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# **Natural history of chronic gastritis in a Population-based cohort**

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**Short title:** Natural history of chronic gastritis

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## **ABSTRACT**

**Objective:** To describe and explore the natural history of *H. pylori* infection and chronic gastritis in terms of gastric mucosal atrophy and ulcer development over time in a population-based cohort.

**Material and Methods:** A population-based cohort of 314 volunteers was re-screened (median follow-up interval of 8.4 y) with gastroduodenoscopy with biopsy, assessment of *H. pylori* status, analysis of pepsinogens, and monitoring of NSAID use and alcohol and smoking habits.

**Results:** The incidence of duodenal or prepyloric ulcer was 0.45 per 100 person years and was associated with weekly NSAID use (OR 27.8), weekly alcohol consumption (OR 19.4) and smoking (OR 31.0), but not with *H. pylori* status. De novo infection with *H. pylori* was not observed, and the infection had disappeared in 11 of 113 subjects. Among subjects with chronic gastritis, the incidence of atrophy of the corpus mucosa was 1.4 per 100 person years. Atrophy development was related to age (OR 1.23) and to the severity of chronic inflammation in the corpus mucosa at baseline (OR 8.98). Substituting atrophy for subnormal S-pepsinogen I/S-pepsinogen II gave similar results.

**Conclusions:** In this cohort, the minimum incidence of ulcer was 0.45 per 100 person years. Smoking, alcohol and NSAIDs, but not *H. pylori* infection was significant risk factors. The incidence of atrophy of the corpus mucosa was 1.4 per 100 person years with a positive relation to age and to the degree of chronic inflammation at baseline. Atrophy was stationary in advanced stages.

**Keywords:** cohort, endoscopy, gastritis, incidence, peptic ulcer, prospective.

## INTRODUCTION

More than half of the world's population is infected with *Helicobacter pylori* (*H. pylori*), the primary cause of chronic gastritis (1-6). Chronic gastritis is associated with peptic ulcer and in advanced stages with an increased risk of developing gastric adenocarcinoma. The incidence of gastric adenocarcinoma has decreased in developed countries, but in Europe more than 100,000 people still die each year from this cancer (5, 7). The main risk factor for the development of adenocarcinoma is atrophy of the gastric mucosa, especially when atrophy involves the corpus (8-13). Severe atrophy of the corpus mucosa can also lead to intrinsic factor deficiency with subsequent vitamin B12 deficiency and hyperhomocysteinaemia (14). When the atrophy is antrum sparing with hypergastrinaemia, it is associated with an increased risk of enterochromaffin-like (ECL) cell neuroendocrine tumours, as observed among patients with pernicious anaemia (15).

The prevalence of atrophic gastritis in the general population has been assessed by screening gastric function. Specifically, screening involves analysis of S-pepsinogen I (PGI) or the S-pepsinogen I/S-pepsinogen II ratio (PGI/PGII), with subnormal levels indicating atrophy of the gastric corpus mucosa (16). According to the results of screening with these surrogate markers the overall prevalence of atrophy of the corpus mucosa among adults in parts of Europe and New Zealand ranges from 3–6% and increases with age (17-19).

According to the results of histomorphological studies the prevalence of atrophy of the corpus mucosa ranges between 10–37% in the general population in northern Europe (20-24). The corresponding prevalence of severe atrophy is 2–7% (20, 21, 23, 24). In a high-risk Chinese population, the prevalence of atrophy of the corpus mucosa (regardless of severity) is 26–66% (25).

Several studies have documented the natural history of chronic gastritis in patient series (26-29), but there are few population-based studies (28, 30, 31). The progression of *H. pylori*-associated chronic non-atrophic gastritis to atrophic gastritis is slow, and long-term observation is needed to obtain reliable quantitative data (5, 8, 32). However, the longer the observation interval, the fewer the number of subjects available for re-examination. This is of particular concern amongst the elderly, who have the highest incidence of atrophy.

The reported prevalence of gastric ulcer is 1–3% among dyspeptic patients (33, 34) and approximately 2% in population-based cohorts (24, 35). The corresponding figures for duodenal ulcer are 1–3% among dyspeptic patients (33, 34) and 1–2% in population-based cohorts (24, 35). One population-based study reported an ulcer prevalence of 8% in subjects with dyspepsia and 4% in subjects without dyspepsia (36).

