Relation between *Helicobacter pylori* infection and gastrointestinal symptoms and syndromes

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Abstract

***Background*—Helicobacter pylori** is a human pathogen that colonises the gastric mucosa and causes permanent gastric inflammation.

***Aims*—To assess the symptoms of *H pylori* infection in an adult unselected population.**

***Subjects*—A random sample of 3589 adult Danes who were examined in 1982 and 1987 (n=2987).**

***Methods*—Abdominal symptoms within the preceding year were recorded at both attendances. Circulating IgG antibodies against *H pylori* in serum samples drawn in 1982 were measured by using in-house indirect enzyme linked immunosorbent assays (ELISA).**

***Results*—People with increased levels of IgG antibodies to *H pylori* were more likely than uninfected individuals to report heartburn (odds ratio (OR) = 1.26, 95% confidence interval (CI) 1.03–1.54) and abdominal pain characterised by daily length (OR = 1.33, 95% CI 0.92–1.91), nocturnal occurrence (OR = 1.62, 95% CI 1.19–2.19), spring aggravation (OR = 1.68, 95% CI 0.70–4.05), and no relation to meals (OR = 0.62, 95% CI 0.43–0.91) or stress (OR = 0.69, 95% CI 0.50–0.95). The inclusion of people with increased levels of IgG antibodies to *H pylori*, but without upper dyspepsia, at study entry significantly increased the likelihood of reporting upper dyspepsia at follow up (OR = 1.71, 95% CI 1.24–2.36). People with epigastric pain and increased levels of IgM antibodies to *H pylori* only indicative of acute *H pylori* infection were more likely to report nocturnal pain, heartburn, nausea, and vomiting.**

***Conclusions*—*H pylori* infection may precede the development of dyspepsia and is associated with a variety of gastrointestinal symptoms in people with no history of peptic ulcer disease.**

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Although the clinical picture of acute *Helicobacter pylori* infection has been described in detail in a few anecdotal reports,[1–3] there is still considerable doubt as to whether chronic *H pylori* infection causes gastrointestinal symptoms in people without peptic ulcer disease.[4 5] Previous research regarding this issue has led to conflicting results.[4] Some studies have shown that *H pylori* infection rates are slightly higher in people with non-ulcer dyspepsia (NUD) than in asymptomatic people.[6–10] Other groups have succeeded in linking specific gastrointestinal symptoms, such as postprandial bloating and belching, to the presence of *H pylori* in the gastric mucosa.[9–12] Finally, there have been reports of symptom relief in people with dyspepsia who were successfully treated for *H pylori* infection,[13 14] but these results were questioned recently.[15 16]

Other studies have, however, failed to demonstrate any relation between *H pylori* infection and gastrointestinal symptoms and specific *H pylori* related dyspepsia has not yet been identified.[8 9 17–19] Moreover, attempts to relate *H pylori* infection status to specific NUD subtypes, that is, reflux-like dyspepsia, ulcer-like dyspepsia, and dysmotility-like dyspepsia, have generally failed.[14 17 19 20]

Assessment of the symptoms of acute *H pylori* infection poses other problems. Acute infection occurs primarily in childhood and is rarely seen in adults. Most such cases remain undiagnosed. Consequently, it has been difficult to attain a consistent clinical image of this condition. Nevertheless, it is preferable that clinicians diagnose the infection immediately after the bacteria have colonised the gastric mucosa, as early diagnosis and treatment may lower the risk of peptic ulcer disease or gastric cancer later in life.[21]

The aim of this study was to assess the symptoms of serologically diagnosed acute and chronic *H pylori* infections in an unselected adult population, with special reference to the prevalence and incidence of upper dyspepsia (UD).

Materials and Methods

STUDY POPULATION AND ACQUISITION OF SERUM SAMPLES

In October 1982 an age and sex stratified sample consisting of 4807 men and women, born in 1922, 1932, 1942, and 1952 (age 30, 40, 50, and 60 years), residing in the western part of Copenhagen County, was drawn from the National Danish Civil Registration System, in which all people living in Denmark are registered by a unique 10-digit number. The distribution of sex, age, occupation, and marital status in the sampling area was compared with national statistics to ensure sample validity.[22]

All sample members received a standard letter containing information about the project and were invited to a general health examination.

