
Article:
Ford, AC orcid.org/0000-0001-6371-4359, Bercik, P, Morgan, DG et al. (3 more authors) (2014) The Rome III Criteria for the Diagnosis of Functional Dyspepsia in Secondary Care Are Not Superior to Previous Definitions. Gastroenterology, 146 (4). pp. 932-940. ISSN 0016-5085

https://doi.org/10.1053/j.gastro.2014.01.014

TITLE PAGE

Title: The Rome III Criteria for the Diagnosis of Functional Dyspepsia in Secondary Care are not Superior to Previous Definitions

Short title: Rome III Criteria for Functional Dyspepsia.

Authors: Alexander C Ford[1, 2], Premysl Bercik[3], David G Morgan[4], Carolina Bolino[3], Maria Ines Pintos-Sanchez[3], Paul Moayyedi[3].

[1]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

[3]Farncombe Family Digestive Health Research Institute, Gastroenterology Division, McMaster University, Health Sciences Center, Hamilton, Ontario, Canada.

[4]Gastroenterology Department, St. Joseph's Healthcare, Hamilton, Ontario, Canada.

Grant support: Canadian Association of Gastroenterology (the study sponsor had no role in the study design, collection, analysis, or interpretation of data).

Abbreviations:

BMI	body mass index
CI	confidence interval
EPS	epigastric pain syndrome
FD	functional dyspepsia
GI	gastrointestinal
LR	likelihood ratio

PDS	postprandial distress syndrome
SD	standard deviation

Correspondence: Dr. Alex Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132684963

Facsimile: +441132429722

Disclosures: ACF: none to declare. PB: is a recipient of a Hamilton Health Sciences Early Career Award. DGM: none to declare. CB: none to declare. MIP-S: none to declare. PM: none to declare.

Writing assistance: None

Author contributions: ACF, PB, DGM, CB, MIP-S, and PM conceived and drafted the study. ACF, CB, and MIP-S collected all data. ACF analyzed and interpreted the

data. PM provided statistical advice and support. ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

Word count: 6294

ABSTRACT

Background & aims: Although the Rome III criteria for functional dyspepsia were defined 7 years ago, they have yet to be validated in a rigorous study. We addressed this issue in a secondary-care population.

Methods: We analyzed complete symptom, upper gastrointestinal (GI) endoscopy, and histology data from 1452 consecutive adult patients with GI symptoms at 2 hospitals in Hamilton, Ontario. Assessors were blinded to symptom status. Individuals with normal upper GI endoscopy and histopathology findings from analyses of biopsy specimens were classified as having no organic GI disease. The reference standard used to define presence of true FD was epigastric pain, early satiety or post-prandial fullness, and no organic GI disease. Sensitivity, specificity, and positive and negative likelihood ratios (LRs), with 95% confidence intervals (CIs), were calculated.

Results: Of the 1452 patients, 722 (49.7%) met Rome III criteria for FD. Endoscopy revealed organic GI disease in 170 patients (23.5%) who met the Rome III criteria. The Rome III criteria identified patients with functional dyspepsia with 60.7% sensitivity, 68.7% specificity, a positive LR of 1.94 (95% CI, 1.69–2.22), and a negative LR of 0.57 (95% CI, 0.52–0.63). In contrast, the Rome II criteria identified patients with functional dyspepsia with 71.4% sensitivity, 55.6% specificity, a positive LR of 1.61 (95% CI, 1.45–1.78), and a negative LR of 0.51 (95% CI, 0.45–0.58). The area under a receiver operating characteristics curves did not differ significantly for any of the diagnostic criteria for functional dyspepsia.

Conclusions: In a validation study of 1452 patients with GI symptoms, the Rome III criteria performed only modestly in identifying those with functional dyspepsia, and were not significantly superior to previous definitions.

Keywords: Functional dyspepsia; Rome III criteria; accuracy; sensitivity; specificity

INTRODUCTION

Dyspepsia is a symptom complex referable to the upper gastrointestinal (GI) tract. The prevalence of dyspepsia in the community varies between 5% and 40%, depending on the geographical region under study, but also on the criteria used to define its presence. [1-4] The condition has significant implications both for sufferers, due to impaired quality of life and sickness absence from work, [5-9] and society as a whole, due to medical expenses arising from managing the condition. A recent questionnaire survey reported that the mean yearly cost of dyspepsia to patients was almost $700, [10] and burden of illness studies in the USA estimated that there were almost 2 million physician visits in 2009 as a result of dyspepsia, [11] and >30% of endoscopies were performed with dyspepsia as the main indication. [12] Despite this, dyspepsia does not appear to impact adversely on survival. [13, 14]

The cost of managing dyspepsia may be reduced if upper GI symptoms could accurately distinguish between organic and functional dyspepsia (FD), but a systematic review has suggested that symptoms perform poorly in this regard. [15] The commonest organic finding at upper GI endoscopy in Western populations with dyspepsia is erosive esophagitis, [16] and over the last 20 years definitions of the condition have been refined substantially, [17-20] with the main aim of excluding patients with gastro-esophageal reflux disease (GERD), in an attempt to enrich the number of patients with FD.

The latest definition of FD is the Rome III criteria, [18] which consist of one or more of the following symptoms: epigastric pain or burning, postprandial fullness after a normal sized meal, or early satiety. This is stricter than previous definitions of FD in excluding patients with reflux symptoms, and should therefore classify fewer

patients with GERD incorrectly as having FD. The Rome III criteria were published over 7 years ago and yet there has been little in the way of validation of these criteria. We have therefore evaluated their accuracy in identifying patients with FD in a secondary care setting. We also compared Rome III with previous definitions of FD to assess whether they are superior to other approaches, and in particular whether they perform better in excluding patients with erosive esophagitis.

