

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Changes in prevalence of Helicobacter pylori in Japan from 2008 to 2018: a repeated cross-sectional study
<b>AUTHORS</b>	Abiko, Soichiro; Hirayama, Yoji; Otaki, Junji; Harada, Yoshimi; Kawakami, Kohei; Toi, Takahiro; Takamiya, Tomoko; Kawai, Takashi

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Zamani, Mohammad Tehran University of Medical Sciences
<b>REVIEW RETURNED</b>	12-Dec-2021

<b>GENERAL COMMENTS</b>	Despite a large population included, assessed outcomes do not satisfy the reviewer to accept the study for BMJ Open. Being prospective study, assessing risk factors, etc., are important subjects in this level.
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<b>REVIEWER</b>	Khoder, Ghalia University of Sharjah
<b>REVIEW RETURNED</b>	17-Jan-2022

<b>GENERAL COMMENTS</b>	<p>Dear Authors,</p> <p>I would like to thank you for the great efforts you have invested in this research paper. I was extremely interested in reading the manuscript as well as the project idea. From reading the manuscript, I have noticed that the whole project was well structured. However, several modifications in different parts of the manuscript need to be considered.</p> <p>I would advise to take in consideration the following major and minor comments in your next resubmission.</p> <p>Major comments:</p> <ol style="list-style-type: none"><li>1. Line 55: Add a reference to gastric diseases associated to Helicobacter pylori and remove immune thrombocytopenia.</li><li>2. Authors has not discussed how serum samples were collected and stored and tested using the E-plate Eiken H. pylori antibody. More technical details are requested in the material and method as well as how the results were read?</li><li>3. The male and female distribution is not balanced to analyze the impact of the sex on the H. pylori infection rate.</li><li>4. Add the figure number to the used figures.</li></ol> <p>Minor comments:</p> <ol style="list-style-type: none"><li>1. Line 1: Japan must be written in capital letter.</li><li>2. Line 41: what do the authors mean by non-patients? do you mean health participants?</li></ol>
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	<p>3. Line 57: Moreover, eradication therapy of H. pylori instead of ``they recognized eradication therapy`` ?? please revise the English language of this sentence.</p> <p>4. Line 62: Please revise the English language in the sentence ``H. pylori could be involved in 90%``.</p> <p>5. Line 138 and line 141: Add ``and`` between (n=134) and ambiguous data (n =154).</p> <p>5. Line 149: H. pylori-infected (infected must not be in italic).</p> <p>6. Line 262: H. pylori must be written in italic.</p>
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<b>REVIEWER</b>	Baburin, Alex National Institute for Health Development, Tallinn, Estonia.
<b>REVIEW RETURNED</b>	09-May-2022

<b>GENERAL COMMENTS</b>	<p>BMJ Open peer review</p> <p>The paper by Abiko and others is describing trends in Helicobacter pylori prevalence in Japan from 2008 to 2018. The topic is important for Japan and other countries where incidence and mortality of gastric cancer are high. The analysis of H. pylori trends enables to assess if any of the measures taken during the observed period has had any effect.</p> <p>In my opinion this paper needs language revision.</p> <p>Line 57/58 revise the sentence Moreover, they recognized eradication therapy for H. pylori in asymptomatic populations as efficient for preventing... Suggestion: Moreover, they recognized the effectiveness of eradication therapy for HP in asymptomatic populations for preventing ...</p> <p>Line 62. Revise the sentence. moreover, H. pylori could be involved &gt; 90% in Japan. Suggestion: moreover, H. pylori could be involved in more than 90% of cases in Japan.</p> <p>Line 83. Revise the sentence: Watanabe et al. suggested that the declining trend of the H. pylori prevalence in Japan appears to become dull. I could not find in the cited article any reference to a dull trend. The exact meaning of dull in this context is not entirely clear.</p> <p>Line 97. Revise the sentence: Participants' data, including medical questionnaires and blood test results, were anonymously obtained from the annual health checkup database of the health insurance society.</p> <p>I understand that authors meant that anonymized data was obtained and not that data was obtained by an unidentified person.</p> <p>Methods section</p> <p>In the methods section there was no mentioning why the joinpoint regression was used to analyze this data or what kind of information was hoped to get from the possible joinpoints. The Joinpoint Regression Program enables to choose different tests for detection of changes - for example the permutation test or the BIC test. As a default the permutation test is used, which is less sensitive than BIC and therefore fewer joinpoints will be detected.</p>
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	<p>The permutation test is suitable for assessment of long term trends. On the other hand, the BIC test is better suited to detect subtle changes. As the data of this study has been made available as open data, more information about the analysis would help to repeat the results of this research.</p> <p>Results section</p> <p>Line140/141. Possibly missing word “or”.</p> <p>Line 160. Revise sentence:  “Both trends showed linear upward trends with age”  Maybe substitute “linear upward trends” with “linear increase”.</p> <p>Discussion section</p> <p>Line 177. Revise the sentence. How can something straightforward be also approximate?</p> <p>Line 188/189. Maybe use “in addition” instead of “moreover”.</p> <p>Line 215. What is the meaning of the Joinpoint trend in this sentence? Could it be a trend with joinpoints?</p> <p>Line 239 and elsewhere. Is health society understood unequivocally as a health insurance society? If not, I suggest including word insurance where applicable.</p>
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### VERSION 1 – AUTHOR RESPONSE

