

• CLINICAL RESEARCH •

Epidemiology of gastroesophageal reflux disease: A general population-based study in Xi'an of Northwest China

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Received: 2003-11-21 **Accepted:** 2003-12-16

Abstract

AIM: Gastroesophageal reflux disease (GERD) is a common disorder in the Western population, but detailed population-based data in China are limited. The aim of this study was to understand the epidemiology of symptomatic gastroesophageal reflux (SGER) in adults of Xi'an, a northwestern city of China, and to explore the potential risk factors of GERD.

METHODS: Symptoms suggestive of GERD, functional dyspepsia (FD), irritable bowel syndrome (IBS), upper respiratory diseases and some potential risk factors were investigated in a face-to-face manner in a region-stratified random samples of 2 789 residents aged 18-70 years in Xi'an by using a standardized questionnaire.

RESULTS: With a response rate of 91.8%, the prevalence of SGER was 16.98% (95% CI, 14.2-18.92) in Xi'an adults, and no gender-related difference was observed ($P>0.05$). SGER was more common among subjects aged 30-70 years than in those aged 18-29 years ($P<0.05$). The prevalence of SGER in rural, urban and suburban subjects was 21.07%, 17.44% and 12.12%, respectively, and there was a significant difference between rural, urban and suburban regions ($P<0.05$). Compared with subjects without SGER, the prevalence of symptoms suggestive of FD and IBS, pneumonia, asthma, bronchitis, laryngitis, pharyngitis, chronic cough, wheeze, globus sensation, oral ulcer and snore was significantly increased in subjects with SGER ($P<0.01$). Heavy smoking (OR=4.94; CI, 3.70-6.61), heavy alcohol use (OR=2.85; CI, 1.67-4.49), peptic ulcer (OR=5.76; CI, 3.99-8.32), cerebral palsy (OR=3.97; CI, 1.97-8.00), abdominal operation (OR=2.69; CI, 1.75-4.13), obesity (OR=2.16; CI, 1.47-3.16), excessive food intake (OR=1.43; CI, 1.17-1.75), sweet food (OR=1.23; CI, 0.89-1.54), and consumption of coffee (OR=1.23; CI, 0.76-2.00) were independently associated with SGER. The episodes of GERD were commonly precipitated by dietary factors (66.05%), followed by body posture (26.54%), ill temper (23.72%), fatigue (22.32%) and stress (10.93%).

CONCLUSION: GERD is common in Xi'an's adult population with a mild or moderate degree. The etiology and pathogenesis of GERD are probably associated with FD, IBS, and some respiratory, laryngopharyngeal and odontostological diseases or symptoms. Some lifestyles, diseases and dietary factors are the risk factors of GERD.

Wang JH, Luo JY, Dong L, Gong J, Tong M. Epidemiology of gastroesophageal reflux disease: A general population-based study in Xi'an of Northwest China. *World J Gastroenterol* 2004; 10(11): 1647-1651

<http://www.wjgnet.com/1007-9327/10/1647.asp>

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disorder, and approximately 17-38% of adults in the Western population experienced heartburn and/or acid regurgitation, the main symptoms of GERD, at least once per week; with 4-9% having daily symptoms^[1-3]. Some patients with GERD would develop Barrett's esophagus, intestinal metaplasia of esophageal mucosa that predisposes to adenocarcinoma of the esophagus^[4-8], which has increased rapidly since 1970s^[9,10]. Patients with esophageal carcinoma have been proved to have a low 5-year survival rate^[11,12]. In addition to the risk of cancer, GERD is well recognized to be associated with some upper respiratory diseases, having an adverse impact on the quality of life, and the cost of long-term medical therapy is substantial. Therefore, it is of much importance to understand the prevalence of GERD and to identify the potential risk factors to prevent GERD and GERD-related diseases. As detailed population-based data on GERD in China are currently limited, we aimed in this study to estimate the prevalence of SGER in Xi'an adults, to determine the relationship between GERD and FD, IBS, and upper respiratory diseases, and to explore the risk factors of GERD.

