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TITLE PAGE

Title: No Increase in Prevalence of Somatization in Functional Versus Organic Dyspepsia: A Cross-sectional Survey.

Short running head: Somatization in Dyspepsia.

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Abbreviations:

FD	functional dyspepsia
OD	organic dyspepsia
BMI	body mass index
CI	confidence interval
GI	gastrointestinal
IBS	irritable bowel syndrome
OR	odds ratio
PDS	postprandial distress syndrome
EPS	epigastric pain syndrome

PHQ	Patient Health Questionnaire
SD	standard deviation

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ABSTRACT AND KEYWORDS

Background: Psychological factors are associated with functional gastrointestinal disorders. Literature suggests that somatization is associated with functional dyspepsia. However, the relationship between organic dyspepsia, functional dyspepsia and functional dyspepsia subtypes and somatization is poorly described. We aimed to examine this issue in a cross-sectional study of secondary care patients.

Methods: Demographic and gastrointestinal symptom data were collected from 4224 adult patients via the Rome III questionnaire. Somatization data were collected using the patient health questionnaire-12. Mean somatization score and number of somatic symptoms were compared between patients with organic and functional dyspepsia, and between functional dyspepsia subtypes using analysis of variance. The same comparison was undertaken for the proportion of patients reporting individual somatic symptoms.

Key results: 783 patients met criteria for dyspepsia, of whom 231 (29.5%) had organic disease following upper GI endoscopy. Mean somatization scores and number of somatic symptoms were no higher in functional versus organic dyspepsia ($P = 0.23$; $P = 0.19$). In addition, whilst the prevalence of somatization in FD was relatively high, there was no difference in severity of somatization in FD subgroups.

Conclusions and inferences: Somatization is associated with functional and organic dyspepsia to the same degree. Overall severity of somatization did not appear to vary according to functional dyspepsia subtype.

Keywords: somatization
symptom severity
post-prandial distress
epigastric pain

KEY MESSAGES

- There is no difference in somatization severity between functional and organic dyspepsia, nor is any difference observed across functional dyspepsia subtypes.
- The aim of the study was to compare the prevalence and severity of somatization in organic and function dyspepsia, and to assess any difference between the functional dyspepsia subtypes.
- A cross-sectional study of patients presenting to secondary care GI services. Functional dyspepsia and subtypes were defined according to the Rome III diagnostic criteria after a normal upper GI endoscopy. Somatization data were collected using the PHQ-12 questionnaire.
- Mean somatization scores, and somatization severity were the same in functional dyspepsia and organic dyspepsia. There was no difference in PHQ-12 scores or somatization severity between functional dyspepsia subgroups.

Dyspepsia is a term used to describe a collection of symptoms arising from the upper gastrointestinal (GI) tract. It is a common condition with an estimated population prevalence of 21%, according to results of a recently published systematic review and meta-analysis. (1) It is more common in females than males, and may be associated with smoking, Helicobacter pylori infection, and non-steroidal anti-inflammatory drug use. In addition to its being a commonly encountered problem, it is also associated with detrimental effects on quality of life, and a significant cost to society associated with medication usage and absenteeism. (2-4)

Patients complaining of dyspepsia are subdivided into those with an organic or functional cause, based on the findings at upper GI endoscopy, the latter group having no objective evidence of structural organic pathology to account for their symptoms. The underlying cause of dyspeptic symptoms after upper GI endoscopy will be functional dyspepsia in up to 75% of patients. (5, 6) The current gold-standard for the diagnosis of functional dyspepsia, in the presence of a normal upper GI endoscopy, are the Rome III criteria. (7) These consist of one or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning. As previously mentioned there must be no evidence of structural disease that is likely to explain the symptoms, which must be present for the last 3 months, with onset at least 6 months before the diagnosis.

A substantial overlap between functional dyspepsia and other functional gastrointestinal disorders (FGIDs), including irritable bowel syndrome (IBS), is thought to exist. (8) Similar to IBS, the etiology of functional dyspepsia is poorly understood, but believed to be multi-factorial. Proposed contributory factors include dysmotility, visceral hypersensitivity, excessive gastric acid secretion, Helicobacter pylori infection, and psychosocial factors, including depression and anxiety. (8, 9) Evidence supporting the role of psychological factors in the etiology of functional dyspepsia includes the high placebo

response rate observed in trials of therapy in this condition, (10, 11) and the response to psychological interventions and antidepressants in a subset of patients. (12, 13)