Responses to the comments by Reviewer 1

Despite a large population included, assessed outcomes do not satisfy the reviewer to accept the study for BMJ Open. Being prospective study, assessing risk factors, etc., are important subjects in this level.

Response:

Thank you for your helpful suggestion. We agree that to increase the reliability of the study, it is important to know the characteristics of the participants and the confounding variables. It would be best if we could analyze a prospective cohort. However, we conducted a (retrospective) repeated cross-sectional study with data from a large company’s health insurance society, because participant data could be obtained without burdening them by this way (the participants did not undergo any additional or unusual procedures during their health checkups). Despite of this drawback, we believe our study provides important information, as follows.

First, our study analyzed participants of the same age (35 years old), from the same company, over 10 years. This enabled us to directly monitor changes in the prevalence of H. pylori over 10 years. To our knowledge, there have been no studies to date using this method. Second, in this study we analyzed various workers around Japan. The participants were not hospital visitors or voluntary candidates, and had a variety of social backgrounds. We believe these characteristics of the participants in our study helped us to clarify H. pylori infection rates in the general Japanese population. Third, we used Joinpoint analysis to analyze the infection rates. This made it possible to analyze not just trends in the infection rate by year or age but also changes in the trends.

We hope that our explanation is helpful for reviewing our revised manuscript.

Responses to the comments by Reviewer 2

Thank you for your helpful feedback on our manuscript.

We have addressed your comments as below.

Major comments:

1. Line 55: Add a reference to gastric diseases associated to *Helicobacter pylori* and remove immune thrombocytopenia.

Response:

In accordance with the comment, we have added references to papers regarding the association between gastric diseases and *H. pylori* infection, and removed immune thrombocytopenia. (Page 4, line 60)

The references are as shown below.

chronic gastritis:

1. Wang F, Meng W, Wang B, et al. *Helicobacter pylori*-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014;345(2):196-202. doi: 10.1016/j.canlet.2013.08.016 [published Online First: 2013/08/29]

peptic ulcer:

2. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002;359(9300):14-22. doi: 10.1016/s0140-6736(02)07273-2 [published Online First: 2002/01/26]

MALT lymphoma:

3. Eck M, Schmausser B, Haas R, et al. MALT-type lymphoma of the stomach is associated with *Helicobacter pylori* strains expressing the CagA protein. *Gastroenterology* 1997;112(5):1482-6. doi: 10.1016/s0016-5085(97)70028-3 [published Online First: 1997/05/01]

gastric cancer:

4. Sasazuki S, Inoue M, Iwasaki M, et al. Effect of *Helicobacter pylori* infection combined with CagA and pepsinogen status on gastric cancer development among Japanese men and women: a nested case-control study. *Cancer Epidemiol Biomarkers Prev* 2006;15(7):1341-7. doi: 10.1158/1055-9965.EPI-05-0901 [published Online First: 2006/07/13]

2. Authors has not discussed how serum samples were collected and stored and tested using the E-plate Eiken *H. pylori* antibody. More technical details are requested in the material and method as well as how the results were read?