MATERIALS AND METHODS

Subjects

Xi'an is a northwestern city of China, consisting of 7 administrative districts and 3 counties. Of the administrative districts 4 are in the urban region and 3 in the suburban region, and the counties are all in the rural region. Each district includes numerous neighboring communities including multiple residential areas, and each of the county covers several townships governing a number of villages. Based on the 1997 census data obtained from the local government and the proportion of population within the regions, we randomly selected one or more residential areas or villages in the urban, suburban and rural regions, respectively. Finally, a total of 2 789 subjects entered this survey, including 911 subjects from the urban region, 853 from the suburban region, and 1 025 from the rural region. The proportion of subjects in different regions was similar to that of Xi'an population ($P>0.05$), and the selected samples were matched for age and gender with Xi'an population ($P>0.05$).

Questionnaire

The questionnaire was designed on the basis of previous works from two university hospitals^[13], but modified to suit the local conditions. The modified version contained 8 fractions covering a total of 130 relative questions (items), of which 15 were specifically concerned with the frequency and severity of symptoms suggestive of GERD in the past years. Other questions included those concerning general condition of the subject (self-reported

height and weight), the symptoms suggestive of functional dyspepsia (FD) and irritable bowel syndrome (IBS) in the past year, symptoms or history of respiratory, laryngopharyngeal, and odontostological diseases in the past year; history of illness and operation, personal habits (smoking, alcohol), and dietary habits.

Definitions

The following definitions for symptom categories and diseases were used. Only symptoms occurring in the past year before the interview were considered. (1) Heartburn: a burning pain or burning sensation behind the sternum in the chest. (2) Acid regurgitation: a bitter or sour-tasting fluid reflux into the throat or mouth. (3) Food regurgitation: eaten food reflux into the mouth. Heartburn, acid regurgitation, and food regurgitation were considered to be the main symptoms of GERD. Each of the typical symptoms was estimated according to its severity and frequency, which measured on a 4-score scale. The severity was assessed as follows: 0, none; 1, mild (could be ignored); 2, moderate (could not be ignored but did not affect lifestyle); 3, severe (affected lifestyle). The score of symptom frequency was estimated as follows: 0, none or less than one occasion per month on average; 1, several occasions (1 to 3) a month; 2, several occasions (1 to 6) a week; 3, one or more than one occasions daily. Based on the scores of the severity and frequency of the main GERD symptoms, a total score (range, 0 to 18) of each subject was calculated. (4) SGER: subjects with a total score (St) no less than 3. (5) Chest pain: any pain or discomfort felt inside the chest more than once per month on average but not including any pain caused by diagnosed heart disease. (6) Dysphagia: a feeling that food stuck in the throat or chest more than one per month. (7) Symptoms suggestive of FD and IBS and symptoms of respiratory, laryngopharyngeal, and odontostological diseases: any of these symptoms presented more than once a week on average in the past year. (8) History of diseases or operations: any disease or operation diagnosed or performed in a hospital before the interview. (9) Alcohol use: taking 300 g of alcohol per month. (10) Heavy alcohol use: taking 210 g or more of alcohol per week. (11) Smoking status: defined as current smoking, current non-smoking, and heavy smoking (more than one pack a day). (12) Obesity: a body mass index ≥ 30 kg/m². (13) Coffee and special beverages: drinking more than one cup per day on average. (14) Dietary habits: taking special food more than one servings per day on average.

Training of interviewers

The team of interviewers was constituted mainly by medical students studying preventive medicine in our university, who were trained by the same two professors, one was a physician of gastroenterology and understood well the relative definitions, and the other was a specialist in preventive medicine and had rich experience in survey.

Assessment of feasibility

Before the actual study, a pilot study was conducted among 100 unselected outpatients attending our gastroenterological clinic, to test the appropriateness of the questionnaire and to familiarize the interviewers with the survey procedure and the definitions. The problems that the interviewers encountered during the pilot study were discussed and their solutions were provided accordingly.

