

Format for ANSWERING REVIEWERS

Dec 12, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: : 23327-Edited.doc)

Title: Constipation, hard stools, fecal urgency, and incomplete evacuation, but not diarrhea is associated with diabetes and its related factors

Author: Noriko Ihana-Sugiyama, Naoyoshi Nagata, Ritsuko Yamamoto-Honda, Eiko Izawa, Hiroshi Kajio, Takuro Shimbo, Masafumi Kakei, Naomi Uemura, Junichi Akiyama, Mitsuhiko Noda

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 23327

Response to Reviewer Comments

We thank the reviewers for their valuable feedback. We have revised the manuscript in accordance with the reviewers' comments and we explain our revisions below.

Reviewer #1-1:

The manuscript has low number of diabetic subjects compared to non-diabetic ones as well as type 1 and 2 diabetes are not separately evaluated.

Response:

Thank you for the important suggestion.

According to National Health and Nutrition Examination Survey Japan which is conducted every 4 years by the government, the incidence rate of adult diabetes is 16.2% for male individuals and 9.2% for female individuals in 2013

<http://www.mhlw.go.jp/file/04-Houdouhappyou-10904750-Kenkoukyoku-Gantaisakukeinkouzoushinka/0000068070.pdf> [The prevalence of diabetes for each age was written on

page 17, Figure 21, in Japanese]).

In our study, the rate of diabetes was 12.7%. Although this study was a hospital-based analysis and the subjects were relatively elderly patients, we think the number of patients with diabetes is not much different from that in the general population.

As the reviewer suggested, we could not separate type 1 and type 2 diabetes. In Asia, the incidence of type 1 diabetes is very low compared with Western countries (DIAMOND project Group: Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. *Diabet Med* 23: 857-866, 2006). We wrote this limitation on page 18, lines 332-334, as follows.

“Third, we did not classify diabetes as type 1 or type 2. However, as the prevalence of type 1 diabetes is notably lower than type 2 diabetes in Asia (DIAMOND project Group: Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. *Diabet Med* 23: 857-866, 2006), this omission is likely to have little impact on our results.”

Reviewer #1-2:

Minor comments, in the abstract and result section ORs should be presented with 95% CI and p-values to understand the reliability of results.

Response:

We added 95% CI and p-values in the abstract and results section (pages 5 and 14-15).

Reviewer #1-3:

In the results, non-adjusted ORs should be replaced with adjusted ones.

Response: We added crude OR [COR] values before adjusted OR [AOR] in the results (pages 13-14).

Reviewer #1-4:

Intestinal microbiome are known to interfere with GI symptoms and there are several studies suggestion that it also involve in the pathogenesis of diabetes. However, authors did not discuss any of this point in the manuscript. I suggest that a paragraph of this issue is added.

Response: Thank you for your meaningful suggestion. We added this point in the discussion, as follows (page 18, lines 334-336).

“Fourth, we did not examine intestinal microbiome which might be associated with GI symptoms. In recent studies, intestinal microbiome is known to interfere with GI symptoms and there are several studies suggesting that it is also involved in the pathogenesis of diabetes (Larsen N, Vogensen FK, van den Berg FW, et al. *PLoS ONE*

2010;5:e9085). In particular, chronic diarrhea is associated with lower amounts of *Lactococcus* spp. (Malinen E, Rinttilä T, Kajander K, et al. *Am J Gastroenterol* 2005;100:373–382.). In this study, we did not examine such an important biomarker. Further investigation of these points is needed.”

Reviewer #2:

This manuscript titled “Constipation, Hard Stools, Fecal Urgency, and Incomplete Evacuation, but not diarrhea are Associated with Diabetes and its related factors” gives us informative knowledges about diabetes and related factors and can be published in this magazine.

Response: Thank you for the valuable comment.