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**The PHQ-12 Somatic Symptom scale as a predictor of
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patients with irritable bowel syndrome and symptomatic
diverticular disease**

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4 **The PHQ-12 Somatic Symptom scale as a predictor of**
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7 **symptom severity and consulting behaviour in patients with**
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10 **irritable bowel syndrome and symptomatic diverticular**
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12 **disease**
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22 **Running head: PHQ12 SS, IBS, Diverticular disease and**
23 **consulting behaviour**
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BACKGROUND Anxiety, depression and non-gastrointestinal symptoms are often prominent in IBS but their relative value in patient management has not been quantitatively assessed. We modified the Patient Health Questionnaire 15 (PHQ-15) by excluding the 3 gastrointestinal items to create the PHQ-12 **Somatic Symptom scale (PHQ-12 SS)**.

AIMS To compare the value of the PHQ-12 **SS scale** to the Hospital Anxiety and Depression (HAD) scale in predicting symptoms and patient behaviour in IBS and diverticular disease.

METHODS: We compared 151 healthy volunteers (HV), 319 IBS patients and 296 patients with diverticular disease (DD), 113 asymptomatic [ASYMPDD] and 173 symptomatic DD (SYMPDD).

RESULTS: **PHQ-12 SS** scores for IBS and SYMPDD were significantly higher than HV. Receiver-operator curves showed a **PHQ-12 SS** >6 gave a sensitivity for IBS of 66.4% with a specificity of 94.7% and a Positive Likelihood Ratio (PLR) = 13.2, significantly better than that associated with an HAD anxiety score >7, PLR = 3.0 and depression score >7 PLR = 6.5. **PHQ-12 SS** correlated strongly with IBS severity scale (IBSSS) and GP visits in both IBS and DD.

CONCLUSION: The **PHQ-12 SS scale** is a useful clinical tool which **correlates with** patient behaviour in both IBS and SYMDD.

Key words: Irritable bowel, somatisation, anxiety, depression, diverticular disease, diagnosis, **sensitivity, specificity**

Abbreviations: PHQ15 Patient Health Questionnaire 15, IBS irritable bowel syndrome, DD diverticular disease, ASYMPDD asymptomatic diverticulosis, SYMPDD symptomatic diverticular disease, IBSSS irritable bowel syndrome symptom severity scale

Introduction

When assessing patients with abdominal pain and disturbed bowel habit associated with normal physical findings, it is recommended to assess psychological variables (1). Many will turn out to have important psychological abnormalities and addressing these has been shown to improve management and outcomes (2). Previous studies have tended to emphasise that IBS patients are significantly more anxious and depressed than healthy controls(3-6) and have a higher incidence of previous psychiatric disease (7,8).

Although this is true, anxiety is a major driver of any consultation (9,10) so it is perhaps not surprising that anxiety is not a useful aid in differential diagnosis since it fails to clearly distinguish IBS patients from patients with other gastrointestinal diseases such as colon cancer, coeliac disease, peptic ulcer (11), inflammatory bowel disease(12) or indeed most general medical conditions (13) (14).

There is increasing recognition of the importance of somatisation in determining health care utilisation in IBS (15). Somatisation with multiple somatic complaints is also important in understanding mechanisms of disease since IBS patients can be usefully subdivided into those with low somatisation, in whom there is a predominantly GI cause for their symptoms and those with high somatisation, in which a central cause, associated with visceral hypersensitivity, predominates (16,17). Patients also feel these symptoms are important as recently reported in a survey of 755 IBS patients which showed that non-GI pains were one of the factors along with pain, illness belief and defaecatory difficulties which contribute to patient-assessed severity(18).

While somatisation meeting the criteria laid down in the Diagnostic and Statistical Manual for psychiatric disease (DSM-IV) is uncommon, being found in only 1-2% of primary care patients, a lesser condition of multiple unexplained somatic symptoms, the Physical Symptom Disorder as detected by the Patient Health Questionnaire 15 (19) has an incidence of 10-15% in patients consulting in primary care (20). The Patient

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3 Health Questionnaire 15 is an instrument which records the bothersomeness of 15
4 symptoms including somatic symptoms such as back ache, limb pain and chest pain,
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6 cardiovascular system symptoms such as palpitations and breathlessness as well as
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8 three gastrointestinal (GI) symptoms, namely abdominal pain, nausea and disordered
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10 bowel function, together with sexual dysfunction, lethargy and headaches (Table 1) (21).
11
12 Clinical experience with this instrument in primary care, internal medicine and
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14 gynaecology clinics shows it correlates well with symptom severity across a range of
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16 conditions (21). Our own experience using this instrument in our clinic over the last 4
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18 years suggested that IBS patients score highly, even when it is modified by excluding
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20 the 3 GI specific questions, a scale we call the PHQ-12. We believe that this is useful
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22 because it detects a sensitisation to painful and other somatic non-GI stimuli which is an
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24 important feature of many IBS patients (22,23).
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29 The aim of this study, therefore, was to assess the value of the PHQ-12 score not only in
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31 separating out IBS from other patients but also in predicting both gastrointestinal
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33 symptom severity and patient consulting behaviour.
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35 As a disease control with disturbed bowel habit and pain we also included a group of
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37 older patients with diverticulosis, some of whom were asymptomatic (ASYMPDD) who
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39 provided age-matched controls for those who were symptomatic (SYMPDD).
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Subjects and Methods