METHODS

Participants and Setting

This study was conducted among patients newly referred from primary care to secondary care for consideration of investigation of upper or lower GI symptoms. Unselected consecutive new patients aged ≥16 years were approached in the GI outpatient clinics of McMaster University Medical Center or St. Joseph's Healthcare, two hospitals in Hamilton, Ontario serving a local population of 520,000. During a monitoring period from January 2012 to December 2012, 26% of the referrals to the clinics were tertiary care in nature. There were no exclusion criteria, other than an inability to understand written English. Potentially eligible subjects were provided with a patient information leaflet about the study at their initial clinic visit, prior to consultation with a Gastroenterologist. Those who agreed to participate were asked to provide written informed consent at that visit. The Hamilton Health Sciences and McMaster University research ethics board approved the study in January 2008, and recruitment ended in December 2012. We have previously conducted a validation study of the Rome III criteria for irritable bowel syndrome among individuals with lower GI symptoms undergoing colonoscopy using this dataset. [21] In this study we set out to validate the Rome III criteria for FD among individuals with upper GI symptoms undergoing upper GI endoscopy.

Data Collection and Synthesis

Demographic and Symptom Data

All demographic and symptom data were collected prospectively at the initial clinic visit, and hence prior to referral for upper GI endoscopy. Basic demographic data included age, gender, ethnicity, marital status, educational level, lifestyle (tobacco and alcohol use), height (in meters), and weight (in kilograms), which were used to calculate body mass index (BMI). Symptom data were captured using the Rome III diagnostic questionnaire for the adult functional GI disorders, [22] but we also collected data in order to examine the accuracy of the Rome II criteria, [20] and a broad definition in line with the 1988 working party report, [17] in diagnosing FD. All questionnaire data were entered into a database by a trained researcher, who was not involved with the clinical care of the patients, thus ensuring assessors were blinded to symptom status.

Definitions of FD

The presence or absence of Rome III-defined FD among individual patients was assigned according to the scoring algorithm proposed for use with the Rome III questionnaire, which is detailed in Supplementary Table 1. As the questionnaire contained other symptom items, we were also able to classify the presence or absence of FD according to the following previously accepted gold-standard symptom-based criteria, which preceded the Rome III criteria: the Rome II criteria, [20] and a broad definition of FD (see supplementary Table 1). [17]

The questionnaire also contained the individual symptom items used to subtype Rome III FD, allowing us to classify the presence or absence of epigastric

pain syndrome (EPS) and postprandial distress syndrome (PDS) (Supplementary Table 1). As the definition of EPS is very restrictive, we performed a sensitivity analysis where EPS was defined using only the presence of symptoms >once per week for ≥6 months, without applying the other required features. In addition, as the definition of PDS does not exclude heartburn we performed a sensitivity analysis where those reporting this symptom at a frequency of >once per month were excluded from the definition.

Endoscopic and Histopathological Data

All included patients underwent complete upper GI endoscopy to the second part of the duodenum, using Pentax endoscopes (Pentax Canada, Inc), following a 6-hour fast. The responsible physician performing upper GI endoscopic examinations remained blinded to the questionnaire data of the patient. Findings were recorded using the endoPRO reporting system (Pentax Canada, Inc), and study investigators accessed these reports to record the ultimate endoscopic diagnosis for each included patient. We classified the following findings as being consistent with organic disease at upper GI endoscopy: evidence of erosive esophagitis, Barrett's esophagus, benign esophageal stricture, Schatzki ring, esophageal carcinoma, esophageal candidiasis, gastric ulcer, gastric cancer, or duodenal ulcer. Cystic fundic gland polyps, gastritis diagnosed after histological interpretation of gastric biopsy specimens, or duodenitis, defined as erythema in the duodenum seen at upper GI endoscopy, were not considered to represent organic disease. However, gastric or duodenal erosions were classified as organic in nature, and were reported separately from peptic ulcer, unless there were ≥5 gastric erosions, in which case the patient was classified as having gastric ulcer.

Biopsy specimens were obtained at the discretion of the responsible physician performing the upper GI endoscopy. Experienced GI histopathologists, who remained blinded to the questionnaire data of the patient, interpreted these biopsies. Histopathological findings were recorded using the MEDITECH Healthcare Reporting System (Medical Information Technology Inc, Westwood, MA, USA), and this was accessed by the study investigators in order to record the ultimate histopathological diagnosis. We classified the following findings as being consistent with organic disease at histopathological examination of biopsy specimens: Barrett's esophagus, reflux or eosinophilic esophagitis, esophageal squamous cell or adenocarcinoma, esophageal candidiasis, gastric adenocarcinoma, gastric carcinoid, upper GI Crohn's disease, celiac disease, villous atrophy due to other causes, or duodenal adenocarcinoma.

Definition of Organic Upper GI disease

Using these data we were able to classify patients according to the presence or absence of organic upper GI disease. Individuals with no evidence of organic disease at both upper GI endoscopy and histopathological examination of biopsy specimens were classified as exhibiting no organic upper GI disease, while those with evidence of organic disease at either upper GI endoscopy or histopathological examination of biopsy specimens were classified as exhibiting organic upper GI disease.

