

## Sociodemographic Determinants of Prevalence and Incidence of *Helicobacter pylori* Infection in Portuguese Adults

Joana Bastos,<sup>\*,†</sup> Bárbara Peleteiro,<sup>\*,†</sup> Rita Barros,<sup>‡</sup> Luís Alves,<sup>\*,†,§</sup> Milton Severo,<sup>\*,†</sup> Maria de Fátima Pina,<sup>\*,†,¶</sup> Hugo Pinto,<sup>\*,†</sup> Sandra Carvalho,<sup>\*,†</sup> Ana Marinho,<sup>\*\*</sup> João T. Guimarães,<sup>†,\*\*,††</sup> Ana Azevedo,<sup>\*,†</sup> Carlo La Vecchia,<sup>‡‡,§§</sup> Henrique Barros<sup>\*,†</sup> and Nuno Lunet<sup>\*,†</sup>

<sup>\*</sup>Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal, <sup>†</sup>Institute of Public Health of the University of Porto (ISPUP), Porto, Portugal, <sup>‡</sup>Institute of Molecular Pathology and Immunology (IPATIMUP), University of Porto, Porto, Portugal, <sup>§</sup>St André de Canidelo Family Health Unit, Vila Nova de Gaia, Portugal, <sup>¶</sup>Biomedical Engineering Institute (INEB), University of Porto, Porto, Portugal, <sup>\*\*</sup>Department of Clinical Pathology, Centro Hospitalar de São João, Porto, Portugal, <sup>††</sup>Department of Biochemistry, University of Porto Medical School, Porto, Portugal, <sup>‡‡</sup>Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy, <sup>§§</sup>Department of Medical Sciences and Public Health, Università degli Studi di Milano, Milan, Italy

### Keywords

*Helicobacter pylori* infection, prevalence, incidence, Portugal.

Reprint requests to: Nuno Lunet, Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública, Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, Porto 4200-319, Portugal.  
E-mail: [nlunet@med.up.pt](mailto:nlunet@med.up.pt)

### Abstract

**Background:** Understanding the determinants of *Helicobacter pylori* infection in adults is essential to predict the burden of *H. pylori*-related diseases. We aimed to estimate the prevalence and incidence of *H. pylori* infection and to identify its major sociodemographic correlates in an urban population from the North of Portugal.

**Material and Methods:** A representative sample of noninstitutionalized adult inhabitants of Porto (n = 2067) was evaluated by ELISA (IgG) and a subsample (n = 412) was tested by Western Blot to assess infection with CagA-positive strains. Modified Poisson and Poisson regression models were used to estimate crude and sex-, age-, and education-adjusted prevalence ratios (PR) and incidence rate ratios (RR), respectively.

**Results:** The prevalence of *H. pylori* infection was 84.2% [95% confidence interval (95%CI): 82.4–86.1]. It increased across age-groups in the more educated subjects, (18–30 years: 72.6%; ≥71 years: 88.1%; *p* for trend <0.001) and decreased with education in the younger (≤4 schooling years: 100.0%; ≥10 schooling years: 72.6%; *p* for trend <0.001). Living in a more deprived neighborhood was associated with a higher prevalence of infection, only in the younger (PR = 1.20, 95%CI: 1.03–1.38) and more educated participants (PR = 1.15, 95%CI: 1.03–1.29). Among the infected, the proportion with CagA-positive strains was 61.7% (95%CI: 56.6–66.9). The incidence rate was 3.6/100 person-years (median follow-up: 3 years; 95%CI: 2.1–6.2), lower among the more educated (≥10 vs ≤9: RR = 0.25, 95%CI: 0.06–0.96). The seroreversion rate was 1.0/100 person-years (95%CI: 0.6–1.7).

**Conclusions:** The prevalence of infection among adults is still very high in Portugal, suggesting that stomach cancer rates will remain high over the next few decades.

*Helicobacter pylori* infection is strongly associated with the occurrence of gastric cancer [1], and individuals who are infected with CagA-positive strains are at an even higher risk than those harboring strains without this virulence marker [2].

The frequency of the infection varies appreciably with age and across geographical areas [3]. It is acquired mainly in childhood, though infection may

also occur in adult life [4] and is observed more often among subjects with lower socioeconomic status [5]. Over the last few decades, the prevalence of infection in adult populations declined to below 50% in the more affluent European countries [3], contributing to the steep decline in gastric cancer incidence and mortality [6]. Nevertheless, approximately half the world adult population is infected [7], and about 660,000 of

all cancers diagnosed in 2008 worldwide were attributable to *H. pylori* infection, corresponding to approximately one third of the 2 million cancer cases due to infections [8].

In Portugal, despite a steady decline in mortality over the last four decades [6,9], gastric cancer rates [10] are among the highest in Europe, especially in the North of the country [11], where this study was conducted. The prevalence of *H. pylori* infection in the Portuguese adult population was approximately 90% in the early 1990s [12]; to our knowledge, no surveys of the adult general population were conducted since then, and the available data on the frequency of infection with the more virulent strains is scarce [13,14].

We aimed to estimate the prevalence and the incidence of *H. pylori* infection and the proportion of subjects infected with CagA-positive strains, and to identify the major sociodemographic correlates of infection in an urban population from the North of Portugal.

