

Letter reviewer comments

Reviewer 1

IBD is a chronic and potentially debilitating disease course and can represent a heavy burden for patients, impacting every aspect of the affected individual's life. IBD treatment goals have evolved in the last 15 years. Work-disability rates of IBD patients vary considerably in the literature, with rates between about 3% and 27.1 % reported. The available studies are substantially different with regard to time periods, study design, definitions of disability, geographic area and patient cohorts. Additionally, there are differences in the social-security systems influencing possibly not only access to therapy but also employment and other rates. The manuscript targets the Dutch population and is well conducted and well written.

1. I would add more details about the social-security system in the discussion.

Thank you for reading our manuscript and your nice comments. Your suggestion is in line with requests from the other reviewers, and we have added this information on (Page 8, line 211-219):

"A Dutch law ("Wet werk en inkomen naar arbeidsvermogen" or WIA) prescribes that from the moment Dutch citizens are disabled to work they are entitled to receive a maximum of 170% of their wages during a period of 104 months (generally 100% for 52 weeks, followed by 70% for 52 weeks). If after 104 months the person is still on sick leave the same law prescribes whether patients receive a disability pension. There are two types of disability pension; partial disability (35% - 80% work disability) and full disability (more than 80% work disability). A specialized physician determines the percentage of work disability based on questionnaires and physical examination."

(Page 15, line 412-421):

"When comparing our data from the Dutch social security system with the more widely used Work Productivity and Activity Impairment Questionnaire (WPAI), the main difference lies within the objectivity of the data from the Dutch social security system, since it is assessed by a physician as opposed to the more subjective WPAI, which is patient reported. A main disadvantage of the data from the Dutch social security system is that it makes no distinction between work disability due to IBD or a due to a different cause. Furthermore, the WPAI assesses activity, not solely work related, on a weekly basis, providing more insight into the disease course."

2. I would have some more details/data about biologics introduction as prevention and therapy to prevent WD.

As surgery is an indicator of severe disease, our data corroborates the hypothesis that severity of disease predicts work disability. The cohort we describe have been treated with full access to biological therapy for at least 15 years. If we expected a major effect of the introduction of biologics on work disability we would expect it

to masquerade as a higher risk for work disability with a long disease history (>15 yrs), something we did not observe in our analyses. We did add extra information in the discussion regarding surgical interventions in the era of biological therapy (Page 13, line 361-366): “A recent review has shown that surgical rates have declined since the introduction of biologicals, indicating a beneficial effect of treatment with biologicals on disease outcome^[20]. Our study is not well suited to study this effect, since our most reliable clinical information has been collected after the introduction of biologicals.”

Reviewer 2

In this paper, the Authors investigate the prevalence of and risk factors for partial and full work disability in Dutch patients with inflammatory bowel disease. The manuscript is complete and well written, and it is expected to improve our knowledge of the health economics of IBD. Yet, I have the following comments/suggestions for the Authors:

1. In order to be more informative, the title should be changed to “Prevalence of and risk factors for partial...etc”, since one of the main objectives of the present study is to determine the overall prevalence of work disability in their IBD patients.

We agree with the reviewer, and changed the title into “Prevalence of- and risk factors for work disability in Dutch patients with inflammatory bowel disease”

2. The methods section in the abstract is too short. The Authors should expand on the methods followed to gather data. The Authors should also state clearly the type of study.

We agree with the reviewer and have changed the methods section in the abstract (Page 4, line 113-119):

“Methods: For this retrospective cohort study, we retrieved clinical data from the Dutch IBD Biobank on July 2014, containing electronic patient records of 3,388 IBD patients treated in the eight University Medical Centers in the Netherlands. Prevalence of work disability was assessed in 2,794 IBD patients and compared with the general Dutch population. Multivariate analyses were performed for work disability (sick leave, partial and full disability) and long-term full work disability (>80% work disability for >2 years).”

3. The results section in the abstract is not exhaustive. For instance, the Authors should provide here the confidence intervals for their results, in addition to the most significant results according to disease location and behavior.