In a Finnish follow-up study of dyspeptic patients without ulcer at baseline examination, the incidence of symptomatic ulcer was 7.7% over a ten-year period (37). In another Finnish prospective study of dyspeptic patients, the incidence of ulcer was 21.6% over a 32-year period (26). We are not aware of any population-based prospective endoscopic screening study on the incidence of ulcer.

The aim of this study was to describe and explore the natural history of *H. pylori* infection and chronic gastritis in terms of the dynamics and the development of benign ulcer over a period of eight years in an adult population-based cohort.

## METHODS

### Study population

The study was conducted in accordance with the principals set forth in the Helsinki Declaration and was approved by the Regional ethics committee in the South-east of Sweden. Informed written consent was obtained from all participants.

The prevalence of gastritis, *H. pylori* infection and ulcer disease in this cohort was published as part of a previous study (24). Randomly selected subjects (n = 501) from the general population of Linköping, Sweden, volunteered to undergo oesophago-gastro-duodenoscopy (OGD) with biopsy. The subjects were 35–85 years old, and there were an equal number of women and men at selection. The earlier study was non-interventional in terms of *H. pylori* infection, although infection was eradicated in 15 subjects with newly-detected subclinical ulcer. The researchers planned to re-examine study participants a minimum of eight years after baseline. Of the 501 participants at baseline, 50 had died, 33 had severe disease, 12 were on warfarin treatment, 6 had moved, 4 lost and 12 had undergone treatment for *H. pylori* infection at baseline. Ten subjects who had undergone gastric resection for benign ulcer before baseline were not included in the present study. Furthermore, histological examination was not carried out in 2 subjects at baseline, leaving 372 subjects eligible for re-examination. Of these, 56 refused re-examination. Thus, a total of 316 subjects were re-examined; however, 2 did not complete the re-examination. In the end, a total of 314 of 372 (84.4%) subjects participated in the follow-up examination. None had ulcer at baseline.

Both at baseline and at follow-up, the participants completed a self-administered questionnaire about disease history, body weight and height, current smoking (no/yes), weekly use of spirits or wine (no/yes), and current medications, including the use of aspirin

(regular or low-dose) and other potentially ulcerogenic NSAIDs (weekly use, no/yes). In-hospital diagnoses recorded during the follow-up period, including causes of death, were extracted from local patient files as well as from the records of Statistics Sweden (SCB) and the Swedish National Board of Health and Welfare, including the Regional Cancer Register. During the follow-up interval, one participant was treated for symptomatic duodenal ulcer with *H. pylori* eradication. This participant was not included in the follow-up analysis of chronic gastritis. No participant was diagnosed with gastric neoplasia during the follow-up interval.

At the follow-up examination, participants were asked via the questionnaire (commercial names were listed) whether they had taken antibiotics, proton pump inhibitors or histamine-2 receptor antagonists at any time during the follow-up interval.

### **Endoscopic examination**

The volunteers fasted for at least 6 h before the examination. Blood samples were drawn and OGD was performed after pharyngeal anaesthesia with lidocaine spray (Xylocaine, AstraZeneca, Södertälje, Sweden). Sedation with 2-3 mg intravenously administered midazolam (Dormicum, Roche AB, Stockholm, Sweden) was provided on demand. Triplicate biopsy specimens were collected from the gastric corpus (major, anterior and posterior aspects) and the antrum (within 3 cm of the pylorus). One additional biopsy specimen from each location was analysed for the presence of *H. pylori* using the urease test (CLO-test, Delta West Pty Ltd, Bentley, Australia).

Ulceration was defined endoscopically as a mucosal break with unequivocal depth and a

diameter of at least 3 mm (38). All gastric ulcers were biopsied and their benign nature verified histologically.

### **Histomorphological examination**

After orientation, fixation in neutral formaldehyde, and routine processing of the biopsies, 5- $\mu$ m thick sections cut perpendicular to the surface were stained with haematoxylin and eosin, Alcian blue-periodic acid-Schiff and Giemsa. The density of *H. pylori*, chronic inflammatory infiltrate, inflammatory activity (polymorphonuclear cells), glandular atrophy and intestinal metaplasia were scored at histological examination according to the Sydney system as follows: 0: none, 1: mild, 2: moderate or 3: severe (39). When inflammation or atrophy was present in both the antrum and corpus, gastritis was classified as antrum- or corpus-predominant if there was a 2-point or greater difference between the scores for inflammation (or atrophy), and as pangastritis when there was less than a 2-point difference. Gastritis that was limited strictly to the antrum or corpus was classified accordingly as antrum- or corpus-predominant.