Response:

We included more detailed descriptions of the participants' characteristics and their selection method/ span>, how samples were collected and stored, and interpretation of the test results in the Materials and Methods section of the revised manuscript, as follows. (Page 6, line 106 – Page 7, line 120)

“Japanese law requires all citizens to have some type of health insurance. T company is one of the largest companies in Japan, with many branches. All workers of this company, which includes a wide

variety of people, such as office workers, manual laborers, and people with disabilities, belong to the company's health insurance society. Members of the T company health insurance society undergo serum anti-*Helicobacter pylori* IgG antibody tests. This test was conducted annually on members aged 35 years during their health checkups (approximately 600–1,100 people per year). However, in 2018, the health insurance society offered this test to participants aged 35, 40, 45, and > 50 years. We included members who had undergone serum *H. pylori* antibody tests at their annual health checkups from April 1, 2008, to March 31, 2019, at the age of 35–65 years. Participants' blood samples were taken at their health checkups. Serum was isolated from the samples, and stored at – 80 °C until use. Serum anti-*H. pylori* IgG was measured using an enzyme-linked immunosorbent assay with “E-Plate Eiken *H. pylori* antibody” or “E-Plate II Eiken *H. pylori* antibody” (Eiken Chemical Co. Ltd., Tokyo, Japan). The cut-off level was set at 10 U/mL, with values above this being classified as positive.”

3. The male and female distribution is not balanced to analyze the impact of the sex on the *H. pylori* infection rate.

Response:

We agree with this point. Inequality in the number of male and female participants could have influenced the results, and may be problematic when considering the results as representing the general population. Considering the comment, we decided to change the results by separating the two sexes (men and women). As a result, a continuous time trend was observed in both men and women. In terms of age, a joinpoint was observed at age 54 years (CI: 54–58) for men, and at age 45 years (CI: 45–51) for women in 2018. We modified the text as appropriate throughout the manuscript, as follows. (Page 9, line 168 – Page 10, line 183)

“The 35-year-old analysis

In the 35-year-old analysis, 1,100 out of 7,586 male participants and 190 out of 1,739 female participants were *H. pylori*-infected. In Joinpoint analysis, infection rates showed linear downward trends in both men and women with advanced years (men: 17.5% in 2008 to 10.1% in 2018 (slope –0.66), women: 12.3% in 2008 to 9.2% in 2018 (slope –0.51) [P < 0.05]). These trends lacked joinpoints at which the trend significantly changed (Figure 2).

The 2018 analysis

In the 2018 analysis, 2,432 out of 9,580 male participants and 431 out of 1,854 female participants were infected with *H. pylori*. The infection rates showed trends of increasing positive rates with advanced age in both men and women (men: 11.0% at 35 years to 47.7% at 65 years, women: 10.0% at 35 years to 40.0% at 65 years). These trends had joinpoints at the age of 54 years in men (95% CI: 45–58) and at the age of 45 in women (95% CI: 45–51), with two different trends in the slope before and after the point. Specifically, the first and second trends were 35–54 years (slope = 0.67) and 54–65 years (slope = 1.83) in men, and 35–45 years (slope = 0.30) and 45–65 years (slope = 1.49) in women.”

Minor modifications were also made to the other sections as appropriate.

4. Add the figure number to the used figures.

Response:

We added the figure numbers to the note sections of the figure legends as shown in the example below.

“Figure 1

Note. (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The 2018 analysis: participants aged 35–65 years in 2018.”

Minor comments:

1. Line 1: Japan must be written in capital letter.

Response:

We thank you for pointing out our mistake. We changed “japan” to “Japan” in the revised manuscript. (Page 1, line 1)

2. Line 41: what do the authors mean by non-patients? do you mean health participants?

Response:

We used the word “non-patients” intentionally to emphasize the strength of our study that participants in this study were not patients, in contrast with previous studies in which the participants were patients who were being treated at hospitals. However, this word was deleted upon modification of the paper’s structure.

3. Line 57: Moreover, eradication therapy of H. pylori instead of “they recognized eradication therapy” ?? please revise the English language of this sentence.

Response:

We agree that our expression was ambiguous and might lead to misunderstanding.

In the revised manuscript, we have quoted from the original document of the World Health Organization (WHO) as shown below.

(Reference: IARC Helicobacter pylori Working Group. Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer: International Agency for Research on Cancer 2014: 4)

“Randomized clinical trials have found that H. pylori treatment is effective in preventing gastric cancer, and models indicate that H. pylori screening and treatment strategies would be cost-effective.”

“The Working Group therefore recommends that countries explore the possibility of introducing population-based H. pylori screening and treatment programmes, but cautions that decisions as to whether and how to implement H. pylori testing and treatment must hinge on local considerations of disease burden, other health priorities, and cost-effectiveness analyses.....”

We rewrote the sentence in our manuscript according to this original document, to avoid misunderstanding, as follows. (Page 4, lines 62 – 65)

“Moreover, the WHO has stated that “H. pylori screening and treatment strategies would be cost-effective” for asymptomatic populations to prevent gastric cancer, and has recommended that “countries explore the possibility of introducing population-based H. pylori screening and treatment programmes”.”

