

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058774
Article Type:	Original research
Date Submitted by the Author:	27-Oct-2021
Complete List of Authors:	<p>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 Health Kawai, Takashi; Tokyo Medical University, Department of Gastroenterological Endoscopy</p>
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY, HEALTH ECONOMICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE

SCHOLARONE™
Manuscripts



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.

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

3 **Author names:** Soichiro Abiko¹, Yoji Hirayama¹, Junji Otaki^{2 1}, Yoshimi Harada^{2 1}, Kohei
4 Kawakami¹, Takahiro Toi¹, Tomoko Takamiya³, Takashi Kawai⁴

5 **Author Affiliations:**

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

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

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

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

10 **Corresponding Author:** Soichiro Abiko

11 Email: s_abiko1@tokyo-med.ac.jp

12 **Word count:** 2412

13

14 **ABSTRACT**

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

17 **Design:** Retrospective cross-sectional study.

18 **Setting:** Japanese workers.

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

1
2
3
4
5 20 insurance society who underwent serum *H. pylori* antibody tests in a health checkup from
6
7
8 21 2008 and 2018.

9
10 22 **Measures:** We analyzed the *H. pylori* infection rate among participants aged 35 years from
11
12
13 23 2008 to 2018 and participants aged 35, 40, 45, and 50–65 years in 2018 based on the results
14
15
16 24 of serum antibody tests during the health checkups. In the 2018 analysis, we considered all
17
18
19 25 participants who had undergone eradication treatment for *H. pylori* as infected, regardless of
20
21
22 26 the antibody test results, to reduce the influence of previous treatment. Trend analyses were
23
24
25 27 performed using Joinpoint analysis.

26 28 **Results:** *H. pylori* was detected in 1,290 out of 9,325 participants aged 35 years. The annual
27
28
29 29 infection rates showed a linear downward trend (slope = -0.65) as follows: 16.6% in 2008 to
30
31
32 30 10.1% in 2018. In the 2018 analysis, 2,863 out of 11,434 participants were positive for *H.*
33
34
35 31 *pylori*; moreover, there was an upward trend of the infection rate with advanced age (10.8%
36
37 32 [35 years] to 47.3% [65 years]). The trend showed a Joinpoint, with the trend changing
38
39
40 33 significantly at the age of 50 years (first trend: 35–50 years [slope = 0.57]; second trend: 50–
41
42
43 34 65 years [slope = 1.51]). Although both were upward trends, the second trend was steeper (P
44
45 35 < 0.05).

46
47 36 **Conclusions:** Over the last 11 years, there has been a decrease in the infection rate of *H.*
48
49
50 37 *pylori* in Japanese 35–year olds. The infection rate in 2018 was high with advanced age.
51
52
53 38 There is a consistent declining trend of the *H. pylori* infection rate in Japan.

1
2
3
4
5 39
6
78 **40 Strengths and limitations of this study**
9

- 10 41 • We included very recent data from the general population (non-patients who underwent
11
12 42 medical checkups without special intentions) and applied Joinpoint trend analysis to
13
14
15 43 analyze trends in the *H. pylori* infection rates in Japan.
16
17
18 44 • We enrolled a large number of participants in a single group over a relatively long period.
19
20
21 45 • This study suggests a trend of the infection rate of *H. pylori* using data from 35-year-olds.
22
23
24 46 • In the 2018 analysis, the participants' history of eradication treatment for *H. pylori* was
25
26 47 determined through questionnaires.
27
28
29 48 • This study has limitations regarding the possibility of group bias (including occupational,
30
31 49 sex ratio, and medical history).
32
33

34 50
3536
37 **51 INTRODUCTION**
38

39 52 *Helicobacter pylori* (*H. pylori*) is a gram-negative bacterium that is often found in the human
40
41
42 53 stomach. *H. pylori* is among the causes of chronic gastritis, duodenal ulcers, gastric ulcers,
43
44
45 54 immune thrombocytopenia, gastric mucosa-associated lymphoid tissue lymphoma, and
46
47
48 55 gastric cancer. The International Agency for Research on Cancer Working group, which is a
49
50
51 56 part of the World Health Organization, classified *H. pylori* as a Group 1 carcinogen for gastric
52
53 57 cancer in 1994.¹ Moreover, they recognized eradication therapy for *H. pylori* in
54
55
56
57
58
59
60

1
2
3
4
5 58 asymptomatic populations as efficient for preventing gastric cancer and recommended
6
7
8 59 introducing population-based *H. pylori* screening and treatment programs.²
9

10 60 *H. pylori* test-and-treat strategy for preventing gastric cancer is considered more
11
12
13 61 effective in regions with a high incidence of gastric cancer.³ The incidence and mortality
14
15
16 62 rates of gastric cancer are high; moreover, *H. pylori* could be involved > 90% in Japan.^{4 5}
17
18
19 63 Additionally, the infection rate of *H. pylori* in Japan is higher than that in other developed
20
21
22 64 countries.⁶ Accordingly, the “test-and-treat” strategy for *H. pylori* could be a good measure
23
24
25 65 for preventing gastric cancer in Japan. In 2013, the national health insurance scheme covered
26
27
28 66 the *H. pylori* eradication therapy for chronic gastritis in Japan. Several groups in Japan,
29
30
31 67 including company health insurance societies and local municipalities, have introduced *H.*
32
33
34 68 *pylori* screening tests for asymptomatic people during medical check-ups for the prophylactic
35
36
37 69 intervention of gastric cancer.
38

39
40 71 Decreasing the *H. pylori* infection rate could reduce the incidence rate of gastric
41
42
43 72 cancer⁷ and reduce the positive predictive value of *H. pylori* screening. Therefore, decreasing
44
45
46 73 the *H. pylori* infection rate in the population may negatively affect the cost-effectiveness of
47
48
49 74 the “test-and-treat” strategy for asymptomatic groups. It is important to elucidate the
50
51
52 75 prevalence of *H. pylori* and its trends to predict the infection rate and plan future strategies.
53
54
55 76 There has been a decrease in the worldwide prevalence of *H. pylori*,⁶ with several Japanese
56
57
58
59
60

1
2
3
4
5 77 studies reporting similar results.⁸ However, most of these studies had small sample sizes or
6
7
8 78 included specific participants, including hospital visitors, or meta-analyses. To our
9
10
11 79 knowledge, there have been no recent large-scale studies on the annual prevalence and trend
12
13 80 of infection rates of *H. pylori* in Japan.^{9,8,10} Additionally, several studies have reported that
14
15 81 the *H. pylori* infection rates become steady at approximately 10% in several low-prevalence
16
17
18 82 regions, including European countries.^{6 11 12} Watanabe et al. suggested that the declining
19
20
21 83 trend of the *H. pylori* prevalence in Japan appears to become dull.¹⁰ This study aimed to
22
23
24 84 elucidate the recent trend in the infection rate of *H. pylori* and whether it showed a significant
25
26
27 85 change.

28
29 86 Using data from health checkups in a company health insurance society, this
30
31
32 87 retrospective cross-sectional study aimed to clarify the recent 11-year trend of *H. pylori*
33
34
35 88 infection rate in 35-year-olds and *H. pylori* infection rates in 2018 according to age.

36
37 89

38 39 90 **MATERIALS AND METHODS**

40
41
42 91 Members of the T company health insurance society undergo serum anti-*Helicobacter pylori*
43
44
45 92 IgG antibody tests. This test was conducted annually on members aged 35 years during their
46
47
48 93 health checkups (approximately 600–1,100 people per year). However, in 2018, the society
49
50
51 94 offered this test to participants aged 35, 40, 45, and > 50 years. We included members who
52
53
54 95 had undergone serum *H. pylori* antibody tests at their annual health checkups from April 1,

1
2
3
4
5 96 2008, to March 31, 2019, at the age of 35–65 years. Participants' data, including medical
6
7
8 97 questionnaires and blood test results, were anonymously obtained from the annual health
9
10
11 98 checkup database of the health insurance society. We excluded data from individuals who
12
13 99 refused academic use of their data.
14
15

100

101 **Statistical analysis**

102 First, we analyzed data obtained from 35-year-old participants between 2008 and
103 2018 to determine trends in *H. pylori* infection rates (“35-year-old analysis”), with positive
104 results of serum antibody tests for *H. pylori* indicating *H. pylori* infection. We calculated the
105 annual infection rates based on the antibody test results. Subsequently, we analyzed the trend
106 of the rates. Second, we analyzed data from participants aged 35, 40, 45, and 50–65 years old
107 obtained in 2018 according to age to determine generational differences in the infection rates
108 (“2018 analysis”).

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

1
2
3
4
5 115 We performed Joinpoint Trend Analysis¹³ to identify trends in the infection rate and
6
7
8 116 their changes over time using Joinpoint Regression Program 4.9.0.0.¹⁴ Statistical significance
9
10
11 117 was set at $P < 0.05$. We measured serum anti-*Helicobacter pylori* IgG using enzyme-linked
12
13 118 immunosorbent assay with E-Plate Eiken *H. pylori* antibody or E-Plate II Eiken *H. pylori*
14
15 119 antibody (Eiken Chemical Co. Ltd., Tokyo, Japan). The cut-off level was set at 10 U/mL,¹⁵
16
17
18 120 with values above this value being classified as positive. Data with missing or ambiguous
19
20
21 121 figures were excluded from the analysis.
22
23
24 122

25 26 123 **Patient and public involvement**

27
28
29 124 No patients were involved in this study. T company health insurance society
30
31
32 125 acknowledged the importance of this study concept and allowed the collection of the
33
34 126 participants' data. The results of this study are published as a report.
35
36
37 127

38 39 128 **Ethical approval**

40
41
42 129 This study protocol was reviewed and approved by the Institutional Review Board of
43
44
45 130 Tokyo Medical University (T2019-0044). Following the Ethical Guidelines for Medical and
46
47
48 131 Health Research Involving Human Subjects,¹⁶ the study information was shown on the
49
50
51 132 websites of the institutions where the researchers or participants belonged. Participants'
52
53 133 consent for using data was obtained through an opt-out option.
54
55
56
57
58
59
60

1
2
3
4
5 134
6
7

8 135 **RESULTS**
9

10 136 There were 9,793 and 12,327 participants in the 35-year-old and 2018 analyses, respectively,
11
12
13 137 with 592 participants overlapping in both analyses. In the 35-year-old analysis, 468
14
15 138 participants were excluded for having missing (n = 314) ambiguous data (n = 154) in the
16
17 139 records, with 9,325 participants (7,586 men; 1,739 women) being included in the final
18
19 140 analysis. In the 2018 analysis, 893 participants were excluded for having missing (n = 875)
20
21 141 ambiguous data (n = 18) in the records, with 11,434 participants (9,580 men; 1,854 women)
22
23 142 being included in the final analysis (Figure 1).
24
25
26
27
28

29 143
30

31 144
32
33

34 145
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

147 **The 35-year-old analysis**

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

154 **The 2018 analysis**

155 In the 2018 analysis, 2,863 (2,432 male; 431 female) participants were infected with
156 *H. pylori*. The infection rates showed a trend of increasing positive rates with advanced age
157 (10.8% in 35 years to 47.3% in 65 years). This trend had a Joinpoint at the age of 50 years
158 (95% CI: 45–57), with two different trends in the slope before and after the point. Specifically,
159 the first and second trends were 35–50 years (slope = 0.57) and 50–65 years (slope = 1.51).
160 Both trends showed linear upward trends with age, with the second trend being significantly
161 steeper than the first trend (P < 0.05) (Figure 3).

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

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

1
2
3
4
5 167 upward trend with advanced age, moreover, analysis of men, but not women, showed a
6
7
8 168 Joinpoint at the age of 54 years (95% CI: 45–58 years) (Supplementary Figure 1).
9

10 169

11
12
13 170

14
15 171 **DISCUSSION**

16
17
18 172 This study investigated the trend in the prevalence of *H. pylori* infection in Japan based on
19
20
21 173 large-scale health checkup data. In the 35-year-old analysis, the infection rate showed a linear
22
23
24 174 declining trend from 2008 to 2018. This demonstrates a declining trend of the *H. pylori*
25
26 175 infection rate in this large Japanese general population.
27

28
29 176

30
31 177 In the 35-year-old analysis, the infection rate straightforwardly reached
32
33
34 178 approximately 10%; further, this downward trend did not significantly change during the
35
36
37 179 observation period. In the 35-year-old analysis, the infection rates were significantly less
38
39
40 180 affected by eradication treatment; therefore, this finding could well describe the trend of the
41
42
43 181 incidence rate of *H. pylori* infections in Japan. If the downward trend (slope = 0.65) observed
44
45 182 in the 35-year-old analysis continues, the infection rate will reach nearly zero around 2035.
46
47
48 183 Contrastingly, recent studies on junior high school students (age: 12–15 years) in Japan have
49
50
51 184 demonstrated that the infection rate of this generation when they reach 35 years at around
52
53 185 2035 will be approximately 3–5%,¹⁷⁻²⁰ which is higher than our prediction. This
54
55
56
57
58
59
60

1
2
3
4
5 186 inconsistency suggests that the decrease in the infection rate may have slowed down.
6
7

8 187

9
10 188 In the 2018 analysis, the infection rate increased with advanced age; moreover, there

11
12
13 189 was a declining trend in the prevalence rate of *H. pylori* in the Japanese general population.

14
15 190 Further, there was a Joinpoint at the age of 50 years, which indicates a change affecting the

16
17
18 191 *H. pylori* infection near this age (Figure 3). Chronic *H. pylori* infection is mostly established

19
20
21 192 in the human stomach during childhood.^{21 22} Drinking water and family members are among

22
23
24 193 the sources of *H. pylori* infection.²³ From the late 1960s to the 1970s, which is when people

25
26 194 aged 50 years in 2018 spent their childhood, Japan experienced rapid economic growth and

27
28
29 195 urbanization. Accordingly, there was a rapid increase in water supply penetration and a

30
31
32 196 decrease in the average number of households.^{24 25} This rapid environmental change may

33
34
35 197 have influenced the establishment of *H. pylori* infection; consequently, there was a rapid

36
37
38 198 decrease in the prevalence of this bacterium during this era. Watanabe et al. revealed changes

39
40
41 199 in the declining trend of *H.pylori* infection rate and indicated an effect of environmental

42
43
44 200 changes on the infection rate,¹⁰ which is consistent with our findings.

