BMJ Open

Changes in prevalence of *Helicobacter pylori* in japan from 2008 to 2018: a retrospective cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058774
Article Type:	Original research
Date Submitted by the Author:	27-Oct-2021
Complete List of Authors:	Abiko, Soichiro; Tokyo Medical University, Department of General Medicine and Primary Care Hirayama, Yoji; Tokyo Medical University, Department of General Medicine and Primary Care Otaki, Junji; Tokyo Medical University, Department of Medical Education; Tokyo Medical University, Department of General Medicine and Primary Care Harada, Yoshimi; Tokyo Medical University, Department of Medical Education; Tokyo Medical University, Department of General Medicine and Primary Care Kawakami, Kohei; Tokyo Medical University, Department of General Medicine and Primary Care Toi, Takahiro; Tokyo Medical University, Department of General Medicine and Primary Care Takamiya, Tomoko; Tokyo Medical University, Department of Preventive Medicine and Public Heatlh Kawai, Takashi; Tokyo Medical University, Department of Gastroenterological Endoscopy
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY, HEALTH ECONOMICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Changes in prevalence of *Helicobacter pylori* in japan from 2008 to 2018: a retrospective cross-sectional study

Author names: Soichiro Abiko[1], Yoji Hirayama[1], Junji Otaki[2 1], Yoshimi Harada[2 1], Kohei Kawakami[1], Takahiro Toi[1], Tomoko Takamiya[3], Takashi Kawai[4]

Author Affiliations:

1. Department of General Medicine and Primary Care, Tokyo Medical University, Tokyo, Japan.

2. Department of Medical Education, Tokyo Medical University, Tokyo, Japan.

3. Department of Preventive Medicine and Public Health, Tokyo Medical University, Tokyo, Japan.

4. Department of Gastroenterological Endoscopy, Tokyo Medical University, Tokyo, Japan.

Corresponding Author: Soichiro Abiko

Email: s_abiko1@tokyo-med.ac.jp

Word count: 2412

ABSTRACT

Objectives: To understand the recent prevalence and trends of *H. pylori* infection rates in the Japanese population.

Design: Retrospective cross-sectional study.

Setting: Japanese workers.

Participants: We included 22,120 members (age: 35–65 years) of the T company health

insurance society who underwent serum *H. pylori* antibody tests in a health checkup from 2008 and 2018.

Measures: We analyzed the *H. pylori* infection rate among participants aged 35 years from 2008 to 2018 and participants aged 35, 40, 45, and 50–65 years in 2018 based on the results of serum antibody tests during the health checkups. In the 2018 analysis, we considered all participants who had undergone eradication treatment for *H. pylori* as infected, regardless of the antibody test results, to reduce the influence of previous treatment. Trend analyses were performed using Joinpoint analysis.

Results: *H. pylori* was detected in 1,290 out of 9,325 participants aged 35 years. The annual infection rates showed a linear downward trend (slope = -0.65) as follows: 16.6% in 2008 to 10.1% in 2018. In the 2018 analysis, 2,863 out of 11,434 participants were positive for *H. pylori*; moreover, there was an upward trend of the infection rate with advanced age (10.8% [35 years] to 47.3% [65 years]). The trend showed a Joinpoint, with the trend changing significantly at the age of 50 years (first trend: 35–50 years [slope = 0.57]; second trend: 50–65 years [slope = 1.51]). Although both were upward trends, the second trend was steeper ($P < 0.05$).

Conclusions: Over the last 11 years, there has been a decrease in the infection rate of *H. pylori* in Japanese 35–year olds. The infection rate in 2018 was high with advanced age**.** There is a consistent declining trend of the *H. pylori* infection rate in Japan.

Strengths and limitations of this study

- We included very recent data from the general population (non-patients who underwent medical checkups without special intentions) and applied Joinpoint trend analysis to analyze trends in the *H. pylori* infection rates in Japan.
- We enrolled a large number of participants in a single group over a relatively long period.
- This study suggests a trend of the infection rate of *H. pylori* using data from 35-year-olds.
- In the 2018 analysis, the participants' history of eradication treatment for *H.* pylori was determined through questionnaires.
- This study has limitations regarding the possibility of group bias (including occupational, sex ratio, and medical history).

INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacterium that is often found in the human stomach. *H. pylori* is among the causes of chronic gastritis, duodenal ulcers, gastric ulcers, immune thrombocytopenia, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. The International Agency for Research on Cancer Working group, which is a part of the World Health Organization, classified *H. pylori* as a Group 1 carcinogen for gastric cancer in 1994.[1] Moreover, they recognized eradication therapy for *H. pylori* in

asymptomatic populations as efficient for preventing gastric cancer and recommended introducing population-based *H. pylori* screening and treatment programs.[2]

H. pylori test-and-treat strategy for preventing gastric cancer is considered more effective in regions with a high incidence of gastric cancer.[3] The incidence and mortality rates of gastric cancer are high; moreover, *H. pylori* could be involved > 90% in Japan.[4 5] Additionally, the infection rate of *H. pylori* in Japan is higher than that in other developed countries. [6] Accordingly, the "test-and-treat" strategy for *H. pylori* could be a good measure for preventing gastric cancer in Japan. In 2013, the national health insurance scheme covered the *H. pylori* eradication therapy for chronic gastritis in Japan. Several groups in Japan, including company health insurance societies and local municipalities, have introduced *H. pylori* screening tests for asymptomatic people during medical check-ups for the prophylactic intervention of gastric cancer.

Decreasing the *H. pylori* infection rate could reduce the incidence rate of gastric cancer[7] and reduce the positive predictive value of *H. pylori* screening. Therefore, decreasing the *H. pylori* infection rate in the population may negatively affect the cost-effectiveness of the "test-and-treat" strategy for asymptomatic groups. It is important to elucidate the prevalence of *H. pylori* and its trends to predict the infection rate and plan future strategies. There has been a decrease in the worldwide prevalence of *H. pylori*,[6] with several Japanese

studies reporting similar results.[8] However, most of these studies had small sample sizes or included specific participants, including hospital visitors, or meta-analyses. To our knowledge, there have been no recent large-scale studies on the annual prevalence and trend of infection rates of *H. pylori* in Japan. [9,8,10] Additionally, several studies have reported that the *H. pylori* infection rates become steady at approximately 10% in several low-prevalence regions, including European countries. [6 11 12] Watanabe et al. suggested that the declining trend of the *H. pylori* prevalence in Japan appears to become dull.[10] This study aimed to elucidate the recent trend in the infection rate of *H. pylori* and whether it showed a significant change.

Using data from health checkups in a company health insurance society, this retrospective cross-sectional study aimed to clarify the recent 11-year trend of *H. pylori* infection rate in 35-year-olds and *H. pylori* infection rates in 2018 according to age.

MATERIALS AND METHODS

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 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' data, including medical questionnaires and blood test results, were anonymously obtained from the annual health checkup database of the health insurance society. We excluded data from individuals who refused academic use of their data.

Statistical analysis

First, we analyzed data obtained from 35-year-old participants between 2008 and 2018 to determine trends in *H. pylori* infection rates ("35-year-old analysis"), with positive results of serum antibody tests for *H. pylori* indicating *H. pylori* infection. We calculated the annual infection rates based on the antibody test results. Subsequently, we analyzed the trend of the rates. Second, we analyzed data from participants aged 35, 40, 45, and 50–65 years old obtained in 2018 according to age to determine generational differences in the infection rates ("2018 analysis").

In the 2018 analysis, participants who tested positive for antibodies were considered as infected. Further, to reduce the influence of eradication treatment on the infection rate, all participants with a history of eradication treatment of *H. pylori* infection were defined as positive regardless of their tests results for *H. pylori* antibody, with the assumption that a history of eradication treatment indicates a previous infection. Similarly, we analyzed sex differences in both analyses.

We performed Joinpoint Trend Analysis[13] to identify trends in the infection rate and their changes over time using Joinpoint Regression Program 4.9.0.0.[14] Statistical significance was set at $P < 0.05$. We measured serum anti-*Helicobacter pylori* IgG using 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,[15] with values above this value being classified as positive. Data with missing or ambiguous figures were excluded from the analysis.

Patient and public involvement

No patients were involved in this study. T company health insurance society acknowledged the importance of this study concept and allowed the collection of the participants' data. The results of this study are published as a report.

Ethical approval

This study protocol was reviewed and approved by the Institutional Review Board of Tokyo Medical University (T2019-0044). Following the Ethical Guidelines for Medical and Health Research Involving Human Subjects,[16] the study information was shown on the websites of the institutions where the researchers or participants belonged. Participants' consent for using data was obtained through an opt-out option.

RESULTS

There were 9,793 and 12,327 participants in the 35-year-old and 2018 analyses, respectively, with 592 participants overlapping in both analyses. In the 35-year-old analysis, 468 participants were excluded for having missing (n = 314) ambiguous data (n = 154) in the records, with 9,325 participants (7,586 men; 1,739 women) being included in the final analysis. In the 2018 analysis, 893 participants were excluded for having missing (n = 875) ambiguous data (n = 18) in the records, with 11,434 participants (9,580 men; 1,854 women) being included in the final analysis (Figure 1).

The 35-year-old analysis

In the 35-year-old analysis, 1,290 (1,100 male; 190 female) participants were *H. pylori-infected*. In Joinpoint analysis, infection rates showed a linear downward trend with advanced years (16.6% in 2008 to 10.1% in 2018, with a slope of -0.65 [$P < 0.05$]). This trend lacked a Joinpoint at which the trend significantly changed (Figure 2).

The 2018 analysis

In the 2018 analysis, 2,863 (2,432 male; 431 female) participants were infected with *H. pylori*. The infection rates showed a trend of increasing positive rates with advanced age (10.8% in 35 years to 47.3% in 65 years). This trend had a Joinpoint at the age of 50 years (95% CI: 45–57), with two different trends in the slope before and after the point. Specifically, the first and second trends were 35–50 years (slope = 0.57) and 50–65 years (slope = 1.51). Both trends showed linear upward trends with age, with the second trend being significantly steeper than the first trend ($P < 0.05$) (Figure 3).

Sex difference in the trends of *H.pylori* infection rate

In the 35-year-old analysis, there were no significant sex differences in terms of the trend in the infection rate. In the 2018 analysis, the infection rates in both sexes showed an

upward trend with advanced age, moreover, analysis of men, but not women, showed a Joinpoint at the age of 54 years (95% CI: 45–58 years) (Supplementary Figure 1).

DISCUSSION

This study investigated the trend in the prevalence of *H. pylori* infection in Japan based on large-scale health checkup data. In the 35-year-old analysis, the infection rate showed a linear declining trend from 2008 to 2018. This demonstrates a declining trend of the *H. pylori* infection rate in this large Japanese general population.

In the 35-year-old analysis, the infection rate straightforwardly reached approximately 10%; further, this downward trend did not significantly change during the observation period. In the 35-year-old analysis, the infection rates were significantly less affected by eradication treatment; therefore, this finding could well describe the trend of the incidence rate of *H. pylori* infections in Japan. If the downward trend (slope = 0.65) observed in the 35-year-old analysis continues, the infection rate will reach nearly zero around 2035. Contrastingly, recent studies on junior high school students (age: 12–15 years) in Japan have demonstrated that the infection rate of this generation when they reach 35 years at around 2035 will be approximately 3–5%,[17-20] which is higher than our prediction. This

inconsistency suggests that the decrease in the infection rate may have slowed down.

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. Further, there was a Joinpoint at the age of 50 years, which indicates a change affecting the *H. pylori* infection near this age (Figure 3). Chronic *H. pylori* infection is mostly established in the human stomach during childhood.[21 22] Drinking water and family members are among the sources of *H. pylori* infection.[23] 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 a rapid increase in water supply penetration and a decrease in the average number of households.[24 25] This rapid environmental change may have influenced the establishment of *H. pylori* infection; consequently, there was a rapid decrease in the prevalence of this bacterium during this era. Watanabe et al. revealed changes in the declining trend of *H.pylori* infection rate and indicated an effect of environmental changes on the infection rate,[10] which is consistent with our findings.

