Author's response to reviews

Title: Prevalence and risk factors of Helicobacter pylori infection in Korea; Nationwide multicenter study over 13 years

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Author's response to reviews: see over
Dear Dr Edoardo Savarino:

RE : MS: 1334941980892913  Prevalence and risk factors of *Helicobacter Pylori* infection in Korea ; Nationwide multicenter Study Over 13 Years

coauthored by
Seon Hee Lim, Jin-Won Kwon, Gwang Ha Kim, Jung Mook Kang, Min Jeong Park, Jeong Yoon Yim, Heung Up Kim, Gwang Ho Baik, Geom Seog Seo, Jeong Eun Shin, and Young-Eun Joo

Thank you very much for giving us an opportunity for revision. Your helpful comments have been addressed in the discussion. We would also like to thank for your valuable comments that helped us improve our manuscript. Changes have been marked in **BOLD** in the revised manuscript to avoid any confusion.

**Reply to each reviewer’s comments**

**A. Reviewer 1**

Major Compulsory Revisions
1. It is stated in the “comparison of trends of seroprevalence” section that the trends were compared using the published data of 1998 and 2005. Thus, it should be cleared how the authors manage to divide the study population into 8 birth cohort intervals with relative seroprevalence values for 1998, 2005 and 2011 when such values are not reported in the studies of 1998 and 2005.

**Answer.** Thank you for the your accurate and helpful comments. Prof. Nayoung Kim (the corresponding author of the present manuscript) worked as one member of Scientific Committee of Korean Helicobacter Study Group (KHSG) since its opening in 1997 and collected the relevant raw data from the national survey in 1998 (blood sample and questionnaire). These data were analyzed with help of prof. Hyung Sik Ahn in Korea University and Nayoung Kim presented the results at the Annual Meeting of Helicobacter Study Group in May, 1999. Parts of these data were published by Kim N, Kim JG, Jin Ho Kim JH, et al. under the title of “Risk factors of *Helicobacter pylori* infection in asymptomatic Korean population” (Korean J Intern Med 2000;59:376-387). In 2005, Nayoung Kim compared these data with the 2005 Cohort with permission of prof. In Sik Chung, the President of Korean Helicobacter and Upper Gastrointestinal Research (this name has been changed from KHSG), which was constructed in 7 provinces with the same serology kit as the present manuscript. During this study period in 2005 Nayoung Kim became the Director of Scientific Committee of KHUGR. The article entitled “Seroprevalence of *Helicobacter pylori* in South Korea.” (Helicobacter 2007;12:333-340 authored by Yim JY, Kim N, Choi SH, et al) has been cited over 65 times. When the raw data was collected in the same way in 2011, birth cohort analysis was performed using the raw data of 1998, 2005 and 2011. I added this sentence “**For this analysis, relevant data from 1998 and 2005 were obtained from the authors and reconstructed for the analysis of birth cohort.”** to
the part of “analysis of cohort effects” in the methods section [page 7 line 8] to clarify the issue.

2. In table 3 reporting the risk factors, the total number of included subjects is 10796. However, the total of subjects divided by household income is 9449, by education is 10188, by BMI 10657, etc. The authors should explain how come there is lacking data about patients when considering each risk factor. Patients with incomplete data should be excluded for the analysis.

*Answer.* We are sorry for not explaining this in detail. *H. pylori* seroprevalence in this manuscript was evaluated for all data with some missing values for demographic and social-economic information as the reviewer mentioned. In case of multivariable logistic regression, if patients have missing data for risk factors, they were excluded automatically in the process of statistic computation, so total subject number of real statistic computation of multivariable logistic regression was 16,770 for table 2 and 8,688 for table 3. We wanted to show to readers all data including missing value for integrity of the data. We mentioned the number of subjects for logistic regression in the bottom of each table as follows; **Total subject number of real statistic computation of multivariable logistic regression was 16,770 for table 2 and 8,688 for table 3.** [page 24 and 25]

3. The decrease of prevalence divided by age (intervals of 10 years), as shown in figure 2C, was statistically significant from 1998 to 2005 (and thus also between 1998 and 2011), but was not significant between 2005 and 2011. This important result should be stressed in the discussion, since although there is a reduction in the last 6 years, this is not statistically
significant.

