Gastric Cancer is Related to Early *Helicobacter pylori* Infection in a High-Prevalence Country

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**Abstract**

Background and Aims: Chile ranks fifth in the world among countries with the highest incidence of gastric cancer. The aim was to quantify the association between *Helicobacter pylori* infection and gastric cancer mortality at the county of residence. Methods: A cross-sectional household survey, a probability sample of the Chilean adult population, provided 2,615 participants in whom serum *H. pylori* IgG antibodies were measured (ELISA). The spatial pattern of 48,367 deaths due to gastric cancer which occurred from 1985 to 2002 was analyzed using a hierarchical Poisson regression model; 333 counties were categorized as low, medium, and high gastric cancer mortality with median gastric cancer death rates of 11.4, 19.1, and 26.0 per 100,000 inhabitants, respectively. The association between *H. pylori* positivity and gastric cancer mortality in the county of residence was assessed by multivariate Poisson regression for complex samples.

**Introduction**

There is abundant evidence of the association between chronic infection with *Helicobacter pylori* and the development of gastric cancer (1-5). Some population-based studies showed that high levels of *H. pylori* infection were not accompanied by high gastric cancer mortality, the so-called African (6-8) and Asian enigmas (9). The wide variation in the risk of gastric cancer mortality in Chile, with a relatively homogeneous population, would permit us to assess the epidemiology of gastric cancer (13). Accordingly, the main objective of the present study was to quantify the association between *H. pylori* infection and gastric cancer mortality at the county of residence.

**Materials and Methods**

**Study Population.** The 2003 National Health Survey was a national cross-sectional household survey of 3,619 people based on a multistage stratified random sample of the Chilean population over 17 years of age. Only one participant was selected per household, using the Kish method to choose the responding individual (14). Participants completed several specific health questionnaires (history of diabetes, hypertension, peptic ulcer, gastroesophageal reflux, and smoking), physical examinations (blood pressure and anthropometry), and laboratory analyses (fasting glucose, lipid profile, hepatitis A, B, C, and hemoglobin). Available sera from participants were used for measuring antibodies to *H. pylori*. Blood samples were centrifuged and frozen at −30°C until they were transported to the central laboratory at the Pontificia Universidad Católica de Chile, where they were kept at −80°C until processing. Sera for 2,615 subjects, corresponding to 72.2% of the target sample, were available for analysis. Participants were similar to nonparticipants with regard to age (<45 years old, 62.9% and 60%, respectively), sex (men, 47.9% and 51.6%, respectively), area of residence (residing in rural areas, 14.4% and 11.4%, respectively), and

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socioeconomic status (<8 years of schooling, 25.1% and 25.5%, respectively). None of the differences reached statistical significance.

**Determination of IgG Anti-\(H. pylori\).** Serum samples were analyzed with a commercial immunoassay for the detection of IgG antibodies to \(H. pylori\) (Bioelisa Helicobacter, Biokit SA, Barcelona, Spain). Briefly, serum samples were diluted (1:200) and 100 \(\mu L\) aliquots were transferred to each well of a plate coated with inactivated \(H. pylori\) antigens. Plates were then incubated at 37°C for 45 min and washed. Next, 100 \(\mu L\) of the conjugate (horseradish peroxidase-labeled rabbit antibodies to human IgG) was added to each well. The plates were washed again under the previous conditions and 100 \(\mu L\) of substrate solution with tetramethylbenzidine was added to each well. After 25 min of incubation at room temperature, the reaction was stopped with 10 \(\mu L\) of \(H_2SO_4\) 1 N. Finally, the color developed was measured spectrophotometrically at 450 nm in the next 30 min. The cutoff values were based on the standard value of the test calibrators, according to the instructions of the manufacturer, and expressed as arbitrary units per milliliter.