In addition to anxiety and depression, somatization, which is characterized by the presence of multiple and variable physical symptoms that cannot be explained by a detectable physical disorder, (14-16) is often more common in patients with FGIDs compared with controls. (17, 18) There have been several studies reporting high levels of somatization among patients with functional dyspepsia, (19-21) but few have assessed whether this is more than that which is observed in patients with an organic cause of dyspepsia. (22) In addition, data concerning whether the degree of somatization varies according to the subtypes of post-prandial distress syndrome (PDS) or epigastric pain syndrome (EPS) are sparse. (20)

We have therefore examined this issue in a large cohort of patients who met the Rome III criteria for functional dyspepsia and who underwent upper GI endoscopy to elucidate the underlying cause. We postulated that the severity of somatization would be greater in those with functional, compared with organic dyspepsia, and that this may vary between dyspepsia subtypes, particularly those with overlapping symptoms who met criteria for both PDS and EPS, as they must report a greater number of symptoms to meet criteria for both subtypes.

MATERIALS AND METHODS

Participants and Setting

All individuals who participated in the study were newly referred from primary care to secondary care for consideration of investigation of GI symptoms. Unselected consecutive patients aged 16 years or over, recruited at two GI outpatient clinics at either McMaster University Medical Center or St. Joseph's Healthcare, in Hamilton, Ontario, Canada, were approached about the study. These hospitals serve a local population of 520,000 people. The only exclusion to participation was an inability to understand written English. At the first clinic visit, prior to the consultation with a gastroenterologist, individuals were presented with a study information sheet explaining the nature of the study. Those who agreed to take part provided written informed consent at this visit. The study was approved by both the Hamilton Health Sciences and McMaster University research ethics boards in January 2008, and data collection continued up to December 2012. We have previously used this dataset to validate the Rome III criteria for functional dyspepsia and IBS, as well as to examine the characteristics of patients meeting criteria for one of the functional bowel disorders, and to examine the interplay between IBS and somatization. (5, 17, 23, 24)

Data Collection and Synthesis

Symptom and Demographic Data

Once informed consent was obtained, symptom and demographic data were collected via a questionnaire. Demographic data collected included gender, age, ethnicity, marital status, educational level, tobacco and alcohol use, weight (in kilograms) and height (in meters), which were used to calculate body mass index (BMI). Symptom data were collected

using the validated Rome III diagnostic questionnaire for adult functional GI disorders. (25) This questionnaire was used to record the frequency of individual upper GI symptoms using a Likert scale.

Definition of Organic and Functional Dyspepsia

The presence of dyspepsia was defined using the Rome III criteria. (7) Patients were classified as having organic dyspepsia if they met the Rome III criteria for dyspepsia, with symptoms of any duration, but structural findings were detected at upper GI endoscopy that would explain the symptoms, or were classified as having functional dyspepsia if they met the Rome III criteria, with symptoms present for the last 3 months, with onset at least 6 months before the diagnosis but upper GI endoscopy was structurally normal. Organic causes of dyspepsia included erosive esophagitis, Barrett's esophagus, esophageal ring or stricture, esophageal candidiasis, eosinophilic esophagitis, esophageal adenocarcinoma or squamous cell carcinoma, gastric adenocarcinoma, peptic ulcer disease, celiac disease or upper GI Crohn's disease.

Individuals were classified as having functional dyspepsia if they met the Rome III criteria and had a normal upper GI endoscopy. Functional dyspepsia was subtyped into post-prandial distress syndrome (PDS), epigastric pain syndrome (EPS), or overlap (where symptoms compatible with both subtypes were reported) using the scoring systems recommended by the questionnaire. For a diagnosis of PDS either of bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week or early satiation that prevents finishing a regular meal was required. To meet criteria for EPS patients had to report intermittent pain or burning localized to the epigastrium of at least moderate severity at least once per week, which was not relieved by defecation or passage of flatus.

Definition of Somatization Severity Using the Patient Health Questionnaire (PHQ)

Somatization data were collected using the PHQ-15, which is derived from the validated full PHQ. (26, 27) The PHQ-15 enquires about the presence of 15 somatic symptoms (or symptom clusters) over the last 4 weeks, which contribute to >90% of physical complaints reported in the outpatient environment. (28) Three of the 15 somatic items included in the PHQ-15 questionnaire relate to the GI tract, and these were therefore excluded to avoid any overestimation of the severity of somatization among a group of patients who were already consulting with GI symptoms, to form the PHQ-12 (Appendix 1). This approach has been used by other investigators when assessing prevalence and severity of somatization among patients with GI symptoms. (29) Each individual was asked to rate the severity of each symptom as "not bothered at all" (scored as 0), "bothered a little" (scored as 1), or "bothered a lot" (scored as 2). Therefore the total PHQ-12 score ranges from a minimum of 0 to a maximum of 24. Somatization severity was categorized, using the total PHQ-12 score, into high (total PHQ-12 ≥13), medium (8-12), low (4-7) and minimal (≤3) levels of somatization severity, an approach we have used previously, (17) but which has not been validated formally.