Participants in the 35-year-old analysis were born after 1973; therefore, they may have not undergone rapid environmental changes as those in 1955–1972. The 35-year-old analysis revealed a recent gradual decrease in the *H. pylori* infection rate. This suggests that

factors other than hygiene and family structure may influence infection establishment. As aforementioned, *H. pylori* infections are likely to be established during childhood through parent-to-child transmission.[22] In addition to hygienic and environmental improvements, the spread of ready-made baby food after around 1970 may have contributed to the decreased *H. pylori* infection rate.[26] With the recently increasing recognition of *H. pylori* in the general population and coverage of eradication treatment through national insurance, there has been an increase in the number of *H. pylori* eradication treatments in Japan.[27] If treatment decreases the infection rate in child-rearing generation, it could accelerate the declining speed of the infection rates in the next generations.

In the 2018 analysis, men, but not women, showed a Joinpoint trend. This suggests sex differences in the trend of *H. pylori* infection; however, given the sex bias in the number of participants (9580 men and 1854 women), we cannot conclude about the sex difference. This should be investigated in future studies.

When conducting *H. pylori* screening tests for prophylactic purposes, the prevalence in a target group should be considered to evaluate the effectiveness of the strategy. We observed a decreasing infection rate of *H. pylori* in Japan. In the future, the infection rate may reach zero; accordingly, there would be a decreased importance of screening tests for

this bacterium in asymptomatic people. A study on the cost-effectiveness of the test-and-treatment strategy for *H. pylori* revealed that it remained effective even with a low infection rate of approximately 5%.[28] Our findings could inform future public health strategies. Moreover, considering the decrease in *H. pylori* prevalence, *H. pylori* infection-negative gastric cancer has lately been receiving attention.[29 30 31] Research for risk factors of gastric cancer other than *H. pylori* is also needed.

Limitations

This study has several limitations. First, there might have been selective bias, including age, sex, occupation, region, and nationality (possibly including several workers who were born and raised in countries other than Japan). Several studies have analyzed differences in the infection rates according to sex, occupation, and region, with a study reporting a higher infection rate in men; however, there remains no consensus regarding these biases.[32-34] A recent study showed that employees in a large company are in better health than those in a small one.[35] The size of the target group could have yielded a bias. However, this study could have insignificant healthy candidate bias since we targeted all health society members. We could not determine the number structure of all society members, which could limit the generalization of our findings to the general population. Heterogeneity of age gaps between age groups and limitation of the target ages may have weakened analyses, especially

in younger age groups. Additionally, the history of *H. pylori* eradication may have influenced our findings. In 2008, T company insurance society performed serum *H. pylori* antibody screening tests for all its members. Therefore, there may have been a higher proportion of post-eradication cases in our study than in the general population. We attempted to reduce the influence of eradication treatment by classifying patients who underwent eradication treatment as infected. However, history information acquired through a self-reported questionnaire could have contained inaccuracies, including recall bias.[36] In the 35-year-old analysis, we could not obtain information regarding previous eradication treatment. Moreover, we performed analysis based on the assumption that the rate of eradication treatment among participants in the 35-year-old analysis was low due to their younger age and that treatment has an insignificant influence on the infection rate. A follow-up survey of the same society between 2018 and 2020 showed that the rate of eradication treatment was 0.9%, 2.1%, and 1.4% in 2018, 2019, and 2020, respectively. Although this supports our assumption, it indicates the possibility of errors of 1%–2 % in the infection rates of the 35-year-old analysis. Additionally, previous medical history; medications; and measurement biases, including test characteristics and threshold application in the test (including high-negative issues), could have influenced our results.[37 38]

CONCLUSION

Our findings demonstrated a decrease in the infection rate of H. pylori among 35-year-olds in Japan from 2008 to 2018. The infection rate of *H. pylori* may continue to decrease in the future. We expect the infection rate of *H. pylori* to continue decreasing, and it would be difficult to rely solely on the *H. pylori* test and treatment strategy to achieve gastric cancer prevention. Other risk factors of gastric cancer other than *H. pylori* should be considered.

Acknowledgment

We would like to acknowledge the T company health insurance society. We would like to thank Editage (www.editage.com) for the English language editing.

Footnotes

Contributors: SA designed the study, analyzed the data, and drafted the manuscript. Y Hirayama contributed to the study design and performed general supervision of a whole study. JO, Y Harada, and T Toi assisted in conducting the study, interpreting the results, and revising the manuscript. KK and TK contributed to data collection and provided advice and opinions from an expert perspective. TT contributed to data analysis and revising the manuscript from statistical and public health perspectives. All authors read and approved the final manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: None declared.

Patient consent for publication: Not required.

Ethics approval: The institutional review boards of Tokyo Medical University (T2019-0044)

Provenance and peer review: Not commissioned; externally peer-reviewed.

Data sharing statement: Data is available in a public, open access repository.

Figshare, https://figshare.com/s/e94123c7270ca1e09084,

DOI: 10.6084/m9.figshare.14594571, CC BY

REFERENCES

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, Liver Flukes and Helicobacter pylori. Lyon (FR): International Agency for Research on Cancer 1994.

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

3. Ford AC, Forman D, Hunt RH, et al. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174. doi: 10.1136/bmj.g3174

4. Center for Cancer Control and Information Services, National Cancer Center. CANCER STATISTICS IN JAPAN '19 [updated 17 April 2020. Available from: https://ganjoho.jp/en/professional/statistics/brochure/2019_en.html accessed 22 Dec 2020.

5. Matsuo T, Ito M, Takata S, et al. Low prevalence of Helicobacter pylori-negative gastric cancer among Japanese. *Helicobacter* 2011;16(6):415-9. doi: 10.1111/j.1523-5378.2011.00889.x [published Online First: 2011/11/09]

6. Peleteiro B, Bastos A, Ferro A, et al. Prevalence of Helicobacter pylori infection worldwide: a systematic review of studies with national coverage. *Dig Dis Sci* 2014;59(8):1698-709. doi: 10.1007/s10620-014-3063-0 [published Online First: 2014/02/25]

7. Tsuda M, Asaka M, Kato M, et al. Effect on Helicobacter pylori eradication therapy against gastric cancer in Japan. *Helicobacter* 2017;22(5) doi: 10.1111/hel.12415 [published Online First: 2017/08/05]

8. Wang C, Nishiyama T, Kikuchi S, 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. doi: 10.1038/s41598-017-15490-7 [published Online First: 2017/11/16]

9. Inoue M. Changing epidemiology of Helicobacter pylori in Japan. *Gastric Cancer* 2017;20(Suppl 1):3-7. doi: 10.1007/s10120-016-0658-5 [published Online First: 2016/10/21]

10. Watanabe M, Ito H, Hosono S, et al. Declining trends in prevalence of Helicobacter pylori infection by birth-year in a Japanese population. *Cancer Sci* 2015;106(12):1738-43. doi: 10.1111/cas.12821 [published Online First: 2015/09/24]

11. Carmack SW, Genta RM. Helicobacter pylori seroprevalence in symptomatic veterans: a study of 7310 patients over 11 years. *Helicobacter* 2009;14(4):298-302. doi: 10.1111/j.1523-5378.2009.00693.x

12. den Hoed CM, Vila AJ, Holster IL, et al. Helicobacter pylori and the birth cohort effect: evidence for stabilized colonization rates in childhood. *Helicobacter*

2011;16(5):405-9. doi: 10.1111/j.1523-5378.2011.00854.x [published Online First: 2011/09/20]

13. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335-51. doi: 10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z [published Online First: 2000/01/29]

14. Joinpoint Regression Program [program]. Version 4.9.0.0 version: Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute., March 2021.

15. Komatsu Y, Sugiyama T, Asaka M. Helicobacter pylori kansenshindan ni okeru nihonjinkabu wo siyou sita ELISA kit " E-plate eiken H.pylori koutai" no yuyousei no kentou [Study of effectiveness of E-plate eiken which is ELAISA kit using Japanese strain in diagnose of Helicobacter pylori infection]. *The Journal of Clinical Laboratory Instruments and Reagents* 2001;24(5):331-35.

16. Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health Research Involving Human Subjects 2015 [Available from: https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf accessed 6 Dec 2020.

17. Kusano C, Gotoda T, Ishikawa H, et al. The administrative project of Helicobacter pylori

infection screening among junior high school students in an area of Japan with a high incidence of gastric cancer. *Gastric Cancer* 2017;20(Suppl 1):16-19. doi: 10.1007/s10120-017-0688-7 [published Online First: 2017/01/18]

18. Honma H, Nakayama Y, Kato S, et al. Clinical features of Helicobacter pylori antibody-positive junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2018:e12559. doi: 10.1111/hel.12559 [published Online First: 2018/12/06]
19. Nakayama Y, Lin Y, Hongo M, et al. Helicobacter pylori infection and its related factors in junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2017;22(2) doi: 10.1111/hel.12363 [published Online First: 2016/10/28]
20. Kakiuchi T, Matsuo M, Endo H, et al. A Helicobacter pylori screening and treatment program to eliminate gastric cancer among junior high school students in Saga Prefecture: a preliminary report. *J Gastroenterol* 2019 doi: 10.1007/s00535-019-01559-9 [published Online First: 2019/02/17]
21. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and Helicobacter pylori. *J Infect Dis* 1993;168(1):219-21. doi: 10.1093/infdis/168.1.219
22. O'Ryan ML, Lucero Y, Rabello M, et al. Persistent and transient Helicobacter pylori infections in early childhood. *Clin Infect Dis* 2015;61(2):211-8. doi: 10.1093/cid/civ256
23. Ueda M, Kikuchi S, Kasugai T, et al. Helicobacter pylori risk associated with childhood

home environment. *Cancer Sci* 2003;94(10):914-8. doi: 10.1111/j.1349-7006.2003.tb01375.x [published Online First: 2003/10/15]

24. JAPAN WATER WORKS ASSOCIATION. Water Supply in Japan 2017 [Available from: http://www.jwwa.or.jp/jigyou/kaigai_file/2017WaterSupplyInJapan.pdf accessed Dec 22 2020.

25. Ministry of Health, Labour and Welfare. General Welfare and Labour Japan [Available from: https://www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf accessed 1st Oct 2020.

26. Council JBF. Seisan Tokei [Production statistics] Japan [Available from: https://www.baby-food.jp/link/ayumi-jikei.html accessed 11 Dec 2020.

27. Hiroi S, Sugano K, Tanaka S, et al. Impact of health insurance coverage for Helicobacter pylori gastritis on the trends in eradication therapy in Japan: retrospective observational study and simulation study based on real-world data. *BMJ Open* 2017;7(7):e015855. doi: 10.1136/bmjopen-2017-015855 [published Online First: 2017/08/02]

28. Kowada A. Cost-effectiveness of Helicobacter pylori screening followed by eradication treatment for employees in Japan. *Epidemiol Infect* 2018;146(14):1834-40. doi: 10.1017/S095026881800208X [published Online First: 2018/07/31]

29. Kato S, Matsukura N, Tsukada K, et al. Helicobacter pylori infection-negative gastric

cancer in Japanese hospital patients: Incidence and pathological characteristics. *Cancer Sci* 2007;98(6):790-94. doi: https://doi.org/10.1111/j.1349-7006.2007.00478.x

30. Yamamoto Y, Fujisaki J, Omae M, et al. Helicobacter pylori-negative gastric cancer: characteristics and endoscopic findings. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society* 2015;27(5):551-61. doi: 10.1111/den.12471 [published Online First: 2015/03/27]

31. Takita M, Ohata K, Inamoto R, et al. Endoscopic and histological features of Helicobacter pylori-negative differentiated gastric adenocarcinoma arising in the antrum. *JGH open : an open access journal of gastroenterology and hepatology* 2021;5(4):470-77. doi: 10.1002/jgh3.12518 [published Online First: 2021/04/17]

32. Kheyre H, Morais S, Ferro A, et al. The occupational risk of Helicobacter pylori infection: a systematic review. *Int Arch Occup Environ Health* 2018;91(6):657-74. doi: 10.1007/s00420-018-1315-6

33. Ueda J, Gosho M, Inui Y, et al. Prevalence of Helicobacter pylori infection by birth year and geographic area in Japan. *Helicobacter* 2014;19(2):105-10. doi: 10.1111/hel.12110 [published Online First: 2014/02/11]

34. Ferro A, Morais S, Pelucchi C, et al. Sex differences in the prevalence of Helicobacter pylori infection: an individual participant data pooled analysis (StoP Project). *Eur J*

Gastroenterol Hepatol 2019;31(5):593-98. doi: 10.1097/MEG.0000000000001389 [published Online First: 2019/03/07]

35. Kanamori S, Tsuji T, Takamiya T, et al. Size of company of the longest-held job and mortality in older Japanese adults: A 6-year follow-up study from the Japan Gerontological Evaluation Study. *J Occup Health* 2020;62(1):e12115. doi: 10.1002/1348-9585.12115 [published Online First: 2020/06/10]

36. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43(1):87-91. doi: 10.1016/0895-4356(90)90060-3

37. Miftahussurur M, Yamaoka Y. Diagnostic Methods of Helicobacter pylori Infection for Epidemiological Studies: Critical Importance of Indirect Test Validation. *BioMed research international* 2016;2016:4819423. doi: 10.1155/2016/4819423 [published Online First: 2016/02/24]

38. Inoue M, Sawada N, Goto A, et al. High-Negative Anti-Helicobacter pylori IgG Antibody Titers and Long-Term Risk of Gastric Cancer: Results from a Large-Scale Population-Based Cohort Study in Japan. *Cancer Epidemiol Biomarkers Prev* 2020;29(2):420-26. doi: 10.1158/1055-9965.EPI-19-0993 [published Online First: 2019/12/13]

FIGURE LEGENDS

Figure 1

Numbers of participants

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.