In a preliminary study, we evaluated immune response to \(H. pylori\) through the measurement of specific antibodies directed against a whole cell preparation of \(H. pylori\) with a noncommercial immunoassay (15). Serum positivity on that study was defined on the basis of cutoff values established by the mean + 3 SD of a normal population from the United States. In a recent study, we compared the noncommercial immunoassay with the commercial assay used in the current study and determined a sensitivity of 90% and a specificity of 50% for the adult group (16). Because variation in sensitivity and specificity according to age has been previously reported, we further extended our analysis by including an older population and the best cutoff values were chosen based on receiver operator curves, with a cutoff value of 72.79 arbitrary units/mL for IgG, reaching a sensitivity and specificity of 87.5% and 62%, respectively. In this evaluation, the gold standard for the ELISA was the presence of \(H. pylori\) in the stomach as determined by histology.

**Statistical Analysis.** The adjusted prevalence rates of \(H. pylori\) were calculated using the sampling weights from the two-stage sampling design and adjusted for poststratification population totals using the 2003 Chilean population. In view of the complex sample design, the SE and 95% confidence intervals (CI) were calculated with a Taylor linear approximation method using SAS version 8 (17). For international comparison purposes, a direct standardization was done to estimate the overall \(H. pylori\) prevalence, by considering the age and gender world population structure as proposed by Doll and Cook (18).

**Gastric Cancer Mortality Estimation.** Computerized information about deaths from gastric cancer between 1985 and 2002 (48,367 deaths), registered separately for the 333 Chilean counties, was obtained from the Ministry of Health (12). Estimates of the population (~15 million inhabitants), stratified by age, sex, and county were obtained from the National Institute of Statistics (19). Relative risk of gastric cancer at the county level was estimated by an internal age/sex standardization of the gastric cancer cumulative rate using the 1985 to 2002 national average rates as reference. The spatial pattern of relative risk was analyzed using a Bayesian hierarchical Poisson regression model. In addition to a classical Standardized Mortality Ratio (SMR) estimates, two statistical models differing in the form of the variability of relative risk were adjusted. Model 1 assumed a nonspatial pattern (unstructured variability), whereas model 2 used a combination of unstructured variability and spatial dependence (structured variability). This spatial variability was taken into account by considering an intrinsic conditional autoregressive prior distribution (20). Model 2 can be represented by:

\[
O_i \sim \text{Poisson}(\mu_i) \\
\log \mu_i = \log E_i + x_0 + b_i + h_i
\]

where, \(x_0\) is the intercept that represents the log of the baseline risk of gastric cancer throughout the study area, \(b_i\) is the random area-specific effect in the log of relative risk explained by the neighbors of the \(i^{th}\) county, and \(h_i\) is the area-specific random effect not explained by neighbors of the \(i^{th}\) county. Posterior inference was done by using Markov chain Monte Carlo techniques and the WinBUGS program (21). Convergences were evaluated based on standard criteria using the BOA program (22). Comparison and selection of models were based on the deviance information criterion (23). The

![Figure 1. Spatial distribution of the risk of gastric cancer mortality in 333 Chilean counties (1985-2002).](image)
H. pylori infection was higher for men and women residing in areas of high (77.4%) versus low gastric cancer incidence (64.3%); high incidence of gastric cancer, study participants presented a $P = 0.01$. Among the 17- to 24-year-olds residing in counties with a low incidence of gastric cancer (Table 2). By age 17, 75% of residents from counties with a high incidence of gastric cancer had serologic evidence of H. pylori infection, whereas people from counties with a low incidence of gastric cancer reached that level of infection only after 35 years of age (Fig. 2).