45
46
47 201

48
49
50 202 Participants in the 35-year-old analysis were born after 1973; therefore, they may

51
52
53 203 have not undergone rapid environmental changes as those in 1955–1972. The 35-year-old

54
55
56 204 analysis revealed a recent gradual decrease in the *H. pylori* infection rate. This suggests that

1
2
3
4
5 205 factors other than hygiene and family structure may influence infection establishment. As
6
7
8 206 aforementioned, *H. pylori* infections are likely to be established during childhood through
9
10 207 parent-to-child transmission.²² In addition to hygienic and environmental improvements, the
11
12
13 208 spread of ready-made baby food after around 1970 may have contributed to the decreased *H.*
14
15 209 *pylori* infection rate.²⁶ With the recently increasing recognition of *H. pylori* in the general
16
17
18 210 population and coverage of eradication treatment through national insurance, there has been
19
20
21 211 an increase in the number of *H. pylori* eradication treatments in Japan.²⁷ If treatment
22
23
24 212 decreases the infection rate in child-rearing generation, it could accelerate the declining speed
25
26 213 of the infection rates in the next generations.

27
28
29 214

30
31 215 In the 2018 analysis, men, but not women, showed a Joinpoint trend. This suggests
32
33
34 216 sex differences in the trend of *H. pylori* infection; however, given the sex bias in the number
35
36
37 217 of participants (9580 men and 1854 women), we cannot conclude about the sex difference.
38
39
40 218 This should be investigated in future studies.

41
42 219

43
44
45 220 When conducting *H. pylori* screening tests for prophylactic purposes, the prevalence
46
47
48 221 in a target group should be considered to evaluate the effectiveness of the strategy. We
49
50
51 222 observed a decreasing infection rate of *H. pylori* in Japan. In the future, the infection rate
52
53 223 may reach zero; accordingly, there would be a decreased importance of screening tests for

1
2
3
4
5 224 this bacterium in asymptomatic people. A study on the cost-effectiveness of the test-and-
6
7
8 225 treatment strategy for *H. pylori* revealed that it remained effective even with a low infection
9
10
11 226 rate of approximately 5%.²⁸ Our findings could inform future public health strategies.
12
13 227 Moreover, considering the decrease in *H. pylori* prevalence, *H. pylori* infection-negative
14
15 228 gastric cancer has lately been receiving attention.^{29 30 31} Research for risk factors of gastric
16
17
18 229 cancer other than *H. pylori* is also needed.
19
20
21 230

22 231 **Limitations**

23
24
25
26 232 This study has several limitations. First, there might have been selective bias,
27
28
29 233 including age, sex, occupation, region, and nationality (possibly including several workers
30
31
32 234 who were born and raised in countries other than Japan). Several studies have analyzed
33
34
35 235 differences in the infection rates according to sex, occupation, and region, with a study
36
37
38 236 reporting a higher infection rate in men; however, there remains no consensus regarding these
39
40
41 237 biases.³²⁻³⁴ A recent study showed that employees in a large company are in better health than
42
43
44 238 those in a small one.³⁵ The size of the target group could have yielded a bias. However, this
45
46
47 239 study could have insignificant healthy candidate bias since we targeted all health society
48
49
50 240 members. We could not determine the number structure of all society members, which could
51
52
53 241 limit the generalization of our findings to the general population. Heterogeneity of age gaps
54
55
56 242 between age groups and limitation of the target ages may have weakened analyses, especially
57
58
59
60

1
2
3
4
5 243 in younger age groups. Additionally, the history of *H. pylori* eradication may have influenced
6
7
8 244 our findings. In 2008, T company insurance society performed serum *H. pylori* antibody
9
10 245 screening tests for all its members. Therefore, there may have been a higher proportion of
11
12
13 246 post-eradication cases in our study than in the general population. We attempted to reduce
14
15
16 247 the influence of eradication treatment by classifying patients who underwent eradication
17
18 248 treatment as infected. However, history information acquired through a self-reported
19
20
21 249 questionnaire could have contained inaccuracies, including recall bias.³⁶ In the 35-year-old
22
23
24 250 analysis, we could not obtain information regarding previous eradication treatment.
25
26 251 Moreover, we performed analysis based on the assumption that the rate of eradication
27
28
29 252 treatment among participants in the 35-year-old analysis was low due to their younger age
30
31
32 253 and that treatment has an insignificant influence on the infection rate. A follow-up survey of
33
34 254 the same society between 2018 and 2020 showed that the rate of eradication treatment was
35
36
37 255 0.9%, 2.1%, and 1.4% in 2018, 2019, and 2020, respectively. Although this supports our
38
39
40 256 assumption, it indicates the possibility of errors of 1%–2 % in the infection rates of the 35-
41
42
43 257 year-old analysis. Additionally, previous medical history; medications; and measurement
44
45 258 biases, including test characteristics and threshold application in the test (including high-
46
47
48 259 negative issues), could have influenced our results.^{37 38}

260

261 **CONCLUSION**

1
2
3
4
5 262 Our findings demonstrated a decrease in the infection rate of *H. pylori* among 35-year-olds
6
7
8 263 in Japan from 2008 to 2018. The infection rate of *H. pylori* may continue to decrease in the
9
10
11 264 future. We expect the infection rate of *H. pylori* to continue decreasing, and it would be
12
13 265 difficult to rely solely on the *H. pylori* test and treatment strategy to achieve gastric cancer
14
15 266 prevention. Other risk factors of gastric cancer other than *H. pylori* should be considered.
16
17
18 267

21 268 **Acknowledgment**

22
23 269 We would like to acknowledge the T company health insurance society. We would like to
24
25
26 270 thank Editage (www.editage.com) for the English language editing.
27
28

29 271

30
31 272

34 273 **Footnotes**

35
36
37 274 **Contributors:** SA designed the study, analyzed the data, and drafted the manuscript. Y
38
39 275 Hirayama contributed to the study design and performed general supervision of a whole study.
40
41
42 276 JO, Y Harada, and T Toi assisted in conducting the study, interpreting the results, and
43
44
45 277 revising the manuscript. KK and TK contributed to data collection and provided advice and
46
47
48 278 opinions from an expert perspective. TT contributed to data analysis and revising the
49
50 279 manuscript from statistical and public health perspectives. All authors read and approved the
51
52
53 280 final manuscript.
54
55
56
57
58
59
60

1
2
3
4
5 281

6
7
8 282 **Funding:** This research received no specific grant from any funding agency in the public,
9
10 283 commercial, or not-for-profit sectors.

11
12
13 284

14
15 285 **Competing interests:** None declared.

16
17
18 286

19
20
21 287 **Patient consent for publication:** Not required.

22
23
24 288

25
26 289 **Ethics approval:** The institutional review boards of Tokyo Medical University (T2019-
27
28 0044)

29
30
31 291

32
33
34 292 **Provenance and peer review:** Not commissioned; externally peer-reviewed.

35
36
37 293

38
39 294 **Data sharing statement:** Data is available in a public, open access repository.

40
41
42 295 Figshare, <https://figshare.com/s/e94123c7270ca1e09084>,

43
44
45 296 DOI: 10.6084/m9.figshare.14594571, CC BY

46
47
48 297

49
50
51 298

52
53 299 **REFERENCES**

- 1
2
3
4
5 300 1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes,
6
7
8 301 Liver Flukes and *Helicobacter pylori*. Lyon (FR): International Agency for Research
9
10 302 on Cancer 1994.
- 11
12
13 303 2. IARC *Helicobacter pylori* Working Group. *Helicobacter pylori* Eradication as a Strategy for
14
15 304 Preventing Gastric Cancer: International Agency for Research on Cancer 2014.
- 16
17
18 305 3. Ford AC, Forman D, Hunt RH, et al. *Helicobacter pylori* eradication therapy to prevent
19
20 306 gastric cancer in healthy asymptomatic infected individuals: systematic review and
21
22 307 meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174. doi:
23
24 308 10.1136/bmj.g3174
- 25
26
27
28
29 309 4. Center for Cancer Control and Information Services, National Cancer Center. CANCER
30
31 310 STATISTICS IN JAPAN '19 [updated 17 April 2020. Available from:
32
33 311 https://ganjoho.jp/en/professional/statistics/brochure/2019_en.html accessed 22
34
35 312 Dec 2020.
- 36
37
38
39 313 5. Matsuo T, Ito M, Takata S, et al. Low prevalence of *Helicobacter pylori*-negative gastric
40
41 314 cancer among Japanese. *Helicobacter* 2011;16(6):415-9. doi: 10.1111/j.1523-
42
43 315 5378.2011.00889.x [published Online First: 2011/11/09]
- 44
45
46
47 316 6. Peleteiro B, Bastos A, Ferro A, et al. Prevalence of *Helicobacter pylori* infection worldwide:
48
49 317 a systematic review of studies with national coverage. *Dig Dis Sci* 2014;59(8):1698-
50
51 318 709. doi: 10.1007/s10620-014-3063-0 [published Online First: 2014/02/25]
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5 319 7. Tsuda M, Asaka M, Kato M, et al. Effect on *Helicobacter pylori* eradication therapy against
6
7 320 gastric cancer in Japan. *Helicobacter* 2017;22(5) doi: 10.1111/hel.12415 [published
8
9
10 321 Online First: 2017/08/05]
11
12
13 322 8. Wang C, Nishiyama T, Kikuchi S, et al. Changing trends in the prevalence of *H. pylori*
14
15 323 infection in Japan (1908-2003): a systematic review and meta-regression analysis
16
17
18 324 of 170,752 individuals. *Sci Rep* 2017;7(1):15491. doi: 10.1038/s41598-017-
19
20
21 325 15490-7 [published Online First: 2017/11/16]
22
23
24 326 9. Inoue M. Changing epidemiology of *Helicobacter pylori* in Japan. *Gastric Cancer*
25
26 327 2017;20(Suppl 1):3-7. doi: 10.1007/s10120-016-0658-5 [published Online First:
27
28
29 328 2016/10/21]
30
31
32 329 10. Watanabe M, Ito H, Hosono S, et al. Declining trends in prevalence of *Helicobacter*
33
34 330 *pylori* infection by birth-year in a Japanese population. *Cancer Sci*
35
36
37 331 2015;106(12):1738-43. doi: 10.1111/cas.12821 [published Online First:
38
39
40 332 2015/09/24]
41
42
43 333 11. Carmack SW, Genta RM. *Helicobacter pylori* seroprevalence in symptomatic veterans:
44
45 334 a study of 7310 patients over 11 years. *Helicobacter* 2009;14(4):298-302. doi:
46
47
48 335 10.1111/j.1523-5378.2009.00693.x
49
50
51 336 12. den Hoed CM, Vila AJ, Holster IL, et al. *Helicobacter pylori* and the birth cohort effect:
52
53 337 evidence for stabilized colonization rates in childhood. *Helicobacter*
54
55
56
57
58
59
60

- 1
2
3
4
5 338 2011;16(5):405-9. doi: 10.1111/j.1523-5378.2011.00854.x [published Online
6
7
8 339 First: 2011/09/20]
9
10 340 13. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with
11
12 341 applications to cancer rates. *Stat Med* 2000;19(3):335-51. doi: 10.1002/(sici)1097-
13
14 342 0258(20000215)19:3<335::aid-sim336>3.0.co;2-z [published Online First:
15
16 343 2000/01/29]
17
18
19
20 344 14. Joinpoint Regression Program [program]. Version 4.9.0.0 version: Statistical
21
22 345 Methodology and Applications Branch, Surveillance Research Program, National
23
24 346 Cancer Institute., March 2021.
25
26
27
28 347 15. Komatsu Y, Sugiyama T, Asaka M. Helicobacter pylori kansenshinden ni okeru
29
30 348 nihonjinkabu wo siyou sita ELISA kit " E-plate eiken H.pylori koutai" no yuyousei no
31
32 349 kentou [Study of effectiveness of E-plate eiken which is ELAISA kit using Japanese
33
34 350 strain in diagnose of Helicobacter pylori infection]. *The Journal of Clinical Laboratory*
35
36 351 *Instruments and Reagents* 2001;24(5):331-35.
37
38
39
40 352 16. Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health
41
42 353 Research Involving Human Subjects 2015 [Available from:
43
44 354 [https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf)
45
46 355 [Daijinkanboukouseikagakuka/0000080278.pdf](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf) accessed 6 Dec 2020.
47
48
49
50
51
52 356 17. Kusano C, Gotoda T, Ishikawa H, et al. The administrative project of Helicobacter pylori
53
54
55
56
57
58
59
60

- 1
2
3
4
5 357 infection screening among junior high school students in an area of Japan with a
6
7
8 358 high incidence of gastric cancer. *Gastric Cancer* 2017;20(Suppl 1):16-19. doi:
9
10 359 10.1007/s10120-017-0688-7 [published Online First: 2017/01/18]
11
12
13 360 18. Honma H, Nakayama Y, Kato S, et al. Clinical features of *Helicobacter pylori* antibody-
14
15 361 positive junior high school students in Nagano Prefecture, Japan. *Helicobacter*
16
17
18 362 2018:e12559. doi: 10.1111/hel.12559 [published Online First: 2018/12/06]
19
20
21 363 19. Nakayama Y, Lin Y, Hongo M, et al. *Helicobacter pylori* infection and its related factors
22
23 364 in junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2017;22(2)
24
25
26 365 doi: 10.1111/hel.12363 [published Online First: 2016/10/28]
27
28
29 366 20. Kakiuchi T, Matsuo M, Endo H, et al. A *Helicobacter pylori* screening and treatment
30
31 367 program to eliminate gastric cancer among junior high school students in Saga
32
33
34 368 Prefecture: a preliminary report. *J Gastroenterol* 2019 doi: 10.1007/s00535-019-
35
36
37 369 01559-9 [published Online First: 2019/02/17]
38
39
40 370 21. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and *Helicobacter pylori*. *J*
41
42 371 *Infect Dis* 1993;168(1):219-21. doi: 10.1093/infdis/168.1.219
43
44
45 372 22. O'Ryan ML, Lucero Y, Rabello M, et al. Persistent and transient *Helicobacter pylori*
46
47 373 infections in early childhood. *Clin Infect Dis* 2015;61(2):211-8. doi:
48
49
50 374 10.1093/cid/civ256
51
52
53 375 23. Ueda M, Kikuchi S, Kasugai T, et al. *Helicobacter pylori* risk associated with childhood
54
55
56
57
58
59
60

