Author's response to reviews

Title: Lifestyle factors affecting gastroesophageal reflux disease symptoms: a cross-sectional study of healthy 19864 adults using FSSG scores.

Authors:

Nobutake Yamamichi (nyamamic-tky@umin.ac.jp)
Satoshi Mochizuki (tguinn@mail.goo.ne.jp)
Itsuko Asada-Hirayama (tguinn@mail.goo.ne.jp)
Rie Mikami-Matsuda (tguinn@mail.goo.ne.jp)
Takeshi Shimamoto (tguinn@mail.goo.ne.jp)
Maki Konno-Shimizu (tguinn@mail.goo.ne.jp)
Yu Takahashi (tguinn@mail.goo.ne.jp)
Chihiro Takeuchi (tguinn@mail.goo.ne.jp)
Keiko Niimi (tguinn@mail.goo.ne.jp)
Satoshi Ono (tguinn@mail.goo.ne.jp)
Shinya Kodashima (tguinn@mail.goo.ne.jp)
Chihiro Minatsuki (tguinn@mail.goo.ne.jp)
Mitsuhiro Fujishiro (tguinn@mail.goo.ne.jp)
Toru Mitsushima (tguinn@mail.goo.ne.jp)
Kazuhiko Koike (tguinn@mail.goo.ne.jp)

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Author's response to reviews: see over
Dear Editor of *BMC Gastroenterology*

We enclose herewith our manuscript entitled “Lifestyle factors affecting gastroesophageal reflux disease symptoms: a cross-sectional study of healthy 19864 adults using FSSG scores.” by Nobutake Yamamichi, Satoshi Mochizuki, Itsuko Asada-Hirayama, Rie Mikami-Matsuda, Takeshi Shimamoto, Maki Konno-Shimizu, Yu Takahashi, Chihiro Takeuchi, Keiko Niimi, Satoshi Ono, Shinya Kodashima, Chihiro Minatsuki, Mitsuhiro Fujishiro, Toru Mitsushima, and Kazuhiko Koike. We believe our finding would be of great interest to a broad section of the readership of your journal.

Outlines of our work are as follows.

The aim of our study is to elucidate background lifestyle factors affecting gastroesophageal reflux disease (GERD) symptoms, using a large-scale cohort of healthy adults in Japan. The total study population of 19864 subjects comprised of 11493 men and 8371 women with a mean age of 50.2 ± 9.4 years. 371 proton pump inhibitor (PPI) users (239 men and 132 women with a mean age of 55.8 ± 9.9 years, range 27-87 years) and 539 H$_2$-receptor antagonist (H$_2$RA) users (332 men and 207 women with a mean age of 52.9 ± 9.8 years, range 27-87 years) were subcategorized and analyzed independently. Using FSSG (Frequency Scale for the Symptoms of GERD) score as a response variable (*J Gastroenterol* 2004:39:888-891), 25
lifestyle-related factors including age and gender were univariately evaluated by Student’s t-test or Pearson’s correlation coefficient. Multiple linear regression was further applied for multivariate analysis.

Average FSSG scores of subjects were 4.8 ± 5.2 for the total subjects, 9.0 ± 7.3 for the PPI users, and 8.2 ± 6.6 for the H₂RA users. Both the PPI and H₂RA users have obviously higher FSSG scores than total study participants (p<0.0001). By analysis of the total population, positively correlated factors and standardized coefficient (β) for FSSG scores are inadequate sleep (β=0.158), use of digestive drugs (β=0.0972 for PPIs, β=0.0903 for H₂RAs, and β=0.104 for others), increased body weight in adulthood (β=0.081), dinner just before bedtime (β=0.061), habit of midnight snack (β=0.055), lower body mass index (β=0.054), NSAID users (β=0.051), female gender (β=0.048), lack of breakfast (β=0.045), lack of physical exercise (β=0.035), younger age (β=0.033), antihyperglycemic agents non-users (β=0.026), habit of quick eating (β=0.025), alcohol drinking (β=0.025), history of gastrectomy (β=0.024), history of cardiovascular disease (β=0.020), and smoking (β=0.018). Poor quality of sleep and irregular dietary habits shows strongest correlation with FSSG scores. On the contrary, influences of alcohol consumption and habitual smoking were not so strong; other eight lifestyle-related factors concerning quality of sleep and dietary habits showed much stronger effect upon FSSG scores.

For antacid users, average FSSG scores of subjects are 9.0 ± 7.3 for the PPI users and 8.2 ± 6.6 for the H₂RA users. Both of users have obviously higher FSSG scores than those of total study participants (4.8 ± 5.2; p<0.0001). Positively correlated
factors of PPI users are female gender ($\beta=0.198$), inadequate sleep ($\beta=0.150$), lack of breakfast ($\beta=0.146$), antihypertensive agents non-users ($\beta=0.134$), and dinner just before bedtime ($\beta=0.129$), whereas those of H$_2$RA users are inadequate sleep ($\beta=0.248$), habit of midnight snack ($\beta=0.160$), anticoagulants non-users ($\beta=0.106$), and antihypertensive agents non-users ($\beta=0.095$). From our results, it is strongly suggested that present-day usual medication of PPI or H$_2$RA cannot fully relieve the GERD symptoms.