## Materials and Methods

Noninstitutionalized adult dwellers in the city of Porto were recruited between January 1999 and December 2003 and re-evaluated between May 2005 and September 2008, as part of the EPIPorto cohort. A detailed description of the general selection procedures and participants' characteristics has been published elsewhere [15,16]. In brief, participants were recruited by random digit dialing using households as the sampling frame, followed by simple random sampling to select one eligible person among permanent residents in each household, without allowing replacement of refusals. The participants underwent a questionnaire evaluation, physical examination, and blood collection at the Department of Clinical Epidemiology, Predictive Medicine and Public Health of the University of Porto Medical School, Porto, Portugal.

A flowchart describing the participants considered for the different components of the present study is presented in Fig. 1.

The EPIPorto cohort included 2485 participants aged above 18, corresponding to a participation proportion of 70% [16]. A venous blood sample was available for 2067 subjects (83.2%). Participants from whom a blood sample was not available were older (median age: 58 vs 55 years,  $p < .001$ ) and less educated (median number of education years: 6 vs 8 years,  $p < .001$ ). The groups were similar regarding sex distribution (males: 39.5% vs 37.8%,  $p = .529$ ).

To assess the incidence of infection during follow-up, a venous blood sample was collected from 114 participants (40.6% of those without evidence of infection

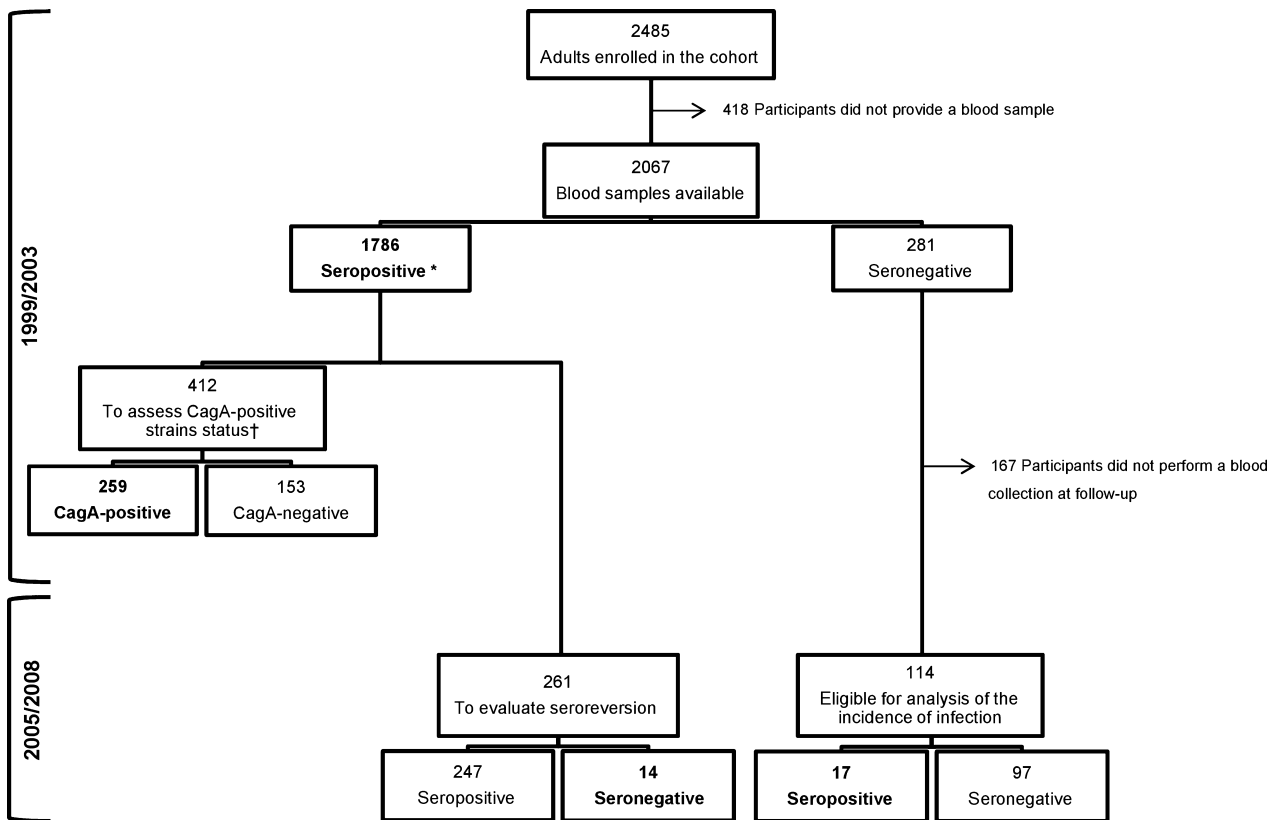
at the baseline evaluation; median follow-up: 3 years). Participants that tested negative for infection at baseline and from whom a blood sample was not available at follow-up were significantly older (median age: 54 vs 41 years,  $p < .001$ ) and less educated (median number of education years: 11 vs 12 years,  $p = .031$ ). The sex distribution was not significantly different between these two groups (males: 31.7% vs 36.8%,  $p = .374$ ).

To quantify the seroreversion rate, a random representative sample, stratified according to sex, age, and education, of individuals classified as infected at baseline and re-evaluated at follow-up ( $n = 261$ , median follow-up: 5 years) was obtained.

