Helicobacter pylori infection, intake of analgesics or anti-inflammatory medication, and personal factors in relation to dyspeptic symptoms in patients of a general practitioner

GÜNTER BODE

HERMANN BRENNER

GUIDO ADLER

DIETRICH ROTHENBACHER

SUMMARY

Background. *Several studies have assessed the relationship between Helicobacter pylori infection and dyspeptic symptoms in highly selected patient populations and they have yielded inconsistent results.*

Aim. *To investigate the relationship between current H. pylori infection, intake of analgesics or anti-inflammatory medication, and personal factors with dyspeptic symptoms in a large, unselected patient population of a general practitioner (GP).*

Method. *Consecutive patients of a GP were invited to participate in a cross-sectional study regardless of the reason for their visit. Active infection with H. pylori was measured using the ¹³C-urea breath test (¹³C-UBT). A standardised questionnaire covering demographic, socioeconomic and lifestyle factors, and dyspeptic symptoms was completed by the patients. The number and severity of dyspeptic symptoms were quantified using a symptom score.*

Results. *Five hundred and one out of 531 eligible patients returned their questionnaires; a response rate of 94.4%. The prevalence of H. pylori infection, as indicated by a positive ¹³C-UBT, was 21.1% and was unrelated to dyspeptic symptoms. After adjustment for potential confounders by multiple logistic regression, a symptom score in the upper quartile of the symptom score distribution was significantly associated with female sex (odds ratio [OR] = 1.8, 95% confidence interval [CI] = 1.1 to 3.0) and intake of analgesics or anti-inflammatory drugs other than non-steroidal anti-inflammatory drugs (NSAIDs) (OR = 2.3, 95% CI = 1.1 to 4.7). Older age (60 to 79 years) was associated with fewer symptoms (OR = 0.4, 95% CI = 0.2 to 0.9) when compared with the youngest age group (15 to 39 years).*

Conclusion. *Female sex, younger age, and intake of analgesics or anti-inflammatory drugs other than NSAIDs, but not H. pylori infection, were independently associated with dyspeptic symptoms in this population.*

Keywords: dyspeptic symptoms; Helicobacter pylori; analgesics; anti-inflammatory drugs; observational study.

Introduction

FUNCTIONAL dyspepsia is a very common complaint of patients presenting in both hospital and general practice in Western countries. It has been estimated to account for a fifth of all visits to general practitioners (GPs).[1]

The aetiology and pathophysiology of functional dyspepsia are poorly understood and many factors have been suggested as possible aetiopathogenic mechanisms. Among these are gastrointestinal motor abnormalities, hypersensitivity of the afferent nerves of the gut, psychological disturbances, and *Helicobacter pylori* infection.[2-4]

However, until now no specific dyspeptic symptoms have been shown to be associated with *H. pylori* infection in the absence of ulcers.[5] Multiple studies on the relationship between chronic *H. pylori* infection and symptoms of dyspepsia have been performed in highly selected patient populations (typically patients who underwent gastroscopy), which limits the generalisability of these results. It is therefore not surprising that these studies have led to controversial results.[6-8] Furthermore, in many cases these studies did not take other factors into account, such as use of analgesics or personal factors, that may be related to the risk of dyspepsia.

The objectives of this study were to investigate the role of *H. pylori* infection and intake of analgesics or anti-inflammatory medication and personal factors as potential determinants for dyspeptic symptoms in an unselected patient population attending a GP.

Method

Study population and study design

This analysis is part of a study investigating prevalence, risk factors, and effects of *H. pylori* infection in a sample of consecutive patients of a GP. The study design and results concerning risk factors of infection have been described elsewhere.[9,10] Briefly, all patients aged 15 to 79 years old who consulted a GP on certain days of the week from June to September 1996 were invited to participate in this study regardless of the reason for their visit. The GP's office was located in a suburban community with approximately 15 000 inhabitants near the town of Ulm in Southern Germany. Essentially, everyone in Germany is covered by health insurance and everybody has access to health care. The ambulant care is provided by registered primary care physicians. Every patient can choose whom to consult among all registered physicians.

The study was approved by the Ethics Board of the University of Ulm. Informed consent of the patient was obtained in each case.

