

Manuscript ID: 42375

“Fatigue in adolescents with inflammatory bowel disease”

Dear Prof. Ruo-Yu Ma,

In good order we received the e-mail that contained the comments concerning our manuscript. We thank you and the reviewers for the feedback and opportunity to revise our manuscript for publication in *World Journal of Gastroenterology*.

Please find herewith a new version of the manuscript that was revised according to the suggestions and comments of the reviewers. Below we provide a detailed, point-by-point response to the comments of the reviewers.

We uploaded both a clean revised version of the manuscript and a revised version with the changes marked in yellow.

We hope that the manuscript in its present form fulfills the criteria to be publishable in the *World Journal of Gastroenterology*.

Sincerely yours,

Els Van de Vijver
(on behalf of the rest of team)

Manuscript ID: 42375
Title: "Fatigue in adolescents with pediatric inflammatory bowel disease."
Re: Detailed response to the comments of reviewer 1.

- (1) Background. In the last sentence of the first paragraph, "is" should be "are".
We corrected this in the text of our manuscript.
- (2) Methods. Consider using PRISMA guidelines when reporting systematic review/meta-analysis. If PRISMA guidelines were used, please state this in the methods section.
We added this information in our manuscript: "The guidelines of the PRISMA 2009 Statement have been adopted."
- (3) Results. I have a few suggestions/needed corrections for Figure 1: list the database and sources in the first 2 boxes. I would consider moving the "records excluded" box to come off the "papers after removal of duplicates" box.
We agree with the reviewer and adjusted Figure 1 as suggested.
- (4) Additionally you have 70 included in the "paper screened on title". The subsequent boxes do not sum to 70 (69). Please correct this.
We corrected the numbers accordingly.
- (5) Would also consider listing the reasons why articles are excluded.
We added the reason for exclusion.
- (6) Have the authors considered excluding the study listed as poor quality in table 2? If there are unique properties of that study, these could be outlined in the body of the text. If there are no unique or redeeming qualities of that study, would exclude, stating so in the methods section.
We did not consider to exclude the study of Nicholas because pooling of data wasn't possible anyway, and the study was one of the few that had fatigue as outcome measurement.
- (7) Where is the discussion on sleep? It is only briefly mentioned in the discussion section. If many of these studies include sleep, this should be given more discussion in the result section. If sleep is not mentioned in multiple papers studied, this can also be mentioned. If possible, include in table 1.
Only one study has sleep/sleep quality as outcome measurement, other studies used questionnaires to evaluate the feeling of fatigue. Table 1 describes for each study the outcome measurements.
- (8) Minor typos (missing period, Extra "C", missing comma) are found on page 14 under the headings "family support" and "psychological variables". Please correct.
We corrected the typos.

(9) Discussion Are you offering figure 2 as a model of your own, or is this a known model?

This is a model of our own.

(10) Why is IMPACT III separate from KINDL/TACQOL/others in figure 2?

IMPACT-III is a disease-specific quality-of-life questionnaire and KINDL/TACQOL/others are generic quality-of-life questionnaires.

(11) I think Figure 2 should have more discussion in the body of the text. How is this more useful from other models? What gaps would this model address? Why do we need another model?

We added the following text: The model depicted in figure 2 addresses the various etiological factors and the connection with fatigue-related diagnostic tests mentioned in this paper. It points out the importance of fatigue being multifaceted and this fatigue model could act as a guide on which to base treatment interventions.

(12) Under “biological factors“ the first sentence starting “fatigue is a common finding“ needs reference.

We added the correct reference.

(13) More discussion on sleep should be included in the systematic review. In the concluding paragraph, the authors emphatically note that increased sleeping problems and anxiety are associated with fatigue. I would recommend that more discussion be given both

We changed the text in the manuscript:” The papers that sought correlations between psychobehavioral factors and fatigue showed conflicting results. One paper (13) linked anxiety, depression and lack of family support with IBD-related fatigue, while another paper failed to show that depression occurs more often in adolescents with IBD than in their healthy peers (6). Sleep disorders can affect the feeling of being tired, as shown in 2 of the included papers. Sleep deprivation leads to more anxiety and depression and to an increase in somatic complaints and aggressive behavior (12, 15, 17). Sleep itself was not often a research objective; only one study had sleeping problems as an outcome measurement (15), while a German study only reported a trend towards prolonged sleep duration in patients with mild IBD compared to healthy controls (8).

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Re: Detailed response to the comments of reviewer 2.

Abstract:

- (1) The Authors wrote: "We performed an electronic search in Medline and Embase from inception to May 2017 using the search term "fatigue" OR related keywords." Please specify related keywords. I also think that fatigue was used in combination with "IBD" and "adolescents" (at least). Please clarify. In fact, I found this in the "Methods" section. Therefore, it would not be difficult to mention more details in the Abstract as well.