Serum samples were kept frozen at  $-20^{\circ}\text{C}$  until analysis. Assessment of anti-*Helicobacter pylori* IgG titers on serum was performed by ELISA (anti-*Helicobacter pylori* ELISA (IgG), Euroimmun, Lubeck, Germany; sensitivity: 100%, specificity: 94% [17]). The participants' infection status was classified as negative if the antibody concentration was lower than 16 RU/ml, borderline if the antibody concentration was equal or higher than 16 RU/mL and lower than 22 RU/mL, and positive if the antibody concentration was 22 RU/mL or higher. For the present analysis, subjects having borderline results were considered infected.

To quantify the prevalence of infection with CagA-positive strains at baseline, a subsample of 412 participants classified as infected according to the anti-*Helicobacter pylori* IgG titers, randomly selected to be representative of the infected individuals at the baseline regarding sex, age, and education, was further tested by Western Blot (Helico Blot 2.1; Genelabs Diagnostics®, Singapore, Singapore). CagA seropositivity was evaluated following the criteria recommended by the manufacturer: presence of the 116 kD band (CagA) with one or more of the following bands: 89 kD (VacA), 37 kD, 35 kD, 30 kD (UreA), and 19.5 kD together.

Education was recorded as completed years of schooling. Occupations were classified by major professional groups, according to the National Classification of Occupations – version 1994 (NCO-94) [18] and grouped in three categories: upper white-collar, lower white-collar, and blue-collar. The upper white-collar category comprised individuals classified in the upper three major groups of the NCO-94: executive civil servants, industrial directors and executives; professionals and scientists; and middle management and technicians. The lower white-collar category comprised individuals classified in the fourth and fifth major groups of the NCO-94: administrative and related workers and service and sales workers. The blue-collar category comprised individuals classified in the sixth to ninth major groups of the NCO-94. These major groups



**Figure 1** Flowchart describing the participants included in the analyses. \*The participants' infection status was classified as negative if the antibody concentration was lower than 16 RU/mL, borderline if the antibody concentration was equal or higher than 16 RU/mL and lower than 22 RU/mL, and positive if the antibody concentration was 22 RU/mL or higher. For analysis, subjects having borderline results were considered infected. †CagA seropositivity was evaluated following the criteria recommended by the manufacturer: presence of the 116 kD band (CagA) with one or more of the following bands: 89 kD (VacA), 37 kD, 35 kD, 30 kD (UreA), and 19.5 kD together.

included farmers and skilled agricultural, fisheries workers, skilled workers, craftsmen and similar, machine operators and assembly workers, and unskilled workers. Retired participants were classified considering their previous main occupation. Similarly, housewives and currently unemployed subjects reporting a previous occupation were included in the analysis using this information [19]. Housewives and unemployed at the time of data collection who did not report a previous occupation were included in an additional category, named 'Other'.

To assess the neighborhood's socioeconomic class statistical census tracts defined by the National Census 2001, broadly equivalent to a city block in an urban setting, were used as a proxy of neighborhoods [20]. Self-reported addresses were used to georeference individuals to a specific neighborhood. The socioeconomic characterization of neighborhoods was based on aggregated data from the National Census 2001, available at the statistical subsection level. Based on statistical criteria

and consensus between investigators, 11 variables related to buildings, households, families, and individuals were selected in order to characterize three distinct socioeconomic dimensions of the neighborhood: age, education/occupation, and housing characteristics. Latent class analysis models were used to uncover socioeconomically heterogeneous and discrete groups of neighborhoods [21]. The final model identified three socioeconomic classes. Whereas class 1 neighborhoods had the better socioeconomic position, classes 2 and 3 had increasingly worse socioeconomic profiles. Further details on these methods may be provided by the authors on request.

Height was measured to the nearest centimeter in the standing position using a wall stadiometer. For analysis, the participants' height was categorized according to the sex-specific tertiles of its distribution.

Information on refrigerator ownership was collected by asking the subjects if they had refrigerator at home and for how many years. For analysis, the participants

were classified as having a refrigerator during all, or only part of their lives.

Proportions were compared using the  $\chi^2$  test or Fisher's exact test, when appropriate. Trends across ordered groups were analyzed using the  $\chi^2$  test for trends.

The modified Poisson regression [22], with a robust estimator of the standard error, and Poisson regression were used to estimate sex-, age-, and education-adjusted prevalence ratios (PR) and incidence rate ratios (RR), respectively, with the corresponding 95% confidence intervals (CI). To compute the incidence rate and the RR estimates, the time at risk was defined as the difference between the date of the second evaluation and the date of the first evaluation when participants were not infected at follow-up or half of this difference for participants infected during the follow-up. To estimate the seroreversion rate, the time at risk was defined as the whole follow-up if the participants remained infected or half this time for those that seroreverted.

All analyses were conducted using STATA<sup>®</sup>, version 9.2, (StataCorp LP, TX, USA), considering sampling weights to account for differences between our sample and the known age and sex structure of the population of Porto [23].