Multivariate Analysis. Univariate analyses of relative risk of H. pylori infection were calculated using Poisson regression with robust estimates of the variance (24). The main explicatory variable analyzed was residence in a county with high gastric cancer mortality; we also explored the association of H. pylori with the 2003 poverty level in the county of residence, i.e., the proportion of the population living below the poverty line (percentage of individuals whose income was insufficient to buy two basic food baskets; ref. 25). Both were county-level variables. Individual-based variables studied were sex, age, educational level (high, medium, and low as a proxy for socioeconomic status), zone of residence at the time of the survey (urban county, >2,000 inhabitants, and rural county, <2,000 inhabitants), tobacco smoking, and antibodies to anti–hepatitis A (proxy for enteric contamination). Variables statistically significant in the univariable analysis were later included in multivariable models to estimate prevalence rate ratios (PRR)—Poisson regression model for complex samples using SPSS version 13. Only those variables that remained significant were left in the final model. The significance level for each test was set to $\alpha = 5\%$.

Results

H. pylori prevalence in adults (>17 years old) was 73.0% (95% CI, 70.0-76.0%); 73.4% adjusted for the world population (18). H. pylori infection was significantly higher in men, peaked from ages 45 to 64, and dropped among study participants ages 65 and older. It was also higher among people of low socioeconomic status and those with hepatitis A antibodies (Table 1). The occurrence of H. pylori did not differ according to reports of frequent regurgitation or pyrosis (reported by 25.6%), or by history of medical diagnoses of peptic ulcer (reported by 4.7%), or smoking (Table 1). H. pylori prevalence was higher among people residing in counties in the high or medium tertiles of poverty versus those residing in counties in the lowest tertile of poverty (75.9%, 76.7%, and 66.3%, respectively; Table 1).

Mean IgG levels (in arbitrary units) were similar among residents of counties with high, medium, and low gastric cancer mortalities: 188.6 (95% CI, 171.8-205.7), 192.0 (95% CI, 177.2-206.7), and 166.0 (95% CI, 149.6-182.4), respectively. Although among 17- to 24-year-olds, IgG levels were significantly higher in residents in counties with high versus low gastric cancer incidences: 182.6 (95% CI, 138.6-226.6) and 92.3 (95% CI, 62.8-121.8), respectively.

H. pylori infection presented a significant and positive association with the gastric cancer mortality of the residence area, as indicated by $\chi^2$ test for trend (Table 2). H. pylori prevalence was higher for men and women residing in areas of high gastric cancer incidence [men from areas of high (81.9%) versus low gastric cancer incidence (72.7%); $P = 0.04$; women from high (77.4%) versus low gastric cancer incidence (64.3%); $P = 0.01$]. Among the 17- to 24-year-olds residing in counties with a high incidence of gastric cancer, study participants presented a level of H. pylori infection twice as high as those from counties with a low incidence of gastric cancer (Table 2). By age 17, 75% of residents from counties with a high incidence of gastric cancer had serologic evidence of H. pylori infection, whereas people from counties with a low incidence of gastric cancer reached that level of infection only after 35 years of age (Fig. 2). H. pylori infection declined at older ages in all counties, but declined earlier among counties with a high versus low incidence of gastric cancer (declining point started at 38 and 49 years old, respectively).

The multivariate Poisson regression analysis indicated a significant effect of gastric cancer mortality, age, gastric cancer mortality × age interaction, and gender on the degree of H. pylori infection. The corresponding score statistics ($P$) were 13.95 (0.001), 16.19 (0.001), 16.90 (0.010), and 6.48 (0.011), respectively. For educational level, the score statistic ($P$) was 5.02 (0.081), suggesting the absence of differences in the degree of H. pylori infection across socioeconomic levels, after controlling for gastric cancer mortality, age, and gender (Table 3). Poverty level in the county of residence was not significant in the multivariable analysis. The score statistic ($P$) was 2.06 (0.36) and, therefore, it was not included in the final model. The PRR’s, resulting from the multivariate Poisson analysis, are shown in Table 3. These results confirm the