Survey design and response rate

According to the list of selected subjects and guiding by the members of residents or village's committee, all subjects were interviewed face to face at their home by the interviewers. The completed questionnaires were checked and kept by same physician. The absent subjects were registered and two reminder

interviews were conducted at weekly intervals. Finally, the survey was closed after 16 wk. Among the 2 789 selected subjects, 74 had moved away, 58 could not be interviewed due to their absence during the survey period, 6 died, and 91 explicitly refused to participate in the study. A total of 2 560 subjects were successfully interviewed within a period of 4 mo, resulting in a response rate of 91.8%. There was no difference between the responders and non-responders with respect to their age and gender ($P>0.05$), and the constitution of the non-responder in different regions was reasonably similar ($P>0.05$). Twenty-eight individuals were subsequently excluded from the analysis because of inadequately questionnaires. Data from 2 532 questionnaires were entered in a computer.

Statistical analysis

The questionnaires were coded for analysis, and the data were entered in a computer and analyzed by using DBASE software. The prevalence was derived with 95% confidence intervals (95%CI). Comparison of the data was performed using EP15.0 χ^2 test. The odds ratios (OR) and 95% CI for each significant variable in the final model were calculated from the coefficients estimated in the logistic regression model. All P values were two-tailed, with the level of statistical significance specified at 0.05.

RESULTS

Main symptoms of GERD

The prevalence of heartburn for at least once monthly, weekly and daily episodes was 10.98% (278/2 532), 4.07% (103/2 532) and 1.66% (42/2 532), respectively. That for acid regurgitation monthly was 21.01% (532/2 532), weekly 7.78% (197/2 532), and daily 3.53% (89/2 532). For food regurgitation, the prevalence was 8.57% (217/2 532), 3.28% (83/2 532), and 1.42% (36/2 532) for at least one occasion monthly, weekly, and daily, respectively.

Symptomatic gastroesophageal reflux

The distribution of the total score of main GERD symptoms in the responders is shown in Table 1. The prevalence of SGER was 16.98% (95%CI, 14.20-18.92), of which, 13.11%, 2.92%, and 0.95% were considered as mild, moderate, and severe, respectively. Responders with SGER were more likely to be a mild or moderate degree.

Table 1 The distribution of total score of main GERD symptoms of responders ($n=2 532$)

Total score (St)	Responders (n)	Rate (%)
≥ 3	2 102	83.02
≥ 3 (SGER)	430	16.98
3-7 (mild)	332	13.11
8-12 (moderate)	74	2.92
13-18 (severe)	24	0.95

Relationship between SGER and gender, age, and region

There was no statistically significant difference between men and women in the prevalence of GERD (61.71% vs 17.25%, $P>0.05$), and the ratio of male/female was 1:1.03. The prevalence of SGER was relatively constant across each of 10-year age interval (Table 2, χ^2 for trend; $P=0.075$), but by cutting χ^2 apart, we found that the prevalence of GERD was significantly higher in the responders aged 30-70 years than in those aged 18-29 years ($\chi^2=4.40$, $P<0.05$), and the group aged 50-59 years had the highest prevalence of SGER (21.39%). The responders in the urban and rural regions were more likely than the responders in suburban regions to have SGER (21.07% and 17.44% vs 12.12%, $P<0.05$). However, SGER was similarly prevalent in the urban and rural regions ($P>0.05$).

Table 2 The prevalence of SGER in each age group

Age group (yr)	Responders (n)	Responders with SGER (n)	Prevalence of SGER(%)
<20	64	9	14.06
20-29	517	73	14.12
30-39	621	106	17.07
40-49	584	100	17.12
50-59	360	77	21.39
60-69	354	60	16.95
70	32	5	15.63
18-70	2 532	430	16.98

Association between SGER and respiratory, laryngopharyngeal, and odontostological diseases

Table 3 summarized the prevalence of some respiratory, laryngopharyngeal, and odontostological diseases or symptoms in responders with and without SGER. The responders with SGER reported a higher prevalence of pneumonia, asthma, bronchitis, pharyngitis, laryngitis, chronic cough, wheeze, globus sensation, oral ulcer, and snore than the responders without SGER.

