Dear Editors

We would like to thank you for considering our manuscript **"Epidemiology of Upper Gastrointestinal Bleeding Risk Factors in Korea: A Large Population-Based Study"** for publication in **"*World Journal of Gastroenterology*".** We would also like to thank the reviewer for the thorough examination of our manuscript and excellent comments which have helped us to improve our manuscript. We have addressed the reviewer's comments below.
I hope that you and the reviewers will find the revision satisfactory. We thank the reviewers for their constructive suggestions and look forward to having our manuscript published in "***World Journal of Gastroenterology***".

Sincerely yours,

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Responses to the comments of Reviewer #1

This new manuscript has been examined. The design of this study does not appear to be inclusive. The discussion by the authors is very speculative.

Major Issues:

#1. Why is age not listed as a comorbid condition?

→ **Responses;** The reviewer has correctly pointed out that old age is an important risk factor of upper gastrointestinal bleeding (UGIB). However, to provide further information of the prevalence of risk factors for specific age groups, we aimed to investigate the prevalence of possible UGIB risk factors stratified by age groups

#2. Why is gastroesophageal reflux disease not included as a comorbid condition?

→ **Responses;** As the reviewer correctly indicated, gastroesophageal reflux disease (GERD) has been reported to be associated UGIB. To address the issue, we included GERD as a risk factor of UGIB. Accordingly, we revised methods, results, discussion sections, and tables to reflect changes occurred by adding GERD. Also, we cited following reference regarding GERD and UGIB.

Tielleman et al. Epidemiology and Risk Factors for Upper Gastrointestinal Bleeding. Gastrointest Endosc Clin N Am 2015;25:415-428.

#3. It is well known that COX-2 inhibitors (especially in higher doses) cause gastrointestinal bleeding. It is not clear why these agents were not included in this analysis.

→ **Responses;** As the reviewer has pointed, COX-2 inhibitors are known to cause UGIB especially in high dose. However, it is generally accepted that COX-2 inhibitors causes less mucosal injuries, peptic ulcer, and clinically significant complications.[1-5] And, COX-2 inhibitors had been considered as a prophylactic option for the NSAIDs-related

gastrointestinal mucosal injury.[6] In addition, recent meta-analysis identified benefit of COX-2 inhibitors in the prevention of ulcer complications including bleeding.[7] Considering those findings and guidelines, we included COX-2 inhibitors as a prophylactic option of NSAID-related UGIB, not as a risk factor of UGIB. Additionally, we cited the references in the manuscript.

1. Rostom et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2007; 5: 818-28.

2. Hooper et al. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. BMJ 2004; 329:948.

3. Chan et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet. 2010;376:173–179.

4. Kellner et al. Celecoxib and diclofenac plus omeprazole are similarly effective in the treatment of arthritis in patients at high GI risk in the CONDOR Trial. Open Rheumatol J. 2013;7:96–100.

5. Brooks J, Warburton R, Beales IL. Prevention of upper gastrointestinal haemorrhage: current controversies and clinical guidance. Therapeutic advances in chronic disease 2013;4:206-222.

6. Lanza et al. Guidelines for prevention of NSAID-related ulcer complications. The American journal of gastroenterology 2009;104:728-738.

7. Yuan et al. Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity. Aliment Pharmacol Ther 2016;43:1262-75.

#4. It is unclear why the authors have not studied newer pharmacologic agents, such as Rivaroxaban.

→ **Responses;** As the reviewer has pointed, newer anticoagulants such as rivaroxaban must be considered as a UGIB risk factor. In fact, we included not only warfarin but also rivaroxaban, dabigatran, and apixaban. However, we described the values for prevalence of those drugs limited to warfarin by mistake. Therefore, we indicated that the values are prevalence for those anticoagulants in the method, results sections and footnote of the tables

"Concomitant drugs included oral aspirin [3, 8, 11, 15, 21], other antiplatelet agents including cilostazol and clopidogrel [3, 11], NSAIDs [3, 8, 10, 11, 16, 29], steroids [3, 19], anticoagulants including warfarin, rivaroxaban, dabigatran, and apixaban [3, 10, 11], and selective serotonin reuptake inhibitors (SSRIs)"

#5. Under "Definition of variables", the authors list codes "defined" as patients with osteoarthritis. Do the author mean "accepted as" patients with osteoarthritis? It is unlikely that these ICD-10 codes are based on strict criteria for the diagnosis of osteoarthritis. It is likely that the patients had chronic joint pain. Do the authors know whether other origins such as Vitamin D deficiency had been excluded? If not, this is a speculative diagnosis.