Definition of Anxiety or Depression

Anxiety and depression data were collected using the hospital anxiety and depression scale (HADS). This 14-item questionnaire consists of seven questions screening for presence of anxiety symptoms, and seven for depression symptoms, with a four point response ranging from 0 to 3. The total HAD score ranges from a minimum of 0 to a maximum of 21 for both anxiety and depression. Severity was categorized, according to total HAD score, into normal (total HAD depression or anxiety score 0-7), borderline normal (8-11), and abnormal (≥11). (30)

Statistical Analysis

The mean PHQ-12 score and the total number of individual somatic symptom items reported were compared between patients with organic and functional dyspepsia, as well as between functional dyspepsia subtypes (PDS, EPS, and overlap) using an independent samples t-test, or one way analysis of variance. The number of patients reporting each of the 12 individual somatic symptom items was compared between those with functional and organic dyspepsia. The number of patients with a high level of somatization severity was compared between organic and functional dyspepsia groups, and between functional dyspepsia subtypes. These comparisons were conducted using a χ^2 test. Due to multiple testing, a two tailed P value of <0.01 was considered statistically significant. We compared the prevalence of each of the individual symptom items from the PHQ-12 between those with and without functional dyspepsia using multivariate logistic regression controlling for all demographic data and lifestyle factors, with the results expressed as odds ratios (ORs) along with 95 % confidence intervals (CIs). All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Of 5978 patients attending the two outpatient clinics, 4224 (70.7%) gave informed consent and were recruited into the study. Of these, 2977 provided complete somatization data, of whom 783 (26.3%) reported symptoms compatible with dyspepsia (mean age 46.9 years (range 16-90 years), 531 (67.8%) female), and were therefore eligible for inclusion in this study. Of these individuals, 231 (29.5%) had organic findings that would explain their symptoms, and the remaining 552 were classified as having functional dyspepsia. Among those with functional dyspepsia, 489 (67.7%) had PDS, 16 (2.2%) EPS, and 33 (4.6%) had overlap. The remaining 14 patients did not provide complete dyspepsia symptom data, meaning that subtyping was not possible. Those with organic dyspepsia were significantly older and less likely to be female, but there were no significant differences in other demographic variables between the two groups (Supplementary Table 1).

Prevalence of Individual PHQ-12 Somatic Symptom Items Among Patients with Organic and Functional Dyspepsia

Of the 12 somatic symptom items listed on the PHQ-12 at a level of "bothered a lot", none were reported at a significantly greater frequency by functional compared with organic dyspepsia patients (Table 1). This remained the case after multivariate logistic regression controlling for demographic and lifestyle factors. The commonest item reported among patients with functional dyspepsia was feeling tired or low in energy (506 (95.3%) individuals), followed by trouble sleeping (441 (83.1%) subjects), and back pain (422 (80.8%) patients). When prevalence of each symptom item was examined among functional dyspepsia patients according to subtype, chest pain was significantly commoner among those with PDS or EPS compared with those with overlap, and shortness of breath and trouble sleeping were significantly commoner among those with PDS (Table 2).

PHQ-12 Scores and Somatization Severity Among Patients with Organic or Functional Dyspepsia

There were 574 patients who provided complete somatization data, allowing the total PHQ-12 score and number of symptom items reported to be assessed, of whom 407 (70.9%) had functional dyspepsia. There was no difference in mean PHQ-12 scores in functional (10.2), compared with organic, dyspepsia patients (9.6) (P = 0.23) (Table 3). In addition the mean number of somatic symptoms reported was almost identical between functional and organic groups (6.9 vs. 6.6 (P = 0.19)). When levels of somatization were compared, there were 127 (31.2%) functional dyspepsia patients with a high level compared to 47 (28.1%) organic dyspepsia patients (P = 0.47). Total PHQ-12 scores in organic and functional dyspepsia patients as a proportion of the total number in each group are illustrated in Figure 1. There were no differences in mean HAD depression (6.4 vs. 6.2, P = 0.63) or anxiety (8.9 vs. 8.4, P = 0.16) scores in functional or organic dyspepsia patients, nor were there any difference in the proportion of patients in either group with depression or anxiety according to HADS.

