Review Article

Sex-differences in the prevalence of *Helicobacter pylori* infection in pediatric and adult populations: Systematic review and meta-analysis of 244 studies

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**A B S T R A C T**

**Background:** The main outcome of *Helicobacter pylori* infection, i.e. gastric cancer, is more frequent in men, but there is no comprehensive synthesis of the evidence on a potential role of sex in the acquisition and/or persistence of infection.

**Aims:** To quantify the association between sex and *H. pylori* infection in pediatric and adult populations, through systematic review and meta-analysis.

**Methods:** PubMed® was searched, from inception to September 2015, to identify population-based studies reporting the prevalence and/or incidence of *H. pylori* infection in both sexes. Odds ratios (OR) or data to compute them were extracted; adjusted estimates were preferred, whenever available. The DerSimonian and Laird method was used to compute summary estimates and respective 95% confidence intervals (95%CI); separately for children and adults.

**Results:** Among a total of 244 studies, mostly cross-sectional, male sex was associated with a greater prevalence of *H. pylori* infection, both in children (102 studies, OR = 1.06, 95%CI: 1.01, 1.12, I² = 43.7%) and adults (169 studies, OR = 1.12, 95%CI: 1.09, 1.15, I² = 68.5%). An underrepresentation of studies showing a negative association between male sex and infection was observed (Egger’s test: p = 0.006).

**Conclusions:** Although further research is needed to understand the mechanisms by which sex may influence the acquisition and/or persistence of infection, our results support a small contribution of sex differences in the prevalence of infection to the male predominance of *H. pylori*-related outcomes, including gastric cancer.

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1. Introduction

It is estimated that half of the adult population is infected with *Helicobacter pylori* [1], but prevalences range between 20% and 90% across regions [2]. In less affluent settings, incidence rates are generally high during childhood and prevalence increases steeply in this period, whereas in more developed countries, the rates of infection are lower and the proportion of people infected increases more gradually throughout life [3].

*H. pylori* infection is the most important risk factor for gastric cancer, and is estimated to account for approximately 80% of all cases worldwide [4], and 90% for noncardia cancers [5]. Gastric cancer is twice more frequent among men than in women [6], which could reflect sex-differences in the prevalence of *H. pylori*. The most recent meta-analysis on the association between sex and *H. pylori* infection was published in 2006 [7]. It included 28 studies with at least 500 participants, and showed that the prevalence of *H. pylori* infection was significantly higher in males, but only among adults. Since then, several studies have been conducted, expanding the range of available evidence on the subject, and an update of previous reviews may allow for a better understanding of the potential role of sex in the acquisition and/or persistence of infection. Therefore, we aimed to quantify the association between sex and *H. pylori* infection in pediatric and adult populations, through systematic review and meta-analysis.

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2. Material and methods

2.1. Systematic review of the literature

2.1.1. Identification and selection of the studies

A panel of three researchers (AI, AF, SM) conducted a search on PubMed®, from inception to September 2015, to identify original population-based studies reporting on the association between sex and *H. pylori* infection or providing sex-specific data on the prevalence and/or incidence of *H. pylori* infection. The references retrieved were analyzed independently by two reviewers, in line with pre-defined criteria to determine eligibility for inclusion (Fig. 1). When more than one report referred to the same study, the one presenting the results with more detail (e.g., regarding the prevalence according to age strata), or providing data for the largest sample was considered, although any of the reports could be used to obtain information on the study characteristics. Disagreements between reviewers were resolved by consensus or after discussion with another reviewer (BP).

The criteria for exclusion of studies were the following: (1) papers not written in English, Portuguese, Spanish, French, Italian or Polish; (2) research not involving humans (e.g., in vitro or animal research); (3) non-eligible publication types, such as reviews, editorials, comments, guidelines or case reports; (4) studies specifically evaluating samples expected to yield biased estimates of the prevalence of *H. pylori* infection in the general population (e.g., subjects undergoing endoscopy for purposes other than screening; blood donors, university students, health care professionals); (5) studies including only *H. pylori*-infected subjects (e.g., eradication trials); (6) studies with data not related to *H. pylori* prevalence and/or incidence or addressing other outcomes (e.g., cost-effectiveness analyses); (7) studies with a non-systematic assessment of *H. pylori* infection in biological samples (e.g., self-reported information, secondary data on infection status retrieved from laboratory databases); (8) studies not evaluating samples from both sexes or not presenting sex-specific data; (9) multiple reports of the same study or studies evaluating the same sample.

2.1.2. Data extraction

Two investigators (AI, SM) evaluated independently the selected studies to extract data regarding sampling procedures, sample characteristics and assessment of *H. pylori* infection status. Differences in the data extracted by the investigators were discussed until consensus and involving a third researcher (BP) whenever necessary.