This study took place at Nottingham University Hospital NHS Trust, Nottingham and the Wythenshawe Hospital, South Manchester between July 2006 and September 2008. The IBS group, who all met the Rome II IBS criteria(24) were part of a larger IBS genetics and biomarker study approved by the Nottingham Research Ethics Committee which also approved the diverticular patient survey.

IBS patients

We recruited 148 IBS with diarrhoea (D-IBS) and 132 IBS with constipation (C-IBS) and 39 patients with a history compatible with post-infective IBS (PI-IBS) from our outpatient clinics but excluded those with mixed bowel habits (25). These had all completed full negative evaluation for other diseases in the Gastroenterology Out-Patient Clinic and were then invited to take part in the study. As recruitment of IBS patients continued we also recruited a total of 151 age and gender matched healthy volunteers.

Diverticulosis patients

We also recruited 296 patients with diverticulosis as a disease control. These patients were identified from our database which includes patients being seen in Nottingham University Hospital NHS Trust with a diagnosis of diverticulosis made either by radiological or endoscopic means as well as from the membership of the National Diverticulitis support group. Of these 113 were asymptomatic without any abdominal pain or discomfort [ASYMPDD] and 173 had abdominal pain or discomfort [SYMPDD]).

Questionnaires

All IBS patients completed the IBS Severity Score questionnaire (IBSS), a simple 5 point scale which uses visual analogue scales to express severity of pain, bloating, as well as dissatisfaction with bowel habit and how much IBS symptoms interference with life (26). We also used the Hospital Anxiety and Depression Scale (HAD) (27) together with a modified Talley Bowel Symptom Questionnaire (28) allowing the diagnosis of IBS

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3 according to the Rome II criteria (29) which was the current gold standard at the time
4 of starting the study. In addition, they also filled out the Patient Health Questionnaire
5 15 (PHQ-15) (Table 1) which asks about the bothersomeness of a range of symptoms
6 (21). Since the PHQ15 contains three questions directly related to gastrointestinal
7 symptoms (constipation or loose bowels, abdominal pain and nausea or indigestion)
8 which would automatically give a high score we calculated a PHQ-12 SS score in which
9 these 3 items were excluded. All diverticulosis patients also completed the bowel
10 symptom questionnaire as well as the HAD and the full PHQ-15. Healthy volunteers also
11 completed the same questionnaires except the IBSSS. The modified Talley Bowel
12 Symptom Questionnaire was used to exclude any who met IBS criteria.
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26 **Data Analysis and Statistics**

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28 All data was entered from the original paper questionnaires into Excel spread sheets and
29 verified by two individuals to check for transcribing errors. Data was then imported into
30 SPSS Version 15 for analysis.
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34 All parameters were assessed for abnormality of distribution. Age, IBS severity score,
35 PHQ-12 SS and HAD were normally distributed while bowel symptoms were not.
36 Normally distributed data is expressed as mean \pm standard error of the mean and
37 differences between groups were assessed by an initial overall analysis of variance
38 (ANOVA) followed by post hoc comparisons using the Tukey test. Correlation was
39 performed using the Pearson correlation coefficient. Non parametric data is presented in
40 the text as median (range). The Kruskal-Wallis nonparametric analysis of variance was
41 used to assess overall group differences and post hoc comparisons were evaluated using
42 Dunn's multiple comparison test.
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53 Approximately 3% of data was missing owing to undecipherable or missing responses,
54 but the numbers on which each assessment is made is indicated in the text. Multivariate
55 analysis was also undertaken to assess the relative importance of the factors shown in
56 univariate analysis to be significantly associated with outcomes of interest, namely IBSS,
57 doctor visits and PHQ12. Backward logistic regression was used including initially PHQ-12
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3 SS, age, anxiety and depression to predict IBSS in IBS groups only. PHQ-12 SS, age,
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5 anxiety and depression were also used to predict doctor visits and bloating both in the
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7 entire group and also within each patient group. Initially we used binary logistic
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9 regression to predict dichotomous outcomes (IBSS above 296, abnormal values of
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11 anxiety, depression, presence of bloating, doctor visits >2/year) and then used linear
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13 regression to derive predictive equations to help understand the relative importance of
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15 each variable for the various outcomes of interest (IBSS, doctor visits, PHQ12, bloating).
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17 Standard receiver-operator curves were constructed to determine the optimum cut-off of
18
19 the PHQ-12 SS for distinguishing IBS from healthy volunteers and to compare the
20
21 efficacy of the different scores in discriminating IBS from HV. We also calculated the
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23 Positive and Negative Likelihood ratios which respectively indicate by how much the
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25 probability of having IBS is increased by having an elevated score or how much it
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27 decreases if the score is normal. These measures have the advantage over positive and
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29 negative predictive values of being independent of the proportion of IBS in the initial
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31 sample. It is generally considered that to be useful a diagnostic test should have a PLR in
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33 excess of 2, with a value >10 being considered excellent, thus the tissue
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35 transglutaminase test has a PLR of 11. Similarly to be useful the Negative Likelihood
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37 Ratio should be <0.2, again the tissue transglutaminase test has a NLR of 0.09. As will
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39 be seen by these criteria the PHQ-12 SS performs well.
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45 **Inclusion and Exclusion Criteria**