- 1
2
3
4
5 376 home environment. *Cancer Sci* 2003;94(10):914-8. doi: 10.1111/j.1349-
6
7
8 377 7006.2003.tb01375.x [published Online First: 2003/10/15]
9
10 378 24. JAPAN WATER WORKS ASSOCIATION. Water Supply in Japan 2017 [Available from:
11
12
13 379 http://www.jwwa.or.jp/jigyoku/kaigai_file/2017WaterSupplyInJapan.pdf accessed
14
15 380 Dec 22 2020.
16
17
18 381 25. Ministry of Health, Labour and Welfare. General Welfare and Labour Japan [Available
19
20
21 382 from: <https://www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf> accessed 1st Oct
22
23 383 2020.
24
25
26 384 26. Council JBF. Seisan Tokei [Production statistics] Japan [Available from:
27
28
29 385 <https://www.baby-food.jp/link/ayumi-jikei.html> accessed 11 Dec 2020.
30
31
32 386 27. Hiroi S, Sugano K, Tanaka S, et al. Impact of health insurance coverage for *Helicobacter*
33
34 387 *pylori* gastritis on the trends in eradication therapy in Japan: retrospective
35
36 388 observational study and simulation study based on real-world data. *BMJ Open*
37
38
39 389 2017;7(7):e015855. doi: 10.1136/bmjopen-2017-015855 [published Online First:
40
41
42 390 2017/08/02]
43
44
45 391 28. Kowada A. Cost-effectiveness of *Helicobacter pylori* screening followed by eradication
46
47 392 treatment for employees in Japan. *Epidemiol Infect* 2018;146(14):1834-40. doi:
48
49
50 393 10.1017/S095026881800208X [published Online First: 2018/07/31]
51
52
53 394 29. Kato S, Matsukura N, Tsukada K, et al. *Helicobacter pylori* infection-negative gastric
54
55
56
57
58
59
60

- 1
2
3
4
5 395 cancer in Japanese hospital patients: Incidence and pathological characteristics.
6
7 396 *Cancer Sci* 2007;98(6):790-94. doi: <https://doi.org/10.1111/j.1349->
8
9 397 7006.2007.00478.x
10
11
12
13 398 30. Yamamoto Y, Fujisaki J, Omae M, et al. Helicobacter pylori-negative gastric cancer:
14
15 399 characteristics and endoscopic findings. *Digestive endoscopy : official journal of the*
16
17 400 *Japan Gastroenterological Endoscopy Society* 2015;27(5):551-61. doi:
18
19 401 10.1111/den.12471 [published Online First: 2015/03/27]
20
21
22
23 402 31. Takita M, Ohata K, Inamoto R, et al. Endoscopic and histological features of Helicobacter
24
25 403 pylori-negative differentiated gastric adenocarcinoma arising in the antrum. *JGH*
26
27 404 *open : an open access journal of gastroenterology and hepatology* 2021;5(4):470-
28
29 405 77. doi: 10.1002/jgh3.12518 [published Online First: 2021/04/17]
30
31
32
33
34 406 32. Kheyre H, Morais S, Ferro A, et al. The occupational risk of Helicobacter pylori infection:
35
36 407 a systematic review. *Int Arch Occup Environ Health* 2018;91(6):657-74. doi:
37
38 408 10.1007/s00420-018-1315-6
39
40
41
42 409 33. Ueda J, Gosho M, Inui Y, et al. Prevalence of Helicobacter pylori infection by birth year
43
44 410 and geographic area in Japan. *Helicobacter* 2014;19(2):105-10. doi:
45
46 411 10.1111/hel.12110 [published Online First: 2014/02/11]
47
48
49
50 412 34. Ferro A, Morais S, Pelucchi C, et al. Sex differences in the prevalence of Helicobacter
51
52 413 pylori infection: an individual participant data pooled analysis (StoP Project). *Eur J*

1
2
3
4
5 414 *Gastroenterol Hepatol* 2019;31(5):593-98. doi: 10.1097/MEG.0000000000001389

6
7
8 415 [published Online First: 2019/03/07]

9
10 416 35. Kanamori S, Tsuji T, Takamiya T, et al. Size of company of the longest-held job and

11
12
13 417 mortality in older Japanese adults: A 6-year follow-up study from the Japan

14
15
16 418 Gerontological Evaluation Study. *J Occup Health* 2020;62(1):e12115. doi:

17
18 419 10.1002/1348-9585.12115 [published Online First: 2020/06/10]

19
20
21 420 36. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43(1):87-91.

22
23
24 421 doi: 10.1016/0895-4356(90)90060-3

25
26 422 37. Miftahussurur M, Yamaoka Y. Diagnostic Methods of Helicobacter pylori Infection for

27
28
29 423 Epidemiological Studies: Critical Importance of Indirect Test Validation. *BioMed*

30
31
32 424 *research international* 2016;2016:4819423. doi: 10.1155/2016/4819423

33
34
35 425 [published Online First: 2016/02/24]

36
37 426 38. Inoue M, Sawada N, Goto A, et al. High-Negative Anti-Helicobacter pylori IgG Antibody

38
39
40 427 Titers and Long-Term Risk of Gastric Cancer: Results from a Large-Scale Population-

41
42
43 428 Based Cohort Study in Japan. *Cancer Epidemiol Biomarkers Prev* 2020;29(2):420-

44
45 429 26. doi: 10.1158/1055-9965.EPI-19-0993 [published Online First: 2019/12/13]

46
47 430

48
49
50 431

51
52
53 432 **FIGURE LEGENDS**

54
55 433 **Figure 1**

1
2
3
4
5 434 *Numbers of participants*

6
7
8 435

9
10 436 *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The
11
12
13 437 2018 analysis: participants aged 35–65 years in 2018.

14
15
16 438

17
18 439 **Figure 2**

19
20 440 *Infection rates of Helicobacter pylori at 35 years old from 2008 to 2018 (n = 9,325)*

21
22
23 441

24
25 442 *Note.* Infection rates at 35 years linearly decreased from 16.6% in 2008 to 10.1% in 2018,
26
27
28 443 with a slope of -0.65. There was no Joinpoint. “*” in the graph legend indicates a
29
30 444 significant difference in the slope from zero at the alpha = 0.05 level.

31
32
33 445

34
35 446 **Figure 3**

36 447 *Infection rates of Helicobacter pylori according to age in 2018 (n = 11,434)*

37
38 448

39
40 449 *Note.* Infection rates increased in two trends: 10.8% at 35 years to 18.2% at 50 years with a
41
42 450 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
43
44
45 451 Joinpoint at the age of 50 years. “*” in the graph legend indicates a significant difference in
46
47
48 452 the slope from zero at the alpha = 0.05 level.

49
50 453

51
52 454 **Supplementary Figure 1**

53 455 *Sex difference in the trends of Helicobacter pylori infection rate in 2018*

54
55 456

1
2
3
4
5 457 *Note.* The two graphs show trends of *the H. pylori* positive rate according to age in 2018 in
6
7
8 458 men and women. There were two trends and Joinpoint in men aged 54 years but not in women.
9
10 459 “*” in the graph legend indicates a significant difference in the slope from zero at the alpha
11
12
13 460 = 0.05 level.
14
15

16 461
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

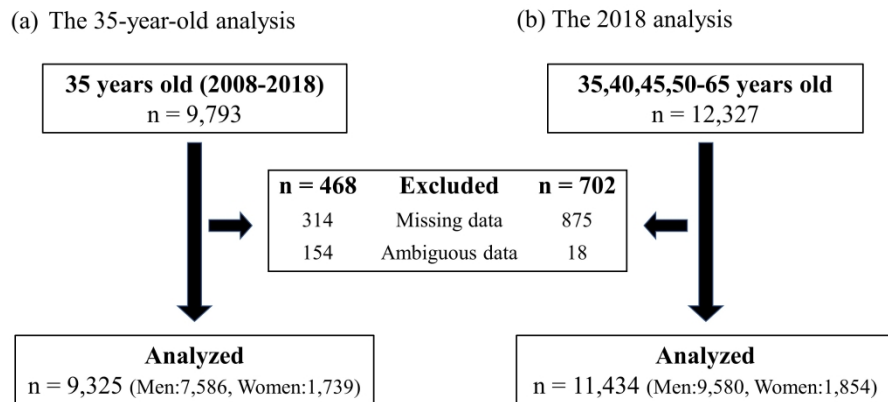
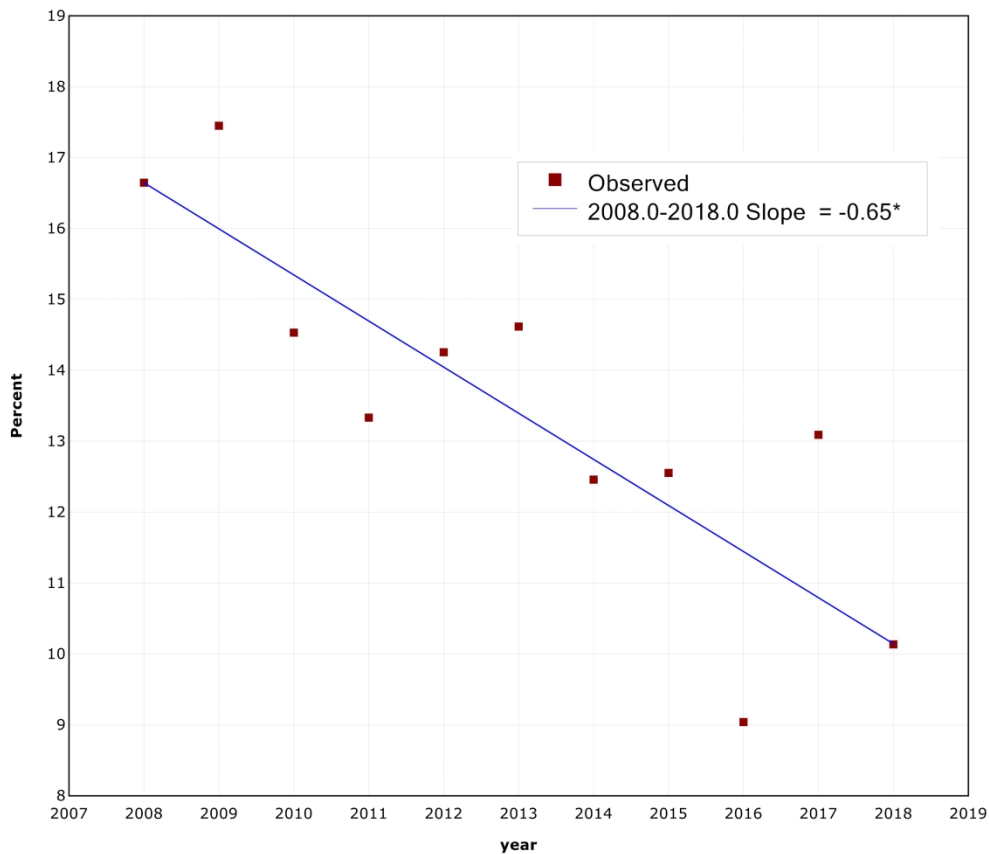


Figure 1: *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The 2018 analysis: participants aged 35–65 years in 2018.

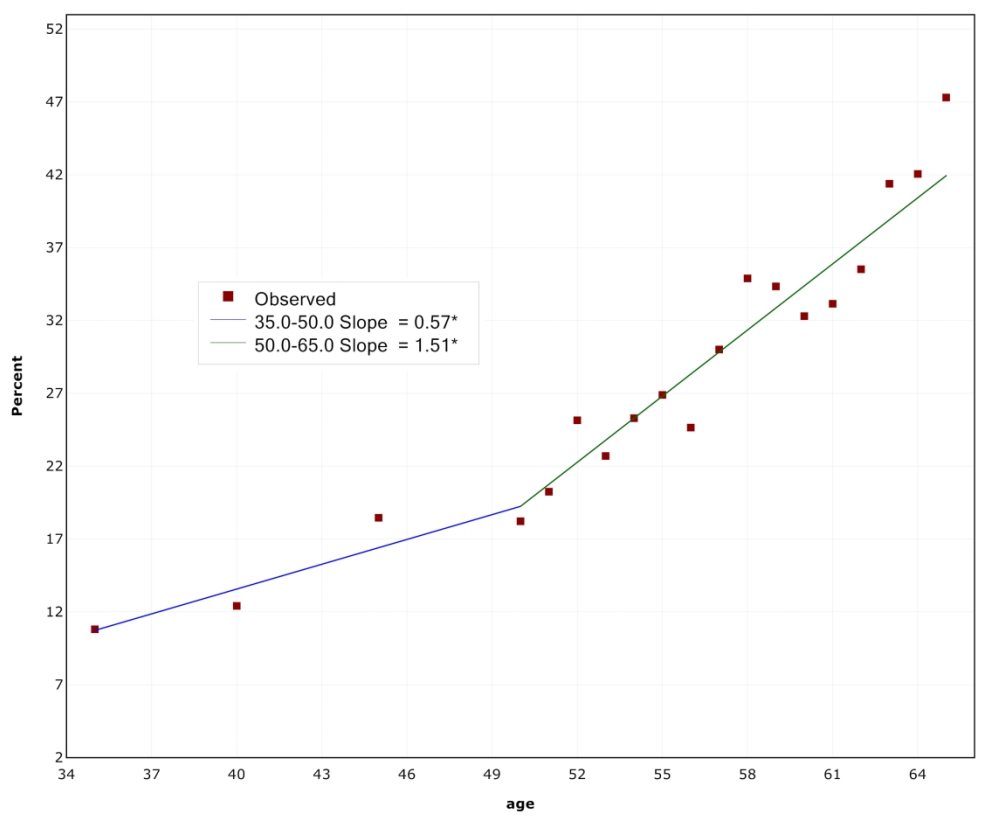
338x190mm (300 x 300 DPI)



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.