4. Line 62: Please revise the English language in the sentence “H. pylori could be involved in 90%”.

Response:

We modified the sentence to “H. pylori infection is thought to be involved in more than 90%...”. (Page 4, lines 69 – 70)

5. Line 138 and line 141: Add “and” between (n=134) and ambiguous data (n =154).

Response:

We added “or” on Page 9, lines 162 and 165 instead of “and” by the context of the sentences.

6. Line 149: H. pylori-infected (infected must not be in italic).

Response:

We modified “H. pylori-infected” to “H. pylori-infected” in the revised manuscript. (Page 9, line 170)

7. Line 262: H. pylori must be written in italic.

Response:

We have corrected this mistake. (Page 16, line 289)

Responses to the comments by Reviewer 3

Thank you for your helpful feedback on our manuscript.

We have addressed your comments as below.

In my opinion this paper needs language revision.

Response:

We have made language revisions regarding the points you mentioned, consulting with our native English-speaking language proofreader. We believe our manuscript is now more readable and robust.

Line 57/58 revise the sentence

Moreover, they recognized eradication therapy for H. pylori in asymptomatic populations as efficient for preventing...

Suggestion: Moreover, they recognized the effectiveness of eradication therapy for HP in asymptomatic populations for preventing ...

Response:

Thank you for this advice. We modified these sentences directly quoting from the original WHO working group report to make our point clear. Reviewer 2 also mentioned the same point.

Please see our response to minor comment no. 3 of Reviewer 2 for more details.

Line 62. Revise the sentence.

moreover, H. pylori could be involved > 90% in Japan.

Suggestion: moreover, H. pylori could be involved in more than 90% of cases in Japan.

Response:

We modified the sentence to “H. pylori infection is thought to be involved in more than 90%...” (Page 4, line 70).

Line 83. Revise the sentence:

Watanabe et al. suggested that the declining trend of the H. pylori prevalence in Japan appears to become dull.

I could not find in the cited article any reference to a dull trend. The exact meaning of dull in this context is not entirely clear.

Response:

Thank you for pointing this out. We agree that this sentence is ambiguous. Although Watanabe et al. did not directly mention the dulling of the declining trend, the results of their study showed three trends: the birth-year percent change (BPC) =  $-1.15\%$  in patients born between 1927 and 1949, BPC =  $-4.59\%$  in patients born between 1949 and 1961, and BPC =  $-2.04\%$  in patients born between 1961 and 1988. This indicated that after a rapid decrease in infection rates in those born between 1949 and 1961, the rate of decrease has slowed down. We rewrote this sentence including detailed facts and figures from their study for clarification, as follows. (Page 5, line 90 – Page 6, line 96)

“Watanabe et al. analyzed the prevalence of H. pylori infection by birth-year among first-visit outpatients between 2005 to 2013 in Nagoya, Japan. The results showed three trends: the birth-year percent change (BPC) =  $-1.15\%$  in patients born between 1927 and 1949, BPC =  $-4.59\%$  in patients born between 1949 and 1961, and BPC =  $-2.04\%$  in patients born between 1961 and 1988, indicating that after a rapid decrease in infection rates in those born between 1949 and 1961, the rate of decrease has slowed down.”

Line 97. Revise the sentence:

Participants' data, including medical questionnaires and blood test results, were anonymously obtained from the annual health checkup database of the health insurance society.

I understand that authors meant that anonymized data was obtained and not that data was obtained by an unidentified person.

Response:

We agree that this sentence is unclear. To clarify the meaning and avoid misunderstanding, we modified the sentence as follows. (Page 7, lines 120–122)

“Anonymized participants' data, including medical questionnaires and blood test results, were obtained...”

Methods section

In the methods section there was no mentioning why the joinpoint regression was used to analyze this data or what kind of information was hoped to get from the possible joinpoints. The Joinpoint Regression Program enables to choose different tests for detection of changes - for example the permutation test or the BIC test. As a default the permutation test is used, which is less sensitive than BIC and therefore fewer joinpoints will be detected. The permutation test is suitable for assessment of long term trends. On the other hand, the BIC test is better suited to detect subtle changes. As the



data of this study has been made available as open data, more information about the analysis would help to repeat the results of this research.

Response:

Thank you very much for your important and insightful comments. We assumed that there may be a change in the decreasing trend of *H. pylori* prevalence in Japan based on the results of previous studies, as listed below.

