Author's response to reviews

Title: Upper Gastrointestinal Bleeding due to Peptic Ulcer Disease is Not Associated with Air Pollution: A Case-Crossover Study

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Version: 2 Date: 13 August 2015

Author's response to reviews:

Editor's comment:

Dear Team,

After careful consideration I believe that paper MS: 5759376451748308 might be suitable for publication in BMC Gastro.

1. Comments to the author

Please respond to the comments raised by the reviewer; in particular those, regarding data on H. pylori infection and NSAID use.

Response: We thank the editors and the reviewers for the thoughtful comments and insightful review of the manuscript. The revised manuscript is considerably improved. Unfortunately, we are not able to study the role of NSAID and H. pylori in our study because this data is not available in the database. We emphasized this in the limitation section of the grant.

b. Comments to the editor

I believe that the paper is well written and presents novel data in intelligible fashion on bleeding related to PUD. I think that after addressing the comments raised by one of the reviewers, the paper might be suitable for publication in BMC Gastro.

Response: Thank you. Please see our response to the reviewers.
Reviewer: Leif Percival P Andersen
Reviewer's report:
I have read the paper and find it very good and well written.
The purpose is clear and well defined and the methods are appropriate and well described.
Data and tables are sound and clear.
Discussion and conclusion are well balanced and limitations of the work is clearly stated.
Title and abstract cover the findings sufficiently. I think the paper can be accepted as it is.
Response: Dr. Andersen thank you for reviewing our manuscript. We appreciate your time and effort in reading the manuscript.

Reviewer: Ilva Daugule
Reviewer's report:
The idea about the association between gastrointestinal bleeding and air pollution is interesting and original, therefore also negative results (observed in the study) could be of importance.
The design is original, although complicated for individuals not involved in environmental research. The main conclusion – no association between air pollution and upper GI bleeding – is clear. The study could be improved by analysis of other factors that could influence gastrointestinal bleeding.

Major Compulsory Revisions
Multiple regression analysis could be performed to evaluate the impact of other factors (age, comorbidities, season, possibly – H.pylori infection).

Response:
Dr. Daugule, thank you for reviewing our manuscript and providing insightful comments. Our primary analysis focused on the entire population. However, you have astutely pointed out that the effect of air pollution on UGIB secondary to PUD maybe associated with other factors. Our only caution is that with each additional analyses we introduce the risk of multiple comparison error. In response, we conducted a series of new conditional logistic regression models that were stratified by age (above and below 70 years, which was the median age of our population), sex (male versus female) and season (summer, fall, winter, and spring). Consistent with our primary analysis, the majority of the findings for age, sex and season were null. We did not assess for H. pylori because this data was not available for our study population. We did not assess for comorbidities because of our concern for introducing multiple comparison error. The results for age, sex, and season are included in the appendices.

Minor Essential Revisions
• Conclusions – no need to repeat hypothesis.

Response: This is a good point and we have revised the conclusion section accordingly.

• Add references in the following sentences:

Despite advances in management, the risk for mortality among patients with this condition ranges from 2.2% upward to 14%.

The primary risk factors for PUD are non-steroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori. However, a significant proportion of PUD is not explained by these risk factors.

Response: These citations are now added.

Discretionary Revisions

• The author could add some ideas in discussion part, how air pollution could promote ulcer bleeding.

Response: This topic has been added to the discussion. Please see the first paragraph.

• The role of comorbidities, seasonality, age and complications could be more analysed in respect to air pollution.

If possible, data about H. pylori infection could also be extrapolated from the databases – this could help to differentiate H. pylori related ulcers and other ulcers. May be there is an association between air pollution and only non-H. pylori ulcers.

Response: We have included analyses for age, sex, and season (see appendices). We did not analyze comorbidities because of our concern for introducing multiple comparison error. Ideally, we would have analyzed the cohort for H. pylori status and NSAID exposure. Unfortunately, this data is not available in the database. Consequently, this remains a limitation of our results, and thus we have emphasized this in the limitations section of our discussion.

The level of air pollution differs in both cities – how this could affect differences in discovery and replication cohort.

Response: The reviewer is correct to point out that air pollution levels are different between cities. For example, the median daily levels of SO2, CO, NO2 and PM10 were significantly higher in Calgary than in Edmonton. In part, this is due to differences in sources of air pollution exposures between the two studies. But, this may also be explained by the location that monitor stations are situated in the two cities (e.g. nearness to traffic). Differences in actual exposures and in misclassification of exposure may result in variation of results; however, this would be more meaningful if we observed greater differences in significant associations between the two cities.

• The following sentence in discussion part is misleading – it seems that the
authors suggests that acute exposure actually triggers an UGIB. Try to change the sentence.
Our discovery and replication cohorts did not demonstrate any statistically significant associations suggesting that acute exposure triggers an UGIB secondary to PUD.
Response: We have changed this sentence.