The natural course of *Helicobacter pylori* in gastritis, peptic ulcer disease and reflux oesophagitis in a population-based prospective cohort: The Sørreisa Gastrointestinal Disorder Study

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Abbreviations: *H. pylori* = *Helicobacter pylori,* OR = Odds ratio, CI = Confidence interval, ASA = Acetylsalicylic acid, NSAIDs = Non-steroid anti-inflammatory drugs, PU = Peptic ulcer, GORD = Gastro-oesophageal reflux disease.

ABSTRACT

Objective To study the natural course of *Helicobacter pylori* (*H. pylori*) and its associations to morphological changes of the gastric mucosa, peptic ulcer (PU) and reflux oesophagitis.

Design Prospective population-based cohort study in Norway (1987-2004), following 361 subjects from a general population with *H. pylori* assessment, upper endoscopy and a questionnaire on gastrointestinal symptoms.

Results *H. pylori* was strongly associated with neutrophilic (odds ratio (OR) 23.79 (95% CI 11.64-48.61)) and mononuclear infiltration (OR 9.43 (5.12-17.36)), moderately with atrophy of the antrum (OR 1.98 (1.17-3.34)), but not associated with atrophy of the gastric body or intestinal metaplasia. Elimination, whatever reason, of *H. pylori* was associated with regression of both gastric inflammation and atrophy, whereas intestinal metaplasia progressed. *H. pylori* was positively associated with PU (OR 2.92 (1.18-7.26)) and negatively associated with oesophagitis (0.34 (0.17-0.68)) in men but not in women. Men ran a higher risk than women of both PU and oesophagitis.

Conclusions This is the first prospective population based study to show that *Helicobacter pylori* is associated with inflammation of the gastric mucosa, which regresses after *H. pylori* elimination. The impact of *H. pylori* on more chronic morphological changes is less obvious, and eliminating *H. pylori* does not cause regression of intestinal metaplasia. *H. pylori* is only a moderate risk factor for peptic ulcer, and other risk factors deserve more attention. The protective effect of *H. pylori* on erosive oesophagitis implies that the future burden of reflux disease may rise with decreasing prevalence of *H. pylori*.

INTRODUCTION

The natural course of hosting *Helicobacter pylori* is not well studied, as it was first described by Marshall and Warren in 1984.[1] Since then time has had to pass in order to address the question properly.

H. pylori is recognised as a carcinogen and is close to being a necessary, but not a sufficient cause of gastric cancer, as host and environmental factors also contribute.[2] Even though *H. pylori* leads to inflammation, atrophy and metaplasia, only a small minority of persons hosting *H. pylori* develop gastric cancer.[3]

H. pylori is a sufficient, yet not a necessary cause of peptic ulcer (PU) and inflammation of the gastric mucosa.[4 5] With decreasing prevalence, the role of *H. pylori* as the major risk factor for PU disease is challenged in Western Europe, Australia, and the United States.[6-8]

The role of *H. pylori* in gastro-oesophageal reflux disease (GORD) is unclear. Both a lack of association and a beneficial effect of hosting *H. pylori* are reported.[4]

Prospective cohort studies published in this field are scarce, and most are based on serologic assessment of *H. pylori*.

The objectives of this study was to assess the role of *H. pylori* on morphological changes of the gastric mucosa, and to assess whether *H. pylori* in a general population is a risk factor for the development of peptic ulcer or reflux oesophagitis.

METHODS

Setting

The Sørreisa Gastrointestinal Disorder Study addresses a general, adult population in the municipality of Sørreisa, Northern Norway. The population of Sørreisa is about 3500 and is comparable with the general population of Norway regarding age and gender distribution, income and educational levels.

Participants

In 1987, a questionnaire on gastrointestinal disorders and lifestyle was sent to all 2068 adult citizens, of which 1802 answered. Results of this cross-sectional study have been published earlier.[9-13] Dyspepsia was reported by 495 subjects, who were invited to partake in upper endoscopy together with a control group matched for gender and ten-year age group. The aim in 1987 was to focus on non-ulcer dyspepsia, therefore subjects with a previous history of known abdominal conditions, such as PU, gallstones and kidney stones were excluded from the study. A previous history of coronary heart disease was also an exclusion criterion due to the risk of complications at upper endoscopy. Among subjects reporting dyspepsia, 137 were excluded, of which 68 had a history of PU. Eventually, 309 subjects reporting dyspepsia and 310 controls underwent upper endoscopy (Figure 1).

