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Sociodemographic, Lifestyle and Medical Factors Associated with *Helicobacter Pylori* Infection

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ABSTRACT

Background & Aims: The prevalence of *Helicobacter pylori* (*H. pylori*) infection is higher in developing countries and is often linked to lower socioeconomic status. Few studies have investigated the association between *H. pylori* and individual level characteristics in Europe, where several countries have a high prevalence of *H. pylori* infection. The study aimed to identify risk factors for *H. pylori* infection among adults in a large clinical trial in Latvia.

Methods: 1,855 participants (40-64 years) of the "Multicenter randomized study of *H. pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality" (GISTAR study) in Latvia tested for *H. pylori* IgG antibodies were included in a cross-sectional analysis. Sociodemographic, lifestyle and medical factors were compared for participants seropositive (*H. pylori*+) and seronegative. Mutually adjusted odds ratios (OR) were calculated for *H. pylori*+ and factors significant in univariate analysis (education, smoking, binge drinking, several dietary habits, history of *H. pylori* eradication and disease), adjusting for age, gender and income.

Results: Of the participants 1,044 (55.4%) were *H. pylori* seropositive. The infection was associated with current (OR: 1.34, 95%CI: 1.01-1.78) and former (OR: 1.38; 95%CI: 1.03-1.85) smoking, binge drinking (OR: 1.35; 95%CI: 1.03-1.78), having ≥200g dairy daily (OR: 1.37; 95%CI: 1.11-1.69), and very hot food/drinks (OR: 1.32; 95%CI: 1.03-1.69) and inversely with ≥400g vegetables/fruit daily (OR: 0.76; 95%CI: 0.60-0.96), history of *H. pylori* eradication (OR: 0.57; 95%CI: 0.39-0.84), peptic ulcer (OR: 0.55; 95%CI: 0.38-0.80) and cardiovascular disease (OR: 0.78; 95%CI: 0.61-0.99).

Conclusions: After mutual adjustment, *H. pylori* seropositivity was associated with lifestyle and in particular dietary factors rather than socioeconomic indicators in contrast to the majority of other studies.

Key words: *Helicobacter pylori* – risk factors – socioeconomic factors – life style – diet – Latvia.

Abbreviations: BMI: body mass index; *H. pylori: Helicobacter pylori*; NSAIDs: non-steroidal anti-inflammatory drugs; PPIs: proton pump inhibitors.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is an established risk factor for atrophic gastritis, peptic ulcer disease and gastric cancer, and has been classified as a Group I carcinogen by International Agency for Research on Cancer (IARC) [1]. Although it is believed that most *H. pylori* carriers will not develop clinical symptoms in their lifetime, studies show that they have an up to six times higher risk of developing gastric cancer [2].

Helicobacter pylori infection has a global prevalence of 50% with significant variation by population [3]. Overall, rates of *H. pylori* infection are higher in developing countries and have been linked to lower socioeconomic status [3, 4]. The association between *H. pylori* infection and lower socioeconomic status, including crowding and sanitation, has been reported in several studies for children and adults, especially in low- and middle-income countries [3, 5, 6]. However, the association was not consistent especially in a few studies from high-income countries [7, 8].

Potential associations between *H. pylori* infection and other factors vary greatly by geographic location. For example, some studies have reported a higher *H. pylori* prevalence among current smokers and drinkers [3, 9], while others have found the contrary [10, 11]. Similarly, an association between low intake of fruit and vegetables and higher *H. pylori* prevalence

was reported in some studies [12, 13], but not others [14, 15]. Although dietary factors such as vegetable and salt intake have been linked to the development of gastric cancer and may potentiate the carcinogenic effects of *H. pylori* [16, 17], there seem to be no consistent findings on dietary factors and the prevalence of *H. pylori* infection.

Helicobacter pylori has been implicated as a risk factor for several extragastric diseases, with positive associations reported but not limited to coronary artery disease, stroke, metabolic syndrome, diabetes mellitus, autoimmune thyroid disease, and an inverse correlation with asthma [18-20] .

Studies covering a wide range of factors potentially associated with *H. pylori* other than socioeconomic status and living conditions have been lacking in Europe, especially in Central and Eastern European regions, where in some areas, the infection rate remains high despite being classified as high-income countries [1, 21]. One such country is Latvia, which has a high prevalence of *H. pylori* (up to 79% in the general adult population) and a high burden of related disease - gastric atrophy and gastric cancer [22].

Previous analysis done by our study group on pilot study data showed some factors to be associated with *H. pylori* infection [23]. The current analysis includes medical history and a wider range of lifestyle and dietary factors in more detail.

The aim of our study was to determine potential risk factors for *H. pylori* infection in Latvia by comparing comprehensive information on sociodemographic, lifestyle and medical characteristics between participants with and without *H. pylori* infection in a cross-sectional analysis. Knowledge of socioeconomic, lifestyle, and health-related factors that may increase the risk of *H. pylori* infection could provide insight into the multifactorial process behind the acquisition and persistence of the infection.