Also included was a questionnaire, to be completed in advance,[22] concerning abdominal symptoms within the preceding year and previously diagnosed gastrointestinal disorders. Repeated requests were made in cases of non-response.

The sample size was reduced to 4581 Danes because 226 people of foreign extraction were excluded. Between November 1982 and February 1984 3608 people (78.8%) entered the study. All responders had a general medical examination, including ultrasound assessment of the gall bladder.[22] Serum samples were drawn from 3589 responders and stored at −20°C pending analysis. There was a slight over-representation of tobacco smokers and people with short duration of schooling and poor social status in the non-responder group.[23]

After five years, all those attending the initial study were re-invited to a re-examination that was conducted between December 1987 and November 1988. One hundred and ten people had died and 85.4% of the eligible population (n=2987/3498) attended the follow up examination. There was a significant difference in response rate among men because of a low attendance rate among 65 year olds, and a high attendance rate among those aged 45.[24] Furthermore, non-responders were more likely than responders to be current tobacco smokers and originate from poor social strata.[25] Medical examination, symptom questionnaires, and ultrasound assessment of the gall bladder were repeated.[26]

The project was approved by the Regional Research Ethics Commitee of Copenhagen County.

ANTIBODY DETECTION AND INTERPRETATION OF ANTIBODY PATTERNS

All serum samples drawn in 1982 were thawed for the first time and analysed in June 1993. Circulating IgG antibodies against a low molecular weight (LMW) fraction of *H pylori* antigens[27] and circulating IgM and IgA antibodies directed against heat stable (HS) *H pylori* antigens were measured in duplicate by using an in-house indirect enzyme linked immunosorbent assay (ELISA).[28] The IgG serology assay had previously been validated in 151 adult Danes with dyspeptic symptoms. This group was comparable to the present study population as regard sociodemographic factors and ethnicity.[27] The sensitivity and specificity, at cut-off points <100 ELISA units (Eu) for seronegativity and ≥400 Eu for seropositivity, were 98.5 and 54.0%, respectively. The IgG serology assay predicted a history of peptic ulcer disease in this population when using the same cut-off points for seronegativity and seropositivity.[29] Previous validation of the IgM serology assay in 167 persons with dyspepsia, of which 96 were *H pylori* positive on biopsy based tests, showed a sensitivity of 67.7% and a specificity of 33.3% when cut-off points for seronegativity and seropositivity were assigned at <100 Eu and ≥200 Eu, respectively.[28] Similar cut-off points for seronegativity and seropositivity were used for the IgG and the IgM serology in the present study.

For the IgA serology, cut-off points for seronegativity and seropositivity were assigned at <100 Eu and ≥100 Eu.[29] Borderline cases were those with antibody levels between cut-off points for seronegativity and seropositivity. People with increased levels of IgG antibodies to *H pylori* were assumed to harbour a chronic *H pylori* infection regardless of IgM or IgA antibody values. Increased levels of IgM antibodies to *H pylori* unaccompanied by an increase in IgG and IgA antibody levels were interpreted as a serological sign of acute *H pylori* infection.[1]

ABDOMINAL SYMPTOMS WITHIN THE YEAR PRECEDING STUDY ENTRY IN 1982

All participants were asked about the occurrence of abdominal pain, heartburn, acid regurgitation, nausea, and vomiting within the year preceding study entry in 1982 (one year period prevalence). Except for abdominal pain, all abdominal symptoms were assessed on a four-point ordinal scale (never, occasionally, frequently, daily or almost constantly). Statements of occasional, frequent, or constant symptoms were considered affirmative answers and symptom scores were subsequently collapsed into simple dichotome variables (no, yes). Abdominal pain was recorded on a three-point ordinal scale (never, occasionally, frequently). Subsequently, this scale was reduced to a simple dichotomous variable by categorising statements of occasional and frequent pain as affirmative answers. Abdominal pain was further characterised according to location (non-epigastric, epigastric), duration (minutes, hours, days, varying), seasonal occurrence (winter, spring, summer, autumn), nocturnal occurrence (no, yes), pain aggravating factors (no, eating, drinking, smoking, hunger, mental stress), and pain relieving factors (no, defaecation, eating, drinking, gastrointestinal drugs, non-opioid analgesics). Finally, a history of abdominal pain, that is, recurrent abdominal pain in the years preceding the year of study entry (life-time prevalence of abdominal pain), was treated as a dichotomous variable (no, yes).