In 2004 we readdressed the population of Sørreisa in order to collect data by means of a questionnaire survey on gastrointestinal disorders, stool samples for detection of *H. pylori*, as well as upper endoscopy.

Predictor variables

Helicobacter pylori

The presence of *H. pylori* in 1987 was diagnosed by culture of biopsies obtained at upper endoscopy. We have revised these results by reassessing biopsies from 1987 for the presence of *H. pylori*, with the investigator blinded to the previous findings. Specimens were formalin-fixed and paraffin-embedded according to standard procedures, and cut into 3-4 μm sections for conventional histology (haematoxylin–eosin stained) and for staining with periodic acid-Schiff. The slides were evaluated by an experienced

pathologist (co-author SES) and assessed for the presence *of H. pylori*. Subjects testing *H. pylori* negative in 1987 were recoded to *H. pylori* positive if their biopsies from 1987 revealed *H. pylori*-like organisms.

In 2004, *H. pylori* presence was assessed by antigen detection in stool samples using a commercial ELISA kit (*H. pylori* STaR, DakoCytomation, Glostrup, Denmark) with a known sensitivity of 98% and specificity of 94%.[14]

Questionnaire data – 1987

Age, in ten-year age groups, was used as a categorical variable in analyses of PU and oesophagitis. Dyspepsia was assessed with the questions ”Have you ever had abdominal pain located in the upper abdomen for at least 2 weeks?“ and ”Have you ever had heartburn or acid regurgitation almost daily for at least 1 week?”.[9] A positive answer to one or both questions defined dyspepsia. Responders scored their financial situation as “Very good”, “Good”, “Difficult” or “Very difficult”. Physical exercise for at least 20 minutes to the extend of breaking sweat or shortness of breath was measured as “Seldom or never”, “Weekly”, “Several times a week” or “Almost daily”. In subsequent analyses the variables on financial situation and physical exercise were dichotomised with the first two and the last two categories pooled. Smoking habits were assessed by the question “Do you smoke cigarettes daily (yes or no)?” Alcohol consumption was measured as sporadic consumption, and the threshold for a positive answer was thus low. Both alcohol consumption and smoking were quantified in the questionnaire, as was information on previous smoking habits, but analyses taking this into consideration did not change the results compared with analyses using the simple dichotomous variables.

Stress was scored by the question “Have you, for the last two months, felt incapable of handling your problems?” Options for answer were “Seldom or never”, “Sometimes”, “Often”, and “Always”. Only 5 subjects answered “Always” and in the analyses the two last categories have been pooled. The use of non-steroid anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) was assessed dichotomously by asking if such drugs were used often. Participants were also asked if they used antacids or H2-antagonists.

Outcome variables

Morphological changes in the gastric mucosa were assessed in biopsy specimens obtained at endoscopy in 1987 and 2004, and scored according to the upgraded Sydney classification.[15] Biopsy samples were processed as described above.

Peptic ulcer was a composite of either self-reported ulcer in the questionnaire in 2004 or ulcer diagnosed at endoscopy in 1987 or 2004. Only 31 reported or were found to have PU; 12 had gastric ulcer, 11 had duodenal ulcer and 8 had both types. The numbers were too small to justify analyses stratified by type of ulcer. Oesophagitis was scored according to the Los Angeles classification,[16] but later dichotomized as the presence or absence of mucosal erosions.

Statistical methods

The morphological variables of the Sydney classification were scored on an ordinal scale; 0; Normal, 1; Mild, 2; Moderate 3; Marked. In the analyses of predictors of morphological appearance, we have used binary logistic regression (category 1-3 versus 0), as neither ordinal nor multinomial logistic regression models fit the data. For the analyses of variance of the changes between 1987 and 2004 in the Sydney classification scores, we have considered the scale of the Sydney classification to be continuous and have used the mean scores and changes of mean scores in the analyses.

Dichotomous outcome variables were analysed with logistic regression. The numbers of outcome-positive cases in the analyses of PU and oesophagitis were small (varying from 6 to 60) and the predictor variables of interest were too many to fit into a single multiple logistic regression model. Therefore, each outcome variable was analysed in three steps as follows: 1) Univariable analyses of all predictors of interest, 2) A maximum of 4 predictors with a p value less than 0.25 were then included in 2-3 intermediary multiple logistic regression models (forced entry). Demographic variables such as age, gender and financial situation were considered in one model, whereas other risk factors such as *H. pylori*, smoking and alcohol consumption were analysed in 1-2 separate models. 3) The most significant predictors from the intermediary analyses, in addition to clinically relevant predictors (e.g. *H. pylori* and dyspepsia) made up the final multiple logistic regression models (forced entry).

