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ORIGINAL ARTICLE

Significance of serological atrophic gastritis on proton pump inhibitor prescriptions and referrals to gastroscopy in the general population

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Key words
atrophic gastritis, gastroscopy, *Helicobacter pylori*, pepsinogen, proton pump inhibitors.

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Abstract

Background and Aim: We aimed to investigate whether individuals with low pepsinogen I levels differed from those with normal pepsinogen I levels in terms of proton pump inhibitors (PPIs) use, referral to gastroscopy, and findings on gastroscopy.

Methods: Serum pepsinogen I was measured in 518 persons (mean age 51.6, SD 8.8; 49% women). A medical chart review focused on PPI prescriptions and gastroscopic findings in the follow-up period.

Results: Patients with serological atrophic gastritis (pepsinogen I < 28 μg/L) had higher body mass index (27.5 *vs* 26.2 kg/m^2; $P = 0.007$), were less likely to be current smokers (8% *vs* 17%; $P = 0.025$), and had higher prevalence of *Helicobacter pylori* seropositivity (57% *vs* 36%; $P < 0.001$) compared with those without. During follow-up (mean 21.4 years, SD 6.5 years), the patients with serological atrophic gastritis had more often findings of atrophic gastritis or gastric polyps on gastroscopy (20% *vs* 8%; $P < 0.001$), despite no differences in the mean number of gastroscopies per 1000 person-years (33 *vs* 23; $P = 0.19$) and the mean prescribed PPI dose (omeprazole equivalents) per year (1064 mg *vs* 1046 mg; $P = 0.95$). Persons with serological atrophic gastritis had lower odds of being prescribed PPIs at least once (odds ratio [95% confidence interval]: 0.58 [0.35–0.96]), but there was no significant difference in the chance of being referred to gastroscopy at least once (1.15 [0.70–1.96]).

Conclusion: Persons with serological atrophic gastritis were less likely to be prescribed PPIs. Persons with serological atrophic gastritis had more often gastric polyps and atrophic gastritis when referred to gastroscopy.

Introduction

Pepsinogen is a single polypeptide enzyme secreted by gastric chief cells and is converted by gastric acid in the gastric lumen into active pepsin. Inflammation of the gastric mucosa and its progression toward atrophic gastritis is correlated with reduced circulating pepsinogen I levels, and low levels indicate the presence of gastric atrophy.[1] Furthermore, low pepsinogen I levels have been associated with increased risk for non-cardia gastric cancer[2,3] and could possibly be used for screening in risk populations.[4]

Patients referred to endoscopy and diagnosed with chronic atrophic gastritis have been shown to present with a wide range of gastrointestinal symptoms prior to referral.[5] In general, patients with premalignant gastric lesions and atrophic gastritis are often asymptomatic[6] or have less frequent symptoms of gastroesophageal reflux disease[7] and less severe endoscopic findings of gastroesophageal reflux disease[8] than persons with normal pepsinogen I levels.

At the population level, there is uncertainty about whether individuals with low pepsinogen I levels differ from those with normal pepsinogen I levels with regard to experiencing gastrointestinal symptoms, the use of proton pump inhibitors (PPIs), and the chance of being referred for gastroscopy.

The overarching aim of this study was to explore whether individuals with serological atrophic gastritis differed from individuals without in regard to healthcare utilization for upper gastrointestinal disorders. More specific aims were to prospectively evaluate the use of proton pump inhibitors, referral to gastroscopy, and findings on gastroscopy.

Methods

Study design. A prospective cohort study with follow-up evaluation of clinical data (endoscopy and drug prescriptions).

Study subjects. This study is part of the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study conducted in Northern Sweden. MONICA is a project initiated by the World Health Organization to study how cardiovascular risk factors change in a population over time and how that affects mortality rates. Data were collected between 1990 and 2009 in seven surveys from individuals aged 25–74 years (the initial two surveys had the age-range of 25–64 years).[9] This study focused on the population living in the Region of Västerbotten in Sweden who participated in the MONICA study between 1990 and 2009 ($n = 558$). Between the sampling date and the introduction of digital records in the Region of Västerbotten in the year 1996, 24 participants were deceased and excluded due to lack of follow-up data. At the time of the blood sample, data on body mass index (BMI) and concurrent medications were collected by questionnaire. PPIs, histamine H_2 receptor blockers, and other anti-acids may interact with pepsinogen levels,[10] and 15 persons who used these drugs at the time of the blood sample were excluded. In the final data analysis, 519 subjects were included (Fig. 1). During the study period, pepsinogen testing was not available in clinical routine in the Region of Västerbotten.