→ **Responses;** As the reviewer has correctly pointed, ICD-10 codes for medical claims are not fully based on the diagnostic criteria of the diseases. In primary care, osteoarthritis is often diagnosed based on history taking and physical exam only, and blood test and X-ray is not always indicated if other types of join pain is not suspected. Therefore, there is possibility that the subjects who were categorized as having osteoarthritis based on ICD-10 codes may not meet all the diagnostic criteria of osteoarthritis, and can include other diseases which can mimic osteoarthritis (e.g. Mild rheumatoid arthritis or Vitamin D deficiency, which can also present with joint pain). However, physician's claim for reimbursement with ICD 10 codes of osteoarthritis means that they are apt to take NSAIDs more frequently, even when they do not actually meet diagnostic criteria of osteoarthritis. Therefore, we think our categorization is still relevant considering our study objective which aims to estimate those who are at high risk of UGIB.

Even though the claims data are not as accurate as clinical data which is collected prospectively with the predefined study protocol, it has other strengths. Sample size can be very large and the study population can be representative of the source population. In

addition, it reflect 'real world' situation, enhancing the generalizability of the findings, than studies performed in selected institutions.[5] Nevertheless, to address the inaccuracy of osteoarthritis diagnosis defined by ICD-10, we described the limitation as follows in the Discussion section;

"Finally, ICD-10 codes based definition of osteoarthritis may not meet the specific diagnostic criteria. However, claims with such osteoarthritis diagnosis are usually made with clinical features which are consistent with symptoms and signs of osteoarthritis, and are accompanied by prescription of NSAIDS, which increases the risk of UGIB. In addition, claims data has its own strengths in terms of large sample size, representativeness, and generalizability to the real world setting."

1. Nasef SA, Shaaban AA, Mould-Quevedo J, Ismail TA. The cost-effectiveness of celecoxib versus non-steroidal anti-inflammatory drugs plus proton-pump inhibitors in the treatment of osteoarthritis in Saudi Arabia. Health economics review 2015;5:53.
2. Laine L, Harper S, Simon T, Bath R, Johanson J, Schwartz H, Stern S, Quan H, Bolognese J. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. Gastroenterology 1999;117:776-783.
3. Lee Bh, Shin B-J, Kim DJ, Lee JC, Suk KS, Park Y-S, Kim K-W, Cho KJ, Shin K-y, Koh M-s, Moon S-H. Gastrointestinal Risk Assessment in the Patients Taking Nonsteroidal Anti-inflammarory Drugs for Lumbar Spinal Disease. Journal of Korean Society of Spine Surgery 2011;18:239.
4. Lee SH, Han CD, Yang IH, Ha CW. Prescription pattern of NSAIDs and the prevalence of NSAID-induced gastrointestinal risk factors of orthopaedic patients in clinical practice in Korea. Journal of Korean medical science 2011;26:561-567.
5. Lee J et al. Cohort Profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. International journal of epidemiology 2016 [Epub ahead of Print]

#6. The authors' definition of sedentary lifestyle needs clarification. The first part of the definition "did not exercise" is clear. The second part of the definition "did not walk more that 30 minutes a week" is unclear (e.g. this is less than 4.5 minutes daily). In

Supplementary Table 3, we see that 13.54% of individuals aged 20-24 years are in the category "Sedentary Lifestyle"; are the authors suggesting that 13.54% of 20-24 year-olds are bedridden?

→ **Responses;** To address the comment #5 of reviewer 2, we decided to exclude sedentary lifestyle from the UGIB risk factors. Please, see the response to the comments #5 of reviewer 2 below.