Data collection

¹³C-urea breath test. Infection status was determined by ¹³C-urea breath test (¹³C-UBT), which indicates current infection with *H.*

pylori. Two breath samples were collected, an initial breath sample and a second breath sample 30 minutes after administration of 75 mg non-radioactive labelled ^{13}C-urea (Mass Trace, Woburn, MA) in 200 ml of apple juice (pH = 2.2 to 2.4). The breath samples were analysed with an isotope selective non-dispersive infrared spectrometer (IRIS; Wagner-Analytical-Systems, Bremen, Germany). A change of the ^{13}C-value over baseline of more than 5‰ was considered positive. The accuracy of the ^{13}C-UBT in adults is very high and the test as employed in this study has been demonstrated to show perfect concordance with culture and urease tests.[11]

Self-administered questionnaire. The patients were asked to fill out a standardised questionnaire during the practice visit before the ^{13}C-UBT was performed. In addition, medical information was taken from the patient's record. The questionnaire comprised information regarding demographic and socioeconomic factors of the patient; medical history, including family history and history of medication; data concerning housing and living conditions; and lifestyle factors. It was checked for completeness and plausibility by trained research assistants.

Current intake of analgesics or anti-inflammatory drugs was evaluated using the questionnaire and the patients' charts. We distinguished between non-steroidal anti-inflammatory drug (NSAID) medication (including aspirin) and other analgesics or anti-inflammatory drugs (the latter were mainly paracetamol, opioid analgesics, antihistamines, and various others).

Evaluation of symptoms

The questionnaire included information on the following symptoms: epigastric pain, nausea, vomiting, flatulence, postprandial fullness, belching, heartburn, lack of appetite, and early satiety during meals. Frequency of symptoms within the past three months was ascertained on a four-level ordinal scale ('never', 'rarely', 'sometimes', and 'often'). We then calculated a sum score of dyspeptic symptoms according to their reported frequency (never = 0 points, rarely = 1 point, sometimes = 2 points, and often = 3 points) leading to a maximal symptom score of 27 points.

Statistical analysis

We first carried out descriptive analyses of the distribution of sociodemographic factors and the frequency of various gastrointestinal symptoms in the study population. To assess the association of *H. pylori* infection and other factors with the distribution of the symptom score, the sum score was divided according to quartiles. We compared the distribution of the symptom score between *H. pylori*-infected and non-infected patients and between levels of other factors by calculating a Mantel–Haenszel chi-squared statistic after adjustment for age.[12] The following factors, which were suspected to be potential risk factors of dyspeptic symptoms on the basis of previous studies, were considered: sex (male/female), age (three categories), current intake of analgesics or anti-inflammatory medication other than NSAIDs (yes/no), intake of NSAIDs (yes/no), school education (nine years or fewer/more than nine years), and smoking status (never, ex-smoker, current smoker). We then employed unconditional logistic regression to assess the independent association of *H. pylori* infection and other factors with a dyspeptic symptom score within the upper quartile after simultaneously controlling for the covariates. All statistical procedures were carried out with the SAS statistical software package.[13]

Results

In total, 501 out of the 531 eligible patients returned their ques-

tionnaires (response rate = 94.4%). Patients treated with antibiotic therapy within the past four weeks and patients who were diagnosed with *H. pylori* infection and who reported previous specific treatment of infection prior to this study (*n* = 24) were excluded to avoid a false negative test result, as were 26 patients who reported a history of peptic ulcer and six patients who had had surgery of the stomach, leading to a final sample size of 445 patients. The sociodemographic and medical characteristics of the patients are listed in Table 1.

The main reasons for consulting the GP were: musculoskeletal pain (34%), screening examinations (17%), acute infections (11.5%), gastrointestinal diseases (6.6%) and allergic diseases (6.6%).

Figure 1 shows the frequency of self-reported symptoms within the past three months. The two most frequently reported symptoms were flatulence (often = 14.4%) and feeling of postprandial fullness (often = 12.2%); the two least frequently reported symptoms were vomiting (never = 87.8%) and lack of appetite (never = 78.4%).

The distribution of the abdominal symptom score varied significantly among the different age groups (see Table 2). Patients in the age categories 15 to 39 years and 40 to 59 years had higher levels of the symptom score more often than patients in the oldest age group from 60 to 79 years (*P* = 0.005). Therefore, all comparisons of distribution of symptoms between levels of the various other determinants were done after adjustment for age.