In the logistic regression models we tested interaction between gender and the other predictor variables, because of a skewed risk of both peptic ulcer and oesophagitis between genders.

RESULTS

Among the 619 subjects enrolled in the Sørreisa Gastrointestinal Disorder Study who underwent endoscopy in 1987, 361 provided information at follow-up in 2004. Responders provided data in one or more parts of the study; questionnaire, *H. pylori* testing or endoscopy. Thus the numbers of participants in the different analyses vary (Figure 1). Table 1 presents baseline characteristics of the questionnaire responders as well as the subgroup who accepted upper endoscopy, between which there were no significant differences (data not shown).

The slight predominance of men (55.7%) in the study and the prevalence of dyspepsia of about 50 % reflect the study design of 1987. The response was somewhat higher in the older age group. The histological assessment of biopsies from the gastric mucosa revealed that marked changes were a rare finding and normal mucosa was the most common finding.

Risk factors for gastric mucosal inflammation, atrophy and metaplasia

Possible risk factors of gastritis in 1987 and their association with morphological changes measured by the Sydney classification in 2004 are presented in multivariable analyses in Table 2.

H. pylori was a strong predictor of neutrophilic and mononuclear infiltration, and was also a significant, but not strong predictor of atrophy of the antrum. Increasing age, but not *H. pylori,* was a risk factor for atrophy of the gastric body and for intestinal metaplasia. Daily smoking was an independent risk factor for atrophy of the gastric body and intestinal metaplasia. No gender differences or interaction between predictor variables were seen (data not shown).

Morphological changes in relation to persistence or change of *H. pylori* presence

A total of 272 subjects were tested for *H. pylori* both in 1987 and in 2004, and the persistence or changes of the occurrence of *H. pylori* are presented in table 3.

Among the 140 subjects originally *H. pylori* positive in the cohort, 39 (28%) had become negative, and 19 of these reported having had triple therapy (9 women, 10 men). The remaining 20 subjects (14%) may have cleared *H. pylori* spontaneously or by antibiotic treatment not directed at *H. pylori* eradication. Among 132 originally *H. pylori* negative subjects, 18 (14 %) contracted *H. pylori* between 1987 and 2004.

The morphological changes of the gastric mucosa during the period of follow-up are addressed in table 4. In subjects persistently negative for *H. pylori*, a slight increase in mononuclear infiltration, atrophy of the antrum and intestinal metaplasia was seen. These changes are attributed to increased age and form the basis for the adjustment of the changes in the other groups.

It appears that persistence or change of *H. pylori* is an important predictor of inflammation, as the model fit parameter, R^2, is 0.29 for neutrophilic infiltration and 0.27 for mononuclear infiltration. In contrast, *H. pylori* has a modest role as risk factor for the development of atrophy and intestinal metaplasia, with R^2 values of 0.02 and 0.03 respectively.

In subjects persistently hosting *H. pylori*, signs of inflammation increased significantly, whereas atrophy and intestinal metaplasia did not. These patterns were even more pronounced in subjects contracting *H. pylori* after 1987. In the *H. pylori* elimination group, signs of inflammation and atrophy decreased, but the grade of intestinal metaplasia increased.

Adding smoking habits to the model presented in table 4 revealed that continuous smoking is strongly associated with increasing atrophy of the gastric body ($p = 0.004$) and that cessation of smoking causes regression of mononuclear infiltration ($p = 0.044$). Otherwise, smoking did not change the results (data not shown).

Risk factors for the occurrence of peptic ulcer

PUs were reported by or found in 31 (8.9%) of the study subjects, 21 (68%) of whom were *H. pylori* positive in 1987. Ulcers were more frequent in men (n = 25) than in women (n = 6).

Table 5 shows the results of both univariable and multivariable logistic regression analyses. In analyses including both genders, being male was strongly associated with PU, whereas *H. pylori* and smoking were moderate risk factors. In analyses stratified by gender, *H. pylori* was a significant risk factor for PU only in men. In women, the use of ASA was the only independent risk factor for PU.