PHQ-12 Scores and Somatization Severity Among Functional Dyspepsia Patients According to Subtype

When the effect of functional dyspepsia subtype on somatization was studied, mean PHQ-12 scores were higher in patients with PDS (10.3) compared with EPS (8.5), or overlap (8.7) respectively, although this comparison failed to achieve statistical significance (P = 0.06) (Table 4). There was also a trend towards the mean total number of somatic symptom items reported being significantly higher in patients with PDS (7.1), compared with EPS (5.7), or overlap (6.2) (P = 0.04). Finally, when somatization severity was assessed according to functional dyspepsia subtype, the prevalence of a high level of somatization was greatest in

patients with PDS, but again this did not reach statistical significance (P = 0.03). Total PHQ-12 scores in each subtype as a proportion of the total number in each group are illustrated in Figure 2. Again, there were no significant differences in mean anxiety or depression score between the three subgroups (9.0 PDS, vs. 8.1 EPS, vs. 7.9 overlap, P = 0.33 for anxiety, and 6.3 PDS, 5.3 EPS, 5.0 overlap, P = 0.26 for depression). Furthermore, there were no differences in the proportion of patients meeting criteria for anxiety or depression in any of the three subtypes (P = 0.38 and P = 0.36 respectively).

DISCUSSION

This study has demonstrated no overall difference in the prevalence or severity of somatization between patients with functional and organic dyspepsia. In addition, there was no difference in the number of somatic symptoms reported between the two groups. When considering individual somatic symptoms, the prevalence of these was not significantly higher among those with functional dyspepsia. Being tired or low in energy was the most commonly reported somatic symptom among all dyspepsia patients, regardless of endoscopy findings. Despite our hypothesis that functional dyspepsia patients with overlap would demonstrate highest levels of somatization, no differences were observed between the three groups for mean total somatization score, or the mean number of somatic symptom items reported. Chest pain was more commonly reported in PDS and EPS than overlap, and shortness of breath and trouble sleeping among those with PDS.

We included a well-characterized group of patients in this study, with rigorous definitions of both organic and functional dyspepsia. The large number of patients included is another strength. The total number of patients with functional dyspepsia included was almost three times that of the only other cross-sectional study to examine the relationship between somatization and functional dyspepsia subgroups using the Rome III criteria. (20) Recruited patients were both consecutive and unselected, meaning that our results are likely to be generalizable to usual clinical practice. We also used validated questionnaires to collect data. Although the original PHQ-15 has been validated, (31) the PHQ-12 utilized in this study has not been fully validated as screening tool for somatization. However, Patel et al. and Spiller et al. have used the PHQ-12 for assessing somatization in IBS and diverticular disease patients, (17, 29) and found it to be a useful clinical tool to assess behavior.

Given that this was a cross-sectional study, an obvious weakness is that causality cannot be implied by our results. Furthermore, as the PHQ-12 is a self-administered

questionnaire, and there was no clinical assessment to confirm that individual somatic symptoms were indeed without medical explanation, it is possible that our results may overestimate the prevalence of somatization in the study population. In addition, due to the strict Rome III definition of EPS, which excludes patients felt to meet criteria for IBS, the numbers in the EPS and overlap groups were small, and this may have led to a lack of power to detect any significant differences in somatization between the three subgroups. As the PHQ-12 questionnaire includes symptoms such as chest pain, which may be more likely to be reported by those with organic conditions such as erosive esophagitis or esophageal stricture, and tiredness or lack of energy may be more likely in those with Crohn's disease or upper GI malignancy, this may have led to some of the failure to detect any differences in somatization levels between the two groups. However, it should be noted that chest pain was reported by similar proportions of patients with organic and functional dyspepsia, and there were only two patients with esophageal cancer, one patient with gastric adenocarcinoma, and one patient with Crohn's disease in the organic dyspepsia group, so this is unlikely to have impacted our results. Finally, as this study was conducted among a referral population, the results may not be generalizable to subjects in the community or primary care.

In keeping with other studies investigating this issue (19-22), our findings confirm that the prevalence of somatization in functional dyspepsia is relatively high, with one in three patients meeting criteria for high levels of somatization. However, most of these previous studies reported somatization in functional dyspepsia only, or in comparison with a normal control group, rather than with a group of patients with organic dyspepsia. (19-21) The only study we are aware of that has assessed somatization in patients with both functional and organic dyspepsia used the revised symptom checklist 90 in a much smaller study sample of 30 patients with organic dyspepsia, 30 patients with functional dyspepsia, and 30 healthy controls. (22) With only 60 patients recruited from a university hospital, this

may mean that the population studied was a more highly selected group. Interestingly, the authors observed that, although somatization scores were significantly greater among those with functional dyspepsia compared with organic dyspepsia, somatization scores among those with organic dyspepsia were significantly higher than among normal healthy controls.