UPPER DYSPEPSIA DEFINITIONS

Different definitions of upper dyspepsia (UD) were used in the present study. Firstly, the definition proposed by Colin-Jones was applied: upper abdominal pain, heartburn, nausea, vomiting, or other symptoms considered to be referrable to the proximal alimentary tract.[30] Secondly, a UD classification based on the definition recently suggested by Talley[31] (persistent or recurrent pain or abdominal discomfort centred in the upper abdomen) was tested. When using the latter definition, people with symptoms of gastro-oesophageal reflux disease (GORD) and people with concomitant irritable bowel syndrome (IBS) were not regarded as having UD.[31] Finally, participants were diagnosed with UD if they had experienced at least one of the following symptoms: epigastric pain, heartburn, or acid regurgitation.[32]

UD prevalence refers to the percentage of participants who fulfilled these criteria at study

entry in 1982, whereas incident cases of UD were those without UD at study entry who met the UD criteria at follow up in 1987.

REPRODUCIBILITY OF THE SYMPTOM QUESTIONNAIRE

The reproducibility of the symptom questionnaire was tested in a sex and age stratified sample consisting of 170 participants drawn from the study population who were asked to complete an identical symptom questionnaire approximately two weeks after the first examination.

POSSIBLE CONFOUNDING FACTORS INCLUDED IN MULTIVARIATE ANALYSES

To avoid any possible confounding effects of other gastrointestinal disorders causing abdominal symptoms, analyses on the relation between abdominal symptoms, UD prevalence, and *H pylori* infection were controlled for the effect of having biliary disease, IBS, or a history of peptic ulcer disease (PUD) at study entry. Likewise, analyses on the association between *H pylori* infection and UD incidence were controlled for a history of incident cases of PUD, biliary disease, and IBS within the observation period. Only those who reported an ulcer verified by endoscopy, x-ray, or surgery were diagnosed as having PUD.[33] By combining the outcome of the ultrasound assessment of the gall bladder with the participant's statements on prior cholecystectomy, at both attendances gall bladder status was classified as: normal, cholecystectomised, or gallstones.[22 26] Participants were diagnosed with IBS if they had abdominal pain and at least one of the following symptoms: changing stool consistency, borborygmi, or bloating.[34]

Information was obtained concerning sociodemographic factors, lifestyle practices, body mass index (BMI), and ingestion of nonsteroid anti-inflammatory drugs (NSAIDs) at study entry.[35]

STATISTICAL METHODS

The SPSS statistical package for Windows was used.[36] The relation between *H pylori* infection and upper gastrointestinal symptoms and syndromes was assessed in the entire study population. The symptomatology of acute *H pylori* infection, as indicated by increased levels of IgM antibodies to *H pylori* only, was examined in 333 participants who had epigastric pain at study entry.

Abdominal symptoms in 1982, UD prevalence in 1982, and UD incidence in 1987 were placed as the dependent variables in a series of logistic regression analyses. IgG and IgM antibody measurements were transformed into nominal scales according to cut-off levels (seronegative, borderline, seropositive) and used as explanatory variables. To obtain independent estimates of the impact of *H pylori* infection on upper gastrointestinal symptoms, sex, age, BMI, current tobacco smoking, cumulated weekly alcohol consumption, daily coffee and tea intake, use of NSAIDs, familial social status, marital status, housing density, and occupational energy expenditure at study

TABLE 1 *Seroprevalence‡ of increased IgG antibodies to H pylori according to sex and age at study entry in 1982*

Age† (years)	IgG seropositivity % (n) [*]	
	Men	Women
30	12.9 (451)	13.7 (454)
40	27.2 (471)	24.3 (456)
50	25.6 (461)	30.4 (448)
60	37.1 (450)	37.4 (398)
All	25.7 (1833)	26.1 (1756)

[*]Tests for trend with age: both significant with p values <0.001.
†Age at the time of sampling in 1982.
‡Prevalence of increased IgG antibody levels (≥400 ELISA units) to *H pylori*.

entry were subsequently included as possible confounding factors into multivariate logistic regression models, together with PUD, biliary disease, and IBS.