Risk factors for oesophagitis

In all, 80 (29.5 %) of the 271 subjects who underwent upper endoscopy, 60 men and 20 women, were found to have oesophagitis. Table 6 presents results of logistic regression analyses of risk factors for oesophagitis. *H. pylori* was a protective factor for the development of oesophagitis in men independent of smoking, but not in women. Male gender was independently associated with oesophagitis.

DISCUSSION

In this prospective cohort study we have followed 361 patients over a period of 17 years and compared risk factors in 1987 with clinical and endoscopic end-points in 2004. We found that hosting *H. pylori* was a major risk factor for neutrophilic and mononuclear infiltration of the gastric mucosa but not for atrophy of the gastric body and intestinal metaplasia. Elimination of *H. pylori* caused regression of gastritis and atrophy, but not regression of intestinal metaplasia once it had developed. *H. pylori* was a moderate risk factor for PU and a protective factor of oesophagitis in men but not in women. However, the power of the estimate for women was low. Smoking was an independent risk factor for peptic ulcer, atrophy and intestinal metaplasia.

Limitations and strengths

The case–control design of the endoscopy examinations in 1987 implies that the prevalence of dyspepsia in the study population was 50% at start, which represent a selection bias, as the prevalence of *H. pylori* in the 1987 cohort of 48% (unadjusted) probably is somewhat higher than what would be expected in the general population. However, the high prevalence of *H. pylori* in the study population is also a reflection of the prevalence at the time of selection, and of the fact that response was highest in the higher age-groups.

Few studies have addressed *H. pylori* occurrence in a general population in a prospective cohort study, without informing or treating positive subjects. Some cohort studies are based on *H. pylori* serology obtained from samples collected in previous population-based studies.[17 18] Studies using serology tend to overestimate the actual prevalence of *H. pylori*. In contrast, the bacteriological culture used for *H. pylori* detection in our study in 1987 is believed to underestimate the prevalence. We have improved the accuracy of the prevalence measurements from 1987 by a revised assessment of *H. pylori*. The morphological assessment of biopsies from gastric mucosa from both 1987 and 2004 also adds strength to our study.

The outcome measure of PU is partly self-reported, a method that tends to overestimate PU disease by approximately 15%.[9] An implication of this is that the interpretation of risk factors of PU should be done with care, especially in women where the number of ulcers was low.

In the analysis of risk factors for oesophagitis we chose a dichotomous score as this was more suitable for the limited number of cases. In addition, dichotomising the scale minimises observer variation, which is prominent in upper endoscopy.[19] All endoscopies in 2004 in this study were carried out by the one of the authors (AMA), thus optimizing the internal validity, but not necessarily the external validity of the study.

Stratification by gender in the analyses of PU and oesophagitis results in smaller groups and subsequent loss of power, which especially is a concern in the analyses concerning women.

Interpretation

Gastritis

H. pylori was strongly associated with inflammation of the gastric mucosa, which is a finding often reported.[20] The association with atrophy and intestinal metaplasia was weaker. Atrophy and intestinal metaplasia develop over a longer period of time than does inflammation, and these chronic changes are associated with spontaneous elimination of *H. pylori*.[21] Even a follow-up of 17 years may be too short to avoid misclassification of *H. pylori* presence, and to fully comprise the role of *H. pylori*. The role of smoking in gastric inflammation and atrophy is controversial. A recent study showed smoking to be protective against gastric atrophy in *H. pylori* infected patients,[22] whereas others report smoking to be a risk factor for gastric atrophy.[23] These are cross-sectional studies, whereas our study is a prospective cohort study addressing changes over time, which strengthen our finding of smoking being harmful.

Persistence and change of *H. pylori*

Our finding of 13% contracting *H. pylori* over 17 years may be a slight overestimation, as the detection in 2004 by monoclonal *H. pylori* antigen in stool samples is a more sensitive diagnostic tool than the 1987 method of culture and histology.[24] However, our findings demonstrates that *H. pylori* can be contracted in adulthood. Of similar interest is that 20 (14%) originally *H. pylori* positive had un-intended cleared *H. pylori*. Other studies support our finding that un-intended elimination of *H. pylori* seems to be more common than the contraction of *H. pylori* in adult life.[25 26]

Subjects who were persistently negative for *H. pylori* also developed some degree of intestinal metaplasia, which seems to be part of the normal ageing process. It is, however, also possible that some of these subjects had been *H. pylori* positive with spontaneous clearance prior to 1987. Of further importance is that elimination of *H. pylori* is associated with regression of most morphological changes except for intestinal metaplasia, supporting the idea of a "point of no return" in the pathogenesis of *H. pylori* leading to precancerous lesions.[21]