(Page 5, line 129-130):

The abstract is a short description of the paper, and to give a good overview we do not show the exact effect sizes for all of our results. We have supplemented the results for which we do show effect sizes with CI's. Full details in terms of effect size

and confidence intervals for all results can be found in the results section of the full paper.

4. Table 1 is not only about the demographic characteristics, as clinical features are included. The Authors should change the title to “Demographic and clinical,,,,,etc”.

We agree with the reviewer and changed it into (Page 23, line 622-623):

“Demographic and clinical characteristics in patients with Crohn’s disease and ulcerative colitis”

5. In Table 3, the title should be changed to “Univariate and multivariate regression analyses of full and partial work disability in patients with Crohn’s disease”.

Thank you for the suggestion. We changed it.

6. In table 4, the title should be changed to “Univariate and multivariate regression analyses of work disability in patients with ulcerative colitis”.

Thank you for the suggestion. We changed it.

7. In table 5, the title should be changed to “Univariate and multivariate regression analyses of full and partial work disability in patients with ulcerative colitis”.

Thank you for the suggestion. We changed it.

8. In Tables 2-5, the abbreviation TNF should be explained in the legend as “Tumor necrosis factor alpha”.

Thank you for the suggestion. We changed it.

9. In the discussion section, the Authors should expand on the surprising results of more prevalent disability in patients with history of anti-TNF use. Did those patients receive anti-TNF drugs as rescue therapy (most likely) or as “top-down” therapy (less likely)?

Thank you for this suggestion. We added extra information in the discussion section. (Page 13, line 371-378):

“While it has been established that anti-TNF α and/or immunomodulators are generally used to maintain remission in patients with IBD, our study found an association between use of anti-TNF α use and (full) work disability. This could be due to selection bias, as all patients were treated in tertiary referral centers, with most of them having extensive disease involvement (Montreal classification; 47% L3 and 58% E3). Therefore, it is likely that patients receiving anti-TNF α and immunomodulator therapy are patients with more severe disease, receiving “rescue therapy” rather than “top-down therapy”.”

10. Furthermore, the Authors should provide their explanation of why is it that the use of immunomodulators (well established to help maintain remission in patients with IBD, and thus possibly decrease work disability) is associated with higher work disability. Could this be secondary to more severe disease rather than the use of these drugs per se? This is important to answer because otherwise the potential reader would get the wrong message.

We agree with the reviewer and made this more clear in the discussion. See our answer and adjustments at question 9.

11. The conclusions are weak; the Authors should provide their perspectives and suggestions for future studies.

We appreciate the prompt by the reviewer to provide stronger conclusions, but we remain cautious because of the specialized character of our cohort. We did add the following to the discussion (Page 16, line 430-432):

"In future studies web-based follow-up of Patient-Reported Outcome Measurements (PROMs) including clinical disease activity scores, could be promising tool for detecting a decline in work activity due to disease activity."

Reviewer 3

In this study, clinical data were retrieved from Dutch IBD Biobank consisting of less than 3.500 patients who received the treatment in 8 University Medical Centers in the Netherlands. Authors focused on patients disability in more than 2700 patients compared with the normal Dutch population. Among disabilities sick leave, partial and full disability as well as long duration of disability were concerned. It was found that work disability was higher in CD and UC patients, especially females and in those who were less educated with extra-manifestations compared to general Dutch population. The lower education level as well as disease complications were associated with long-term full disability. It is concluded that early assessment of work disability should be screened to predict the risk for work disability among IBD patients and to reduce the overall cost of the therapy. This study analyzes a large cohort of IBD patients and points out an important complication of human IBD pertaining to the prevalence of work disability in these patients. Although the number of evaluations is impressive and in general, this paper is fine, the minor points are addressed to Authors for the improvement of this paper in the form presented. Minor comments

1. The major issue that needs clarification for patients enrolled to this study is at least, more Authors commentaries to the question whether the cause of disability solely reflects the IBD as predominant disease or another, perhaps, age-related comorbidities or pre-associated diseases can interfere with those considered as truly IBD patients. Authors should comment in the text of Introduction, how they tried to cope with this problem.