Figure 2

Infection rates of Helicobacter pylori at 35 years old from 2008 to 2018 (n = 9,325)

Note. Infection rates at 35 years linearly decreased from 16.6% in 2008 to 10.1% in 2018, with a slope of -0.65. There was no Joinpoint. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

Figure 3

Infection rates of Helicobacter pylori according to age in 2018 (n = 11,434)

Note. Infection rates increased in two trends: 10.8% at 35 years to 18.2% at 50 years with a slope of 0.57; 18.2% at 50 years to 47.3% at 65 years old with a slope of 1.51. There was a Joinpoint at the age of 50 years. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

Supplementary Figure 1

Sex difference in the trends of Helicobacter pylori infection rate in 2018

Note. The two graphs show trends of *the H. pylori* positive rate according to age in 2018 in men and women. There were two trends and Joinpoint in men aged 54 years but not in women. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

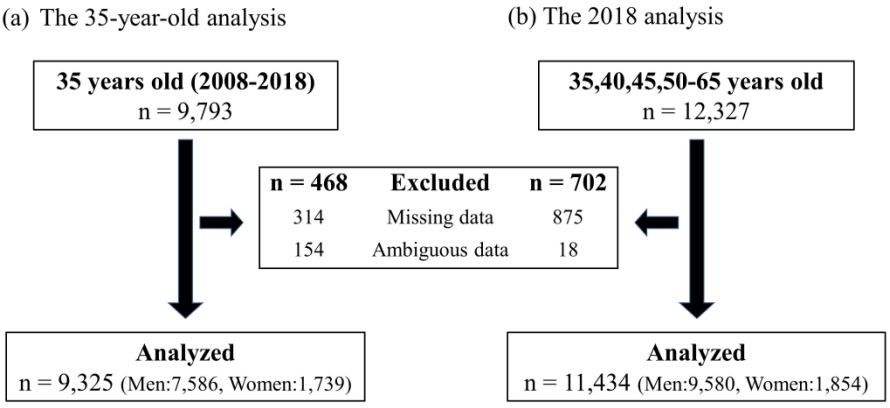
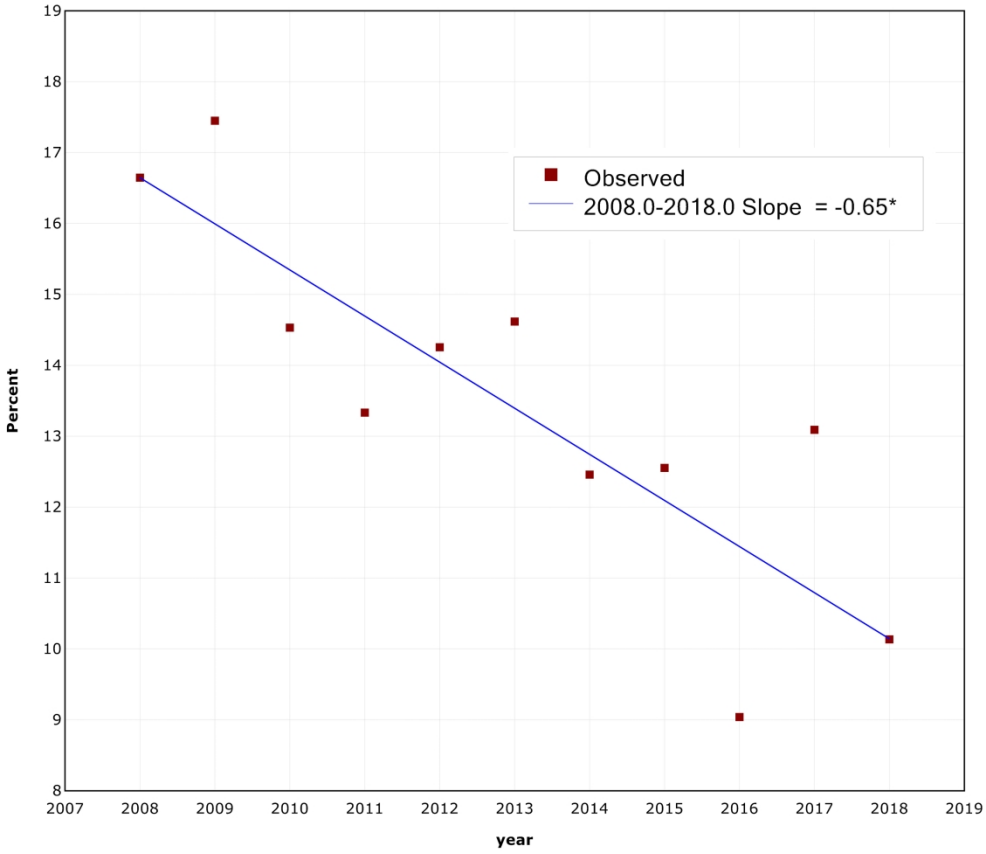


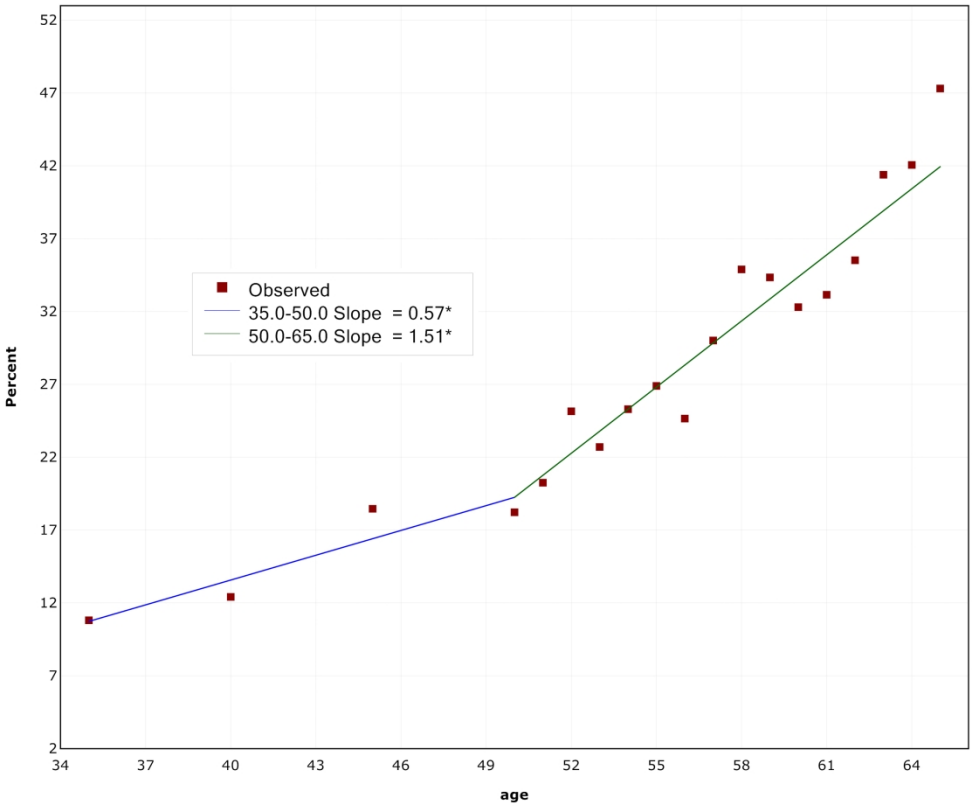
Figure 1: *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The 2018 analysis: participants aged 35–65 years in 2018.

338x190mm (300 x 300 DPI)



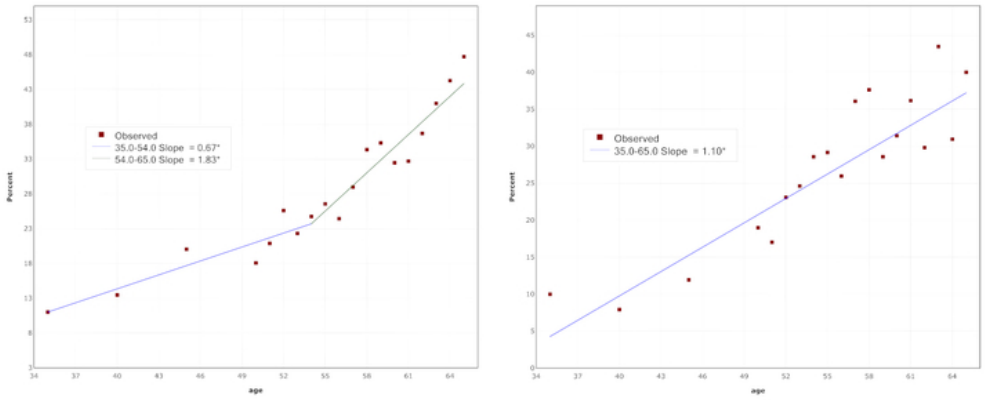
Note. Infection rates at 35 years linearly decreased from 16.6% in 2008 to 10.1% in 2018, with a slope of -0.65. There was no Joinpoint. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

141x122mm (600 x 600 DPI)



Note. Infection rates increased in two trends: 10.8% at 35 years to 18.2% at 50 years with a slope of 0.57; 18.2% at 50 years to 47.3% at 65 years old with a slope of 1.51. There was a Joinpoint at the age of 50 years. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

126x104mm (600 x 600 DPI)



Men Women

Note. The two graphs show trends of the H. pylori positive rate according to age in 2018 in men and women. There were two trends and Joinpoint in men aged 54 years but not in women. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

30x13mm (600 x 600 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	1-2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	5-7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5-6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-7
Bias	#9	Describe any efforts to address potential sources of bias	13-14
Study size	#10	Explain how the study size was arrived at	n/a

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	n/a
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6-7
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8-9
Participants	#13b	Give reasons for non-participation at each stage	8
Participants	#13c	Consider use of a flow diagram	8
Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5-6, 13-

		clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	14
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8-9
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	8-9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13-14

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13

Other Information

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

BMJ Open

Changes in prevalence of *Helicobacter pylori* in Japan from 2008 to 2018: a repeated cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058774.R1
Article Type:	Original research
Date Submitted by the Author:	14-Jul-2022
Complete List of Authors:	Abiko, Soichiro; Tokyo Medical University, Department of General Medicine and Primary Care Hirayama, Yoji; Tokyo Medical University, Department of General Medicine and Primary Care Otaki, Junji; Tokyo Medical University, Department of Medical Education; Tokyo Medical University, Department of General Medicine and Primary Care Harada, Yoshimi; Tokyo Medical University, Department of Medical Education; Tokyo Medical University, Department of General Medicine and Primary Care Kawakami, Kohei; Tokyo Medical University, Department of General Medicine and Primary Care Toi, Takahiro; Tokyo Medical University, Department of General Medicine and Primary Care Takamiya, Tomoko; Tokyo Medical University, Department of Preventive Medicine and Public Heatlh Kawai, Takashi; Tokyo Medical University, Department of Gastroenterological Endoscopy
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Gastroenterology and hepatology, Health policy
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY, HEALTH ECONOMICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Changes in prevalence of *Helicobacter pylori* in Japan from 2008 to 2018: a repeated cross-sectional study

Author names: Soichiro Abiko[1], Yoji Hirayama[1], Junji Otaki[2 1], Yoshimi Harada[2 1], Kohei Kawakami[1], Takahiro Toi[1], Tomoko Takamiya[3], Takashi Kawai[4]

Author Affiliations:

1. Department of General Medicine and Primary Care, Tokyo Medical University, Tokyo, Japan.

2. Department of Medical Education, Tokyo Medical University, Tokyo, Japan.

3. Department of Preventive Medicine and Public Health, Tokyo Medical University, Tokyo, Japan.

4. Department of Gastroenterological Endoscopy, Tokyo Medical University, Tokyo, Japan.

Corresponding Author: Soichiro Abiko

Email: s_abiko1@tokyo-med.ac.jp

Word count: 2,919

ABSTRACT

Objectives: To understand the recent prevalence and time-trends of *Helicobacter pylori* infection rates in the Japanese population.