Odds ratios (ORs) were calculated as the natural antilogarithm of the coefficient (β) for the separate variables of the fitted regression model. Ninety five per cent confidence intervals (CIs) for ORs were computed from the equation:

$$CI = [e^{\beta \pm 1.96 \; SE(\beta)}]$$

where β is the coefficient and SE is the standard error of the fitted model. The percentage of abdominal pain recordings that could be attributed to *H pylori* infection (the population attributable risk per cent (PAR %)) was calculated from the prevalence data by using the following equation:

$$PAR \; \% = (P_e(OR-1)/P_e(OR-1)+1) \times 100$$

where P_e is the proportion of people with increased IgG antibody levels and OR is the odds ratio of abdominal pain in IgG seropositive people compared with non-infected individuals.[37] The reproducibility of the symptom questionnaire was tested with the kappa statistic method.[36]

Results

REPRODUCIBILITY OF THE QUESTIONNAIRE

All questionnaires from the 170 participants who received a second questionnaire were returned within an average time of 16.7 days (range nine to 43 days) after the first examination. The overall kappa value (±2 SD) was 0.75 (0.71–0.79) and ranged from 0.57 (pain duration) to 0.89 (seasonal pain occurrence).

INCREASED LEVELS OF IgG ANTIBODIES TO *H PYLORI* (CHRONIC *H PYLORI* INFECTION)

The prevalence of increased IgG antibody levels to *H pylori* according to sex and age at study entry is shown in table 1.

Abdominal pain

People with increased levels of IgG antibodies to *H pylori* were more likely than non-infected individuals to have a history of abdominal pain and report abdominal pain within the preceding year (table 2). Sex had a significant interaction effect on these relations. Thus, having

TABLE 2 *One year and life-time prevalence of abdominal pain, abdominal pain characteristics and the seroprevalence of IgG antibodies to H pylori in 1982: crude and multivariate adjusted odds ratios (OR)‡*

Symptoms and IgG antibody status	n (%)	Unadjusted OR	Sex and age adjusted OR	Multivariate adjusted OR	95% CI§
History of abdominal pain (life-time prevalence)¶					
IgG seronegative	248 (12.5)	1.0	1.0	1.0	–
IgG borderline	84 (12.4)	0.99	0.99	0.92	(0.68–1.25)
IgG seropositive	165 (17.8)	1.51	1.47	1.18	(0.91–1.54)
Abdominal pain within the preceding year (one-year period prevalence)*					
IgG seronegative	229 (11.5)	1.0	1.0	1.0	–
IgG borderline	74 (10.9)	0.94	0.96	0.89	(0.63–1.24)
IgG seropositive	128 (13.8)	1.23	1.27	1.23	(0.91–1.65)
Epigastric pain					
IgG seronegative	356 (42.1)	1.0	1.0	1.0	–
IgG borderline	123 (40.9)	0.95	0.89	0.89	(0.67–1.18)
IgG seropositive	188 (45.2)	1.13	0.99	0.92	(0.70–1.19)
Nocturnal pain					
IgG seronegative	237 (28.1)	1.0	1.0	1.0	–
IgG borderline	118 (39.3)	1.66	1.58	1.62	(1.19–2.19)
IgG seropositive	155 (37.3)	1.52	1.36	1.13	(0.85–1.51)
Pain duration†					
Minutes	153 (32.0)	1.0	1.0	1.0	–
Days	101 (43.7)	1.65	1.53	1.33	(0.92–1.91)
Factors aggravating pain					
Spring*					
IgG seronegative	45 (51.7)	1.0	1.0	1.0	–
IgG borderline	19 (51.4)	0.99	1.05	1.20	(0.44–3.26)
IgG seropositive	44 (67.7)	1.96	2.14	1.68	(0.70–4.05)
Autumn					
IgG seronegative	55 (63.2)	1.0	1.0	1.0	–
IgG borderline	29 (78.4)	2.11	2.01	3.29	(0.99–11.0)
IgG seropositive	42 (64.6)	1.06	0.97	0.68	(0.27–1.69)
Drinking					
IgG seronegative	201 (34.9)	1.0	1.0	1.0	–
IgG borderline	54 (28.0)	0.72	0.71	0.81	(0.55–1.20)
IgG seropositive	78 (27.8)	0.72	0.74	0.71	(0.50–1.01)
Eating					
IgG seronegative	231 (40.1)	1.0	1.0	1.0	–
IgG borderline	63 (32.6)	0.72	0.67	0.62	(0.43–0.91)
IgG seropositive	134 (47.7)	1.36	1.08	1.06	(0.76–1.47)
Mental stress					
IgG seronegative	350 (60.8)	1.0	1.0	1.0	–
IgG borderline	108 (56.0)	0.82	0.81	0.84	(0.59–1.20)
IgG seropositive	145 (51.6)	0.69	0.72	0.69	(0.50–0.95)

*Significant in women in multivariate analyses.

