

December 30, 2019

**RE: World Journal of Gastroenterology Manuscript review of Manuscript NO: 52433**

Dear Editor-in-Chief,

We are submitting our revised manuscript entitled “ *Trends and Risk Factors of Elderly-onset Crohn’s Disease: A Nationwide Cohort Study*” for consideration of publication in *World Journal of Gastroenterology*.

We appreciate the valuable and insightful comments from the reviewer. We responded to each of the comments made and incorporated all modifications suggested by the reviewer into the revised manuscript. Changes to the revised manuscript have been highlighted ([underlined and in blue](#)). Please let us know if you have any further suggestion for changes. I anticipate favorable response from the review board.

Sincerely,

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## **Point-by-Point Response to the Reviewer's comment:**

We thank the reviewers for their thoughtful and expert review of our manuscript and for their valuable and insightful comments. We responded to each of the comments made and incorporated all modifications suggested by the reviewers into the revised manuscript. Changes to the revised manuscript have been highlighted ([underlined and in blue](#)). Our response to the Reviewers' comments is as follows:

### **● Reviewer 1:**

#### **COMMENTS:**

Moon et al. investigated the trends and environmental risk factors of Crohn's disease diagnosed in persons aged >40 years in South Korea. They found four risk factors including ex-smoking, anemia, CKD, and lower BMI, and three possible protective factors (alcohol consumption, physical activity, and dyslipidemia) for Crohn's disease age > 40 years. The study is interesting and the manuscript is well-written. My comments are listed below:

#### **Major points:**

1. Not all variables were included in the multivariate analysis. The authors should explain why they choose the listed risk factors, not the others for the analysis? Other variables, such as blood sugar, dietary intake nutrition ratio, and platelets, may be also associated with risk of Crohn's disease.

#### **Response:**

Thank you for your comment. We identified all variables available in the claim data (National Health Insurance Service data). Unfortunately, the claim data does not include information on platelet and dietary intake nutrition ratios. The risk of elderly-onset Crohn's disease according to income status, diabetes mellitus, fasting glucose levels, hypertension, serum cholesterol and metabolic syndrome were also investigated and we described the results in Supplementary

table1. Except for the factors mentioned in the results, the variables were not significant in increasing the risk of Crohn's disease.

Furthermore, as you have thoughtfully suggested other variables to be adjusted in multivariate analysis, we performed further analysis with additional adjustments for age, sex, diabetes, hypertension, smoking, alcohol consumption, regular exercise, BMI, anemia, chronic kidney disease, and dyslipidemia. The results are expressed in revised figure 2 and 3. The trend and statistical significance remained consistent.

2. The authors stated that smoking, anemia, CKD, and lower BMI were risk factors, while drinking, physical exercise, and dyslipidemia were protective factors. Is this appropriate? Actually, whether these factors are the causes or consequences of Crohn's disease remains uncertain. For example, Crohn's disease may induce anemia and low BMI as well.

**Response:**

Thank you for your critical comments. All variables, including smoking, anemia, CKD, BMI, drinking, exercise and dyslipidemia, were collected in 2009, the index year when the study population received the national health check-up. People diagnosed with Crohn's disease before the health check-up or in the first year of enrollment were excluded. However, anemia and underweight are often considered early symptoms of Crohn's disease. Therefore, it is assumed that Crohn's disease diagnosed within one year of the index year has no causal relationship with possible risk factors. Factors associated with elderly-onset Crohn's disease were ahead of time in the diagnosis of Crohn's disease, allowing us to assume a causal relationship. However, since temporal relationship do not necessarily explain causality, we have revised the manuscript to carefully interpret the results, taking into account that the time of onset of the disease at baseline is 7-8 years depending on the variable.

3. Is it possible to perform a subgroup analysis of the severity of Crohn's disease to enrich the conclusions?

**Response:**

Thank you for your valuable comment. Unfortunately, the risk of elderly-onset Crohn's disease

based on the severity could not be demonstrated because the NHI database had no information regarding the severity of the disease. This is an intrinsic limitation of this study due to the nature of claim data in Korea. We have made further comments on this limitation on the revised version.