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47 All subjects in the IBS study underwent a screening medical examination including a
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49 general physical examination and screening blood tests including full blood count, serum
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51 calcium and endomysial antibodies to exclude underlying diseases. In the course of the
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53 three year study, two supposed IBS patients were shown to have coeliac disease and
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55 excluded but no other conditions were identified. Exclusion criteria were serious
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57 concomitant disease, bleeding or clotting disorders, previous gastrointestinal surgery
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59 (other than appendectomy or cholecystectomy), history of alcohol or drug dependence
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and pregnancy. Healthy volunteers were excluded if they had IBS symptoms or had

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3 gastroenteritis within the previous 6 months. As this was part of a larger genetic study,
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5 only Caucasians were included to avoid heterogeneity due to racial differences. Subjects
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7 in the diverticulosis group were not subjected to systematic screening for this study but
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9 had already been investigated for their original presenting complaint. Any with a
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11 diagnosis of bowel cancer or other serious gastrointestinal disease were excluded.
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Results

Demographics and bowel symptoms (Table 2)

In accordance with our planned age and sex matching there are no differences in age and gender between our healthy volunteers (HV) and the IBS groups except that C-IBS were slightly more likely to be female (93%) compared to PI-IBS (70%) and D-IBS (67.2%), Chi squared $p < 0.001$. Symptomatic diverticular patients (SYMPDD) were likewise female predominant (78%) while in the asymptomatic DD patient group (ASYMPDD) gender was more even with only 56% female (Chi squared $p < 0.0001$). The diverticular patients as expected were significantly older than the IBS and HV groups.

As required by the IBS classification used there were significant differences in bowel frequency and the proportion of days with loose and hard stool in the IBS subgroups. The diverticular patients had significantly more days with both loose and hard stool than healthy volunteers, even those patients not troubled by abdominal pain. SYMPDD had fewer days pain than both CIBS and DIBS, both $p < 0.001$. By definition ASYMDD did not report recurrent abdominal pain.

Somatisation scores

The most striking difference was the clear separation of the 3 groups of IBS patients by the PHQ-12 SS scores (Figure 1, Table 3 and [Supplementary Figure 1](#)) from both healthy volunteers, and from the ASYMPDD group.

A receiver-operating curve comparing all IBS patients with HV (Figure 2) gave an ROC score of 0.88. A cut-off of >6 was chosen to give the best combination of sensitivity 66.4% and specificity 94.7%. This gave an excellent Positive Likelihood Ratio of 13.2, with a Negative Likelihood Ratio of 0.3.

Using the cut off of >6 (Table 4) 67% of all IBS patients considered as a single group had abnormally elevated values compared with only 54.8% of the SYMPDD patients. [As the supplementary figure shows most of the ASYMPDD had values within the normal range.](#)

Performance of anxiety and depression scores

Although anxiety and depression did differ between the IBS groups and healthy volunteers there was a greater overlap than for PHQ-12 SS (Table 3 & 4). The ROC area under the curve for anxiety was less than for the PHQ-12 SS at 0.8 and, using the standard cut off of >7, sensitivity was 72.4% and specificity 74.8% for all IBS versus HV. The PLH was less good than for the PHQ-12 SS at 2.9 and a NLR of 0.4. The ROC area for depression was similar at 0.8 but using the standard cut off of >7 gave a sensitivity of only 36% with specificity of 93.4% (PLR 5.5 and a NLR 0.7). Thus the PHQ-12 SS score was approximately three times as likely to be abnormally high in IBS than depression and 1.3X as likely to be elevated compared to anxiety.

As Table 4 shows 54.8% SYMPDD had abnormal PHQ-12 SS compared with just 26.6 % in ASYMPDD, Chi-squared 27.0 versus SYMPDD, $p < 0.001$.