†IgG antibody status was used as the dependent variable. Other pain episodes were not associated with *H pylori* infection.

‡The upper odds ratio represents the risk of having the symptom in IgG borderline cases compared with IgG seronegative people. The lower odds ratio is the corresponding risk in IgG seropositive people compared with IgG seronegative people.

§Confidence intervals for multivariate adjusted odds ratios.

¶Significant in men in multivariate analyses.

increased levels of IgG antibodies to *H pylori* significantly increased the likelihood of reporting abdominal pain within the preceding year in women (multivariate adjusted OR 1.46 (1.01–2.14)), whereas this relation was not seen in men (multivariate adjusted OR 1.01 (0.63–1.61)). Seropositivity for IgG antibodies to *H pylori* was associated with a history of abdominal pain in men (multivariate adjusted OR 1.59 (1.07–2.35)) but not in women (multivariate adjusted OR 0.93 (0.65–1.34)). The proportion of abdominal pain reports that could be attributed to *H pylori* infection (the PAR %) was 9.9% in men with a history of abdominal pain and 7.2% in women with abdominal pain within the preceding year.

Abdominal pain characteristics
When pain characteristics were assessed in participants who reported abdominal pain within the preceding year at study entry (n=431), a pain pattern became evident in people with increased levels of IgG antibodies to *H pylori*. IgG seropositive people most often described pain episodes that lasted for days and occurred predominantly at night. Pain was often aggravated in spring and was unlikely to be provoked by meals or mental stress (table 2). IgG antibody status was not associated with

having pain that could be relieved by defaecation, eating, drinking, or medication.

Other symptoms referrable to the upper gastrointestinal tract
Whereas acid regurgitation and nausea were not associated with *H pylori* infection, vomiting and heartburn were seen more often in IgG seropositive people than in non-infected individuals. The relation with heartburn persisted in multivariate analyses (IgG borderline versus IgG seronegative: OR 1.26 (1.03–1.54)).

Prevalence and incidence of upper dyspepsia
Regardless of how UD was defined, the relation between UD prevalence and *H pylori* infection did not reach significance (table 3). Nevertheless, there was a tendency towards higher UD incidence rates with all three UD definitions in people with increased levels of IgG antibodies and no sign of UD at study entry. When the authors' definition was examined, people with increased levels of IgG antibodies at study entry suffered a significant 71% increased risk of reporting UD at follow up when compared with IgG seronegative individuals despite control for first-time diagnosed ulcers within the same time period (table 3).

TABLE 3 *Prevalence of upper dyspepsia (UD) in 1982, incidence of UD in 1987 and seroprevalence of IgG antibodies to H pylori in 1982: crude and multivariate adjusted odds ratios (OR)‡ by UD definitions★*

UD definitions★ and IgG antibody status	n (%)	Unadjusted OR‡	Sex and age adjusted OR‡	Multivariate adjusted OR‡	95% CI†
Colin-Jones' definition					
UD prevalence (1982)					
IgG seronegative	940 (47.4)	1.0	1.0	1.0	–
IgG borderline	320 (47.4)	0.99	1.04	1.02	(0.84–1.24)
IgG seropositive	455 (49.0)	1.07	1.18	1.12	(0.93–1.35)
UD incidence (1987)					
IgG seronegative	154 (17.5)	1.0	1.0	1.0	–
IgG borderline	60 (20.5)	1.28	1.38	1.17	(0.78–1.75)
IgG seropositive	75 (19.5)	1.13	1.32	1.37	(0.96–1.97)
Talley's definition					
UD prevalence (1982)					
IgG seronegative	465 (36.4)	1.0	1.0	1.0	–
IgG borderline	157 (36.5)	1.03	0.89	1.02	(0.80–1.30)
IgG seropositive	225 (37.3)	1.14	1.07	0.97	(0.78–1.21)
UD incidence (1987)					
IgG seronegative	75 (12.0)	1.0	1.0	1.0	–
IgG borderline	34 (17.3)	1.23	1.37	1.28	(0.86–1.91)
IgG seropositive	37 (13.8)	1.20	1.44	1.46	(1.02–2.10)
Authors' definition					
UD prevalence (1982)					
IgG seronegative	991 (49.9)	1.0	1.0	1.0	–
IgG borderline	346 (51.2)	1.10	1.10	1.11	(0.92–1.34)
IgG seropositive	478 (51.5)	1.14	1.13	1.03	(0.86–1.23)
UD incidence (1987)					
IgG seronegative	181 (21.6)	1.0	1.0	1.0	–
IgG borderline	63 (23.2)	1.05	1.62	1.15	(0.80–1.65)
IgG seropositive	102 (27.9)	1.42	1.23	1.71	(1.24–2.36)