Data collection. The digital medical record system (NCS cross) used in the Region Västerbotten covers all three hospitals (Umeå, Skellefteå and Lycksele) and all primary care centers in the region. NCS cross started in 1992 but was not fully introduced until 2006. Complete information on endoscopy was available from 1996 for the hospitals in Umeå and Lycksele, and from 2003 in Skellefteå. The observation period for collecting data on endoscopies and drug prescriptions started when data were available in the medical records (or after the sample date for those subjects who participated after the NCS cross was introduced). The observation period ended if the person moved out of Region Västerbotten, died, or at the end of the year 2021. For gastroscopies performed at the hospitals, information on the date of investigation, cause of referral, and documented findings on endoscopy were collected. The macroscopic findings on gastroscopy were categorized based on how the endoscopist documented the findings in the medical record and were categorized into the variables: esophagitis, gastritis, and gastric polyps. In cases where biopsies were taken and the pathologist judged the biopsy as atrophic gastritis, the patient was classified as having histologically verified atrophic gastritis. The number of gastroscopies is presented as the number per 1000 person-years. All drugs prescribed by clinicians in Region Västerbotten are registered in the prescriptions module in the digital medical record system, and complete data were available since 2006. Therefore, all prescriptions of PPIs were collected from 2006 (or after the sample date) to the end of the observation period and calculated as mean doses per year based on omeprazole equivalents.[11] Information on other anti-acid drugs (H_2 receptor antagonists) and nonsteroidal anti-inflammatory drugs (NSAIDs) was collected if they had been prescribed at least once in the observation period. The indication for the PPI prescription was noted based on the information from the medical records and from the text on the drug prescription. The data were collected by author TP, who was blinded to all the blood sample results at the time of the data collection.

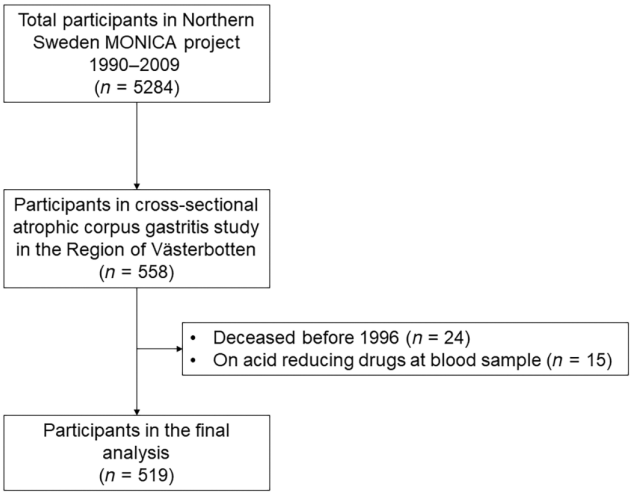

Figure 1 An overview of the study design and study participants.

Blood analysis. Two immunoenzymometric assay tests were used to analyze pepsinogen I in this study. Gastroset PG-I (Orion Diagnostica, Espoo, Finland) was used for samples from 1990, 1994, and 1999, and PG-I Enzyme-Linked Immunoassay Kit (Biohit Oy, Helsinki, Finland) for samples from 2004, 2009, and 2014.[9] A comparison of these two tests was conducted by reusing serum from earlier samplings and comparing the values of pepsinogen I when using the new kit. The tests were deemed comparable when using 28 μg/L as a cutoff value for serologic atrophic gastritis.[10] The test kit used for detecting antibodies against *Helicobacter pylori* was an immunoblot (Helicoblot 2.1; Genelab Diagnostics, Singapore), which has a sensitivity of 95–99% and a specificity of 93–98%.[12,13]

Statistical methods. We used the χ^2-test for the comparison of categorical data. Continuous data were presented as means with SD and, when appropriate, as medians with 25th–75th percentiles. Student's *t*-test and Mann–Whitney test were used for the comparison of continuous data. Based on the "ABCD" method for risk stratification for gastric cancer,[14] we divided the study participants based on *H. pylori* seropositivity and/or serological atrophic gastritis into Group A (normal pepsinogen levels and *H. pylori* seronegative), Group B (normal pepsinogen levels and *H. pylori* seropositive), Group C (low pepsinogen levels and *H. pylori* seropositive), and Group D (low pepsinogen levels and *H. pylori* seronegative), and compared healthcare utilization for Groups B, C, and D in comparison with Group A. Finally, multivariable logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CI) for the association between serological atrophic gastritis (independent/exposure) and various healthcare utilization (dependent/outcome). All models were adjusted for age (continuous), gender (male *vs* female), BMI (obesity ≥30 kg/m^2 *vs* non-obese <30 kg/m^2), *H. pylori* seropositivity, prescription of NSAID ≥2 times in the observation period, and smoking status (current smoker at sample date). Healthcare utilization outcome variables include being prescribed PPIs at least once (yes/no), being referred to

gastroscopy at least once (yes/no), and having the findings of gastric polyps or atrophic gastritis on gastroscopy (yes/no). A *P*-value <0.05 was considered statistically significant. For data analysis, we used IBM SPSS version 27.0.