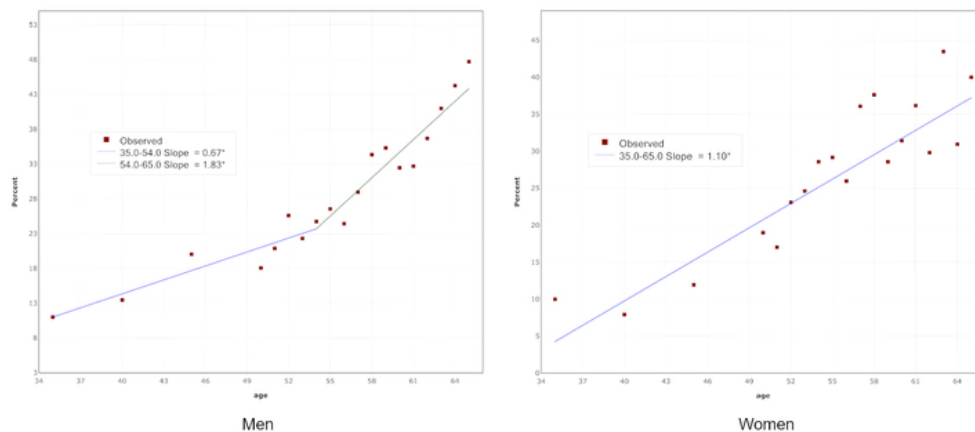
141x122mm (600 x 600 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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)



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 sectional reporting guidelines, and cite them as:

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

			Page
		Reporting Item	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

1	Quantitative	#11	Explain how quantitative variables were handled in the	n/a
2				
3	variables		analyses. If applicable, describe which groupings were chosen,	
4				
5			and why	
6				
7				
8				
9	Statistical	#12a	Describe all statistical methods, including those used to control	6-7
10				
11	methods		for confounding	
12				
13				
14	Statistical	#12b	Describe any methods used to examine subgroups and	6-7
15				
16	methods		interactions	
17				
18				
19	Statistical	#12c	Explain how missing data were addressed	7
20				
21	methods			
22				
23				
24				
25	Statistical	#12d	If applicable, describe analytical methods taking account of	n/a
26				
27	methods		sampling strategy	
28				
29				
30	Statistical	#12e	Describe any sensitivity analyses	n/a
31				
32	methods			
33				
34				
35				
36	Results			
37				
38				
39	Participants	#13a	Report numbers of individuals at each stage of study—eg	8-9
40				
41			numbers potentially eligible, examined for eligibility, confirmed	
42				
43			eligible, included in the study, completing follow-up, and	
44				
45			analysed. Give information separately for for exposed and	
46				
47			unexposed groups if applicable.	
48				
49				
50				
51	Participants	#13b	Give reasons for non-participation at each stage	8
52				
53				
54	Participants	#13c	Consider use of a flow diagram	8
55				
56				
57	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5-6, 13-
58				
59				
60				

clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.

1			14
2			
3			
4			
5			
6			
7			
8	Descriptive data	#14b	8-9
9		Indicate number of participants with missing data for each	
10		variable of interest	
11			
12			
13	Outcome data	#15	8-9
14		Report numbers of outcome events or summary measures.	
15		Give information separately for exposed and unexposed	
16		groups if applicable.	
17			
18			
19			
20			
21	Main results	#16a	8-9
22		Give unadjusted estimates and, if applicable, confounder-	
23		adjusted estimates and their precision (eg, 95% confidence	
24		interval). Make clear which confounders were adjusted for and	
25		why they were included	
26			
27			
28			
29			
30			
31	Main results	#16b	n/a
32		Report category boundaries when continuous variables were	
33		categorized	
34			
35			
36	Main results	#16c	n/a
37		If relevant, consider translating estimates of relative risk into	
38		absolute risk for a meaningful time period	
39			
40			
41			
42	Other analyses	#17	9-10
43		Report other analyses done—e.g., analyses of subgroups and	
44		interactions, and sensitivity analyses	
45			
46			
47	Discussion		
48			
49			
50	Key results	#18	10
51		Summarise key results with reference to study objectives	
52			
53	Limitations	#19	13-14
54		Discuss limitations of the study, taking into account sources of	
55		potential bias or imprecision. Discuss both direction and	
56		magnitude of any potential bias.	
57			
58			
59			
60			

1	Interpretation	#20	Give a cautious overall interpretation considering objectives,	10-14
2			limitations, multiplicity of analyses, results from similar studies,	
3			and other relevant evidence.	
4				
5				
6				
7				
8				
9	Generalisability	#21	Discuss the generalisability (external validity) of the study	13
10			results	
11				
12				
13				
14	Other Information			
15				
16				
17	Funding	#22	Give the source of funding and the role of the funders for the	16
18			present study and, if applicable, for the original study on which	
19			the present article is based	
20				
21				
22				
23				
24				

25 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License
26 CC-BY. This checklist was completed on 20. September 2021 using <https://www.goodreports.org/>, a
27 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Health 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

SCHOLARONE™
Manuscripts



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.

1
2
3
4
5 1 **Changes in prevalence of *Helicobacter pylori* in Japan from 2008 to 2018: a repeated**
6
7
8 2 **cross-sectional study**

9
10 3 **Author names:** Soichiro Abiko¹, Yoji Hirayama¹, Junji Otaki^{2 1}, Yoshimi Harada^{2 1}, Kohei
11
12
13 4 Kawakami¹, Takahiro Toi¹, Tomoko Takamiya³, Takashi Kawai⁴

14
15
16 5 **Author Affiliations:**

- 17
18 6 1. Department of General Medicine and Primary Care, Tokyo Medical University, Tokyo,
19
20
21 7 Japan.
22
23 8 2. Department of Medical Education, Tokyo Medical University, Tokyo, Japan.
24
25
26 9 3. Department of Preventive Medicine and Public Health, Tokyo Medical University, Tokyo,
27
28
29 10 Japan.
30
31 11 4. Department of Gastroenterological Endoscopy, Tokyo Medical University, Tokyo, Japan.
32
33

34 12 **Corresponding Author:** Soichiro Abiko

35
36
37 13 Email: s_abiko1@tokyo-med.ac.jp
38

39
40 14 **Word count:** 2,919
41

42 15
43
44

45 16 **ABSTRACT**

46
47 17 **Objectives:** To understand the recent prevalence and time-trends of *Helicobacter pylori*
48
49
50 18 infection rates in the Japanese population.
51

52
53 19 **Design:** Repeated cross-sectional study
54
55
56
57
58
59
60

1
2
3
4
5 20 **Participants:** A total of 22,120 workers (age: 35–65 years) from one Japanese company,
6
7
8 21 who underwent serum *H. pylori* antibody tests in a health checkup between 2008 and 2018.
9

10 22 **Measures:** *H. pylori* infection rates among participants aged 35 years from 2008 to 2018,
11
12
13 23 and participants aged 35, 40, 45, and 50–65 years in 2018, based on the results of serum
14
15
16 24 antibody tests were analyzed. In the 2018 analysis, in addition to the antibody test results, all
17
18
19 25 participants who had undergone eradication treatment for *H. pylori* were considered as
20
21 26 infected. Trends were examined using Joinpoint analysis.
22

23
24 27 **Results:** *H. pylori* were detected in 1,100 of 7,586 male, and 190 of 1,739 female participants
25
26 28 aged 35 years. Annual infection rates among those aged 35 years showed linear downward
27
28
29 29 trends as follows: men, 17.5% in 2008 to 10.1% in 2018 (slope: -0.66); women, 12.3% in
30
31
32 30 2008 to 9.2% in 2018 (slope: -0.51) without joinpoints. In the 2018 analysis, 2,432 of 9,580
33
34 31 men and 431 of 1,854 women were *H. pylori* positive. Infection rates tended to increase with
35
36
37 32 older age (men: 11.0% [35 years] to 47.7% [65 years], women: 10.0% [35 years] to 40.0%
38
39
40 33 [65 years]), and showed joinpoints in both sexes (men: 54 years, women: 45 years). Although
41
42 34 both the first and second trends were upward, the second trends for both men and women
43
44
45 35 were steeper than the first trends ($P < 0.05$).
46

47 36 **Conclusions:** Our study demonstrated that in the previous 11 years, infection rates of *H.*
48
49
50 37 *pylori* in Japanese 35-year-old male and female workers have constantly decreased, and
51
52
53 38 furthermore, analysis of various age groups showed joinpoints around 50 years, suggesting a
54
55
56

1
2
3
4
5 39 consistent declining trend in *H. pylori* infection rates in Japan.
6
7
8 40

9
10 41 **Strengths and limitations of this study**

11
12
13 42 • This study presents a recent 11-year time trend of *H. pylori* infection rates based on *H.*
14
15 43 *pylori* serum antibody test results of 35-year-old workers from one large company with many
16
17
18 44 branches around Japan, using Joinpoint trend analysis, suggesting a consistent declining
19
20
21 45 trend in *H. pylori* infection rates in both men and women in Japan.
22

23 46
24
25
26 47 • The 2018 data compared infection rates by age group (35, 40, 45, and 50–65 years), taking
27
28
29 48 into account the history of *H. pylori* eradication treatment obtained by a questionnaire, in
30
31
32 49 addition to antibody testing, demonstrating a joinpoint at around 50 years for both men and
33
34
35 50 women, and a substantially lower infection rate in younger participants.
36

37 51
38
39 52 • The main limitation of this study is the generalizability of the results to the general
40
41
42 53 Japanese population because the study subjects were company employees.
43
44

45 54

46
47 55

48
49
50 56 **INTRODUCTION**

51
52
53 57 *Helicobacter pylori* (*H. pylori*) is a gram-negative bacterium that is often found in the human
54
55
56

1
2
3
4
5 58 stomach. *H. pylori* infection is known to be closely associated with chronic gastritis,
6
7
8 59 duodenal ulcers, gastric ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and
9
10 60 gastric cancer.^{1 2 3 4} The International Agency for Research on Cancer Working group, which
11
12
13 61 is a part of the World Health Organization (WHO), classified *H. pylori* as a Group 1
14
15 62 carcinogen for gastric cancer in 1994.⁵ Moreover, the WHO has stated that “*H. pylori*
16
17
18 63 screening and treatment strategies would be cost-effective” for asymptomatic populations to
19
20
21 64 prevent gastric cancer, and has recommended that “countries explore the possibility of
22
23
24 65 introducing population-based *H. pylori* screening and treatment programmes”.⁶
25
26 66
27
28
29 67 *H. pylori* test-and-treat strategy for preventing gastric cancer is considered more effective in
30
31
32 68 regions with a high incidence of gastric cancer.⁷ The incidence and mortality rates of gastric
33
34
35 69 cancer are relatively high in Japan compared with other countries. Moreover, *H. pylori*
36
37
38 70 infection is thought to be involved in more than 90% of gastric cancer cases in Japan.^{8 9} In
39
40
41 71 addition, the infection rate of *H. pylori* in Japan is higher than that in other developed
42
43
44 72 countries.¹⁰ Accordingly, the “test-and-treat” strategy for *H. pylori* could be a good measure
45
46
47 73 for preventing gastric cancer in Japan. In 2013, the national health insurance scheme covered
48
49
50 74 the *H. pylori* eradication therapy for chronic gastritis in Japan. Several groups in Japan,
51
52
53 75 including company health insurance societies and local municipalities, have introduced *H.*
54
55
56 76 *pylori* screening tests for asymptomatic people during medical check-ups for the prophylactic

1
2
3
4
5 77 intervention of gastric cancer.
6
7

8 78
9

10 79 Decreasing the *H. pylori* infection rate could reduce the incidence rate of gastric cancer¹¹ and
11

12
13 80 reduce the positive predictive value of *H. pylori* screening. Therefore, decreasing the *H.*
14

15 81 *pylori* infection rate in the population may negatively affect the cost-effectiveness of the
16

17
18 82 “test-and-treat” strategy for asymptomatic groups. It is important to elucidate the current
19

20
21 83 prevalence of *H. pylori* infection and its trends over time, to predict future infection rates and
22

23
24 84 plan test strategies for the future. There has been a decrease in the worldwide prevalence of
25

26 85 *H. pylori*,¹⁰ with several Japanese studies reporting similar results.¹² However, most of these
27

28
29 86 studies had small sample sizes or included specific participants, including hospital visitors.
30

31 87 To our knowledge, there have been no recent large-scale studies on the prevalence and time-
32

33
34 88 trend of infection rates of *H. pylori* in Japan.^{12 13 14} In addition, several studies have reported
35

36
37 89 that the *H. pylori* infection rates become steady at approximately 10% in several low-
38

39
40 90 prevalence regions, including European countries.^{10 15 16} Watanabe et al. analyzed the
41

42 91 prevalence of *H. pylori* infection by birth-year among first-visit outpatients between 2005 to
43

44
45 92 2013 in Nagoya, Japan. The results showed three trends: the birth-year percent change (BPC)
46

47 93 = -1.15% in patients born between 1927 and 1949, BPC = -4.59% in patients born between
48

49
50 94 1949 and 1961, and BPC = -2.04% in patients born between 1961 and 1988, indicating that
51

52
53 95 after a rapid decrease in infection rates in those born between 1949 and 1961, the rate of
54

1
2
3
4
5 96 decrease has slowed down.¹⁴ Our present study aimed to elucidate the recent trends in the
6
7 97 infection rates of *H. pylori*, including the rates after 2013, which is the year that the health
8
9
10 98 insurance system in Japan began to cover *H. pylori* eradication therapy for chronic gastritis,
11
12
13 99 and whether they showed significant changes with time.
14
15

100

18 101 Using data from health checkups in a company health insurance society, this repeated cross-
19
20
21 102 sectional study aimed to clarify the recent 11-year trend of *H. pylori* infection rate in 35-year-
22
23
24 103 olds and *H. pylori* infection rates in 2018 according to age, stratified by sex.
25
26

104

105 MATERIALS AND METHODS

31 106 Japanese law requires all citizens to have some type of health insurance. T company is one
32
33
34 107 of the largest companies in Japan, with many branches. All workers of this company, which
35
36
37 108 includes a wide variety of people, such as office workers, manual laborers, and people with
38
39
40 109 disabilities, belong to the company's health insurance society. Members of the T company
41
42 110 health insurance society undergo serum anti-*Helicobacter pylori* IgG antibody tests. This test
43
44
45 111 was conducted annually on members aged 35 years during their health checkups
46
47
48 112 (approximately 600–1,100 people per year). However, in 2018, the health insurance society
49
50
51 113 offered this test to participants aged 35, 40, 45, and > 50 years. We included members who
52
53 114 had undergone serum *H. pylori* antibody tests at their annual health checkups from April 1,
54
55
56
57
58
59
60

1
2
3
4
5 115 2008, to March 31, 2019, at the age of 35–65 years. Participants' blood samples were taken
6
7
8 116 at their health checkups. Serum was isolated from the samples, and stored at –80 °C until
9
10 117 use. Serum anti-*H. pylori* IgG was measured using an enzyme-linked immunosorbent assay
11
12
13 118 with “E-Plate Eiken *H. pylori* antibody” or “E-Plate II Eiken *H. pylori* antibody” (Eiken
14
15
16 119 Chemical Co. Ltd., Tokyo, Japan). The cut-off level was set at 10 U/mL,¹⁷ with values above
17
18 120 this being classified as positive. Anonymized participants' data, including medical
19
20
21 121 questionnaires and blood test results, were obtained from the annual health checkup database
22
23
24 122 of the health insurance society. We excluded data from individuals who refused academic
25
26 123 use of their data.
27
28

29 124

31 125 **Statistical analysis**

32
33
34 126 First, data obtained from 35-year-old participants between 2008 and 2018 were analyzed to
35
36
37 127 determine time-trends in *H. pylori* infection rates (“35-year-old analysis”) stratified by sex.
38
39
40 128 Positive results of serum antibody tests for *H. pylori* were defined as *H. pylori* infection.
41
42
43 129 Annual infection rates were calculated based on the antibody test results. Subsequently, we
44
45 130 analyzed the time-trend of the rates.
46
47

48 131

49
50 132 Second, we analyzed data from participants aged 35, 40, 45, and 50–65 years old obtained in
51
52
53 133 2018 according to age stratified by sex to determine generational differences in the infection
54
55
56

1
2
3
4
5 134 rates (“2018 analysis”). In the 2018 analysis, participants who tested positive for antibodies
6
7
8 135 were considered as infected. Further, to reduce the influence of eradication treatment on the
9
10 136 infection rate, all participants with a history of eradication treatment of *H. pylori* infection
11
12
13 137 were defined as positive regardless of their tests results for *H. pylori* antibody, with the
14
15
16 138 assumption that a history of eradication treatment indicates a previous infection.

