Epidemiological and clinical features of functional dyspepsia in a region with a high incidence of esophageal cancer in China

Nan Hu[1], Kun Wang[1], Li Zhang[1], Zuo-Jing Liu[1], Zhu Jin[1], Rong-Li Cui[1], He-Jun Zhang[1], Zhong-Hu He[2], Yang Ke[2], Li-Ping Duan[1]

[1]Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China;
[2]Department of Gastroenterology, Peking University Cancer Hospital and Institute, Beijing 100142, China.

Abstract

Background: Functional dyspepsia (FD) has rarely been investigated in areas with a high prevalence of esophageal squamous cell carcinoma (ESCC). This study aims to reveal the epidemiological and clinical features of FD and organic dyspepsia (OD) in such a population.

Methods: A middle-aged and elderly population-based study was conducted in a region with a high incidence of ESCC. All participants completed the Gastroesophageal Reflux Disease Questionnaire and Functional Gastrointestinal Disease Rome III Diagnostic Questionnaire, and they underwent gastroscopy. After exclusion of gastroesophageal reflux disease, uninvestigated dyspepsia (UID) was divided into OD and FD for further analyses.

Results: A total of 2916 participants were enrolled from July 2013 to March 2014 in China. We detected 166 UID cases with questionnaires, in which 17 patients with OD and 149 with FD were diagnosed via gastroscopy. OD cases presented as reflux esophagitis (RE), ESCC, and duodenal ulcer. Heartburn (52.94%) and reflux (29.41%) were common in OD, but no symptomatic differences were found between FD and OD. Male sex, low education level, and liquid food were the risk factors for OD, while frequent fresh vegetable consumption was a protective factor. FD included 56 (37.58%) cases of postprandial distress syndrome (PDS), 52 (34.89%) of epigastric pain syndrome (EPS), nine (6.04%) of PDS + EPS, and 32 (21.48%) of FD + functional esophageal disorders. The *Helicobacter pylori* infection rate in FD patients was not higher than that in the control group (34.23% *vs.* 42.26%, $P = 0.240$). Frequent spicy food consumption was associated with PDS (odds ratio [OR]: 2.088, 95% confidence interval [CI]: 1.028–4.243), while consumption of deep well water was protective for PDS (OR: 0.431, 95% CI: 0.251–0.741).

Conclusions: The prevalence of FD was 5.11% in the studied population. Gastroscopy should be prescribed for dyspepsia patients in case that ESCC and RE would be missed in UID cases diagnosed solely by the Rome III questionnaire.

Trial Registration: ClinicalTrials.gov, NCT01688908; https://clinicaltrials.gov/ct2/show/record/NCT01688908.

Keywords: Epidemiology; Esophageal squamous cell carcinoma; Functional dyspepsia; Gastroscopy; General population

Introduction

Functional dyspepsia (FD) is characterized by symptoms such as postprandial fullness, early satiation, epigastric pain, and burning without any identified structural abnormalities.[1] Although FD is non-fatal, its symptoms are often chronic and recurrent, which seriously impairs patients' quality of life, resulting in repeated medical visits as well as heavy economic burden. The prevalence of FD varies considerably among different areas and populations, ranging from 5% to 40% worldwide.[2,3] Approximately 10% to 40% of residents in Western and 5% to 30% of Asian countries have been diagnosed with FD.[3,4] FD is common in China, with a prevalence varying geographically from 2.4% to 23.5%.[5-9]

The Hua County in Henan province in China is an area with a high incidence of esophageal squamous cell carcinoma (ESCC), with the highest ESCC mortality among the world.[10,11] A high prevalence of gastroesophageal reflux disease (GERD) is also observed in this area.[12] However, the epidemiological characteristics of FD and the validity of the Rome III diagnostic questionnaire for FD in this area have not yet been reported. Patients with dyspepsia symptoms defined by the Rome III

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001584

Correspondence to: Dr. Li-Ping Duan, Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China
E-Mail: duanlp@bjmu.edu.cn
Dr. Yang Ke, Department of Gastroenterology, Peking University Cancer Hospital and Institute, Beijing 100142, China
E-Mail: keyang@bjmu.edu.cn

Chinese Medical Journal 2021;134(12)

Received: 02-03-2021 **Edited by:** Yan-Jie Yin and Xiu-Yuan Hao

criteria in the absence of a gastroscopy examination are diagnosed with uninvestigated dyspepsia (UID). A better understanding of the prevalence and the features of UID in this population through a questionnaire and a further characterization of FD and organic dyspepsia (OD) through gastroscopy will promote diagnosis and treatment as well as help alleviate the burden of FD.

Therefore, this study aimed to investigate the prevalence of FD in a middle-aged and elderly population from Hua County and the features of misdiagnosed organic diseases. The relationship between FD and *Helicobacter pylori* infection was also analyzed.

Methods

Ethical approval

This study was approved by the Ethical Committee of Peking University Cancer Hospital and Institute (No. 2011101110). All participants agreed to the research process and provided written informed consent.

Study population

Participants of this study were all recruited from Hua County, Henan Province, China. Since 2012, a general population-based randomized controlled trial (RCT) has been carried out in this area, and gastroscopic screening has been conducted among middle-aged and elderly (45–69 years old) residents to assess esophageal cancer (clinical trial: NCT01688908).[13] There are 968 villages in this area, of which 846 villages have a population between 500 and 3000. Among the 846 villages, 668 villages were randomly selected as the target villages and were randomly divided into a control arm and a screening arm (334 villages for each). A total of 2916 participants from the screening arm of the RCT were consecutively recruited for our study from July 2013 to March 2014, and also as part of the RCT. Exclusion criteria for this study included a history of malignancy; mental illness; hepatitis B virus, hepatitis C virus, and human immunodeficiency virus infection; and gastroscopy in the past 5 years. None of the participants had undergone *H. pylori* screening or eradication treatment.

Questionnaires and interview

All participants were interviewed face-to-face by trained researchers and the following questionnaires were completed: case report form [Supplementary Table 1, http://links.lww.com/CM9/A616], the Chinese version of the Adult Functional Gastrointestinal Disease Rome III Diagnostic Questionnaire [Supplementary Table 2, http://links.lww.com/CM9/A616],[14] and the Chinese version of the Gastroesophageal Reflux Disease Questionnaire (GerdQ) [Supplementary Table 3, http://links.lww.com/CM9/A616]. FD was diagnosed if the patient suffered from bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning in the past 3 months, and the symptoms had started at least 6 months before diagnosis. It could be further divided into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). PDS was defined as the symptom of postprandial fullness or early satiation that occured several times per week. And the diagnostic criterion of PDS was the upper abdominal pain that happened at least once per week. Functional esophageal disorders (FED) include functional heartburn, functional chest pain of presumed esophageal origin, functional dysphagia, and globus hystericus. GERD was diagnosed if a patient obtained a GerdQ score ≥ 8[15,16] [Supplementary Tables 4–6, http://links.lww.com/CM9/A616].