Similarly abnormal anxiety/ depression was seen in 71.7%/ 39.3% of the SYMPDD patients significantly greater than the 38.9%/ 23.0% of the ASYMPDD group, Chi-squared 27.3 / 8.2, $p < 0.001$ / 0.01 respectively .

Predicting IBS symptom severity score (IBSS)

Restricting analysis just to IBS patients showed that PHQ-12 SS correlated more strongly with IBS severity scale (IBSS) than anxiety or depression ($r = 0.41$ versus 0.29 and 0.34, all $p < 0.00$, $n = 309$). Binary logistic regression showed PHQ-12 SS, lower age and depression were all independent predictors of IBSS > 296 , $p < 0.000$, 0.001 and 0.01 respectively. Predictably anxiety correlated with depression and was not an independent predictor of IBSS. Multiple regression showed that each 1 point rise in PHQ-12 SS or depression score increased IBSS by 8.3 and 7.1 points respectively while each additional decade of age reduced the score 13 points. Put another way each 1 standard deviation (SD) rise in depression increased IBSS 0.28 SD while each 1 SD rise in PHQ-12 SS

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3 increased IBSS 0.31 SD again showing that PHQ12 is a more important predictor of
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5 IBSS than depression.
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9 **Predicting visits to doctors: role of age, PHQ12, anxiety and depression**

10 IBS patients reported visiting their doctor for their abdominal symptoms an average of
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12 2.2(0.2) times in the previous year, significantly more than the ASYMPDD patients
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14 0.3(0.1) and SYMPDD patients 1.4(0.2) $p < 0.0001$ and 0.002 respectively.
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17 Considering the IBS patients separately, GP visits correlated with negatively with age
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19 ($r = -0.19$) $p = 0.001$, and positively with PHQ-12 SS ($r = 0.17$), $p = 0.002$ anxiety ($r = 0.12$),
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21 $p = 0.03$ and depression, ($r = 0.18$) $p = 0.001$, $n = 310$. Gender did not significantly influence
22
23 the number of visits. Binary logistic regression using age, PHQ-12 SS, anxiety and
24
25 depression to predict 2 or more doctor visits per year showed that neither gender nor
26
27 anxiety nor depression were independent predictors but that age and PHQ-12 SS were.
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29 Multiple linear regression showed that visits increased 0.23 /year for each unit rise in
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31 PHQ-12 SS and fell 0.28 visits / year for each advancing decade of life.
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34 The pattern in diverticular disease was slightly different with only PHQ-12 SS showing an
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36 independent effect on doctor visits on binary logistic regression. Multiple regression
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38 showed that visits increased 0.17 /year for each unit rise in PHQ-12 SS.
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41 Within the diverticulosis there were 19 patients with more severe symptoms. This group
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43 reported prolonged periods of pain lasting > 24 hours with fever for which they had sought
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45 medical attention and received antibiotic treatment. These 19 were predominantly
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47 female (16/19) and significantly younger than the other DD patients being 61.6 ± 2.8 ,
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49 $p < 0.001$. These patients reported visiting their doctor more at 2.2(0.3) visits/year than
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51 the remaining SYMPDD excluding these 19 who visited 0.8(0.2) times or ASYMPDD
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53 patients 0.3(0.1) visits, $p < 0.01$ and 0.0001 respectively. They had significantly higher
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55 PHQ-12 SS scores at 10.3 ± 1.1 compared to the remaining SYMPDD patients as a whole
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57 7.1 ± 0.3 , $p < 0.01$ and the ASYMPDD at 5.0 ± 0.3 , $p < 0.001$
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Predicting PHQ-12 SS

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3 Within the entire study group PHQ-12 SS correlated with both anxiety $r= 0.54$ and
4 depression $r=0.55$ $p<0.001$ $n=583$. Multiple logistic regression in all subjects also
5 showed that depression and anxiety and female gender were all significant independent
6 predictors of having a PHQ-12 SS score greater than **the cutoff of >6** , p for all variables
7 <0.0001 . Linear regression showed that for each unit rise in anxiety score, PHQ-12 SS
8 rose 0.29 , and 0.39 for each unit rise in depression score. Females scored on average
9 6.8 ± 0.2 points, significantly greater than males who scored 5.1 ± 0.2 , $p<0.001$. PHQ-12
10 SS score fell slightly with increasing age but this was not significant, $p=0.52$.

21 **Predicting bloating and abnormal bowel function**

22
23 86% of IBS patients reported being troubled by abdominal distension or bloating
24 significantly more than ASYMPDD (24%) and SYMPDD (68%), both $p<0.001$. PHQ-12 SS
25 scores correlated more strongly than anxiety or depression with days with bloating ($r=$
26 0.48 versus $r=0.43$ and 0.33 , all $p<0.000$, $n=582$). Multiple logistic regression showed
27 that advancing age and male gender were independently protective, Odds ratio for being
28 troubled by bloating 0.99 ($p<0.03$) and 0.62 ($p<0.000$), while anxiety and PHQ-12 SS
29 showed a modest adverse effect, Odd's Ratio 1.1 and 1.2 , both $p<0.000$. Advancing
30 years also reduced the incidence of loose stools with every decade of age reducing the
31 number of days with loose stool on average 0.4 days/ week, $p<0.001$. Male gender in
32 contrast significantly increased the frequency by 1.1 days/ week, $p<0.001$.