Design: Repeated cross-sectional study

Participants: A total of 22,120 workers (age: 35–65 years) from one Japanese company, who underwent serum *H. pylori* antibody tests in a health checkup between 2008 and 2018.

Measures: *H. pylori* infection rates among participants aged 35 years from 2008 to 2018, and participants aged 35, 40, 45, and 50–65 years in 2018, based on the results of serum antibody tests were analyzed. In the 2018 analysis, in addition to the antibody test results, all participants who had undergone eradication treatment for *H. pylori* were considered as infected. Trends were examined using Joinpoint analysis.

Results: *H. pylori* were detected in 1,100 of 7,586 male, and 190 of 1,739 female participants aged 35 years. Annual infection rates among those aged 35 years showed linear downward trends as follows: 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) without joinpoints. In the 2018 analysis, 2,432 of 9,580 men and 431 of 1,854 women were *H. pylori* positive. Infection rates tended to increase with older age (men: 11.0% [35 years] to 47.7% [65 years], women: 10.0% [35 years] to 40.0% [65 years]), and showed joinpoints in both sexes (men: 54 years, women: 45 years). Although both the first and second trends were upward, the second trends for both men and women were steeper than the first trends ($P < 0.05$).

Conclusions: Our study demonstrated that in the previous 11 years, infection rates of *H. pylori* in Japanese 35-year-old male and female workers have constantly decreased, and furthermore, analysis of various age groups showed joinpoints around 50 years, suggesting a

consistent declining trend in *H. pylori* infection rates in Japan.

Strengths and limitations of this study

• This study presents a recent 11-year time trend of *H. pylori* infection rates based on *H. pylori* serum antibody test results of 35-year-old workers from one large company with many branches around Japan, using Joinpoint trend analysis, suggesting a consistent declining trend in *H. pylori* infection rates in both men and women in Japan.

• The 2018 data compared infection rates by age group (35, 40, 45, and 50–65 years), taking into account the history of *H. pylori* eradication treatment obtained by a questionnaire, in addition to antibody testing, demonstrating a joinpoint at around 50 years for both men and women, and a substantially lower infection rate in younger participants.

• The main limitation of this study is the generalizability of the results to the general Japanese population because the study subjects were company employees.

INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacterium that is often found in the human

stomach. *H. pylori* infection is known to be closely associated with chronic gastritis, duodenal ulcers, gastric ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[1 2 3 4] The International Agency for Research on Cancer Working group, which is a part of the World Health Organization (WHO), classified *H. pylori* as a Group 1 carcinogen for gastric cancer in 1994.[5] 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".[6]

H. pylori test-and-treat strategy for preventing gastric cancer is considered more effective in regions with a high incidence of gastric cancer.[7] The incidence and mortality rates of gastric cancer are relatively high in Japan compared with other countries. Moreover, *H. pylori* infection is thought to be involved in more than 90% of gastric cancer cases in Japan.[8 9] In addition, the infection rate of *H. pylori* in Japan is higher than that in other developed countries.[10] Accordingly, the "test-and-treat" strategy for *H. pylori* could be a good measure for preventing gastric cancer in Japan. In 2013, the national health insurance scheme covered the *H. pylori* eradication therapy for chronic gastritis in Japan. Several groups in Japan, including company health insurance societies and local municipalities, have introduced *H. pylori* screening tests for asymptomatic people during medical check-ups for the prophylactic

intervention of gastric cancer.

Decreasing the *H. pylori* infection rate could reduce the incidence rate of gastric cancer[11] and reduce the positive predictive value of *H. pylori* screening. Therefore, decreasing the *H. pylori* infection rate in the population may negatively affect the cost-effectiveness of the "test-and-treat" strategy for asymptomatic groups. It is important to elucidate the current prevalence of *H. pylori* infection and its trends over time, to predict future infection rates and plan test strategies for the future. There has been a decrease in the worldwide prevalence of *H. pylori*,[10] with several Japanese studies reporting similar results.[12] However, most of these studies had small sample sizes or included specific participants, including hospital visitors. To our knowledge, there have been no recent large-scale studies on the prevalence and time-trend of infection rates of *H. pylori* in Japan.[12 13 14] In addition, several studies have reported that the *H. pylori* infection rates become steady at approximately 10% in several low-prevalence regions, including European countries.[10 15 16] 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.[14] Our present study aimed to elucidate the recent trends in the infection rates of *H. pylori*, including the rates after 2013, which is the year that the health insurance system in Japan began to cover *H. pylori* eradication therapy for chronic gastritis, and whether they showed significant changes with time.

Using data from health checkups in a company health insurance society, this repeated cross-sectional study aimed to clarify the recent 11-year trend of *H. pylori* infection rate in 35-year-olds and *H. pylori* infection rates in 2018 according to age, stratified by sex.

MATERIALS AND METHODS

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,[17] with values above this being classified as positive. Anonymized participants' data, including medical questionnaires and blood test results, were obtained from the annual health checkup database of the health insurance society. We excluded data from individuals who refused academic use of their data.

Statistical analysis

First, data obtained from 35-year-old participants between 2008 and 2018 were analyzed to determine time-trends in *H. pylori* infection rates ("35-year-old analysis") stratified by sex. Positive results of serum antibody tests for *H. pylori* were defined as *H. pylori* infection. Annual infection rates were calculated based on the antibody test results. Subsequently, we analyzed the time-trend of the rates.

Second, we analyzed data from participants aged 35, 40, 45, and 50–65 years old obtained in 2018 according to age stratified by sex to determine generational differences in the infection

rates ("2018 analysis"). In the 2018 analysis, participants who tested positive for antibodies were considered as infected. Further, to reduce the influence of eradication treatment on the infection rate, all participants with a history of eradication treatment of *H. pylori* infection were defined as positive regardless of their tests results for *H. pylori* antibody, with the assumption that a history of eradication treatment indicates a previous infection.

We performed Joinpoint Trend Analysis[18] to identify trends in the infection rate and their changes over time using Joinpoint Regression Program 4.9.0.0.[19] 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. Linear Model was selected in the analyses. Statistical significance was set at $P < 0.05$. Data with missing or ambiguous figures were excluded from the analysis.

Patient and public involvement

After discussions with representatives of the health insurance society about this study, the health insurance society acknowledged the importance of the concept of our study, and permitted us to collect and use participant data from its database. The results of this study are published as a report.

Ethical approval

This study protocol was reviewed and approved by the Institutional Review Board of Tokyo Medical University (T2019-0044). Following the Ethical Guidelines for Medical and Health Research Involving Human Subjects,[20] the study information was shown on the websites of the institutions where the researchers or participants belonged. Participants' consent for using data was obtained through an opt-out option.

RESULTS

There were 9,793 and 12,327 participants in the 35-year-old and 2018 analyses, respectively, with 592 participants overlapping in both analyses. In the 35-year-old analysis, 468 participants were excluded for having missing (n = 314) or ambiguous data (n = 154) in the records, with 9,325 participants (7,586 men; 1,739 women) being included in the final analysis. In the 2018 analysis, 893 participants were excluded for having missing (n = 875) or ambiguous data (n = 18) in the records, with 11,434 participants (9,580 men; 1,854 women) being included in the final analysis (Figure 1).

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. Both first and second trends showed a linear increase with age, with the second trends being significantly steeper than the first trends ($P < 0.05$) (Figure 3).

DISCUSSION

This study investigated the 11-year time-trend from 2008 to 2018, and the trend by age in 2018 regarding the prevalence of *H. pylori* infection in Japanese workers stratified by sex

based on large-scale health checkup data. In the 35-year-old analysis, the infection rate showed a linear declining trend from 2008 to 2018 both in men and women. This provided a good estimate of the *H. pylori* infection trends in Japan, as this study was conducted among workers in a large company with branch offices throughout Japan, and its workers, including workers in the branch offices, were the subjects of this study.

In the 35-year-old analysis, the infection rate decreased linearly to approximately 10% both in men and women; further, this downward trend did not significantly change during the observation period. We assumed that the participants in this analysis, who were all 35 years old were less affected by eradication treatment than older participants; and therefore, the results may closely reflect the actual trend of the incidence rate of *H. pylori* infections in Japan. If the downward trends (slope = −0.65 in men or slope = −0.51 in women) observed in the 35-year-old analysis continues, the infection rate is expected to reach nearly zero by about 2035. In contrast, recent studies on junior high school students (aged: 12–15 years) in Japan have demonstrated that the infection rate of this generation when they reach 35 years at about 2035 will be approximately 3% to 5%,[21 22 23 24] which is higher than our prediction. This inconsistency suggests that the decrease in the infection rate may have slowed down.

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. Furthermore, there were joinpoints around the age of 50 years (54 years in men [95% CI: 45–58] and 45 years in women [95% CI: 45–51]), which implies the existence of some type of change affecting the *H. pylori* infection rate in people of this generations (Figure 3). Chronic *H. pylori* infection is mostly established in the human stomach during childhood.[25 26] Drinking water and family members are among the sources of *H. pylori* infection.[27] 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 a rapid increase in water supply penetration and a decrease in the average number of households.[28 29] These rapid environmental changes may have influenced the establishment of *H. pylori* infection; consequently, there was a rapid decrease in the prevalence of this bacterium during this era. Watanabe et al. revealed changes in the declining trend of *H. pylori* infection rate and indicated an effect of environmental changes on the infection rate,[14] which is consistent with our findings.

Participants in the 35-year-old analysis were born after 1973; therefore, they may have not experienced the rapid environmental changes that those who were born during the period of high economic growth (1955–1972) had experienced. The 35-year-old analysis revealed a recent gradual decrease in the *H. pylori* infection rate. This suggests that factors other than

hygiene and family structure may influence infection establishment. As aforementioned, *H. pylori* infections are likely to be established during childhood through parent-to-child transmission.[26] In addition to hygienic and environmental improvements, the spread of ready-made baby food after around 1970 may have contributed to the decreased *H. pylori* infection rate.[30] With the recently increasing recognition of *H. pylori* in the general population and coverage of eradication treatment through national insurance, there has been an increase in the number of *H. pylori* eradication treatments in Japan.[31] If treatment decreases the infection rate in child-rearing generation, it could accelerate the declining speed of the infection rates in the next generations.

When conducting *H. pylori* screening tests for prophylactic purposes, the prevalence in a target group should be considered to evaluate the effectiveness of the strategy. We observed a decreasing infection rate of *H. pylori* in Japan. In the future, the infection rate may reach zero; accordingly, there would be a decreased importance of screening tests for this bacterium in asymptomatic people. A study on the cost-effectiveness of the test-and-treatment strategy for *H. pylori* revealed that it remained effective even with a low infection rate of approximately 5%.[32] Our findings could inform future public health strategies. Moreover, considering the decrease in *H. pylori* prevalence, *H. pylori* infection-negative gastric cancer has lately been receiving attention.[33 34 35] Research for risk factors of gastric cancer other

than *H. pylori* is also needed.

