Author's response to reviews

Title: Psychopathological features of irritable bowel syndrome patients with and without functional dyspepsia: a cross sectional study

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Version: 2 Date: 11 November 2010

Author's response to reviews: see over
Dear Dr. Robin Cassady-Cain,

we thank the two Reviewers for their in depth analysis of our work. Many of the queries have been appreciated and several suggestions have been useful to improve the revised text.

We submit the revised manuscript conforming to the journal style, that takes into consideration the comments and suggestions of the reviewers. Changes have been underlined to facilitate the Editors. As requested, it has been outlined that written informed consent was obtained from all the participants. Also, Table 1 was graphically modified. All authors read and approved the final manuscript. Enclosed is the point by point response to the Reviewers’ comments.

On behalf of all contributing Authors,

with best regards,

Prof Enrico Corazziari

Point by point response

Reviewer Michael Crowell

Major Compulsory Revisions:

1. The primary limitations of the study are the small sample size, and the large number of exploratory analyses in different subgroupings. Due to the small sample sizes, special care should be taken in interpreting the lack of significant findings between the subgroup analyses, especially between the PDS and EPS. Another major concern is the repeated analysis of the FD data as a combined group and then separately as PDS and EPS. These limitations may limit the generalizability and reproducibility of the findings in the clinical setting. Due to the very small sample size for this subgroup comparison, the conclusion that there was “…no significant difference between IBS patients with PDS and IBS patients with EPS…” is not warranted by the data presented in this study.

For the reasons indicated by the reviewer we decided to dismiss our second aim (“to evaluate the psychopathological differences, if any, between IBS patients featuring the two Rome III-defined FD subtypes, i.e. postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS)” and present our findings regarding PDS and EPS as preliminary results of a study in progress in which we are increasing the sample size. These results have to be considered provisional and encourage us to continue in future research. Therefore the sentence “…no significant difference between IBS patients with PDS and IBS patients with EPS…” was replaced with a more appropriate one (see Discussion section).

2. Please explain why the raw scores were used rather than normalized T-scores? The T-scores would allow for better interpretation compared to normal values.

We agree. However, conversion of the raw scores to normalized T-scores, which takes sociodemographic factors into account, is usually made following the US manual (Derogatis LR: The SCL-90-R Administration, Scoring, and Procedures Manual II. Clinical Psychometric Research: Towson, MD, USA; 1983.), i.e. using the US standardization sample described by Derogatis, which is a non-psychiatric patient normative sample. In view of the fact that in Italy, up to now, no such standardization sample (with gender- and age-appropriate norms for conversion to normalized t-scores) has been obtained, we decided to use raw scores, as in most Italian studies (e.g. Marucci S, Pettinelli C: Soul place and body shape: a new treatment for alimentary behavior disorders in a shared place of care. Biological Medicine

3. Medians should be reported with their associated interquartile ranges in the Results section of the paper or a table to allow the reader to evaluate the variability within the groups.

We arranged this point (see Results section).

4. Was the distribution of scale scores evaluated for normality? If so, how? Is this why a non-parametric statistic used for the comparison of SCL-90 scales? If T-scores were used the distribution would be approximately normal and allow the use of parametric tests.

The distribution of scale scores was evaluated for normality by means of the Kolmogorov-Smirnov normality test (P-values < 0.05). Thus, a non-parametric test was used to compare the SCI-90-R scales.

5. The P-value for the comparison of the SCL-90 subscales should be adjusted for multiple comparisons or it should be stated that these adjustments were not made and why in the Statistical analysis section.

In the present paper we do not use multiple comparisons, as comparisons are made either between IBS and IBS+FD patients or between PDS and EPS patients.

6. How was the sample size chosen for the study? The number of combined IBS+FD patients seems quite small for the statistical analyses, but adequate. More concerning is the very small sample size used for the FD subgroup comparisons. The sample size is much too small conclude that a negative statistical finding infers that there is no differences between subgroups. The lack of significant findings may be solely due to lack of statistical power to identify differences (Type II error). The discussion and conclusion should clearly state this fact and not over state that there were no differences between subgroups.

With regard to IBS and IBS+FD patients, an estimate of power is included below. The power analysis was carried out using NCSS PASS Statistical Software (version 2008). We considered the global severity index (GGI) as the main variable of the SCL-90-R, as it is reflects the general psychopathological symptom level of the individuals, and we used an α = 0.05. Using Mann-Whitney U test with N = 26+56 (= 82) the power was 0.87. The sample size is adequate for the study purpose. Even if we had considered a lower N = 26+26 (= 52) the power of the study would have been 0.79, which is very close to the usual requested value of 0.80 in clinical studies. With regard to PDS and EPS subgroup, see our response to query 1.

7. Discussion, 2nd paragraph. In the sentence “The present study shows a high frequency of overlap between IBS and FD, equal to 31.7%, with no significant difference between PDS and EPS, supporting previous findings.” it is not clear what is meant by “with no significant difference between PDS and EPS, supporting previous findings”. Please clarify.

We acknowledge a mistake in the citation. We realized that this sentence erroneously remained from a previous version of the manuscript. It has been properly corrected in the current version: “Overlap between IBS and upper gastrointestinal symptoms can be observed in both FD subtypes, PDS and EPS, but EPS alone seems to have a lower chance of overlap with IBS [5]. The present study shows a high frequency of overlap between IBS and FD, equal to 31.7%, supporting previous findings [2,25]. Moreover, it shows no difference in terms of IBS-FD overlap between PDS
and EPS, but this result should be interpreted with caution, considering the small sample size of the two FD subgroups”.