46 **Predicting symptoms in diverticular disease**

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48 Binary logistic regression showed both gender, anxiety and PHQ-12 SS were significant
49 ($p<0.001$) independent predictors of having symptoms with each 1 unit rise in Anxiety
50 or PHQ-12 SS score increasing the risk of having symptoms 19% and 11% respectively,
51 while females were at 2.3 fold increased risk compared to males
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Discussion

This is the first study using the modified PHQ15 to evaluate a large group of patients with gastrointestinal symptoms. After excluding the three items which cover gastrointestinal symptoms, we found that the modified scale, which we have called the **PHQ-12 SS**, clearly distinguishes IBS patients from healthy volunteers. Although the sensitivity of **PHQ-12 SS** for identifying IBS in general, using a cut off of >6, was only 66%, the specificity was 95%, which would be very helpful in a clinical setting such as outpatients in which IBS is very common. Since in our study IBS accounted for about 2/3 of the group we would expect similar performance in a clinical setting and a normal **PHQ-12 SS** score would be against a diagnosis of IBS and prompt further tests.

We believe that a high **PHQ-12 SS** indicates heightened awareness of bodily symptoms. Earlier studies suggested that visceral hypersensitivity(VH) is a significant component in at least 50% of IBS patients who experience a range of stimuli such as rectal distension or colonic contraction as more painful than normal subjects(30,31,31,32). These studies suggested that VH did not extend to somatic pain, however more recently the overlap of IBS with fibromyalgia has been recognised and there have been some major advances in understanding the neurological basis of VH which may reflect defective anti-nociceptive systems(33-35). The descending inhibitory pathways, which are normally activated to reduce sensation from the viscera, appear defective in IBS. Some of the most effective treatments in IBS, the tricyclic antidepressants, have been shown to produce changes in brain activation suggesting they may restore this anti-nociceptive activity(36). A similar defect may underlie fibromyalgia (37). Failure to inhibit noxious signals may be a more generalised defect and clinically IBS patients are known to consult frequently not only for bowel symptoms but also for non GI symptoms(38) (39) (40) and also receive more treatments such as antibiotics for non GI complaints(41). Excessive awareness of signals from many parts of the body other than the gut are detected by the **PHQ-12 SS** scale which provides a rapid and useful clinical assessment.

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3 One of the authors, (RS) has been using this for over 4 years in his clinic and this study
4 confirms the clinical impression that this is more useful than anxiety and depression
5 scales which are elevated in patients with organic as well as functional disease (42).
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9 One reason why the PHQ-12 SS more clearly separates IBS from the other groups is
10 that it may be a way of detecting generalised hypersensitivity, which is a key feature in
11 at least half of IBS patients and seems to predict the more severe symptoms(43).
12
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15 The recognition that multiple somatic complaints are frequently seen in IBS patients is
16 also of considerable importance from a management point of view. This is because they
17 significantly add to the burden of illness as well as leading to inappropriate referral and
18 even unnecessary treatment (44-46). Thus patients with IBS are over-represented in
19 gynaecological and urological clinics and it has been shown that they are also subjected
20 to an excess of surgical procedures (47) . These non-GI complaints are also a major
21 cause of concern to patients themselves who often fear that other disease is being
22 overlooked. It has been shown that these symptoms can be just as intrusive as the
23 gastroenterological symptoms (48) . Furthermore these features have diagnostic utility
24 as it has been shown that the more non-colonic symptoms of which a patient complains,
25 the more secure the diagnosis of IBS becomes (49) .
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39 Although both IBS and DD patients suffer abdominal pain and disturbed bowel habit,
40 there are important differences, including the structurally abnormal bowel and the effect
41 of advancing age which increases the prevalence of symptomatic diverticular disease but
42 reduces IBS prevalence. Our previous studies show that using the Rome II criteria only a
43 minority (15%) of SYMDD patients meet Rome criteria for IBS largely because their pain
44 was not relieved by defecation nor closely linked to stool consistency or frequency. A
45 recent survey in Olmstead county found a somewhat higher prevalence but even so only
46 29% of patients with diverticulosis meet the Rome II criteria for IBS compared to 13% in
47 the population overall (50). PHQ-12 SS scores in both asymptomatic and symptomatic
48 patients with diverticulosis in the current study were higher than healthy controls but
49 lower compared to IBS patients despite their greater age and their having a similar
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3 disturbance of bowel habit as judged by the number of days per week with hard or loose
4 stools. This discrepancy supports the idea that the symptoms in at least some DD
5 patients are related to the associated peripheral abnormality, namely muscular
6 hypertrophy and altered innervation (51) which is absent in IBS, where symptoms are
7 mainly driven by central abnormalities of sensory processing and interpretation. The
8 higher PHQ-12 SS score in the small subgroup with a history of fever, pain lasting >24hr
9 and prescription of antibiotics is intriguing. It may represent a group with somatisation
10 who seek and get more medical attention but alternatively it may indicate that recurrent
11 pain from acute diverticulitis leads to generalised hypersensitivity. Only a prospective
12 study with objective rather than the current subjective criteria for diagnosing
13 diverticulitis could answer this question.
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Completing the PHQ-12 SS takes only a few minutes and we believe is a valuable
addition to the clinical assessment of patients . Not only is the physician gaining useful
data, but the patient becomes re-assured that their medical attendants are familiar with
these additional features of their condition, which can be so disabling.