To date only one study has investigated the variation in somatization severity between the Rome III-defined functional dyspepsia subgroups. (20) In contrast to our results, the authors reported higher somatization, anxiety, and depression scores in overlap patients, compared with EPS or PDS patients, which is in line with our hypothesis. Reasons for the differences observed between this study and our own are speculative, but it should be pointed out that there were 64 individuals in the overlap group in this study, compared with only 32 in our study. It is also unclear why we observed a relatively high level of symptom reporting in those with both organic and functional dyspepsia. Whether this is a primary phenomenon among patients with dyspepsia, or a secondary effect due the impact of upper GI symptoms on psychological health will need to be investigated in future studies.

In summary, anxiety, depression, and somatization are associated with functional and organic dyspepsia to the same degree. Overall severity of somatization did not appear to vary according to functional dyspepsia subtype, although power for these subgroup analyses was limited. Previous investigators have demonstrated that the addition of somatic symptoms, anxiety, or depression data to current symptom-based criteria may improve the ability of clinicians to discriminate between IBS and other organic causes of lower GI symptoms. (29, 32) However, our findings suggest that incorporating the presence of somatization, anxiety or depression into future iterations of diagnostic criteria will not lead to any increased ability to discriminate between functional and organic causes of dyspepsia.

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Guarantor of the article: DJG is guarantor.

Specific author contributions: DJG, PB, DGM, CB, MIP-S, PM, and ACF conceived and drafted the study. ACF, CB, and MIP-S collected all data. DJG and 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.

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REFERENCES

1. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. Gut. 2014.

2. Mahadeva S, Yadav H, Rampal S, Everett SM, Goh KL. Ethnic variation, epidemiological factors and quality of life impairment associated with dyspepsia in urban Malaysia. Aliment Pharmacol Ther. 2010;31(10):1141-51.

3. Halder SLS, Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ. Impact of functional gastrointestinal disorders on health-related quality of life: a population-based case–control study. Alimentary Pharmacology & Therapeutics. 2004;19(2):233-42.

4. Brook RA, Kleinman NL, Choung RS, Melkonian AK, Smeeding JE, Talley NJ. Functional Dyspepsia Impacts Absenteeism and Direct and Indirect Costs. Clinical Gastroenterology and Hepatology.8(6):498-503.

5. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. The Rome III criteria for the diagnosis of functional dyspepsia in secondary care are not superior to previous definitions. Gastroenterology. 2014;146:932-40.

6. 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(10):830-7, 7.e1-2.

7. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, et al. Functional gastroduodenal disorders. Gastroenterology. 2006;130(5):1466-79.

8. Fujiwara Y, Arakawa T. Overlap in patients with dyspepsia/functional dyspepsia. Journal of neurogastroenterology and motility. 2014;20(4):447-57.

9. Miwa H, Watari J, Fukui H, Oshima T, Tomita T, Sakurai J, et al. Current understanding of pathogenesis of functional dyspepsia. Journal of gastroenterology and hepatology. 2011;26 Suppl 3:53-60.

10. Talley NJ, Locke GR, Lahr BD, Zinsmeister AR, Cohard-Radice M, D'Elia TV, et al. Predictors of the placebo response in functional dyspepsia. Aliment Pharmacol Ther. 2006;23(7):923-36.

11. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. Gastroenterology. 2004;127(5):1329-37.

12. Wu JC CP, Chan Y, Lai LH, Ching J, Chan A, Sung J, Chan FKL. A randomized, double-blind, placebo-controlled trial of low dose imipramine for treatment of refractory functional dyspepsia. . Gastroenterology. 2011;140 (suppl 1):S50.

13. Haag S, Senf W, Tagay S, Langkafel M, Braun-Lang U, Pietsch A, et al. Is there a benefit from intensified medical and psychological interventions in patients with functional dyspepsia not responding to conventional therapy? Aliment Pharmacol Ther. 2007;25(8):973-86.

14. Organization TWH. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. 1993.

15. De Gucht V, Fischler B. Somatization: a critical review of conceptual and methodological issues. Psychosomatics. 2002;43(1):1-9.