17
18 139
19
20
21 140 We performed Joinpoint Trend Analysis¹⁸ to identify trends in the infection rate and their
22
23
24 141 changes over time using Joinpoint Regression Program 4.9.0.0.¹⁹ We used the permutation
25
26
27 142 test to select the optimal number of joinpoints in the 35-year-old analysis, whereas we used
28
29 143 the Bayesian Information Criterion (BIC) in the 2018 analysis. Linear Model was selected in
30
31
32 144 the analyses. Statistical significance was set at $P < 0.05$. Data with missing or ambiguous
33
34
35 145 figures were excluded from the analysis.

36
37 146

38 39 147 **Patient and public involvement**

40
41
42 148 After discussions with representatives of the health insurance society about this study, the
43
44
45 149 health insurance society acknowledged the importance of the concept of our study, and
46
47
48 150 permitted us to collect and use participant data from its database. The results of this study are
49
50
51 151 published as a report.

52
53 152
54
55
56
57
58
59
60

153 **Ethical approval**

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

159

160 **RESULTS**

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

168

169 **The 35-year-old analysis**

170 In the 35-year-old analysis, 1,100 out of 7,586 male participants and 190 out of 1,739 female
171 participants were *H. pylori*-infected. In Joinpoint analysis, infection rates showed linear

1
2
3
4
5 172 downward trends in both men and women with advanced years (men: 17.5% in 2008 to
6
7
8 173 10.1% in 2018 (slope -0.66), women: 12.3% in 2008 to 9.2% in 2018 (slope -0.51) [$P <$
9
10 174 0.05]). These trends lacked joinpoints at which the trend significantly changed (Figure 2).
11
12

13 175

16 176 **The 2018 analysis**

17
18 177 In the 2018 analysis, 2,432 out of 9,580 male participants and 431 out of 1,854 female
19
20
21 178 participants were infected with *H. pylori*. The infection rates showed trends of increasing
22
23
24 179 positive rates with advanced age in both men and women (men: 11.0% at 35 years to 47.7%
25
26 180 at 65 years, women: 10.0% at 35 years to 40.0% at 65 years). These trends had joinpoints at
27
28
29 181 the age of 54 years in men (95% CI: 45–58) and at the age of 45 in women (95% CI: 45–51),
30
31
32 182 with two different trends in the slope before and after the point. Specifically, the first and
33
34 183 second trends were 35–54 years (slope = 0.67) and 54–65 years (slope = 1.83) in men, and
35
36
37 184 35–45 years (slope = 0.30) and 45–65 years (slope = 1.49) in women. Both first and second
38
39
40 185 trends showed a linear increase with age, with the second trends being significantly steeper
41
42 186 than the first trends ($P < 0.05$) (Figure 3).
43
44

45 187

47 188 **DISCUSSION**

48
49
50 189 This study investigated the 11-year time-trend from 2008 to 2018, and the trend by age in
51
52
53 190 2018 regarding the prevalence of *H. pylori* infection in Japanese workers stratified by sex
54
55
56
57
58
59
60

1
2
3
4
5 191 based on large-scale health checkup data. In the 35-year-old analysis, the infection rate
6
7
8 192 showed a linear declining trend from 2008 to 2018 both in men and women. This provided a
9
10 193 good estimate of the *H. pylori* infection trends in Japan, as this study was conducted among
11
12
13 194 workers in a large company with branch offices throughout Japan, and its workers, including
14
15
16 195 workers in the branch offices, were the subjects of this study.
17

18 196
19
20
21 197 In the 35-year-old analysis, the infection rate decreased linearly to approximately 10% both
22
23
24 198 in men and women; further, this downward trend did not significantly change during the
25
26
27 199 observation period. We assumed that the participants in this analysis, who were all 35 years
28
29
30 200 old were less affected by eradication treatment than older participants; and therefore, the
31
32
33 201 results may closely reflect the actual trend of the incidence rate of *H. pylori* infections in
34
35
36 202 Japan. If the downward trends (slope = -0.65 in men or slope = -0.51 in women) observed
37
38
39 203 in the 35-year-old analysis continues, the infection rate is expected to reach nearly zero by
40
41
42 204 about 2035. In contrast, recent studies on junior high school students (aged: 12–15 years) in
43
44
45 205 Japan have demonstrated that the infection rate of this generation when they reach 35 years
46
47
48 206 at about 2035 will be approximately 3% to 5%,^{21 22 23 24} which is higher than our prediction.
49
50
51 207 This inconsistency suggests that the decrease in the infection rate may have slowed down.

52
53 208
54
55
56 209 In the 2018 analysis, the infection rates in both sexes increased with advanced age. This also
57
58
59
60

1
2
3
4
5 210 indicated declining trends in the prevalence rate of *H. pylori* over the years. Furthermore,
6
7
8 211 there were joinpoints around the age of 50 years (54 years in men [95% CI: 45–58] and 45
9
10 212 years in women [95% CI: 45–51]), which implies the existence of some type of change
11
12
13 213 affecting the *H. pylori* infection rate in people of this generations (Figure 3). Chronic *H.*
14
15 214 *pylori* infection is mostly established in the human stomach during childhood.^{25 26} Drinking
16
17
18 215 water and family members are among the sources of *H. pylori* infection.²⁷ From the late 1960s
19
20
21 216 to the 1970s, which is when people aged 50 years in 2018 spent their childhood, Japan
22
23
24 217 experienced rapid economic growth and urbanization. Accordingly, there was a rapid
25
26 218 increase in water supply penetration and a decrease in the average number of households.²⁸
27
28
29 219 ²⁹ These rapid environmental changes may have influenced the establishment of *H. pylori*
30
31 220 infection; consequently, there was a rapid decrease in the prevalence of this bacterium during
32
33
34 221 this era. Watanabe et al. revealed changes in the declining trend of *H. pylori* infection rate
35
36
37 222 and indicated an effect of environmental changes on the infection rate,¹⁴ which is consistent
38
39
40 223 with our findings.

41
42 224

43
44
45 225 Participants in the 35-year-old analysis were born after 1973; therefore, they may have not
46
47
48 226 experienced the rapid environmental changes that those who were born during the period of
49
50
51 227 high economic growth (1955–1972) had experienced. The 35-year-old analysis revealed a
52
53 228 recent gradual decrease in the *H. pylori* infection rate. This suggests that factors other than

1
2
3
4
5 229 hygiene and family structure may influence infection establishment. As aforementioned, *H.*
6
7
8 230 *pylori* infections are likely to be established during childhood through parent-to-child
9
10 231 transmission.²⁶ In addition to hygienic and environmental improvements, the spread of ready-
11
12
13 232 made baby food after around 1970 may have contributed to the decreased *H. pylori* infection
14
15 233 rate.³⁰ With the recently increasing recognition of *H. pylori* in the general population and
16
17
18 234 coverage of eradication treatment through national insurance, there has been an increase in
19
20
21 235 the number of *H. pylori* eradication treatments in Japan.³¹ If treatment decreases the infection
22
23
24 236 rate in child-rearing generation, it could accelerate the declining speed of the infection rates
25
26 237 in the next generations.

28
29 238

30
31 239 When conducting *H. pylori* screening tests for prophylactic purposes, the prevalence in a
32
33
34 240 target group should be considered to evaluate the effectiveness of the strategy. We observed
35
36
37 241 a decreasing infection rate of *H. pylori* in Japan. In the future, the infection rate may reach
38
39
40 242 zero; accordingly, there would be a decreased importance of screening tests for this bacterium
41
42 243 in asymptomatic people. A study on the cost-effectiveness of the test-and-treatment strategy
43
44
45 244 for *H. pylori* revealed that it remained effective even with a low infection rate of
46
47
48 245 approximately 5%.³² Our findings could inform future public health strategies. Moreover,
49
50 246 considering the decrease in *H. pylori* prevalence, *H. pylori* infection-negative gastric cancer
51
52
53 247 has lately been receiving attention.^{33 34 35} Research for risk factors of gastric cancer other

1
2
3
4
5 248 than *H. pylori* is also needed.
6
7

8 249
9

10 250 **Limitations**

11
12
13 251 This study has several limitations. First, there might have been selection bias, including age,
14
15 252 sex, occupation, region, and nationality (possibly including several workers who were born
16
17 253 and raised in countries other than Japan). Several studies have analyzed differences in the
18
19 254 infection rates according to sex, occupation, and region, with a study reporting a higher
20
21 255 infection rate in men; however, there remains no consensus regarding these biases.^{36 37 38} Our
22
23 256 present study included participants of an unequal number of each sex. This was one reason
24
25 257 why we conducted separate analyses for each sex. A recent study showed that employees in
26
27 258 a large company are in better health than those in a small one.³⁹ As the target group of this
28
29 259 study were employees of a large company, there is the possibility of such bias. Heterogeneity
30
31 260 of age gaps between age groups and limitation of the target ages may have weakened analyses,
32
33 261 especially in younger age groups. However, the present study targeted all health insurance
34
35 262 society members working in a large company operating throughout Japan, and therefore, we
36
37 263 were able to include subjects from various age groups and regions throughout Japan. Second,
38
39 264 the history of *H. pylori* eradication may have influenced our findings. In 2008, T company
40
41 265 health insurance society performed serum *H. pylori* antibody screening tests for all its
42
43 266 members. Therefore, there may have been a higher proportion of post-eradication cases in
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5 267 our study than in the general population. We attempted to reduce the influence of eradication
6
7
8 268 treatment by classifying patients who underwent eradication treatment as infected. However,
9
10 269 history information acquired through a self-reported questionnaire could have contained
11
12
13 270 inaccuracies, including recall bias.⁴⁰ In the 35-year-old analysis, we could not obtain
14
15
16 271 information regarding previous eradication treatment of the participants. We hence analyzed
17
18 272 the data based on the assumption that the rate of eradication treatment among participants in
19
20
21 273 the 35-year-old analysis was low, due to their younger age, and therefore would not
22
23
24 274 significantly affect the influence rate. The health insurance society collected and reported, as
25
26 275 part of their health services, that the rate of 35-year-old participants who had previously
27
28 276 undergone eradication treatment (both men and women) was 0.9%, 2.1%, and 1.4% in 2018,
29
30
31 277 2019, and 2020, respectively. Although this supports our assumption, it indicates the
32
33
34 278 possibility of errors of 1%–2 % from eradication treatment in the infection rates of the 35-
35
36
37 279 year-old analysis. In addition, previous medical history; medications; and measurement
38
39
40 280 biases, including test characteristics and threshold application in the test (including high-
41
42 281 negative issues), could have influenced our results.^{41 42} The limitations mentioned above may
43
44
45 282 hinder the generalization of our findings to the Japanese general population.
46
47
48 283

49
50 284 However, the present study collected data of 35-year-olds from 2009 to 2018, and data also
51
52
53 285 of various age groups from 2018, and this information was analyzed using a robust statistical
54
55
56
57
58
59
60

1
2
3
4
5 286 method called joinpoint analysis, demonstrating important findings for considering future *H.*
6
7
8 287 *pylori* eradication therapy targets.
9

10 288

13 289 **CONCLUSION**

15 290 Our study showed a constant decreasing time-trend in the infection rate of *H. pylori* among
16
17
18 291 35-year-old workers in Japan from 2008 to 2018. This time-trend indicates that the infection
19
20
21 292 rate of *H. pylori* may continue to decrease in the future. Trends in the infection rate by age
22
23
24 293 in 2018 indicated the possibility of a slowing down of the rate of decrease in the prevalence
25
26 294 of *H. pylori* in Japan. In populations with few *H. pylori*-positive individuals, the efficiency
27
28
29 295 of measures to routinely test for antibodies is low, and therefore, it would be difficult to rely
30
31
32 296 solely on the *H. pylori* test and treatment strategy to achieve gastric cancer prevention. We
33
34 297 believe that the data regarding changes in the prevalence of *H. pylori* over the years observed
35
36
37 298 in Japan could be useful for other countries with a high incidence of *H. pylori* infection, in
38
39
40 299 planning future eradication strategies.
41

42 300

45 301 **Acknowledgments**

46
47 302 We would like to acknowledge the T company health insurance society. We would like to
48
49
50 303 thank the Center for International Education and Research of Tokyo Medical University for
51
52
53 304 English language editing.
54
55
56
57
58
59
60

1
2
3
4
5 305
6
7

8 306 **Footnotes**
9

10 307 **Contributors:** SA designed the study, analyzed the data, and drafted the manuscript. Y

11
12 308 Hirayama contributed to the study design and performed general supervision of the whole

13
14
15 309 study. JO, Y Harada, and T Toi assisted in conducting the study, interpreting the results, and

16
17
18 310 revising the manuscript. KK and TK contributed to data collection and provided advice and

19
20
21 311 opinions from an expert perspective. TT contributed to data analysis and revising the

22
23 312 manuscript from statistical and public health perspectives. All authors read and approved the

24
25
26 313 final manuscript.
27
28

29 314
30

31 315 **Funding:** This research received no specific grant from any funding agency in the public,

32
33
34 316 commercial, or not-for-profit sectors.
35
36

37 317
38

39 318 **Competing interests:** None declared.
40
41

42 319
43
44

45 320 **Patient consent for publication:** Not required.
46
47

48 321
49

50 322 **Ethics approval:** The institutional review boards of Tokyo Medical University (T2019-

51
52
53 323 0044)
54
55
56
57
58
59
60

324

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

326

327 **Data sharing statement:** Data is available in a public, open access repository. ⁴³