Table 3 shows the association of potential risk factors with the distribution of the symptom score after adjustment for age. Overall, 94 out of the 445 patients had a positive ^{13}C-UBT (21.1%). No association was seen between current *H. pylori* infection status and distribution of the symptom score. Female sex was significantly associated with a higher symptom score

Table 1. Study population by personal and medical characteristics (total n = 445).

| Characteristic	n	Percentage
Sex		
Male	162	36.4
Female	283	63.6
Age (years)		
15–39	211	47.4
40–59	143	32.1
60–79	91	20.4
School education		
Ongoing	15	3.4
9 years or less	190	42.6
10–11 years	141	31.8
12 years or more	98	22.0
Family status		
Single	128	28.8
Married	277	62.4
Divorced/widowed	39	8.8
Main reason for presentation to the GP		
Musculoskeletal pain	119	34.3
Screening examination	59	17.0
Acute infection	40	11.5
Gastrointestinal diseases	23	6.6
Allergic diseases	23	6.6
Current intake of analgesics or anti-inflammatory drugs		
No	339	76.2
Yes	106	23.8
NSAIDs	68	–
Others	38	–
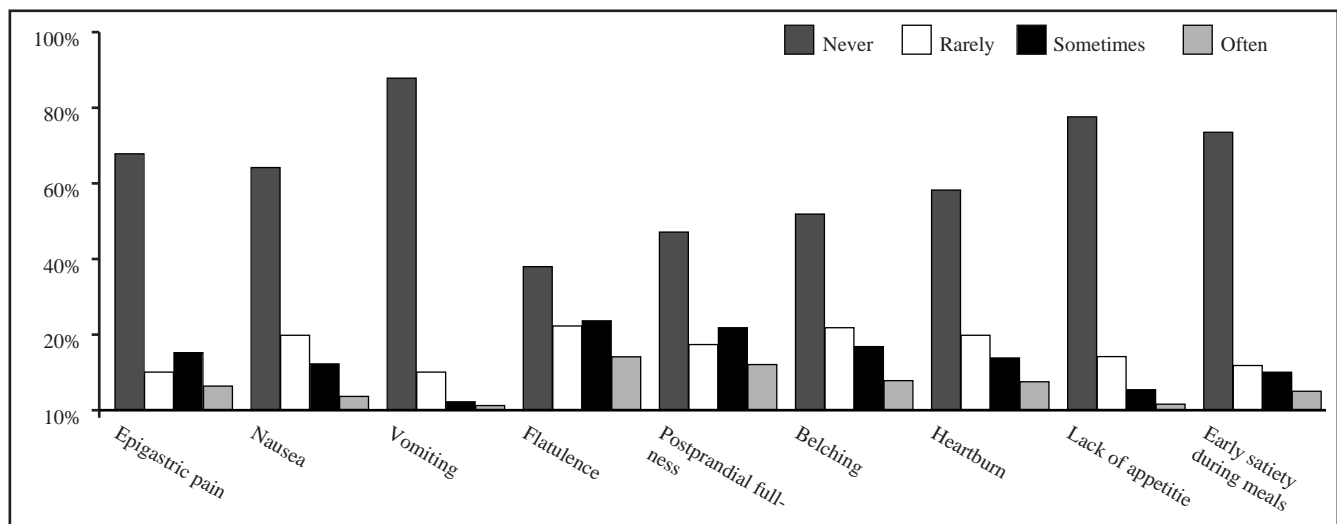
Figure 1. Frequency of self-reported symptoms during past three months.

Table 2. Distribution of abdominal symptom score according to age.

		Abdominal symptom score (%)				
Age (years)	n	0 to <2	≥2 to <4	≥4 to <9	≥9 to 27	P-value[a]
15–39	211	20.4	18.0	35.1	26.5	
40–59	143	20.3	24.5	30.1	25.2	
60–79	91	35.2	28.6	23.1	13.2	0.005
Overall	445	23.4	22.2	31.0	23.4	

[a]Chi-squared for difference among age categories.

compared with male sex; school education showed no association. Patients taking NSAIDs or other analgesic or anti-inflammatory drugs showed a tendency towards higher symptom scores when compared with patients without current intake of such drugs. This tendency was most evident in patients taking analgesics or other anti-inflammatory drugs; however, it is important to note that very few patients taking NSAIDs did so on a daily basis (2%), whereas most of them took them sometimes.

Smoking status showed no significant association with the distribution of the abdominal symptom score.