METHODS

Study population

A total of 4,620 participants aged 40 to 64 years were enrolled in the main study of the "Multicenter randomized study of *H. pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality (the GISTAR study)" in four study centers in Latvia from March 2016 to December 2018 [22]. Individuals were invited using patient lists of general practitioners in areas of local recruitment centers and contacted through phone or mail. Participants signed an informed consent form and were examined by a study physician upon enrolment. Ten participants were excluded, as they had a personal history of gastric cancer, gastric resection due to benign disease, *H. pylori* eradication therapy within the past 12 months, presence of alarm symptoms of digestive or other disease, or signs of serious disease requiring immediate management. A total of 4,610 participants completed a questionnaire on socio-demographic characteristics, lifestyle (exercise, diet, smoking, alcohol consumption) and medical history (body mass index (BMI), history of disease, use of medication). After completing the questionnaire, study participants were randomly allocated either to the intervention or control group within the GISTAR study. The 1,885 participants of the intervention group were tested for *H. pylori* IgG group antibodies by ELISA (Eiken Chemical, Tokyo, Japan). Those positive for *H. pylori* were offered eradication therapy as part of the intervention. For the current study questionnaire data and *H. pylori* serology from the 1,885 participants of the intervention group was used (Fig. 1).

The GISTAR study protocol was approved by the Ethics Committee of the International Agency for Research on Cancer (IEC 12–36) and the Central Medical Ethics Committee of Latvia (01–29.1/11). The study protocol is registered in the clinicaltrials.gov database (NCT02047994).

For the purpose of the current cross-sectional analyses, participants were divided into two groups based on serology: seropositive and seronegative for *H. pylori*. Self-reported socio-demographic, lifestyle, and medical data obtained from the GISTAR questionnaire was used to characterize *H. pylori* seropositive and *H. pylori* seronegative groups.

Sociodemographic characteristics included age (median in years), gender, nationality (Latvian, Russian, other), level of education (primary or lower, upper secondary, professional vocational, higher education), monthly household income per household member after tax (less than 250, 250-500, more than 500 Euros), and employment status (employed, unemployed, retired, handicapped).

Lifestyle characteristics included smoking habits (current, former and non-smoker), binge drinking, physical activity and dietary habits. Binge drinking was defined as having at least 200 g of alcohol (ethanol content at least 40%) in one

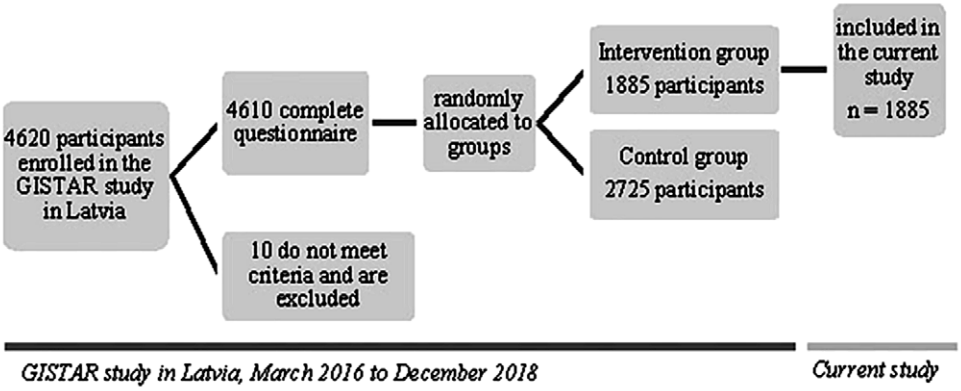

Fig. 1. Visual representation of the main GISTAR study in Latvia and the current study.

sitting during the past year (none, less than once a month, or at least once a month, with the last category qualifying as binge drinking) [24]. Physical activity was assessed by the duration of moderate (at least 150 minutes per week) and intensive (at least 75 minutes per week) physical activity at work and during free time according to the recommendations of the World Health Organization (WHO) on the amount of exercise necessary to decrease the risk of non-communicable disease [25].

Dietary habits were assessed based on self-reports of consuming at least 400 g of fruit and/or vegetables daily during the past week (yes, no) according to the recommendations of WHO and the Food and Agriculture Organization of the United Nations (FAO) on minimum fruit and vegetable intake [26]; at least 200 g of dairy daily during the past week (yes, no); consumption of portions (1 portion = 100 g) of red meat and poultry daily, assisted by visual representations of portions; consumption of very hot food and/or drinks, spicy food at least once a week (yes, no); addition of extra salt to food (never, sometimes, or always); and the frequency of consumption of several products on a daily basis during an average week in the past year (at least one, two to three, four to five, or six to seven days per week): fish, quark, kefir, eggs, legumes, pickled, cured, salted and/or smoked products, allium vegetables, instant coffee, ground coffee, black or green tea, and sweetened beverages.

Self-reported medical history included the use of drugs during the past month (proton pump inhibitors (PPIs), aspirin, antihypertensive and non-steroidal anti-inflammatory drugs (NSAIDs)), history of *H. pylori* eradication, abdominal or pelvic surgery, and of diseases potentially associated with *H. pylori* reported in other studies [18, 19]: cardiovascular (myocardial infarction, stroke, arterial hypertension), gastrointestinal (peptic ulcer, inflammatory bowel disease, autoimmune gastritis, gallstones), thyroid, and respiratory disease (bronchial asthma, chronic obstructive pulmonary disease), as well as type 2 diabetes mellitus, B12 deficiency anemia, hemolytic anemia, and thrombocytopenia. Height, weight and abdominal circumference were measured on site.

Body mass index (BMI) [weight (kg)/height (m)^2] was calculated and split into three categories: ≤ 24.9 kg/m^2 (normal or underweight), between 25.0 and 29.9 kg/m2 (overweight), and ≥30.0 kg/m^2 (obese). Characteristics of the seropositive and seronegative for *H. pylori* participants were compared using Pearson chi-square and Mann Whitney tests. The percent of participants in each group was presented. Medians and inter-quartile range was used for the analysis of age, as the variable was not normally distributed.