- Watanabe M, et al. Declining trends in prevalence of *Helicobacter pylori* infection by birth-year in a Japanese population. *Cancer Sci* 2015;106(12):1738-43.
- den Hoed CM, et al. *Helicobacter pylori* and the birth cohort effect: evidence for stabilized colonization rates in childhood. *Helicobacter* 2011;16(5):405-9
- Wang C, et al. Changing trends in the prevalence of *H. pylori* infection in Japan (1908-2003): a systematic review and meta-regression analysis of 170,752 individuals. *Sci Rep* 2017;7(1):15491.

To detect the changes, we used Joinpoint analysis in this study.

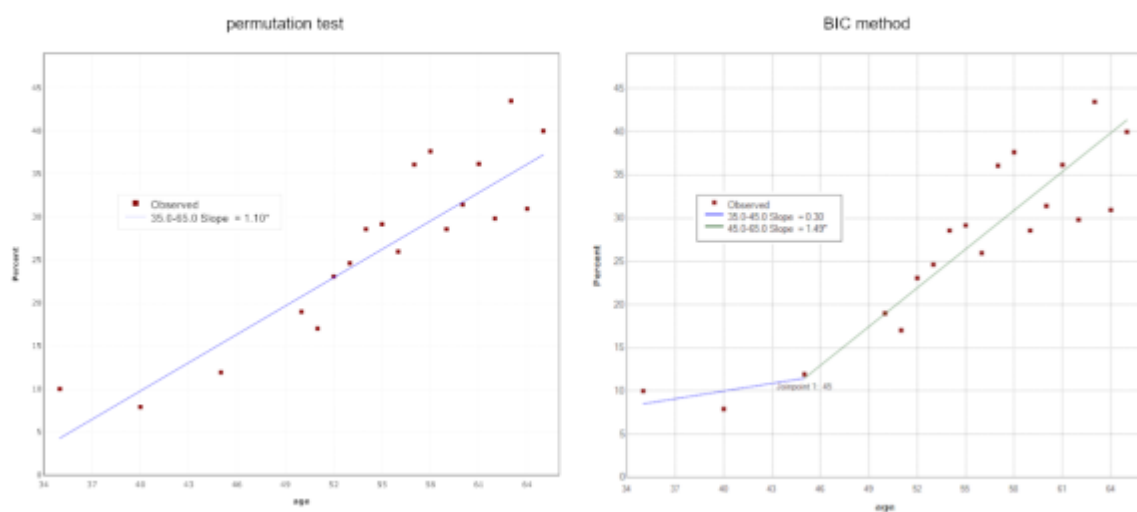
In accordance with your advice, we used the permutation test to detect changes in the analysis of yearly trends of infection rates of 35-year-old participants, because we assumed that the permutation test is suited to the analysis of long-term trends with few joinpoints. We used BIC methods in the analysis of the infection rates by age in 2018 with the assumption that BIC is more sensitive to small changes in small data. Overall, there were no major differences affecting the study results between the two methods. However, the trend of infection rates by age in women in 2018 had a joinpoint using the BIC method, which was not detected with the permutation test. We rewrote the manuscript according to the results obtained from the analysis mentioned above.

In addition, we added the following sentence to the statistical analysis section. (Page 8, lines 140–143)

“We used the permutation test to select the optimal number of joinpoints in the 35-year-old analysis, whereas we used the Bayesian Information Criterion (BIC) in the 2018 analysis.”

A comparison of results of the permutation test and those of BIC in women in 2018 is shown below.

Women in 2018



Results section

Line 140/141. Possibly missing word “or”.

Response:

We added the word “or” to this sentence. (Page 9, line 165)

Line 160. Revise sentence:

“Both trends showed linear upward trends with age”

Maybe substitute “linear upward trends” with “linear increase”.

Response:

We corrected “linear upward trends” to “linear increase” as suggested. (Page 10, line 184)

Discussion section

Line 177. Revise the sentence. How can something straightforward be also approximate?

Response:

We rewrote this sentence as “the infection rate decreased linearly to approximately 10%”, following the suggestion from our language proofreader. We hope this change has made this sentence clear. (Page 11, line 196)

Line 188/189. Maybe use “in addition” instead of “moreover”.

Response:

We agree that this sentence was unclear, and hence we separated the sentence into two sentences, as shown below. (Page 11, lines 208–209)

“In the 2018 analysis, the infection rate increased with advanced age; moreover, there was a declining trend in the prevalence rate of *H. pylori* in the Japanese general population.”