Microscopic examination was performed by a single experienced pathologist who was blinded to the other data. Kappa analysis of the “blinded” repeat evaluation of the Sydney system scores of biopsy sections from the antrum and corpus in 50 participants (30 with chronic gastritis and 20 without gastritis) at baseline yielded a Cohen’s Kappa statistic of 0.782 and 0.821 for chronic inflammation, 0.882 and 0.735 for inflammatory activity, 0.640 and 1.000 for atrophy and 0.839 and 1.000 for intestinal metaplasia, respectively.

Corresponding values for the density of *H. pylori* were 0.897 and 0.824, respectively.

*H. pylori* status was classified as positive when more than one of the following occurred: *H. pylori* identified by light microscopic examination; a positive urease test; an elevated level of *H. pylori* antibodies.

### **Blood analysis**

Blood samples were stored at -80°C until analysis. Serum pepsinogen concentrations were measured with a sandwich enzyme immunoassay (ELISA) utilizing PGI- and PGII-specific capture antibodies and a secondary horseradish peroxidase detection antibody (GastroPanel<sup>®</sup>, Biohit Diagnostics, Helsinki, Finland). There is no cross reactivity between the two assays. The reference interval is 30.0-120.0 µg/L for PGI, 3.0-10.0 µg/L for PGII and 3.0-20.0 for the ratio PGI/PGII. PGI/PGII values lower than 3.0 were considered indicative of significant atrophy of the gastric corpus mucosa.

Serum IgG antibodies to *H. pylori* were analysed by ELISA as described previously (40) and reported as relative OD, that is, as a percent of positive standards (normal upper limit, 5%).

### **Statistical analysis**

Continuous numerical data were summarised as median (range). The Mann-Whitney U-test was used to compare non-paired data, and the Wilcoxon signed rank test was used for paired data. Fisher's exact test or the chi-square test was used as appropriate to compare categorical data. McNemar's test was used for paired binominal data. Logistic regression analysis, including forward stepwise regression, was performed using incident ulcer, atrophy of the gastric mucosa and subnormal (< 3.0) PGI/PGII as the dependent variable. Goodness-of-fit was tested using the Hosmer-Lemeshow statistic. Odds ratios (OR) derived from logistic

regression analyses are reported with the 95% confidence interval (41). Gender, age at baseline, difference in BMI between baseline and follow-up, follow-up interval (months), *H. pylori* status at baseline and follow-up, weekly use of NSAIDs (no/yes) at follow-up, smoking (no/yes) at follow-up and weekly consumption of alcohol (no/yes) at follow-up were included as independent variables in all logistic regression analyses. The degree of inflammation in the corpus mucosa at baseline was an additional independent variable in the analysis that used atrophy of the corpus mucosa as the dependent variable. A two-sided P-value < 0.05 was considered significant.

## RESULTS

Median age of the cohort was 58.0 (37.0-81.0) years at baseline and 66.4 (45.3–89.8) years at follow-up examination, with no difference between the sexes. Of the 314 participants, 144 were women. Although the intention was to apply a minimum follow-up interval of 96 months (8 years), 41 participants were examined 88-95 months after baseline. The median follow-up interval was 101 (54-175) months, corresponding to 2657.5 person years. Table 1 shows the frequencies of putative risk factors for gastritis or ulcer. The median BMI was 24.4 (17.9–40.9) kg/m<sup>2</sup> at baseline and 25.1 (18.0–43.0) kg/m<sup>2</sup> at follow-up (P < 0.001).