328

329

330 REFERENCES

- 331 1. Wang F, Meng W, Wang B, et al. Helicobacter pylori-induced gastric inflammation and
332 gastric cancer. *Cancer Lett* 2014;345(2):196-202. doi: 10.1016/j.canlet.2013.08.016
333 [published Online First: 2013/08/29]
- 334 2. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal
335 anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*
336 2002;359(9300):14-22. doi: 10.1016/s0140-6736(02)07273-2 [published Online
337 First: 2002/01/26]
- 338 3. Eck M, Schmausser B, Haas R, et al. MALT-type lymphoma of the stomach is associated
339 with Helicobacter pylori strains expressing the CagA protein. *Gastroenterology*
340 1997;112(5):1482-6. doi: 10.1016/s0016-5085(97)70028-3 [published Online First:
341 1997/05/01]
- 342 4. Sasazuki S, Inoue M, Iwasaki M, et al. Effect of Helicobacter pylori infection combined

- 1
2
3
4
5 343 with CagA and pepsinogen status on gastric cancer development among Japanese
6
7
8 344 men and women: a nested case-control study. *Cancer Epidemiol Biomarkers Prev*
9
10 345 2006;15(7):1341-7. doi: 10.1158/1055-9965.EPI-05-0901 [published Online First:
11
12
13 346 2006/07/13]
- 14
15 347 5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes,
16
17
18 348 Liver Flukes and *Helicobacter pylori*. Lyon (FR): International Agency for Research
19
20
21 349 on Cancer 1994.
- 22
23 350 6. IARC *Helicobacter pylori* Working Group. *Helicobacter pylori* Eradication as a Strategy
24
25
26 351 for Preventing Gastric Cancer: International Agency for Research on Cancer 2014.
- 27
28
29 352 7. Ford AC, Forman D, Hunt RH, et al. *Helicobacter pylori* eradication therapy to prevent
30
31
32 353 gastric cancer in healthy asymptomatic infected individuals: systematic review and
33
34 354 meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174. doi:
35
36 355 10.1136/bmj.g3174
- 37
38
39 356 8. Center for Cancer Control and Information Services, National Cancer Center. CANCER
40
41
42 357 STATISTICS IN JAPAN '19 [updated 17 April 2020. Available from:
43
44 358 https://ganjoho.jp/en/professional/statistics/brochure/2019_en.html accessed 22 Dec
45
46 359 2020.
- 47
48
49 360 9. Matsuo T, Ito M, Takata S, et al. Low prevalence of *Helicobacter pylori*-negative gastric
50
51
52 361 cancer among Japanese. *Helicobacter* 2011;16(6):415-9. doi: 10.1111/j.1523-

- 1
2
3
4
5 362 5378.2011.00889.x [published Online First: 2011/11/09]
6
7
8 363 10. Peleteiro B, Bastos A, Ferro A, et al. Prevalence of Helicobacter pylori infection
9
10 364 worldwide: a systematic review of studies with national coverage. *Dig Dis Sci*
11
12 365 2014;59(8):1698-709. doi: 10.1007/s10620-014-3063-0 [published Online First:
13
14 366 2014/02/25]
15
16
17
18 367 11. Tsuda M, Asaka M, Kato M, et al. Effect on Helicobacter pylori eradication therapy
19
20 368 against gastric cancer in Japan. *Helicobacter* 2017;22(5) doi: 10.1111/hel.12415
21
22 369 [published Online First: 2017/08/05]
23
24
25
26 370 12. Wang C, Nishiyama T, Kikuchi S, et al. Changing trends in the prevalence of H. pylori
27
28 371 infection in Japan (1908-2003): a systematic review and meta-regression analysis of
29
30 372 170,752 individuals. *Sci Rep* 2017;7(1):15491. doi: 10.1038/s41598-017-15490-7
31
32 373 [published Online First: 2017/11/16]
33
34
35
36
37 374 13. Inoue M. Changing epidemiology of Helicobacter pylori in Japan. *Gastric Cancer*
38
39 375 2017;20(Suppl 1):3-7. doi: 10.1007/s10120-016-0658-5 [published Online First:
40
41 376 2016/10/21]
42
43
44
45 377 14. Watanabe M, Ito H, Hosono S, et al. Declining trends in prevalence of Helicobacter pylori
46
47 378 infection by birth-year in a Japanese population. *Cancer Sci* 2015;106(12):1738-43.
48
49 379 doi: 10.1111/cas.12821 [published Online First: 2015/09/24]
50
51
52
53 380 15. Carmack SW, Genta RM. Helicobacter pylori seroprevalence in symptomatic veterans: a
54
55
56
57
58
59
60

- 1
2
3
4
5 381 study of 7310 patients over 11 years. *Helicobacter* 2009;14(4):298-302. doi:
6
7
8 382 10.1111/j.1523-5378.2009.00693.x
9
10 383 16. den Hoed CM, Vila AJ, Holster IL, et al. Helicobacter pylori and the birth cohort effect:
11
12 384 evidence for stabilized colonization rates in childhood. *Helicobacter* 2011;16(5):405-
13
14 385 9. doi: 10.1111/j.1523-5378.2011.00854.x [published Online First: 2011/09/20]
15
16
17
18 386 17. Komatsu Y, Sugiyama T, Asaka M. Helicobacter pylori kansenshingan ni okeru
19
20 387 nihonjinkabu wo siyou sita ELISA kit " E-plate eiken H.pylori koutai" no yuyousei
21
22 388 no kentou [Study of effectiveness of E-plate eiken which is ELAISA kit using
23
24 389 Japanese strain in diagnose of Helicobacter pylori infection]. *The Journal of Clinical*
25
26 390 *Laboratory Instruments and Reagents* 2001;24(5):331-35.
27
28
29
30
31 391 18. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with
32
33 392 applications to cancer rates. *Stat Med* 2000;19(3):335-51. doi: 10.1002/(sici)1097-
34
35 393 0258(20000215)19:3<335::aid-sim336>3.0.co;2-z [published Online First:
36
37 394 2000/01/29]
38
39
40
41
42 395 19. Joinpoint Regression Program [program]. Version 4.9.0.0 version: Statistical
43
44 396 Methodology and Applications Branch, Surveillance Research Program, National
45
46 397 Cancer Institute., March 2021.
47
48
49
50 398 20. Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health
51
52 399 Research Involving Human Subjects 2015 [Available from:
53
54
55
56
57
58
59
60

- 1
2
3
4
5 400 <https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000->
6
7
8 401 [Daijinkanboukouseikagakuka/0000080278.pdf](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf) accessed 6 Dec 2020.
9
10 402 21. Kusano C, Gotoda T, Ishikawa H, et al. The administrative project of *Helicobacter pylori*
11
12
13 403 infection screening among junior high school students in an area of Japan with a high
14
15 404 incidence of gastric cancer. *Gastric Cancer* 2017;20(Suppl 1):16-19. doi:
16
17 405 10.1007/s10120-017-0688-7 [published Online First: 2017/01/18]
18
19
20
21 406 22. Honma H, Nakayama Y, Kato S, et al. Clinical features of *Helicobacter pylori* antibody-
22
23
24 407 positive junior high school students in Nagano Prefecture, Japan. *Helicobacter*
25
26 408 2018:e12559. doi: 10.1111/hel.12559 [published Online First: 2018/12/06]
27
28
29 409 23. Nakayama Y, Lin Y, Hongo M, et al. *Helicobacter pylori* infection and its related factors
30
31 410 in junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2017;22(2)
32
33 411 doi: 10.1111/hel.12363 [published Online First: 2016/10/28]
34
35
36
37 412 24. Kakiuchi T, Matsuo M, Endo H, et al. A *Helicobacter pylori* screening and treatment
38
39 413 program to eliminate gastric cancer among junior high school students in Saga
40
41 414 Prefecture: a preliminary report. *J Gastroenterol* 2019 doi: 10.1007/s00535-019-
42
43 415 01559-9 [published Online First: 2019/02/17]
44
45
46
47 416 25. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and *Helicobacter pylori*. *J*
48
49 417 *Infect Dis* 1993;168(1):219-21. doi: 10.1093/infdis/168.1.219
50
51
52
53 418 26. O'Ryan ML, Lucero Y, Rabello M, et al. Persistent and transient *Helicobacter pylori*
54
55
56
57
58
59
60

- 1
2
3
4
5 419 infections in early childhood. *Clin Infect Dis* 2015;61(2):211-8. doi:
6
7
8 420 10.1093/cid/civ256
9
10 421 27. Ueda M, Kikuchi S, Kasugai T, et al. Helicobacter pylori risk associated with childhood
11
12 home environment. *Cancer Sci* 2003;94(10):914-8. doi: 10.1111/j.1349-
13 422 7006.2003.tb01375.x [published Online First: 2003/10/15]
14
15 423
16
17 424 28. JAPAN WATER WORKS ASSOCIATION. Water Supply in Japan 2017 [Available
18
19 from: http://www.jwwa.or.jp/jigyoku/kaigai_file/2017WaterSupplyInJapan.pdf
20
21 425
22 accessed Dec 22 2020.
23
24 426
25
26 427 29. Ministry of Health, Labour and Welfare. General Welfare and Labour Japan [Available
27
28 from: <https://www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf> accessed 1st Oct 2020.
29
30 428
31 429 30. Council JBF. Seisan Tokei [Production statistics] Japan [Available from:
32
33 <https://www.baby-food.jp/link/ayumi-jikei.html> accessed 11 Dec 2020.
34
35 430
36
37 431 31. Hiroi S, Sugano K, Tanaka S, et al. Impact of health insurance coverage for Helicobacter
38
39 432 pylori gastritis on the trends in eradication therapy in Japan: retrospective
40
41 433 observational study and simulation study based on real-world data. *BMJ Open*
42
43 434 2017;7(7):e015855. doi: 10.1136/bmjopen-2017-015855 [published Online First:
44
45 435 2017/08/02]
46
47
48
49 436 32. Kowada A. Cost-effectiveness of Helicobacter pylori screening followed by eradication
50
51 437 treatment for employees in Japan. *Epidemiol Infect* 2018;146(14):1834-40. doi:
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5 438 10.1017/S095026881800208X [published Online First: 2018/07/31]
6
7
8 439 33. Kato S, Matsukura N, Tsukada K, et al. Helicobacter pylori infection-negative gastric
9
10 440 cancer in Japanese hospital patients: Incidence and pathological characteristics.
11
12
13 441 *Cancer Sci* 2007;98(6):790-94. doi: <https://doi.org/10.1111/j.1349->
14
15 442 7006.2007.00478.x
16
17
18 443 34. Yamamoto Y, Fujisaki J, Omae M, et al. Helicobacter pylori-negative gastric cancer:
19
20 444 characteristics and endoscopic findings. *Digestive endoscopy : official journal of the*
21
22
23 445 *Japan Gastroenterological Endoscopy Society* 2015;27(5):551-61. doi:
24
25 446 10.1111/den.12471 [published Online First: 2015/03/27]
26
27
28
29 447 35. Takita M, Ohata K, Inamoto R, et al. Endoscopic and histological features of Helicobacter
30
31 448 pylori-negative differentiated gastric adenocarcinoma arising in the antrum. *JGH*
32
33 449 *open : an open access journal of gastroenterology and hepatology* 2021;5(4):470-77.
34
35 450 doi: 10.1002/jgh3.12518 [published Online First: 2021/04/17]
36
37
38
39 451 36. Kheyre H, Morais S, Ferro A, et al. The occupational risk of Helicobacter pylori infection:
40
41 452 a systematic review. *Int Arch Occup Environ Health* 2018;91(6):657-74. doi:
42
43 453 10.1007/s00420-018-1315-6
44
45
46
47 454 37. Ueda J, Gosho M, Inui Y, et al. Prevalence of Helicobacter pylori infection by birth year
48
49 455 and geographic area in Japan. *Helicobacter* 2014;19(2):105-10. doi:
50
51 456 10.1111/hel.12110 [published Online First: 2014/02/11]
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5 457 38. Ferro A, Morais S, Pelucchi C, et al. Sex differences in the prevalence of *Helicobacter*
6
7
8 458 *pylori* infection: an individual participant data pooled analysis (StoP Project). *Eur J*
9
10 459 *Gastroenterol Hepatol* 2019;31(5):593-98. doi: 10.1097/MEG.0000000000001389
11
12
13 460 [published Online First: 2019/03/07]
- 14
15
16 461 39. Kanamori S, Tsuji T, Takamiya T, et al. Size of company of the longest-held job and
17
18 462 mortality in older Japanese adults: A 6-year follow-up study from the Japan
19
20
21 463 Gerontological Evaluation Study. *J Occup Health* 2020;62(1):e12115. doi:
22
23
24 464 10.1002/1348-9585.12115 [published Online First: 2020/06/10]
- 25
26 465 40. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43(1):87-91.
27
28
29 466 doi: 10.1016/0895-4356(90)90060-3
- 30
31 467 41. Miftahussurur M, Yamaoka Y. Diagnostic Methods of *Helicobacter pylori* Infection for
32
33
34 468 Epidemiological Studies: Critical Importance of Indirect Test Validation. *BioMed*
35
36
37 469 *research international* 2016;2016:4819423. doi: 10.1155/2016/4819423 [published
38
39
40 470 Online First: 2016/02/24]
- 41
42 471 42. Inoue M, Sawada N, Goto A, et al. High-Negative Anti-*Helicobacter pylori* IgG Antibody
43
44
45 472 Titers and Long-Term Risk of Gastric Cancer: Results from a Large-Scale
46
47
48 473 Population-Based Cohort Study in Japan. *Cancer Epidemiol Biomarkers Prev*
49
50
51 474 2020;29(2):420-26. doi: 10.1158/1055-9965.EPI-19-0993 [published Online First:
52
53 475 2019/12/13]
- 54
55
56
57
58
59
60

1
2
3
4
5 476 [dataset] 43. Soichiro A. Data from: Changes in prevalence of *Helicobacter pylori* in Japan
6
7
8 477 from 2008 to 2018: a repeated cross-sectional study, figshare, July 13, 2022
9
10 478 <https://doi.org/10.6084/m9.figshare.14594571.v2>
11
12

13 479

14
15 480

16
17
18 481 **FIGURE LEGENDS**

19
20
21 482 **Figure 1**

22
23 483 *Numbers of participants*

24
25
26 484

27
28
29 485 Figure 1

30
31 486 *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The

32
33 487 2018 analysis: participants aged 35–65 years in 2018.
34
35
36

37 488

38
39 489

40
41
42 490 **Figure 2:**

43
44 491 *Infection rates of *Helicobacter pylori* at 35 years old from 2008 to 2018 (men: n = 7,586,*