This study was approved by the Swedish Ethical Board (DNR 2020-02674) and includes no intervention. All subjects gave written informed consent including permission to check their medical records for diseases and prescription of drugs.

Results

Baseline characteristics. At baseline (at the time of blood sampling), the mean age of the study participants was 51.6 years (SD 8.8 years). There was an equal proportion of women and men in the study; 16.5% had a BMI ≥30 kg/m^2, 81 subjects (15.6%) were current smokers, and 39% were seropositive for *H. pylori* infection. One out of six individuals ($n = 91$) were classified as having serological atrophic gastritis. Compared with subjects with normal pepsinogen I level, those with serological atrophic gastritis were more obese (BMI ≥30 kg/m^2, 24.4% *vs* 14.8%), were more often seropositive for *H. pylori* (57.1% *vs* 35.5%), and were less current smokers (7.7% *vs* 17.3%) (Table 1).

Healthcare utilization for upper gastrointestinal disorders during the follow-up period. Table 2 shows various healthcare utilization for upper gastrointestinal disorders during the mean follow-up period of 21.4 years (SD 6.5). The follow-up period was similar for the serologic atrophic gastritis and normal pepsinogen group (mean [SD], 20.8 [5.8] *vs* 21.7 [5.2] years, respectively). A quarter underwent one or more gastroscopies, with no differences in the number of gastroscopies between the two groups (serological atrophic gastritis *vs* normal pepsinogen 29.7% *vs* 24.1%, $P = 0.262$). Among 130 patients with at least one gastroscopy in the follow-up period, 17 patients (13.1%) had histologically verified atrophic gastritis, 26 patients (20%) had nonspecific gastritis and 17 patients (13.1%) had gastric polyps. A total of 52 (40%) of the participants who underwent gastroscopy had any gastritis and/or gastric polyps. Twenty-one had esophagitis according to the gastroscopy, but the presence did not associate with pepsinogen I levels. One individual was diagnosed with gastric cancer (a non-cardia cancer) and had both serological atrophic gastritis and seropositivity for *H. pylori* at baseline. Nearly half of the population received a prescription for PPI treatment at least once. The prescription pattern of PPIs, histamine H_2 receptor blockers, or NSAIDs did not differ between individuals with serological atrophic gastritis and individuals with normal pepsinogen levels. Individuals prescribed with a PPI equivalent dose per year of 1–1000 mg had significantly less serological atrophic gastritis (15% *vs* 29%, $P = 0.006$), whereas individuals prescribed 1001–2000 mg PPI equivalent dose per year had more serological atrophic gastritis (12% *vs* 5%, $P = 0.014$) (Fig. 2). Persons who had been prescribed PPIs at least once were also more often prescribed NSAIDs (at least once) compared with persons who were not prescribed PPI (74% *vs* 47%; $P < 0.001$), and there was a positive correlation between cumulative dose of PPI and number of NSAID prescriptions ($R^2 = 0.318$; $P < 0.001$).

Indications for PPI prescription in the follow-up period. Among those who had at least one prescription for PPI ($n = 256$), a documented indication for the prescription in the medical record (or in the prescription) was only found in 129 patients (50%) (Table 3). The proportion of patients with a documented reason for PPI prescription in the medical record was significantly higher in the group with normal pepsinogen I levels than those with serological atrophic gastritis (55% *vs* 23%; $P < 0.001$).

Table 1 Characteristics of the participants with serological atrophic gastritis (pepsinogen I < 28 μg/L) *versus* those with normal pepsinogen I levels who had serum pepsinogen I measurements at baseline ($n = 519$).