8. **Discussion. Limitations should be discussed more fully.**

Following the reviewer’s advice, we modified our Discussion section to underline the limitations of this study.

9. **Figure 1. Please double check the significance for the Phobic Anxiety subscale as the differences seem extremely small?**

We double checked the significance for the Phobic Anxiety subscale. It is correct.

**Reviewer Laurie Keefer**

**Major Compulsory Revisions:**

1. **An estimate of power and a justification that the relatively small sample size is adequate should be included**

See our response to query 6 of Reviewer #1.

2. **While differences were found between groups, they are not really clinically significant-- scores on the SCL90R fell within the normal range for several variables. I wonder whether a nonparametric statistic might be more useful, i.e. comparing functional v. dysfunctional SCL90 X group.**

In order to evaluate differences between groups, we already used a non-parametric test (Mann-Whitney U test). GSI and eight of the nine scores showed a well defined and statistically significant difference between IBS alone and IBS+FD. For the comparison between PDS and EPS see response to query 1 of Reviewer #1. With regard to a possible comparison between functional vs dysfunctional SCL90 X group, it seems a very interesting suggestion to further examine in more depth.

3. **The authors conclude that the IBS+FD group have a greater severity of psychopathology than IBS alone-- however, they failed to control for other known variables affecting this link including symptom severity and quality of life impairment. While I realize that not all of the common questionnaires have been validated in Italian, it still would have been appropriate to get a patient or physician rating of symptom severity or functional impairment, etc.**

We agree. However, we decided not to hand out questionnaires on Health Related Quality of Life (HRQOL) or Global Assessment of Functioning (GAF) – a possibility we had previously taken into consideration – in order to prevent a reduction of patients’ compliance. In fact, patients were already asked to fill out two questionnaires, which require approximately 15 minutes each to be completed (Rome II Modular Questionnaire, consisting of 38 items, and SCL-90-R questionnaire, consisting of 90 items). Moreover, we did not hand out questionnaires on symptom severity, since there are no validated ones in Italian for functional GI disorders, as the reviewer has already pointed out. In order to make up for this shortcoming, we evaluated the duration of illness as a sort of “surrogate” index of symptom severity, but found no significant difference between IBS and IBS+FD groups.

4. **It may have been more compelling to have included a group of FD patients alone to tease out the “contribution” FD has to the association between IBS and psychopathology.**

Aim of the study was to assess the psychopathological difference, if any, between IBS alone and IBS-FD comorbidity. The inclusion of a FD group could be of interest, however it is not known whether pathophisiology of FD alone is the same of FD as comorbidity of IBS. Thus, no firm conclusion can be reached by simply excluding the contribution of FD alone.

**Minor Essential Revisions:**

1. **The authors should include in their discussion the potential limitation of having >10% of their sample being referred from other gastroenterologists-- this implies that the patients in this group were more distressed or refractory and may have biased the results. This is particularly important because of the small sample size.**
Discussion section was revised in accordance. We compared the main demographic and clinical characteristics of the 11.0% of patients referred from other gastroenterologists and the remaining 89.0% of patients (either referred from primary care or self-referred). No significant difference between the two groups of patients was found in terms of gender (females: 66.7% vs 83.6%, \( P = 0.22 \)), mean age (40.2 ± 12.3 years vs 41.8 ± 12.8 years, \( P = 0.72 \)) and median score of the GSI (0.71 vs 0.74, \( P = 0.76 \)). This finding was not unexpected, as our study was performed in a third level gastroenterological centre with a long history of research on functional GI disorders: in our experience, referral from other gastroenterologists is quite common and does not necessarily imply that patients have a greater symptom severity or are more difficult to treat.

2. **Antidepressant therapies are commonly used in refractory functional gi disorders-- what proportion of your patients were already using psychological medications and how might this have affected the findings.**

During the study period, only 2.43% (2/82) of patients were undergoing treatment with antidepressants (Amitryptiline in low doses, i.e. 20-25 mg/die). As a result, it can be assumed that the effect of psychological medications on our findings is negligible.

3. **The authors should justify the breakdown of FD patients by subtype-- are there theoretical reasons why these groups might be expected to differ? Also, why not breakdown the IBS patients by subtype too then (IBS-D, IBS-C, etc.)? Again, a larger sample may have been more useful in this regard.**

According to recent studies, FD appears to include different types of patients with distinct underlying pathophysiology who require different management: associations between symptom patterns and delayed gastric emptying (Talley NJ, Zinsmeister AR, Schleck CD: *Dyspepsia and dyspepsia subgroups. A population based study. Gastroenterology* 1992, **102**:1259-68.; Talley NJ, Boyce P, Jones M: *Identification of distinct upper and lower gastrointestinal symptom groupings in the urban population. Gut* 1998, **42**:690-5.), impaired fundic accommodation (McColl KE, el-Nujumi A, Murray L: *The Helicobacter pylori breath test: a surrogate marker for peptic ulcer disease in dyspeptic patients. Gut* 1997, **40**:302-6.) and visceral hypersensitivity has been shown (Klauser AG, Voderholzer WA, Knesewitsch PA: *What is behind dyspepsia? Dig Dis Sci* 1993, **38**:147-54.). Therefore, it seemed of some interest to evaluate whether different FD subtypes differed not only in pathophysiology, but also in psychopathology (which is likely, as functional GI disorders are currently viewed as multifactorial disorders in which physiological, psychological and social factors are strictly intertwined). This may have important consequences on therapeutic approaches, improving patients’ well-being. Accordingly, the suggested breakdown of IBS patients in subtypes would certainly add other relevant information, but the sample size has not allowed to further subanalyze the data. A future study with a larger sample size is warranted.