All of the factors significantly associated with seropositivity for *H. pylori* in univariate analysis were included in a multiple binary logistic regression model with subsequent calculation of odds ratios (OR) and 95% confidence intervals (95% CI), adjusting for the potential confounders of age and gender, as well as income, which has previously been linked to *H. pylori* [3]. Significance at $\alpha < 0.10$ level was considered as statistically significant in univariate analysis and at $\alpha < 0.05$ level for multivariate analysis. Statistical analysis was performed using SPSS software, version 21.0 [27].

Additional analyses were carried out for education and thyroid disease, because the association with *H. pylori* lost significance in multivariate analysis, as well as for the consumption of dairy and a history of cardiovascular disease for potential confounding factors. Participants reporting a history of *H. pylori* eradication were divided into two groups – those seropositive and seronegative for *H. pylori* to determine whether any factors were associated with being seropositive despite reporting a history of eradication. Pearson chi-square and Mann Whitney or Kruskal-Wallis tests were used to identify differences in factors included in multivariate analysis.

RESULTS

The data of 1,885 participants were eligible for analysis (Fig. 1). The median age of participants was 52 years and 62.3% were women. Of the participants 1,044 (55.4%) were seropositive for *H. pylori*. Seropositivity for *H. pylori* was most prevalent in the lowest education group and decreased with increasing level of education (Table I).

Seropositivity for *H. pylori* was more common among current and former smokers than nonsmokers, as well as those with binge drinking behavior. Participants consuming at least 200 g of dairy daily, very hot food and/or drinks, and adding extra salt to food were more likely, but those consuming at least 400 g of fruit and/or vegetables daily were less likely to be seropositive for *H. pylori*. Participants having pickled products six to seven days a week were more likely to be seropositive for *H. pylori* (Table II).

Participants reporting a history of *H. pylori* eradication, peptic ulcer, cardiovascular and thyroid disease were less likely to be seropositive for *H. pylori* (Table III).

Additional analysis showed that participants with higher levels of education were more likely to consume at least 400 g of fruit and/or vegetables daily, less likely to add extra salt to food, have hot foods and/or drinks, report a history of peptic ulcer and cardiovascular disease, and to smoke (Supplementary file S1). The only factor other than seropositivity for *H. pylori* significantly associated with the consumption of at least 200 g of dairy daily was the consumption of at least 400 g of fruit and/or vegetables daily (Supplementary file S2).

Of the 146 (7.8%) participants reporting a history of *H. pylori* eradication 58 (39.7%) were seropositive for *H. pylori*. There were no significant differences in age, gender, education, and income between those *H. pylori* seropositive and seronegative reporting a history of *H. pylori* eradication (Supplementary file S3).

A history of cardiovascular disease was associated with older age, but inversely with higher education and the consumption of very hot food and/or drinks in the past week (Supplementary file S4). Those reporting thyroid disease were more likely to be nonsmokers, not engage in binge drinking, and seemed more likely to report a history of *H. pylori* eradication (17.8% vs. 12.5% respectively, p=0.06) (Supplementary file S5). These factors were also associated with a lower likelihood of seropositivity for *H. pylori* (Table II).

In multivariate analysis statistically significant positive associations were observed between seropositivity for *H. pylori* and current and former smoking, binge drinking, having at least 200 g of dairy daily, and very hot food and/or drinks. Seropositivity for *H. pylori* was inversely associated with the

Table I. Sociodemographic characteristics of the study population and participants seropositive and seronegative for *Helicobacter pylori*

Variable, n (%)	Study population n = 1,885	*H. pylori* + n = 1,044	*H. pylori* - n = 841	p*
Male gender	711 (37.7)	406 (38.9)	305 (36.3)	0.24
Age (years), median, IQR	52, 12	52, 12	52, 12	0.82
Education				
primary or lower (0-9 years)	77 (4.1)	50 (4.8)	27 (3.2)	0.03
upper secondary (10-12 years)	333 (17.7)	190 (18.2)	143 (17.0)	
professional vocational	860 (45.6)	490 (46.9)	370 (44.0)	
higher	615 (32.6)	314 (30.1)	301 (35.8)	
Income (Euros)[a]				
<250	461 (28.1)	260 (28.3)	201 (27.9)	0.98
250-500	899 (54.9)	503 (54.8)	396 (55.0)	
>500	278 (17.0)	155 (16.9)	123 (17.1)	
Employment				
Unemployed	145 (7.7)	80 (7.7)	65 (7.7)	0.56
Employed	1555 (82.5)	865 (82.9)	690 (82.0)	
Retired	100 (5.3)	58 (5.6)	42 (5.0)	
Handicapped	85 (4.5)	41 (3.9)	44 (5.2)	

*Differences obtained using χ^2 test comparing seropositive for *Helicobacter pylori* participants (*H. pylori* +) and seronegative participants (*H. pylori* -). IQR: interquartile range. [a] monthly household income per household member after tax

consumption of at least 400 g of vegetables and/or fruit daily, history of *H. pylori* eradication, peptic ulcer disease, and cardiovascular disease (Table IV). Age, gender and income were not significantly associated with seropositivity for *H. pylori* in multivariate analysis.