16. De Gucht V, Maes S. Explaining medically unexplained symptoms: toward a multidimensional, theory-based approach to somatization. J Psychosom Res. 2006;60(4):349-52.

17. Patel P, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P, et al. Irritable bowel syndrome is significantly associated with somatisation in 840 patients, which may drive bloating. Aliment Pharmacol Ther. 2015;41(5):449-58.

18. Vu J, Kushnir V, Cassell B, Gyawali CP, Sayuk GS. The impact of psychiatric and extraintestinal comorbidity on quality of life and bowel symptom burden in functional GI disorders. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2014;26(9):1323-32.

19. Jones MP, Sharp LK, Crowell MD. Psychosocial correlates of symptoms in functional dyspepsia. Clin Gastroenterol Hepatol. 2005;3(6):521-8.

20. Hsu YC, Liou JM, Liao SC, Yang TH, Wu HT, Hsu WL, et al. Psychopathology and personality trait in subgroups of functional dyspepsia based on Rome III criteria. Am J Gastroenterol. 2009;104(10):2534-42.

21. Van Oudenhove L, Vandenberghe J, Geeraerts B, Vos R, Persoons P, Fischler B, et al. Determinants of symptoms in functional dyspepsia: gastric sensorimotor function, psychosocial factors or somatisation? Gut. 2008;57(12):1666-73.

22. Faramarzi M, Kheirkhah F, Shokri-Shirvani J, Mosavi S, Zarini S. Psychological factors in patients with peptic ulcerand functional dyspepsia. Caspian journal of internal medicine. 2014;5(2):71-6.

23. 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;145:1262-70.

24. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Characteristics of functional bowel disorder patients: A cross-sectional survey using the Rome III criteria. Aliment Pharmacol Ther. 2014;39:312-21.

25. Whitehead WE, and the Validation Working Team Committee in association with the Rome Questionnaire C. Development and validation of the Rome III diagnostic questionnaire. In: Drossman DA, editorRome III: The functional gastrointestinal disorders, 3rd editionVirginia: Degnon Associates Inc. 2006:835-53.

26. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999;282(18):1737-44.

27. Spitzer RL, Williams JB, Kroenke K, Hornyak R, McMurray J. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. Am J Obstet Gynecol. 2000;183(3):759-69.

28. Kroenke K, Arrington ME, Mangelsdorff AD. The prevalence of symptoms in medical outpatients and the adequacy of therapy. Arch Intern Med. 1990;150(8):1685-9.

29. Spiller RC, Humes DJ, Campbell E, Hastings M, Neal KR, Dukes GE, et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. Aliment Pharmacol Ther. 2010;32(6):811-20.

30. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-70.

31. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. 2002;64:258-66.

32. Jones MP, Chey WD, Singh S, Gong H, Shringarpure R, Hoe N, et al. A biomarker panel and psychological morbidity differentiates the irritable bowel syndrome from health and provides novel pathophysiological leads. Aliment Pharmacol Ther. 2014;39(4):426-37.

APPENDICES

PHQ-12 QUESTIONNAIRE

Please answer all the questions below:

During the past 4 weeks how much have you been bothered by any of the following problems?

	No	A little	A lot
a. Back pain	□	□	□
b. Arm, leg, joint (hip, knee etc) pain	□	□	□
c. Period pain / period problems	□	□	□
d. Headaches	□	□	□
e. Chest pain	□	□	□
f. Dizziness	□	□	□
g. Fainting spells	□	□	□
h. Heart pounding / racing	□	□	□
i. Shortness of breath	□	□	□
j. Pain / problems during intercourse	□	□	□
k. Feeling tired or low in energy	□	□	□
l. Trouble sleeping	□	□	□

SUPPORTING INFORMATION

Supplementary Table 1. Characteristics of 552 Functional Dyspepsia Patients Compared with 170 Organic Dyspepsia Patients.

	Functional dyspepsia (n = 552)	Organic dyspepsia (n = 231)	P Value *
Mean age	45.4	50.3	<0.001
Number of females (%)	396 (71.7)	135 (58.4)	<0.001
White Caucasian ethnicity (%)	466 (85.7)	208 (91.6)	0.04
Marital status (%)			
Married or co-habiting	304 (55.5)	141 (13.3)	
Divorced	84 (15.3)	33 (14.3)	
Never married	140 (25.5)	46 (20.0)	
Widowed	20 (3.6)	10 (4.3)	0.34
Educational level (%)			
Elementary	29 (5.3)	16 (6.9)	
High school	171 (31.5)	76 (32.9)	
College or technical school	172 (31.7)	77 (33.3)	
University	119 (21.9)	38 (16.5)	
Postgraduate	52 (9.6)	19 (8.2)	0.46
Alcohol user (%)	274 (49.7)	121 (52.6)	0.46
Tobacco user (%)	153 (27.8)	68 (29.4)	0.64
H. pylori-positive	37(6.7)	21 (9.1)	0.25
Mean BMI	26.8	27.3	0.22

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

TABLES

Table 1. Prevalence of Individual PHQ-12 Somatic Symptom Items in Functional Dyspepsia Patients Compared with Organic Dyspepsia Patients.