Reference Standard

The reference standard used to define the presence of true FD was the presence of any of epigastric pain or burning, postprandial fullness, or early satiety in a patient who exhibited no evidence of organic upper GI disease after upper GI

endoscopy and histological interpretation of biopsies (if obtained) that would explain these symptoms. The reference standard used to define presence of EPS was the presence of any degree of epigastric pain or burning, in a patient who exhibited no evidence of organic upper GI disease after upper GI endoscopy and normal histological interpretation of biopsies (if obtained). The reference standard used to define PDS was the presence of any degree of postprandial fullness or early satiety, again in a patient who exhibited no evidence of organic upper GI disease after upper GI endoscopy and histological interpretation of biopsies (if obtained).

Statistical Analysis

In order to assess whether those who underwent upper GI endoscopy were representative of all patients seen in the two GI outpatient clinics demographic data were compared between those undergoing upper GI endoscopy who completed the symptom questionnaire, and those who completed the symptom questionnaire but did not undergo upper GI endoscopy, using a χ^2 test for categorical data, and an independent samples *t*-test for continuous data, with a mean and standard deviation (SD). Due to multiple comparisons a 2-tailed P value of <0.01 was considered statistically significant for these analyses. We compared organic findings in those meeting the Rome III criteria for FD with those who did not, as well as according to FD symptom subtype, using Fisher's exact test, as numbers in each cell were relatively small. These statistical analyses were performed using SPSS for Windows version 19.0 (SPSS Inc, Chicago, IL, USA).

The primary aim of the study was to describe the performance of the Rome III criteria for FD in evaluating the presence of true FD versus the reference standard. However, we also wanted to compare the performance of the Rome III criteria for FD

with previously available symptom-based diagnostic criteria including the Rome II criteria, and a broad definition of FD, as well as the performance of the Rome III FD symptom subtypes of EPS and PDS. The sensitivity, specificity, and positive and negative predictive values, and their 95% confidence intervals (CIs), were calculated for each of these using a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA). The positive likelihood ratio (LR) and negative LR, and their 95% CIs, were also calculated using the same spreadsheet. The positive LR can be calculated from the formula: positive LR = sensitivity / (1-specificity), while the negative LR is derived from the formula: negative LR = (1-sensitivity) / specificity. These calculations were checked using Meta-DiSc® version 1.4 (Universidad Complutense, Madrid, Spain). The area under a receiver operating characteristics curve, with a 95% CI, was calculated for each of these three definitions of FD using SPSS for Windows version 19.0 (SPSS Inc, Chicago, IL, USA), and this was compared between the three using a one-way analysis of variance.

RESULTS

There were a total of 4224 consecutive new patients who gave informed consent and were recruited into the study between January 2008 and December 2012 (Figure 1). The mean age of recruited subjects was 47.6 years (range 16 to 93 years) and 2617 (62.0%) were female. In total, 1605 (38.0%) of these 4224 patients underwent complete endoscopic evaluation for their upper GI symptoms. The mean age among those undergoing upper GI endoscopy was 48.9 years (range 16 to 91), and 1018 (63.4%) were female.

Characteristics of Included Individuals

There were 1452 individuals providing complete symptom, upper GI endoscopy, and histology data. Demographic data of all these patients, compared with the 2619 subjects who did not undergo upper GI endoscopy, are provided in Table 1. Those undergoing upper GI endoscopy were slightly older, were less likely to be White Caucasian, and were more likely to meet the Rome III criteria for FD, but there were no other significant differences in demographics between the two groups.

In total, 722 (49.7%) of the 1452 patients undergoing upper GI endoscopy met the Rome III criteria for FD. The mean age of these 722 individuals was 46.4 years, and 496 (68.7%) were female. Organic pathology was detected at upper GI endoscopy in 170 (23.5%) of the 722 patients meeting the Rome III criteria for FD, with 29 individuals demonstrating more than one pathology. Erosive esophagitis and peptic ulcer disease were the commonest, occurring in 11.2% and 7.8% of individuals respectively, while gastro-esophageal malignancy was extremely rare, occurring in only two patients (0.28%). The prevalence of individual organic findings after upper

GI endoscopy and examination of biopsies, where obtained, in those who met the Rome III criteria for FD, compared with those who did not, are detailed in Table 2. The only significant difference was the prevalence of eosinophilic esophagitis, which was commoner among those who did not meet the Rome III criteria for FD (1.6% versus 0.1%, P = 0.003).

Of the 722 individuals with dyspepsia, 24 (3.3%) met criteria for EPS alone, 663 (91.8%) met criteria for PDS alone, and 35 (4.8%) met criteria for both EPS and PDS, giving a prevalence for EPS among those undergoing endoscopy of 4.1%, compared with 48.1% for PDS. Organic findings according to FD symptom subtype are provided in Table 3. When the less restrictive definition of EPS was used there were 851 individuals with dyspepsia, 153 (18.0%) of whom met criteria for EPS alone, 347 (40.8%) met criteria for PDS alone, and 351 (41.2%) met criteria for both EPS and PDS. This gave a prevalence of EPS among those undergoing endoscopy of 34.7%, compared with 48.1% for PDS.

Validation of the Rome III Criteria for FD

Among the 909 patients with a diagnosis of FD according to the reference standard following upper GI endoscopy, 552 met the Rome III criteria for FD, giving a sensitivity of 60.7% (Table 4). Among 543 subjects who were not judged to have FD according to the reference standard, 373 did not meet the Rome III criteria, giving a specificity of 68.7%. The positive LR of the Rome III criteria for the diagnosis of FD was therefore 1.94 (95% CI 1.69 to 2.22), while the negative LR was 0.57 (95% CI 0.52 to 0.63). The area under the receiver operating characteristics curve for the Rome III criteria was 0.65 (95% CI 0.62 to 0.68).