★See text for definition.
†95% Confidence intervals for multivarite adjusted odds ratios.
‡The upper odds ratio represents the risk of having the symptom in IgG borderline cases compared with IgG seronegative people. The lower odds ratio is the corresponding risk in IgG seropositive people compared with IgG seronegative people.

The corresponding figure was 46% when Talley's definition of UD was applied.

Prevalence and incidence of peptic ulcer disease, and H pylori infection status at study entry
People who were seropositive for IgG antibodies to *H pylori* at study entry were more likely than uninfected individuals to have a history of PUD (prevalent ulcer) and to develop a first-time diagnosed (incident) ulcer within the five year observation period. When adjusted for possible confounders the odds ratios for prevalent and incident PUD were 4.2 (2.8–6.3) and 2.6 (1.1–6.2), respectively, for people with seropositive IgG antibody levels compared with people who were IgG seronegative.

INCREASED LEVELS OF IgM ANTIBODIES TO *H PYLORI* ONLY (ACUTE *H PYLORI* INFECTION)
Gastrointestinal symptoms were not reported more often in people with increased levels of IgM antibodies to *H pylori* only than in non-infected people. However, in a subgroup of 333 participants who had epigastric pain at study entry, nocturnal pain and heartburn were reported significantly more often in people with borderline increased levels solely of IgM antibodies to *H pylori* than in non-infected individuals (table 4). Sex specific analyses, moreover, showed that men with borderline increased IgM antibodies to *H pylori* were more likely than non-infected men to complain of nausea, vomiting, and pain that was induced by drinking. These relations were not seen in women (table 4).

Discussion
Numerous obstacles hamper the study of the relation between *H pylori* infection and abdominal symptoms. Most cases of *H pylori* infection are silent and, although abdominal symptoms are commonplace, not all dyspeptic patients seek medical advice.[38] To examine the association between *H pylori* infection and abdominal symptoms, unselected general populations rather than patients must be examined, as the latter may lead to Berkson's bias.[39] Dyspeptic patients are liable to self-medicate with bismuth containing compounds, antacids, and antisecretory drugs that affect *H pylori* infection rates. If *H pylori* infection contributes little to the overall occurrence of abdominal symptoms, large-scale studies must be adopted. Non-invasive detection methods are necessary for large-scale screening for *H pylori* infection,[40] but may not be as reliable as biopsy based methods. Symptom assessments must be meticulous as *H pylori* infection may induce some abdominal symptoms while other symptoms may not be associated with the infection. Moreover, to assess the association between *H pylori* infection and NUD, *H pylori* related organic disease must be ruled out.

Whereas the sensitivity of the IgG serology used in this study was high, the specificity was relatively low. Consequently, some of the participants who tested IgG negative were probably infected with *H pylori*. The low specificity would, however, mask a possible effect of *H pylori* on gastrointestinal symptomatology as symptoms caused by *H pylori* may also be reported by people who tested IgG seronegative. The diagnostic accuracy of commercially available serology kits varies considerably between different laboratories.[41] The specificity of the present assay, however, was only slightly lower than that which could be obtained with commercially available detection kits in this study population.[42]

TABLE 4 *Prevalence of abdominal symptoms in 333 Danes with epigastric pain at study entry in 1982 and seroprevalence of increased IgM antibodies to H pylori only: multivariate adjusted odds ratios (OR)* ⋆