This work is a very large-scale study comprising about 20000 subjects, and is characteristic that our analysis focused on the GERD symptoms alone. Compared with many studies evaluating the correlation between endoscopic reflux esophagitis and background factors, our work therefore should reflect the property of NERD (non-erosive reflux disease) patients, who are at present thought to occupy more than half of all GERD patients. We believe our study should shed light on the pathophysiology of GERD symptoms, and would also lead to the prevention of bothersome epigastralgia from the viewpoint of lifestyle factors.

This manuscript consists of original data which are not under consideration for publication elsewhere, and has been carefully checked and approved by all the listed authors.

Our manuscript was once submitted to the *BMC Medicine*, and according to the editor’s recommendation, we now submit the revised manuscript to *BMC Gastroenterology*. According to the reviewers’ comment, we revised our manuscript
as follows.

**Comment of Reviewer 1**

1. Some additional informations are needed to allow a final evaluation in particular for the clinical application of the study results. Some data regarding the clinical outcome of the enrolled patients should be useful to better support the present results. For example the relationship between the sleep disturbancies and the GERD symptoms (did sleep disturbancies change after PPI treatment?)

   Our large cohort study is a cross-sectional one based on the questionnaire and symptom scores (FSSG). Because it is not a prospective or intervention study, it is difficult to evaluate the clinical application precisely. According to the result of our present study, we are now planning to perform a prospective study investigating the effect of sleeping drugs upon the GERD patients with sleep disturbance, which will be reported in the future.

2. The authors stated that drugs did not influence the clinical presentation (symptoms score) of the disease; however no information regarding treatment dose and duration are provided. Did different doses and/or type of drug (different PPI) influence the results?

   We did not state that drug did not influence the clinical presentation (symptoms score), but stated that present-day drugs could not fully relieve the symptoms (The 3rd part titled “Medication of PPIs or H₂RAs is not enough to relieve the GERD
symptoms” in the DISCUSSION).

For PPI drugs, omeprazole (20mg/day), lansoprazole (15mg/day), and rabeprazole (10mg/day) are mostly used in Japan, as only these three drugs are officially allowed to use in Japan. In this study, however, we do not have information about dose or duration of PPI medication in each subject, which is the limitation of our study.

**Comment of Reviewer 2**

1. Abstract has too many details in methods and results.

   According to the indication, both methods (from 76 words to 67 words) and results (from 171 words to 166 words) were shortened.

2. Introduction needs a clear couple of questions to be answered.

   We interpreted this “Introduction” as “Background”. According to the suggestion, two sentences in “BACKGROUND” were changed as follows.

   In our present cross-sectional study comprising about 20,000 healthy adults, the correlation between GERD symptoms and background variables were strictly analyzed, especially focused on lifestyle factors.

   Therefore, it is one of our aims to analyze the correlation between GERD symptoms and background variables, especially focused on lifestyle factors.
In this study, we additionally evaluated the efficacy of antacids, proton pump inhibitor (PPI) and histamine H₂-receptor antagonist (H₂RA), both of which are world-wide most popular drugs used for GERD treatment.

Besides, another aim of our study is to evaluate the efficacy of proton pump inhibitor (PPI) and histamine H₂-receptor antagonist (H₂RA), both of which are world-wide most popular drugs used for GERD treatment.

3. In Methods, content of the questionnaires itself should be presented in a figure or table, not in the text.

According to the indication, questionnaires including FSSG were presented in figure 1, and removed them from the text.

4. Results should be related to the questions formulated after 2. and need to be presented more concise, with referral to tables

According to the indication, all the four paragraphs of RESULT were shortened. In the 1st "Characteristics of Study Subjects" paragraph, redundant description was omitted with referral to Figure 1. In the 2nd "Positively Correlated Factors of FSSG scores among the total 19864 subjects" paragraph, values of standardized coefficient were omitted, with referral to Table 1 and Table 2. In the 3rd “Positively Correlated Factors of FSSG scores among the PPI users” paragraph and the 4th “Positively Correlated Factors of FSSG scores among the 539 H₂RA users” paragraphs, values of
standardized coefficient were also omitted, with referral to Table S1 and Table S2. Consequently, we could make RESULT much more concise (from 725 words to 628 words).

5. Discussion again repeats too many details, try to focus on major positive and negative findings and what others found on this.

   According to the indication, DISCUSSION was shortened. Especially in the 1st "Many lifestyle-related factors show strong correlation with GERD symptoms" paragraph, redundant description was omitted with referral to Table 2.

   Consequently, we could make DISCUSSION more concise (from 1094 words to 1050 words).

6. Conclusion repeats again

   Though some repeats are inevitable in CONCLUSION, we omitted redundant description and tried to shorten the CONCLUSION. Finally, word count of CONCLUSION decreased from 68 words to 51 words.

   We believe this manuscript should be of great interest to a broad section of the readership of *BMC Gastroenterology.* Please do not hesitate to contact me when you require anything further. Thank you for your consideration.
Yours sincerely,

Nobutake Yamamichi, M.D., Ph.D.

Department of Gastroenterology,
Graduate School of Medicine,
University of Tokyo, Tokyo, Japan
7-3-1, Hongo, Bunkyo-ku, Tokyo,
Japan (zip code: 113-8655)
Tel: +81-3-3815-5411 (ext 33019)
Fax: +81-3-5800-8806
E-mail: nyamamic-tky@umin.ac.jp