Validation of the Rome III Symptom Subtypes for FD

We also compared the performance of the two dyspepsia symptom subtypes, EPS and PDS, against their reference standards. We report the results of these analyses in the supplementary materials provided online.

Degree of Overlap Between FD Symptom Subtypes

Among the 552 individuals who met the Rome III criteria for FD, and who were confirmed as having FD according to the gold-standard, complete symptom data were available for EPS and PDS subtypes in 538. Of these, 16 (3.0%) met criteria for EPS alone, 489 (90.9%) met criteria for PDS alone, and 33 (6.1%) met criteria for both. When the less restrictive definition of EPS was used, the degree of overlap increased considerably, with 16 (3.0%) patients having EPS alone, 241 (44.8%) meeting criteria for PDS alone, and 281 (52.2%) meeting criteria for both.

Validation of the Rome II Criteria for FD

Among the 947 patients with a diagnosis of FD according to the reference standard, 676 met the Rome II criteria for FD, giving a sensitivity of 71.4% (Table 4). Among 550 subjects who were not judged to have FD according to the reference standard, 306 did not meet the Rome II criteria, giving a specificity of 55.6%. The positive LR of the Rome II criteria for the diagnosis of FD was therefore 1.61 (95% CI 1.45 to 1.78), while the negative LR was 0.51 (95% CI 0.45 to 0.58). The area under the receiver operating characteristics curve for the Rome II criteria was 0.64 (95% CI 0.61 to 0.67).

Validation of a Broad Definition of FD

Among the 988 patients with a diagnosis of FD according to the reference standard following upper GI endoscopy, 909 met the broad definition for FD, giving a sensitivity of 92.0% (Table 4). Among 559 subjects who were not judged to have FD according to the reference standard, 160 did not report symptoms compatible with a broad definition of FD, giving a specificity of 28.6%. The positive LR of a broad definition of FD was therefore 1.29 (95% CI 1.22 to 1.36), while the negative LR was 0.28 (95% CI 0.22 to 0.36). The area under the receiver operating characteristics curve for a broad definition of FD was 0.61 (95% CI 0.58 to 0.64).

Comparison of the Definitions of FD

There was no statistically significant difference between the area under the receiver operating characteristics curve for Rome III, Rome II or a broad definition of FD (P = 0.15, repeated measures one-way analysis of variance).

Prevalence of Erosive Esophagitis According to FD Definition

Among the 722 patients with Rome III-defined FD, 81 (11.2%; 95% CI 9.1% to 13.7%) were found to have erosive esophagitis at upper GI endoscopy. This compared with 104 (11.2%; 95% CI 9.3% to 13.4%) of 931 subjects meeting the Rome II criteria for FD, and 157 of (11.8%; 95% CI 10.2% to 13.7%) 1327 individuals who reported symptoms compatible with a broad definition of FD.

DISCUSSION

This study has attempted to validate the Rome III criteria for FD against an accepted reference standard. It has demonstrated that these criteria perform only modestly in predicting a diagnosis of FD in a patient with upper GI symptoms, with their presence increasing the likelihood of having FD by around two-fold, whilst their absence reduces the likelihood of FD by approximately 40%. When the individual symptom subtypes of EPS and PDS were examined, the presence of EPS increased the likelihood of FD by over six-fold, but the negative LR was poor at 0.94. The less restrictive definition of EPS performed much better, in terms of the negative LR which was 0.50, and the positive LR remained above 4. The criteria for PDS performed similarly in terms of negative LR, but the positive LR was less than 3. Refining the criteria for PDS led to an improvement in the positive, but not the negative, LR. Prevalence of the EPS subtype was only 4% in our primary analysis, due to the restrictive nature of the Rome III definition. When the definition was relaxed in our sensitivity analysis the prevalence increased to almost 35%. In both analyses >50% of individuals with EPS also met criteria for PDS, questioning the clinical relevance of these subtypes.

The Rome III criteria performed similarly to the Rome II criteria, in terms of the positive and negative LRs obtained. However, the positive LR of the Rome III criteria was higher than that for a broad definition of FD, although the negative LR for a broad definition was lower. Analysis of the area under the receiver operating characteristics curve for all three diagnostic criteria demonstrated very similar results, with overlapping 95% CIs, and there was no statistically significant difference in their performance. Despite one of the rationales for the revision of the Rome III criteria

being to allow separation of FD and GERD more clearly, almost identical proportions of patients meeting criteria for each of the different definitions of FD we studied were found to have erosive esophagitis at upper GI endoscopy.

Strengths of this study include the large sample size, with >1400 individuals undergoing upper GI endoscopy and providing complete symptom data. We also validated the two FD symptom subtypes of EPS and PDS, and performed a sensitivity analysis using a less restrictive definition of EPS, and a more restrictive definition of PDS. In addition, the study was designed to adhere closely to the STARD guidelines for the reporting of studies of diagnostic accuracy, with consecutive patients recruited, assessors blinded, and an accepted reference standard used. Finally, the fact that the majority of patients we recruited were unselected referrals to secondary care means that the results are likely to be generalizable to Gastroenterologists consulting with individuals with suspected FD in usual clinical practice, but not to a primary care setting, where many patients with FD are managed.