Table 4 shows the results of the multivariate analysis as obtained by means of logistic regression. Odds ratios (ORs) and 95% confidence intervals (CIs) for having a high symptom score given the various risk factors were calculated after adjustment for covariates. *H. pylori* infection was not related to the occurrence of a high symptom score (OR = 0.9, 95% CI = 0.5 to 1.6). Female sex showed an OR of 1.8 (95% CI = 1.1 to 3.0).

Intake of analgesics or anti-inflammatory drugs in general was positively associated with a symptom score in the upper quartile (OR = 1.8, 95% CI = 1.1 to 2.9). When medication was evaluated more specifically, current intake of NSAIDs showed an OR of 1.5 (95% CI = 0.8 to 2.8) and an OR of 2.3 (95% CI = 1.1 to 4.7) for intake of other analgesics or anti-inflammatory drugs. Furthermore, a high symptom score was significantly less frequent (OR = 0.4, 95% CI = 0.2 to 0.8) in the oldest age category compared with the 15 to 39 years age group.

In addition, we found none of the various single symptoms statistically associated with the current *H. pylori* infection status. Also, taking heartburn out of the summary score did not alter the results (data not shown).

Discussion

This study, conducted in a GP's patient population without a history of peptic ulcer, showed that current *H. pylori* infection was not associated with the occurrence of dyspeptic symptoms as evaluated using an integrated sum score. In addition, we found no single symptom more likely to occur in *H. pylori*-positive patients when compared with *H pylori*-negative patients. Apart from sex and age, use of analgesics or anti-inflammatory medication in general was significantly associated with the occurrence of abdominal symptoms.

The relationship between *H. pylori* infection and dyspeptic symptoms is still discussed controversially. A positive association may be restricted to a subset of infected patients.[4] Eradication of *H. pylori* infection has successfully reduced dyspeptic symptoms in highly selected patient populations.[8] It is unquestionable that *H. pylori* infection is related to dyspeptic symptoms in patients with a history of peptic ulcer[7] and with active peptic ulcer.[14] However, our study suggests that *H. pylori* infection may not be a relevant cause of non-ulcer dyspeptic symptoms in a general patient population. This study is consistent with a recent report of a general population sample of the United Kingdom[15] and with the lack of improvement of symptoms in a recently reported randomised double-blind placebo-controlled trial with 12 months follow-up after *H. pylori* eradication.[16] In concordance with our data, the infection does not seem to produce abdominal symptoms in children in whom a causal role should be easier to identify than in adults because other causes of gastric symptoms, such as smoking and non-steroidal anti-inflammatory drugs, have not been taken into account.[17]

Table 3. Association of various factors with abdominal symptom score.

		Abdominal symptom score (%)				
Factor	*n*	0 to <2	≥2 to <4	≥4 to <9	≥9 to 27	P-value
Infection with *H. pylori*						
No	351	21.7	23.1	31.3	23.9	
Yes	94	29.8	19.2	29.8	21.2	0.448[a]
Sex						
Male	162	29.6	22.2	31.5	16.7	
Female	283	19.8	22.3	30.7	27.2	0.034
School education						
9 years or less	190	27.9	20.5	27.4	24.2	
More than 10 years/ongoing	254	20.1	23.6	33.5	22.8	0.200
Intake of analgesics						
No	339	25.7	22.7	30.9	20.9	
Yes						
Any	106	16.0	20.8	32.1	31.1	0.017[b]
NSAIDs	68	16.2	19.1	36.8	27.9	0.105[c]
Others	38	15.8	23.7	23.7	36.8	0.068[c]
Smoking status						
Never	220	20.9	24.5	32.7	21.8	
Ex-smoker	109	30.3	24.8	23.9	21.1	
Current smoker	115	21.7	15.6	34.8	27.8	0.368

[a]Pooled P-value of Mantel–Haenszel chi-squared for association of factor with abdominal symptom score categories after adjustment for age (general association); [b]reference category; [c]compared with reference category only.

Table 4. Adjusted odds ratios for having a high symptom score (9–27 compared with 0–8 points) according to H. pylori infection, intake of analgesics or anti-inflammatory medication, and personal factors.