Peptic ulcer

We found *H. pylori* to be a moderate predictor of PU only in men, who were also at a higher risk of having PU than women. The male to female ratios of PU vary in different studies, but is mostly higher than 1.[27 28] The estimated risk of PU associated with *H. pylori* found by us is lower than reported elsewhere,[17 29] which may reflect the population-based design of the study. However, this is also an indication of the importance of considering other causes than *H. pylori* when dealing with PU patients in a time of decreasing *H. pylori* prevalence.[30 31] Smoking predicts PU in multivariable analyses including both genders. A Danish cohort study also reported smoking to be an important risk factor for PU.[17] and smoking has been recognised as a risk factor for PU even before the discovery of *H. pylori.*[32] The use of alcohol is considered a risk factor for PU,[5 33] a finding that we were not able to confirm. It is well documented that both NSAIDs and ASA are associated with increased risk of PU.[33 34] We found ASA use to be a risk factor for PU in women but not in men. In a relatively small observational study such as ours there may well be a selection bias towards ASA and NSAID use among subjects with a "healthy" stomach, thus masking the harmful effect.

Increasing age was not a risk factor for PU, yet we saw a peak of ulcer occurrence in the age group of 40-49 years regardless of *H. pylori* status (data not shown). Other epidemiological studies have reported an increasing risk of ulcers with increasing age.[35 36]

Reflux oesophagitis

The role of *H. pylori* in oesophagitis is ambiguous. Pan-gastritis caused by *H. pylori* decreases acid secretion, could be protective against development of oesophagitis.[4] We found *H. pylori* to be protective of oesophagitis in men only. Men were also at higher risk of oesophagitis than women, a finding earlier reported in a case-control study,[37] as well as in a population-based cross-sectional study.[38]

CONCLUSION

Following a general population for 17 years reveals that *H. pylori* is strongly associated with inflammation of the gastric mucosa, moderately associated to atrophy of the antrum, but not to atrophy of the gastric body or intestinal metaplasia. Eliminating H. pylori causes regression of signs of inflammation, but does not normalize intestinal metaplasia. *H. pylori* is only a moderate risk factor for PU in men, whereas in women the use of ASA seems more important. Men run a higher risk than women of both peptic ulcer and oesophagitis. The protective effect of *H. pylori* against the development of oesophagitis in men may imply a future increased burden of GORD.

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Competing interests: None

Ethical considerations: The Regional Committee for Medical Research Ethics approved the study. Licence to register the participants was granted by the Norwegian Data Inspectorate. Participants gave written informed consent.

