II ratio ≤ 3).

Results

In most of the studies, the prevalence of *H. pylori* infection was higher among men, particularly among older individuals, as depicted in Supplementary Figs 1–3 (Supplemental digital content 1, *http://links.lww.com/EJGH/A399*).

For the association between sex (men vs. women) and *H. pylori* infection, the summary adjusted OR was 1.33 (95% CI: 1.04–1.70; $I^2 = 56.5\%$) and the summary adjusted PR was 1.05 (95% CI: 1.00–1.10; $I^2 = 63.0\%$; Fig. 2, Table 1). The summary OR and PR were essentially the same when using the crude estimates (1.32, 95% CI: 1.06–1.66; $I^2 = 65.9\%$ and 1.05, 95% CI: 1.00–1.10; $I^2 = 67.3\%$, respectively) or when smoking status was not considered in the multivariable analysis of each individual study (1.32, 95% CI: 1.07–1.62; $I^2 = 53.8\%$ and 1.05, 95% CI: 1.00–1.09; $I^2 = 55.5\%$, respectively). Visual inspection of the funnel plot and respective Egger's test ($P = 0.470$ and 0.675 for summary OR and PR, respectively) were not suggestive of publication bias (Fig. 3).

Greater OR and PR estimates were observed among studies with hospital-based controls (adjusted summary OR: 1.51, 95% CI: 1.17–1.93 and PR: 1.10 95% CI: 1.02–1.19) and among older age groups, particularly those older than 55 years of age (OR: 1.67, 95% CI: 1.08–2.62 and PR: 1.09, 95% CI: 1.00–1.18 for > 65 vs. ≤ 55 years; Table 1). The association was stronger among hospital controls older than 65 years (OR: 2.07, 95% CI: 1.05–4.09 and PR: 1.19, 95% CI: 1.02–1.38). Among population-based controls, the odds and prevalence of infection increased with age (OR: 1.07, 95% CI: 0.69–1.67 and PR: 1.02, 95% CI: 0.96–1.09 for those younger than 55 years; OR: 1.43, 95% CI: 0.76–2.70 and PR: 1.04, 95% CI: 0.95–1.14 for those older than 65 years), although not being statistically significant among any specific age group, except for men with 56–65 years who had a 5% significantly higher prevalence of infection compared with women (adjusted summary OR: 1.33, 95% CI: 0.81–2.17 and PR: 1.05, 95% CI: 1.00–1.11). Significantly higher odds and prevalence of infection were observed in men from studies belonging to European countries (adjusted summary OR: 1.66, 95% CI: 1.36–2.03 and PR: 1.06, 95% CI: 1.01–1.12).

When defining *H. pylori* infection considering the presence of gastric atrophy defined by histological examination or measurement of serum PG, in six studies, the summary adjusted OR and PR estimates were 1.62 (95% CI: 1.23–2.13) and 1.13 (95% CI: 1.03–1.25), respectively (Table 1).

Discussion

The present individual participant data pooled analysis shows that, after adjusting for age, social class, and smoking status, men had a 33% greater odds of infection with *H. pylori* than women, though this corresponds to a prevalence of infection only 5% higher among men.

These results are generally consistent with previous meta-analyses on this topic. The most recent review by Ibrahim *et al.* [7], which included 169 studies evaluating adult general populations regardless of sample size, found a significant OR of 1.12. However, only 54 estimates were adjusted; among these, strategies to control confounding varied widely, and many did not report OR estimates adjusted for smoking. On the other hand, the meta-analysis by de Martel and Parsonnet [6], based on 18 studies with at least 500 adult participants and ORs adjusted for at least age and an individual measure of socioeconomic status, found a 16% increased odds of *H. pylori* infection for men. In a systematic review performed by Zamani *et al.* [31], the worldwide prevalence of *H. pylori* infection was estimated at 46.3% (95% CI: 42.1–50.5) among men and 42.7% (95% CI: 39.0–46.5) in women, though this study did not provide adjusted estimates for the sex differences. Although none of the previous meta-analyses found evidence of publication bias through visual inspection of a funnel plot and Egger's regression asymmetry tests, Ibrahim *et al.* [7] found that there was a much higher number of studies from which only crude ORs could be retrieved or calculated than reports with adjusted estimates. Furthermore, although de Martel and Parsonnet [6] attempted to obtain primary data from authors when information on sex associations was not present, data from eight eligible studies were unavailable. The present analysis is not affected by publication bias, as confirmed by the symmetric funnel plot and Egger's test, mainly because the original studies were not selected based on their results regarding the relation between sex and *H. pylori* infection, and data needed for a sound and homogeneous assessment of this relation were available from all the studies included.