DISCUSSION

Studies have reported higher rates of *H. pylori* infection with lower socioeconomic status including low household income [3, 4, 9]. In most studies a higher level of education was found to be inversely associated with *H. pylori* [9, 28]. Although seropositivity for *H. pylori* was less common among those with a higher education in our study, the relationship was no longer significant after adjusting for covariates. Additional sensitivity analyses showed that higher levels of education were associated with factors also associated with seropositivity for *H. pylori* in univariate analysis. Of these factors most remained significantly associated with seropositivity for *H. pylori* in multivariate analysis, suggesting the association between seropositivity for *H. pylori* and education was confounded by other lifestyle and dietary factors. Higher education was also associated with higher income.

No differences were found for income level and employment status. However, it must be noted that general indicators of economic wealth may be imprecise in accurately assessing the socioeconomic status of each participant, as although Latvia has seen comparatively rapid economic growth over the past decade, there is still a high shadow economy index (22% of the GDP in 2017) [29]. The main component of the shadow economy index is the underreporting of salaries or "envelope-wages" (45.5%) [29], which may have led to the underreporting of income in our study. Circumstances created by decreasing income inequality (GINI coefficient) and economic growth post-crisis could also explain the lack of an association between seropositivity for *H. pylori*, income and unemployment, with a tendency toward a relationship with education and factors indirectly linked to education (lifestyle) instead. Around the time of recruitment, Latvia had the fourth highest GINI coefficient in the EU-28, indicating a significant level of income inequality [30].

Given the above, lifestyle characteristics may better serve as indicators of socioeconomic and educational status in the current study population. This could be used to explain why significant associations remained between *H. pylori* and lifestyle or dietary characteristics but not income and education in multivariate analysis.

The association between *H. pylori*, smoking, and binge drinking in both univariate and multivariate analysis might be attributable to lower education and socioeconomic status. When comparing these lifestyle habits by the levels of education and income in the study population, we observed that while smoking was less prevalent among individuals with higher levels of education ($p<0.001$) and higher income ($p=0.04$), binge drinking was more common with increasing income level ($p<0.001$) and showed no significant association with the level of education ($p=0.34$). In most other studies no significant relationships were found for smoking, alcohol consumption, and *H. pylori* [3, 9], except for a select few [10, 11].

In our study *H. pylori* was significantly associated with several dietary factors, which have also been investigated as independent risk factors for gastric cancer.

In univariate analysis *H. pylori* was associated with several habits related to increased salt intake (adding extra salt to

Table II. Lifestyle characteristics in the study population and the group of participants seropositive and seronegative for *Helicobacter pylori*

Variable, n (%)	Study population n = 1,885	*H. pylori* + n = 1,044	*H. pylori* - n = 841	p*
Smoking				<0.01
Current	398 (21.1)	243 (23.3)	155 (18.5)	
Former	364 (19.3)	218 (20.9)	146 (17.4)	
Non-smoker	1,120 (59.5)	582 (55.8)	538 (64.1)	
Binge drinking[a]				<0.01
None	1213 (64.4)	640 (61.3)	573 (68.1)	
Less than monthly	246 (13.1)	141 (13.5)	105 (12.5)	
at least monthly	426 (22.6)	263 (25.2)	163 (19.4)	
BMI				0.36
≤24.9 kg/m^2	451 (24.3)	258 (25.0)	193 (23.4)	
25-29.9 kg/m^2	724 (39.0)	410 (39.7)	314 (38.1)	
≥30 kg/m^2	683 (36.8)	365 (35.3)	318 (38.5)	
Dietary habits				
≥ 200g dairy daily (past week)	1,149 (61.0)	660 (63.2)	489 (58.1)	0.03
≥ 400g fruit and/or vegetables daily (past week)	1,292 (68.5)	691 (66.2)	601 (71.5)	0.01
Very hot food and/or drinks (past week)	449 (23.8)	273 (26.1)	176 (20.9)	0.01
Spicy food (past week)	392 (20.8)	230 (22)	162 (19.3)	0.14
Addition of extra salt to food				<0.01
Never	1390 (73.7)	741 (71)	649 (77.2)	
Sometimes or always	495 (26.3)	303 (29)	192 (22.8)	
Pickled products (days per week)				0.06
≤ one	326 (17.3)	180 (17.2)	146 (17.4)	
2-3	416 (22.1)	232 (22.2)	184 (21.9)	
4-5	1058 (56.1)	573 (54.9)	485 (57.7)	
6-7	85 (4.5)	59 (5.7)	26 (3.1)	
Meat products (days per week)				0.05
≤ one	284 (15.1)	159 (15.2)	125 (14.9)	
2-3	235 (12.5)	119 (11.4)	116 (13.8)	
4-5	1035 (54.9)	562 (53.8)	473 (56.2)	
6-7	331 (17.6)	204 (19.5)	127 (15.1)	
Eggs (days per week)				0.08
≤ one	40 (2.1)	17 (1.6)	23 (2.7)	
2-3	144 (7.6)	72 (6.9)	72 (8.6)	
4-5	1363 (72.3)	754 (72.2)	609 (72.4)	
6-7	338 (17.9)	201 (19.3)	137 (16.3)	

[a] frequency of binge drinking in the past year- at least 200 g of liquor (alcohol content at least 40%) in one sitting during the past year. Seropositive for *Helicobacter pylori* participants (*H. pylori* +) and seronegative participants (*H. pylori* -). BMI: body mass index. *Differences obtained using χ^2 test comparing HP+ and HP- groups.