### Table 1. Prevalence of H. pylori by age, sex, and selected characteristics in a sample of 2,615 people (Chile 2003)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>H. pylori – positive (n = 1,950)</th>
<th>Positivity, % (95% CI)*</th>
<th>H. pylori+/ H. pylori−, PRR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,042</td>
<td>69.7 (65.3-73.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>908</td>
<td>76.8 (72.3-80.8)</td>
<td>1.1 (1.01-1.20)</td>
</tr>
<tr>
<td>Age (x² for trend, 8.2; P = 0.004)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-24</td>
<td>217</td>
<td>62.0 (53.5-69.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>25-44</td>
<td>639</td>
<td>76.8 (72.0-80.9)</td>
<td>1.24 (1.06-1.44)</td>
</tr>
<tr>
<td>45-64</td>
<td>654</td>
<td>78.1 (72.5-82.8)</td>
<td>1.26 (1.07-1.47)</td>
</tr>
<tr>
<td>65 and older</td>
<td>440</td>
<td>67.1 (61.6-72.2)</td>
<td>1.08 (0.92-1.27)</td>
</tr>
<tr>
<td>Educational level † (x² for trend, 15.5; P &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>238</td>
<td>65.2 (56.8-72.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Medium</td>
<td>947</td>
<td>74.3 (69.9-78.2)</td>
<td>1.14 (0.99-1.31)</td>
</tr>
<tr>
<td>Low</td>
<td>765</td>
<td>76.3 (71.0-80.9)</td>
<td>1.17 (1.01-1.34)</td>
</tr>
<tr>
<td>Zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>1,568</td>
<td>72.3 (68.9-75.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Rural</td>
<td>382</td>
<td>77.9 (71.0-83.6)</td>
<td>1.08 (0.98-1.18)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>88</td>
<td>59.0 (48.2-69.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive</td>
<td>635</td>
<td>74.5 (68.9-79.4)</td>
<td>1.26 (1.04-1.53)</td>
</tr>
<tr>
<td>Obesity</td>
<td>No</td>
<td>71.5 (67.6-75.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>524</td>
<td>78.5 (73.6-82.7)</td>
<td>1.15 (1.04-1.27)</td>
</tr>
<tr>
<td>Gastroesophageal reflux or pyrosis</td>
<td>1,421</td>
<td>73.2 (69.4-76.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>500</td>
<td>72.8 (67.7-77.4)</td>
<td>0.99 (0.91-1.09)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>1,797</td>
<td>73.5 (70.3-76.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>153</td>
<td>69.5 (58.1-78.9)</td>
<td>0.94 (0.81-1.09)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>71.3 (67.1-75.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>876</td>
<td>76.5 (72.5-80.0)</td>
<td>1.31 (0.98-1.76)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>No</td>
<td>72.1 (66.2-77.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>438</td>
<td>77.2 (72.3-81.5)</td>
<td>1.31 (0.89-1.92)</td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
<td>74.5 (70.7-78.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>645</td>
<td>70.8 (65.9-75.3)</td>
<td>0.83 (0.61-1.13)</td>
</tr>
<tr>
<td>Poverty level in county of residence ‡</td>
<td>Low</td>
<td>542 (66.3 (63.0-69.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Medium</td>
<td>670</td>
<td>76.7 (74.0-80.0)</td>
<td>1.16 (1.09-1.23)</td>
</tr>
<tr>
<td>High</td>
<td>649</td>
<td>75.9 (73.0-79.0)</td>
<td>1.15 (1.08-1.22)</td>
</tr>
</tbody>
</table>

NOTE: Prevalence was age/sex-standardized to the 2003 Chilean population.