Limitations

This study has several limitations. First, there might have been selection bias, including age, sex, occupation, region, and nationality (possibly including several workers who were born and raised in countries other than Japan). Several studies have analyzed differences in the infection rates according to sex, occupation, and region, with a study reporting a higher infection rate in men; however, there remains no consensus regarding these biases.[36 37 38] Our present study included participants of an unequal number of each sex. This was one reason why we conducted separate analyses for each sex. A recent study showed that employees in a large company are in better health than those in a small one.[39] As the target group of this study were employees of a large company, there is the possibility of such bias. Heterogeneity of age gaps between age groups and limitation of the target ages may have weakened analyses, especially in younger age groups. However, the present study targeted all health insurance society members working in a large company operating throughout Japan, and therefore, we were able to include subjects from various age groups and regions throughout Japan. Second, the history of *H. pylori* eradication may have influenced our findings. In 2008, T company health insurance society performed serum *H. pylori* antibody screening tests for all its members. Therefore, there may have been a higher proportion of post-eradication cases in

our study than in the general population. We attempted to reduce the influence of eradication treatment by classifying patients who underwent eradication treatment as infected. However, history information acquired through a self-reported questionnaire could have contained inaccuracies, including recall bias.[40] In the 35-year-old analysis, we could not obtain information regarding previous eradication treatment of the participants. We hence analyzed the data based on the assumption that the rate of eradication treatment among participants in the 35-year-old analysis was low, due to their younger age, and therefore would not significantly affect the influence rate. The health insurance society collected and reported, as part of their health services, that the rate of 35-year-old participants who had previously undergone eradication treatment (both men and women) was 0.9%, 2.1%, and 1.4% in 2018, 2019, and 2020, respectively. Although this supports our assumption, it indicates the possibility of errors of 1%–2 % from eradication treatment in the infection rates of the 35-year-old analysis. In addition, previous medical history; medications; and measurement biases, including test characteristics and threshold application in the test (including high-negative issues), could have influenced our results.[41 42] The limitations mentioned above may hinder the generalization of our findings to the Japanese general population.

However, the present study collected data of 35-year-olds from 2009 to 2018, and data also of various age groups from 2018, and this information was analyzed using a robust statistical

method called joinpoint analysis, demonstrating important findings for considering future *H. pylori* eradication therapy targets.

CONCLUSION

Our study showed a constant decreasing time-trend in the infection rate of *H. pylori* among 35-year-old workers in Japan from 2008 to 2018. This time-trend indicates that the infection rate of *H. pylori* may continue to decrease in the future. Trends in the infection rate by age in 2018 indicated the possibility of a slowing down of the rate of decrease in the prevalence of *H. pylori* in Japan. In populations with few *H. pylori*-positive individuals, the efficiency of measures to routinely test for antibodies is low, and therefore, it would be difficult to rely solely on the *H. pylori* test and treatment strategy to achieve gastric cancer prevention. We believe that the data regarding changes in the prevalence of *H. pylori* over the years observed in Japan could be useful for other countries with a high incidence of *H. pylori* infection, in planning future eradication strategies.

Acknowledgments

We would like to acknowledge the T company health insurance society. We would like to thank the Center for International Education and Research of Tokyo Medical University for English language editing.

Footnotes

Contributors: SA designed the study, analyzed the data, and drafted the manuscript. Y Hirayama contributed to the study design and performed general supervision of the whole study. JO, Y Harada, and T Toi assisted in conducting the study, interpreting the results, and revising the manuscript. KK and TK contributed to data collection and provided advice and opinions from an expert perspective. TT contributed to data analysis and revising the manuscript from statistical and public health perspectives. All authors read and approved the final manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: None declared.

Patient consent for publication: Not required.

Ethics approval: The institutional review boards of Tokyo Medical University (T2019-0044)

Provenance and peer review: Not commissioned; externally peer-reviewed.

Data sharing statement: Data is available in a public, open access repository. [43]

REFERENCES

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]

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]

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]

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]

5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, Liver Flukes and Helicobacter pylori. Lyon (FR): International Agency for Research on Cancer 1994.

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

7. Ford AC, Forman D, Hunt RH, et al. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174. doi: 10.1136/bmj.g3174

8. Center for Cancer Control and Information Services, National Cancer Center. CANCER STATISTICS IN JAPAN '19 [updated 17 April 2020. Available from: https://ganjoho.jp/en/professional/statistics/brochure/2019_en.html accessed 22 Dec 2020.

9. Matsuo T, Ito M, Takata S, et al. Low prevalence of Helicobacter pylori-negative gastric cancer among Japanese. *Helicobacter* 2011;16(6):415-9. doi: 10.1111/j.1523-

5378.2011.00889.x [published Online First: 2011/11/09]

10. Peleteiro B, Bastos A, Ferro A, et al. Prevalence of Helicobacter pylori infection worldwide: a systematic review of studies with national coverage. *Dig Dis Sci* 2014;59(8):1698-709. doi: 10.1007/s10620-014-3063-0 [published Online First: 2014/02/25]

11. Tsuda M, Asaka M, Kato M, et al. Effect on Helicobacter pylori eradication therapy against gastric cancer in Japan. *Helicobacter* 2017;22(5) doi: 10.1111/hel.12415 [published Online First: 2017/08/05]

12. Wang C, Nishiyama T, Kikuchi S, 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. doi: 10.1038/s41598-017-15490-7 [published Online First: 2017/11/16]

13. Inoue M. Changing epidemiology of Helicobacter pylori in Japan. *Gastric Cancer* 2017;20(Suppl 1):3-7. doi: 10.1007/s10120-016-0658-5 [published Online First: 2016/10/21]

14. Watanabe M, Ito H, Hosono S, et al. Declining trends in prevalence of Helicobacter pylori infection by birth-year in a Japanese population. *Cancer Sci* 2015;106(12):1738-43. doi: 10.1111/cas.12821 [published Online First: 2015/09/24]

15. Carmack SW, Genta RM. Helicobacter pylori seroprevalence in symptomatic veterans: a

study of 7310 patients over 11 years. *Helicobacter* 2009;14(4):298-302. doi: 10.1111/j.1523-5378.2009.00693.x

16. den Hoed CM, Vila AJ, Holster IL, et al. Helicobacter pylori and the birth cohort effect: evidence for stabilized colonization rates in childhood. *Helicobacter* 2011;16(5):405-9. doi: 10.1111/j.1523-5378.2011.00854.x [published Online First: 2011/09/20]

17. Komatsu Y, Sugiyama T, Asaka M. Helicobacter pylori kansenshindan ni okeru nihonjinkabu wo siyou sita ELISA kit " E-plate eiken H.pylori koutai" no yuyousei no kentou [Study of effectiveness of E-plate eiken which is ELAISA kit using Japanese strain in diagnose of Helicobacter pylori infection]. *The Journal of Clinical Laboratory Instruments and Reagents* 2001;24(5):331-35.

18. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335-51. doi: 10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z [published Online First: 2000/01/29]

19. Joinpoint Regression Program [program]. Version 4.9.0.0 version: Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute., March 2021.

20. Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health Research Involving Human Subjects 2015 [Available from:

https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf accessed 6 Dec 2020.

21. Kusano C, Gotoda T, Ishikawa H, et al. The administrative project of Helicobacter pylori infection screening among junior high school students in an area of Japan with a high incidence of gastric cancer. *Gastric Cancer* 2017;20(Suppl 1):16-19. doi: 10.1007/s10120-017-0688-7 [published Online First: 2017/01/18]

22. Honma H, Nakayama Y, Kato S, et al. Clinical features of Helicobacter pylori antibody-positive junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2018:e12559. doi: 10.1111/hel.12559 [published Online First: 2018/12/06]

23. Nakayama Y, Lin Y, Hongo M, et al. Helicobacter pylori infection and its related factors in junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2017;22(2) doi: 10.1111/hel.12363 [published Online First: 2016/10/28]

24. Kakiuchi T, Matsuo M, Endo H, et al. A Helicobacter pylori screening and treatment program to eliminate gastric cancer among junior high school students in Saga Prefecture: a preliminary report. *J Gastroenterol* 2019 doi: 10.1007/s00535-019-01559-9 [published Online First: 2019/02/17]

25. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and Helicobacter pylori. *J Infect Dis* 1993;168(1):219-21. doi: 10.1093/infdis/168.1.219

26. O'Ryan ML, Lucero Y, Rabello M, et al. Persistent and transient Helicobacter pylori

infections in early childhood. *Clin Infect Dis* 2015;61(2):211-8. doi: 10.1093/cid/civ256

27. Ueda M, Kikuchi S, Kasugai T, et al. Helicobacter pylori risk associated with childhood home environment. *Cancer Sci* 2003;94(10):914-8. doi: 10.1111/j.1349-7006.2003.tb01375.x [published Online First: 2003/10/15]

28. JAPAN WATER WORKS ASSOCIATION. Water Supply in Japan 2017 [Available from: http://www.jwwa.or.jp/jigyou/kaigai_file/2017WaterSupplyInJapan.pdf accessed Dec 22 2020.

29. Ministry of Health, Labour and Welfare. General Welfare and Labour Japan [Available from: https://www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf accessed 1st Oct 2020.

30. Council JBF. Seisan Tokei [Production statistics] Japan [Available from: https://www.baby-food.jp/link/ayumi-jikei.html accessed 11 Dec 2020.

31. Hiroi S, Sugano K, Tanaka S, et al. Impact of health insurance coverage for Helicobacter pylori gastritis on the trends in eradication therapy in Japan: retrospective observational study and simulation study based on real-world data. *BMJ Open* 2017;7(7):e015855. doi: 10.1136/bmjopen-2017-015855 [published Online First: 2017/08/02]

32. Kowada A. Cost-effectiveness of Helicobacter pylori screening followed by eradication treatment for employees in Japan. *Epidemiol Infect* 2018;146(14):1834-40. doi:

10.1017/S095026881800208X [published Online First: 2018/07/31]

33. Kato S, Matsukura N, Tsukada K, et al. Helicobacter pylori infection-negative gastric cancer in Japanese hospital patients: Incidence and pathological characteristics. *Cancer Sci* 2007;98(6):790-94. doi: https://doi.org/10.1111/j.1349-7006.2007.00478.x

34. Yamamoto Y, Fujisaki J, Omae M, et al. Helicobacter pylori-negative gastric cancer: characteristics and endoscopic findings. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society* 2015;27(5):551-61. doi: 10.1111/den.12471 [published Online First: 2015/03/27]

35. Takita M, Ohata K, Inamoto R, et al. Endoscopic and histological features of Helicobacter pylori-negative differentiated gastric adenocarcinoma arising in the antrum. *JGH open : an open access journal of gastroenterology and hepatology* 2021;5(4):470-77. doi: 10.1002/jgh3.12518 [published Online First: 2021/04/17]

36. Kheyre H, Morais S, Ferro A, et al. The occupational risk of Helicobacter pylori infection: a systematic review. *Int Arch Occup Environ Health* 2018;91(6):657-74. doi: 10.1007/s00420-018-1315-6

37. Ueda J, Gosho M, Inui Y, et al. Prevalence of Helicobacter pylori infection by birth year and geographic area in Japan. *Helicobacter* 2014;19(2):105-10. doi: 10.1111/hel.12110 [published Online First: 2014/02/11]

38. Ferro A, Morais S, Pelucchi C, et al. Sex differences in the prevalence of Helicobacter pylori infection: an individual participant data pooled analysis (StoP Project). *Eur J Gastroenterol Hepatol* 2019;31(5):593-98. doi: 10.1097/MEG.0000000000001389 [published Online First: 2019/03/07]

39. Kanamori S, Tsuji T, Takamiya T, et al. Size of company of the longest-held job and mortality in older Japanese adults: A 6-year follow-up study from the Japan Gerontological Evaluation Study. *J Occup Health* 2020;62(1):e12115. doi: 10.1002/1348-9585.12115 [published Online First: 2020/06/10]

40. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43(1):87-91. doi: 10.1016/0895-4356(90)90060-3

41. Miftahussurur M, Yamaoka Y. Diagnostic Methods of Helicobacter pylori Infection for Epidemiological Studies: Critical Importance of Indirect Test Validation. *BioMed research international* 2016;2016:4819423. doi: 10.1155/2016/4819423 [published Online First: 2016/02/24]

42. Inoue M, Sawada N, Goto A, et al. High-Negative Anti-Helicobacter pylori IgG Antibody Titers and Long-Term Risk of Gastric Cancer: Results from a Large-Scale Population-Based Cohort Study in Japan. *Cancer Epidemiol Biomarkers Prev* 2020;29(2):420-26. doi: 10.1158/1055-9965.EPI-19-0993 [published Online First: 2019/12/13]

[dataset] 43. Soichiro A. Data from: Changes in prevalence of Helicobacter pylori in Japan from 2008 to 2018: a repeated cross-sectional study, figshare, July 13, 2022 https://doi.org/10.6084/m9.figshare.14594571.v2

FIGURE LEGENDS

Figure 1

Numbers of participants

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.