## Results

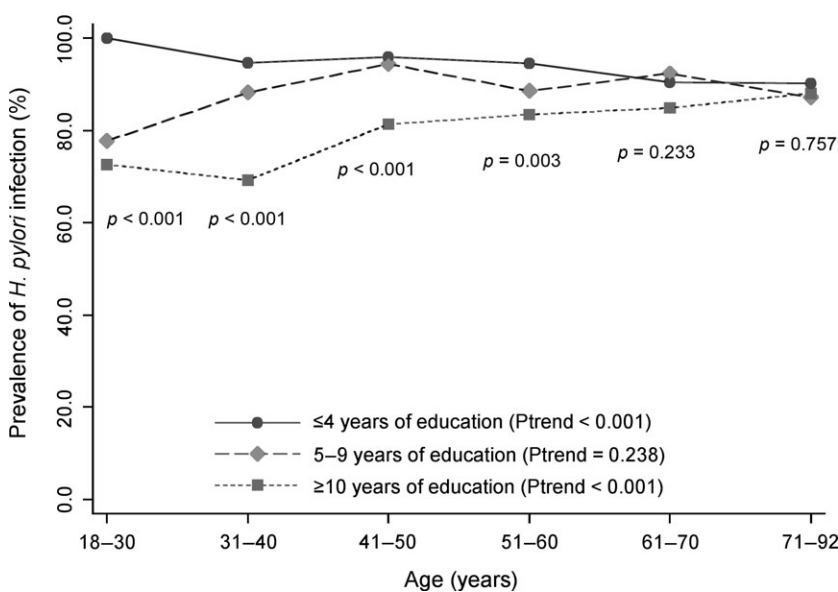
### Prevalence of *H. pylori* Infection

At baseline, the prevalence of *H. pylori* infection was 84.2% (95%CI: 82.4–86.1%). It increased with age in the subjects with  $\geq 10$  schooling years (from 72.6% in

the age-group 18–30 years to 88.1% in those aged  $\geq 71$  years,  $p$  for trend  $< 0.001$ ), whereas a decline was observed among those with  $\leq 4$  schooling years (from 100.0% in the age-group 18–30 years to 90.2% in the participants aged  $\geq 71$  years,  $p$  for trend  $< 0.001$ ). The prevalence was lower in the more educated subjects, though the differences across the levels of education decreased with age, from nearly 30% in the younger to less than 5% in the older (Fig. 2).

As shown in Table 1, the association between most of the participants' sociodemographic characteristics and *H. pylori* infection differed significantly across age and education groups. Among individuals aged 18–40 years, the more educated ( $\geq 10$  vs  $\leq 4$  schooling years: adjusted PR = 0.74, 95%CI: 0.66–0.83) and those having refrigerator all their lives (adjusted PR = 0.78, 95%CI: 0.67–0.91) were less likely to be infected, while those living in more deprived neighborhoods were more likely to be infected (most versus least deprived: adjusted PR = 1.20, 95%CI: 1.03–1.38). In subjects aged 41–60 years, the more educated ones were also significantly less likely to be infected ( $\geq 10$  vs  $\leq 4$  schooling years: adjusted PR = 0.86, 95%CI: 0.82–0.91) and those living in more deprived neighborhoods were more frequently infected (most versus least deprived: adjusted PR = 1.14, 95%CI: 1.07–1.22). In the group of participants aged above 60 years, infection was more frequent in males (adjusted PR = 1.06, 95%CI: 1.01–1.11).

Among more educated subjects, the prevalence of infection increased with age (61–92 vs 18–40 years: adjusted PR = 1.21, 95%CI: 1.10–1.33); the participants living in more deprived neighborhoods (most versus least deprived: adjusted PR = 1.15, 95%CI: 1.03–1.29)



**Figure 2** Prevalence of *Helicobacter pylori* infection according to age and education. P refers to the comparisons of the prevalence of *H. pylori* infection between different levels of education, within each age-group. P for trend refers to the pattern of the prevalence of *H. pylori* infection across age-groups, in each education strata.

**Table 1** Association between sociodemographic characteristics and prevalence of infection, defined by the titers of anti-*Helicobacter pylori* serum IgG<sup>a</sup>