Our study yielded a greater OR estimate than those from previous meta-analyses [6,7]. This can be explained by the fact that the included studies comprised both hospital and population-based controls, and the former

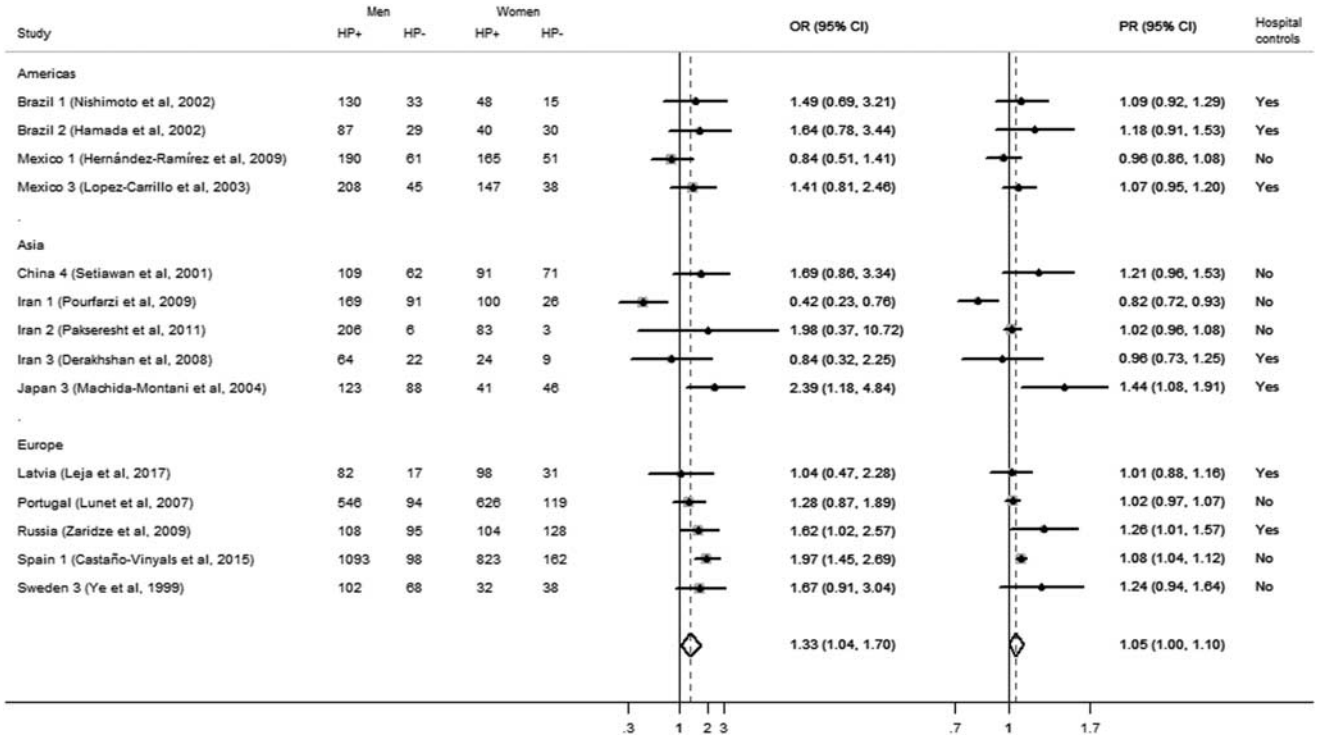

Fig. 2. Study-specific and summary adjusted[a] odds ratios (ORs) and prevalence ratios (PRs), and corresponding 95% confidence intervals (CIs), for the association between sex and *Helicobacter pylori* infection in the Stomach Cancer Pooling (StoP) Project consortium. CI confidence interval, HP + , infected with *Helicobacter pylori*, HP – , not infected with *Helicobacter pylori*, OR, odds ratio, PR, prevalence ratio. [a]OR and PR for males vs. females, adjusted for age, social class (study-specific low, intermediate, and high, based on education, income, or occupation), and smoking (never and ever).