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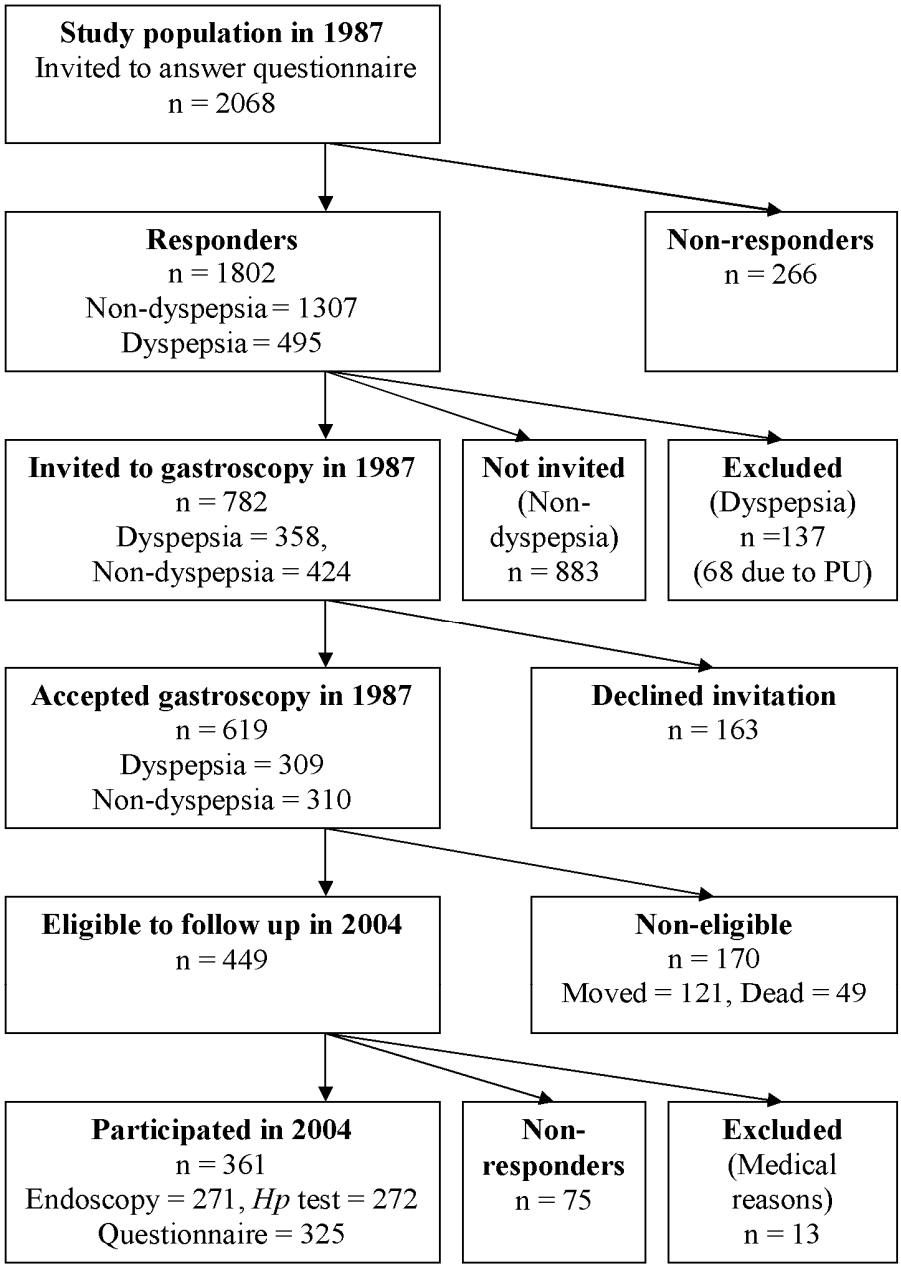
Figure 1: Overview of study subjects
in the Sørreisa Gastrointestinal Disorder Study in 1987 and 2004



Hp: *Helicobacter pylori*, PU: Peptic ulcer.

Table 1. Baseline characteristics of the cohort of 361 subjects answering the questionnaire in 1987 and the subgroup of 271 subjects examined with upper endoscopy in 2004.

Risk factors in 1987		Questionnaire responders N (%) 361[a]	Upper endoscopy participants N (%) 271[a]
Gender	Male	201 (55.7%)	157 (57.9%)
	Female	160 (44.3%)	114 (42%)
Age group	20-39	158 (43.8%)	117 (43.2%)
	40-69	203 (55.7%)	154 (56.8%)
H. pylori presence		176 (48%)	141 (52%)
Dyspepsia		185 (51.2%)	146 (53.9%)
Financial situation	Difficult	61 (16.9%)	46 (17.6%)
	Good	290 (82.6%)	215 (82.4%)
Daily smoking		139 (38.5%)	102 (37.6%)
Alcohol consumption		319 (88.6%)	243 (90%)
Stress	Seldom or never	240 (68.8%)	183 (69.8%)
	Sometimes	98 (28.1%)	70 (26.7%)
	Often or more	11 (3.2%)	9 (3.4%)
Physical exercise	Weekly or more	183 (52%)	144 (53.9%)
	Seldom or never	169 (48%)	123 (46.1%)
ASA use		49 (14.1%)	38 (14.6%)
NSAID use		12 (3.5%)	10 (4%)
Antacid use		67 (18.9%)	54 (20.3%)
H2 antagonist use		8 (2.3%)	7 (2.7%)

[a]Due to missing values in the questionnaire in 1987, the frequencies of the risk factors are measured among valid answers, varying between 340-361 (questionnaire responders) and 253-270 (upper endoscopy participants).

Table 2. Predictors of morphological appearance in biopsies from the pyloric antrum and body stomach according to the updated Sydney classification. Multivariable logistic regression[a].