45
46 492 *women: n= 1,739)*

47
48
49 493

50
51
52 494 Figure 2

1
2
3
4
5 495 *Note.* Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to
6
7
8 496 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51).
9
10 497 There were no joinpoints. “*” in the graph legend indicates a significant difference in the
11
12
13 498 slope from zero at the alpha = 0.05 level.
14
15
16 499
17
18 500
19
20

21 **Figure 3**

22
23 502 *Infection rates of Helicobacter pylori according to age in 2018 (men: n = 9,580, women:*
24
25
26 503 *n=1,854)*
27
28
29 504

30
31 Figure 3

32
33
34 506 *Note.* Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67];
35
36
37 507 second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30];
38
39
40 508 second trend: 45–65 years [slope = 1.49]. “*” in the graph legend indicates a significant
41
42 509 difference in the slope from zero at the alpha = 0.05 level.
43
44
45 510
46
47
48 511
49
50
51
52
53
54
55
56
57
58
59
60

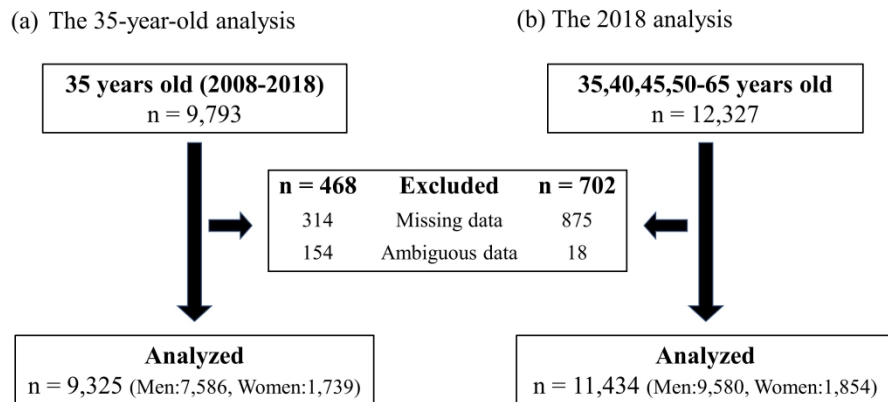


Figure 1: *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The 2018 analysis: participants aged 35–65 years in 2018.

338x190mm (300 x 300 DPI)

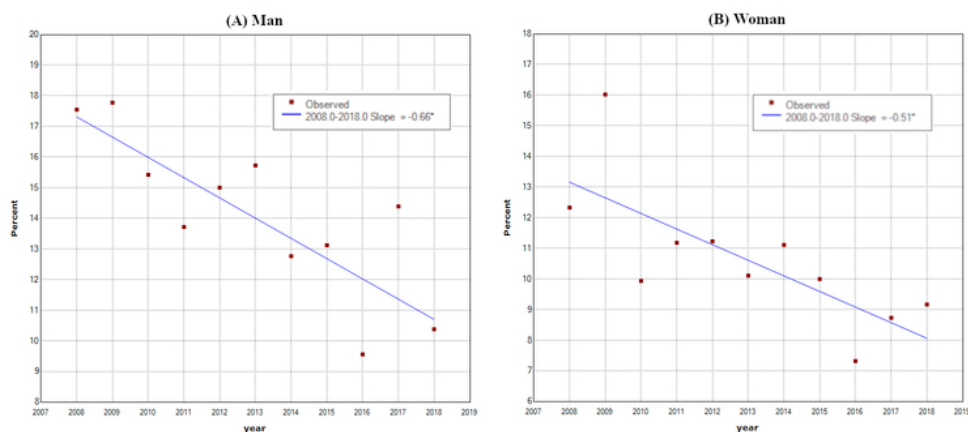


Figure 2: Note. Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51). There were no joinpoints. "*" in the graph legend indicates a significant difference in the slope from zero at the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

32x14mm (600 x 600 DPI)

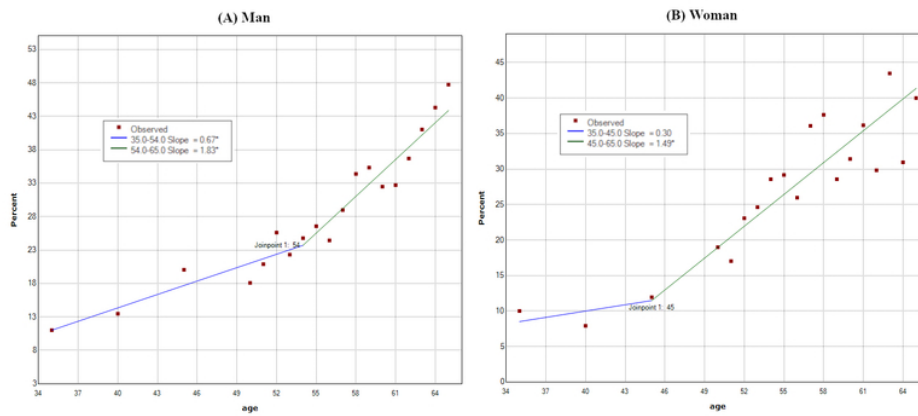


Figure 3: Note. Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67]; second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30]; second trend: 45–65 years [slope = 1.49]. "*" in the graph legend indicates a significant difference 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 sectional reporting guidelines, and cite them as:

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

			Page
	Reporting Item		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

1	Quantitative	#11	Explain how quantitative variables were handled in the	n/a
2				
3	variables		analyses. If applicable, describe which groupings were chosen,	
4				
5			and why	
6				
7				
8				
9	Statistical	#12a	Describe all statistical methods, including those used to control	7-8
10				
11	methods		for confounding	
12				
13				
14	Statistical	#12b	Describe any methods used to examine subgroups and	7-8
15				
16	methods		interactions	
17				
18				
19	Statistical	#12c	Explain how missing data were addressed	7
20				
21	methods			
22				
23				
24				
25	Statistical	#12d	If applicable, describe analytical methods taking account of	n/a
26				
27	methods		sampling strategy	
28				
29				
30	Statistical	#12e	Describe any sensitivity analyses	n/a
31				
32	methods			
33				
34				
35				
36	Results			
37				
38				
39	Participants	#13a	Report numbers of individuals at each stage of study—eg	9-10
40				
41			numbers potentially eligible, examined for eligibility, confirmed	
42				
43			eligible, included in the study, completing follow-up, and	
44				
45			analysed. Give information separately for for exposed and	
46				
47			unexposed groups if applicable.	
48				
49				
50				
51	Participants	#13b	Give reasons for non-participation at each stage	9
52				
53				
54	Participants	#13c	Consider use of a flow diagram	9
55				
56				
57	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	6-7, 14-
58				
59				
60				

1		clinical, social) and information on exposures and potential	15
2			
3		confounders. Give information separately for exposed and	
4			
5		unexposed groups if applicable.	
6			
7			
8	Descriptive data	#14b Indicate number of participants with missing data for each	9-10
9			
10		variable of interest	
11			
12			
13	Outcome data	#15 Report numbers of outcome events or summary measures.	9-10
14			
15		Give information separately for exposed and unexposed	
16			
17		groups if applicable.	
18			
19			
20			
21	Main results	#16a Give unadjusted estimates and, if applicable, confounder-	9-10
22			
23		adjusted estimates and their precision (eg, 95% confidence	
24			
25		interval). Make clear which confounders were adjusted for and	
26			
27		why they were included	
28			
29			
30			
31	Main results	#16b Report category boundaries when continuous variables were	n/a
32			
33		categorized	
34			
35			
36	Main results	#16c If relevant, consider translating estimates of relative risk into	n/a
37			
38		absolute risk for a meaningful time period	
39			
40			
41			
42	Other analyses	#17 Report other analyses done—e.g., analyses of subgroups and	n/a
43			
44		interactions, and sensitivity analyses	
45			
46			
47	Discussion		
48			
49			
50	Key results	#18 Summarise key results with reference to study objectives	11-12
51			
52			
53	Limitations	#19 Discuss limitations of the study, taking into account sources of	14-15
54			
55		potential bias or imprecision. Discuss both direction and	
56			
57		magnitude of any potential bias.	
58			
59			
60			

1	Interpretation	#20	Give a cautious overall interpretation considering objectives,	10-15
2			limitations, multiplicity of analyses, results from similar studies,	
3			and other relevant evidence.	
4				
5				
6				
7				
8				
9	Generalisability	#21	Discuss the generalisability (external validity) of the study	15
10			results	
11				
12				
13				
14	Other Information			
15				
16				
17	Funding	#22	Give the source of funding and the role of the funders for the	n/a
18			present study and, if applicable, for the original study on which	
19			the present article is based	
20				
21				
22				
23				
24				

25 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License
26 CC-BY. This checklist was completed on 20. September 2021 using <https://www.goodreports.org/>, a
27 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Health 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

SCHOLARONE™
Manuscripts



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.

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

3 **Author names:** Soichiro Abiko¹, Yoji Hirayama¹, Junji Otaki^{2 1}, Yoshimi Harada^{2 1}, Kohei
4 Kawakami¹, Takahiro Toi¹, Tomoko Takamiya³, Takashi Kawai⁴

5 **Author Affiliations:**

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

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

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

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

12 **Corresponding Author:** Soichiro Abiko

13 Email: s_abiko1@tokyo-med.ac.jp

14 **Word count:** 2,903

15
16 **ABSTRACT**

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

19 **Design:** Repeated cross-sectional study

1
2
3
4
5 20 **Participants:** A total of 22,120 workers (age: 35–65 years) from one Japanese company,
6
7
8 21 who underwent serum *H. pylori* antibody tests in a health checkup between 2008 and 2018.

9
10 22 **Measures:** *H. pylori* infection rates among participants aged 35 years from 2008 to 2018,
11
12
13 23 and participants aged 35, 40, 45, and 50–65 years in 2018, based on the results of serum
14
15
16 24 antibody tests were analyzed. In the 2018 analysis, in addition to the antibody test results, all
17
18
19 25 participants who had undergone eradication treatment for *H. pylori* were considered as
20
21
22 26 infected. Trends were examined using Joinpoint analysis.

23
24 27 **Results:** *H. pylori* were detected in 1,100 of 7,586 male, and 190 of 1,739 female participants
25
26
27 28 aged 35 years. Annual infection rates among those aged 35 years showed linear downward
28
29
30 29 trends as follows: men, 17.5% in 2008 to 10.1% in 2018 (slope: -0.66); women, 12.3% in
31
32
33 30 2008 to 9.2% in 2018 (slope: -0.51) without joinpoints. In the 2018 analysis, 2,432 of 9,580
34
35
36 31 men and 431 of 1,854 women were *H. pylori* positive. Infection rates tended to increase with
37
38
39 32 older age (men: 11.0% [35 years] to 47.7% [65 years], women: 10.0% [35 years] to 40.0%
40
41
42 33 [65 years]), and showed joinpoints in both sexes (men: 54 years, women: 45 years). Although
43
44
45 34 both the first and second trends were upward, the second trends for both men and women
46
47
48 35 were steeper than the first trends ($P < 0.05$).

49
50 36 **Conclusions:** Our study demonstrated that in the previous 11 years, infection rates of *H.*
51
52
53 37 *pylori* in Japanese 35-year-old male and female workers have constantly decreased, and
54
55
56 38 furthermore, analysis of various age groups showed joinpoints around 50 years, suggesting a

1
2
3
4
5 39 consistent declining trend in *H. pylori* infection rates in Japan.
6
7
8 40

9 10 41 **Strengths and limitations of this study**

11
12
13 42 • This study presents a recent 11-year time trend of *H. pylori* infection rates based on *H.*
14
15 43 *pylori* serum antibody test results of 35-year-old workers from one large company with many
16
17
18 44 branches around Japan, using Joinpoint trend analysis.
19

20
21 45
22
23 46 • The 2018 data compared infection rates by age group (35, 40, 45, and 50–65 years), taking
24
25
26 47 into account the history of *H. pylori* eradication treatment obtained by a questionnaire, in
27
28
29 48 addition to antibody testing.
30

31 49
32
33
34 50 • The main limitation of this study is the generalizability of the results to the general
35
36
37 51 Japanese population because the study subjects were company employees.
38
39
40 52

41
42
43
44
45 53

46 54 **INTRODUCTION**

47 55 *Helicobacter pylori* (*H. pylori*) is a gram-negative bacterium that is often found in the human
48
49
50 56 stomach. *H. pylori* infection is known to be closely associated with chronic gastritis,
51
52
53 57 duodenal ulcers, gastric ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and
54
55
56
57
58
59
60

1
2
3
4
5 58 gastric cancer.^{1 2 3 4} The International Agency for Research on Cancer Working group, which
6
7
8 59 is a part of the World Health Organization (WHO), classified *H. pylori* as a Group 1
9
10
11 60 carcinogen for gastric cancer in 1994.⁵ Moreover, the WHO has stated that “*H. pylori*
12
13 61 screening and treatment strategies would be cost-effective” for asymptomatic populations to
14
15
16 62 prevent gastric cancer, and has recommended that “countries explore the possibility of
17
18 63 introducing population-based *H. pylori* screening and treatment programmes”.⁶
19
20
21 64
22
23
24 65 *H. pylori* test-and-treat strategy for preventing gastric cancer is considered more effective in
25
26 66 regions with a high incidence of gastric cancer.⁷ The incidence and mortality rates of gastric
27
28
29 67 cancer are relatively high in Japan compared with other countries. Moreover, *H. pylori*
30
31
32 68 infection is thought to be involved in more than 90% of gastric cancer cases in Japan.^{8 9} In
33
34
35 69 addition, the infection rate of *H. pylori* in Japan is higher than that in other developed
36
37
38 70 countries.¹⁰ Accordingly, the “test-and-treat” strategy for *H. pylori* could be a good measure
39
40
41 71 for preventing gastric cancer in Japan. In 2013, the national health insurance scheme covered
42
43
44 72 the *H. pylori* eradication therapy for chronic gastritis in Japan. Several groups in Japan,
45
46
47 73 including company health insurance societies and local municipalities, have introduced *H.*
48
49
50 74 *pylori* screening tests for asymptomatic people during medical check-ups for the prophylactic
51
52
53 75 intervention of gastric cancer.
54
55
56
57
58
59
60 76