### Incidence of ulcer

At the follow-up examination, prepyloric ulcer was diagnosed in 4 and duodenal ulcer in 7 participants. In addition, 1 subject had received *H. pylori* eradication therapy for a symptomatic duodenal ulcer 54 months before the planned follow-up examination. Thus, a total of 12 participants were diagnosed with ulcer, yielding an incidence of 0.45 per 100 person years among all 314 participants. The corresponding figure was 0.58 per 100 person

years among 141 participants with chronic gastritis (follow-up interval 1201.9 person years). Putative risk factors in participants with ulcer are listed in Table 2. Of the 12 participants with ulcer, 5 were women. Of 5 participants with ulcer and negative *H. pylori* status, 1 had only positive *H. pylori* serology and 1 had only histologically diagnosed *H. pylori*. Urea breath test and biopsy cultures were negative in these 5 participants. Two of these used NSAIDs every week, another 3 consumed alcohol every week, and 1 was a smoker at follow-up.

Among the 11 participants with incident subclinical ulcer, there was no significant change in the weekly use of NSAIDs (2 vs. 5,  $P=0.250$ ), weekly consumption of alcohol (6 vs. 8,  $P=0.625$ ) or smoking (6 vs. 5,  $P=0.999$ ) between the baseline and follow-up examinations.

Logistic regression analysis showed an association between incident ulcer and weekly use of NSAIDs (OR 27.8 [4.2-184.6]), weekly consumption of alcohol (OR 19.4 [3.3-114.3]) and smoking (OR 31.0 [5.3-182.2]) at follow-up. There was no significant relation to *H. pylori* status.

### **Course of chronic gastritis**

At baseline, 173 participants had neither *H. pylori* infection nor gastritis. At the follow-up examination, none of these 173 had positive *H. pylori* status; however, 15 had chronic gastritis, 14 mild and 1 moderate (pangastritis without atrophy). The frequency of NSAID use, alcohol consumption and smoking did not differ between baseline and follow-up in these 15 participants.

Twenty-seven participants had chronic gastritis without *H. pylori* infection at baseline. Of these, 21 had mild gastritis, which had disappeared in 16 and was unchanged in 5 at follow-up

examination. Of the remaining 6 participants, 4 had moderate-to-severe corpus-predominant atrophic gastritis, 1 had moderate antrum-predominant atrophic gastritis and 1 had moderate non-atrophic pangastritis at baseline. In the latter 2, gastritis had resolved at follow-up, whereas it was unchanged in those with moderate-to-severe corpus-predominant atrophic gastritis. The frequency of NSAID use, alcohol consumption and smoking did not differ between baseline and follow-up in these 27 participants, and none had acquired *H. pylori* infection.

Gastritis with positive *H. pylori* status was present in 113 participants at baseline (one participant treated for ulcer during the follow-up interval excluded). The topographic types and severity of gastritis at baseline and follow-up are shown in Table 3.

In 11 participants (9.7%), the *H. pylori* status had changed from positive to negative (Table 4). The degree of chronic gastritis was unchanged in 4 (one with moderate atrophic corpus-predominant gastritis) of these 11 participants, and there was progress from mild atrophy (antrum-predominant in 1 and corpus-predominant in 1) to severe atrophy of the corpus mucosa in 2 participants.

Table 5 shows the development of atrophy among participants with chronic gastritis.

Regarding the corpus mucosa, there was a decrease in the frequency of none-to-mild atrophy (from 93.5% to 87.7 %) and an increase in the frequency of moderate-to-severe atrophy (from 6.5% to 12.2%). Regarding the antral mucosa, the frequency of non-atrophic gastritis increased the frequency of mild-to-moderate atrophy decreased and the frequency of severe atrophy increased. Among participants with gastritis and positive *H. pylori* status at baseline, the results were similar. There was an increase in moderate-to-severe atrophy of the corpus

mucosa from 4.5% to 11.6%, ( $P < 0.001$ ).

Thirteen of 113 participants with chronic gastritis without atrophy of the corpus mucosa at baseline (regardless of *H. pylori* status) had developed atrophy of the corpus mucosa, yielding an incidence of 1.4 per 100 person years. Thirteen of 93 participants with *H. pylori* associated chronic gastritis without atrophy of the corpus mucosa at baseline developed atrophy of the corpus mucosa, resulting in an incidence of 1.1 per 100 person years for this group.