	According to the participants' age (years)						According to the participants' education (years)					
	18-40		41-60		61-92		≤4		5-9		≥10	
	All participants % (95% CI)	PR <sup>b</sup> (95% CI)	%	PR <sup>b</sup> (95% CI)	%	PR <sup>b</sup> (95% CI)	%	PR <sup>d</sup> (95% CI)	%	PR <sup>d</sup> (95% CI)	%	PR <sup>d</sup> (95% CI)
Sex												
Female	83.7 (81.4-85.9)	1.00 [ref.] <sup>e</sup>	88.8	1.00 [ref.] <sup>e</sup>	87.5	1.00 [ref.] <sup>e</sup>	91.5	1.00 [ref.] <sup>f</sup>	87.6	1.00 [ref.] <sup>f</sup>	75.8	1.00 [ref.] <sup>f</sup>
Male	85.0 (81.9-88.0)	1.00 (0.89-1.13)	89.3	1.02 (0.97-1.07)	92.2	1.06 (1.01-1.11)	94.2	1.03 (0.99-1.08)	90.0	1.04 (0.96-1.11)	77.6	1.02 (0.93-1.11)
Age (years)												
18-40	75.3 (71.0-79.6)	—	—	—	—	—	95.6	1.00 [ref.] <sup>g</sup>	84.6	1.00 [ref.] <sup>g</sup>	71.2	1.00 [ref.] <sup>g</sup>
41-60	89.0 (86.9-91.1)	—	—	—	—	—	95.0	0.99 (0.90-1.08)	91.8	1.09 (0.98-1.20)	82.4	1.16 (1.06-1.26)
61-92	89.5 (87.4-91.6)	—	—	—	—	—	90.4	0.94 (0.86-1.03)	90.4	1.07 (0.96-1.19)	86.1	1.21 (1.10-1.33)
Education (years) <sup>h</sup>												
≤4	92.4 (90.5-94.3)	1.00 [ref.] <sup>g</sup>	95.0	1.00 [ref.] <sup>g</sup>	90.4	1.00 [ref.] <sup>g</sup>	—	—	—	—	—	—
5-9	88.8 (85.5-92.1)	0.88 (0.77-1.01)	91.8	0.96 (0.92-1.01)	90.4	0.99 (0.94-1.05)	—	—	—	—	—	—
≥10	76.6 (73.3-80.0)	0.74 (0.66-0.83)	82.4	0.86 (0.82-0.91)	86.1	0.94 (0.88-1.01)	0.008	—	—	—	—	—
Occupation <sup>i</sup>												
Upper white-collar	79.3 (75.8-82.8)	1.00 [ref.]	84.9	1.00 [ref.]	90.3	1.00 [ref.]	90.2	1.00 [ref.]	92.7	1.00 [ref.]	77.2	1.00 [ref.]
Lower white-collar	84.0 (80.3-87.8)	1.10 (0.93-1.31)	86.1	0.95 (0.87-1.04)	87.2	0.91 (0.83-1.00)	91.8	1.03 (0.88-1.21)	87.3	0.96 (0.89-1.04)	74.1	0.97 (0.86-1.10)
Blue-collar	91.5 (89.7-93.9)	1.17 (0.97-1.41)	95.0	1.01 (0.93-1.10)	90.6	0.94 (0.87-1.03)	92.6	1.04 (0.90-1.21)	89.0	1.01 (0.92-1.10)	89.2	1.18 (1.02-1.37)
Other	80.3 (74.9-87.0)	1.04 (0.87-1.24)	95.3	1.05 (0.95-1.16)	88.6	0.95 (0.86-1.06)	0.006	1.06 (0.90-1.25)	86.4	0.95 (0.82-1.10)	73.5	1.02 (0.88-1.18)
Neighborhood <sup>j</sup>												
1 (the least deprived)	81.2 (77.2-85.2)	1.00 [ref.] <sup>g</sup>	84.5	1.00 [ref.] <sup>g</sup>	88.7	1.00 [ref.] <sup>g</sup>	92.7	1.00 [ref.] <sup>g</sup>	89.9	1.00 [ref.] <sup>g</sup>	75.7	1.00 [ref.] <sup>g</sup>
2	83.6 (81.0-86.2)	0.97 (0.84-1.13)	89.2	1.06 (0.99-1.13)	89.1	1.01 (0.94-1.08)	91.5	0.99 (0.92-1.05)	88.5	0.98 (0.90-1.07)	75.3	0.99 (0.90-1.10)
3 (the most deprived)	91.0 (87.6-94.4)	1.20 (1.03-1.38)	96.3	1.14 (1.07-1.22)	89.0	1.00 (0.92-1.09)	0.021	1.00 (0.93-1.07)	91.0	1.00 (0.90-1.12)	87.5	1.15 (1.03-1.29)
Height <sup>k,l</sup>												
1st third	89.0 (86.3-91.6)	1.00 [ref.]	92.4	1.00 [ref.]	89.5	1.00 [ref.]	92.7	1.00 [ref.]	90.0	1.00 [ref.]	79.8	1.00 [ref.]
2nd third	85.9 (83.0-88.8)	1.03 (0.88-1.21)	87.5	0.98 (0.92-1.03)	89.2	1.00 (0.94-1.05)	90.8	0.97 (0.93-1.02)	90.2	1.01 (0.93-1.09)	80.1	1.03 (0.91-1.15)
3rd third	79.4 (75.8-83.0)	0.94 (0.80-1.10)	87.2	0.99 (0.94-1.06)	90.0	1.02 (0.96-1.08)	0.216	1.01 (0.96-1.06)	85.9	0.97 (0.88-1.08)	74.2	0.97 (0.86-1.09)
Refrigerator ownership <sup>m</sup>												
Not during all their lives	91.3 (88.3-94.3)	1.00 [ref.]	89.4	1.00 [ref.]	91.6	1.00 [ref.]	91.4	1.00 [ref.]	96.5	1.00 [ref.]	84.8	1.00 [ref.]
During all their lives	76.6 (71.7-81.4)	0.78 (0.67-0.91)	84.5	0.99 (0.90-1.09)	100.0	1.10 (1.04-1.17)	<0.001	1.09 (1.04-1.16)	82.6	0.89 (0.81-0.97)	72.8	0.98 (0.84-1.14)

<sup>a</sup>For analysis, subjects having borderline results were considered infected.

<sup>b</sup>Adjusted for sex and education, except if otherwise specified.

<sup>c</sup>p for interaction.

<sup>d</sup>Adjusted for sex, and age, except if otherwise specified.

<sup>e</sup>Only adjusted for education.

<sup>f</sup>Only adjusted for age.

<sup>g</sup>Only adjusted for sex.

<sup>h</sup>n = 2064 due to missing data.

<sup>i</sup>n = 2063 due to missing data.

<sup>j</sup>n = 1928 due to missing data.

<sup>k</sup>n = 2046 due to missing data.