Variable	Overall ($n = 519$)	Serological atrophic gastritis ($n = 91$)	Normal pepsinogen I levels ($n = 428$)	*P*-value
Mean age at baseline, years (SD)	51.6 (8.8)	52.9 (9.2)	51.3 (8.7)	0.12
Women, *n* (%)	254 (49.0)	40 (42.9)	213 (50.2)	0.20
Hospital, *n* (%)				0.61
Umeå	239 (46.1)	41 (45.0)	198 (46.3)	
Skellefteå	197 (37.8)	38 (41.8)	159 (37.1)	
Lycksele	83 (16.0)	12 (13.2)	71 (16.6)	
Body mass index (kg/m^2), mean (SD)	26.4 (4.1)	27.5 (4.8)	26.2 (3.8)	0.007
Body mass index categories (kg/m^2); *n* (%)				0.04
<25.0	215 (41.7)	29 (32.2)	186 (43.7)	
25.0–29.9	216 (41.9)	39 (43.3)	177 (41.5)	
≥30.0	85 (16.5)	22 (24.4)	63 (14.8)	
Smoking status				0.07
Nonsmokers, *n* (%)	282 (54.3)	54 (59.3)	74 (17.3)	
Former smokers, *n* (%)	156 (30.1)	30 (33.0)	126 (29.4)	
Current smokers, *n* (%)	81 (15.6)	7 (7.7)	228 (53.3)	
Seropositive for *Helicobacter pylori* at baseline, *n* (%)	204 (39.3)	52 (57.1)	152 (35.5)	<0.001

P-values calculated for the difference between serologic atrophic gastritis and normal pepsinogen group by χ^2 test and Student's *t*-test.

Table 2 Health care utilization for upper gastrointestinal disorders during the follow-up period for participants with serological atrophic gastritis (pepsinogen I < 28 μg/L) and those with normal pepsinogen I (pepsinogen I ≥ 28 μg/L) levels.

	Overall ($n = 519$)	Serological atrophic gastritis ($n = 91$)	Normal pepsinogen I levels ($n = 428$)	Serological atrophic gastritis *versus* normal pepsinogen I *P*-value
Mean observation time, years (SD)	21.4 (6.5)	20.8 (5.8)	21.7 (5.2)	0.208
Gastroscopies per 1000 person-years, mean (SD)	25 (68)	33 (72)	23 (67)	0.188
Gastroscopies per 1000 person-years, median (1Q–3Q)	0 (0–0)	0 (0–58)	0 (0–0)	0.149
One or more gastroscopies, *n* (%)	130 (25.0)	27 (29.7)	103 (24.1)	0.262
Diagnosis of esophagitis on gastroscopy, *n* (%)	21 (16.1)	3 (11.1)	18 (17.4)	0.563
Diagnosis of gastritis on gastroscopy, *n* (%)	41 (31.5)	14 (51.9)	27 (26.2)	*0.011*
Histologically verified atrophic gastritis, *n* (%)	17 (13.1)	9 (33.3)	8 (7.8)	*0.002*
Diagnosis of gastric polyps on gastroscopy, *n* (%)	27 (20.8)	6 (22.2)	11 (10.7)	0.121
Endoscopically gastritis or gastric polyps, *n* (%)	52 (40.0)	18 (66.7)	34 (33.0)	*<0.001*
Cumulative PPI dose per year, mg omeprazole, mean (SD)	1050 (2577)	1064 (2395)	1046 (2616)	0.952
Cumulative PPI dose per year, mg omeprazole, median (1Q–3Q)	0 (0–694)	0 (0–1050)	17 (0–662)	0.397
One or more PPI prescriptions, *n* (%)	256 (49.3)	39 (43)	217 (51)	0.174
One or more H_2-antagonist prescriptions, *n* (%)	26 (5.0)	7 (7.7)	19 (4.4)	0.192
Median number of more H_2-antagonist prescriptions (1Q–3Q)	0 (0–0)	0 (0–0)	0 (0–0)	0.209
One or more NSAID prescriptions, *n* (%)	315	58 (64)	257 (60)	0.513
Median number of NSAID prescription (1Q–3Q)	2 (0–3)	2 (0–3)	2 (0–3)	0.832

P-values calculated for the difference between serologic atrophic gastritis and normal pepsinogen group by χ^2 test, Fischer's exact test, Student's *t*-test, and Mann–Whitney test. A *P*-value <0.05 was considered statistically significant.
NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Indications for gastroscopy in the follow-up period. The indications for gastroscopy did not differ between individuals with serological atrophic gastritis and individuals with normal pepsinogen I levels except for the indication of anemia, which was more common in subjects with serological atrophic gastritis (Table 4).

Healthcare utilization based on the "ABCD" classification. Table 5 presents the outcome of classifying the individuals according to the "ABCD" method for risk stratification for gastric cancer. Males were significantly more common in patients in Group D (serologic atrophic gastritis and negative *H. pylori* serology) compared with Group A (normal pepsinogen I levels and negative *H. pylori* serology). BMI was higher in Group D compared with Group A (mean [SD] 28.1 [5.7] *vs* 26.2 [3.9] kg/m^2).