Table 3 The prevalence of respiratory, laryngopharyngeal, and odontostological diseases or symptoms in responders with and without SGER

Disease or symptom	Responders with SGER (n=430)		Responders without SGER (n=2 102)		P value
	n	Rate (%)	n	Rate (%)	
Pneumonia	12	2.79	15	0.73	<0.01
Asthma	28	6.51	46	2.19	<0.01
Bronchitis	66	15.35	187	8.90	<0.01
Pharyngitis	35	8.14	82	3.90	<0.01
Laryngitis	102	23.73	248	11.80	<0.01
Chronic cough	92	21.40	232	11.04	<0.01
Wheeze	33	7.67	80	3.80	<0.01
Globus sensation	102	23.72	104	4.95	<0.01
Oral ulcer	77	17.91	162	7.71	<0.01
Snore	121	28.14	362	12.27	<0.01

Relationship between SGER and other common gastrointestinal symptoms

The prevalence rate of pain behind the sternum, dysphagia,

retching, nausea, vomiting, epigastric discomfort, epigastric fullness, epigastric pain, diarrhoea, and constipation in responders with SGER was significantly higher than that in the responders without SGER ($P<0.01$, Table 4).

Table 4 Other common gastrointestinal symptoms in responders with and without GERD

Symptom	Responders with SGER (n=430)		Responders without SGER (n=2 102)		P value
	n	Rate (%)	n	Rate (%)	
Pain behind breastbone	100	23.25	84	4.14	<0.01
Dysphagia	24	5.58	20	0.95	<0.01
Retching	164	38.14	228	10.85	<0.01
Nausea	137	31.86	148	7.04	<0.01
Vomiting	78	18.14	71	3.38	<0.01
Epigastric discomfort	161	37.44	216	10.28	<0.01
Epigastric fullness	201	46.74	303	14.41	<0.01
Epigastric pain	122	28.37	147	6.99	<0.01
Diarrhoea	59	13.72	102	5.07	<0.01
Constipation	93	21.63	199	9.47	<0.01

The potential risk factors

The data obtained from Table 5 showed that heavy smoking (OR=4.94; CI, 3.70-6.61), heavy alcohol use (OR=2.85; CI, 1.67-4.49), peptic ulcer (OR=5.76; CI, 3.99-8.32), abdominal operation (OR=2.69; CI, 1.75-4.13) were strongly associated with SGER; obesity (OR=2.16; CI, 1.47-3.16) was moderately associated. The association between SGER and current smoking (OR=1.27; CI, 1.17-1.38), excessive food intake (OR=1.43; CI, 1.17-1.75), sweet food (OR=1.23; CI, 0.98-1.54), and coffee (OR=1.23; CI, 0.76-2.00) still existed, but it was mild. The prevalence of SGER was not influenced by tea (OR=1.13; CI, 0.91-1.44), pepper food (OR=1.07; CI, 0.86-1.32), and fat intake (OR=1.00; CI, 0.81-1.23).

Precipitating factors for SGER

Of 430 responders with SGER, 79.07% (340/432) reported the episodes of SGER with specially precipitating factors. Some dietary factors (sweet foods, peppery foods, fat or oil foods, and sour beverage) were the most common precipitating factors (66.05%), followed by body posture (26.54%), ill temper (23.72%), fatigue (22.32%), and stress (10.93%).

Table 5 The Association Between SGER and Selected Risk Factors

Selected risk factors	Factor exposure			Non-factor exposure			P value	OR ¹ (95%CI)
	Responders n	Responders with SGER n	Rate (%)	Responders n	Responders with SGER n	Rate (%)		
Current smoking	992	189	19.05	1 540	241	15.65	<0.05	1.27(1.17-1.38)
Heavy smoking	219	99	45.21	2 313	320	13.84	<0.01	4.94(3.70-6.61)
Heavy alcohol use	74	26	35.14	2 458	404	16.44	<0.01	2.85(1.67-4.49)
Peptic ulcer	59	31	52.54	2 473	399	16.13	<0.01	5.76(3.99-8.32)
Abdominal operation	99	34	34.34	2 433	396	16.28	<0.01	2.69(1.75-4.13)
Erebral palsy	18	8	44.44	2 514	422	16.78	<0.01	3.97(1.97-8.00)
Obesity	139	41	29.50	2 392	389	16.26	<0.01	2.16(1.47-3.16)
Over intake	614	129	21.01	1 918	301	15.69	<0.01	1.43(1.17-1.75)
Sweet food	695	133	19.14	1 837	297	16.17	>0.05	1.23(0.98-1.54)
Coffee	85	17	20.00	2 447	413	16.88	>0.05	1.23 0.76-2.00)
Tea	798	145	18.17	1 734	285	16.44	>0.05	1.13(0.91-1.44)
Pepper food	1 533	266	17.35	999	164	16.42	>0.05	1.07(0.86-1.32)
Fat intake	1 065	181	17.00	1 467	249	16.97	>0.05	1.00(0.81-1.23)