* SEs and 95% CIs estimated with the Taylor expansion method.
† PRR from Poisson regression with robust estimate of the variance error.
‡ Educational level is a proxy for socioeconomic status.
§ Percentage of the population living below the poverty level in the county of residence.
Table 2. Prevalence of IgG anti–H. pylori among people residing in counties of high, medium, or low mortality of gastric cancer

<table>
<thead>
<tr>
<th>Age</th>
<th>High gastric cancer, n = 1,306 (95% CI)*</th>
<th>Medium gastric cancer, n = 882 (95% CI)*</th>
<th>Low gastric cancer, n = 427 (95% CI)*</th>
<th>Medium gastric cancer/low gastric cancer, PRR (95% CI)*</th>
<th>High gastric cancer/low gastric cancer, PRR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-24</td>
<td>79.7 (72.2-85.6)</td>
<td>49.3 (36.7-62.0)</td>
<td>39.8 (19.6-64.2)</td>
<td>1.2 (0.6-2.4)</td>
<td>2.0 (1.1-3.7)</td>
</tr>
<tr>
<td>25-44</td>
<td>82.6 (76.1-87.7)</td>
<td>75.4 (67.3-82.0)</td>
<td>65.4 (52.6-76.3)</td>
<td>1.1 (0.9-1.4)</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td>45-64</td>
<td>79.3 (73.4-84.1)</td>
<td>80.3 (72.2-86.5)</td>
<td>70.0 (47.9-85.5)</td>
<td>1.15 (0.9-1.5)</td>
<td>1.1 (0.9-1.4)</td>
</tr>
<tr>
<td>≥65</td>
<td>68.1 (61.3-74.2)</td>
<td>64.4 (54.6-73.1)</td>
<td>71.4 (55.8-83.3)</td>
<td>0.69 (0.7-1.3)</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>79.7 (76.4-82.6)</td>
<td>70.7 (65.4-75.5)</td>
<td>62.3 (53.8-70.2)</td>
<td>1.1 (0.9-1.3)</td>
<td>1.3 (1.1-1.5)</td>
</tr>
</tbody>
</table>

*SEs and 95% CI estimated with the Taylor expansion method.

Discussion

The national prevalence of H. pylori infection standardized for the world population for ages 20 to 60 was 74.5%. This high level of H. pylori infection may explain why Chile has the highest rate of gastric cancer mortality in the Americas, and is among the top five countries in the world with regard to gastric cancer mortality (11). This study confirmed, at the ecological level, the association between H. pylori and gastric cancer; in the counties with high gastric cancer mortality, H. pylori prevalence was significantly higher than in those with low gastric cancer mortality (79.7% and 62.3%, respectively). This difference was even higher at younger ages (17-24 years) in which H. pylori prevalence was twice as high among people residing in counties of high compared with those residing in counties of low gastric cancer mortality (79.7% and 39.8%, respectively). This result might have been higher had we studied younger subjects (<17 years old). In a previous study, Armijo showed that the only risk factors for gastric cancer in Chile were tobacco use and the duration of residence in zones with a high gastric cancer mortality before turning 25 years old (26). The earlier age at which H. pylori infection begins to decline in counties of high gastric cancer mortality may reflect the earlier installation of atrophy and the longer time at risk of developing gastric cancer.

The inconsistencies that have been described in the association between H. pylori and gastric cancer at the population level (27, 28) may be explained in part by the lack of accuracy in serologic testing and by variations in study conditions. We did not find a spatial association between gastric cancer and H. pylori when analyzed at the level of large conglomerates—the 13 regions of the country—the association was only evident in smaller geographic units, that is, the 333 counties. The use of large populations may explain the lack of association between H. pylori and gastric cancer in Mexico (27). A recent study in Colombia (28) reports an equal infection rate of H. pylori in areas of high (Pasto) and low (Tumaco) risk for gastric cancer (59.7% and 58.6%, respectively). This apparent paradox could be explained by racial differences (as stated by the authors, Pasto is predominantly Spanish-American, whereas Tumaco is predominantly African-Spanish ancestry) or the environmental differences between the two cities (Pasto is at a high altitude in the Andean mountains and is mostly agricultural, whereas Tumaco is by the Pacific coast). In our study, the population was highly homogeneous, mostly Spanish-American, we controlled by individual socioeconomic status and by county poverty level, and included participants from counties from all over Chile, and this could have diluted the effect of unmeasured potential confounders.