Figure 2:

Infection rates of Helicobacter pylori at 35 years old from 2008 to 2018 (men: n = 7,586, women: n= 1,739)

Figure 2

Note. Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51). There were no joinpoints. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

Figure 3

Infection rates of Helicobacter pylori according to age in 2018 (men: n = 9,580, women: n=1,854)

Figure 3

Note. Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67]; second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30]; second trend: 45–65 years [slope = 1.49]). "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

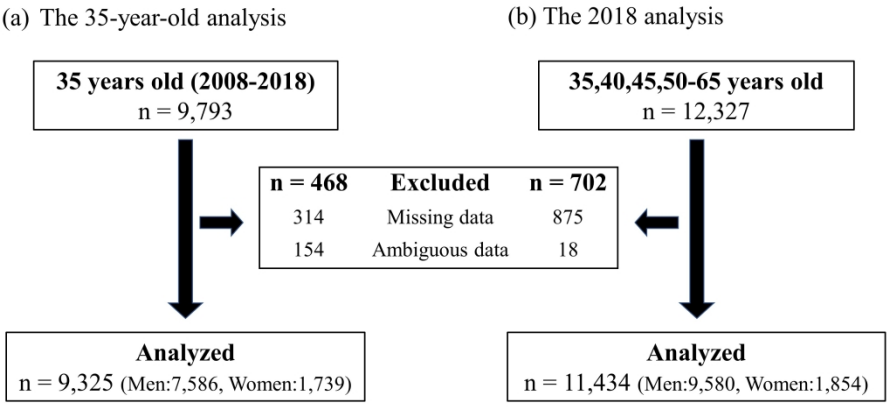


Figure 1: *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The 2018 analysis: participants aged 35–65 years in 2018.

338x190mm (300 x 300 DPI)

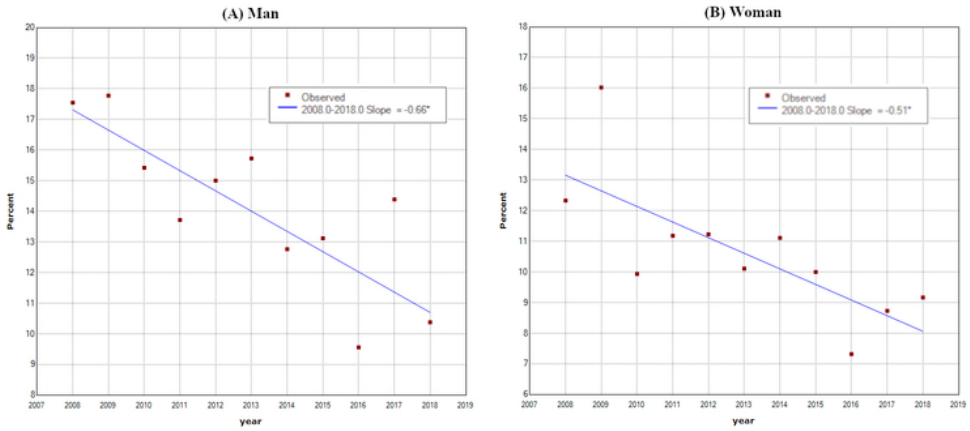


Figure 2: Note. Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51). There were no joinpoints. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

32x14mm (600 x 600 DPI)

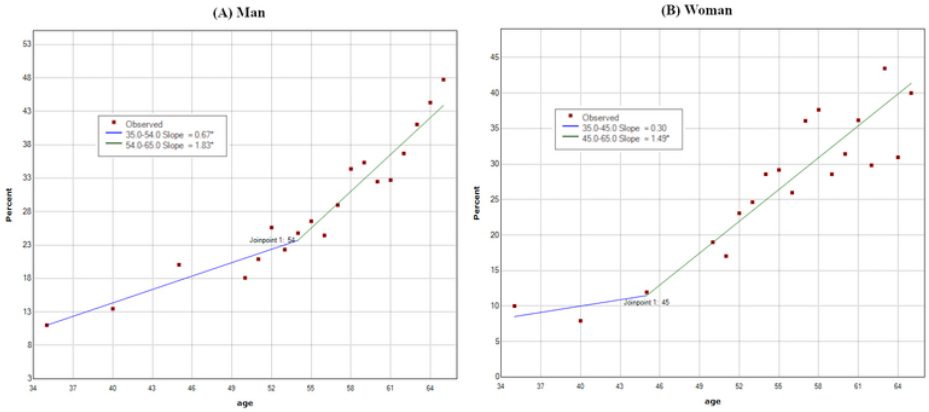


Figure 3: Note. Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67]; second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30]; second trend: 45–65 years [slope = 1.49]). "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

35x15mm (600 x 600 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	1-3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-8
Bias	#9	Describe any efforts to address potential sources of bias	14-15
Study size	#10	Explain how the study size was arrived at	n/a

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	n/a
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9-10
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	9
Descriptive data	#14a	Give characteristics of study participants (eg demographic,	6-7, 14-

		clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	15
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9-10
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	9-10
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11-12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14-15

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n/a

BMJ Open

Changes in prevalence of *Helicobacter pylori* in Japan from 2008 to 2018: a repeated cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058774.R2
Article Type:	Original research
Date Submitted by the Author:	05-Aug-2022
Complete List of Authors:	Abiko, Soichiro; Tokyo Medical University, Department of General Medicine and Primary Care Hirayama, Yoji; Tokyo Medical University, Department of General Medicine and Primary Care Otaki, Junji; Tokyo Medical University, Department of Medical Education; Tokyo Medical University, Department of General Medicine and Primary Care Harada, Yoshimi; Tokyo Medical University, Department of Medical Education; Tokyo Medical University, Department of General Medicine and Primary Care Kawakami, Kohei; Tokyo Medical University, Department of General Medicine and Primary Care Toi, Takahiro; Tokyo Medical University, Department of General Medicine and Primary Care Takamiya, Tomoko; Tokyo Medical University, Department of Preventive Medicine and Public Heatlh Kawai, Takashi; Tokyo Medical University, Department of Gastroenterological Endoscopy
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Gastroenterology and hepatology, Health policy
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY, HEALTH ECONOMICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Changes in prevalence of *Helicobacter pylori* in Japan from 2008 to 2018: a repeated cross-sectional study

Author names: Soichiro Abiko[1], Yoji Hirayama[1], Junji Otaki[2 1], Yoshimi Harada[2 1], Kohei Kawakami[1], Takahiro Toi[1], Tomoko Takamiya[3], Takashi Kawai[4]

Author Affiliations:

1. Department of General Medicine and Primary Care, Tokyo Medical University, Tokyo, Japan.

2. Department of Medical Education, Tokyo Medical University, Tokyo, Japan.

3. Department of Preventive Medicine and Public Health, Tokyo Medical University, Tokyo, Japan.

4. Department of Gastroenterological Endoscopy, Tokyo Medical University, Tokyo, Japan.

Corresponding Author: Soichiro Abiko

Email: s_abiko1@tokyo-med.ac.jp

Word count: 2,903

ABSTRACT

Objectives: To understand the recent prevalence and time-trends of *Helicobacter pylori* infection rates in the Japanese population.

Design: Repeated cross-sectional study

Participants: A total of 22,120 workers (age: 35–65 years) from one Japanese company, who underwent serum *H. pylori* antibody tests in a health checkup between 2008 and 2018.

Measures: *H. pylori* infection rates among participants aged 35 years from 2008 to 2018, and participants aged 35, 40, 45, and 50–65 years in 2018, based on the results of serum antibody tests were analyzed. In the 2018 analysis, in addition to the antibody test results, all participants who had undergone eradication treatment for *H. pylori* were considered as infected. Trends were examined using Joinpoint analysis.

Results: *H. pylori* were detected in 1,100 of 7,586 male, and 190 of 1,739 female participants aged 35 years. Annual infection rates among those aged 35 years showed linear downward trends as follows: 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) without joinpoints. In the 2018 analysis, 2,432 of 9,580 men and 431 of 1,854 women were *H. pylori* positive. Infection rates tended to increase with older age (men: 11.0% [35 years] to 47.7% [65 years], women: 10.0% [35 years] to 40.0% [65 years]), and showed joinpoints in both sexes (men: 54 years, women: 45 years). Although both the first and second trends were upward, the second trends for both men and women were steeper than the first trends ($P < 0.05$).

Conclusions: Our study demonstrated that in the previous 11 years, infection rates of *H. pylori* in Japanese 35-year-old male and female workers have constantly decreased, and furthermore, analysis of various age groups showed joinpoints around 50 years, suggesting a

consistent declining trend in *H. pylori* infection rates in Japan.

Strengths and limitations of this study

• This study presents a recent 11-year time trend of *H. pylori* infection rates based on *H. pylori* serum antibody test results of 35-year-old workers from one large company with many branches around Japan, using Joinpoint trend analysis.

• The 2018 data compared infection rates by age group (35, 40, 45, and 50–65 years), taking into account the history of *H. pylori* eradication treatment obtained by a questionnaire, in addition to antibody testing.

• The main limitation of this study is the generalizability of the results to the general Japanese population because the study subjects were company employees.

INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacterium that is often found in the human stomach. *H. pylori* infection is known to be closely associated with chronic gastritis, duodenal ulcers, gastric ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and

gastric cancer.[1 2 3 4] The International Agency for Research on Cancer Working group, which is a part of the World Health Organization (WHO), classified *H. pylori* as a Group 1 carcinogen for gastric cancer in 1994.[5] 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".[6]

H. pylori test-and-treat strategy for preventing gastric cancer is considered more effective in regions with a high incidence of gastric cancer.[7] The incidence and mortality rates of gastric cancer are relatively high in Japan compared with other countries. Moreover, *H. pylori* infection is thought to be involved in more than 90% of gastric cancer cases in Japan.[8 9] In addition, the infection rate of *H. pylori* in Japan is higher than that in other developed countries.[10] Accordingly, the "test-and-treat" strategy for *H. pylori* could be a good measure for preventing gastric cancer in Japan. In 2013, the national health insurance scheme covered the *H. pylori* eradication therapy for chronic gastritis in Japan. Several groups in Japan, including company health insurance societies and local municipalities, have introduced *H. pylori* screening tests for asymptomatic people during medical check-ups for the prophylactic intervention of gastric cancer.

Decreasing the *H. pylori* infection rate could reduce the incidence rate of gastric cancer[11] and reduce the positive predictive value of *H. pylori* screening. Therefore, decreasing the *H. pylori* infection rate in the population may negatively affect the cost-effectiveness of the "test-and-treat" strategy for asymptomatic groups. It is important to elucidate the current prevalence of *H. pylori* infection and its trends over time, to predict future infection rates and plan test strategies for the future. There has been a decrease in the worldwide prevalence of *H. pylori*,[10] with several Japanese studies reporting similar results.[12] However, most of these studies had small sample sizes or included specific participants, including hospital visitors. To our knowledge, there have been no recent large-scale studies on the prevalence and time-trend of infection rates of *H. pylori* in Japan.[12 13 14] In addition, several studies have reported that the *H. pylori* infection rates become steady at approximately 10% in several low-prevalence regions, including European countries.[10 15 16] 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.[14] Our present study aimed to elucidate the recent trends in the infection rates of *H. pylori*, including the rates after 2013, which is the year that the health

insurance system in Japan began to cover *H. pylori* eradication therapy for chronic gastritis, and whether they showed significant changes with time.