Gastroscopy and pathology

Standardized gastroscopy was performed for all participants by trained gastroenterologists. Biopsies were obtained from regions with abnormalities or the mid-esophagus and gastric antrum if no lesions were found. Hematoxylin and eosin staining was used to make a histopathological diagnosis and *H. pylori* was detected via Warthin-Starry staining. Histopathological diagnosis was made by three experienced pathologists from Gastroenterology Department of Peking University Third Hospital. *H. pylori* infection was determined according to the "Chinese consensus on chronic gastritis" (Shanghai, 2017),[17] while gastric, esophageal, and cardiac cancers were diagnosed based on the "2010 World Health Organization Classification of Digestive System Tumors."[18]

Statistics

We established an Epidata 2.0 database with all the collected data. Statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using the Kruskal-Wallis test, while categorical variables were evaluated using Chi-square or Fisher exact tests. Moreover, all variables were analyzed by univariate logistic regression. Variables with a P value < 0.2 were further included in the multivariate logistic regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. P values < 0.05 were considered statistically significant.

Results

Prevalence of UID and FD

A total of 2916 participants (aged 56.92 ± 6.87 years, male/female ratio = 1436/1480) were enrolled. They all completed the questionnaire and underwent a gastroscopy. Of the 2916 participants, 1705 (58.47%) had upper gastrointestinal (GI) symptoms, including heartburn, postprandial fullness, belching, nausea, and reflux. 166 (5.69%) cases of UID and 310 (10.63%) cases of GERD were preliminarily identified by the Rome III and GerdQ questionnaires, respectively. Gastroscopy revealed 342 (11.73%) cases of organic diseases, including 17 (0.58%) cases of ESCC, two (0.07%) cases of gastric cancer, one (0.03%) case of cardiac cancer, 30 (1.03%) cases of gastric ulcer, 22 (0.75%) cases of duodenal ulcer (DU), and 270 (9.26%) cases of reflux esophagitis (RE) [Figure 1].

After combining the questionnaire and gastroscopy results, 149 (5.11%) patients were diagnosed as FD and 140

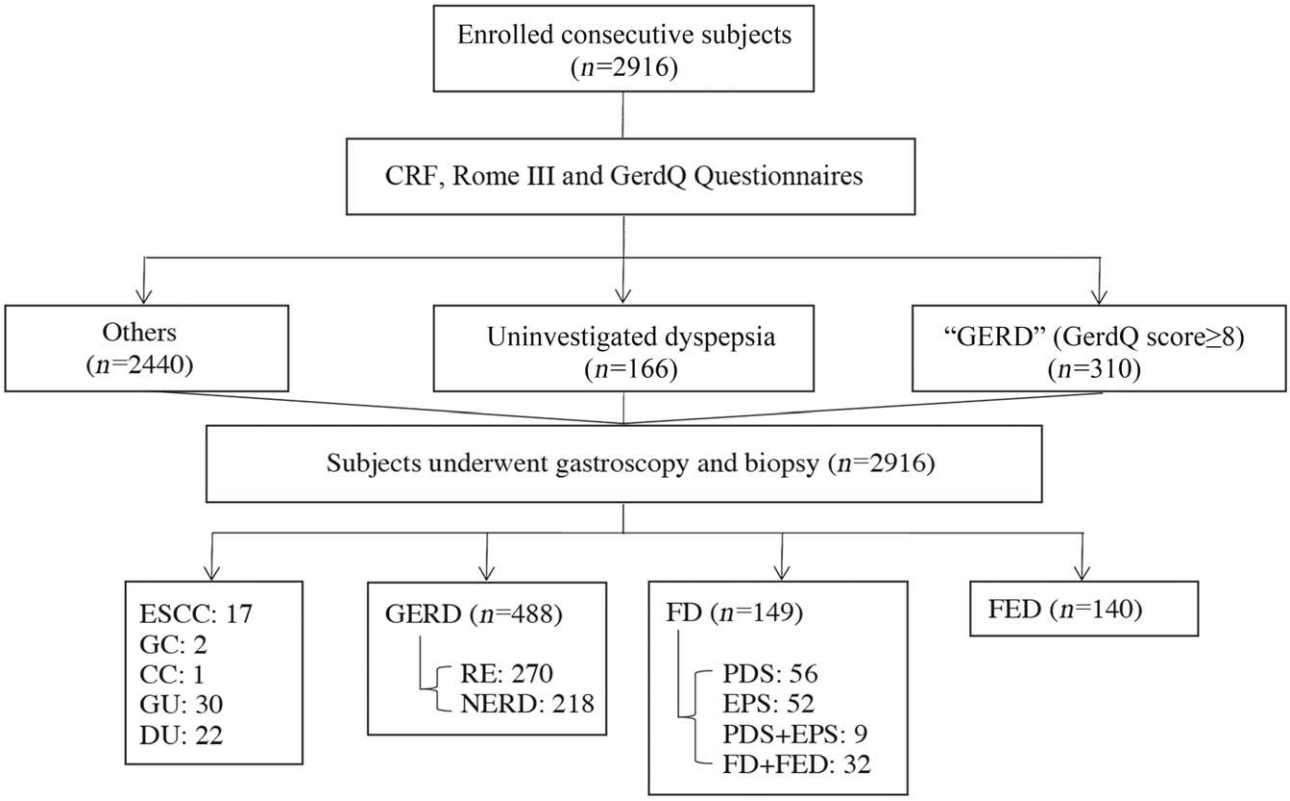

Figure 1: Study flow chart and the distribution of upper GI tract diseases based on questionnaire and gastroscopy findings. CC: Cardiac cancer; CRF: Case report form; DU: Duodenal ulcer; EPS: Epigastric pain syndrome; ESCC: Esophageal squamous cell cancer; FD: Functional dyspepsia; FED: Functional esophageal diseases; FD + FED: Co-occurrence of FD and FED; GI: Gastrointestinal; GerdQ: Gastroesophageal Reflux Disease Questionnaire; GC: Gastric cancer; GU: Gastric ulcer; NERD: Non-erosive reflux disease; PDS: Postprandial distress syndrome; PDS + EPS: Co-occurrence of PDS and EPS; Rome III: The Chinese version of the Adult Functional Gastrointestinal Disease Rome III Diagnostic Questionnaire; RE: Reflux esophagitis.