Future studies should assess the value of these scores when combined with alarm
symptoms and the Rome criteria in reducing the need for unnecessary investigations in
this important group of patients.

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Statement of interests

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Table 1: PHQ12 Questionnaire

The PHQ15 questionnaire asks about the bothersomeness of each symptom, scored 0= Not bothered at all, 1 = bothered a little, 2 =bothered a lot.

The PHQ12 excludes the first 3 GI questions

- Stomach pain
- Constipation, loose bowels, or diarrhoea
- Nausea, gas, or indigestion
- Back pain
- Pain in your arms, legs, or joints (knees, hips, etc)
- Menstrual cramps or other problems with your periods (Women only)
- Headaches
- Chest pain
- Dizziness
- Fainting spells
- Feeling your heart pound or race
- Shortness of breath
- Pain or problems during sexual intercourse
- Feeling tired or having low energy
- Trouble sleeping

Table 2
Demographics and Bowel Habit in the healthy volunteers and patients with IBS or Diverticulosis

	† p=	HV	PI- IBS	D-IBS	C-IBS	ASYMPDD	SYMPDD
N		151	39	148	132	113	173
Gender F/M	0.000	115/36	27/12	96/52	123/9 **	64/49 ***	135/38
Age	0.000	37.9±1 .1	42.1± 2.4	47.4± 1.0 ***	42.5±1. 1*	73.7±0.9 *** ^a	69.8±0.8 *** ^a
BM/da y	0.000	1.0 (0-5)	3.0 (0-7) ***	4.0 (0-12) ***	1.0 (0-5) *** ^b	1 (1-5) *** ^c	2 (1-5) ***
Days /wk loose BM	0.000	0 (0-5)	3 (0-7) ***	5 (0-7) ***	0.0 (0-7) *** ^b	3(1-7) *** ^d	5 (1-7) ***
Days/ wk hard BM	0.000	0 (0-7)	2 (0-7) ***	1 (0-7) *	3 (0-7) *** ^b	5 (1-7) ***	3 (1-7) ***
Days/ wk pain	0.000	0	4 (0-7) ***	3 (0-7) **	4 (0-7) ***	0 ^e	2 (0-7) *** ^f

Legend to Table 2

HV= healthy volunteer, PI-IBS= post infectious IBS, IBS-D= IBS with diarrhoea, IBS-C= IBS with constipation, SYMPDD= symptomatic diverticular disease, ASYMPDD= asymptomatic diverticulosis.† ANOVA Kruskal-Wallis test except Age which being normally distributed was analysed using ANOVA

Age =Age in years Mean ±SEM

BM / Day = Bowel movements per day Median (range)

Days /wk loose BM = Days per week with loose bowel movements Median(range)

Days/wk hard BM =Days per week hard bowel movements Median (range)

Difference from HV *** p<0.001, ** p<0.01 * p<0.05. ^a P<0.0001 versus IBS ^b p<0.0001 versus D-IBS ^c p<0.0001 versus SYMPDD ^d p<0.05 versus SYMPDD ^e p<0.0001 versus SYMPDD ^f p<0.001 versus D-IBS and C-IBS

Table 3: Somatisation (PHQ12), anxiety and depression scores in healthy volunteers and patients with IBS or Diverticulosis

	ANOV A p=	HV	PI-IBS	D-IBS	C-IBS	ASYM PDD	SYMP DD
N		151	39	148	132	113	173
PHQ12	0.000	3.2± 0.2	8.2±0 .3 ***	8.0±0 .3***	8.4±0 .3***	5.0±0 .3*** ^a	7.4 ±0.3* ** ^b
Anxiety	0.000	4.8± 0.2	8.3±0 .6 ***	8.6±0 .3 ***	9.7±0 .4 ***	5.6±0 .3 ^c	8.9±0 .3*** ^b
Depres sion	0.000	2.1± 0.2	5.1±0 .6 ***	5.7±0 .3 ***	5.6±0 .3 ***	4.4±0 .3*** ^g	5.8. ±0.3 *** ^b