PHQ-12 somatic symptom item ("reported as bothered a lot")	Functional Dyspepsia	Organic Dyspepsia	P value*	Adjusted OR (95% CI)
Back pain (%)	422/522 (80.8)	163/223 (73.1)	0.02	1.39 (0.92 – 2.11)
Arm, leg, or joint pain (%)	386/528 (73.1)	160/220 (72.7)	0.92	1.07 (0.72 – 1.59)
Period pain or period problems (%)†	146/352 (41.5)	46/123 (37.4)	0.43	0.85 (0.48 – 1.48)
Headaches (%)	380/522 (72.8)	143/220 (65.0)	0.03	1.15 (0.77 – 1.70)
Chest pain (%)	294/515 (57.1)	119/220 (54.1)	0.45	1.28 (0.89 – 1.83)
Dizziness (%)	331/515 (64.3)	128/221 (57.9)	0.10	1.14 (0.79 – 1.64)
Fainting spells (%)	78/507 (15.4)	28/216 (13.0)	0.40	1.48 (0.85 – 2.58)
Heart pounding or racing (%)	268/520 (51.5)	107/220 (48.6)	0.47	1.05 (0.74 – 1.49)
Shortness of breath (%)	302/523 (57.7)	134/220 (60.9)	0.42	0.91 (0.64 – 1.31)
Pain or problems during intercourse (%)	127/489 (26.0)	63/210 (30.0)	0.27	0.68 (0.45 – 1.02)
Tired or low in energy (%)	506/531 (95.3)	207/225 (92.0)	0.07	1.42 (0.70 – 2.90)
Trouble sleeping (%)	441/531 (83.1)	183/225 (81.3)	0.57	1.25 (0.80 – 1.94)

*P value for Pearson χ^2.

†Female patients only.

Table 2. Prevalence of Individual PHQ-12 Somatic Symptom Items Among Functional Dyspepsia Patients According to Subtype.

PHQ-12 somatic symptom item ("reported as bothered a lot")	PDS	EPS	Overlap	P value*
Back pain (%)	378/462 (81.8)	11/14 (78.6)	23/33 (69.7)	0.23
Arm, leg, or joint pain (%)	350/468 (74.8)	8/15 (53.3)	19/33 (57.6)	0.02
Period pain or period problems (%)†	127/308 (41.2)	4/8 (50.0)	13/27 (48.1)	0.70
Headaches (%)	337/462 (72.9)	10/14 (71.4)	26/33 (78.8)	0.76
Chest pain (%)	275/455 (60.4)	7/14 (50.0)	5/33 (15.2)	<0.001
Dizziness (%)	293/456 (64.3)	7/13 (53.8)	24/33 (72.7)	0.44
Fainting spells (%)	71/448 (15.8)	1/14 (7.1)	4/33 (12.1)	0.58
Heart pounding or racing (%)	241/460 (52.4)	6/14 (42.9)	15/33 (45.5)	0.59
Shortness of breath (%)	278/462 (60.2)	7/15 (46.7)	11/33 (33.3)	0.007
Pain or problems during intercourse (%)	113/430 (26.3)	1/14 (7.1)	9/33 (27.3)	0.27
Tired or low in energy (%)	447/470 (95.1)	15/15 (100.0)	33/33 (100.0)	0.29
Trouble sleeping (%)	397/470 (84.5)	9/15 (60.0)	23/33 (69.7)	0.003

*P value for Pearson χ^2.for trend.

†Female patients only.

Table 3. Somatization Levels and Severity, and Anxiety and Depression Scores in Functional Dyspepsia Patients Compared with Organic Dyspepsia Patients.

	Functional Dyspepsia (n = 407)	Organic Dyspepsia (n = 167)	P value*
Mean PHQ-12 score (SD)	10.2(4.4)	9.6 (4.8)	0.23
Mean number of somatic symptom items reported (SD)	6.9 (2.5)	6.6 (2.7)	0.19
High level of somatization severity	127 (31.2)	47 (28.1)	0.47

*P value for independent samples t-test, or Pearson χ^2 test.