⇒

“In the 2018 analysis, the infection rates in both sexes increased with advanced age. This also indicated declining trends in the prevalence rate of *H. pylori* over the years.”

Line 215. What is the meaning of the Joinpoint trend in this sentence? Could it be a trend with joinpoints?

Response:

Thank you for your comment. We have deleted this sentence, or more precisely, the whole paragraph according to the changes in the structure of the manuscript.

Line 239 and elsewhere. Is health society understood unequivocally as a health insurance society? If not, I suggest including word insurance where applicable.

Response:

We have changed “health society” to “health insurance society” throughout the revised manuscript.

Thank you again for giving us the opportunity to strengthen our manuscript with your insightful advice, and for taking your time to review our revised manuscript.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Baburin, Alex National Institute for Health Development, Tallinn, Estonia.
<b>REVIEW RETURNED</b>	22-Jul-2022

<b>GENERAL COMMENTS</b>	<p>Minor corrections/suggestions in order to facilitate the ease of reading.</p> <p>In line 148, page 8 consider shorter sentence "Health insurance society acknowledged the importance of our study, and permitted us to collect and use participant data from its database."</p> <p>In line 172, page 10 consider replacing advanced years with "increasing years" or "advancing years" or something better. At first reading it associated with the age of participants and not the calendar years.</p> <p>Line 193, page 11. Consider shorter sentence "The subjects of this study were workers in a large company, including workers in the branch offices."</p> <p>Line 202, page 11. Consider using "and" instead of "or" in (slope = -0.65 in men or slope = -0.51 in women).</p> <p>Lines 217 to 221, page 12. There are four instances of using the word rapid in one paragraph. Consider other options - steep, fast, sharp, etc.</p> <p>In line 274, page 15. There is a term "the influence rate". Shouldn't it be the incidence rate?</p>
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### VERSION 2 – AUTHOR RESPONSE

Responses to the comments by Reviewer 3

Thank you for your helpful feedback and suggestions regarding our manuscript.

We have addressed your comments and revised the manuscript as explained below.

We believe that the changes have made our manuscript more readable.

1. In line 148, page 8 consider shorter sentence "Health insurance society acknowledged the importance of our study, and permitted us to collect and use participant data from its database."

Response:

In accordance with your suggestion, we revised the sentence to reduce the redundancy and make it more readable, as shown below. (page 8, lines 145 – 147)

“After discussions with representatives of the health insurance society about this study, the health insurance society acknowledged the importance of our study, and permitted us to collect and use participant data from its database.”

2. In line 172, page 10 consider replacing advanced years with "increasing years" or "advancing years" or something better. At first reading it associated with the age of participants and not the calendar years.

Response:

We agree that the word “advanced year” may cause misunderstanding. In this sentence, we meant the calendar year. Therefore, we replace “advanced year” with “increasing year” in the revised manuscript. (page 9, line 169)

3. Line 193, page 11. Consider shorter sentence "The subjects of this study were workers in a large company, including workers in the branch offices."

Response:

We revised the sentence based on your suggestion, as shown below. (pages 10 – 11, lines 189 – 191)

“This provided a good estimate of the H. pylori infection trends in Japan, as the subjects of this study were workers in a large company, including workers in the branch offices. “

4. Line 202, page 11. Consider using "and" instead of "or" in (slope =  $-0.65$  in men or slope =  $-0.51$  in women).

Response:

In accordance with the comment, we rewrote the sentence using “and” instead of “or”. (page 11, line 198)

5. Lines 217 to 221, page 12. There are four instances of using the word rapid in one paragraph. Consider other options - steep, fast, sharp, etc.

Response:

Thank you for your suggestion. We rewrote the sentences using different words instead of repeatedly using the word "rapid", as follows. (page 11, lines 211 – 217)

"From the late 1960s to the 1970s, which is when people aged 50 years in 2018 spent their childhood, Japan experienced rapid economic growth and urbanization. Accordingly, there was an accelerated increase in water supply and a decrease in the average number of households.<sup>28</sup> <sup>29</sup> These fast environmental changes may have influenced the establishment of *H. pylori* infection; consequently, there was a sharp decrease in the prevalence of this bacterial infection during this era.  
"

6. In line 274, page 15. There is a term "the influence rate". Shouldn't it be the incidence rate?

Response:

We apologize for the mistake. This was corrected to "the infection rate". (page 15, line 270)

Thank you again for your helpful suggestions and comments, and for taking the time to re-review our revised manuscript, which we believe is now a better representation of our work.