*Answer.* Thank you for the accurate comment. We added that issue with an explanation to “second limitation” in the discussion section [page 14 line 6~] as follows; “*Nonetheless, the study subjects in 1998 involved a relatively lower population from Seoul and Gyeonggi, (capital city and its near city) compared with the population in 2005 and 2011. Generally, people in capital cities have higher socioeconomic conditions than those living in other areas. It may account for much higher seroprevalence in 1998 compared with 2005/2011. However, the change of seroprevalence by the strata (e.g. age, sex, region, etc) over time periods may indicate that our overall result is not much influenced by a different proportion of subjects from provinces.”

4. According to figure 2A there is a statistically significant reduction only between data from 1998 and 2011. It is not clear whether there is also a statistically significant reduction between 2005 and 2011. This point should be clarified.

*Answer.* Following the reviewer’s comment, we added Confidence Interval to each seroprevalence to “Comparison of seroprevalence~” in the result section [page 9 line 7~] as follows; “The overall seroprevalence of *H. pylori* infection was 54.4% (95% CI: 53.5-55.4%) in 2011 which is significantly decreased from 66.9 % (95% CI: 65.4-68.6%) in 1998, and 59.6 % (95% CI: 58.5-60.7%) in 2005 (p < 0.001) (Fig. 2). *There was statistically significant reduction both between 1998 and 2005, and between 2005 and 2011.*” Thank you!
5. The English spelling and grammar should be reviewed by a native English-speaker.

*Answer.* The 1st manuscript was actually already reviewed by a native speaker through an agency of a professional language editing service. However, it looked like it was not enough. Following the reviewer’s comment, the English spelling and grammar has been reviewed again by another native English-speaker.

Minor Essential Revisions

6. As reported in the methods section, patients underwent only questionnaire testing and seroprevalence of infection. However during the study the authors report also blood test values (Cholesterol, glucose, triglyceride) and anthropometric values (weight, BMI). These evaluations (physical examination, blood testing, etc.) should be mentioned in the methods section.

*Answer.* Thank you for the kind comment. Following the reviewer’s comment, following statements were inserted in the methods section [page 5 and 6] under the small title of Clinical and laboratory evaluations; “Anthropometric measurements (weight and height) were done by trained nurses using a standardized protocol. Blood samples were obtained from the antecubital vein in the morning after overnight fasting and serum samples were separated after centrifugation. Serum cholesterol, triglyceride, and fasting glucose were measured by an automatic analyser, Alisei® (Seac, Pomezia, Italy). To compare these results according to seropositivity of *H. Pylori*, we categorized the level of total cholesterol
(TC) as normal (≤240 mg/dl) and abnormal (>240 mg/dl), triglyceride (TG) as ≤150 mg/dl and >150 mg/dl, and fasting glucose as ≤100 mg/dl and >100 mg/dl, respectively.”

7. Was the questionnaire used the same as for the previous studies?

*Answer.* Yes the questionnaire in this study was the same one as previous two studies, and we added the phrase “which was the same as previous study’s [9]” in the methods section.[page 5 line 7]

8. In the “Analysis of cohort effects” section the Authors state that “the data from 1998 was considered to be those in 1999 because the successive cross-sectional data should span with same interval”. Doesn’t reducing the time interval from 7 to 6 years modify the statistical validity and result? The Authors should comment such statistical adjustment.

*Answer.* With all respect, your comment is quite right, so we added this limitation to the discussion section [page 14 line 13~] as follows; “Third, for the generation of synthetic cohort, cross-sectional data should have the same interval. However, our data did not have the same interval as the previous data. This is the reason why we considered the data from 1998 as equivalent to those from 1999. This intentional modification could have caused bias, but we think that the bias may be negligible because *H. pylori* seroprevalence was not changed much by one-year.”
9. Figure 3 line H has a wrong symbol.