Weaknesses of the study include the fact that we did not mandate endoscopy in all individuals with upper GI symptoms as part of the study design. This means that patients were managed according to the judgment of the physician they were consulting with. There were a total of 750 patients who also met the Rome III criteria for FD but who did not undergo endoscopy, and if the diagnosis were also correct in this group of patients then the true positive rate of the Rome III criteria will have been artificially reduced, leading to an underestimation of their accuracy. In addition, those who did undergo endoscopy and provide complete symptom data were not entirely representative of the entire study population, with an under representation of White Caucasians, younger individuals, and alcohol users. However, in most cases the absolute differences in demographic data between those undergoing endoscopy and

providing complete symptom data and those who did not were modest. The reference standard included symptom data from the questionnaire, although if anything this would have led to an overestimation of the accuracy of the Rome III criteria for FD. As the presence of any degree of erosive esophagitis at upper GI endoscopy was classed as an organic disease, regardless of correlation with symptoms, this may have led to misclassification of patients with true FD as organic disease, hence underestimating the sensitivity and positive predictive value of the Rome III criteria. Finally, the decision to take biopsies at upper GI endoscopy was in the hands of the responsible physician, and there is likely to be considerable variability between individual endoscopists in the reporting of macroscopic findings thought to be representative of duodenitis, meaning that some other patients may have been misclassified as having functional, rather than organic, disease. However, given that we did not classify histologic gastritis as organic disease, and we treated gastric and duodenal erosions as organic disease, it is unlikely that that these issues will have led to any great degree of misclassification.

As this study was conducted within usual clinical practice, and there is no accepted gold-standard for the diagnosis of FD, other than a normal endoscopy, we did not mandate a minimum diagnostic work-up such as complete blood count, C-reactive protein, celiac serology, abdominal ultrasound scan, or gastric scintigraphy in all individuals. Our study assumed that where initial blood tests were abnormal, these would have prompted the responsible physician to request further appropriate investigations to exclude organic disease. However, where celiac serology was positive, distal duodenal biopsy was performed, and those individuals with celiac disease were classified as having organic disease within our analyses. The relevance of these issues is debatable. A previous meta-analysis has demonstrated that the

prevalence of celiac disease in patients with dyspeptic symptoms is no higher than among individuals without, [23] emptying rates during gastric scintigraphy appear to correlate poorly with symptoms, [24] and the yield of abdominal ultrasound in detecting relevant organic pathology in dyspeptic patients with a normal upper GI endoscopy was <5% in one primary care-based study. [25]

There have been few studies that have attempted to validate the Rome III criteria for FD, to our knowledge, to date. In a small study from Malaysia, Lee *et al.* applied a Malaysian translation of the Rome III questionnaire for the functional GI disorders in primary care. [26] The authors reported that 19 patients met criteria for FD, of whom 16 had a negative endoscopy, giving a positive predictive value of 84%. In a larger Pakistani study, 191 patients fulfilling Rome III criteria for FD underwent upper GI endoscopy, and true FD was confirmed in 136, giving a positive predictive value of 71%. [27] However, as neither of these studies reported endoscopic findings among those without Rome III FD the positive and negative LRs cannot be calculated.

A previous meta-analysis of population-based studies that performed endoscopy in subjects with dyspepsia reported that 23.6% had clinically significant findings after investigation. [16] Despite being conducted in a secondary care setting, the proportion of individuals who met the Rome III criteria for FD with organic disease at endoscopy in our study was almost identical. The commonest organic findings were erosive esophagitis or peptic ulcer disease, with upper GI malignancy occurring in <0.3%. In a large primary care-based study that performed upper GI endoscopy in over 2700 patients with Rome II FD, 23% had organic disease and only 0.2% gastro-esophageal malignancy. [28] These data are remarkably consistent, highlighting the fact that three-quarters of individuals who meet criteria for FD have

no organic explanation for their symptoms detected at endoscopy, and reinforcing that upper GI cancer is extremely rare in patients with dyspepsia.

The FD symptom subtypes were developed as a result of factor analysis studies, [29-31] as well as reports that up to 80% of patients reported symptom aggravation after ingestion of a meal, [32] and the observation that response to therapy differed by symptom subgroup in clinical trials of proton pump inhibitors in FD. [33] Novel therapies for dyspepsia continue to be developed and tested based on these subtypes. [34, 35] Despite this, the proportion of patients who met criteria for EPS and PDS who demonstrated organic findings after upper GI endoscopy in our study was broadly comparable. When one also considers the substantial degree of overlap we, and others, [36, 37] have observed between EPS and PDS, this suggests that the division of FD into subtypes may be artificial and of little clinical utility.

The Rome criteria are due to be revised in 2016. In terms of their accuracy in predicting a diagnosis of FD after upper GI endoscopy, the sensitivity analyses we conducted suggest that further refinement based on the addition or exclusion of other symptom items are unlikely to enhance their performance to any great extent. Our data could therefore be interpreted as calling into question the rationale for the Rome process as a whole, suggesting that an entirely new approach may be required. They also support the assertions of others that the division of FD into subtypes are, at present, potentially arbitrary in secondary care and should, perhaps, be reconsidered. In addition, the EPS subtype appears to be too restrictive, with only a very small proportion of individuals with FD meeting criteria for EPS, a finding that has been reported elsewhere. [38]

In the future, the incorporation of biomarkers into the diagnostic criteria for FD may improve their accuracy in predicting true FD, and also allow clearer

separation between the proposed subtypes. One potential candidate is the presence of duodenal eosinophilia which has been associated with FD. [39] Some investigators have demonstrated that symptoms in FD appear to be related to meal ingestion, [32, 40] suggesting the inclusion of questions that explore a temporal association between symptoms and food intake may be fruitful as part of the Rome IV process. However, this may lead to confusion with gastroparesis, in which postprandial pain is also common. [41] Another approach could be the inclusion of other GI or non-GI symptoms within the Rome IV criteria. A Japanese study reported that the use of concomitant lower GI symptoms suggestive of a functional bowel disorder accurately predicted the presence of FD, [42] while van Oudenhove *et al.* have shown that the incorporation of psychosocial factors such as anxiety, depression, and somatization may enhance the accuracy of current diagnostic criteria. [43]

In summary, all of the diagnostic criteria we examined performed only modestly in predicting a diagnosis of FD, and the prevalence of erosive esophagitis was almost identical when a broad definition of FD, which includes heartburn, was used compared with the Rome III criteria, which exclude heartburn from the definition. These data highlight the fact that, despite continued attempts to better discriminate between functional and organic causes of dyspepsia, a definitive approach to this diagnostic dilemma remains elusive.