Difference from HV * p<0.05, ** p<0.01, *** p<0.001 ^a p<0.001 versus all IBS and symptomatic DD ^b p<0.001 versus ASYMPDD ^c p<0.002 versus PI-IBS and p<0.001 versus IBS-C, IBS-D and SYMPDD

Table 4: Percentage of subjects with abnormal values for somatisation , anxiety or depression

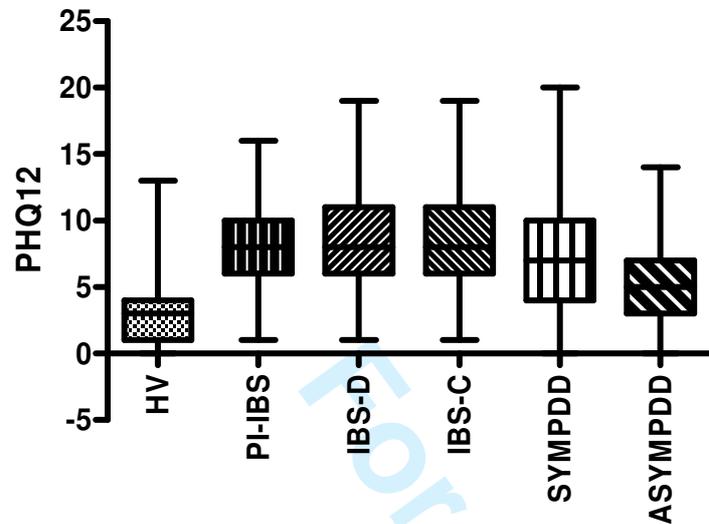
	Chi- suar ed p=	HV	PI-IBS	IBS-D	IBS-C	ASYM PDD	SYMP DD
PHQ12	0.000	5.3	71.8 ***	65.5 ***	67.4 ***	26.6	54.8 ^a
Anxiety	0.000	25.2	69.2 ***	70.3 ***	75.8 ***	38.9	71.7 ^a
Depressi on	0.000	6.6	30.8 ***	40.5 ***	32.6 ***	23.0	39.3 ^b

*** p<0.001 versus healthy volunteers ^a p<0.001 versus ASYMPDD ^b p<0.01 versus ASYMPDD

% IBS patients with abnormal PHQ12, Anxiety and Depression were significantly greater than HV while %SYMPDD were significantly greater than ASYMPDD for all three variables.

Figure 1 Somatisation (PHQ12) scores in IBS and Diverticular disease (DD) compared to healthy volunteers

Box and whiskers plot showing median and interquartile ranges together with extreme values



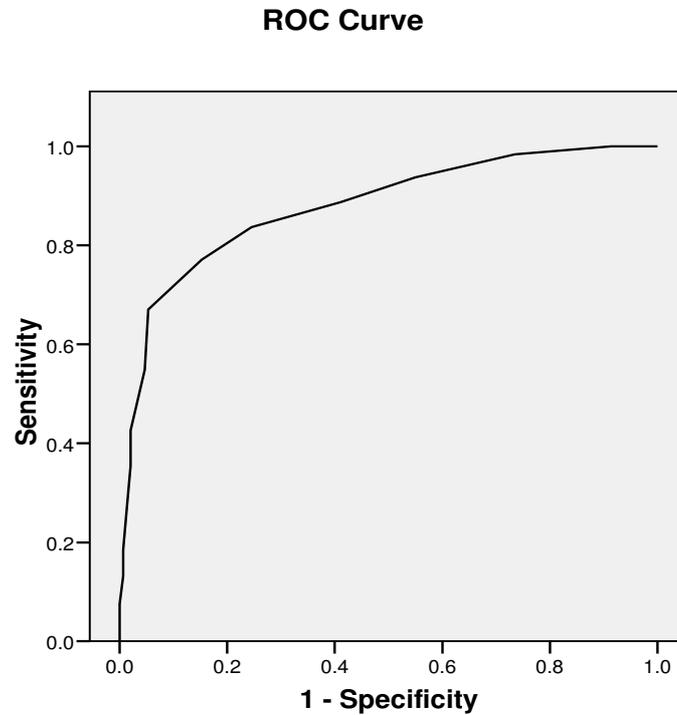
Key: Healthy volunteer HV, Postinfective IBS PI-IBS, IBS with diarrhoea IBS-D, IBS with constipation IBS-C, Symptomatic diverticular disease SYMPDD, Asymptomatic diverticulosis ASYMPDD.

All groups were significantly different from HV $p < 0.001$, ASYMPDD were significantly less than SYMPDD and all IBS groups, $p < 0.001$

Figure 2

Receiver Operating Curve for distinguishing IBS from healthy volunteers showing sensitivity versus 1-specificity for varying cut off values.