Logistic regression analysis was performed that included all participants with chronic gastritis at baseline. With newly developed atrophy of the corpus mucosa at follow-up examination as the dependent variable, there was a positive association with age at baseline (OR 1.23 [1.08-1.45]) and with more than mild inflammation in the corpus mucosa at baseline (OR 8.98 [1.41-57.23]). When using newly developed atrophy or progression of atrophy of the corpus mucosa as the dependent variable, there was also an association with age at baseline (OR 1.12 [1.04-1.28]) and with the presence of more than mild inflammation in the corpus mucosa at baseline (OR 5.49 [1.68-17.92]). None of the other independent variables at baseline or follow-up examination (sex, BMI, follow-up interval, weekly use of NSAIDs, smoking, weekly consumption of alcohol and *H. pylori* status) were related to newly developed or progression of atrophy of the corpus mucosa.

Using newly developed intestinal metaplasia of the corpus mucosa as the dependent variable, the results were similar to those found using newly developed atrophy as the dependent variable: there was a significant positive association with age and with the presence of more than mild inflammation in the corpus mucosa at baseline.

With atrophy of the antral mucosa as dependent variable along with the independent variables mentioned above there were no significant correlations.

### **Pepsinogens at baseline and at follow-up**

Table 6 shows the PGI/PGII ratios and the frequency of subnormal (< 3.0) PGI/PGII ratios.

The PGI/PGII ratio decreased significantly in all groups. The frequency of subnormal PGI/PGII ratios was unchanged in participants without gastritis and in participants with gastritis without atrophy of the corpus.

Logistic regression analysis was performed that included all participants with chronic gastritis at baseline. Using a newly developed subnormal PGI/PGII ratio (< 3.0) as the dependent variable, there was a positive association with age at baseline (OR 1.13 [1.02-1.45]) and with more than mild inflammation in the corpus mucosa at baseline (OR 22.27 [4.75-104.50]). No other independent variable from baseline or follow-up examination was associated with the development of subnormal PGI/PGII.

## **DISCUSSION**

The aim of this study was to describe and explore the natural history of *H. pylori* infection and chronic gastritis in terms of the dynamics and the development of ulcer. Of 372 eligible subjects, 314 (84.4%) were re-examined after 2657.5 person years. With a longer interval, participation rate would have been lower due to co-morbidity and deaths. On the other hand, since the evolution of chronic gastritis is a slow process, a shorter interval might have been insufficient for documenting progression into atrophy (5, 8, 9, 32).

None of the participants acquired *H. pylori* infection during the follow-up interval. This is

consistent with the observation that de novo infection generally occurs in childhood or youth (28, 42, 43). In a review of 15 population-based publications, Xia et al. found that the annual rate of seroconversion and seroreversion of *H. pylori* infection among adults was 0.2–3.8% and 0.0–2.8%, respectively (42). In a histological study by Niemala et al. 5 of 39 patients (12.8%) became *H. pylori*-negative over a 10-year period (44). Another patient-based histological follow-up study by Villako et al. (n = 139) showed that *H. pylori* infestation had disappeared in the antrum and corpus of 9% and 10%, respectively, over a six-year period. The corresponding frequencies for acquiring *H. pylori* infestation were 9% and 11%, respectively (45).

In the present study, *H. pylori* status changed from positive to negative in 11 of 113 participants (9.7%). One of these 11 participants had unchanged moderate atrophic corpus-predominant gastritis, and two progressed from mild to severe atrophy of the corpus mucosa. In these three participants, the disappearance of the *H. pylori* infection may be explained by the fact that development of significant atrophy can be associated with the disappearance of the *H. pylori* infection (2). None of the other 8 participants developed significant atrophy. Underreporting of antibiotic use might explain some of these cases.

The incidence of ulcer was 0.45 per 100 person years. This figure must be considered an approximation, since subclinical ulcers may have occurred and resolved during the follow-up interval (24). The incidence is somewhat lower than that reported in other studies from the 1990s (26, 37). In a study of 454 outpatients, Sipponen et al. found a 10-year cumulative risk of ulcer of 10.6% among patients with chronic gastritis and of 0.8% in patients without gastritis (37). In the present study, the incidence of ulcer was 0.58 per 100 person years among participants with chronic gastritis. The study by Sipponen et al. only included patients

with dyspepsia, which might explain the difference.