Individuals with serological atrophic gastritis (Group C + D) were more commonly referred to gastroscopy compared with individuals with normal pepsinogen I levels and negative for *H. pylori* serology (29.6% *vs* 19.3%; $P = 0.04$). In those with a gastroscopic examination, the presence of gastritis was significantly more common in Group B (40.0%) and Group C + D (50.0%) *versus* Group A (13.2%), and histological atrophic gastritis was significantly more common in Group C + D (32.1%) versus Group A (7.5%). The presence of esophagitis did not differ between the groups (range 0–5.8%; $P = 0.152$; Table 5). There was a significant *P*-trend with increased risk for A to D for being referred to gastroscopy at least once, having gastritis, having verified atrophic gastritis, and having either verified atrophic gastritis or gastric polyps (Table 5).

In the observation period, only three patients with both *H. pylori* positivity and serological atrophic gastritis were treated for *H. pylori* infection (PPI with two antibiotics for 1–2 weeks). In the whole study population, 10% of the subjects with *H. pylori* positivity were treated for *H. pylori* infection. There was no significant difference in the proportion of patients who received treatment for *H. pylori* infection between patients with serological atrophic gastritis and persons with normal pepsinogen I levels (6% *vs* 11%; $P = 0.417$). Only 4% of the subjects who were seronegative for *H. pylori* and had normal pepsinogen I levels had verified atrophic gastritis or gastric polys on gastroscopy compared with one out of five with serological atrophic gastritis ($P < 0.001$) (Table 5).

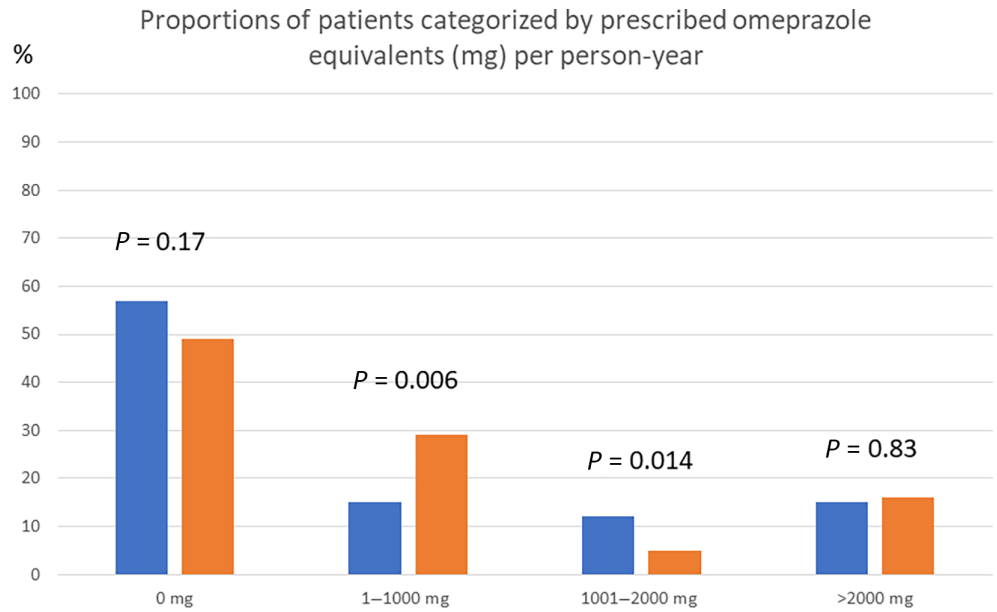

Figure 2 Proportion of patients categorized by prescribed omeprazole equivalents (mg) per person-year. (■), Serological atrophic gastritis ($n = 91$); (■), normal pepsinogen I levels ($n = 428$).

Table 3 Among those who had at least once received a prescription for proton pump inhibitors (PPIs) ($n = 256$), a documented reason for PPI prescriptions in the medical records was presented in 129 patients and are presented in the table.

	Serological atrophic gastritis ($n = 39$)	Normal pepsinogen I ($n = 217$)	*P*-value
Any documented indications, *n* (%)	9 (23)	120 (55)	<0.001
Prophylaxis, *n* (%)	0 (0)	43 (36)	0.03
Gastroesophageal reflux, *n* (%)	4 (44)	35 (29)	0.45
Gastritis, *n* (%)	4 (44)	29 (24)	0.23
Dyspepsia, *n* (%)	0 (0)	8 (7)	>0.99
Gastric or duodenal ulcers, *n* (%)	2 (22)	7 (6)	0.12

P-values calculated for the difference between serologic atrophic gastritis and normal pepsinogen groups by Fischer's exact test. Some patients had more than one indication.

Table 4 Indications for gastroscopy in persons with serological atrophic gastritis (pepsinogen 1 < 28 μg/L) and persons with normal pepsinogen 1 (pepsinogen I ≥ 28 μg/L) levels.