ACKNOWLEDGEMENTS

We are grateful to June Urquhart for entry of questionnaire data and administering questionnaires to patients attending clinic, and Sandra Arthur for administering questionnaires to patients attending clinic.

REFERENCES

1. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, Whitehead WE, Janssens J, Funch-Jensen P, Corazziari E, Richter JE, Koch GG. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569-1580.

2. 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.

3. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Initial poor quality of life and new onset of dyspepsia: Results from a longitudinal 10-year follow-up study. Gut 2007;56:321-327.

4. Jones RH, Lydeard SE, Hobbs FDR, Kenkre JE, Williams EI, Jones SJ, Repper JA, Caldow JL, Dunwoodie WMB, Bottomley JM. Dyspepsia in England and Scotland. Gut 1990;31:401-405.

5. Brook RA, Kleinman NL, Choung RS, Melkonian AK, Smeeding JE, Talley NJ. Functional dyspepsia impacts absenteeism and direct and indirect costs. Clin Gastroenterol Hepatol 2010;8:498-503.

6. Camilleri M, Dubois D, Coulie B, Jones M, Kahrilas PJ, Rentz AM, Sonnenberg A, Stanghellini V, Stewart WF, Tack J, Talley NJ, Whitehead W,

Revicki DA. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: Results of the US Upper Gastrointestinal Study. Clin Gastroenterol Hepatol 2005;3:543-552.

7. Halder SLS, Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ, III. Impact of functional gastrointestinal disorders on health-related quality of life: A population-based case-control study. Aliment Pharmacol Ther 2004;19:233-242.

8. Mahadeva S, Yadav H, Rampal S, Goh KL. Risk factors associated with dyspepsia in a rural Asian population and its impact on quality of life. Am J Gastroenterol 2010;105:904-912.

9. Mahadeva S, Yadav H, Rampal S, Everett SM, Goh K-L. Ethnic variation, epidemiological factors and quality of life impairment associated with dyspepsia in urban Malaysia. Aliment Pharmacol Ther 2010;31:1141-1151.

10. Lacy BE, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: The economic impact to patients. Aliment Pharmacol Ther 2013;38:170-177.

11. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, COOK SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179-1187.

12. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: Overall and upper gastrointestinal diseases. Gastroenterology 2009;136:376-386.

13. Chang JY, Locke III GR, McNally MA, Halder SL, Schleck CD, Zinsmeister AR, Talley NJ. Impact of functional gastrointestinal disorders on survival in the community. Am J Gastroenterol 2010;105:822-832.

14. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Effect of dyspepsia on survival: A longitudinal 10-year follow-up study. Am J Gastroenterol 2012;107:912-921.

15. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? JAMA 2006;295:1566-1576.

16. 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.

17. Colin-Jones DG, Bloom B, Bodemar G, Crean G, Freston J, Malagelada J, Nyren O, Petersen H, Piper D. Management of dyspepsia: Report of a working party. Lancet 1988;331:576-579.

18. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional gastroduodenal disorders. Gastroenterology 2006;130:1466-1479.

19. Talley NJ, Colin-Jones DG, Koch KL, Koch M, Nyren O, Stanghellini V. Functional dyspepsia: A classification with guidelines for diagnosis and management. Gastroenterology International 1991;4:145-160.

20. Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GNJ. Functional gastroduodenal disorders. Gut 1999;45 (suppl 2):37-42.

21. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gastroenterology 2013;145:1262-1270.

22. Whitehead WE, and the Validation Working Team Committee in association with the Rome Questionnaire Committee. Development and validation of the Rome III diagnostic questionnaire. In: Drossman DA, editor Rome III: The functional gastrointestinal disorders, 3rd edition Virginia: Degnon Associates Inc 2006;835-853.

23. Ford AC, Ching E, Moayyedi P. Meta-analysis: Yield of diagnostic tests for coeliac disease in dyspepsia. Aliment Pharmacol Ther 2009;30:28-36.

24. Talley NJ, Locke III GR, Lahr BD, Zinsmeister AR, Tougas G, Ligozio G, Rojavin MA, Tack J. Functional dyspepsia, delayed gastric emptying, and impaired quality of life. Gut 2006;55:933-939.

25. Heikkinen M, Rasanen H, Farkkila M. Clinical value of ultrasound in the evaluation of dyspepsia in primary health care. Scand J Gastroenterol 2005;40:980-984.

26. Lee YY, Wahab N, Mustaffa N, Daud N, Mohd Noor N, Shaaban J, Chua AS. A Rome III survey of functional dyspepsia among the ethnic Malays in a primary care setting. BMC Gastroenterol 2013;13:84.

27. Abid S, Siddiqui S, Jafri W. Discriminant value of Rome III questionnaire in dyspeptic patients. Saudi J Gastroenterol 2011;17:129-133.

28. Vakil N, Talley NJ, Veldhuyzen van Zanten S, Flook N, Persson T, Bjorck E, Lind T, Bolling-Sternevald E. Cost of detecting malignant lesions by endoscopy in 2741 primary care dyspeptic patients without alarm symptoms. Clin Gastroenterol Hepatol 2009;7:756-761.