Table 1. Risk of *Helicobacter pylori* infection in males vs. females stratified by sociodemographic characteristics

	H. pylori infection					*H. pylori* infection or gastric atrophy[c]				
Study characteristics	*N*	OR[a] (95% CI)	I^2 (%)	PR[a] (95% CI)	I^2 (%)	*N*	OR[a] (95% CI)	I^2 (%)	PR[a] (95% CI)	I^2 (%)
All studies	14	1.33 (1.04–1.70)	56.5	1.05 (1.00–1.10)	63.0	6[b]	1.62 (1.23–2.13)	0.0	1.13 (1.03–1.25)	34.4
Population type										
Hospital-based	7	1.51 (1.17–1.93)	0.0	1.10 (1.02–1.19)	23.4	5	1.69 (1.25–2.29)	0.0	1.15 (1.03–1.28)	47.4
Population-based	7	1.21 (0.80–1.85)	76.2	1.02 (0.96–1.08)	74.0	1	1.30 (0.66–2.57)	NA	1.10 (0.87–1.38)	NA
Age group (years)										
≤55	14	1.25 (0.98–1.59)	2.0	1.03 (0.99–1.08)	9.7	6	1.49 (1.01–2.19)	6.0	1.11 (0.99–1.24)	0.0
>55 to ≤65	14	1.51 (1.13–2.02)	0.0	1.06 (1.01–1.11)	0.0	6	1.60 (0.93–2.75)	0.0	1.11 (0.98–1.25)	0.0
>65	14	1.67 (1.08–2.62)	56.6	1.09 (1.00–1.18)	59.5	6	2.18 (0.65–7.33)	0.0	1.31 (1.05–1.64)	58.6
Geographic location										
Europe	5	1.66 (1.36–2.03)	0.0	1.06 (1.01–1.12)	44.3	2	1.35 (0.89–2.06)	6.0	1.09 (0.89–1.36)	65.6
Asia	5	1.17 (0.55–2.51)	76.6	1.04 (0.89–1.22)	78.6	2	1.70 (0.99–2.92)	17.9	1.22 (0.97–1.54)	41.2
Americas	4	1.22 (0.89–1.67)	4.5	1.04 (0.97–1.12)	4.2	2	2.28 (1.22–4.26)	0.0	1.14 (0.99–1.32)	30.3

CI, confidence interval; *N*, number of studies; NA, not applicable; OR, odds ratio; PG, pepsinogens; PR, prevalence ratio.
[a]Adjusted for age (except for the age strata), social class (study-specific: low, intermediate, and high, based on education, income, or occupation) and smoking (never and ever).
[b]Corresponding to studies Brazil 1 [11], Brazil 2 [12], China 4 [13], Japan 3 [17], Latvia [18], and Russia [22]. Summary adjusted OR (95% CI): 1.62 (1.24–2.12) and PR (95% CI): 1.15 (1.04–1.27), respectively, for *Helicobacter pylori* infection defined by IgG serum titers and multiplex serology.
[c]Evaluated through histological examination or measured by serum pepsinogen levels (PG I≤70 and PG I/II ratio≤3).

had a higher overall OR. On the contrary, we found that summary OR estimates increased with age, and the differences in relation to previous meta-analyses may reflect differences in the age distribution of the participants. This is expectedly higher in the studies that take part in the StoP project, as controls were often selected to match the age of gastric cancer cases, which was particularly evident among hospital-based controls. Nevertheless, we were able to compute summary PR estimates, which add to the available evidence on this topic a more meaningful estimate of the magnitude of the association than ORs. In fact, a 5% higher prevalence among men shows more clearly that an incidence of gastric cancer twice higher among men can hardly be explained by sex differences in the prevalence of infection. Sex differences are more pronounced among cancers of the intestinal type [32], and previous studies suggest that they become more evident as the carcinogenic cascade progresses; the male/female ratio is very close to 1 in *H. pylori*-related chronic gastritis, increasing gradually through the steps of atrophic gastritis and intestinal metaplasia, and reaching a maximum male predominance in glandular dysplasia and adenocarcinoma [33]. This is