	Serological atrophic gastritis ($n = 27$)	Normal pepsinogen I ($n = 103$)	*P*-value
Anemia, *n* (%)	9 (33.1)	10 (9.7)	0.004
Dysphagia, *n* (%)	1 (3.7)	13 (12.6)	0.29
Dyspepsia, *n* (%)	10 (37.0)	38 (36.9)	>0.99
Gastroesophageal reflux, *n* (%)	4 (14.8)	20 (19.4)	0.78
Gastrointestinal bleeding, *n*	3 (11.1)	15 (14.6)	0.76
Weight loss, *n*	1 (3.7)	1 (1.0)	0.37
Other[†], *n*	3 (11.1)	7 (6.8)	0.43

[†]Other reasons include amyloidosis, screening for hereditary cancer, chest pain, and trauma.
P-values calculated for the difference between serologic atrophic gastritis and normal pepsinogen groups by Fischer's exact test. Some patients had more than one indication.

Table 5 Characteristics and health care utilization comparing patients according to the "ABCD" method for risk stratification for gastric cancer by a combination of *Helicobacter pylori* positivity and/or serological atrophic gastritis (pepsinogen 1 < 28 μg/L).

Variable	Group A ($n = 275$)	Group B ($n = 152$)	Group C ($n = 52$)	Group D ($n = 39$)	Group B *versus* Group A, OR (95% CI)	Group C + D *versus* Group A, OR (95% CI)	*P*-trend (A to D)
Baseline characteristics							
Mean age, years (SD)	49.5 (8.6)	54.6 (7.8)*	55.6 (7.5)*	49.3 (10.1)	*1.07 (1.05–1.10)*	*1.04 (1.01–1.08)*	Not calculated
Women; *n* (%)	139 (50.5)	76 (50.0)	28 (53.8)	11 (28.2)*	0.98 (0.65–1.49)	0.72 (0.44–1.18)	0.089
Body mass index (kg/m^2), mean (SD)	26.2 (3.9)	26.1 (3.7)	26.9 (4.0)	28.1 (5.7)*	0.98 (0.93–1.03)	*1.06 (1.00–1.23)*	Not calculated
Current smokers, *n* (%)	42 (15.3)	32 (21.1)	5 (9.6)	2 (5.1)	1.18 (0.69–2.03)	0.43 (0.20–1.01)	0.177
Healthcare utilization during follow-up							
One or more gastroscopies, *n* (%)	53 (19.3)	50 (32.9)	16 (30.8)	11 (28.2)	*1.86 (1.16–2.99)*	1.74 (0.99–3.05)	*0.012*
Diagnosis of esophagitis on gastroscopy, *n* (%)	11 (4.0)	7 (4.6)	3 (5.8)	0 (0)	0.52 (0.17–1.60)	0.34 (0.08–1.48)	0.152
Diagnosis of gastritis on gastroscopy, *n* (%)	7 (13.2)	20 (40.0)	9 (56.3)	5 (45.5)	*3.64 (1.32–10.0)*	*7.41 (2.14–25.6)*	*<0.001*
Histologically verified atrophic gastritis, *n* (%)	4 (7.5)	4 (8.0)	5 (31.3)	4 (36.5)	0.85 (0.19–3.85)	*6.41 (1.43–28.8)*	*0.002*
Diagnosis of gastric polyps on gastroscopy, *n* (%)	9 (17.0)	2 (4.0)	1 (6.3)	5 (45.5)	*0.12 (0.02–0.70)*	0.83 (0.23–2.95)	0.267
Endoscopically verified gastritis or gastric polyps, *n* (%)	12 (4.4)	22 (14.5)	10 (19.2)	8 (20.5)	*2.44 (1.03–5.79)*	*7.25 (2.40–21.9)*	*<0.001*
One or more PPI prescriptions, *n* (%)	127 (46.2)	89 (58.6)	23 (44.2)	16 (41.0)	*1.60 (1.05–2.44)*	0.71 (0.43–1.17)	0.953
Mean PPI dose per year, mg omeprazole (SD)	1028 (2745)	1067 (2379)	1280 (2880)	780 (1510)	1.00 (0.87–1.16)	0.94 (0.80–1.14)	Not calculated

Group A: Normal pepsinogen 1 and seronegative for *H. pylori*. *Group B*: Normal pepsinogen 1 and seropositive for *H. pylori*. *Group C*: Serological atrophic gastritis and seropositive for *H. pylori*. *Group D*: Serological atrophic gastritis and seronegative for *H. pylori*. A *P*-value <0.05 was considered statistically significant.