¹OR ~ RR2.6: a strong association; OR=1.7-2.5: a moderate association; OR=1.2-1.6: a mild association; OR=0.9-1.1: no association.

DISCUSSION

Population-based research well suits the purpose of investigating the epidemiology of gastroesophageal reflux disease, which is a common disorder in the community. The diagnosis could be made on the basis of its specific symptoms of heartburn and acid regurgitation without further diagnostic test^[14]. Thus, the methodology utilizing a self-reported questionnaire has become popular in population-based study of GERD^[1-3]. However, this kind of research can be limited by the varied ability of the interviewees to comprehend the definitions used and also by the relatively low response rates. Our research was conducted face to face in subjects' home with the guidance by the members of local community, therefore a high response rate (91.8%) was insured, significant responder bias was avoided, and the definitions were understood accurately assisted by the explanation provided by the trained interviewers, making possible a semi-quantitative diagnosis of SGER which was made by quantifying not only the frequency, but also the severity of main GERD symptoms so as to exclude those subjects with trivial symptoms. The prevalence of heartburn for at least weekly episodes in our study was 4.07%, similar to the prevalence rates reported in other two studies in Asia^[15,16], but was lower than those of Western population, such as the rate of 17.8% in Americans^[2], 14.7% in Australians^[17], 15% in Finlanders^[18] and 11.76% in Belgians^[19].

In the past few years, there has been an increase in the frequency of GERD in Asia, but the related information remains scarce^[20]. The prevalence of GERD in Western adult population varied between 17% and 38%, depending on the definitions and methodology used^[1,2,3]. A community-based study showed that the ethnic-adjusted prevalence of GERD was 1.6% in Singapore, in which GERD was defined as the presence of heartburn and/or acid regurgitation at least once a month^[15]. The prevalence of SGER was 16.98% in the present study. Although these studies are not comparable because of differences in methodologies and definitions used, the different prevalence of GERD may suggest that the prevalence of GERD actually varies between these populations. These differences were probably caused by genetic factors, environmental factors, dietary habits, and health habits. In our study, the variation of the prevalence of SGER in different regions was more likely to be explained by these factors. We found that the prevalence rate of SGER did not differ between men and women, which agreed with many studies^[1,2,15]. Our data also suggested that elder subjects were more likely to have SGER. The reasons are mainly that old people had a poor esophageal acid clearance and decreased defense mechanisms against reflux of acid gastric contents on the esophageal mucosa^[21,22].

The association between GERD and atypical reflux symptoms^[2], FD^[1,15,17,1], and IBS^[23-26] was assessed in some studies, but no related studies were conducted in China. The high prevalence of atypical reflux symptoms (pain behind the sternum and dysphagia) and symptoms suggestive of FD (retching, nausea, vomiting, epigastric discomfort, epigastric fullness, *etc.*), and IBS (epigastric pain, diarrhoea, and constipation.) in the responders with SGER in this population-based study confirmed the association among these symptoms. Subjects with aggravated dysphagia and pain behind the sternum caused by heart or coronary diseases were excluded in the analysis, so to some extent, the high prevalence of non-obstructive dysphagia and non-cardiac chest pain in subjects with SGER suggested that these two symptoms might be a late sequela of GERD. The considerable overlap among symptoms suggestive of GERD, FD and IBS may imply the same etiology and pathogenesis in these diseases. This conclusion, however, needs to be tested by further clinical and experimental studies.