We adjusted this in the abstract as follows: We performed an electronic search in Medline and EMBASE from their inception to May 2017 using the search term "fatigue" or the related keywords "physical impairment" AND "inflammatory bowel disease" with the filter "child" (age 0-18 years). Cross-sectional and case-control studies were included. We restricted our search to studies published in English . We used the PRISMA checklist and flow diagram. Duplicate articles identified were manually deleted using End Note. To identify further relevant studies, we checked the reference lists of the selected articles.

- (2) I did not find the systematic review registration number.

This review was not registered. Completed reviews cannot be registered anymore.

Background:

- (1) The first sentence starts with the reference nr. 6. References below 6 do not appear before. I researched and found reference nr. 1 in the Figure 2, which appears much later on (page 16). Please renumber the references accordingly, in the order they appear in the text.

- (2) The authors wrote "The ultimate goal in IBD treatment is to reach disease remission as early as possible." Please specify how you define remission.

We changed "disease remission" into "clinical remission"; as this is the first goal, endoscopic remission and normalization of blood and fecal markers are the next steps.

Methods:

- (1) The first heading is "Identification and selection of studies" and the second one is "Study selection". Please rename.

We deleted "Study selection" and merged the two paragraphs.

- (2) The authors wrote “We restricted our search to studies published in English only”. Please insert this sentence in the Abstract as well.

We adjusted the abstract as mentioned above (Abstract 1)

- (3) Please insert that you used the “PRISMA guidelines” in this section and also in the Abstract.

We added this information in our manuscript:” The guidelines of the PRISMA 2009 Statement have been adopted.”

Results:

- (1) First paper in table 1: it is mentioned that “adolescents with IBD are fatigued , even when clinical remission is reached”. Maybe this finding should be discussed/emphasized in the “Discussion”, as clinical remission only is not enough for deep remission. As mentioned in Table 2, and later on in the text, only clinical remission was assessed in some of the studies. Maybe deep remission would have an impact on less fatigue.

We agree with the reviewer and added in the discussion: “Adolescents in clinical remission are fatigued, but deep remission was not assessed: deep remission could have an impact on less fatigue.”

- (2) Studies in Table 1 include not only adolescents, but also children aged of 6 years, 7 years, 8 years and so on. Maybe it would be better to consider this for the title and related sentences reporting on adolescents.

We agree with the reviewer and adjusted the title and related sentences accordingly.

- (3) Adolescents with IBD report no more sleeping problems or overtiredness than their healthy peers (21). Another study (11) found that general fatigue and sleep/rest fatigue were frequently observed in pediatric IBD patients compared to healthy control subjects, even when their disease was in remission. The German study (13) reported that “a trend towards shorter duration of physical activity and significantly prolonged sleep duration in patients with mild IBD compared to controls, but there was no statistical significant difference (13)”. These observations could be commented more in depth in the “Discussion”, as the first sentence in the “Discussion paragraph” states that “This review demonstrates that fatigue, exhaustion, diminished physical activity and trouble sleeping are more common in adolescents with IBD than in healthy peers.”. About sleep, there was not always the case. 4. “The Finnish study amongst 160 adolescents used a visual analogue scale (VAS) to measure disease activity. Adolescents with severe IBD (VAS scores above 3) had significantly more trouble falling asleep (41% vs 22%), feeling overtired (80% vs 44%) and longer sleep duration than adolescents with less active disease (VAS score below 3). In this study, the results of the self-reported questionnaires and the parent reports had a close similarity when the adolescents had

higher VAS scores, but this was less so in the parent-adolescent pairs with mild IBD symptoms." Please add here reference nr 21, which is missing.

We agree with the reviewer and added the following sentences in the discussion: "This review demonstrates that fatigue, exhaustion and, diminished physical activity and trouble sleeping are more common in children and adolescents with IBD than in their healthy peers"... "Sleep itself was not often a research objective: only one study had sleeping problems as an outcome measurement, while a German study only reported a trend towards prolonged sleep duration in patients with mild IBD compared to healthy controls." The correct reference is added.

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Re: Detailed response to the comments of reviewer 3.

- (1) The word relations in the Results of the ABSTRACT should be relationships
We corrected "relations" into "relationships".
- (2) The use of subheadings in the INTRODUCTION is not standard. Suggest to remove this.
We removed the subheadings as suggested.
- (3) At the bottom of page 12, a sentence concludes with the words wearable. Should this be followed by another word (device?)
We added the word "device".
- (4) At the bottom of page 13, "no" should be "not"
The Editing office changed this sentence.
- (5) In the first paragraph of page 14, the letter c should be deleted
We deleted the typo extra letter "c".
- (6) The titles for the figures and Tables could be more comprehensive.
We adjusted the titles.