Using data from health checkups in a company health insurance society, this repeated cross-sectional study aimed to clarify the recent 11-year trend of *H. pylori* infection rate in 35-year-olds and *H. pylori* infection rates in 2018 according to age, stratified by sex.

MATERIALS AND METHODS

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,[17] with values above this being classified as positive. Anonymized participants' data, including medical questionnaires and blood test results, were obtained from the annual health checkup database of the health insurance society. We excluded data from individuals who refused academic use of their data.

Statistical analysis

First, data obtained from 35-year-old participants between 2008 and 2018 were analyzed to determine time-trends in *H. pylori* infection rates ("35-year-old analysis") stratified by sex. Positive results of serum antibody tests for *H. pylori* were defined as *H. pylori* infection. Annual infection rates were calculated based on the antibody test results. Subsequently, we analyzed the time-trend of the rates.

Second, we analyzed data from participants aged 35, 40, 45, and 50–65 years old obtained in 2018 according to age stratified by sex to determine generational differences in the infection rates ("2018 analysis"). In the 2018 analysis, participants who tested positive for antibodies were considered as infected. Further, to reduce the influence of eradication treatment on the

infection rate, all participants with a history of eradication treatment of *H. pylori* infection were defined as positive regardless of their tests results for *H. pylori* antibody, with the assumption that a history of eradication treatment indicates a previous infection.

We performed Joinpoint Trend Analysis[18] to identify trends in the infection rate and their changes over time using Joinpoint Regression Program 4.9.0.0.[19] 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. Linear Model was selected in the analyses. Statistical significance was set at $P < 0.05$. Data with missing or ambiguous figures were excluded from the analysis.

Patient and public involvement

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. The results of this study are published as a report.

Ethical approval

This study protocol was reviewed and approved by the Institutional Review Board of Tokyo

Medical University (T2019-0044). Following the Ethical Guidelines for Medical and Health Research Involving Human Subjects,[20] the study information was shown on the websites of the institutions where the researchers or participants belonged. Participants' consent for using data was obtained through an opt-out option.

RESULTS

There were 9,793 and 12,327 participants in the 35-year-old and 2018 analyses, respectively, with 592 participants overlapping in both analyses. In the 35-year-old analysis, 468 participants were excluded for having missing (n = 314) or ambiguous data (n = 154) in the records, with 9,325 participants (7,586 men; 1,739 women) being included in the final analysis. In the 2018 analysis, 893 participants were excluded for having missing (n = 875) or ambiguous data (n = 18) in the records, with 11,434 participants (9,580 men; 1,854 women) being included in the final analysis (Figure 1).

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 increasing 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. Both first and second trends showed a linear increase with age, with the second trends being significantly steeper than the first trends ($P < 0.05$) (Figure 3).

DISCUSSION

This study investigated the 11-year time-trend from 2008 to 2018, and the trend by age in 2018 regarding the prevalence of *H. pylori* infection in Japanese workers stratified by sex based on large-scale health checkup data. In the 35-year-old analysis, the infection rate showed a linear declining trend from 2008 to 2018 both in men and women. 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.

In the 35-year-old analysis, the infection rate decreased linearly to approximately 10% both in men and women; further, this downward trend did not significantly change during the observation period. We assumed that the participants in this analysis, who were all 35 years old were less affected by eradication treatment than older participants; and therefore, the results may closely reflect the actual trend of the incidence rate of *H. pylori* infections in Japan. If the downward trends (slope = –0.65 in men and slope = –0.51 in women) observed in the 35-year-old analysis continues, the infection rate is expected to reach nearly zero by about 2035. In contrast, recent studies on junior high school students (aged: 12–15 years) in Japan have demonstrated that the infection rate of this generation when they reach 35 years at about 2035 will be approximately 3% to 5%,[21 22 23 24] which is higher than our prediction. This inconsistency suggests that the decrease in the infection rate may have slowed down.

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. Furthermore, there were joinpoints around the age of 50 years (54 years in men [95% CI: 45–58] and 45 years in women [95% CI: 45–51]), which implies the existence of some type of change

affecting the *H. pylori* infection rate in people of this generations (Figure 3). Chronic *H. pylori* infection is mostly established in the human stomach during childhood.[25 26] Drinking water and family members are among the sources of *H. pylori* infection.[27] 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.[28 29] 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. Watanabe et al. revealed changes in the declining trend of *H. pylori* infection rate and indicated an effect of environmental changes on the infection rate,[14] which is consistent with our findings.

Participants in the 35-year-old analysis were born after 1973; therefore, they may have not experienced the rapid environmental changes that those who were born during the period of high economic growth (1955–1972) had experienced. The 35-year-old analysis revealed a recent gradual decrease in the *H. pylori* infection rate. This suggests that factors other than hygiene and family structure may influence infection establishment. As aforementioned, *H. pylori* infections are likely to be established during childhood through parent-to-child transmission.[26] In addition to hygienic and environmental improvements, the spread of ready-

made baby food after around 1970 may have contributed to the decreased *H. pylori* infection rate.[30] With the recently increasing recognition of *H. pylori* in the general population and coverage of eradication treatment through national insurance, there has been an increase in the number of *H. pylori* eradication treatments in Japan.[31] If treatment decreases the infection rate in child-rearing generation, it could accelerate the declining speed of the infection rates in the next generations.

When conducting *H. pylori* screening tests for prophylactic purposes, the prevalence in a target group should be considered to evaluate the effectiveness of the strategy. We observed a decreasing infection rate of *H. pylori* in Japan. In the future, the infection rate may reach zero; accordingly, there would be a decreased importance of screening tests for this bacterium in asymptomatic people. A study on the cost-effectiveness of the test-and-treatment strategy for *H. pylori* revealed that it remained effective even with a low infection rate of approximately 5%.[32] Our findings could inform future public health strategies. Moreover, considering the decrease in *H. pylori* prevalence, *H. pylori* infection-negative gastric cancer has lately been receiving attention.[33 34 35] Research for risk factors of gastric cancer other than *H. pylori* is also needed.

Limitations

This study has several limitations. First, there might have been selection bias, including age, sex, occupation, region, and nationality (possibly including several workers who were born and raised in countries other than Japan). Several studies have analyzed differences in the infection rates according to sex, occupation, and region, with a study reporting a higher infection rate in men; however, there remains no consensus regarding these biases.[36 37 38] Our present study included participants of an unequal number of each sex. This was one reason why we conducted separate analyses for each sex. A recent study showed that employees in a large company are in better health than those in a small one.[39] As the target group of this study were employees of a large company, there is the possibility of such bias. Heterogeneity of age gaps between age groups and limitation of the target ages may have weakened analyses, especially in younger age groups. However, the present study targeted all health insurance society members working in a large company operating throughout Japan, and therefore, we were able to include subjects from various age groups and regions throughout Japan. Second, the history of *H. pylori* eradication may have influenced our findings. In 2008, T company health insurance society performed serum *H. pylori* antibody screening tests for all its members. Therefore, there may have been a higher proportion of post-eradication cases in our study than in the general population. We attempted to reduce the influence of eradication treatment by classifying patients who underwent eradication treatment as infected. However, history information acquired through a self-reported questionnaire could have contained

inaccuracies, including recall bias.[40] In the 35-year-old analysis, we could not obtain information regarding previous eradication treatment of the participants. We hence analyzed the data based on the assumption that the rate of eradication treatment among participants in the 35-year-old analysis was low, due to their younger age, and therefore would not significantly affect the infection rate. The health insurance society collected and reported, as part of their health services, that the rate of 35-year-old participants who had previously undergone eradication treatment (both men and women) was 0.9%, 2.1%, and 1.4% in 2018, 2019, and 2020, respectively. Although this supports our assumption, it indicates the possibility of errors of 1%–2 % from eradication treatment in the infection rates of the 35-year-old analysis. In addition, previous medical history; medications; and measurement biases, including test characteristics and threshold application in the test (including high-negative issues), could have influenced our results.[41 42] The limitations mentioned above may hinder the generalization of our findings to the Japanese general population.

However, the present study collected data of 35-year-olds from 2009 to 2018, and data also of various age groups from 2018, and this information was analyzed using a robust statistical method called joinpoint analysis, demonstrating important findings for considering future *H. pylori* eradication therapy targets.

CONCLUSION

Our study showed a constant decreasing time-trend in the infection rate of *H. pylori* among 35-year-old workers in Japan from 2008 to 2018 [43]. This time-trend indicates that the infection rate of *H. pylori* may continue to decrease in the future. Trends in the infection rate by age in 2018 indicated the possibility of a slowing down of the rate of decrease in the prevalence of *H. pylori* in Japan. In populations with few *H. pylori*-positive individuals, the efficiency of measures to routinely test for antibodies is low, and therefore, it would be difficult to rely solely on the *H. pylori* test and treatment strategy to achieve gastric cancer prevention. We believe that the data regarding changes in the prevalence of *H. pylori* over the years observed in Japan could be useful for other countries with a high incidence of *H. pylori* infection, in planning future eradication strategies.

Acknowledgments

We would like to acknowledge the T company health insurance society. We would like to thank the Center for International Education and Research of Tokyo Medical University for English language editing.

Footnotes

Contributors: SA designed the study, analyzed the data, and drafted the manuscript. Y

Hirayama contributed to the study design and performed general supervision of the whole study. JO, Y Harada, and T Toi assisted in conducting the study, interpreting the results, and revising the manuscript. KK and TK contributed to data collection and provided advice and opinions from an expert perspective. TT contributed to data analysis and revising the manuscript from statistical and public health perspectives. All authors read and approved the final manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: None declared.

Patient consent for publication: Not required.

Ethics approval: The institutional review boards of Tokyo Medical University (T2019-0044)

Provenance and peer review: Not commissioned; externally peer-reviewed.

Data sharing statement: Data is available in a public, open access repository. [43]

REFERENCES

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]

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]

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]

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]

5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, Liver Flukes and Helicobacter pylori. Lyon (FR): International Agency for Research on Cancer 1994.

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

7. Ford AC, Forman D, Hunt RH, et al. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174. doi: 10.1136/bmj.g3174

8. Center for Cancer Control and Information Services, National Cancer Center. CANCER STATISTICS IN JAPAN '19 [updated 17 April 2020. Available from: https://ganjoho.jp/en/professional/statistics/brochure/2019_en.html accessed 22 Dec 2020.

9. Matsuo T, Ito M, Takata S, et al. Low prevalence of Helicobacter pylori-negative gastric cancer among Japanese. *Helicobacter* 2011;16(6):415-9. doi: 10.1111/j.1523-5378.2011.00889.x [published Online First: 2011/11/09]

10. Peleteiro B, Bastos A, Ferro A, et al. Prevalence of Helicobacter pylori infection worldwide: a systematic review of studies with national coverage. *Dig Dis Sci*

2014;59(8):1698-709. doi: 10.1007/s10620-014-3063-0 [published Online First: 2014/02/25]

11. Tsuda M, Asaka M, Kato M, et al. Effect on Helicobacter pylori eradication therapy against gastric cancer in Japan. *Helicobacter* 2017;22(5) doi: 10.1111/hel.12415 [published Online First: 2017/08/05]

12. Wang C, Nishiyama T, Kikuchi S, 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. doi: 10.1038/s41598-017-15490-7 [published Online First: 2017/11/16]

13. Inoue M. Changing epidemiology of Helicobacter pylori in Japan. *Gastric Cancer* 2017;20(Suppl 1):3-7. doi: 10.1007/s10120-016-0658-5 [published Online First: 2016/10/21]

14. Watanabe M, Ito H, Hosono S, et al. Declining trends in prevalence of Helicobacter pylori infection by birth-year in a Japanese population. *Cancer Sci* 2015;106(12):1738-43. doi: 10.1111/cas.12821 [published Online First: 2015/09/24]

15. Carmack SW, Genta RM. Helicobacter pylori seroprevalence in symptomatic veterans: a study of 7310 patients over 11 years. *Helicobacter* 2009;14(4):298-302. doi: 10.1111/j.1523-5378.2009.00693.x

16. den Hoed CM, Vila AJ, Holster IL, et al. Helicobacter pylori and the birth cohort effect:

evidence for stabilized colonization rates in childhood. *Helicobacter* 2011;16(5):405-9. doi: 10.1111/j.1523-5378.2011.00854.x [published Online First: 2011/09/20]

17. Komatsu Y, Sugiyama T, Asaka M. Helicobacter pylori kansenshindan ni okeru nihonjinkabu wo siyou sita ELISA kit " E-plate eiken H.pylori koutai" no yuyousei no kentou [Study of effectiveness of E-plate eiken which is ELAISA kit using Japanese strain in diagnose of Helicobacter pylori infection]. *The Journal of Clinical Laboratory Instruments and Reagents* 2001;24(5):331-35.

18. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335-51. doi: 10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z [published Online First: 2000/01/29]

19. Joinpoint Regression Program [program]. Version 4.9.0.0 version: Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute., March 2021.

20. Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health Research Involving Human Subjects 2015 [Available from: https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf accessed 6 Dec 2020.

21. Kusano C, Gotoda T, Ishikawa H, et al. The administrative project of Helicobacter pylori

infection screening among junior high school students in an area of Japan with a high incidence of gastric cancer. *Gastric Cancer* 2017;20(Suppl 1):16-19. doi: 10.1007/s10120-017-0688-7 [published Online First: 2017/01/18]

22. Honma H, Nakayama Y, Kato S, et al. Clinical features of Helicobacter pylori antibody-positive junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2018:e12559. doi: 10.1111/hel.12559 [published Online First: 2018/12/06]

23. Nakayama Y, Lin Y, Hongo M, et al. Helicobacter pylori infection and its related factors in junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2017;22(2) doi: 10.1111/hel.12363 [published Online First: 2016/10/28]

24. Kakiuchi T, Matsuo M, Endo H, et al. A Helicobacter pylori screening and treatment program to eliminate gastric cancer among junior high school students in Saga Prefecture: a preliminary report. *J Gastroenterol* 2019 doi: 10.1007/s00535-019-01559-9 [published Online First: 2019/02/17]

25. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and Helicobacter pylori. *J Infect Dis* 1993;168(1):219-21. doi: 10.1093/infdis/168.1.219

26. O'Ryan ML, Lucero Y, Rabello M, et al. Persistent and transient Helicobacter pylori infections in early childhood. *Clin Infect Dis* 2015;61(2):211-8. doi: 10.1093/cid/civ256

27. Ueda M, Kikuchi S, Kasugai T, et al. Helicobacter pylori risk associated with childhood

home environment. *Cancer Sci* 2003;94(10):914-8. doi: 10.1111/j.1349-7006.2003.tb01375.x [published Online First: 2003/10/15]

28. JAPAN WATER WORKS ASSOCIATION. Water Supply in Japan 2017 [Available from: http://www.jwwa.or.jp/jigyou/kaigai_file/2017WaterSupplyInJapan.pdf accessed Dec 22 2020.

29. Ministry of Health, Labour and Welfare. General Welfare and Labour Japan [Available from: https://www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf accessed 1st Oct 2020.

30. Council JBF. Seisan Tokei [Production statistics] Japan [Available from: https://www.baby-food.jp/link/ayumi-jikei.html accessed 11 Dec 2020.

31. Hiroi S, Sugano K, Tanaka S, et al. Impact of health insurance coverage for Helicobacter pylori gastritis on the trends in eradication therapy in Japan: retrospective observational study and simulation study based on real-world data. *BMJ Open* 2017;7(7):e015855. doi: 10.1136/bmjopen-2017-015855 [published Online First: 2017/08/02]

32. Kowada A. Cost-effectiveness of Helicobacter pylori screening followed by eradication treatment for employees in Japan. *Epidemiol Infect* 2018;146(14):1834-40. doi: 10.1017/S095026881800208X [published Online First: 2018/07/31]

33. Kato S, Matsukura N, Tsukada K, et al. Helicobacter pylori infection-negative gastric cancer in Japanese hospital patients: Incidence and pathological characteristics.

Cancer Sci 2007;98(6):790-94. doi: https://doi.org/10.1111/j.1349-7006.2007.00478.x

34. Yamamoto Y, Fujisaki J, Omae M, et al. Helicobacter pylori-negative gastric cancer: characteristics and endoscopic findings. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society* 2015;27(5):551-61. doi: 10.1111/den.12471 [published Online First: 2015/03/27]

35. Takita M, Ohata K, Inamoto R, et al. Endoscopic and histological features of Helicobacter pylori-negative differentiated gastric adenocarcinoma arising in the antrum. *JGH open : an open access journal of gastroenterology and hepatology* 2021;5(4):470-77. doi: 10.1002/jgh3.12518 [published Online First: 2021/04/17]

36. Kheyre H, Morais S, Ferro A, et al. The occupational risk of Helicobacter pylori infection: a systematic review. *Int Arch Occup Environ Health* 2018;91(6):657-74. doi: 10.1007/s00420-018-1315-6

37. Ueda J, Gosho M, Inui Y, et al. Prevalence of Helicobacter pylori infection by birth year and geographic area in Japan. *Helicobacter* 2014;19(2):105-10. doi: 10.1111/hel.12110 [published Online First: 2014/02/11]

38. Ferro A, Morais S, Pelucchi C, et al. Sex differences in the prevalence of Helicobacter pylori infection: an individual participant data pooled analysis (StoP Project). *Eur J Gastroenterol Hepatol* 2019;31(5):593-98. doi: 10.1097/MEG.0000000000001389

[published Online First: 2019/03/07]

39. Kanamori S, Tsuji T, Takamiya T, et al. Size of company of the longest-held job and mortality in older Japanese adults: A 6-year follow-up study from the Japan Gerontological Evaluation Study. *J Occup Health* 2020;62(1):e12115. doi: 10.1002/1348-9585.12115 [published Online First: 2020/06/10]

40. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43(1):87-91. doi: 10.1016/0895-4356(90)90060-3

41. Miftahussurur M, Yamaoka Y. Diagnostic Methods of Helicobacter pylori Infection for Epidemiological Studies: Critical Importance of Indirect Test Validation. *BioMed research international* 2016;2016:4819423. doi: 10.1155/2016/4819423 [published Online First: 2016/02/24]

42. Inoue M, Sawada N, Goto A, et al. High-Negative Anti-Helicobacter pylori IgG Antibody Titers and Long-Term Risk of Gastric Cancer: Results from a Large-Scale Population-Based Cohort Study in Japan. *Cancer Epidemiol Biomarkers Prev* 2020;29(2):420-26. doi: 10.1158/1055-9965.EPI-19-0993 [published Online First: 2019/12/13]

[dataset] 43. Soichiro A. Data from: Changes in prevalence of Helicobacter pylori in Japan from 2008 to 2018: a repeated cross-sectional study, figshare, July 13, 2022 https://doi.org/10.6084/m9.figshare.14594571.v2

FIGURE LEGENDS

Figure 1

Numbers of participants

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.

Figure 2:

Infection rates of Helicobacter pylori at 35 years old from 2008 to 2018 (men: n = 7,586, women: n= 1,739)

Figure 2

Note. Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51). There were no joinpoints. "*" in the graph legend indicates a significant difference in the

slope from zero at the alpha = 0.05 level.

Figure 3

Infection rates of Helicobacter pylori according to age in 2018 (men: n = 9,580, women: n=1,854)

Figure 3

Note. Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67]; second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30]; second trend: 45–65 years [slope = 1.49]). "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

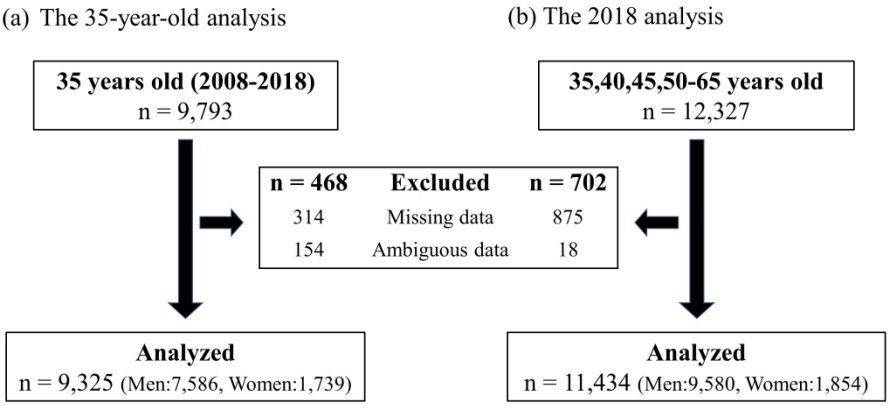


Figure 1: *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The 2018 analysis: participants aged 35–65 years in 2018.

338x190mm (300 x 300 DPI)

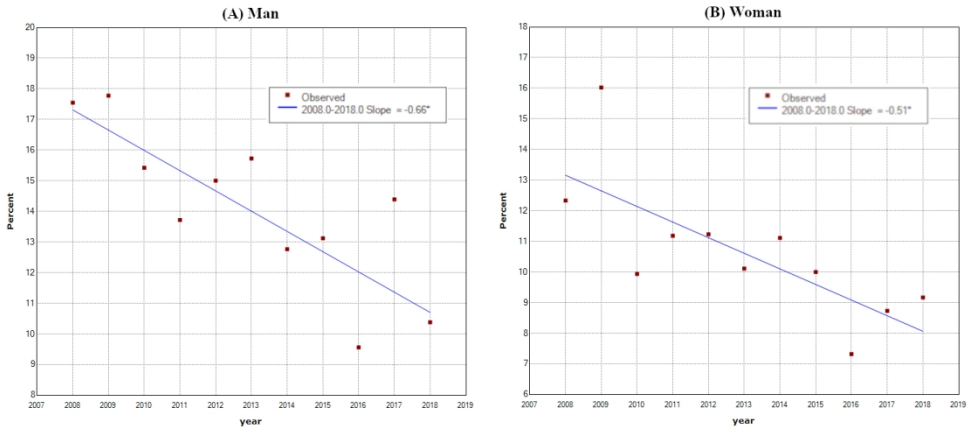


Figure 2: Note. Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51). There were no joinpoints. "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

32x14mm (1200 x 1200 DPI)

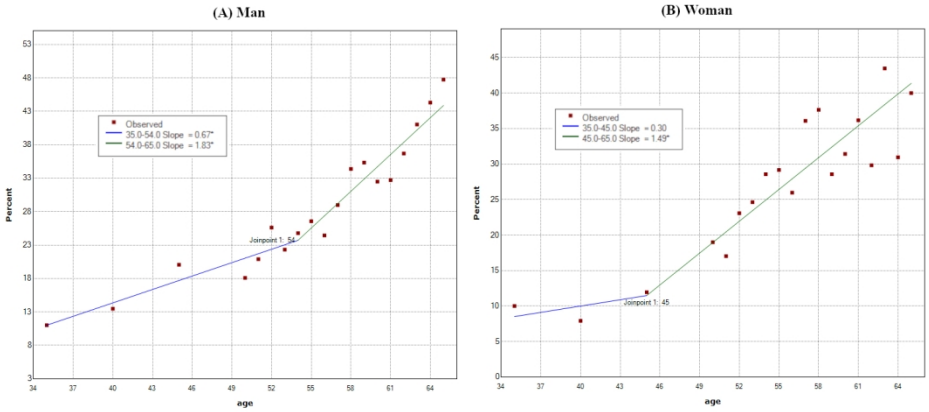


Figure 3: Note. Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67]; second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30]; second trend: 45–65 years [slope = 1.49]). "*" in the graph legend indicates a significant difference in the slope from zero at the alpha = 0.05 level.

35x15mm (1200 x 1200 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	1-3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-8
Bias	#9	Describe any efforts to address potential sources of bias	13-15
Study size	#10	Explain how the study size was arrived at	n/a

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	n/a
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9-10
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	9
Descriptive data	#14a	Give characteristics of study participants (eg demographic,	6, 14-15

		clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9-10
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	9-10
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10-12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13-15

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n/a