Clinical studies have shown a cause-effect relationship between GERD and some respiratory, laryngopharyngeal, and odontostological diseases or symptoms^[27-32]. This association was further confirmed by our population-based research. Therefore, when a general medical therapy failed to improve the patients' conditions, a 24-h pH monitoring was necessary to detect pathological reflux, and a medical antireflux treatment would be more effective to relieve these conditions with pathological reflux^[28].

Laboratory studies demonstrated a correlation between both weight and body mass index with gastroesophageal reflux^[33,34]. This correlation was still held in our population-based study. Cigarette smoking could reduce lower esophageal sphincter pressure and predispose strain-induced reflux^[35,36]. Our research confirmed the association between smoking and SGER, and the association was weaker when cigarette consumption was decreased. We also observed a more than twofold increase in the prevalence of SGER in heavy alcohol users (42.9%) as compared with non-drinkers (15.7%). Although weight loss, smoking and drinking cessation have been recommended for patients with GERD, some patients reported improvement in their symptoms by doing so^[37], a multicentre-randomized clinical trial is still needed to certify the efficacy of these therapies for GERD.

We also found that GERD was strongly associated with peptic ulcer, post abdominal operation conditions (cholecystectomy and gastrectomy), and cerebral palsy (intellectually disabled and sequela of apoplexy) which were not reported by the other population-based studies. High gastric acid output and abnormal gastric empty are responsible for the increased prevalence of GERD in patients with peptic ulcer. Abdominal operations change the normal anatomic structure of upper gastrointestinal tract and commonly cause alkaline reflux. The main reasons for the high prevalence of SGER in individuals with cerebral palsy were the abnormal motility of esophagus or gastric tract of these patients and a number of common medications used (calcium channel blockers and tricyclic antidepressants) which promote GER by relaxing the lower esophageal sphincter^[38,39].

Consumption of special foods such as fat, chocolate, mints, coffee, onion, citrus fruit and tomato products and eating habits have been shown to be associated with temporary GER or relaxed LES in laboratory settings^[40-42]. However, our population-based study demonstrated that excessive food intake, sweet foods, and coffee were only weakly associated with SGER and no positive association was observed between SGER and fat intake, tea, and peppery foods. Our results were partly similar to the observation by Paul and his colleagues, whose nationwide population-based case-control study showed that GER symptoms and the risk of adenocarcinoma of esophagus or gastric cardia were not associated with dietary factors^[43]. The main explanation is that the quantity of these special foods was difficult to be accurately assessed in population-based study other than in a laboratory experiment. Another conceivable explanation is that the consumption of these foods might not be enough in quantity and/or frequency to cause GERD symptoms. The finding that episodes of SGER were commonly precipitated by dietary factors in our study also supports the above explanations.

In summary, GERD is common in Xi'an adult population, and a significant health problem in the community. The etiology and pathogenesis of GERD are probably associated with FD, IBS, and some respiratory, laryngopharyngeal and odontostological diseases or symptoms. Some life habits, diseases and dietary factors are the risk factors for GERD, and avoidance of these risk factors should be recommended as a primary prevention therapy of GERD.