Estimates of the association between sex and *H. pylori* infection were extracted from the articles selected, with the necessary detail to analyze separately the data referring to children and adults. Studies were considered to evaluate children or adults when the median, mean or mid-point of participants’ age was <18 or ≥18 years, respectively; when no age-specific estimates were available, the studies were included in the group that corresponded to the median, mean and mid-point of participants’ age.

When cross-sectional data was available for different moments of evaluation of the same cohort study (e.g. baseline and end of follow-up), each of these observations was treated as independent from the remaining.

Adjusted odds ratio (OR) and respective 95% confidence intervals (95%CI) were directly abstracted whenever available; when a study provided OR estimates adjusted for a different number of potential confounders, the one adjusted for the largest number of variables was selected. Otherwise, crude estimates or the information needed to compute them, along with 95%CI, were extracted.

Study design was classified as cross-sectional (including the baseline evaluation of cohort studies and pre-intervention evaluations of randomized controlled trials), case-control or cohort. Study year was defined by the year in which cross-sectional evaluations or baseline evaluations of longitudinal studies were conducted or by the mid-point of the period of data collection, when it spanned over more than one year. When the period of data collection was not reported, we assumed the publication year minus the median difference between the publication year and date of data collection in the articles for which that information was available.

For each study, the type of sample used to detect *H. pylori* infection status was recorded and grouped into: serum (for measurement of IgG antibody level), biopsy (evaluated through histology, rapid urease test or culture), breath (assessed by urea breath test), stool (evaluated by stool antigen tests) or mixed samples (using any combination of the previous).

2.2. Meta-analysis

The meta-analyses were performed separately for children and adults. The DerSimonian and Laird method was used to compute summary OR estimates of the association between sex and *H. pylori* infection (males vs. females) and respective 95%CI. Heterogeneity was quantified using the I² statistic [8]. Visual inspection of the funnel plots and Egger’s regression asymmetry test were used for assessment of publication bias [9]. Stratified analyses according to age group, sample size (using 500 subjects as the cut-off, corresponding to the inclusion criteria used in the previous meta-analysis on the topic [7]), geographic location, type of study, type of sample used to detect *H. pylori* infection status, publication year (using 2006 as the cut-off, corresponding to the publication date of the most recent systematic review on the topic [7]), and survey year (using 1998 as the cut-off, corresponding to the median of the studies included in the systematic review). Meta-regression was also conducted to investigate the joint effect of these variables on heterogeneity [10]. The statistical analysis was performed with STATA®, version 11.2 (Stata Corporation, College Station, TX, USA).

3. Results

A total of 244 studies were included in the meta-analysis, providing 102 estimates for children and 169 for adults (from which 26 recruited both children and adults without providing separate estimates according to age group) (Fig. 1 and Supplementary Table 1). Most targeted school-aged children and middle-aged adults. The studies evaluated recruited between 37 and 183,970 participants, were published from 1991 to 2016, and referred to data collected between 1971 and 2014. The great majority of the studies was conducted in Asian countries. A cross-sectional design and the evaluation of serum samples to assess *H. pylori* infection status were the most frequent.

3.1. Studies in children

Taking into account the 102 estimates retrieved for children, the overall summary OR was 1.06 (95%CI: 1.01, 1.12), with moderate heterogeneity ($I^2 = 43.7\%$) (Fig. 2). Using only adjusted estimates, the summary OR was 1.08 (95%CI: 0.96, 1.23), 23 estimates, $I^2 = 68.9\%$, whereas a summary OR of 1.05 (95%CI: 1.00, 1.12), 79 estimates, $I^2 = 26.6\%$, was obtained when using only crude estimates. The visual inspection of the corresponding funnel plot (Fig. 3) suggests an underrepresentation of smaller studies with negative associations, in accordance with Egger's regression asymmetry test ($p = 0.006$).

Stratified results are presented in Table 1. The association between male sex and *H. pylori* infection was stronger in studies with a smaller sample size (OR = 1.14, 95%CI: 1.05, 1.24, 61 estimates, $I^2 = 25.8\%$), in those conducted in Africa (OR = 1.27, 95%CI: 1.04, 1.54, 9 estimates, $I^2 = 50.9\%$), in those using stool samples to
detect infection status (OR = 1.25, 95%CI: 1.04, 1.50, 14 estimates, $I^2 = 44.8\%$), in studies performed after 1998 (OR = 1.08, 95%CI: 1.01, 1.15, 62 estimates, $I^2 = 51.0\%$), and published before 2006 (OR = 1.08, 95%CI: 1.00, 1.17, 58 estimates, $I^2 = 49.3\%$). Meta-regression showed no significant impact of these variables on heterogeneity.