Overall, weekly use of NSAIDs and smoking decreased, whereas alcohol consumption increased (Table 1). There was no significant change in the occurrence of risk factors among the 11 participants with incident subclinical ulcer. Multivariable analysis showed that the occurrence of ulcer was dependent on these three risk factors, but not on *H. pylori* status. The latter finding could be explained by the low number of detected ulcers. However, others have recently reported a relatively high proportion of idiopathic uncomplicated ulcers in the general population (35) as well as among patients with bleeding ulcer (46). We found that 3 of 12 ulcers were idiopathic. In our prevalence (baseline) study published in 2000, which included 501 volunteers, prepyloric or duodenal ulcer was diagnosed in 13 (2.6%) participants, 12 of whom had positive *H. pylori* status (24). In the Kalixanda population based prevalence study (n = 1,001) published in 2006, 4.1% had benign ulcer (20 gastric and 21 duodenal) (35). Eight (38.1%) subjects with duodenal ulcer lacked evidence of *H. pylori* infection. Five (25.0%) of the gastric ulcers and 4 (19.0%) of the duodenal ulcers were classified as idiopathic. Smoking, NSAID intake and high BMI were risk factors for gastric ulcer, and smoking, NSAID use and *H. pylori* infection were risk factors for duodenal ulcer (35).

Atrophy of the gastric corpus mucosa is a major risk factor for the development of adenocarcinoma (8-10). It may also lead to hyperhomocysteinemia, which may be associated with cardiovascular disease (14). As shown in this study and in a study by Siurala et al. (30), age and the degree of inflammation in the corpus mucosa are independent determinants of atrophy development.

Among participants with chronic gastritis without atrophy of the corpus mucosa, the incidence of atrophy of the corpus mucosa was 1.4 per 100 person years. The corresponding

figure for participants with *H. pylori*-associated chronic gastritis was 1.1 per 100 person years. There are very few histomorphological studies of the incidence of atrophic gastritis. Orniston et al. found that 2 of 50 (4.0%) dyspeptic patients developed atrophy of the gastric corpus mucosa in a 5-year follow-up study (27). Villako et al. published a 12-year endoscopic population-based follow-up study with biopsy data showing that the rates of appearance and disappearance of atrophy in the corpus mucosa were quite similar (28). These findings contrasted with earlier findings by the same group (47).

In an 18-year population-based follow-up study by Maaroos et al., atrophy of the corpus mucosa appeared in 22 of 64 (34.3%) subjects and atrophy of the antral mucosa in 7 (10.9%) (31). We found great variability in the occurrence and degree of antral mucosal atrophy. As illustrated by the Kappa analysis, intra-examiner error was greatest for histomorphological evaluation of antral mucosal atrophy. Furthermore, as indicated by the results of other prospective studies, it seems that regardless of *H. pylori*, even moderate-to-severe antral mucosal atrophy can revert over time (27, 28, 31).

We are not aware of any patient- or population-based study on the natural history of chronic gastritis without *H. pylori* infection. Although at that time, the existence of *H. pylori* was not generally known, in 1982 Orniston et al. reported in a patient-based five-year follow-up study that gastritis is a variable process (27). In the present study, chronic gastritis disappeared in 18 of 27 participants without *H. pylori* infection. Furthermore, chronic gastritis appeared in 15 of 173 participants without gastritis or *H. pylori* infection. It seems that chronic gastritis without *H. pylori* infection is frequently a reversible and temporary condition. This could be explained by variations in the occurrence of risk factors, such as use of NSAIDs, alcohol consumption

and smoking. However, as illustrated in this study, some subjects (4/27) presented with significant corpus-predominant atrophy and negative *H. pylori* status upon initial screening (baseline). The degree of atrophy in these subjects was unchanged at follow-up examination. Among 139 participants with gastritis at baseline, mild atrophy of the corpus mucosa had disappeared in 7 and moderate atrophy in 1.

In general, there was good agreement between the histomorphological findings and the results of the pepsinogen analyses. The PGI/PGII ratio decreased significantly among participants with chronic gastritis as well as in participants without gastritis. The latter finding indicates that PGI/PGII decreases with age even in the absence of chronic gastritis. Although this is still somewhat controversial, other studies have shown similar results (16). The decrease in PGI/PGII levels among participants without gastritis was not paralleled by a decrease in the frequency of subnormal PGI/PGII. An increased incidence of subnormal PGI/PGII was observed only in participants with atrophy of the corpus mucosa.