REFERENCES

- 1 **Kennedy T**, Jones R. The prevalence of gastro-oesophageal reflux symptoms in a UK population and the consultation behaviour of patients with these symptoms. *Aliment Pharmacol Ther* 2000; **14**: 1589-1594
- 2 **Locke GR 3rd**, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County. *Gastroenterology* 1997; **112**: 1448-1456
- 3 **Talley NJ**, Zinsmeister AR, Schleck CD, Melton LJ 3rd. Dyspepsia and dyspepsia subgroups: a population-based study. *Gastroenterology* 1992; **102**: 1259-1268
- 4 **Bytzer P**, Christensen PB, Damkier P, Vinding K, Seersholm N. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. *Am J Gastroenterol* 1999; **94**: 86-91
- 5 **Falk GW**. Barrett's esophagus. *Gastroenterology* 2002; **122**: 1569-1591
- 6 **Buttar NS**, Wang KK, Leontovich O, Westcott JY, Pacifico RJ, Anderson MA, Krishnadath KK, Lutzke LS, Burgart LJ. Chemoprevention of esophageal adenocarcinoma by COX-2 inhibitors in an animal model of Barrett's esophagus. *Gastroenterology* 2002; **122**: 1101-1112
- 7 **Shirvani VN**, Ouatu-Lascar R, Kaur BS, Omary MB, Triadafilopoulos G. Cyclooxygenase 2 expression in Barrett's esophagus and adenocarcinoma: Ex vivo induction by bile salts and acid exposure. *Gastroenterology* 2000; **118**: 487-496
- 8 **Sampliner RE**. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol* 1998; **93**: 1028-1033
- 9 **Devesa SS**, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the united states. *Cancer* 1998; **83**: 2049-2053
- 10 **Cameron AJ**, Lomboy CT. Barrett's esophagus: age, prevalence and extent of columnar epithelium. *Gastroenterology* 1992; **103**: 1241-1245
- 11 **Sampliner RE**. Effect of up to 3 years of high-dose lansoprazole on Barrett's esophagus. *Am J Gastroenterol* 1994; **89**: 1844-1848
- 12 **Sharma P**, Sampliner RE, Camargo E. Normalization of esophageal pH with high-dose proton pump inhibitors therapy dose not result in regression of Barrett's esophagus. *Am J Gastroenterol* 1997; **92**: 582-585
- 13 **Pan GZ**, Xu GM, Ke MY, Han SM, Guo HP, Li ZS, Fang XC, Zou DW, Lu SC, Liu J. Epidemiological study on symptomatic gastroesophageal reflux disease in China: Beijing and Shanghai. *Chin J Dig Dis* 2000; **1**: 2-8
- 14 **Hollenz M**, Stolten M, Labenz J. Prevalence of gastro-oesophageal reflux disease in general practice. *Dtsch Med Wochenschr* 2002; **127**: 1007-1012
- 15 **Ho KY**, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. *Am J Gastroenterol* 1998; **93**: 1816-1822
- 16 **Ho KY**. Gastroesophageal reflux disease is uncommon in Asia: evidence and possible explanations. *World J Gastroenterol* 1999; **5**: 4-6
- 17 **Talley NJ**, Boyce P, Jones M. Identification of distinct upper and lower gastrointestinal symptom groupings in an urban population. *Gut* 1998; **42**: 690-695
- 18 **Isolauri J**, Laippala P. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. *Ann Med* 1995; **27**: 67-70
- 19 **Louis E**, DeLooze D, Deprez P, Hiele M, Urbain D, Pelckmans P, Deviere J, Deltenre M. Heartburn in Belgium: prevalence, impact on daily life, and utilization of medical resources. *Eur J Gastroenterol Hepatol* 2002; **14**: 279-284
- 20 **Lim LG**, Ho KY. Gastroesophageal reflux disease at the turn of millennium. *World J Gastroenterol* 2003; **9**: 2135-2136
- 21 **Huang X**, Zhu HM, Deng CZ, Porro GB, Sangaletti O, Pace F. Gastroesophageal reflux: the features in elderly patients. *World J Gastroenterol* 1999; **5**: 421-423
- 22 **Ter RB**, Johnston BT, Castell DO. Influence of age and gender on gastroesophageal reflux in symptomatic patients. *Dis Esophagus* 1998; **11**: 106-108
- 23 **Pimentel M**, Rossi F, Chow EJ, Ofman J, Fullerton S, Hassard P, Lin HC. Increased prevalence of irritable bowel syndrome in patients with gastroesophageal reflux. *J Clin Gastroenterol* 2002; **34**: 221-224