3.2. Studies in adults

Taking into account the 169 estimates for the association among adults, the overall summary OR was 1.12 (95%CI: 1.09, 1.15), with high heterogeneity ($I^2 = 68.5\%$) (Fig. 4). Conducting similar analysis using only adjusted ORs resulted in a slightly higher point estimate, 1.14 (95%CI: 1.07, 1.21, 31 estimates, $I^2 = 78.0\%$), while similar results were obtained when using only crude estimates (summary OR = 1.12, 95%CI: 1.08, 1.15, 138 estimates, $I^2 = 65.1\%$). Visual inspection of the corresponding funnel plot suggested no publication bias, in accordance with Egger’s regression asymmetry test ($p = 0.379$) (Fig. 5).

The stratified analysis according to population type shows a stronger association between male sex and _H. pylori_ infection when using studies that only recruited adults (summary OR = 1.13, 95%CI: 1.10, 1.17, 143 estimates, $I^2 = 68.4\%$), when compared with those recruiting both children and adults (Table 1). The strongest association between sex and _H. pylori_ infection was found in studies performed in Oceania (summary OR = 1.37, 95%CI: 1.16, 1.64, 10 estimates, $I^2 = 44.8\%$). Higher summary estimates were also observed in those using serum samples to detect infection status (summary OR = 1.14, 95%CI: 1.10, 1.18, 121 estimates, $I^2 = 72.2\%$). No significant differences in the point estimates were found according to age group, sample size, publication year or survey time period. Meta-regression showed no significant impact of these variables on heterogeneity.

Only three cohort studies provided data on the association between sex and _H. pylori_ incidence, one in children and two in adults. Only one study showed a statistically significant positive association among middle-aged adults (relative risk [RR] = 1.64, 95%CI: 1.52, 1.78) [11], whereas the others presented non-significant associations (RR = 1.39, 95%CI: 0.71, 2.71 in adolescents [12] and RR = 0.79, 95%CI: 0.29, 2.18 in adults [13]).
Fig. 2. Forest plot for the association between sex and Helicobacter pylori infection in children, using women as the reference category.

CI—confidence interval; OR—odds ratio.

*Adjusted estimates.
Table 1
Association between sex and Helicobacter pylori infection from studies in children and in adults, according to study characteristics.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of studies</td>
<td>Summary OR (95%CI)</td>
</tr>
<tr>
<td>All studies</td>
<td>102</td>
<td>1.06 (1.01, 1.12)</td>
</tr>
<tr>
<td>Using only adjusted estimates</td>
<td>23</td>
<td>1.08 (0.96, 1.23)</td>
</tr>
<tr>
<td>Using only crude estimates</td>
<td>79</td>
<td>1.05 (1.00, 1.12)</td>
</tr>
<tr>
<td>Population type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only adults</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Both children and adults</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 in children and 18–39 in adults</td>
<td>23</td>
<td>1.10 (0.92, 1.30)</td>
</tr>
<tr>
<td>6–12 in children and 40–69 in adults</td>
<td>62</td>
<td>1.06 (1.00, 1.14)</td>
</tr>
<tr>
<td>13–17 in children and ≥70 in adults</td>
<td>17</td>
<td>1.02 (0.93, 1.13)</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>61</td>
<td>1.14 (1.05, 1.24)</td>
</tr>
<tr>
<td>≥500</td>
<td>41</td>
<td>1.01 (0.94, 1.08)</td>
</tr>
<tr>
<td>Geographic location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>9</td>
<td>1.27 (1.04, 1.54)</td>
</tr>
<tr>
<td>America</td>
<td>26</td>
<td>1.13 (1.00, 1.28)</td>
</tr>
<tr>
<td>Asia</td>
<td>34</td>
<td>1.06 (0.97, 1.15)</td>
</tr>
<tr>
<td>Europe</td>
<td>32</td>
<td>0.95 (0.88, 1.03)</td>
</tr>
<tr>
<td>Oceania</td>
<td>1</td>
<td>1.13 (0.58, 2.21)</td>
</tr>
<tr>
<td>Type of study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>102</td>
<td>1.06 (1.01, 1.12)</td>
</tr>
<tr>
<td>Case-control</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Assessment of H. pylori infection status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>49</td>
<td>1.02 (0.96, 1.09)</td>
</tr>
<tr>
<td>Biopsy</td>
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<td>–</td>
</tr>
<tr>
<td>Breath</td>
<td>34</td>
<td>1.07 (0.95, 1.20)</td>
</tr>
<tr>
<td>Stool</td>
<td>14</td>
<td>1.25 (1.04, 1.50)</td>
</tr>
<tr>
<td>Mixed samples</td>
<td>5</td>
<td>1.09 (0.92, 1.29)</td>
</tr>
<tr>
<td>Publication year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 2006</td>
<td>58</td>
<td>1.08 (1.00, 1.17)</td>
</tr>
<tr>
<td>After 2006</td>
<td>44</td>
<td>1.04 (0.97, 1.11)</td>
</tr>
<tr>
<td>Survey year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1998</td>
<td>40</td>
<td>1.02 (0.93, 1.12)</td>
</tr>
<tr>
<td>After 1998</td>
<td>62</td>
<td>1.08 (1.01, 1.15)</td>
</tr>
</tbody>
</table>