In Chile, men had a 64% greater gastric cancer mortality than women (29.0 and 10.5 gastric cancer deaths per 10^5 inhabitants, respectively; ref. 12) but their H. pylori prevalence was only 9.2% higher (76.8% and 69.7% for men and women, respectively). Other cofactors may explain men’s higher risk: 23% higher smoking rate (48% men and 37% women; ref. 13) and 22% higher abuse of salt in foods (addition of salt to food before tasting was 10.9% and 8.5% for men and women, respectively; ref. 29). The protective role of female hormones has also been proposed (30).

Although H. pylori was marginally more frequent among those subjects with anti–hepatitis A antibodies (relative risk, 1.26; see Table 1), the significance disappeared when adjustments were made for the risk of gastric cancer in the county of...
residence. Hepatitis A infection was unrelated with gastric cancer mortality in the county of residence. The apparent lack of effect of general environmental improvements (almost 100% of basic sanitation and sewage coverage by 2005) in H. pylori prevalence may be explained by the latency in effect due to the chronic condition of H. pylori infection or to a different mechanism of transmission of H. pylori and hepatitis A. Other authors have previously reported the different epidemiologies between H. pylori and hepatitis A (31, 32). The lack of association between H. pylori infection and a history of gastric ulcer may reflect the effect of medical treatment because 85% of these people reported that they had been treated. Finally, variations in H. pylori strains have been proposed as an explanation for the changes in the effect of H. pylori (5). However, we found similar a seroprevalence for Cag A–positive strains in a subsample of 267 subjects residing in counties at high or low risk (66% and 69%, respectively); although the sample size was too small to rule out this possibility.

This is the first national level study of the population distribution of H. pylori infection and its relation with the risk of gastric cancer. We developed a spatial model for gastric cancer mortality in the country of residence. The principal limitation is inherent to the hybrid design, which combines conglomerate variables (risk of gastric cancer in the county of residence) with individual variables (participants’ antibodies against H. pylori). The analysis assigns the risk of county of residence to the individual, which implies some assumptions (homogeneity of risk within the county, permanent residence there, and that other risk factors for gastric cancer were homogeneous within counties). The model used to estimate the baseline gastric cancer mortality in each county has a spatial smoothing function that takes account of the influence of neighbors. Interregional migration in Chile is among the lowest registered. From 1965 to 2000, annual internal migration was only 0.6% in comparison with 1.2% in Argentina, 3.1% in the United Kingdom, and 6.6% in the United States (33). Some diseased individuals from regions at high-risk may migrate to the capital city of Santiago to obtain medical care, artificially elevating cancer rates in the Metropolitan area, whereas simultaneously decreasing the rates in areas with low population density. Thus, migration would attenuate the risk estimates calculated. Gastric cancer at the national level has been extraordinarily stable in the last 20 years; its death rate per 100,000 population was 19.6 in 1984 and 19.0 in 2004, the lowest was 18.6 in 1985, the highest was 21.2 in 1982. At the county level, the rates may vary randomly from year to year associated with small population size. The model adjusts for the random temporal variation in the observed number of cases. We did not study temporal trends because our interest was to obtain a summary measure of risk for the study period. This summary measure may hide trends in risk in some counties. Regarding the quality of mortality data, almost 100% of the deaths recorded in Chile had a death certificate, and the large majority were completed by physicians (34).

The low specificity of the H. pylori ascertainment method may be explained, among other factors, by cross-reactivity with other non–H. pylori infections, by lack of detection of H. pylori in the biopsies (sample error; refs. 35-38), or by spontaneous eradication. Nevertheless, only a minority of infected individuals could eradicate the infection spontaneously (39), except when the development of gastric mucosal atrophy renders the gastric environment hostile to the bacterium. The misclassification of H. pylori status may decrease the association between the exposure and the effect. In conclusion, heterogeneity in H. pylori infection may explain the differences in gastric cancer mortality around Chile.

Acknowledgments

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References

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