food and the consumption of pickled and meat products), but not in multivariate analysis after including a large number of factors. High salt intake has been shown not only to facilitate the colonization of the gastric mucosa by *H. pylori* but also increase inflammation and accelerate carcinogenesis [17, 31]. Beevers et al. [32] reported a correlation between urinary sodium excretion and *H. pylori* infection rates in 2004 in the EUROGAST and INTERSALT study population from ten countries [32]

In our study the association between *H. pylori* and lower fruit and vegetable intake remained strong in multivariate analysis. An association between low intake of fruit and vegetables, and *H. pylori* prevalence has been reported in some epidemiologic studies [12, 13]. A diet rich in fruits and vegetables is considered a protective factor for gastric cancer and the pathogenic effects of *H. pylori*, possibly due to the protective role of carotenoids, folate, vitamin C, and phytochemicals in carcinogenesis [17, 34].

The association between dairy products and *H. pylori* in our study is less straightforward. Other than seropositivity for *H. pylori*, consumption of dairy was only associated with the consumption of fruit and vegetables despite the many other

Table III. Self-reported medical characteristics in the study population and participants seropositive and seronegative for Helicobacter pylori.

Variable, n (%)	Study population n = 1,885	*H. pylori* + n = 1,044	*H. pylori* - n = 841	p*
H. pylori eradication	146 (7.8)	58 (39.7)	88 (60.3)	<0.001
Proton pump inhibitor use (past month)	168 (8.9)	89 (53.0)	79 (47.0)	0.51
Peptic ulcer disease	160 (8.5)	71 (44.4)	89 (55.6)	<0.01
Cardiovascular disease	528 (28.0)	274 (51.9)	254 (48.1)	0.06
Thyroid disease	241 (12.8)	116 (48.1)	125 (51.9)	0.02
Gallstones	155 (8.2)	72 (46.5)	83 (53.5)	0.02
Urticaria	34 (1.8)	13 (38.2)	21 (61.8)	0.04
Glomerulonephritis (past 3 years)	84 (4.5)	37 (44.0)	47 (56.0)	0.03

*Differences obtained using $\chi 2$ test comparing seropositive for *Helicobacter pylori* participants (*H. pylori* +) and seronegative participants (*H. pylori* -).

factors investigated in this study, suggesting its role as a possible independent risk factor.

Milk may serve as a vector for the transmission of *H. pylori* to humans. Reported rates of *H. pylori* in ruminant milk vary from 19% of raw cow milk samples in Iran [35] to 50% in Italy [36]. In Latvia, the use of raw unpasteurized milk is popular, especially in rural areas.

The increased rate of *H. pylori* among those currently consuming more dairy might be a reflection of circumstances allowing for the acquiring of the bacterium in childhood and early adulthood, as *H. pylori* infection is thought to usually occur during childhood, especially with low socioeconomic conditions [3, 5, 6]. If the participants currently reporting higher consumption of dairy products also did so in childhood, the higher rate of *H. pylori* could be explained by infection several decades ago. Despite the claims of officials and milk producers, independent studies in the then Soviet Union occupied Latvia in the 1980s showed high levels of milk contamination with bacteria and industrial chemicals [37]. An alternative hypothesis to that of milk as a vector for *H. pylori* transmission may be that of milk consumption contributing to a more favorable gastric environment for *H. pylori* persistence. We found no association between *H. pylori* infection and the popular fermented milk product "kefir", despite some studies suggesting that certain proteins in fermented milk products possess antibacterial properties [38].

Of the participants reporting a history of peptic ulcer disease 44.4% tested positive for *H. pylori*, indicating that there is considerable potential for decreasing gastric cancer risk by eradicating *H. pylori* according to international guidelines [39, 40].

Although participants reporting a history of *H. pylori* eradication were less likely to test positive for *H. pylori* than those not, the difference between these two groups was larger than expected (39.7% and 56.8% respectively, p<0.001). In supplementary analysis no significant differences in sociodemographic factors were found that explain the relatively high percentage of *H. pylori* positive participants claiming to have undergone *H. pylori* eradication. Possible explanations may include false reports of *H. pylori* eradication (a lack of knowledge on the topic), unsuccessful *H. pylori* eradication, and reinfection.

Helicobacter pylori was less common among participants reporting cardiovascular disease than those not (51.9% and 56.7% respectively, p=0.06). In multivariate analysis *H. pylori* was inversely associated with a history of self-reported cardiovascular disease (p=0.04).

Several studies have been published on *H. pylori* and cardiovascular disease; the most recent meta-analyses in 2017 by Yu et al. [41] reported a significant association with coronary artery disease, and by Rahmani et al. [42] with myocardial infarction. It has been hypothesized that *H. pylori* may facilitate atherosclerosis by promoting chronic inflammation, dyslipidemia and endothelial dysfunction [41].

Another meta-analysis published by Sun et al. [43] in 2016 on prospective cohort studies concluded that although *H. pylori* infection increased the risk of cardiovascular disease events especially in earlier life, this association was no longer significant for studies with follow-up times of 10 or more years, with the effect possibly weakened or masked by other cardiovascular risk factors. In our study the association between *H. pylori* and cardiovascular disease was inverse, despite *H. pylori* having been associated with several known cardiovascular risk factors in univariate analysis (salt intake, smoking, alcohol consumption, and insufficient consumption of vegetables). In additional sensitivity analysis cardiovascular disease was not significantly associated with any of these factors. The only factor that both seropositivity for *H. pylori* and cardiovascular disease were significantly associated with was the level of education, with both less likely in the higher education group. Nevertheless, we cannot exclude reverse causality due to the cross-sectional nature of the current analysis.