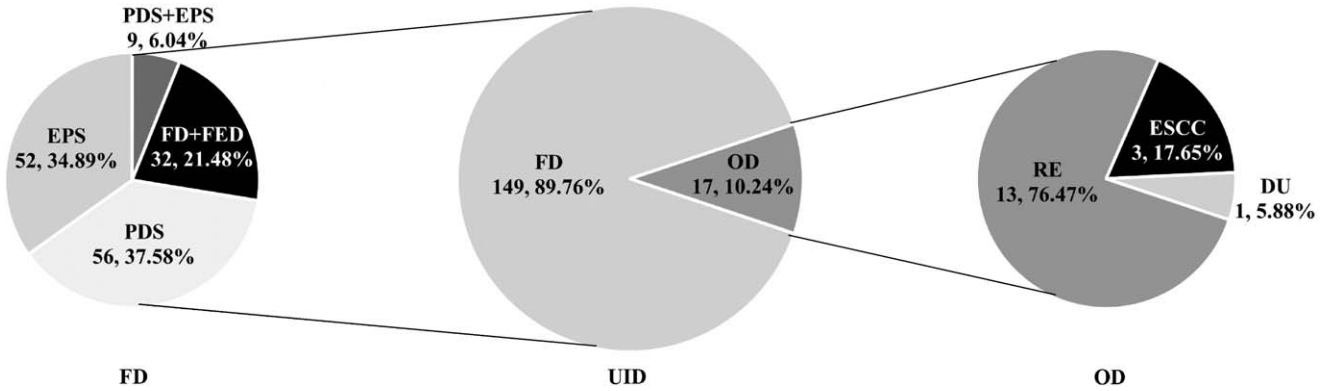

Figure 2: Distribution of FD and OD in UID. DU: Duodenal ulcer; EPS: Epigastric pain syndrome; ESCC: Esophageal squamous cell cancer; FD: Functional dyspepsia; FD + FED: Co-occurrence of FD and functional esophageal disorders; OD: Organic dyspepsia; PDS: Postprandial distress syndrome; PDS + EPS: Co-occurrence of PDS and EPS; RE: Reflux esophagitis; UID: Uninvestigated dyspepsia.

(4.80%) as FED, including 56 (37.58%) patients with PDS, 52 (34.89%) with EPS, and nine (6.04%) with PDS + EPS. Additionally, 32 participants had both FD and FED. Of the patients diagnosed with UID, 10.24% (17/166) of them were in the OD group, including three patients with ESCC, 13 with RE, and one with DU [Figure 2]. We identified 488 GERD (16.74%) cases, including 270 cases of RE and 218 of non-erosive reflux disease. Demographic and clinical characteristics of this population are shown in Table 1 and Supplementary Table 7, http://links.lww.com/CM9/A616. We found that patients with ESCC were significantly older than those with FD and FED. The proportion of males was significantly higher in those with GERD and DU than those with functional disorders. Patients with GERD were exposed to more smoke than those with EPS and FED [Table 1].

Table 1: Demographic and clinical characteristics of the functional and organic diseases.

	Organic diseases ($n = 560$)						FD ($n = 149$)					
	ESCC ($n = 17$)	GC ($n = 2$)	CC ($n = 1$)	GU ($n = 30$)	DU ($n = 22$)	GERD ($n = 488$)	PDS ($n = 56$)	EPS ($n = 52$)	PDS + EPS ($n = 9$)	FD + FED ($n = 32$)	FED ($n = 140$)	*P*
Age (years), mean ± SD	63.47 ± 4.09	64.50 ± 3.54	64	57.27 ± 7.49	58.18 ± 6.63	58.19 ± 6.80	57.89 ± 6.63	56.92 ± 6.71	57.44 ± 6.41	57.50 ± 7.16	55.03 ± 7.10	0.001†
Male sex, *n* (%)	8 (47.06)	1 (50.00)	1 (100)	13 (43.33)	14 (63.64)	314 (64.34)	30 (53.57)	23 (44.23)	3 (33.33)	11 (34.38)	59 (42.14)	<0.001*
BMI (kg/m^2), mean ± SD	25.13 ± 3.44	24.89 ± 1.66	23.12	26.03 ± 7.49	23.71 ± 2.96	25.47 ± 3.36	24.74 ± 3.95	24.72 ± 3.57	24.04 ± 2.14	25.21 ± 3.92	25.34 ± 3.89	0.274†
Marriage (unmarried), *n* (%)	2 (11.76)	0	0	4 (13.33)	4 (18.18)	32 (6.56)	2 (3.57)	1 (1.92)	1 (11.11)	1 (3.13)	9 (6.43)	0.144*
Family size, mean ± SD	3.18 ± 2.30	7.00 ± 2.83	2	3.20 ± 1.88	3.68 ± 2.17	3.59 ± 1.95	3.46 ± 1.64	3.67 ± 2.02	2.56 ± 1.01	3.84 ± 2.08	3.82 ± 2.02	0.233†
Education (primary school or below), *n* (%)	11 (64.71)	1 (50.00)	0	17 (56.67)	17 (77.27)	276 (56.56)	34 (60.71)	27 (51.92)	6 (66.67)	22 (68.75)	92 (65.71)	0.348*
Smoking, *n* (%)	5 (29.41)	0	1 (100)	9 (30.00)	8 (36.36)	207 (42.42)	19 (33.93)	11 (21.15)	2 (22.22)	8 (25.00)	37 (26.43)	0.003*
Alcohol drinking, *n* (%)	3 (17.65)	0	0	4 (13.33)	3 (13.64)	134 (27.46)	14 (25.00)	8 (15.38)	2 (22.22)	4 (12.50)	22 (15.71)	0.067*
Eating fast, *n* (%)	1 (5.88)	1 (50.00)	0	5 (16.67)	2 (9.09)	75 (15.37)	3 (5.36)	7 (13.46)	0	3 (9.38)	16 (11.43)	0.263*
Hot food preference, *n* (%)	4 (23.53)	1 (50.00)	0	4 (13.33)	2 (9.09)	75 (15.37)	4 (7.14)	8 (15.38)	0	5 (15.63)	15 (10.71)	0.287*
Liquid food preference, *n* (%)	3 (17.65)	0	1 (100)	4 (13.33)	4 (18.18)	110 (22.54)	8, 14.29	13 (25.00)	2 (22.22)	4 (12.50)	21 (15.00)	0.512*
Fresh vegetable preference, *n* (%)	16 (94.12)	2 (100)	1 (100)	30 (100.00)	20 (90.91)	462 (94.67)	52 (92.86)	50 (96.15)	9 (100)	32 (100)	135 (96.43)	0.736*
Fresh fruit preference, *n* (%)	6 (35.29)	1 (50.00)	1 (100)	12 (40.00)	9 (40.91)	236 (48.36)	23 (41.07)	28 (53.85)	2 (22.22)	13 (40.63)	58 (41.43)	0.461*
Spicy food preference, *n* (%)	2 (11.76)	0	0	1 (3.33)	2 (9.09)	54 (11.07)	10 (17.86)	4 (7.69)	0	1 (3.13)	5 (3.57)	0.058*
Drinking deep well water, *n* (%)	9 (52.94)	0	1 (100)	18 (60.00)	17 (77.27)	298 (61.07)	23 (41.07)	35 (67.31)	6 (66.67)	23 (71.88)	97 (69.29)	0.007*
Helicobacter pylori positive, *n* (%)	5 (29.41)	0	1 (100)	7 (23.33)	12 (54.55)	169 (34.63)	19 (33.93)	23 (44.23)	1 (11.11)	8 (25.00)	45 (32.14)	0.206*