Table 4. Somatization Levels and Severity, and anxiety and depression scores in 538 Functional Dyspepsia Patients According to Subtype

	PDS (n = 355)	EPS (n = 11)	Overlap (n = 32)	P value*
Mean PHQ-12 score (SD)	10.3 (4.4)	8.5 (4.4)	8.7 (3.5)	0.06
Mean number of somatic symptom items reported (SD)	7.1 (2.5)	5.7 (2.6)	6.2 (2.2)	0.04
High level of somatization severity	119 (33.5)	2 (18.2)	4 (12.5)	0.03

*P value for one way analysis of variance, or Pearson χ^2 test for trend.

FIGURES

Figure 1. Total PHQ-12 scores in Functional Dyspepsia Patients Compared with Organic Dyspepsia Patients.

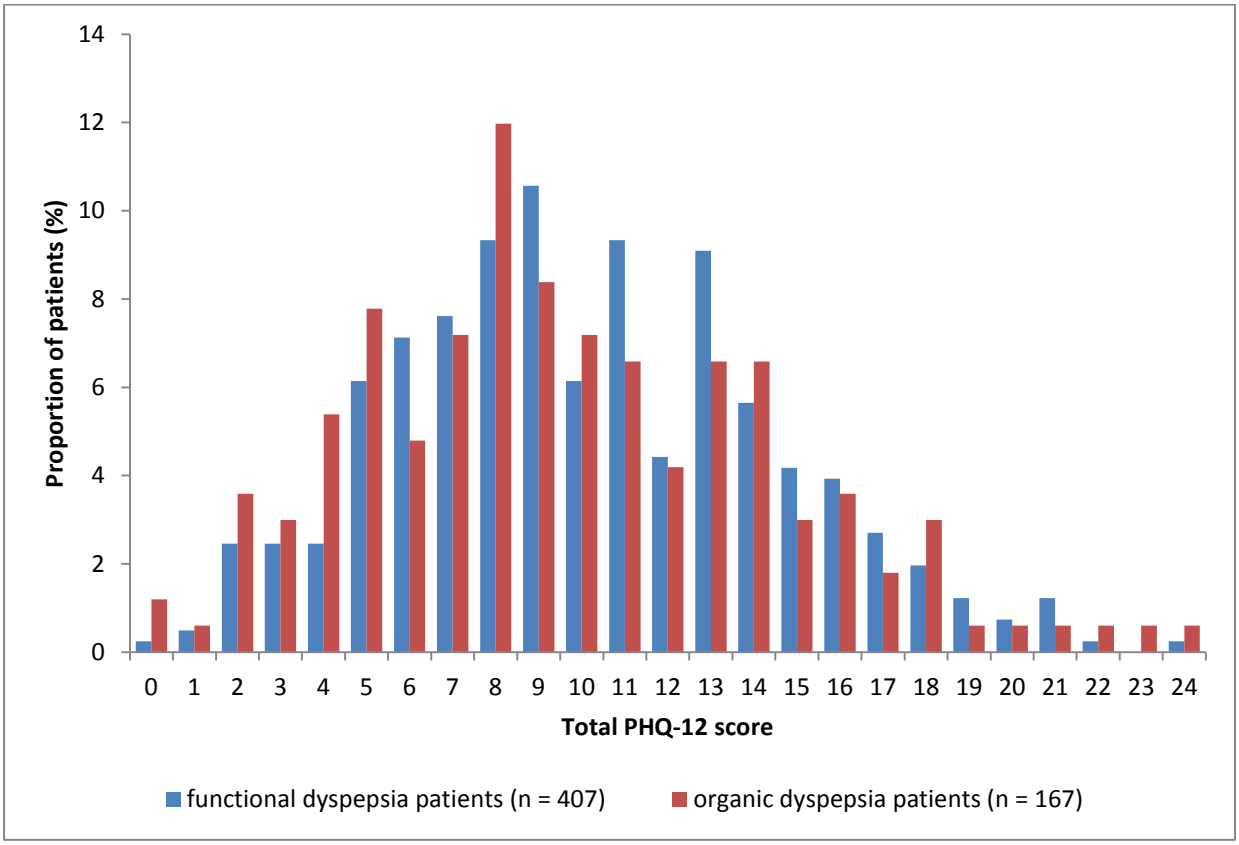

Figure 2. Total PHQ-12 scores in Functional Dyspepsia Patients According to Subtype.