In univariate analysis participants reporting a history of thyroid disease were less likely to test positive for *H. pylori* than those reporting none (48.1% and 56.4% respectively, p=0.02). Although *H. pylori* has been linked to autoimmune thyroid disease in other studies, we were not able to investigate it in our study as we did not have information on the type of thyroid disease (autoimmune disease or inactive nodules). In multivariate analysis this association was no longer significant (p=0.06). Those reporting thyroid disease were less likely to engage in habits (smoking, binge drinking) which were associated with being seropositive for *H. pylori* and were

Table IV. Factors associated with Helicobacter pylori infection in the study population included in multivariate analysis, adjusted for age, gender and income

Variable	OR	95% CI	p
Education			
primary or lower (0-9 years)	1.38	0.79-2.41	0.25
upper secondary (10-12 years)	1.17	0.86-1.59	0.30
professional vocational	1.20	0.94-1.53	0.14
higher	Ref		
Smoking			
current	1.34	1.01-1.78	0.04
former	1.38	1.03-1.85	0.03
non-smoker	Ref		
Binge drinking[a]			
no	Ref		
less than monthly	1.37	0.99-1.89	0.06
at least monthly	1.35	1.03-1.78	0.03
Dietary habits			
Dairy ≥ 200g daily	1.37	1.11-1.69	<0.01
Vegetables / fruit ≥ 400g daily	0.76	0.60-0.96	0.02
Very hot food /drinks	1.32	1.03-1.69	0.03
Adding extra salt to food	1.21	0.95-1.54	0.13
Pickled products			
≤ once a week	Ref		
2-3 days	1.03	0.74-1.43	0.88
4-5 days	0.87	0.65-1.16	0.33
6-7 days a week	1.58	0.89-2.83	0.12
Meat products			
≤ once a week	Ref		
2-3 days	0.79	0.53-1.16	0.22
4-5 days	0.81	0.60-1.09	0.17
6-7 days a week	1.05	0.72-1.53	0.79
H. pylori eradication	0.57	0.39-0.84	0.01
Thyroid disease	0.79	0.58-1.08	0.14
Cardiovascular disease	0.78	0.61-0.99	0.04
Peptic ulcer disease	0.55	0.38-0.80	<0.01
Gallstones	0.79	0.55-1.15	0.22
Urticaria	0.64	0.29-1.39	0.26
Glomerulonephritis	0.61	0.36-1.03	0.07

H. pylori+ participants seropositive for *Helicobacter pylori*; ref: reference value; OR: odds ratio; CI: confidence interval. a frequency of binge drinking in the past year at least 200g of liquor (alcohol content at least 40%) in one sitting during the past year.

more likely to report a history of *H. pylori* eradication. This suggests a possible link between health-associated behaviors and the ability to recall history of disease and could potentially explain why the reporting of other diseases (e.g. urticaria, glomerulonephritis) was also associated with a lower likelihood of seropositivity for *H. pylori*. The reporting of the history of disease was not consistently associated with the level of education. The number of participants reporting other diseases of interest was too few for analysis.

This is a unique study investigating a wide range of potential risk factors for *H. pylori* infection in the Central and Eastern European region. The number of factors investigated is a strength of our study, as few studies have been able to include such a wide range of sociodemographic, lifestyle, and medical history data. This may have increased the possibility of identifying associations that may otherwise have gone unnoticed.

Our study also has limitations. Our findings need to be interpreted with caution due to the cross-sectional nature of the study. We cannot therefore conclude whether the lifestyle factors associated with *H. pylori* infection in our study play a role in determining the presence of the infection or whether

they, along with a higher likelihood of *H. pylori* infection, are consequences of, for instance, socioeconomic status or childhood environment. Evaluation of dietary habits was based on participants' memory, can be subject to recall bias, and may not accurately reflect general dietary habits over a longer time period. Therefore, results must be interpreted critically when discussing possible long-term exposures.

Our analysis was a first step in identifying possible associations, describing the findings from a region where such information is limited. Determining cause-and-effect relationships requires further studies.

The factors associated with *H. pylori* in our study have also been implicated in the development of gastric cancer. Since *H. pylori* and other risk factors (certain dietary habits, smoking, alcohol consumption, history of peptic ulcer disease) have a synergistic relationship in the development of gastric cancer, targeting this subset of the population specifically with lifestyle interventions and *H. pylori* eradication may be beneficial in the prevention of cancer.

Collecting data on the current place of residence (urban or rural) and childhood socioeconomic status would have been valuable in interpreting the results pertaining to both sociodemographic and lifestyle factors. Our analyses on self-reported medical history by *H. pylori* status did not include specific data on types of disease, such as subtypes of cardiovascular and thyroid disease, as the number of participants reporting subtypes was not sufficient for analysis. We did not have information to differentiate between active and past peptic ulcer disease.

A detailed description of self-reported medical history including *H. pylori* eradication was added in the latest version of the study questionnaire with the aim of improving participant understanding of medical terms and decreasing recall bias in the future.

Including the factors associated with *H. pylori* seropositivity in our study in future studies could be beneficial in identifying causal relationships with sociodemographic, lifestyle and medical factors in other populations.