* Fisher exact test was applied for comparisons among groups. † Kruskal-Wallis test was applied for comparisons among groups. BMI: Body mass index; CC: Cardiac cancer; DU: Duodenal ulcer; EPS: Epigastric pain syndrome; ESCC: Esophageal squamous cell cancer; FD: Functional dyspepsia; FD + FED: Co-occurrence of FD and FED; FED: Functional esophageal diseases; GC: Gastric cancer; GU: Gastric ulcer; GERD: Gastroesophageal reflux disease; PDS: Postprandial distress syndrome; PDS + EPS: Co-occurrence of PDS and EPS; SD: Standard deviation.

Characteristics of UID

Among the UID cases diagnosed solely by questionnaires, OD were further defined by an endoscopic diagnosis. The most common OD detected in the UID group were RE (13/17) and ESCC (3/17) [Supplementary Table 7, http://links.lww.com/CM9/A616]. The patients typically presented with postprandial fullness (76.47%), heartburn (52.94%), epigastric pain or burning sensations (47.06%), belching (41.18%), and acid reflux (29.41%). There were no significant differences in the symptoms between the OD and FD groups [Supplementary Table 8, http://links.lww.com/CM9/A616]. We found that compared to the FD group, the most prominent risk factor for patients in the OD group was a low level of education (OR: 4.292, 95% CI: 1.028–17.915). In contrast, the protective factor was regular vegetable consumption (OR: 0.127, 95% CI: 0.019–0.858). Compared to the control group, risk factors for patients with OD included the male sex (OR: 4.007, 95% CI: 1.055–15.226, $P = 0.042$), low level of education (OR: 4.771, 95% CI: 1.331–17.099, $P = 0.016$), and frequent liquid food consumption (OR: 2.997, 95% CI: 1.081–8.038, $P = 0.035$) [Table 2].

Characteristics of FD and its subtypes

The most common symptoms of the 149 patients with FD included postprandial fullness (71.14%), epigastric pain or burning sensations (57.05%), belching (37.58%), heartburn (32.89%), and nausea (26.85%). Among these patients, 56 were diagnosed with PDS and 52 with EPS. Common symptoms of PDS included postprandial fullness (89.29%), belching (30.36%), heartburn (26.79%), and early satiation (21.43%). Common symptoms of EPS included epigastric pain or burning (100%), postprandial fullness (42.31%), belching (28.85%), and nausea (25.00%). Patients with PDS + EPS presented with severe upper abdominal symptoms (100% postprandial fullness, 100% epigastric pain or burning sensations, and 55.56% belching). Also, 32 patients presented with significant esophageal-related symptoms and were diagnosed with FED by the Rome III questionnaire and a gastroscopy. Comorbid FED was present in 21.48% of patients with FD; the most common symptoms included postprandial fullness (78.13%), epigastric pain or burning sensations (68.75%), nausea (59.38%), belching (59.38%), heartburn (59.38%), chest pain (53.13%), dysphagia (37.50%), globus hystericus (34.38%), and reflux (31.25%) [Figure 3 and Supplementary Table 9, http://links.lww.com/CM9/A616].

Possible risk factors for FD

Among the 149 FD patients, we detected *H. pylori* in mucosal biopsies in 34.23% (51/149) of patients, which did not differ from the *H. pylori* detection rate of the control group (877/2099, 42.26%, $\chi^2 = 1.380$, $P = 0.240$), nor the subtypes of FD. When we focused on the symptoms, the proportion of patients with nausea (37.25% *vs.* 21.43%, $P = 0.039$) and acid reflux (21.57% *vs.* 8.16%, $P = 0.020$) was significantly higher in FD patients with *H. pylori* infection than those without. Though we could not identify any definitive risk factors for

Table 2: Risk factors for OD compared to those for FD and the control group.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
OD/FD				
Male sex	2.937 (0.986–8.754)	0.053	3.058 (0.733–12.764)	0.125
BMI (kg/m^2)	1.092 (0.967–1.232)	0.156	1.115 (0.978–1.271)	0.105
Education (primary school or below)	3.146 (0.867–11.420)	0.081	4.292 (1.028–17.915)	0.046
Smoking	2.422 (0.874–6.710)	0.089	1.311 (0.344–4.996)	0.692
Liquid food preference	2.465 (0.838–7.247)	0.101	2.552 (0.789–8.247)	0.118
Fresh vegetables preference	0.315 (0.058–1.699)	0.179	0.127 (0.019–0.858)	0.034
OD/control				
Male sex	2.793 (0.981–7.957)	0.054	4.007 (1.055–15.226)	0.042
BMI (kg/m^2)	1.090 (0.958–1.241)	0.191	1.103 (0.968–1.257)	0.140
Education (primary school or below)	3.138 (0.899–10.954)	0.073	4.771 (1.331–17.099)	0.016
Smoking	2.170 (0.833–5.650)	0.113	1.099 (0.329–3.669)	0.878
Liquid food preference	2.557 (0.940–6.959)	0.066	2.997 (1.081–8.308)	0.035

All variables were analyzed by univariate logistic regression. Variables with a *P* value < 0.2 were further included in the multivariate logistic regression analysis. Bold style indicates statistical significance. BMI: Body mass index; CI: Confidence interval; Control: Exclude organic and functional diseases; FD: Functional dyspepsia; OD: Organic dyspepsia; OR: Odds ratio; SD: Standard deviation.