	2004				
	Infiltration		Atrophy		Intestinal
	Neutrophilic	Mononuclear	Antrum	Gastric body	metaplasia
Risk factor in 1987	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI
Age	1.03 (0.996:1.063)	1.02 (0.99:1.05)	1.03 (1.01:1.06)	1.04 (1.01:1.08)	1.07 (1.03:1.11)
Male gender (female ref.)	0.99 (0.50:1.94)	0.85 (0.46:1.57)	0.88 (0.51:1.53)	1.35 (0.65:2.79)	0.84 (0.43:1.67)
H. pylori presence	23.79 (11.64:48.61)	9.43 (5.12:17.36)	1.98 (1.17:3.34)	1.27 (0.64:2.53)	1.60 (0.82:3.12)
ASA use	0.71 (0.28:1.79)	0.80 (0.33:1.91)	0.48 (0.22:1.05)	0.86 (0.31:2.37)	0.91 (0.36:2.30)
Daily smoking	1.33 (0.68:2.63)	0.83 (0.45:1.53)	1.74 (0.99:3.05)	2.46 (1.24:4.88)	2.09 (1.08:4.04)
N	259	259	256	249	259
Model fit; R^2	0.49	0.32	0.10	0.10	0.15

Analyses of interaction between gender and predictor variables were all non-significant for all 5 outcome variables.

[a]The binary outcome variables are coded as Sydney classification category 1-3 versus 0.

Table 3. Persistence and change of *H. pylori* infection between 1987 and 2004.

	2004 [b]		
1987 [a]	*H. pylori* negative (men/women)	*H. pylori* positive (men/women)	Total
H. pylori negative	114 (50/64)[c]	18 (11/7)[c]	132
H. pylori positive	39 (15/24)[c]	101 (50/51)[c]	140
Total	153	119	272

[a]*H. pylori* diagnosis based on bacteriological culture in 1987 and revised after blinded reassessment of histology specimens.

[b]*H. pylori* diagnosis based on antigen detection in stool samples.

[c]Differences between genders are not significant (data not shown).

Table 4. Mean changes in the Sydney classification scores after 17 years according to persistence of, elimination of, or contraction of *H. pylori*, adjusted for natural morphologic changes.

	Infiltration				Atrophy				Intestinal metaplasia	
	Neutrophilic		Mononuclear		Antrum		Gastric body			
H. pylori	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N
Persistently negative[c]										
1987	0.11	83	0.23	83	0.39	77	0.08	80	0.02	83
2004	0.08	90	0.39	90	0.65	89	0.18	87	0.13	90
Change[b]	-0.02	83	0.19	83	0.32	76	0.12	78	0.12	83
Adjusted change (95% CI)	-0.02 (ref) (-0.19: 0.14)		0.19 (ref) (0.04: 0.35)		0.32 (ref) (0.10: 0.53)		0.12 (ref) (-0.01: 0.24)		0.12 (ref) (0.02: 0.22)	
Eliminators										
1987	0.84	31	1.26	31	0.86	28	0.37	30	0.00	31
2004	0.22	32	0.53	32	0.56	32	0.23	31	0.34	32
Change[b]	-0.65	31	-0.74	31	-0.25	28	-0.14	29	0.35	31
Adjusted change (95% CI)	-0.62 (-0.94: -0.30)		-0.94 (-1.23: -0.64)		-0.57 (-0.98: -0.15)		-0.25 (-0.49: -0.02)		0.23 (0.04: 0.43)	
Persistently positive										
1987	0.82	79	1.35	79	0.9	77	0.27	77	0.15	79
2004	1.45	83	1.76	83	1.05	83	0.25	80	0.27	83
Change[b]	0.68	77	0.42	77	0.17	76	0.01	72	0.16	77
Adjusted change (95% CI)	0.70 (0.46: 0.94)		0.22 (0.002: 0.44)		-0.15 (-0.45: 0.16)		-0.10 (-0.27: 0.07)		0.04 (-0.11: 0.18)	
Contractors										
1987	0.10	10	0.3	10	0.44	9	0.13	8	0.5	10
2004	1.09	11	1.36	11	0.80	10	0.50	10	0.36	11
Change[b]	0.90	10	1.1	10	0.44	9	0.25	8	-0.1	10
Adjusted change (95% CI)	0.92 (0.42: 1.43)		0.91 (0.44: 1.37)		0.13 (-0.54: 0.79)		0.14 (-0.26: 0.53)		-0.22 (-0.54: 0.10)	
Model fit R^2	0.29		0.27		0.03		0.02		0.03	

[a]The Sydney classification are scored as; [a]0: normal, 1; mild, 2; moderate 3; marked. The mean reflects this coding.
[b]The changes in mean are calculated at individual level.
[c]Adjusted change is estimated with analysis of variance with subjects persistently *H. pylori* negative as reference category.