	Men (n=159)			Women (n=174)		
Symptoms and IgM antibodies	n (%)	OR⋆	95% CI†	n (%)	OR⋆	95% CI†
Nocturnal pain‡						
IgG seronegative	39 (27.9)	1.0		49 (32.5)	1.0	
IgG borderline	9 (69.2)	5.64	(1.12–28.39)	7 (43.8)	1.88	(0.64–5.53)
IgG seropositive	0 (0)	0.00	–	3 (42.9)	1.53	(0.31–7.33)
Pain aggravated by drinking						
IgG seronegative	50 (45.5)	1.0		39 (31.2)	1.0	
IgG borderline	9 (75.0)	3.98	(0.98–16.15)	4 (30.8)	0.89	(0.16–4.80)
IgG seropositive	2 (40.0)	0.93	(0.14–6.06)	3 (50.0)	2.16	(0.29–16.24)
Nausea						
IgG seronegative	52 (37.1)	1.0		81 (53.6)	1.0	
IgG borderline	10 (76.9)	5.26	(1.30–21.33)	9 (56.3)	0.77	(0.22–2.73)
IgG seropositive	0 (0)	0.00	–	2 (28.6)	0.60	(0.09–4.13)
Vomiting						
IgG seronegative	24 (17.1)	1.0		39 (25.8)	1.0	
IgG borderline	7 (53.8)	4.73	(1.32–16.93)	3 (18.8)	0.34	(0.07–1.79)
IgG seropositive	1 (16.7)	1.09	(0.10–11.55)	0 (0)	0.00	–
Hearburn‡						
IgG seronegative	75 (53.6)	1.0		75 (49.7)	1.0	
IgG borderline	10 (76.9)	3.95	(0.65–23.85)	11 (68.8)	4.08	(0.90–18.43)
IgG seropositive	2 (33.3)	0.25	(0.03–2.43)	3 (42.9)	0.81	(0.13–4.95)

⋆The upper odds ratio represents the risk of having the symptom in IgM borderline cases compared with IgM seronegative people. The lower odds ratio is the corresponding risk in IgM seropositive people compared with IgM seronegative people.
†95% Confidence intervals for multivariate adjusted odds ratios.
‡Odds ratios were significant when men and women were grouped together (IgM borderline > <IgM seronegative: OR nocturnal pain 2.43 (1.01–5.83), OR heartburn 4.11 (1.48–11.41)).

Talley recently pointed out that earlier studies in favour of a causal relation between *H pylori* infection and abdominal symptoms may be biased by inappropriate study designs.[15 43] The population based prospective cohort design applied in this study rules out a number of methodological flaws. The confounding effects of sociodemographic factors, lifestyle practices, and concomitant gastrointestinal disease were controlled for by multivariate logistic regression analyses. Valid assessment of abdominal symptoms is, however, essential as objective outcome measures do not exist. The reproducibility of the questionnaire was substantial as shown by the overall kappa statistic of 0.75. The validity of the symptom questionnaire was previouly examined by comparing the one-year period prevalence of abdominal symptoms with symptom prevalences reported in other studies. Symptom prevalences were found to be valid for the study population.[44] The symptom questionnaire was simple and written in comprehensible language. This method of obtaining data does not depart from the daily routine in clinical practice where doctors mostly accept the patients' answers to simple questions without further elaboration.

A high prevalence of PUD is found in *H pylori* infected dyspeptic individuals.[45 46] The participants did not receive an endoscopic examination when they entered the study and, although gastroscopy is free of charge in Denmark, our results may be biased by the fact that some ulcers were missed. The prevalence of peptic ulcer disease in this study population[33] was only slightly lower than ulcer rates found in a similar Norwegian population undergoing endoscopy because of dyspepsia.[47] Therefore, the number of missed ulcers in this study is probably small.