Factor	Adjusted odds ratio[a] (95% confidence interval)
Helicobacter infection	
No	1.0[b]
Yes	0.9 (0.5–1.6)
Sex	
Male	1.0[b]
Female	1.8 (1.1–3.0)
Age (years)	
15–39	1.0[b]
40–59	0.9 (0.5–1.5)
60–79	0.4 (0.2–0.8)
Intake of analgesics or anti-inflammatory drugs	
No	1.0[b]
Yes	5.6
Any	1.8 (1.1–2.9)
NSAIDs	1.5 (0.8–2.8)
Others	2.3 (1.1–4.7)
School education	
9 years or less	1.0[b]
>10 years/ongoing	0.7 (0.5–1.2)
Smoking status	
Never	1.0[b]
Ex-smoker	1.0 (0.6–1.7)
Current smoker	1.2 (0.7–2.1)

[a]Adjusted for all other variables listed in the table; [b]reference.

In our study, female sex was associated with a higher symptom score even after adjustment for *H. pylori* infection and other personal factors. The mechanism could be related to delayed gastric emptying of solids in women compared with men.[18,19] In fact, these sex differences were largest for flatulence and post-prandial fullness: two symptoms that are associated with dysmotility.

For reasons not identifiable in this study, a high symptom score was found to be inversely related to age. Similar results, especially for ulcer-like pain, have recently been reported by Lai *et al* in a quantitative analysis of symptoms in 348 endoscopically investigated non-ulcer patients.[20] The elderly are known to complain of pain less than younger people, as demonstrated in patients with heart attack or perforated bowel.[21] Also, peptic ulcer appears to be more frequently asymptomatic in the elderly than in younger subjects.[22,23]

Patients taking NSAIDs commonly report dyspepsia.[24-28] Although patients taking NSAIDs more commonly had higher symptom scores than patients who did not take such medication, this association was less strong in our study than for other analgesics or anti-inflammatory drugs. This pattern may appear unexpected at first sight. A plausible explanation could be that people with gastrointestinal complaints already have changed their medication or have been prescribed other analgesics by the doctor. Furthermore, the majority of the patients using NSAIDs did not do so on a daily basis.

Various studies showed that smoking may potentiate gastric aggressive factors and attenuate defensive factors; however, the influence on symptom generation seems to be low.[29-31] In our study, smoking seems to play no major role in symptom generation.

In conclusion, our study shows that dyspeptic symptoms are common in patients of a GP, particularly among young and middle-aged patients and among women. *H. pylori* infection is neither associated with a single abdominal symptom nor associated with an integrated measure of diverse abdominal symptoms in patients without a history of peptic ulcer. Use of analgesics or anti-inflammatory drugs seems to be a more important possible risk factor in this population.