<sup>l</sup>1st third: <153.1 cm, 2nd third: 153.1-158.3 cm, 3rd third: >158.3 cm for females; 1st third: <166.1 cm, 2nd third: 166.1-172.0 cm, 3rd third: >172.0 cm for males.

<sup>m</sup>n = 704 due to missing data.



or having blue-collar occupations (blue-collar versus upper white-collar: PR = 1.18, 95%CI: 1.02–1.37) were also more likely to be infected.

Among the participants with  $\leq 4$  years of schooling, those having refrigerator all their lifetime were more likely to be infected (adjusted PR = 1.09, 95%CI: 1.04–1.16), while an inverse association was observed in those with 5–9 years of schooling (adjusted PR = 0.89, 95%CI: 0.81–0.97). No association was found between height and *H. pylori* infection across strata of age or education.

### Prevalence of Infection with CagA-Positive Strains, Among the *H. pylori*-Infected

In the subsample of infected subjects that were evaluated by Western Blot, the prevalence of infection with CagA-positive strains was 61.7% (95%CI: 56.6–66.9%). The more educated were less likely to be infected with these high-virulence strains ( $\geq 10$  vs  $\leq 9$  schooling years: adjusted PR = 0.81, 95%CI: 0.67–0.99) (Table 2).

### Incidence of *H. pylori* Infection and Seroreversion

A total of 17 of 114 *H. pylori* negative subjects seroconverted over the follow-up period and the incidence rate was 3.6/100 person-years (95%CI: 2.1–6.2). The more educated participants had a lower risk of infection ( $\geq 10$  vs  $\leq 9$  schooling years: adjusted RR = 0.25, 95%CI: 0.06–0.96) (Table 3).

The seroreversion rate was 1.0/100 person-years (95%CI: 0.6–1.7).

## Discussion

Our study shows a high prevalence of *H. pylori* infection in urban Portuguese adults evaluated between 1999 and 2003. Living in a more deprived neighborhood was associated with a higher risk of infection, particularly among younger and more educated participants.

In the last half century, Portugal went through several important economical and societal changes. After the Second World War, the country evolved from a rural to a service economy, and in the 1970s, the political system changed from a dictatorial regime to a democracy. These transitions resulted in an improvement of the living standards, although unequally across the different socioeconomic groups [24]. The pace of these historical changes contributes to understanding the currently high prevalence of infection and the distinct patterns depicted by our results. The comparison of the prevalence of *H. pylori* across different age-groups

**Table 2** Association between sociodemographic characteristics and infection with *Helicobacter pylori* CagA-positive strains, among *H. pylori*-infected subjects<sup>a</sup>

	Infection with CagA-positive strains		
	%	PR (95% CI)	PR (95% CI) <sup>b</sup>
Sex			
Female	61.4	1.00 [ref.]	1.00 [ref.] <sup>c</sup>
Male	62.0	1.01 (0.85–1.19)	1.01 (0.84–1.18)
Age (years)			
18–40	55.5	1.00 [ref.]	1.00 [ref.] <sup>d</sup>
41–92	65.0	1.17 (0.94–1.45)	1.06 (0.84–1.34)
Education (years)			
$\leq 9$	67.6	1.00 [ref.]	1.00 [ref.] <sup>e</sup>
$\geq 10$	53.6	0.79 (0.66–0.96)	0.81 (0.67–0.99)
Occupation			
Upper white-collar	61.0	1.00 [ref.]	1.00 [ref.]
Lower white-collar	64.2	1.05 (0.83–1.33)	0.99 (0.71–1.20)
Blue-collar	65.3	1.07 (0.88–1.30)	0.89 (0.69–1.14)
Other	48.2	0.79 (0.55–1.14)	0.75 (0.51–1.09)
Neighborhood <sup>f</sup>			
1 (the least deprived)	54.5	1.00 [ref.]	1.00 [ref.] <sup>g</sup>
2	64.5	1.18 (0.94–1.48)	1.18 (0.94–1.49)
3 (the most deprived)	65.6	1.20 (0.92–1.56)	1.20 (0.93–1.56)
Height <sup>h</sup>			
1st third	61.4	1.00 [ref.]	1.00 [ref.]
2nd third	60.3	0.98 (0.80–1.20)	1.04 (0.86–1.27)
3rd third	63.4	1.03 (0.84–1.26)	1.18 (0.95–1.47)
Refrigerator availability <sup>i</sup>			
Not during all their lives	69.0	1.00 [ref.]	1.00 [ref.]
During all their lives	54.5	0.79 (0.62–1.01)	0.81 (0.62–1.06)

<sup>a</sup>CagA seropositivity was evaluated following the criteria recommended by the manufacturer: presence of the 116 kD band (CagA) with one or more of the following bands: 89 kD (VacA); 37 kD; 35 kD; 30 kD (UreA), and 19.5 kD together.

<sup>b</sup>Adjusted for sex, age, and education, except if otherwise specified.

<sup>c</sup>Only adjusted for age and education.

<sup>d</sup>Only adjusted for sex and education.

<sup>e</sup>Only adjusted for sex and age.

<sup>f</sup>n = 377 due to missing data.

<sup>g</sup>Only adjusted for sex.

<sup>h</sup>1st third: <153.1 cm, 2nd third: 153.1–158.3 cm, 3rd third: >158.3 cm for females; 1st third: <166.1 cm, 2nd third: 166.1–172.0 cm, 3rd third: >172.0 cm for males.