As with histomorphologically determined atrophy of the corpus mucosa, PGI/PGII levels among subjects with chronic gastritis were positively associated with age and with the degree of inflammation in the corpus mucosa at baseline.

In conclusion, the minimum incidence of ulcer was 0.45 per 100 person years overall and 0.58 per 100 person years among subjects with chronic gastritis. Use of NSAIDs, alcohol consumption and smoking were risk factors for ulcer disease. Idiopathic ulcer occurred in 3 of 12 participants, of whom 5 had negative *H. pylori* status; indeed, *H. pylori* status did not emerge as a significant risk factor. The incidence of atrophy of the corpus mucosa was 1.4 per

100 person years for gastritis overall, and 1.1 per 100 person years for *H. pylori*-associated gastritis. Chronic gastritis with or without *H. pylori* infection was shown to be a variable process in which milder degrees of atrophy of the corpus mucosa could appear or disappear. In contrast, moderate-to-severe atrophy rarely regressed. Age and the degree of chronic inflammation in the gastric corpus mucosa were major risk factors for development of atrophy.

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**Table 1.** Putative risk factors for gastritis or ulcer at baseline and at follow-up in the study population.

Risk factor	No. of responding participants <sup>a,b</sup>	Baseline No. (%)	Follow-up No. (%)	P-value McNemar's test
NSAID, weekly use	281	42 (14.9)	26 (9.3)	0.034
Alcohol, weekly use	281	52 (18.5)	72 (25.6)	0.008
Smoking	286	50 (17.5)	30 (10.5)	0.001
Gastritis with positive <i>H. pylori</i> status	313	113 (36.1)	102 (32.6)	0.001
Gastritis with negative <i>H. pylori</i> status	313	27 (8.6)	32 (10.2)	0.532

a: some participants did not answer all of the lifestyle questions

b: one participant who was diagnosed with and treated for *H. pylori*-associated duodenal ulcer between examinations was excluded.

**Table 2.** Putative risk factors for ulcer at baseline and at follow-up among participants with and without incident ulcer at follow-up examination.

Risk factor	Ulcer <sup>a</sup>	No ulcer <sup>a</sup>	P-value Fisher's exact test
NSAIDs, weekly use at baseline	2/12	46/293	> 0.999
Alcohol, weekly use at baseline	6/12	50/297	0.011
Smoking at baseline	7/12	47/299	0.001
Positive <i>H. pylori</i> status at baseline	7/12	107/302	0.129
NSAIDs, weekly use at follow-up	5/11	21/278	0.001
Alcohol, weekly use at follow-up	8/11	65/275	0.001
Smoking at follow-up	5/11	26/278	0.003
Positive <i>H. pylori</i> status at follow-up	6/11	96/302	0.186

a: some participants did not answer all of the lifestyle questions

**Table 3.** Topography and severity scores for chronic gastritis according to the Sydney system at baseline and at follow-up in 113 participants with positive *H. pylori* status at baseline.

Baseline				Follow-up												
Topography	Severity	Atrophy	No. at baseline	No gastritis	Antrum-predominant				Pangastritis				Corpus-predominant			
					Mild		Moderate-severe		Mild		Moderate-severe		Mild		Moderate-severe	
					Atrophy		Atrophy		Atrophy		Atrophy		Atrophy		Atrophy	
					No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Antrum-predominant	Mild	No	4			1			1		1			1		
		Yes	35	1 <sup>b</sup>		10		2	9		9	2 <sup>b</sup>		1	1	
	Moderate-severe	No	2								2					
		Yes	9	1 <sup>b</sup>		1					3 <sup>a</sup>	2		2		
Pangastritis	Mild	No	17			1			9 <sup>b</sup>		6 <sup>a</sup>				1	
		Yes	3								1		1	1		
	Moderate-severe	No	26	1 <sup>b</sup>	1	3	1	2	3 <sup>b</sup>	2	12			1		
		Yes	5							2 <sup>b</sup>	1			1	1	
Corpus-predominant	Mild	No	1						1 <sup>b</sup>							
		Yes	9						2	1	2			1 <sup>b</sup>	3 <sup>b</sup>	
	Moderate-severe	No														
		Yes	2							1					1 <sup>b</sup>	

a: glandular atrophy could not be evaluated in one participant. b: *H. pylori* status was negative at follow-up examination in one participant.