#7. In the discussion, paragraph 5: the authors state "physicians should always bear in mind the possibility of UGIB, regardless of age". This is an internationally known gastrointestinal journal. This disrespectful comment should be removed.

→ **Responses;** We removed the sentence as suggested by the reviewer. Instead, following paragraph was added;

"Second, our study revealed that a considerable portion of young adults have concurrent multiple risk factors of UGIB. When *H. pylori* infection was considered, more than 10% of the general population aged 35-39"

#8. In the same paragraph, the authors state "Selective COX-2 inhibitors or concurrent prescription of proton pump inhibitors may be a good option". The authors do not mention why they have omitted misoprostol. There indeed is a large literature on cost-benefit analysis for the use of these medications in high-risk patients. If the authors want to mention this field they should include the appropriate references.

→ **Responses;** Thank you for informing us about misoprostol. As the reviewer has pointed out, misoprostol is a good prophylactic option for UGIB. We changed that paragraph and added a reference which identified the better cost-effectiveness of misoprostol.

"Selective COX-2 inhibitors or concurrent prescription of proton pump inhibitors or misoprostol may be a good option for osteoarthritis patients with high risk of UGIB"

Brown et al. A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling. Health technology assessment 2006;10:1-183

#9. In the discussion, Paragraph 6: the authors state that "high-risk subjects should control any modifiable risk factors for UGIB". If the authors have any literature that supports this claim, they should have added the references. (For example there is extensive literature on the possible advantage of H. pylori eradication therapy prior to initiation of treatment with a non-steroidal anti-inflammatory drug.)
Otherwise, the authors' results do support the need for a prospective study to determine whether or not control of modifiable risks factors decreases the risk of upper gastrointestinal bleeding.

→ **Responses;** Thank you for the detailed guidance. As the reviewer has commented, we cited a reference which highlighted H.pylori eradication for UGIB prevention.[1] Also, we cited a reference which indicated positive effect of physical activity against UGIB.[2] However, to the best of our knowledge, there was no published data which recommended smoking cessation or reducing alcohol consumption to prevent UGIB. To consider those references, we changed the paragraph as follows;

"subjects should control any modifiable risk factors of UGIB, such as smoking, heavy drinking, and *H. pylori* infection [27, 35]. Also, further prospective studies are needed to address the issue of other lifestyle modification and UGIB prevention."

1. Brooks J etal. Prevention of upper gastrointestinal haemorrhage: current controversies and clinical guidance. Therapeutic advances in chronic disease 2013;4:206-222.

2. Pahor et al. Physical activity and risk of severe gastrointestinal hemorrhage in older persons. Jama 1994;272:595-599

Minor Issue:

#1. The title is misleading. Since the authors add estimates of the prevalence of gastric H. pylori and then proceed to statistically evaluate this potential effect, this part of their study is modeling not a population-based study.

→ **Responses;** We agree to the reviewer's comment, and changed the title as follows (Simultaneously, we considered the #1 comment of reviewer 2);

"Prevalence of Upper Gastrointestinal Bleeding Risk Factors among the General Population and Osteoarthritis Patients"

#2. In the conclusion, "as well as prevention of H. pylori infection". Do the authors have any information about counseling individuals to prevent H. pylori infection?

→ **Responses;** Thank you for the correction. Our original intention was 'eradication', not 'prevention'. We changed the word 'prevention' to 'eradication';

"We investigated the prevalence of various risk factors of UGIB in the general population and osteoarthritis patients. Physicians should consider individualized risk assessment regardless of age when prescribing drugs or performing procedures that may increase the risk of UGIB, and take necessary measures to reduce modifiable risk factors such as H.pylori eradication or lifestyle counseling.."

Responses to the comments of Reviewer #2

In the presented article the prevalence of possible risk factors of UGIB among general population and patients with osteoarthritis were assessed. The prevalence of risk factors were higher in patients with osteoarthritis compared to general population. My concerns are;

#1-The title of the article does not represent the study. The study mainly compares risk factors of UGIB among general population and patients with osteoarthritis.