CONCLUSIONS

In our study *H. pylori* seropositivity was associated with lifestyle and in particular with dietary factors rather than socioeconomic indicators in contrast to the majority of other studies on the topic. Seropositivity for *H. pylori* was significantly associated with smoking, binge drinking, the consumption of at least 200 g of dairy daily and very hot food and/or drinks, but inversely associated with having at least 400 g of vegetables and/or fruit daily, a history of *H. pylori* eradication, peptic ulcer disease, and cardiovascular disease.

Conflicts of interest: None to declare.

Authors' contributions:J.Y.P, M.L., R.H., R.M., D.S., D.R.E. conceived and designed the study. I.P., S.P., D.S. data acquisition. D.R.E., I.P. statistical analysis. D.R.E., J.Y.P., I.E., L.T., R.M., R.H., M.L. interpreted the results. D.R.E., I.E., L.T., J.Y.P. drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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REFERENCES

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon (FR): International Agency for Research on Cancer; 2012;100B:385-435. Available at:https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Biological-Agents-2012
2. Mbulaiteye SM, Hisada M, El-Omar EM. Helicobacter pylori associated global gastric cancer burden. Front Biosci (Landmark Ed) 2009;14:1490–1504. doi:10.2741/3320
3. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of Helicobacter pylori infection. Helicobacter 2014;19:1-5. doi:10.1111/hel.12165
4. Lim SH, Kwon JW, Kim N, et al. Prevalence and risk factors of Helicobacter pylori infection in Korea: nationwide multicenter study over 13 years. BMC Gastroenterol 2013;13:104. doi:10.1186/1471-230X-13-104
5. Ozbey G, Hanafiah A. Epidemiology, diagnosis, and risk factors of *Helicobacter pylori* infection in children. Euroasian J Hepatogastroenterol 2017;7:34-39. doi:10.5005/jp-journals-10018-1208
6. Khalifa MM, Sharaf RR, Aziz RK. Helicobacter pylori: a poor man's gut pathogen? Gut Pathog 2010;2:2. doi:10.1186/1757-4749-2-2
7. Chi H, Bair MJ, Wu MS, Chiu NC, Hsiao YC, Chang KY. Prevalence of *Helicobacter pylori* infection in high-school students on Lanyu island, Taiwan: risk factor analysis and effect on growth. J Formos Med Assoc 2009;108:929–936. doi:10.1016/S0929-6646(10)60005-8
8. Roma E, Panayiotou J, Pachoula J, et al. Intrafamilial spread of *Helicobacter pylori* infection in Greece. J Clin Gastroenterol 2009;43:711–715. doi:10.1097/MCG.0b013e318192fd8a
9. Zhu Y, Zhou X, Wu J, Su J, Zhang G. Risk factors and prevalence of Helicobacter pylori infection in persistent high incidence area of gastric carcinoma in Yangzhong city. Gastroenterol Res Pract 2014;2014:481365. doi:10.1155/2014/481365
10. Ogihara A, Kikuchi S, Hasegawa A, et al. Relationship between Helicobacter pylori infection and smoking and drinking habits. J Gastroenterol Hepatol 2000;15:271-276. doi:10.1046/j.1440-1746.2000.02077.x
11. Ozaydin N, Turkyilmaz SA, Cali S. Prevalence and risk factors of Helicobacter pylori in Turkey: a nationally-representative, cross-sectional, screening with the ^{13}C-Urea breath test. BMC Public Health 2013;13:1215. doi:10.1186/1471-2458-13-1215
12. Mard SA, Khadem Haghighian H, Sebghatulahi V, Ahmadi B. Dietary Factors in Relation to Helicobacter pylori Infection. Gastroenterol Res Pract 2014;2014:826910. doi:10.1155/2014/826910
13. Jarosz M, Rychlik E, Siuba M, et al. Dietary and socio-economic factors in relation to Helicobacter pylori re-infection. World J Gastroenterol 2009;15:1119-1125. doi:10.3748/wjg.15.1119