Table 5. Association between risks factors in 1987, including *H. pylori* presence, and peptic ulcer in 2004. Logistic regression.

	Peptic ulcer disease 2004											
	Univariable analyses						Multivariable adjusted analyses					
	Women		Men		Both		Women		Men		Both	
Risk factors in 1987	OR	p	OR	p	OR	p	OR	95% CI	OR	95% CI	OR	95% CI
Male gender (female ref.)					3.67	s					4.18	(1.58: 11.03)
Age (ten-year groups) [a]		ns		ns		ns						
Financial situation[d]	1.48	ns	2.45	ns	2.5	s						
H. pylori presence	1.90	ns	2.9	s	2.42	s	1.76	(0.29: 10.78)	2.92	(1.18: 7.26)	2.77	(1.23: 6.24)
Daily smoking	4.42	ns	1.78	ns	2.38	s	3.74	(0.62: 22.50)	1.97	(0.83: 4.73)	2.19	(1.01: 4.76)
Alcohol consumption	-[c]	-[c]	1.61	ns	4.17	ns						
Dyspepsia in 1987	1.11	ns	1.91	ns	1.81	ns	0.72	(0.13: 4.12)	1.79	(0.71: 4.48)	1.44	(0.65: 3.20)
Stress	1.28	ns	1.37	ns	1.17	ns						
Exercise[d]	0.57	ns	1.31	ns	1.22	ns						
NSAID use	3.04	ns	0.0	ns	0.90	ns						
ASA use	7.87	s	0.46	ns	1.19 [b]	ns	7.15	(1.25: 45.03)	0.40	(0.05: 3.30)	1.63	(0.55: 4.88)
Antacid use	2.14	ns	3.69	s	3.08	s						
H2 antagonist use	3.94	ns	0.84	ns	1.27	ns						
Model fit; R2							0.19		0.10		0.14	
n/N							6/154		25/193		31/347	

P values are considered significant if < 0.05. Significance = s. Non-significance = ns.

[a]Age is incorporated in the model as a categorical variable of ten-year age groups. Estimates of the different age groups (not significant) are not presented.

[b]Significant interaction with sex on 5% level.

[c]All 6 female ulcer patients drank alcohol.

[d] Financial situation is coded as "difficult" or "good". Exercise is coded as "weekly or more" or "seldom or never".

Table 6. Association between risks factors in 1987, including *H. pylori* presence, and oesophagitis in 2004. Logistic regression.

	Oesophagitis 2004											
	Univariable analyses						Multivariable adjusted analyses					
	Women		Men		Both		Women		Men		Both	
Risk factors in 1987	OR	p	OR	p	OR	p	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Male gender (female ref.)					2.88	s					2.69	(1.49: 4.86)
Age (ten-year groups)[a]		ns		ns[aa]		ns						
Financial situation[c]	2.34	ns	1.01	ns	1.25	ns						
H. pylori presence	1.63	ns	0.34	s	0.57[b]	s	1.49	(0.53: 4.17)	0.34	(0.17: 0.68)	0.57	(0.33: 0.98)
Daily smoking	2.54	ns	1.25	ns	1.67	ns	2.44	(0.90: 6.61)	1.04	(0.52: 2.09)	1.48	(0.85: 2.59)
Alcohol consumption	4.05	ns	0.93	ns	2	ns						
Dyspepsia in 1987	1	ns	2.35	s	1.84	s	0.93	(0.35: 2.51)	2.58	(1.27: 5.26)	1.79	(1.02: 3.13)
Stress	1.08	ns	0.46	ns	0.59	ns						
Exercise[c]	0.42	ns	0.83	ns	0.77	ns						
NSAID	1.69	ns	0.0	ns	0.60	ns						
ASA	0.86	ns	1.05	ns	0.61	ns						
Antacid	0.94	ns	1.16	ns	1.06	ns						
H2 antagonists	0.61	ns	0.33	ns	0.38 7	ns						
Model fit; R2							0.06		0.14		0.14	
n/N							20/112		60/156		80/268	

P values are considered significant if < 0.05. Significance = s. Non-significance = ns.

[a]Age is incorporated in the model as a categorical variable of ten-year age groups. Estimates of the different age groups (not significant) are not presented.

[b]Significant interaction with sex on 5% level.

[c]Financial situation is coded as “difficult” or “good”. Exercise is coded as “weekly or more” or “seldom or never”.