→ **Responses;** Originally, we planned to investigate the prevalence of UGIB in general population. However, as the reviewer commented, it is more valuable to show risk factors in general population and osteoarthritis patients separately. If the editorial board allows, we would like to change the title as follows (Simultaneously, we considered the #1 minor comment of reviewer 1);

"Prevalence of Upper Gastrointestinal Bleeding Risk Factors among the General Population and Osteoarthritis Patients"

#2-The subjects of the study includes 801,926 from general population aged 20 or more and 93,855 of them were patients with osteoarthritis. If general population includes osteoarthritis patients, the ratios of some conditions (e.g peptic ulcer, NSAIDs use, ..) may increase due to the high ratio in osteoarthritis patients. It may be more valuable to show risk factors in general population and osteoarthritis patients seperately and statistical significance (p values) should have been given.

→ **Responses;** Thank you for the detailed guidance. We agree to the comment that it may be more valuable to show risk factors in general population and osteoarthritis patients seperately and statistical significance.

We subdivided overall subjects into 3 categories; (1) overall population, (2) subjects without osteoarthritis, and (3) osteoarthritis patients

We revised the manuscript, method sections, tables and figures accordingly.

Introduction section;

"In this study, we assessed the prevalence of possible risk factors of UGIB and their age-group specific trend among the general population, and compared the prevalence between the patients with osteoarthritis and others."

Statistical analysis section;

"Subjects aged 20 and above were included in our analysis. First, we calculated the prevalence of each risk factor within the general population and those for osteoarthritic patients and others were compared. To identify subjects with"

"All statistical analyses were conducted using the STATA software version 14.0 (StataCorp., TX)."

#3-It is not given if the ratios of risks factors of UGIB between general population and those with osteoarthritis are statistically significant or not.

→ **Responses;** As the reviewer commented, we revised table 1 to provide p values for the difference in ratios between subjects without osteoarthritis and osteoarthritis patients in Table 1.

#4-The authors stated that corticosteroid use is a risk factor for UGIB and they cited 3 references; 9, 10, 19. But, in all three references, corticosteroid use alone is not associated with UGIB.

→ **Responses;** As the reviewer has correctly indicated, those references investigated multiple UGIB risk factors including corticosteroid simultaneously. We dropped the reference 9 (Piper et al), and 10 (Wolfe et al) which showed that corticosteroid use alone was not significant. However, reference 19 (Gutthann et al) provided significant association between corticosteroid use and complicated peptic ulcer disease regardless of other co-existing risk factors (odds ratio, 2.4; 95% confidence interval, 1.6 to3.6). Also, we cited one more reference which supports corticosteroid as an independent risk factor of UGIB (relative risk, 4.07, 95% confidence interval 3.83 to 4.32).1

1. Tielleman et al. Epidemiology and Risk Factors for Upper Gastrointestinal Bleeding. Gastrointest Endosc Clin N Am 2015;25:415-428.

#5-What is the reference for defining sedentary lifestyle? The authors defined it as those who did not exercise and did not walk more than 30 minutes a week. Is it chosen arbitrarily?

→ **Responses;** We identified only one reference which provided significant preventive effect of physical activity on UGIB. Pahor et al reported elderly subjects with more physically active had lower UGIB risk.[1] They compared those who reported that they did walking, gardening, and doing vigorous physical activity three times per week to those who did not.

In the national health check-up program in Korea, it includes unvalidated 3 questionnaires about physical activities. However, from the survey questionnaires, we could not exactly categorize physical activity as the definition of Pahor et al. Originally, we had decided to define the sedentary lifestyle more strictly to consider those issues.

During the reviewing present study after we got the reviewer's comments, as mentioned above, we could not identify other studies which dealt with sedentary lifestyle for UGIB. Also, the results from study of Pahor et al were obtained from elderly population not from the general population. Therefore, it is too difficult to define the sedentary lifestyle as a UGIB risk factor appropriately.

To make it clear, we decided to exclude sedentary lifestyle from the UGIB risk factor.

The manuscript, figures and tables were revised appropriately after excluding sedentary lifestyle.

1. Pahor et al. Physical activity and risk of severe gastrointestinal hemorrhage in older persons. Jama 1994;272:595-599