CI, confidence interval; OR, adjusted for age, gender, body mass index and smoking status; PPI, proton pump inhibitor.

Risk for healthcare utilization for upper gastrointestinal disorders. In a multivariate analysis, individuals with serological atrophic gastritis had less prescriptions of PPI compared with individuals with normal pepsinogen I (OR 0.58, 95% CI 0.35–0.96), whereas individuals with two or more prescriptions of NSAIDs were more often prescribed PPI compared with those prescribed less (OR 3.04, 95% CI 2.07–4.45) (Table 6).

H. pylori positivity and smoking at baseline were associated with a higher risk for a gastroscopic examination during follow-up (OR 1.60, 95% CI 1.04–2.48, and OR 1.77, 95% CI 1.04–3.01, respectively). As a sensitivity analysis, we restricted the analysis to individuals with baseline data from 1986 and onward, and individuals with serological atrophic gastritis were probably still less often prescribed PPIs at least once (OR 0.45; 95% CI 0.20–1.02). The differences in referral to gastroscopy did not persist.

Discussion

This study is, to our knowledge, the first study that presents data on the significance of serological atrophic gastritis in a general population in an era when pepsinogen testing was not performed in clinical routine in Sweden. In this study, we found that individuals with serological atrophic gastritis were less often prescribed PPIs but had a higher risk of being diagnosed with a gastritis or atrophic gastritis when referred to gastroscopy compared with individuals with normal pepsinogen I levels. Furthermore, we found that the presence of esophagitis on gastroscopy did not differ between those with low *versus* normal pepsinogen I levels.

Our study demonstrates that a person with serological atrophic gastritis and therefore at risk of developing non-cardia gastric cancer do not present more often with conditions that result in a PPI prescription. On the other hand, with the assumption that a subject with low pepsinogen I level has reduced gastric acid production, a remarkably high proportion of subjects with serological atrophic gastritis had at least once been prescribed PPIs. Furthermore, there was no difference in the cumulative prescribed dosage between persons with serological atrophic gastritis and persons with normal pepsinogen levels, and there were no significant differences in having at least one

Table 6 Association between various demographic factors, serological atrophic gastritis (pepsinogen I < 28 μg/L), nonsteroidal anti-inflammatory drug (NSAID) use, and healthcare utilization for upper gastrointestinal disorders (prescribed proton pump inhibitors [PPIs] and referral to gastroscopy).

	PPI prescription ($n = 256$) *versus* no PPI prescription ($n = 263$) aOR (95% CI)	Gastroscopy ($n = 130$) *versus* no gastroscopy ($n = 389$) aOR (95% CI)
Age at baseline (per 1 year increase)	1.02 (0.99–1.04)	1.02 (0.99–1.04)
Men *versus* women	1.39 (0.95–1.28)	1.27 (0.83–1.93)
Body mass index ≥ 30 *versus* <30 kg/m^2	1.28 (0.77–2.12)	1.02 (0.58–1.77)
Current smoker at baseline *versus* nonsmoker at baseline	0.88 (0.53–1.48)	*1.77 (1.04–3.01)*
Seropositive *versus* seronegative for *Helicobacter pylori*	1.46 (0.98–2.19)	*1.60 (1.04–2.48)*
NSAID prescription (≥2 *vs* <2 prescription)	*3.04 (2.07–4.45)*	1.46 (0.96–2.22)
Serological atrophic gastritis *versus* normal pepsinogen I	*0.58 (0.35–0.96)*	1.15 (0.70–1.96)

Models were adjusted for age at baseline, gender, body mass index, smoking at baseline, *H. pylori* serology, NSAID prescriptions, and serological atrophic gastritis. A *P*-value <0.05 was considered statistically significant.

aOR, adjusted odds ratio; CI, confidence interval.

prescription of PPI between Group A and Group C/D when using the "ABCD method." Interestingly, a reason for the indication for PPIs was less often recorded in patients´ notes or the prescriptions in patients with serological atrophic gastritis compared with subjects with normal pepsinogen I levels who were prescribed PPIs. PPI use in older adults with serological atrophic gastritis has been associated with vitamin B12 deficiency,[15] and therefore unnecessary prescriptions of PPIs should be avoided in persons with atrophic gastritis as others with nonacid-related conditions.