14. Mhaskar RS, Ricardo I, Azliyati A, et al. Assessment of Risk Factors of Helicobacter Pylori Infection and Peptic Ulcer Disease. J Glob Infect Dis 2013;5:60-67. doi:10.4103/0974-777X.112288
15. Monno R, De Laurentiis V, Trerotoli P, Roselli AM, Ierardi E, Portincasa P. Helicobacter pylori infection: association with dietary habits and socioeconomic conditions. Clin Res Hepatol Gastroenterol 2019;43:603-607. doi:10.1016/j.clinre.2018.10.002
16. Wang XQ, Yan H, Terry PD, et al. Interaction between dietary factors and Helicobacter pylori infection in noncardia gastric cancer: a population-based case-control study in China. J Am Coll Nutr 2012;31:375-384. doi:10.1080/07315724.2012.10720447
17. Haley KP, Gaddy JA. Nutrition and Helicobacter pylori: Host Diet and Nutritional Immunity Influence Bacterial Virulence and Disease Outcome. Gastroenterol Res Pract 2016;2016:3019362. doi:10.1155/2016/3019362
18. Ražuka-Ebela D, Giupponi B, Franceschi F. Helicobacter pylori and extragastric diseases. Helicobacter 2018;23 Suppl 1:e12520. doi:10.1111/hel.12520
19. Goni E, Franceschi F. Helicobacter pylori and extragastric diseases. Helicobacter 2016;21 Suppl 1:45-48. doi:10.1111/hel.12340
20. Chen C, Xun P, Tsinovoi C, He K. Accumulated evidence on Helicobacter pylori infection and the risk of asthma: a meta-analysis. Ann Allergy Asthma Immunol. 2017;119:137-145. doi:10.1016/j.anai.2017.05.021
21. Roberts SE, Morrison-Rees S, Samuel DG, Thorne K, Akhbari A, Williams JG. Review article: the prevalence of Helicobacter pylori and the incidence of gastric cancer across Europe. Aliment Pharmacol Ther 2016;43:334-345. doi:10.1111/apt.13474
22. Leja M, Park JY, Murillo R, et al. Multicentric randomised study of Helicobacter pylori eradication and pepsinogen testing for prevention of gastric cancer mortality: the GISTAR study. BMJ Open 2017;7:e016999. doi:10.1136/bmjopen-2017-016999
23. Park JY, Polaka I, Parshutin S, et al. Trial profile: pilot study of the multicentre randomised trial of H. pylori eradication and pepsinogen testing for prevention of gastric cancer mortality (the GISTAR Pilot study). Microb Health Dis 2019;1e:165. doi: 10.26355/mhd_201912_165
24. Nugawela MD, Langley T, Szatkowski L, Lewis S. Measuring alcohol consumption in population surveys: a review of international guidelines and comparison with surveys in England. Alcohol Alcohol 2016;51:84-92. doi:10.1093/alcalc/agv073
25. World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization Press; 2010. Available at:https://www.who.int/dietphysicalactivity/global-PA-recs-2010.pdf
26. World Health Organization. Diet, Nutrition and the Prevention of Chronic Diseases. WHO Technical Report Series No. 916. Geneva: World Health Organization Press, 2003. Available at:https://www.who.int/dietphysicalactivity/publications/trs916/en/
27. IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.
28. Epidemiology of, and risk factors for, Helicobacter pylori infection among 3194 asymptomatic subjects in 17 populations. The EUROGAST Study Group. Gut 1993;34:1672-1676. doi:10.1136/gut.34.12.1672
29. Sauka A, Putniņš T. Shadow Economy Index for the Baltic Countries 2009-2017 Stockholm School of Economics in Riga 2019. Available at:https://www.sseriga.edu/shadow-economy-index-baltic-countries
30. Latvia, Statistics in Brief 2018. Riga: Central Statistical Bureau of Latvia; 2018. Available at:https://www.csb.gov.lv/en/statistics/statistics-by-theme/economy/gdp/search-in-theme/298-latvia-statistics-brief-2018
31. Hołubiuk L, Imiela J. Diet and Helicobacter pylori infection. Prz Gastroenterol 2016;11:150-154. doi:10.5114/pg.2016.61487
32. Beevers DG, Lip GYH, Blann AD. Salt intake and Helicobacter pylori infection. J Hypertens 2004;22:1475-1477. doi:10.1097/01.hjh.0000133736.77866.77
33. Monteiro C, Costa AR, Peleteiro B. Sodium intake and Helicobacter pylori infection in the early stages of life. Porto Biomed J 2016;1:52-58. doi:10.1016/j.pbj.2016.05.001
34. Bertuccio P, Rosato V, Andreano A, et al. Dietary patterns and gastric cancer risk: a systematic review and meta-analysis. *Ann Oncol 2013;24:*1450–1458. doi:10.1093/annonc/mdt108
35. Mousavi S, Dehkordi FS, Rahimi E. Virulence factors and antibiotic resistance of Helicobacter pylori isolated from raw milk and unpasteurized dairy products in Iran. J Venom Anim Toxins Incl Trop Dis 2014;20:51. doi:10.1186/1678-9199-20-51
36. Quaglia NC, Dambrosio A, Normanno G, et al. High occurrence of Helicobacter pylori in raw goat, sheep and cow milk inferred by glmM gene: A risk of food-borne infection? Int J Food Microbiol 2008:124:43-47. doi:10.1016/j.ijfoodmicro.2008.02.011
37. Ebela I. Report on the situation of Children in Latvia. Latvian Save the Children „Glābiet bērnus." Riga, 1990.
38. Sachdeva A, Rawat S, Nagpal J. Efficacy of fermented milk and whey proteins in Helicobacter pylori eradication: a review. World J Gastroenterol 2014;20:724-737. doi:10.3748/wjg.v20.i3.724
39. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection – the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30. doi:10.1136/gutjnl-2016-312288
40. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol 2017;112:212-238. doi:10.1038/ajg.2016.563
41. Yu XJ, Yang X, Feng L, Wang LL, Dong QJ. Association between Helicobacter pylori infection and angiographically demonstrated coronary artery disease: a meta-analysis. Exp Ther Med 2017;13:787-793. doi:10.3892/etm.2017.4028
42. Rahmani Y, Mohammadi S, Babanejad M, Rai A, Zalei B, Shahmohammadi A. Association of Helicobacter pylori with presence of myocardial infarction in Iran: a systematic review and meta-analysis. Ethiop J Health Sci 2017;27:433-440. doi:10.4314/ejhs.v27i4.15
43. Sun J, Rangan P, Bhat SS, Liu L. A meta-analysis of the association between Helicobacter pylori infection and risk of coronary heart disease from published prospective studies. Helicobacter 2016;21:11-23. doi:10.1111/hel.12234