29. Fischler B, Tack J, De Gucht V, Shkedy ZI, Persoons P, Molenberghs G, Janssens J. Heterogeneity of symptom pattern, psychosocial factors, and pathophysiological mechanisms in severe functional dyspepsia. Gastroenterology 2003;124:903-910.

30. Westbrook JI, Talley NJ. Empiric clustering of dyspepsia into symptom subgroups: A population-based study. Scand J Gastroenterol 2002;37:917-923.

31. Talley NJ, Boyce P, Jones M. Identification of distinct upper and lower gastrointestinal symptom groupings in an urban population. Gut 1998;42:690-695.

32. Bisschops R, Karamanolis G, Arts J, Caenepeel P, Verbeke K, Janssens J, Tack J. Relationship between symptoms and ingestion of a meal in functional dyspepsia. Gut 2008;57:1495-1503.

33. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in non-ulcer dyspepsia: A systematic review and economic analysis. Gastroenterology 2004;127:1329-1337.

34. Matsueda K, Hongo M, Tack J, Saito Y, Kato H. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. Gut 2012;61:821-828.

35. Tack J, Janssen P, Masaoka T, Farre R, van Oudenhove L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. Clin Gastroenterol Hepatol 2012;10:1239-1245.

36. Vakil N, Halling K, Ohlsson L, Wernersson B. Symptom overlap between postprandial distress and epigastric pain syndromes of the Rome III dyspepsia classification. Am J Gastroenterol 2013;108:767-774.

37. van Kerkhoven LA, Laheij RJ, Meineche-Schmidt V, Veldhuyzen Van Zanten SJ, de Wit NJ, Jansen JB. Functional dyspepsia: Not all roads seem to lead to Rome. J Clin Gastroenterol 2009;43:118-122.

38. Park JM, Choi MG, Cho YK, Lee IS, Kim JI, Kim SW, Chung IS. Functional gastrointestinal disorders diagnosed by Rome III questionnaire in Korea. J Neurogastroenterol Motil 2011;17:279-286.

39. Walker MM, Salehian SS, Murray CE, Rajendran A, Hoare JM, Negus R, Powell N, Talley NJ. Implications of eosinophilia in the normal duodenal biopsy - an association with allergy and functional dyspepsia. Aliment Pharmacol Ther 2010;31:1229-1236.

40. Pilichiewicz AN, Horowitz M, Holtmann G, Talley NJ, Feinle-Bisset C. Relationship between symptoms and dietary patterns in patients with functional dyspepsia. Clin Gastroenterol Hepatol 2009;7:317-322.

41. Cherian D, Sachdeva P, Fisher RS, Parkman HP. Abdominal pain is a frequent symptom of gastroparesis. Clin Gastroenterol Hepatol 2010;8:676-681.

42. Matsuzaki J, Suzuki H, Asakura K, Fukushima Y, Inadomi JM, Takebayashi T, Hibi T. Classification of functional dyspepsia based on concomitant bowel symptoms. Neurogastroenterol Motil 2012;24:325-e164.

43. van Oudenhove L, Holvoet L, Vandenberghe J, Vos R, Tack J. Do we have an alternative for the Rome III gastroduodenal symptom-based subgroups in

functional gastroduodenal disorders? A cluster analysis approach. Neurogastroenterol Motil 2011;23:730-738.

Table 1. Demographics and Baseline Characteristics of Patients Undergoing Upper GI Endoscopy and Providing Complete Rome III Symptom Data, Compared with Those Who Did Not Undergo Upper GI Endoscopy.

	Underwent upper GI endoscopy and provided complete Rome III symptom data (n = 1452)	**Did not undergo upper GI endoscopy (n = 2619)**	**P value***
Mean age (SD)	48.4 (17.1)	46.8 (18.0)	0.005
Mean body mass index (SD)	27.3 (6.2)	26.9 (6.1)	0.03
Female gender (%)	913 (62.9)	1599 (61.1)	0.25
Tobacco user (%)	321 (22.1)	499 (19.1)	0.04
Alcohol user (%)	800 (55.1)	1536 (58.6)	0.01
Marital status (%)			
Married or co-habiting	866 (59.6)	1529 (58.4)	0.47
Divorced or separated	168 (11.6)	288 (11.0)	
Never married	336 (23.1)	636 (24.3)	
Widowed	65 (4.5)	118 (4.5)	

Educational level (%)			
Elementary	67 (4.6)	101 (3.9)	0.12
High school	433 (29.8)	724 (27.6)	
College or technical school	437 (30.1)	756 (28.9)	
University	328 (22.6)	692 (26.4)	
Postgraduate	160 (11.0)	259 (9.9)	
Ethnicity (%)			
White Caucasian	1249 (86.0)	2324 (88.7)	0.002
South Asian	20 (1.4)	38 (1.5)	
Middle-Eastern	27 (1.9)	29 (1.1)	
First Nations	22 (1.5)	16 (0.6)	
African	23 (1.6)	28 (1.1)	
South-East Asian	21 (1.4)	27 (1.0)	
Latin-American	17 (1.2)	18 (0.7)	
Met Rome III criteria for FD (%)	722 (49.7)	750 (28.6)	< 0.001

*P value for independent samples *t*-test for continuous data and Pearson χ^2 for comparison of categorical data.

Table 2. Prevalence of Organic Disease in Patients Meeting the Rome III Criteria for FD, Compared with Those Who Did Not.