We clarify this in the methods section. As stated there, “due to the nature of our data we could not distinguish between work disability solely attributable to IBD, or work disability due to a different cause. However, the median age in our study was 40 years for CD patients and 43 years for UC patients, ages at which age-related comorbidities are generally low.” We added this to the discussion (Page 15, line 404-408).

2. Please clarify in the text of Methods how and from which protocol you have defined in this study and accepted the criteria for the two-types of disability: partial (35%-80%) and full (>80%). Which percentage classification is it based on or maybe this is the national Dutch recommendation?

Thank you for this interesting question. It is indeed a Dutch law that decides the two-types of disability. We added the following to the methods section (Page 8, line 211-219):

“A Dutch law (“Wet werk en inkomen naar arbeidsvermogen” or WIA) prescribes that from the moment Dutch citizens are disabled to work they are entitled to receive a maximum of 170% of their wages during a period of 104 months (generally 100% for 52 weeks, followed by 70% for 52 weeks). If after 104 months the person is still on sick leave the same law prescribes whether patients receive a disability pension. There are two types of disability pension; partial disability (35% - 80% work disability) and full disability (more than 80% work disability). A specialized physician determines the percentage of work disability based on questionnaires and physical examination.”

3. Please clarify in details in the text of Methods what you meant by using the term “lower education” concerning the lack of any school or alimentary education without a higher education (?) and what you meant for the patient therapy by saying “immunomodulator use” ?

Definitions of the variables used can be found in Supplementary Methods 1. Concerning educational level; Patients were classified in two groups; low education (Lower general education; Lower vocational education; General secondary education; Vocational secondary education; Did not finish primary school) and high education (Pre-university secondary education; Vocational post-secondary education; University)

Definition of immunomodulator use: immunomodulators (mercaptopurine, azathioprine, thioguanine or methotrexate). Data on medication use was available for the entire disease course; medication use was therefore defined as medication ‘ever used’

4. According to this study, surgery in IBD patients constitutes a major risk of their long term work disability. It would be worthy to comment, if specific analysis not available, which conventional pharmacological treatment besides biological therapy with anti-TNF- α (i.e. 5-ASA, corticosteroids, azathioprine, 6-mercaptopurine?) led to a partial or full disability in patients who suffered from CD and UC despite the treatment used.

We found an association of tioguanine and methotrexate with work disability in Crohn's disease, but no association with azathioprine or mercaptopurine. We found an association of tioguanine en mercaptopurine with work disability in ulcerative colitis, but not with mesalazine, methotrexate, or azathioprine. Since the number of patients on tioguanine, methotrexate and mercaptopurine are very low in our cohort (due to a fear of liver-related side effects, these drugs are only prescribed incidentally) the confidence intervals for these associations were extremely wide and we felt our power to detect true associations was low. We therefore chose not to report these results in the paper.

Reviewer 4

Excellent original publication.

Thank you for this nice comment.

Reviewer 5

I enjoyed reading this paper, nicely written and tackling an important issue in the health service and in general for the work productivity. My only concern is related tenth arbitrary definitions used in the study, which to my understanding were derived by the actual regulation for work leave in Netherlands.

1. I wonder how this information is valid in other health service context and how it relates to a more widely use methodology to evaluate the work productivity (or not productivity) like WPAI. These potential limitations should be clarified and acknowledged

Thank you for the nice comments. We added the following to the discussion (Page 15, line 412-421):

"When comparing our data from the Dutch social security system with the more widely used Work Productivity and Activity Impairment Questionnaire (WPAI), the main difference lies within the objectivity of the data from the Dutch social security system, since it is assessed by a physician as opposed to the more subjective WPAI, which is patient reported. A main disadvantage of the data from the Dutch social security system is that it makes no distinction between work disability due to IBD or due to a different cause. Furthermore, the WPAI assesses activity, not solely work related, on a weekly basis, providing more insight in the disease course."

Reviewer 6

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