The area under the curve was 0.88. Using a cut off score of >6 gave a Sensitivity of 66.4 % and Specificity of 94.7%.



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For Peer Review

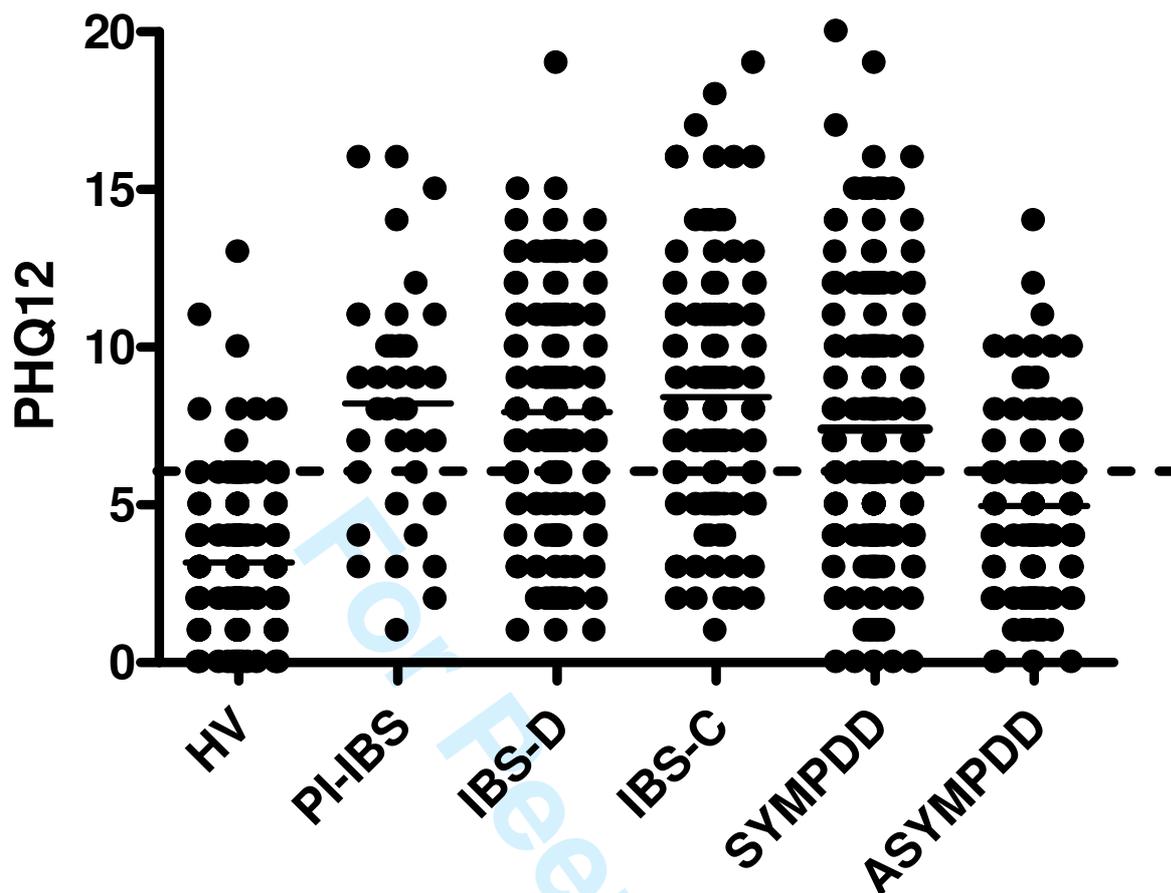


Figure 1 showing individual data points. The horizontal bar shows the median. The dotted line shows the cut off at 6.

There are very few high values in controls. The range in all patient groups is wide but values do correlate with doctor visits and symptom severity in IBS as assessed by the IBSSSS. Most ASYMPDD are within the normal range.

STARD checklist for reporting of studies of diagnostic accuracy
(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	2
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	4
METHODS			
<i>Participants</i>	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	5
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	5
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	5
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	Cross-sectional study
<i>Test methods</i>	7	The reference standard and its rationale.	6
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	9
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	9
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	Self administered
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	NA
<i>Statistical methods</i>	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	ROC
	13	Methods for calculating test reproducibility, if done.	Not done
RESULTS			
<i>Participants</i>	14	When study was performed, including beginning and end dates of recruitment.	between July 2006 and September 2008
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	Table 2
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	All did
<i>Test results</i>	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	simultaneous
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	Table 2
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	NA
	20	Any adverse events from performing the index tests or the reference standard.	None
<i>Estimates</i>	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	Table 4
	22	How indeterminate results, missing data and outliers of the index tests were handled.	NA
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	NA

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	24	Estimates of test reproducibility, if done.	NA
DISCUSSION	25	Discuss the clinical applicability of the study findings.	Page 14

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