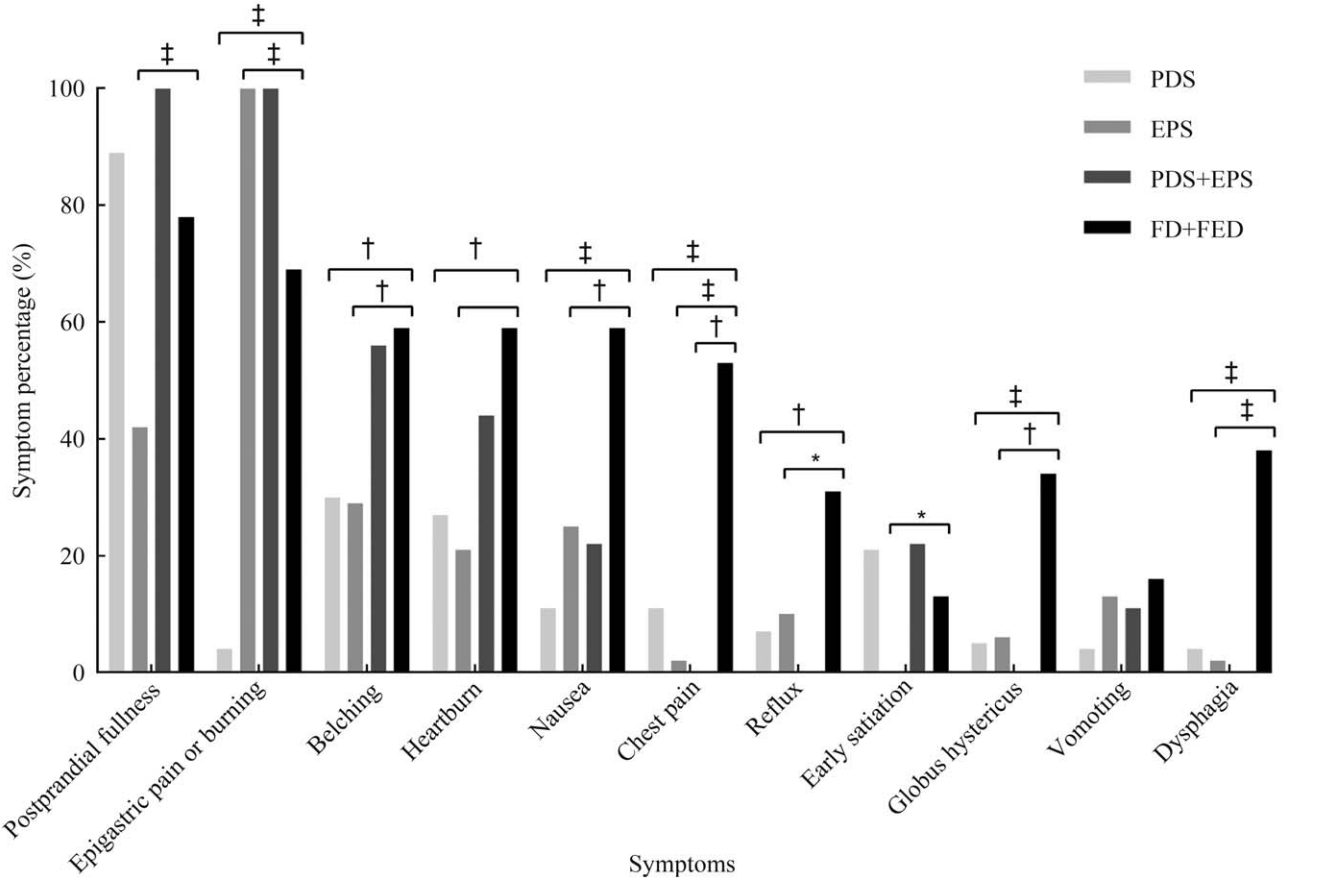

Figure 3: Distribution of symptoms in FD and its subtypes. $^{*}P < 0.050$; $^{\dagger}P < 0.010$; $^{\ddagger}P < 0.001$. EPS: Epigastric pain syndrome; FD + FED: Co-occurrence of functional dyspepsia and functional esophageal disorder; PDS: Postprandial distress syndrome; PDS + EPS: Co-occurrence of PDS and EPS.

patients with FD, some factors seemed to be related to the FD subgroups. For example, frequent spicy food consumption (OR: 2.088, 95% CI: 1.028–4.243) was a risk factor for PDS, while drinking deep well water (OR: 0.431, 95% CI: 0.251–0.741) was protective for PDS [Table 3].

Discussion

The prevalence of FD reported from several studies is dependent on the criterion used for a diagnosis. The Functional Gastrointestinal Disease Rome III Diagnostic

Table 3: Risk factors for FD and its subtypes compared to the control group.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
FD/control				
Age (years)	1.019 (0.994–1.044)	0.133	1.019 (0.994–1.045)	0.135
Marriage (married)	0.482 (0.195–1.195)	0.115	0.440 (0.176–1.100)	0.079
Eating fast	0.587 (0.328–1.050)	0.073	0.616 (0.342–1.107)	0.105
Helicobacter pylori positive	0.711 (0.501–1.008)	0.056	0.723 (0.509–1.026)	0.069
PDS/control				
Age (years)	1.029 (0.989–1.071)	0.155	1.028 (0.987–1.070)	0.181
Eating fast	0.348 (0.108–1.119)	0.077	0.385 (0.116–1.274)	0.118
Hot food preference	0.508 (0.182–1.416)	0.195	0.581 (0.206–1.645)	0.307
Spicy food preference	1.724 (0.859–3.463)	0.126	2.088 (1.028–4.243)	0.042
Drinking deep well water	0.429 (0.250–0.736)	0.002	0.431 (0.251–0.741)	0.002
EPS/control				
Age (years)	1.018 (0.968–1.049)	0.715	1.015 (0.974–1.057)	0.478
Marriage (married)	0.272 (0.037–1.985)	0.199	0.252 (0.034–1.853)	0.176
Liquid food preference	1.563 (0.826–2.957)	0.170	1.592 (0.840–3.018)	0.154
PDS + EPS/control				
Marriage (married)	1.736 (0.216–13.976)	0.604	0.256 (0.035–1.892)	0.182
Family size	0.657 (0.400–1.078)	0.097	0.963 (0.833–1.113)	0.613
Fresh fruit preference	0.334 (0.069–1.611)	0.172	1.384 (0.795–2.409)	0.250
H. pylori positive	0.171 (0.021–1.368)	0.096	1.105 (0.634–1.927)	0.725
FD + FED/control				
Male sex	1.640 (0.787–3.419)	0.187	1.583 (0.758–3.304)	0.221
Spicy food preference	0.256 (0.035–1.883)	0.181	0.269 (0.037–1.982)	0.197
H. pylori positive	0.455 (0.204–1.019)	0.055	0.472 (0.211–1.056)	0.068

All variables were analyzed by univariate logistic regression. Variables with a P value < 0.2 were further included in the multivariate logistic regression analysis. Bold style indicates statistical significance. CI: Confidence interval; Control: Exclude organic and functional diseases; EPS: Epigastric pain syndrome; FD + FED: Co-occurrence of functional dyspepsia and functional esophageal disorder; OR: Odds ratio; PDS: Postprandial distress syndrome; PDS + EPS: Co-occurrence of PDS and EPS; SD: Standard deviation.

