Dear Jin-Lei Wang, Director, Editorial Office,

Please find enclosed the edited and revised manuscript in Word format (file name: WJG7320_edited revised.doc).

Title: Smoking increases the risk of Extraintestinal Manifestations in Crohn´s Disease but not in Ulcerative Colitis – results from a population based cohort at first diagnosis and during the early course of disease

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We thank the Editors and Reviewers for the insightful comments on our manuscript. We have carefully studied the items they have raised. Please find enclosed our answers to their questions and items point by point. The text in the manuscript has been revised in line with the reviewers' suggestions essentially improving the manuscript. All changes in the manuscript are highlighted by underlining.

1. The format has been updated.

2. Revision has been made according to the suggestions of the reviewers

   Comments from reviewer 1:
   1. *The disease phenotype for your patients population is not provided. This is essential for further interpretation. the patient population throughout the results and discussion sections have been grouped loosely and claims of statistical significance made to colonic disease without providing details.*

   We have changed the manuscript due to the reviewer´s suggestion and provide the disease phenotype of our patients in detail now (s. Table 1). In accordance to the study of Vavricka et al., no correlation of colonic disease and any type of EIM was found in our cohort as provided

on page 9. In addition, pancolitis did not increase the risk to develop an EIM in patients with UC as provided in table 5.

We grouped the results now in the same order the different factors are discussed in the discussion section (gender, age, colonic involvement, family history, smoking, surgery.

2. *What treatment did these patients receive at diagnosis and what was the median duration of such treatment. It is now well accepted that in the well-selected patient earlier introduction of immuno-suppressive therapy alters disease course and outcomes.it is therefore unclear from your data whether this cohort received a step up or step down approach and if this could have affected EIM's.*

We thank the reviewer for raising this issue. During the recent years, various data suggest treating severe IBD in a "top-down" regime and early use of immunosuppressive drugs might change the natural history of the disease, especially in CD. Nevertheless, patients of this population based cohort were diagnosed during 2004 and 2008. According to the existing ECCO-guidelines in Europe, the patients were mainly treated with the conventional step-up strategy. We included now the different types of treatment at first diagnosis as well as during the observation period in the manuscript in detail (page 10 and 11). Unfortunately, due to the population-based design of our study, we are not able to give exact details on the median duration of every treatment, as patients are seen by general practitioners and not in tertiary centres to some extent, in particular if they have only few abdominal symptoms and the course of the abdominal disease is mild.

3. *The majority of your EIM's were arthralgias and those which have a strong correlation with disease activity. This makes the above comment even more relevant.*

We absolutely agree with this important comment of the reviewer. Therefore, we included details on the treatment of our patients at first diagnosis and during the observation period in the manuscript (page 10 and 11). However, patients with EIMs - neither suffering from disease-activity dependent EIM nor disease-activity unrelated EIM- were not treated more frequently with immunosuppressive agents (azathioprine, Mtx) or anti-TNF-therapy (infliximab, adalimumab) in contrast to patients without EIM (p=0.82) (page 10).

4. *Smoking has a strong and well established negative impact on Crohn's disease pathogenesis and outcome. How many of the CD patient sand how many UC patients were smokers at diagnosis? Past history and passive smoking history should be mentioned if available or mentioned as confounders.*

Thank you for this important advice. We present now the exact number of smokers and ex-smokers at first diagnosis (page 9). Unfortunately, we do not have data of passive smoking history; therefore we mentioned this point as possible confounder in the discussion section (page 16).

5. *The statistical analysis with most of the results provided does not reach significance. Yet and in a rather illogical manner the reader is suddenly shown strong correlation with EIM. Is this not a function of smoking affecting CD especially if the disease phenotype was*

unfavourable in the first instance? The conclusions thus are circumspect and need to be substantiated through disease phenotype and markers of disease activity (biochemical, radiological and endoscopic).

In patients with CD, three factors were identified to increase the risk to develop an EIM during the early course of the disease with statistically significant results – the need of IBD-related surgery, smoking and an age of 40 years or less at first diagnosis. Only 45 patients were active smokers at first diagnosis, but later in the course, 55 patients reported of active smoking at the time, the EIM was diagnosed for the first time. We could neither find any correlation of phenotype and the development of an EIM nor any correlation of phenotype according to the Vienna Classification and active smoking (p=0.23). But due to the important point of disease activity, the reviewer has mentioned, we added data of remission rates in the manuscript as in the population-based setting biochemical data of activity, regular radiological and endoscopic examinations are not available in a standardized manner (page 11). Remission rates were not different in CD patients suffering from an EIM in contrast to patients without EIMs.

6. *The relevance of discussion of the HLA associations with EIM's on page 13 is illogical when taken in context.*

We thank the reviewer for this important advice and removed this irrelevant section.

Comments from reviewer 2:
1. *In the Results, the authors evaluated the EIM such as arthralgia, arthritis, ocular manifestation, sacroiliitis, pyoderma gangrenosum, erythema nodosum and PSC. However, there were no comments about the perianal lesions such as perianal fistula or abscess. Please describe how many patients in the IBD patients were diagnosed perianal lesions.*

We thank the reviewer for raising this issue. We adapted the manuscript and included the data of perianal lesions at first diagnosis and during the observation period. The presence of perianal fistulas had no influence on the development of EIMs (p=0.72, 95%CI 0.40-3.84) (page 10).

2. *In the Results and Discussion, the EIM was affected by the disease activity of IBD patients. Please described that how many patients were active and inactive disease, and whether there was any difference in the EIM frequency according to the disease activity.*

We could not find any correlation of disease activity and EIMs in general, as rates of clinical remission were not different in patients with or without EIMs during the observation period (we included this issue in the manuscript, s. page 11). In the discussion, we speculate that a higher activity in patients with CD needing surgery at first diagnosis or during the early course of the disease might be an explanation for the association of surgery and EIM´s (page 16).

3. *In the Results (Table 5), there was no difference of EIM frequency in Ulcerative Colitis. Please comment that whether steroid treatment may be affect the EIM state or not. In addition, in Table 4, please comment about the effect of Steroid and Immunosuppressive treatment on the EIM frequency.*

We thank the reviewer for these helpful suggestions. In 76.5% of patients with UC and 63.1% patients with CD receiving corticosteroids, the EIM present at first diagnosis resolved during the observation period. We included these findings now in the manuscript (page 10 and 12).

No correlation was found regarding the reaction on corticosteroid therapy and the development of an EIM during the observation period in both patient groups. These data are now presented in detail on page 10 and 12. In addition, patients with EIMs were not treated more frequently with immunosuppressive agents or anti-TNF-therapy compared to patients without an EIM.

Comments from reviewer 3:

Interesting paper providing additional information on a not marginal aspect of IBD.

We thank the reviewer for his positive assessment of our manuscript.

Comments from reviewer 4:

The paper is informative and original in presenting the prevalence of extraintestinal manifestation of disease in a population of patients at first diagnosis of IBD or the early course of the disease. Undoubtedly, the clinical consequences of the findings are substantial. It is quite well written and only some mistyping are scattered in the paper.

We appreciate the reviewer´s positive assessment of our manuscript and apologize for all typing and grammatical errors. We carefully revised the manuscript. Additionally, the manuscript was revised by a native English-speaker.

3. References and typesetting were corrected. The manuscript was revised by a native speaker of English.

We once again thank all reviewers for their helpful comments and suggestions. We hope that the revised manuscript will be suitable for publication.

Yours sincerely,
Dr. Claudia Ott