<sup>i</sup>n = 215 due to missing data.

suggests that its acquisition has been decreasing in the most recent cohorts, in accordance with observations from other high-income countries where prevalence of infection is low (e.g., United Kingdom, the Netherlands, Finland), intermediate (e.g., Greece), or high (e.g., Japan) [4], although in our study, this pattern only applies to the more educated subjects. This likely reflects general improvements in hygiene practices over time [25], and is also in accordance with the higher prevalence observed in the participants living in more

**Table 3** Association between sociodemographic characteristics and incidence of *Helicobacter pylori* infection<sup>a</sup>

	N	Person-years	Incidence of <i>Helicobacter pylori</i> infection		
			n	RR (95% CI)	RR (95% CI) <sup>b</sup>
<b>Sex</b>					
Female	72	237	10	1.00 [ref.]	1.00 [ref.] <sup>c</sup>
Male	42	162	7	1.00 (0.35–2.85)	0.79 (0.29–2.18)
<b>Age (years)</b>					
18–40	56	183	5	1.00 [ref.]	1.00 [ref.] <sup>d</sup>
41–92	58	216	12	2.28 (0.78–6.65)	1.33 (0.34–5.21)
<b>Education (years)</b>					
≤9	39	139	11	1.00 [ref.]	1.00 [ref.] <sup>e</sup>
≥10	75	260	6	0.23 (0.08–0.66)	0.25 (0.06–0.96)
<b>Occupation</b>					
Upper white-collar	53	177	5	1.00 [ref.]	1.00 [ref.]
Lower white-collar	32	118	8	3.01 (0.91–9.95)	1.87 (0.54–6.60)
Blue-collar	16	58	4	2.71 (0.68–10.75)	1.20 (0.16–8.82)
Other	13	46	0	–	–
<b>Neighborhood<sup>f</sup></b>					
1 (the least deprived)	38	141	4	1.00 [ref.]	1.00 [ref.] <sup>g</sup>
2	53	171	10	1.90 (0.56–6.47)	1.91 (0.56–6.47)
3 (the most deprived)	14	53	2	2.18 (0.36–13.11)	2.22 (0.41–12.0)
<b>Height<sup>h,i</sup></b>					
1st third	31	119	8	1.00 [ref.]	1.00 [ref.]
2nd third	30	118	2	0.21 (0.04–1.01)	0.34 (0.06–1.93)
3rd third	50	148	7	0.84 (0.30–2.39)	2.19 (0.62–7.76)
<b>Refrigerator availability<sup>j</sup></b>					
Not during all their lives	15	36	0	1.00 [ref.]	1.00 [ref.]
During all their lives	43	105	3	–	–

<sup>a</sup>For analysis, subjects having borderline results were considered infected.

<sup>b</sup>Adjusted for sex, age, and education, except if otherwise specified.

<sup>c</sup>Only adjusted for age and education.

<sup>d</sup>Only adjusted for sex and education.

<sup>e</sup>Only adjusted for sex and age.

<sup>f</sup>n = 105 due to missing data.

<sup>g</sup>Only adjusted for sex.

<sup>h</sup>1st third: <153.1 cm, 2nd third: 153.1–158.3 cm, 3rd third: >158.3 cm for females; 1st third: <166.1 cm, 2nd third: 166.1–172.0 cm, 3rd third: >172.0 cm for males.

<sup>i</sup>n = 111 due to missing data.

<sup>j</sup>n = 58 due to missing data.

deprived neighborhoods only among the younger and the more educated. On the other hand, among the participants with a lower education level, the age-specific prevalence resembles more closely those observed in low-and-middle-income countries characterized by high prevalence since young adulthood and possibly lower prevalence among the older subjects due to the high proportion of subjects with chronic atrophic gastritis [26] and intestinal metaplasia [27], and consequent spontaneous disappearance of the infection.

At a population level, height may be used as an indicator of growth, nutrition, and social environment in early life and can also measure socioeconomic status during childhood [28]. In our investigation, *H. pylori*

infection was not associated with height, in accordance with previous observations of non significant independent association between adult height and *H. pylori* infection [29]. However, conflicting findings have been published on this topic. A study from Leeds, UK, found an association between adult height and *H. pylori* infection, but only among women [30], and the authors did not discard the hypothesis of residual confounding. A more recent study found a modest increase in the risk of *H. pylori* infection with height (OR per meter: 0.05; 95% CI: 0.01–0.24) [31].

The availability of a refrigerator reflects both the living conditions in childhood and socioeconomic status. Refrigerators became available in most Portuguese

families between the late 1970s and the early 1980s [32], and its ownership was initially restricted to the higher socioeconomic classes. This exposure is therefore a surrogate for socioeconomic status, but also for the less frequent consumption of salted foods. However, the results were not consistent across the different strata analyzed and are not easily interpretable.

A meta-analysis published in 2006 showed a higher prevalence of *H. pylori* among men than women (OR = 1.16, 95%CI: 1.11–1.22) [33]. Because there is no evidence of sex differences in the acquisition of the infection at young ages, this may be explained by a greater loss of infection among females, possibly due to a greater female exposure to antibiotic treatments throughout life [33,34]. This hypothesis is compatible with our observation of a slightly higher prevalence of infection in men only among the elderly.