Questionnaire is a relatively simple and reliable method for diagnosing FD and is suitable for screening large populations.[19,20] Limited by costs and tolerance, gastroscopy was not available to exclude the OD from UID disease in many studies. The prevalence of UID varies widely worldwide, ranging from 7.0% to 37.7% in Western countries[21] and 7.9% to 30.4% in Asian countries.[4] China has a high incidence of upper GI cancers, such as ESCC and gastric adenocarcinoma.[22,23] This study specifically investigated the middle-aged and elderly population in a region with a high incidence of ESCC. It also revealed possible diagnostic problems that can arise if the diagnosis relies solely on the Rome III questionnaire.

In our study, the UID detection rate by the Rome III questionnaire was 5.69%, of which 10.24% were OD cases. Among these OD cases, RE (13/17) was most frequently diagnosed, followed by ESCC (3/17) and DU (1/17). Our study population presented with distinct characteristics compared to other similar studies. Ford *et al*[24] summarized gastroscopy findings from several dyspepsia studies and revealed that the pooled detection rates of RE, DU, GU, gastric cancer, and esophageal cancer were 13.4%, 3.4%, 3.2%, 0.25%, and 0.1%, respectively. RE was the organic disease that was most commonly missed both in the literature and in our study. The detection rate of ESCC was higher in our OD patients than those in the Ford *et al*[24] study, which could be attributed to the specific population in the present study. Using the Rome III criteria, Xu *et al*[8] found upper GI organic diseases in 11.66% (45/386) of patients with dyspepsia in a rural area of Guangdong, China. Although their OD detection rate was similar to ours, the proportion of DU and GU cases in their study was much higher than ours. Compared to our results (*H. pylori* infection rate was 34.23%), the high *H. pylori* infection rate (55.21%) in that area might explain the OD distribution pattern. Although patients with OD were more likely to have heartburn and acid reflux in Hua County, there was no significant difference in symptoms between patients with OD and FD, suggesting that it is difficult to distinguish them based on questionnaires and clinical presentation. Therefore, patients with similar symptoms should undergo gastroscopy.

In our study, the male sex, low level of education, and frequent liquid food consumption were risk factors for OD, while fresh vegetable consumption was a protective factor. One study by Sardana *et al*[25] found that the intake of pickled and long-term preserved vegetables is a risk factor for esophageal cancer. However, eating both fresh fruits and vegetables was negatively associated with esophageal cancer, with a prominent protective effect of fresh vegetables. These findings are consistent with ours.[12,26-28] Guidelines from Western countries have

suggested that gastroscopy should be performed in patients aged 60 years or older with dyspepsia to exclude organic diseases.[29] However, Chen *et al*[30] reported that in Asia, especially in areas with a high prevalence of *H. pylori* infection and upper GI malignancies, the screening age should be lowered to 35 years or younger. If symptoms, such as acid reflux and heartburn, occur in middle-aged and elderly adults living in an area with a high incidence of ESCC, a gastroscopy should be performed to ensure that a diagnosis of ESCC and/or GERD is not missed.

According to the Rome III criteria, the worldwide prevalence of FD is 7.0% to 15.7%, with patients ranging from 20 to 84 years old.[31] At present, there are few extensive epidemiological studies on FD in the general population in China. In our study, we found that after making a definitive diagnosis by gastroscopy, the prevalence of FD in Hua County is 5.11%, which is not higher than the prevalence previously reported in other Asian populations.[32] Many factors may contribute to variations in worldwide prevalence of FD, such as ethnicity, economy, education, medical conditions, culture, dietary habits, and *H. pylori* infection. FD tends to occur more frequently in young and middle-aged people. Additionally, a fast-paced lifestyle, high work pressure, psychological disorders, and irregular diet may also lead to an increased prevalence of FD.[33] Contrarily, a large proportion of the elderly population has a slow-paced, low-pressure lifestyle in rural areas and the strict exclusion of organic diseases may lower the prevalence of FD. Moreover, many studies have shown that PDS and EPS can co-occur; the distribution of FD subtypes also varies geographically.[32,34,35] In our study, PDS was the most common subtype of FD.

FD symptoms originate in the gastroduodenal region. Tack *et al*[36] reported that the most prevalent symptoms in patients with dyspepsia are postprandial fullness, epigastric pain, early satiation, belching, epigastric burning, nausea, and vomiting. In our study, postprandial fullness and epigastric pain or burning commonly occurred in patients with FD. In addition to the typical dyspepsia symptoms, patients with FD also commonly presented with heartburn, reflux, belching, chest pain, dysphagia, and globus hystericus. Heartburn was not a typical FD symptom, but often co-occurred with it. More than 33% of FD patients report heartburn and reflux.[26] Additionally, belching was found to be more pronounced in patients from all three FD subtypes. Belching is also a common symptom of GERD; frequent belching can easily cause esophageal mucosa damage, leading to GERD. It is currently believed that overlap syndrome is more common among functional GI disorders. In our study, we found that patients with FD had some esophageal symptoms, which could be related to the specific lifestyle and diet of the region. Using the Rome III questionnaire, some patients were diagnosed with FED. We found that the proportion of patients who presented with typical esophageal and dyspepsia symptoms was higher in patients with FD + FED than in those with FD alone. This suggests that for patients with FD who have obvious or refractory symptoms, we should not only strictly exclude GERD but should also test for FED. FD and FED may coexist in patients because they share a similar pathogenesis, such as a motility disorder or visceral hypersensitivity. Further investigation into the causes of this co-occurrence is needed. Because the population of patients investigated in this study were from a region with a high incidence of ESCC, in-depth studies on the characteristics of esophageal diseases were warranted.