**Table 4.** Follow-up data in 11 participants who showed a change from positive to negative *H. pylori* status during the follow-up interval. At follow-up examination, none were infected with *H. pylori* according to histological examination or a urease test of gastric biopsies.

Participant No.	Positive <i>H. pylori</i> serology at follow-up	Antibiotics taken temporarily during follow-up interval	PPI or H2 receptor antagonist taken temporarily during follow-up interval	Chronic gastritis, Type <sup>a</sup> ; severity <sup>b</sup>		Change in severity during follow-up
				Baseline	Follow-up	
7	1	0	0	4 ; 2	4 ; 1	regressed
75	1	1	0	3 ; 2	3 ; 1	regressed
76	0	1	0	6 ; 1	6 ; 3	progressed
140	0	0	1	6 ; 1	6 ; 1	unchanged
160	0	0	0	2 ; 2	0 ; 0	normalised
347	1	1	1	2 ; 1	0 ; 0	normalised
359	1	0	0	6 ; 2	6 ; 2	unchanged
414	1	0	0	3 ; 1	3 ; 1	unchanged
419	0	0	1	3 ; 2	0 ; 0	normalised
442	0	0	0	5 ; 1	3 ; 1	unchanged
459	1	1	1	2 ; 1	4 ; 3	progressed

a: 0 = none; 1 = antrum-predominant without atrophy; 2 = antrum-predominant with atrophy; 3 = pangastritis without atrophy; 4 = pangastritis with atrophy; 5 = corpus-predominant without atrophy; 6 = corpus-predominant with atrophy.

b: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

**Table 5.** Atrophy of the gastric corpus (A) and antral (B) mucosa in the study population was scored using the Sydney classification system at baseline and at follow-up in participants with chronic gastritis with or without positive *H. pylori* status at baseline.

**A**

Atrophy score	Baseline	Follow-up
	No. (%)	No. (%)
None	113 (81.3)	108 (77.7)
Mild	17 (12.2)	14 (10.1)
Moderate	6 (4.3)	12 (8.6)
Severe	3 (2.2)	5 (3.6)
Total <sup>a</sup>	139 (100.0)	139 (100)

a: Atrophy of the corpus mucosa could not be evaluated in 1 of the 140 participants.

P < 0.001 (Chi-square test)

**B**

Atrophy score	Baseline	Follow-up
	No. (%)	No. (%)
None	78 (56.5)	107 (77.5)
Mild	49 (35.5)	25 (18.1)
Moderate	11 (8.0)	1 (0.7)
Severe	0 (0.0)	5 (3.6)
Total <sup>a</sup>	138 (100.0)	138 (99.9)

a: Atrophy of the antral mucosa could not be evaluated in 2 of the 140 participants.

P = 0.142 (Chi-square test)

**Table 6.**

A: The pepsinogen I/pepsinogen II ratio at baseline and at follow-up in subgroups of the study population.

B: The frequency of subnormal (< 3.0) pepsinogen I/pepsinogen II ratios at baseline and at follow-up in subgroups of the study population.

## A

Group	No. of participants examined	Baseline, median (range)	Follow-up, median (range)	P-value Wilcoxon signed rank test
No gastritis	164	11.7 (3.3-23.6)	8.2 (1.2-15.6)	< 0.001
Gastritis without atrophy in corpus	109	8.1 (2-4-18.0) <sup>a</sup>	5.9 (1.6-14.0) <sup>a</sup>	< 0.001
Gastritis with atrophy in corpus (grade 1-3)	25	4.8 (0.8-9.0) <sup>a</sup>	2.9 (0.6-6.9) <sup>a</sup>	< 0.001

a: P < 0.001 as compared with no gastritis (Mann-Whitney U-test).

## B

Group	No. of participants examined	Baseline No. (%)	Follow-up No. (%)	P-value McNemar's test
No gastritis	164	0 (0.0)	1 (0.6)	> 0.999
Gastritis without atrophy in corpus	109	2 (1.8)	7 (6.4)	0.180
Gastritis with atrophy in corpus (grade 1-3)	25	7 (28.0)	14 (56.0)	0.039