Pilotto et al. observed that despite a theoretically expected low acid production, as many as 22% of patients with autoimmune atrophic gastritis report symptoms typical of GERD.[16] However, those patients had overall an inferior clinical benefit of PPIs, and few had a GERD diagnosis based on abnormal esophageal acid exposure, indicating nonacid causes of reflux symptoms in patients with atrophic gastritis. Nonacid-related gastrointestinal symptoms are common but often wrongly treated with PPIs, and in most countries, there is a high prevalence of unnecessary PPI use.[17] The most common reasons for unnecessary PPI use are functional dyspepsia or prophylaxis for concurrent NSAID treatment,[17] and both these indications were also common causes for PPI prescription in the persons with normal pepsinogen I levels in our study. A similar prevalence of gastrointestinal symptoms was reported in patients with and without the findings of atrophic gastritis, intestinal metaplasia, and dysplasia on gastroscopy in a study on patients referred to both upper and lower endoscopy.[6] Using tests for gastrin and pepsinogen in clinical practice to guide PPI therapy could be a tool to prevent the overuse of PPIs.[18]

Previous studies have shown that persons with dyspepsia who are seropositive for *H. pylori* had significantly higher pepsinogen I levels than persons seronegative for *H. pylori*.[19,20] On the contrary, we found that in a population that mirrors the general population, the proportion of patients seropositive for *H. pylori* was instead significantly higher in the group with serological atrophic gastritis. The explanation for this difference is unknown, but perhaps pepsinogen I levels are involved in generating or associated with symptoms of dyspepsia in patients with *H. pylori*.

Pepsinogen I testing in combination with *H. pylori* testing has been suggested as a screening tool to select patients for upper gastrointestinal endoscopy[21] and to screen for non-cardia gastric cancer.[2] The combination of a pepsinogen I level >70 and negative *H. pylori* serology has in two large studies from Japan shown to be associated with almost no risk of developing non-cardia cancer.[22,23] In our study, only one patient was diagnosed with non-cardia gastric cancer, and that patient had serological atrophic gastritis and was seropositive for *H. pylori* prior to diagnosis. Interestingly, using the "ABCD" method,[14] we found an increasing odds ratio from B, C, to D when comparing patients with A for the endoscopic findings "histological serological atrophic gastritis" and the compound outcome "any gastritis or gastric polyps", supporting the use of this method for risk stratification. Furthermore, only one out of three patients with serological atrophic gastritis referred to gastroscopy in our study were verified as having histologically atrophic gastritis, which probably mirrors a lack of taking biopsy during gastroscopy. A risk stratification using pepsinogen testing prior to gastroscopy could facilitate the endoscopist to make accurate decisions about taking biopsy during gastroscopy.

Consistent with previous studies, we found that smoking was associated with higher pepsinogen I levels.[24,25] However, we could not confirm the difference in pepsinogen I levels between former smokers and nonsmokers reported by Razuka-Ebela et al.,[24] but it may be dependent on pack years of smoking and the time since the persons quit smoking. Patients in our study who were current smokers at baseline had higher odds of being referred to gastroscopy at least once. The role of smoking in the pathogenesis of conditions in the upper gastrointestinal tract with and without increased pepsinogen I levels is not known. In a Finnish study, the risk for gastric cancer in male smokers with normal pepsinogen I levels was slightly higher than in the general population (standard incidence ratio 1.13; 95% CI 1.00–1.27).[26]

The strength of this study is that we investigated serological atrophic gastritis in a population that mirrors the general population in a health survey, which was not focused on gastrointestinal disease. In the literature, studies on pepsinogen I levels are mostly performed on patients with gastrointestinal symptoms and/or performed at an endoscopic unit. Another strength of the study is that we had access to all endoscopic investigations and long-term PPI prescriptions in the Region of Västerbotten from the time our medical digital record system was in use, which enabled reliable data on the incidence for gastroscopy and PPI prescriptions.

This study also has several limitations. First, the definition of serological atrophic gastritis was based on only one blood

sample. Second, the study only noted PPIs and histamine H_2 prescribed from medical care, and we have no information on all sporadic users ("over-the-counter") of these drugs. However, the tax-financed medical health system in Sweden, which includes cost support of up to approximately 250 Euro per year for prescribed drugs, means that all long-term PPI users usually get their PPIs through doctor prescriptions.[27] Third, the gastroscopy was performed in clinical practice, and the diagnosis of findings on gastroscopy including gastric polyps and gastritis are dependent on the judgment of several doctors with different experiences of endoscopy. However, all endoscopists were blinded for pepsinogen I and *H. pylori* results. Another important limitation is that we do not have access to the prescription of drugs before 2006 and no data on endoscopies performed before 1996. Finally, this study did not evaluate all clinical parameters. For example, we have no information on the health visits for gastrointestinal-related complaints in primary care.

To conclude, individuals with serological atrophic gastritis were not referred more often for gastroscopy than others but had a higher risk of being diagnosed with gastritis or atrophic gastritis. Persons with normal pepsinogen I levels were more often prescribed PPIs (at least once) compared with patients with serological atrophic gastritis.

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