Previous studies have reported the risk factors of FD as the female sex; low level of education; higher socioeconomic status; the use of tobacco, alcohol, coffee or non-steroidal anti-inflammatory drugs; high-fat diets; consumption of foods containing wheat; and *H. pylori* infections.[21,33,34,37] We found that frequent consumption of spicy foods was a risk factor of PDS, which is consistent with previous findings from India and Iran.[38,39] On the contrary, drinking deep well water tended to be a protective factor for PDS. One study[40] has reported that infectious gastroenteritis is related to secondary dyspepsia and IBS. Patients who drink deep well water may be less prone to post-infectious FD, because the water is cleaner and more sterile than surface or shallow well water. Guidance regarding proper diet and lifestyle changes should be tailored for individual patients with FD based on the specific FD subtype and physiological characteristics of each patient. Although the infection rate of *H. pylori* was not significantly different between patients in the FD and control groups, we found that nausea and reflux symptoms were more severe in *H. pylori*-positive FD patients. This finding was likely caused by inflammation of the gastric mucosa microenvironment induced by *H. pylori* infection. Immune cells and cytokines would have then been stimulated, further exacerbating dyspepsia symptoms. Additionally, numerous studies[41-43] have shown that impaired permeability of the duodenal epithelial mucosal barrier, immune cell infiltration, and mucosal inflammation all play crucial roles in the pathogenesis of FD. The Kyoto Consensus[44] suggests that after *H. pylori* eradication, these symptoms should be relieved. Thus, an individualized assessment and additional studies need to be considered. This study has a limitation. The age range of the population was limited to middle-aged and older people. Therefore, our findings do not fully reflect the full epidemiological features of FD in the region.

Using gastroscopy, we assessed the prevalence of FD in a middle-aged and elderly population from a region with a high incidence of ESCC. We found that the prevalence of UID was 5.69%, while the actual prevalence of FD was 5.11% (mainly PDS). RE and ESCC were the predominant OD that were missed in UID cases diagnosed solely by the Roma III questionnaire. About 20% of patients had FD combined with FED, suggesting that in this area, middle-aged and elderly patients with upper GI symptoms should undergo endoscopies to exclude OD.

Acknowledgements

The authors thank the following collaborators for their contributions to the endoscopy examinations: Chuan-Hai Guo, Li-Xin Zhang, Ying Chen, Yu-Jie He, and Cai-Yun Wang from Anyang Cancer Hospital.

Funding

The study was supported by a grant from the Chinese Charity Project of National Ministry of Health (No. 201202014).

Conflicts of interest

None.