CagA seropositivity has been associated with a substantially increased risk of gastric cancer [2], and CagA-positive strains have been reported to account for 60% to 80% of the infections in Portugal and in other European countries [13,35]. In a recent study from the US, subjects living in neighborhoods with higher house values, and where proportionately more adults had a high school education, and those who were employed had lower odds of being seropositive for CagA-positive strains than those living in neighborhoods with lower levels of these socioeconomic status measures [36]. Despite the overall high prevalence of infection observed in our study, we also showed a tendency for more educated participants and those living in less deprived neighborhoods to have a lower prevalence of infection with the more virulent strains. This may reflect a lower frequency of multiple infections among subjects with a higher socioeconomic status [37].

A recent systematic review [38] showed annual incidence rates of *H. pylori* infection among adults below 1.0% in 17 of 32 studies and between 1.0% and 3.0% in most of the remaining. However, measurement error could account for the apparent cumulative incidence estimates observed in these studies, even in the absence of any true new infections. When applying the most stringent criteria used in the previous report to define incident cases of infection (excluding the participants with borderline results at baseline and considering that a new infection occurred only if there was an increase of at least 4-fold in the antibody concentrations from baseline to follow-up), the incidence rate in our study is 2.0/100 person-years (95%CI: 1.1–4.5). Our conclusion of a high incidence of infection in this adult population is strengthened by the observation of a high rate even when the specificity of the test used to assess the

infection status was further improved, and by the significantly lower incidence rate among the more educated participants. Furthermore, the infection at the second evaluation was assessed for only 41% of individuals not infected at baseline, and those not evaluated tended to be older and less educated, contributing to underestimate the incidence.

In our study, the seroreversion rate was similar to the observed in other developed countries (e.g., Japan, 0.7/100 person-years [39], Denmark, 0.8/100 person-years [40]). Although we considered participants with borderline results as positive for infection, sensitivity analyses excluding individuals with borderline IgG titers or considering borderline results as negative yielded no meaningful differences (data not shown). We also compared antibody concentration of individuals that seroreverted in successive evaluations. Two of these 14 participants had a borderline result in the first evaluation, and the other 12 had IgG titers much higher than the cutoff for positivity (median antibody concentration: 76.5 RU/mL), and none of these individuals presented a borderline result at the second evaluation (median antibody concentration: 12.1 RU/mL). Therefore, these results are more likely to reflect a previous infection that was resolved than misclassification. The small number of participants in which seroreversion was observed does not allow the assessment of its determinants.

Although this is the first investigation assessing the prevalence and incidence of *H. pylori* infection in the general population of Porto, the comparison of our results with estimates published in 1994 for the overall Portuguese population (approximately 84% in individuals aged above 19 years) [12] suggests that the prevalence did not change meaningfully in the last decade. Furthermore, our study is likely to underestimate the true prevalence, especially among the young subjects, because the participants evaluated for infection status tended to be more educated than the remaining. Our estimates are among the highest in the world [7], close to those observed in some Eastern European and South American countries (e.g., 82.0% in Brazil in 2010 [41]; 88.0% in Russia in 1996 [3]; 86.0% in a Cape Verdean immigrants in the Netherlands in 2004 and 2005 [42]). This is in accordance with the high gastric cancer incidence and mortality rates in Portugal, especially in the North [9,11], and with the fact that the decline in mortality only started in the mid-1970s, later than in most developed countries [43].

The recognition of a still high burden of *H. pylori* infection in this setting should serve as a mandate for considering the implementation of evidence-based measures for its prevention and control at a population



level. The infection with *H. pylori* is the most important risk factor for gastric cancer [44] and, according to the recent recommendations from the Maastricht IV/Florence Consensus Report, a screen-and-treat strategy must be explored in areas with a high burden of gastric cancer [45]. However, eradication may only benefit individuals at the early stages of gastric carcinogenesis [46–48], and therefore, risk stratification of patients with premalignant gastric conditions is likely to be necessary [45]. Moreover, resistance to antibiotics used to eradicate *H. pylori* infection is an important problem in some countries [49,50], and this needs to be taken into account when estimating the impact of a population-based approach to prevent gastric cancer through the control of this major risk factor.

The Maastricht IV/Florence Consensus Report [45] also postulated that eradication of *H. pylori* infection is a cost-effective measure for gastric cancer prevention in high-risk settings. This is supported by a recent study according to which a preventive strategy aiming to eliminate gastric cancer in Japan, by the simultaneous measurement of pepsinogen and *H. pylori* antibody combined with eradication of *H. pylori* in all individuals at risk and active surveillance of high-risk subjects (with atrophic gastritis), may reduce the incidence of gastric cancer by more than 80% within 10 years [51]; although in a first phase, this approach is expected to increase national healthcare expenditure, great savings may be achieved by reducing the cost of treating gastric cancer [51]. A recent systematic review of cost-effectiveness studies addressing screening for gastric cancer and/or surveillance of precancerous conditions and lesions concluded that *H. pylori* serology population screening with treatment of positive cases is cost-effective [52].

In conclusion, our results show that the prevalence of *H. pylori* infection in Portugal remains in the upper bound of those observed across European countries. Stomach cancer incidence and mortality rates are likely to remain among the highest in Europe during the next decades, particularly in less educated individuals. Therefore, population-based approaches to control *H. pylori* infection in the Portuguese setting, as a means of preventing gastric cancer, and reducing costs to the health service and society in general, should be considered and, whenever possible, implemented by the health authorities.

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