- 24 **Holtmann G**, Goebell H, Talley NJ. Functional dyspepsia and irritable bowel syndrome: is there a common pathophysiological basis? *Am J Gastroenterol* 1997; **92**: 954-959
- 25 **Stanghellini V**, Tosetti C, Paternico A, De Giorgio R, Barbara G, Salvioli B, Corinaldesi R. Predominant symptoms identify different subgroups in functional dyspepsia. *Am J Gastroenterol* 1999; **94**: 2080-2085
- 26 **Kennedy TM**, Jones RH, Hungin APS, O'flanagan H, Kelly P. Irritable bowel syndrome, gastro-oesophageal reflux, and bronchial hyper-responsiveness in the general population. *Gut* 1998; **43**: 770-774
- 27 **Tomonaga T**, Awad ZT, Filipi CJ, Hinder RA, Selima M, Tercero F, Marsh RE, Shiino Y, Welch R. Symptom predictability of reflux-induced respiratory disease. *Dig Dis Sci* 2002; **47**: 9-14
- 28 **Tauber S**, Gross M, Issing WJ. Association of laryngopharyngeal symptoms with gastroesophageal reflux disease. *Laryngoscope* 2002; **112**: 879-886
- 29 **Jiang SP**, Liang RY, Zeng ZY, Liu QL, Liang YK, Li JG. Effects of antireflux treatment on bronchial hyper-responsiveness and lung function in asthmatic patients with gastroesophageal reflux disease. *World J Gastroenterol* 2003; **9**: 1123-1125
- 30 **Giacchi RJ**, Sullivan D, Rothstein SG. Compliance with anti-reflux therapy in patients with otolaryngologic manifestation of gastroesophageal reflux disease. *Laryngoscope* 2000; **110**: 19-22
- 31 **Branski RC**, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. *Laryngoscope* 2002; **112**: 1019-1024
- 32 **Garcia-Compean D**, Gonzalez MV, Galindo G, Mar DA, Trevino JL, Martinez R, Bosques F, Maldonado H. Prevalence of gastroesophageal reflux disease in patients with extraesophageal symptoms referred from otolaryngology, allergy, and cardiology practices: a prospective study. *Dig Dis* 2000; **18**: 178-182
- 33 **Fisher BL**, Pennathur A, Mutnick JLM, Little AG. Obesity correlates with gastroesophageal reflux. *Dig Dis Sci* 1999; **44**: 2290-2294
- 34 **Locke GR 3rd**, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. The factors associated with symptoms of gastroesophageal reflux. *Am J Med* 1999; **106**: 642-649
- 35 **Pandolfino JE**, Kahrilas PJ. Smoking and gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2000; **12**: 837-842
- 36 **Kadakia SC**, De La Baume HR, Shaffer RT. Effects of transdermal nicotine on lower esophageal sphincter and esophageal motility. *Dig Dis Sci* 1996; **41**: 2130-2134
- 37 **Häuser W**, Grandt D. Tobacco associated gastrointestinal disorders: smoking cessation therapy – a task for gastroenterologists. *Z Gastroenterol* 2002; **40**: 815-821
- 38 **Bohmer CJ**, Klinkenberg-knol EC, Niezen-de Boer RC, Meuwissen SG. The prevalence of gastro-oesophageal reflux disease based on non-specific symptoms in institutionalized, intellectually disabled individuals. *Eur J Gastroenterol Hepatol* 1997; **9**: 187-190
- 39 **Böhmer CJM**, Klinkenberg-Knol EC, Niezen-de Boer MC, Meuwissen SGM. Gastroesophageal reflux disease in intellectually disabled individuals: how often, how serious, how manageable? *Am J Gastroenterol* 2000; **95**: 1868-1872
- 40 **Cranley JP**, Achkar E, Fleshler B. Abnormal lower esophageal sphincter pressure responses in patients with orange juice-induced heartburn. *Am J Gastroenterol* 1986; **81**: 104-106
- 41 **Allen ML**, Mellow MH, Robinson MG, Orr WC. The effect of raw onions on acid reflux and reflux symptoms. *Am J Gastroenterol* 1990; **85**: 377-380
- 42 **Cohen S**, Booth GH Jr. Gastric acid secretion and low-esophageal-sphincter pressure in response to coffee and caffeine. *N Engl J Med* 1975; **293**: 897-899
- 43 **Terry P**, Lagergren J, Wolk A, Nyren O. Reflux-inducing dietary factors and risk of adenocarcinoma of the esophagus and gastric cardia. *Nutrition Cancer* 2000; **38**: 186-191