*Answer.* Thank for your point. We corrected Figure 3.

*The authors really appreciated the reviewer’s kind and accurate comments. Revision based on these comments has improved the accuracy and the quality of the manuscript. We appreciate your efforts.*
B. Reviewer 2

Comment to the Author:

General:

Yet another cross-sectional study, about H pylori epidemiology, in a specific geographical area (three in a row in about 15 years by the same working group), but this time in a larger population and with more variables taken into consideration. However, analysis of epidemiological data seems comprehensive and clear.

Specific:

Major revisions:

a) Patients enrollment is not completely clear. Why did asymptomatic patients undergo H pylori testing? It is not clear if data were collected retrospectively or prospectively.

Answer. Three studies in 1998, 2005 and 2011 have been performed prospectively under well designed protocol, respectively. In the early 2010 when we designed this study, we wanted to know if there would be the another change of H. pylori seroprevalence after 2005 from the last study. Thus the study subjects were collected prospectively during 2011. The institutions participating in this study were healthcare centers for health check-ups, and because of a high seroprevalence in Korea, so H. pylori test is usually included for health check-up in the health care centers in Korea. To clarify the process of subject collection, we mentioned following statement in the methods section [page 5 line 3]; The subjects were enrolled prospectively in 2011 under a predefined protocol.
b) Author should state if patients provided informed consent.

*Answer.* An Informed consent was obtained from each subject in this study. We added this to the methods section [page 5 line 6] like this; “*Informed consent was obtained from each subject.*”

c) Was the questionnaire used validated?

*Answer.* Even though there was no study result about validation of this questionnaire, the questionnaire was designed by the Scientific Committee members of “Korean College of Helicobacter and Upper Gastrointestinal Research” and was used in the many studies about *H. pylori* in Korea.

d) How were patients belonging to the same family unit considered?

*Answer.* Originally data were collected based on the individual level, so there was no information on whether the subjects were in the same family or not in this study.

Discretionary revisions

e) It is known that different geographic areas had different *H pylori* prevalence: according to
previous studies, Seoul had the lowest prevalence compared to the other regions of South Korea. Although seroprevalence showed downward trends in most of areas (as stated in discussion section), is it possible that change of prevalence in the overall population might be influenced by a different proportion of subjects included from the provinces rather than more industrialized areas, over the decades?

*Answer.* We agree with the reviewer’s point. One of limitations of this study was in comparison of seroprevalence over time not within the same population in three time points. We mentioned this matter in “2nd limitation” part of the discussion section [page 14 line 6~] as below;

“Nonetheless, the study subjects in 1998 involved a relatively lower population from Seoul and Gyeonggi, (capital city and its near city) compared with the population in 2005 and 2011. Generally, people in capital cities have higher socioeconomic conditions than those living in other areas. It may account for much higher seroprevalence in 1998 compared with 2005/2011. However, change of seroprevalence by the strata (e.g. age, sex, region, etc) over time periods may indicate that our overall result is not much influenced by different proportions of subjects included from provinces.”

f) I think the manuscript might benefit if the author would discuss why serologic test was used rather than other non-invasive test such as UBT or SAT. (i.e. costs/adherence/PPI usage…)

*Answer.* For comparability of data over three time points, the same diagnostic method, i.e. the serologic test was used. Stool antigen test was not popular in Korea in 1998 and UBT was not appropriate test for young children in 1998’s study. On the other hand, serologic testing has
become common in most healthcare centers in Korea because it is more adherent and less expensive.

g) Have the author got information about how the association between TC and Hp serology was in the previous periods investigated?

Answer. In previous studies, there was no evaluation about the association between TC and HP serology due to lack of data on TC.

The authors really appreciated the reviewer’s kind and accurate comments. Revision based on these comments has improved the accuracy and the quality of the manuscript. We appreciate your efforts.

Sincerely,

Nayoung Kim, M.D., Ph.D.