	Met Rome III criteria for FD (n = 722)	**Did not meet Rome III criteria for FD (n = 730)**	**P value***
Erosive esophagitis (%)	81 (11.2)	109 (14.9)	0.04
Barrett's esophagus (%)	31 (4.3)	33 (4.5)	0.90
Benign esophageal stricture (%)	2 (0.3)	10 (1.4)	0.04
Schatzki ring (%)	8 (1.1)	15 (2.1)	0.21
Esophageal candidiasis (%)	6 (0.8)	7 (1.0)	1.00
Eosinophilic esophagitis (%)	1 (0.1)	12 (1.6)	0.003
Esophageal squamous cell carcinoma (%)	1 (0.1)	2 (0.3)	1.00
Esophageal adenocarcinoma (%)	0 (0)	1 (0.1)	1.00
Gastric ulcer (%)	31 (4.3)	43 (5.9)	0.21
Gastric erosions (%)	9 (1.2)	6 (0.8)	0.59
Gastric carcinoma (%)	1 (0.1)	2 (0.3)	1.00
Duodenal ulcer (%)	13 (1.8)	9 (1.2)	0.50
Duodenal erosions (%)	3 (0.4)	3 (0.4)	0.99
***H. pylori*-positive (%)**	54 (7.5)	53 (7.3)	0.92

Celiac disease (%)	15 (2.1)	22 (3.0)	0.32
Upper GI Crohn's disease (%)	1 (0.1)	2 (0.3)	1.00

*P value for Fisher's exact test for comparison of categorical data.

Table 3. Prevalence of Organic Disease in Patients Meeting the Rome III Criteria for FD, According to Symptom Subtype.

	Met criteria for EPS alone (n = 24)	Met criteria for PDS alone (n = 663)	Met criteria for EPS and PDS (n = 35)
Erosive esophagitis (%)	1 (4.2)	79 (11.9)	1 (2.9)
Barrett's esophagus (%)	2 (8.3)	28 (4.2)	1 (2.9)
Benign esophageal stricture (%)	1 (4.2)	1 (0.2)	0 (0)
Schatzki ring (%)	0 (0)	8 (1.2)	0 (0)
Esophageal candidiasis (%)	1 (4.2)	5 (0.8)	0 (0)
Eosinophilic esophagitis (%)	1 (4.2)	0 (0)	0 (0)
Esophageal squamous cell carcinoma (%)	0 (0)	1 (0.2)	0 (0)
Esophageal adenocarcinoma (%)	0 (0)	0 (0)	0 (0)
Gastric ulcer (%)	1 (4.2)	30 (4.5)	0 (0)
Gastric erosions (%)	0 (0)	9 (1.4)	0 (0)
Gastric carcinoma (%)	0 (0)	1 (0.2)	0 (0)
Duodenal ulcer (%)	0 (0)	13(2.0)	0 (0)
Duodenal erosions (%)	0 (0)	3 (0.5)	0 (0)
***H. pylori*-positive (%)**	2 (8.3)	51 (7.7)	1 (2.9)

Celiac disease (%)	2 (8.3)	13 (2.0)	0 (0)
Upper GI Crohn's disease (%)	0 (0)	1 (0.2)	0 (0)

Table 4. Sensitivity, Specificity, Positive and Negative Predictive Values, and Positive and Negative Likelihood Ratios for the Rome III Criteria, Rome II Criteria, and a Broad Definition of FD.

	Sensitivity (95% CI)	**Specificity (95% CI)**	**Positive predictive value (95% CI)**	**Negative predictive value (95% CI)**	**Positive likelihood ratio (95% CI)**	**Negative likelihood ratio (95% CI)**
Rome III FD	60.7% (57.5% – 63.9%)	68.7% (64.6% – 72.6%)	76.5% (73.2% – 79.4 %)	51.1% (47.4% – 54.8%)	1.94 (1.69 – 2.22)	0.57 (0.52 – 0.63)
Rome III EPS	7.1% (5.4% – 9.2%)	98.9% (98.0% – 99.4%)	84.8% (73.5% – 91.8%)	56.0% (53.4% – 58.5%)	6.63 (3.28 – 13.39)	0.94 (0.92 – 0.96)
Rome III EPS (less restrictive definition)	56.7% (53.0% – 60.3%)	87.3% (84.8% – 89.4%)	79.0% (75.2% – 82.3%)	70.5% (67.7% – 73.2%)	4.46 (3.69 – 5.38)	0.50 (0.45 – 0.54)
Rome III PDS	65.7% (62.4% – 68.9%)	74.9% (71.4% – 78.1%)	76.7% (73.4% – 79.6%)	63.5% (60.1% – 66.9%)	2.62 (2.27 – 3.02)	0.46 (0.41 – 0.51)

Rome III PDS (excluding heartburn)	32.5% (29.3% – 35.8%)	89.6% (87.0% – 91.7%)	79.5% (74.8% – 83.5%)	51.7% (48.7% – 54.6%)	3.12 (2.44 – 4.00)	0.75 (0.71 – 0.80)
Rome II FD	71.4% (68.4% –74.2%)	55.6% (51.5% – 59.7%)	73.5% (70.5% – 76.2%)	53.0% (49.0% – 57.1%)	1.61 (1.45 – 1.78)	0.51 (0.45 – 0.58)
Broad definition of FD	92.0% (90.1% – 93.5%)	28.6% (25.0% – 32.5%)	69.5% (67.0% – 71.9%)	67.0% (60.8% – 72.6%)	1.29 (1.22 – 1.36)	0.28 (0.22 – 0.36)

FIGURE LEGENDS

Figure 1. Flow of Study Participants.