References

1. Penston JG, Pounder RE. A survey of dyspepsia in Great Britain. *Aliment Pharmacol Ther* 1996; **10:** 83-89.
2. Talley NJ, Phillips SF. Non-ulcer dyspepsia: potential causes and pathophysiology. *Ann Intern Med* 1988; **108:** 865-879.
3. Talley NJ, Zinsmeister AR, Schleck CD, Melton III LJ. Dyspepsia and dyspepsia subgroups: A population-based study. *Gastroenterology* 1992; **102:** 1259-1268.
4. Holtmann G, Talley NJ, Goebell H. Association between *H. pylori*, duodenal mechanosensory thresholds, and small intestinal motility in chronic unexplained dyspepsia. *Dig Dis Sci* 1996; **41:** 1285-1291.
5. Mearin F, de Ribot X, Balboa A, *et al*. Does *Helicobacter pylori* infection increase gastric sensitivity in functional dyspepsia? *Gut* 1995; **37:** 47-51.
6. Strauss RM, Wang TC, Kelsey PB. Association of *Helicobacter pylori* infection with dyspeptic symptoms in patients undergoing gastroduodenoscopy. *Am J Med* 1990; **89:** 464-469.
7. Schubert TT, Schubert AB, Ma CK. Symptoms, gastritis, and *Helicobacter pylori* in patients referred for endoscopy. *Gastrointest Endosc* 1992; **38:** 357-360.
8. Gilvarry J, Buckley MJM, Beattie S, *et al*. Eradication of *Helicobacter pylori* affects symptoms in non-ulcer dyspepsia. *Scand J Gastroenterol* 1997; **32:** 535-540.
9. Rothenbacher D, Bode G, Winz T, *et al*. *Helicobacter pylori* in outpatients of a general practitioner: Prevalence and determinants of current infection. *Epidemiol Infect* 1997; **119:** 151-157.
10. Brenner H, Rothenbacher D, Bode G, Adler G. Relation of smoking, alcohol and coffee consumption to active infection with *Helicobacter pylori*: cross sectional study. *BMJ* 1997; **315:** 1489-1492.
11. Ellenrieder V, Glasbrenner B, Stoffels C, *et al*. Qualitative and semi-quantitative value of a modified ^{13}C-urea breath test for identification of *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol* 1997; **9:** 1085-1089.
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22:** 719-748.
13. SAS Institute, Inc. *Release 6.07, 1991*. Cary, NC: SAS Institute.
14. Maxwell AA, Mendall MA, Northfiled TC. Which *Helicobacter pylori*-positive dyspeptics are likely to respond symptomatically to empirical *H. pylori* eradication? *Eur J Gastroenterol Hepatol* 1998; **10:** 265-268.
15. Stone MA, Barnett DB, Mayberry JF. Lack of correlation between self-reported symptoms of dyspepsia and infection with *Helicobacter pylori* in a general population sample. *Eur J Gastroenterol Hepatol* 1998; **10:** 301-304.
16. Talley NJ, Janssens J, Lauritsen K, *et al*. Eradication of *Helicobacter pylori* in functional dyspepsia: randomised double blind placebo controlled trial with 12 months' follow-up. *BMJ* 1999; **318:** 833-837.
17. Bode G, Rothenbacher D, Brenner H, Adler G. *Helicobacter pylori* and abdominal symptoms: a population based study among preschool children in Southern Germany. *Pediatrics* 1998; **101:** 634-637.
18. Stanghellini V, Tosetti C, Paternico A, *et al*. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996; **110:** 1036-1042.
19. Datz FL, Christian PE, Moore JA. Gender-related differences in gastric emptying. *J Nucl Med* 1987; **28:** 1204-1207.
20. Lai ST, Fung KP, Ng FH, Lee KC. A quantitative analysis of symptoms of non-ulcer dyspepsia as related to age, pathology, and *Helicobacter pylori* infection. *Scand J Gastroenterol* 1996; **31:** 1078-1082.
21. Coleman JA, Denham MJ. Perforation of peptic ulcer in the elderly. *Age Aging* 1980; **9:** 157-161.
22. Clinch D, Banerjee AK, Ostick G. Absence of abdominal pain in elderly patients with peptic ulcer. *Age Ageing* 1984; **13:** 120-123.
23. Pounder R. Silent peptic ulceration: deadly silence or golden silence? *Gastroenterology* 1989; **96:** 626-631.
24. Holtmann G, Goebell H, Holtmann M, Talley NY. Dyspepsia in healthy blood donors: patterns of symptoms and associaton with *Helicobacter pylori*. *Dig Dis Sci* 1994; **39:** 1090-1098.
25. Jones STM, Clague RB, Eldridge J, Jones DM. Serological evidence of infection with *Helicobacter pylori* may predict gastrointestinal intolerance to non-steroidal anti-inflammatory drug (NSAID) treatment in rheumatoid arthritis. *Br J Rheumatol* 1991; **30:** 16-20.
26. Talley NJ, Evans YM, Fleming KC, *et al*. Non-steroidal anti-inflammatory drugs and dyspepsia in the elderly. *Dig Dis Sci* 1995; **40:** 1345-1350.
27. Lanza FL, Evans DG, Graham DY. Effect of *H pylori* infection on the severity of gastroduodenal injury after the acute administration of naproxen or aspirin to normal volunteers. *Am J Gastroenterol* 1991; **86:** 735-737.
28. Iglehart IW, Edlow DW, Mills IJ, *et al*. The presence of *Campylobacter pylori* in non-steroidal anti-inflammatory drug associated gastritis. *J Rheumatol* 1989; **16:** 599-603.
29. Iwata F, Zhang XY, Leung FW. Aggravation of gastric mucosal lesions in rat stomach by tobacco cigarette smoke. *Dig Dis Sci* 1995; **40:** 1118-1124.
30. Talley NJ, McNeil D, Piper DW. Environmental factors and chronic unexplained dyspepsia. Association with acetaminophen but not other analgesics, alcohol, coffee, tea or smoking. *Dig Dis Sci* 1988; **33:** 641-648.
31. Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ. Smoking, alcohol and analgesics in dyspepsia and among dyspepsia subgroups: lack of an association in a community. *Gut* 1994; **35:** 619-624.

Address for correspondence

Dr Günter Bode, Department of Epidemiology, University of Ulm, Helmholtzstr 22, D-89081 Ulm, Germany. E-mail: guenter.bode@medizin.uni-ulm.de