References

1. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, *et al*. Functional gastroduodenal disorders. Gastroenterology 2006;130:1466–1479. doi: 10.1053/j.gastro.2005.11.059.
2. Mahadeva S, Goh KL. Epidemiology of functional dyspepsia: a global perspective. World J Gastroenterol 2006;12:2661–2666. doi: 10.3748/wjg.v12.i17.2661.
3. Enck P, Azpiroz F, Boeckxstaens G, Elsenbruch S, Feinle-Bisset C, Holtmann G, *et al*. Functional dyspepsia. Nat Rev Dis Primers 2017;3:17081. doi: 10.1038/nrdp.2017.81.
4. Ghoshal UC, Singh R, Chang FY, Hou X, Wong BCY, Kachintorn U, *et al*. Epidemiology of uninvestigated and functional dyspepsia in Asia: facts and fiction. J Neurogastroenterol Motil 2011;17:235–244. doi: 10.5056/jnm.2011.17.3.235.
5. Zhao Y, Zou D, Wang R, Ma X, Yan X, Man X, *et al*. Dyspepsia and irritable bowel syndrome in China: a population-based endoscopy study of prevalence and impact. Aliment Pharmacol Ther 2010;32:562–572. doi: 10.1111/j.1365-2036.2010.04376.x.
6. Li Y, Nie Y, Sha W, Su H. The link between psychosocial factors and functional dyspepsia: an epidemiological study. Chin Med J (Engl) 2002;115:1082–1084.
7. Zhang AZ, Wang QC, Huang KM, Huang JG, Zhou CH, Sun FQ, *et al*. Prevalence of depression and anxiety in patients with chronic digestive system diseases: a multicenter epidemiological study. World J Gastroenterol 2016;22:9437–9444. doi: 10.3748/wjg.v22.i42.9437.
8. Xu JH, Lai Y, Zhuang LP, Huang CZ, Li CQ, Chen QK, *et al*. Certain dietary habits contribute to the functional dyspepsia in South China Rural Area. Med Sci Monit 2017;23:3942–3951. doi: 10.12659/msm.902705.
9. Dong YY, Chen FX, Yu YB, Du C, Qi QQ, Liu H, *et al*. A school-based study with Rome III criteria on the prevalence of functional gastrointestinal disorders in Chinese college and university students. PLoS One 2013;8:e54183. doi: 10.1371/journal.pone.0054183.
10. Liu M, Liu Z, Cai H, Guo C, Li X, Zhang C, *et al*. A model to identify individuals at high risk for esophageal squamous cell carcinoma and precancerous lesions in regions of high prevalence in China. Clin Gastroenterol Hepatol 2017;15:1538–1546. doi: 10.1016/j.cgh.2017.03.019.
11. Liu Z, Guo C, He Y, Chen Y, Ji P, Fang Z, *et al*. A clinical model predicting the risk of esophageal high-grade lesions in opportunistic screening: a multicenter real-world study in China. Gastrointest Endosc 2020;91:1253–1260. doi: 10.1016/j.gie.2019.12.038.
12. Wang K, Zhang L, He ZH, Liu ZJ, Zhang L, Hu N, *et al*. A population-based survey of gastroesophageal reflux disease in a region with high prevalence of esophageal cancer in China. Chin Med J (Engl) 2019;132:1516–1523. doi: 10.1097/CM9.0000000000000275.
13. He Z, Liu Z, Liu M, Guo C, Xu R, Li F, *et al*. Efficacy of endoscopic screening for esophageal cancer in China (ESECC): design and preliminary results of a population-based randomised controlled trial. Gut 2019;68:198–206. doi: 10.1136/gutjnl-2017-315520.
14. Ghoshal UC, Gwee KA, Chen M, Gong XR, Pratap N, Hou X, *et al*. Development, translation and validation of enhanced Asian Rome III Questionnaires for diagnosis of functional bowel diseases in major Asian languages: a Rome Foundation-Asian Neurogastroenterology and Motility Association Working Team Report. J Neurogastroenterol Motil 2015;21:83–92. doi: 10.5056/jnm14045.
15. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. Global Consensus Group. The montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900–1920. doi: 10.1111/j.1572-0241.2006.00630.x.
16. Lin SR, Xu GM, Hu PJ, Zhou LY, Chen MH, Ke MY, *et al*. Chinese consensus on gastroesophageal reflux disease (GERD): October 2006, Sanya, Hainan Province, China. J Dig Dis 2007;8:162–169. doi: 10.1111/j.1443-9573.2007.00298.x.
17. Gastroenterology Branch of Chinese Medical Association. Chinese consensus on chronic gastritis (Shanghai, 2017). Chin J Dig 2017;37:721–738. doi: 10.3760/cma.j.issn.0254-1432.2017.11.001.
18. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumours of the Digestive System. 2010;World Health Organization,
19. Xiong LS, Shi Q, Gong XR, Cui Y, Chen MH. The spectra, symptom profiles and overlap of Rome III functional gastrointestinal disorders in a tertiary center in South China. J Dig Dis 2014;15:538–544. doi: 10.1111/1751-2980.12178.
20. Kanazawa M, Nakajima S, Oshima T, Whitehead WE, Sperber AD, Palsson OS, *et al*. Validity and reliability of the Japanese Version of the Rome III diagnostic Questionnaire for irritable bowel syndrome and functional dyspepsia. J Neurogastroenterol Motil 2015;21:537–544. doi: 10.5056/jnm15016.
21. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. Gut 2015;64:1049–1057. doi: 10.1136/gutjnl-2014-307843.
22. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. doi: 10.3322/caac.21492.
23. Chen W, Sun K, Zheng R, Zeng H, Zhang S, Xia C, *et al*. Cancer incidence and mortality in China, 2014. Chin J Cancer Res 2018;30:1–12. doi: 10.21147/j.issn.1000-9604.2018.01.01.
24. Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. Clin Gastroenterol Hepatol 2010;8:830–837. doi: 10.1016/j.cgh.2010.05.031.
25. Sardana RK, Chhikara N, Tanwar B, Panghal A. Dietary impact on esophageal cancer in humans: a review. Food Funct 2018;9:1967–1977. doi: 10.1039/c7fo01908d.
26. Richter JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. Gastroenterology 2018;154:267–276. doi: 10.1053/j.gastro.2017.07.045.
27. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut 2018;67:430–440. doi: 10.1136/gutjnl-2016-313589.
28. Kusano M, Hosaka H, Yasuoka H, Kawamura O, Kawada A, Kuribayashi S, *et al*. New endoscopic classification of cascade stomach, a risk factor for reflux esophagitis. J Gastroenterol 2017;52:211–217. doi: 10.1007/s00535-016-1214-0.
29. Moayyedi P, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol 2017;112:988–1013. doi: 10.1038/ajg.2017.154.
30. Chen SL, Gwee KA, Lee JS, Miwa H, Suzuki H, Guo P, *et al*. Systematic review with meta-analysis: prompt endoscopy as the initial management strategy for uninvestigated dyspepsia in Asia. Aliment Pharmacol Ther 2015;41:239–252. doi: 10.1111/apt.13028.
31. Oshima T, Miwa H. Epidemiology of functional gastrointestinal disorders in Japan and in the world. J Neurogastroenterol Motil 2015;21:320–329. doi: 10.5056/jnm14165.
32. Matsuzaki J, Suzuki H, Asakura K, Fukushima Y, Inadomi JM, Takebayashi T, *et al*. Classification of functional dyspepsia based on concomitant bowel symptoms. Neurogastroenterol Motil 2012;24:164–325. doi: 10.1111/j.1365-2982.2011.01859.x.
33. Stanghellini V, Chan FKL, Hasler WL, Malagelada JR, Suzuki H, Tack J, *et al*. Gastroduodenal disorders. Gastroenterology 2016;150:1380–1392. doi: 10.1053/j.gastro.2016.02.011.
34. Kim SE, Kim N, Lee JY, Park KS, Shin JE, Nam K, *et al*. Prevalence and risk factors of functional dyspepsia in health check-up population: a Nationwide Multicenter Prospective Study. J Neurogastroenterol Motil 2018;24:603–613. doi: 10.5056/jnm18068.
35. Carbone F, Vanuytsel T, Tack J. Analysis of postprandial symptom patterns in subgroups of patients with Rome III or Rome IV functional dyspepsia. Clin Gastroenterol Hepatol 2020;18:838–846.e3. doi: 10.1016/j.cgh.2019.07.053.
36. Tack J, Talley NJ. Functional dyspepsia – symptoms, definitions and validity of the Rome III criteria. Nat Rev Gastroenterol Hepatol 2013;10:134–141. doi: 10.1038/nrgastro.2013.14.
37. Duncanson KR, Talley NJ, Walker MM, Burrows TL. Food and functional dyspepsia: a systematic review. J Hum Nutr Diet 2018;31:390–407. doi: 10.1111/jhn.12506.
38. Goktas Z, Koklu S, Dikmen D, Ozturk O, Yilmaz B, Asil M, *et al*. Nutritional habits in functional dyspepsia and its subgroups: a comparative study. Scand J Gastroenterol 2016;51:903–907. doi: 10.3109/00365521.2016.1164238.

39. Saneei P, Sadeghi O, Feizi A, Keshteli AH, Daghaghzadeh H, Esmaillzadeh A, *et al*. Relationship between spicy food intake and chronic uninvestigated dyspepsia in Iranian adults. J Dig Dis 2016;17:28–35. doi: 10.1111/1751-2980.12308.
40. Futagami S, Itoh T, Sakamoto C. Systematic review with meta-analysis: post-infectious functional dyspepsia. Aliment Pharmacol Ther 2015;41:177–188. doi: 10.1111/apt.13006.
41. Vanheel H, Vicario M, Vanuytsel T, Van Oudenhove L, Martinez C, Keita AV, *et al*. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. Gut 2014;63:262–271. doi: 10.1136/gutjnl-2012-303857.
42. Holtmann G, Talley NJ. Functional dyspepsia. Curr Opin Gastroenterol 2015;31:492–498. doi: 10.1097/MOG.0000000000000219.
43. Wauters L, Nightingale S, Talley NJ, Sulaiman B, Walker MM. Functional dyspepsia is associated with duodenal eosinophilia in an Australian paediatric cohort. Aliment Pharmacol Ther 2017;45:1358–1364. doi: 10.1111/apt.14045.
44. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, *et al*. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut 2015;64:1353–1367. doi: 10.1136/gutjnl-2015-309252.

How to cite this article: Hu N, Wang K, Zhang L, Liu ZJ, Jin Z, Cui RL, Zhang HJ, He ZH, Ke Y, Duan LP. Epidemiological and clinical features of functional dyspepsia in a region with a high incidence of esophageal cancer in China. Chin Med J 2021;134:1422–1430. doi: 10.1097/CM9.0000000000001584