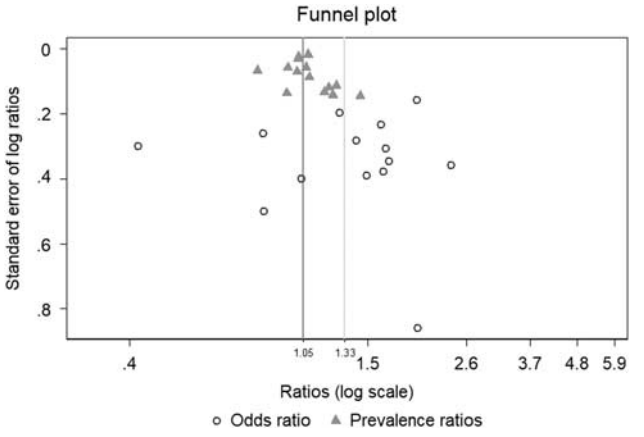

Fig. 3. Funnel plot of the Stomach Cancer Pooling (StoP) studies for the association between sex (male vs. female) and *Helicobacter pylori* infection. Egger's test: $P = 0.470$ (odds ratio) and $P = 0.675$ (prevalence ratio).

supported by our findings of a greater *H. pylori* prevalence when considering the presence of atrophy to further define infection status, particularly in older participants.

Individual participant pooled analyses, such as those performed using the database of the StoP Project [10], may also yield more valid summary estimates than those from meta-analyses of published literature, due to the possibility of a statistical analysis based on more homogenous criteria, including control for confounding [34–36]. In the present pooled analysis we were able to compute for each study estimates for the expectedly most important confounders of this association, though no substantial differences were observed between the summary crude OR or PR and those based on different adjustments.

All studies included in the present pooled analysis defined *H. pylori* infection according to serological methods, which do not measure current infection but infection at some time in life. However, the increasing strength of the association between sex and infection with age suggests that it reflects mostly a relation between persistence of infection rather than with its acquisition, as the latter would result in more pronounced differences at younger ages. The fact that the results were similar when defining infection status considering also the data on gastric atrophy gives further support to this interpretation.

Men from all geographic regions defined in this study had a higher prevalence of infection compared with women, with a higher OR estimate observed for studies from European countries. Ibrahim *et al.* [7] found no differences according to geographical region (America, 26 studies, OR: 1.11, 95% CI: 1.01–1.22); Asia, 82 studies, OR: 1.11, 95% CI: 1.07–1.15; Europe, 49 studies, OR: 1.12, 95% CI: 1.08–1.18), but Zamani *et al.* [31] observed higher prevalences of infection among men with ratios ranging from 1.03 in Latin America and the Caribbean region to 1.16 in Africa, though differences were not statistically significant.

A hypothesis of differential antibiotic exposure between sexes has been put forward to explain the sex differences in *H. pylori* infection. Generally, women have more contact with the health care system [37], which may provide them with an increased opportunity for receiving prescriptions; specifically, over their lifetime, women are more likely than men to obtain antibiotics [38], even if not specifically used for *H. pylori* eradication. A stronger immune response against infection by the presence of estrogens in women was also pointed out as a possible explanation for the sex differences in *H. pylori* infection [6], as well as differences regarding smoking prevalence [7]. However, the inclusion of smoking in the adjusted model did not significantly change the estimates, with a higher prevalence of *H. pylori* infection continuing to be observed among men. With the same set of studies, we were also able to study the association between smoking and the prevalence of infection, adjusting for age, sex funded by the FCT and the "Programa Operacional Capital Humano" (POCH/FSE) and social class, and no significant association was found (OR: 1.08, 95% CI: 0.89–1.32; PR: 1.01, 95% CI: 0.98–1.05) [39]; this is consistent with previous evidence that the male predominance in gastrointestinal adenocarcinomas is similar between smokers and nonsmokers [40]. Moreover, the association between smoking and gastric cancer most likely reflects the effects of tobacco in the later stages of carcinogenesis [41].

Conclusion

This collaborative pooled analysis of individual participant data provides more easily interpreted estimates of the sex differences in the prevalence of *H. pylori* infection as a result of a systematic analysis of each individual study, and the use of detailed and uniform information on major covariates. Moreover, the use of more sensitive criteria to define *H. pylori* infection further elucidated the male predominance of infection at older ages, thus adding to the importance of persistence of infection to the sex difference.

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Conflicts of interest

There are no conflicts of interest.

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