H pylori infection is found frequently in patients with dyspepsia undergoing endoscopy, but in whom no macroscopic lesions are found. Attention has, therefore, been directed to a possible role of *H pylori* infections in the aetiology of NUD. In this study, *H pylori* infection was associated with higher rates of heartburn, vomiting, and specific pain characteristics in people with no history of PUD, biliary disease, or IBS. This symptom cluster is not consistent with any of previously described NUD subtypes, but contains symptoms referrable to reflux-like dyspepsia (heartburn), and ulcer-like dyspepsia (nocturnal pain).[30] The applicability of the NUD subtype definitions has been questioned previously.[32 48] The present findings may further challenge the clinical relevance of this categorisation. Our results may also explain why attempts to link *H pylori* infection to specific NUD subtypes have failed.[14 17 19 20]

Seropositivity for IgG antibodies to *H pylori* at study entry caused an appreciable increase in the risk of reporting UD at follow up in people who did not have UD when they entered the study. The temporal sequence points towards causality. This association reached significance with two of the UD definitions applied (table 2). No consensus has yet been reached on standard definitions of UD.[30 49 50] The definition used by our group was previously applied to this population. UD prevalence was comparable to prevalence rates reported in studies from other Western countries.[32] The increased risk of developing UD in people with *H pylori* infection at study entry and the lack of significant association between *H pylori* infection and UD prevalence is, however, of concern. *H pylori* infection is a progressive disease, which passes through a continuum of different histomorphological states.[40] The duration of the infection could be the decisive factor influencing whether or not abdominal symptoms occur.[21] The increase in symptom occurrence in *H pylori* infected people was modest compared with people who had seronegative IgG antibody levels. Consequently, it could be inferred that the impact of eradicating an existing *H pylori* infection in people with dyspepsia is lim-

ited. Given that the relation between abdominal pain and *H pylori* infection is causal, our results suggest that approximately 7–10% of all cases with abdominal pain would benefit from antimicrobial treatment.

As only a small number of *H pylori* infected people develop dyspepsia, different factors must influence the clinical outcome of infection. Tytgat recently suggested that the extent and activity of the *H pylori* associated gastritis may determine whether dyspepsia occurs.[51] The intensity of gastritis probably reflects both host factors, such as genetic make-up and environmental setting, and bacterial factors, such as the virulence of the infecting strain. Strain specific differences in the relation between *H pylori* infection and abdominal symptoms were not examined in this study. The lack of differentiation between different *H pylori* strains may have resulted in random misclassifications, which inevitably weakens relations and may explain the small magnitude of the risk estimates.

The reports of the interaction of sex on abdominal pain are intriguing. Sex differences in intragastric acidity, se-gastrin, parietal cell mass, and gastric emptying have been reported in humans.[52–54] The relation between *H pylori* infection and these factors is not yet known in detail. Elaborations on the observed interactions, therefore, should await further research.

Symptoms associated with acute *H pylori* infection are present only for a few weeks.[1–3] As we assessed abdominal symptoms within a year, it is possible that symptoms caused by acute *H pylori* infection were masked by other upper gastrointestinal symptoms unrelated to *H pylori* infection. Abdominal symptoms were reported more often only in people with borderline increased IgM antibody levels but not in IgM seropositive people. The significance of borderline increased IgM antibody levels could, however, be questioned. Furthermore, the symptoms of acute *H pylori* infection seen in men with epigastric pain shows a considerable overlap with symptoms of acute gastroenteritis. Cross-reacting antigens have been reported between *H pylori* and *Campylobacter jejuni*, an organism known to cause gastroenteritis.[55] A high cut-off level for IgM seropositivity was applied to lower the risk of including people with *C jejuni* infections. Nevertheless, cross-reactions cannot be ruled out entirely.

No biological mechanism has yet been put forward that adequately explains how *H pylori* may induce abdominal symptoms. Although gastric acid and gastrin secretion are increased in *H pylori* infection,[56] the relation between acid secretion and abdominal symptoms is undetermined.[57] The impact of *H pylori* infection on gastric motility and gastric emptying likewise is equivocal.[58] Pain mechanisms are not known in most gastrointestinal disorders, and this lack of biological mechanism may merely reflect current limitations of knowledge and is hardly an argument against a relation between *H pylori* infection and abdominal symptoms.

In summary, *H pylori* infection seems to precede the development of upper dyspepsia. Seropositivity for IgG antibodies to *H pylori* relates to a variety of abdominal symptoms referrable to the upper gastrointestinal tract. The symptom cluster associated with IgG seropositivity in this population is not consistent with previously described NUD subtypes. *H pylori* infection may give rise to different abdominal syndromes in men and women. Acute *H pylori* infection in adults may be characterised by specific upper gastrointestinal symptoms, particularly in men.

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