CI—confidence interval; OR—odds ratio.

a Includes the baseline evaluation of 29 cohort studies and two randomized controlled trials.
b Includes the baseline evaluation of 23 cohort studies and two randomized controlled trials.
c Includes one study quantifying anti-H. pylori antibodies in saliva.
d Includes one study quantifying anti-H. pylori antibodies in urine.

Fig. 3. Funnel plot for the association between sex and Helicobacter pylori infection in children, using women as the reference category.

OR—odds ratio.

4. Discussion

Our results show a male predominance in H. pylori prevalence in both pediatric and adult populations. The association was stronger in adults than in children, and among the latter publication bias may have contributed to an overestimation of the summary OR.

In the current systematic review, the inclusion criteria were less restrictive than in the previous meta-analysis [7], namely because studies with smaller samples sizes were not excluded, which allowed for the analysis of an overall number of studies nearly 10 times higher, despite searching only one database (PubMed®), and therefore for a more comprehensive assessment of the available evidence on this topic. The present review included studies from all continents, which was one of the limitations identified by the authors of the previous meta-analysis [7], but no regional differences were consistently observed in both age strata.

We opted for excluding studies specifically evaluating samples expected to yield biased estimates of the prevalence of H. pylori infection in the general population. While the exclusion of some populations is consensual, including subjects undergoing endoscopy for purposes other than screening or health care professionals, the exclusion of blood donors may be questioned, as these have been widely used in epidemiological studies as representative of the general population. Although this group of subjects may be a suitable sample to study genetic factors [14], they differ from the general population in several aspects, namely sociodemographic characteristics [14], which are considered the main determinants...
Fig. 4. Forest plot for the association between sex and *Helicobacter pylori* infection in adults, using women as the reference category. CI—confidence interval; OR—odds ratio.

*Adjusted estimates.
for acquiring _H. pylori_ infection [15]. Besides the fact that in some countries blood donors are paid [16], there are guidelines for blood donation [17] that make this population generally healthier than the general population, potentially leading to biased estimates.

Unlike the previous meta-analysis [7], we observed a significantly higher frequency of infection among boys, but this seems to be due essentially to publication bias. In our meta-analysis there was a much higher number of studies from which only crude ORs could be retrieved or calculated than reports of adjusted estimates. This reflects the fact that assessing sex differences in infection status was not an objective of most studies, or that adjusted estimates were more likely to be provided when results showed stronger associations.

Among children, exposure to antibiotics, even to those not specifically indicated for _H. pylori_ eradication, could contribute to clearance of the infection and to explain sex-differences, since a higher incidence of urinary tract infections in girls may be associated with a greater use of antibiotics [18]. Among adults, sex-differences in the prevalence of _H. pylori_ infection may be explained by differences in the exposure to environmental factors such as smoking, which has been associated with an increased risk of _H. pylori_ infection [12,19], and to the failure of _H. pylori_ eradication [20,21]. Since the prevalence of smoking remains higher in men compared with women [22], this is compatible with the sex-differences observed in the prevalence of infection in adults, even in the absence of such an association at younger ages. Physiological differences, namely sex hormones [23], may also affect immunity and the inflammatory response to _H. pylori_ differently in men and women; these hormones can interfere, directly or indirectly, with the cell receptors altering immunological response (immune-modulators) [24].

5. Conclusions

This study provides the most extensive and robust assessment of the sex differences in the prevalence of _H. pylori_ infection. The results confirm the increased prevalence among adult men and are compatible with a lack of association at younger ages. Although further research is needed to understand the mechanisms by which sex may influence the acquisition and/or persistence of infection, our results support a small contribution of sex differences in the prevalence of infection to the male predominance of _H. pylori_-related outcomes, including gastric cancer.

**Conflict of interest**

None declared.

**Acknowledgements**

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jldd.2017.03.019.

**References**