1
2
3
4
5 77 Decreasing the *H. pylori* infection rate could reduce the incidence rate of gastric cancer¹¹ and
6
7
8 78 reduce the positive predictive value of *H. pylori* screening. Therefore, decreasing the *H.*
9
10 79 *pylori* infection rate in the population may negatively affect the cost-effectiveness of the
11
12
13 80 “test-and-treat” strategy for asymptomatic groups. It is important to elucidate the current
14
15
16 81 prevalence of *H. pylori* infection and its trends over time, to predict future infection rates and
17
18
19 82 plan test strategies for the future. There has been a decrease in the worldwide prevalence of
20
21 83 *H. pylori*,¹⁰ with several Japanese studies reporting similar results.¹² However, most of these
22
23
24 84 studies had small sample sizes or included specific participants, including hospital visitors.
25
26
27 85 To our knowledge, there have been no recent large-scale studies on the prevalence and time-
28
29 86 trend of infection rates of *H. pylori* in Japan.^{12 13 14} In addition, several studies have reported
30
31
32 87 that the *H. pylori* infection rates become steady at approximately 10% in several low-
33
34
35 88 prevalence regions, including European countries.^{10 15 16} Watanabe et al. analyzed the
36
37
38 89 prevalence of *H. pylori* infection by birth-year among first-visit outpatients between 2005 to
39
40
41 90 2013 in Nagoya, Japan. The results showed three trends: the birth-year percent change (BPC)
42
43
44 91 = -1.15% in patients born between 1927 and 1949, BPC = -4.59% in patients born between
45
46
47 92 1949 and 1961, and BPC = -2.04% in patients born between 1961 and 1988, indicating that
48
49
50 93 after a rapid decrease in infection rates in those born between 1949 and 1961, the rate of
51
52
53 94 decrease has slowed down.¹⁴ Our present study aimed to elucidate the recent trends in the
54
55
56 95 infection rates of *H. pylori*, including the rates after 2013, which is the year that the health

1
2
3
4
5 96 insurance system in Japan began to cover *H. pylori* eradication therapy for chronic gastritis,
6
7
8 97 and whether they showed significant changes with time.
9

10 98
11
12
13 99 Using data from health checkups in a company health insurance society, this repeated cross-
14
15
16 100 sectional study aimed to clarify the recent 11-year trend of *H. pylori* infection rate in 35-year-
17
18 101 olds and *H. pylori* infection rates in 2018 according to age, stratified by sex.
19
20

21 102

22 23 103 **MATERIALS AND METHODS**

24
25
26 104 Japanese law requires all citizens to have some type of health insurance. T company is one
27
28
29 105 of the largest companies in Japan, with many branches. All workers of this company, which
30
31
32 106 includes a wide variety of people, such as office workers, manual laborers, and people with
33
34 107 disabilities, belong to the company's health insurance society. Members of the T company
35
36
37 108 health insurance society undergo serum anti-*Helicobacter pylori* IgG antibody tests. This test
38
39
40 109 was conducted annually on members aged 35 years during their health checkups
41
42 110 (approximately 600–1,100 people per year). However, in 2018, the health insurance society
43
44
45 111 offered this test to participants aged 35, 40, 45, and > 50 years. We included members who
46
47
48 112 had undergone serum *H. pylori* antibody tests at their annual health checkups from April 1,
49
50 113 2008, to March 31, 2019, at the age of 35–65 years. Participants' blood samples were taken
51
52
53 114 at their health checkups. Serum was isolated from the samples, and stored at –80 °C until
54
55
56
57
58
59
60

1
2
3
4
5 115 use. Serum anti-*H. pylori* IgG was measured using an enzyme-linked immunosorbent assay
6
7
8 116 with “E-Plate Eiken *H. pylori* antibody” or “E-Plate II Eiken *H. pylori* antibody” (Eiken
9
10 117 Chemical Co. Ltd., Tokyo, Japan). The cut-off level was set at 10 U/mL,¹⁷ with values above
11
12
13 118 this being classified as positive. Anonymized participants’ data, including medical
14
15
16 119 questionnaires and blood test results, were obtained from the annual health checkup database
17
18 120 of the health insurance society. We excluded data from individuals who refused academic
19
20
21 121 use of their data.
22
23
24 122

26 123 **Statistical analysis**

28
29 124 First, data obtained from 35-year-old participants between 2008 and 2018 were analyzed to
30
31
32 125 determine time-trends in *H. pylori* infection rates (“35-year-old analysis”) stratified by sex.
33
34 126 Positive results of serum antibody tests for *H. pylori* were defined as *H. pylori* infection.
35
36
37 127 Annual infection rates were calculated based on the antibody test results. Subsequently, we
38
39
40 128 analyzed the time-trend of the rates.
41
42
43 129

44
45 130 Second, we analyzed data from participants aged 35, 40, 45, and 50–65 years old obtained in
46
47
48 131 2018 according to age stratified by sex to determine generational differences in the infection
49
50
51 132 rates (“2018 analysis”). In the 2018 analysis, participants who tested positive for antibodies
52
53 133 were considered as infected. Further, to reduce the influence of eradication treatment on the
54
55
56
57
58
59
60

1
2
3
4
5 134 infection rate, all participants with a history of eradication treatment of *H. pylori* infection
6
7
8 135 were defined as positive regardless of their tests results for *H. pylori* antibody, with the
9
10 136 assumption that a history of eradication treatment indicates a previous infection.
11
12

13 137
14
15 138 We performed Joinpoint Trend Analysis¹⁸ to identify trends in the infection rate and their
16
17
18 139 changes over time using Joinpoint Regression Program 4.9.0.0.¹⁹ We used the permutation
19
20
21 140 test to select the optimal number of joinpoints in the 35-year-old analysis, whereas we used
22
23
24 141 the Bayesian Information Criterion (BIC) in the 2018 analysis. Linear Model was selected in
25
26 142 the analyses. Statistical significance was set at $P < 0.05$. Data with missing or ambiguous
27
28
29 143 figures were excluded from the analysis.
30
31

32 144 33 34 145 **Patient and public involvement**

35
36
37 146 After discussions with representatives of the health insurance society about this study, the
38
39
40 147 health insurance society acknowledged the importance of our study, and permitted us to
41
42
43 148 collect and use participant data from its database. The results of this study are published as a
44
45 149 report.
46
47

48 150 49 50 151 **Ethical approval**

51
52
53 152 This study protocol was reviewed and approved by the Institutional Review Board of Tokyo
54
55
56
57
58
59
60

1
2
3
4
5 153 Medical University (T2019-0044). Following the Ethical Guidelines for Medical and Health
6
7
8 154 Research Involving Human Subjects,²⁰ the study information was shown on the websites of
9
10
11 155 the institutions where the researchers or participants belonged. Participants' consent for using
12
13 156 data was obtained through an opt-out option.
14
15
16
17

18 158 **RESULTS**

19
20
21 159 There were 9,793 and 12,327 participants in the 35-year-old and 2018 analyses, respectively,
22
23
24 160 with 592 participants overlapping in both analyses. In the 35-year-old analysis, 468
25
26 161 participants were excluded for having missing (n = 314) or ambiguous data (n = 154) in the
27
28
29 162 records, with 9,325 participants (7,586 men; 1,739 women) being included in the final
30
31
32 163 analysis. In the 2018 analysis, 893 participants were excluded for having missing (n = 875)
33
34 164 or ambiguous data (n = 18) in the records, with 11,434 participants (9,580 men; 1,854
35
36
37 165 women) being included in the final analysis (Figure 1).
38
39
40
41

42 167 **The 35-year-old analysis**

43
44
45 168 In the 35-year-old analysis, 1,100 out of 7,586 male participants and 190 out of 1,739 female
46
47
48 169 participants were *H. pylori*-infected. In Joinpoint analysis, infection rates showed linear
49
50
51 170 downward trends in both men and women with increasing years (men: 17.5% in 2008 to
52
53 171 10.1% in 2018 (slope -0.66), women: 12.3% in 2008 to 9.2% in 2018 (slope -0.51) [$P <$
54
55
56
57
58
59
60

1
2
3
4
5 172 0.05]). These trends lacked joinpoints at which the trend significantly changed (Figure 2).
6
7

8 173
9

10 174 **The 2018 analysis**

11
12
13 175 In the 2018 analysis, 2,432 out of 9,580 male participants and 431 out of 1,854 female
14
15 176 participants were infected with *H. pylori*. The infection rates showed trends of increasing
16
17
18 177 positive rates with advanced age in both men and women (men: 11.0% at 35 years to 47.7%
19
20
21 178 at 65 years, women: 10.0% at 35 years to 40.0% at 65 years). These trends had joinpoints at
22
23
24 179 the age of 54 years in men (95% CI: 45–58) and at the age of 45 in women (95% CI: 45–51),
25
26 180 with two different trends in the slope before and after the point. Specifically, the first and
27
28
29 181 second trends were 35–54 years (slope = 0.67) and 54–65 years (slope = 1.83) in men, and
30
31 182 35–45 years (slope = 0.30) and 45–65 years (slope = 1.49) in women. Both first and second
32
33
34 183 trends showed a linear increase with age, with the second trends being significantly steeper
35
36
37 184 than the first trends ($P < 0.05$) (Figure 3).
38
39

40 185

41 42 186 **DISCUSSION**

43
44
45 187 This study investigated the 11-year time-trend from 2008 to 2018, and the trend by age in
46
47
48 188 2018 regarding the prevalence of *H. pylori* infection in Japanese workers stratified by sex
49
50
51 189 based on large-scale health checkup data. In the 35-year-old analysis, the infection rate
52
53 190 showed a linear declining trend from 2008 to 2018 both in men and women. This provided a
54
55
56
57
58
59
60

1
2
3
4
5 191 good estimate of the *H. pylori* infection trends in Japan, as the subjects of this study were
6
7
8 192 workers in a large company, including workers in the branch offices.
9

10
11 193
12
13 194 In the 35-year-old analysis, the infection rate decreased linearly to approximately 10% both
14
15 195 in men and women; further, this downward trend did not significantly change during the
16
17
18 196 observation period. We assumed that the participants in this analysis, who were all 35 years
19
20
21 197 old were less affected by eradication treatment than older participants; and therefore, the
22
23
24 198 results may closely reflect the actual trend of the incidence rate of *H. pylori* infections in
25
26 199 Japan. If the downward trends (slope = -0.65 in men and slope = -0.51 in women) observed
27
28
29 200 in the 35-year-old analysis continues, the infection rate is expected to reach nearly zero by
30
31
32 201 about 2035. In contrast, recent studies on junior high school students (aged: 12–15 years) in
33
34
35 202 Japan have demonstrated that the infection rate of this generation when they reach 35 years
36
37 203 at about 2035 will be approximately 3% to 5%,^{21 22 23 24} which is higher than our prediction.
38
39
40 204 This inconsistency suggests that the decrease in the infection rate may have slowed down.
41

42 205
43
44
45 206 In the 2018 analysis, the infection rates in both sexes increased with advanced age. This also
46
47
48 207 indicated declining trends in the prevalence rate of *H. pylori* over the years. Furthermore,
49
50
51 208 there were joinpoints around the age of 50 years (54 years in men [95% CI: 45–58] and 45
52
53 209 years in women [95% CI: 45–51]), which implies the existence of some type of change
54
55
56
57
58
59
60

1
2
3
4
5 210 affecting the *H. pylori* infection rate in people of this generations (Figure 3). Chronic *H.*
6
7
8 211 *pylori* infection is mostly established in the human stomach during childhood.^{25 26} Drinking
9
10
11 212 water and family members are among the sources of *H. pylori* infection.²⁷ From the late 1960s
12
13 213 to the 1970s, which is when people aged 50 years in 2018 spent their childhood, Japan
14
15 214 experienced rapid economic growth and urbanization. Accordingly, there was an accelerated
16
17
18 215 increase in water supply and a decrease in the average number of households.^{28 29} These fast
19
20
21 216 environmental changes may have influenced the establishment of *H. pylori* infection;
22
23
24 217 consequently, there was a sharp decrease in the prevalence of this bacterial infection during
25
26
27 218 this era. Watanabe et al. revealed changes in the declining trend of *H. pylori* infection rate
28
29 219 and indicated an effect of environmental changes on the infection rate,¹⁴ which is consistent
30
31
32 220 with our findings.

33
34 221
35
36
37 222 Participants in the 35-year-old analysis were born after 1973; therefore, they may have not
38
39
40 223 experienced the rapid environmental changes that those who were born during the period of
41
42
43 224 high economic growth (1955–1972) had experienced. The 35-year-old analysis revealed a
44
45
46 225 recent gradual decrease in the *H. pylori* infection rate. This suggests that factors other than
47
48
49 226 hygiene and family structure may influence infection establishment. As aforementioned, *H.*
50
51
52 227 *pylori* infections are likely to be established during childhood through parent-to-child
53
54
55 228 transmission.²⁶ In addition to hygienic and environmental improvements, the spread of ready-

1
2
3
4
5 229 made baby food after around 1970 may have contributed to the decreased *H. pylori* infection
6
7
8 230 rate.³⁰ With the recently increasing recognition of *H. pylori* in the general population and
9
10
11 231 coverage of eradication treatment through national insurance, there has been an increase in
12
13 232 the number of *H. pylori* eradication treatments in Japan.³¹ If treatment decreases the infection
14
15
16 233 rate in child-rearing generation, it could accelerate the declining speed of the infection rates
17
18 234 in the next generations.

20
21 235

22
23
24 236 When conducting *H. pylori* screening tests for prophylactic purposes, the prevalence in a
25
26 237 target group should be considered to evaluate the effectiveness of the strategy. We observed
27
28
29 238 a decreasing infection rate of *H. pylori* in Japan. In the future, the infection rate may reach
30
31
32 239 zero; accordingly, there would be a decreased importance of screening tests for this bacterium
33
34
35 240 in asymptomatic people. A study on the cost-effectiveness of the test-and-treatment strategy
36
37 241 for *H. pylori* revealed that it remained effective even with a low infection rate of
38
39
40 242 approximately 5%.³² Our findings could inform future public health strategies. Moreover,
41
42 243 considering the decrease in *H. pylori* prevalence, *H. pylori* infection-negative gastric cancer
43
44
45 244 has lately been receiving attention.^{33 34 35} Research for risk factors of gastric cancer other
46
47
48 245 than *H. pylori* is also needed.

49
50 246

51
52
53 247 **Limitations**

1
2
3
4
5 248 This study has several limitations. First, there might have been selection bias, including age,
6
7
8 249 sex, occupation, region, and nationality (possibly including several workers who were born
9
10 250 and raised in countries other than Japan). Several studies have analyzed differences in the
11
12
13 251 infection rates according to sex, occupation, and region, with a study reporting a higher
14
15
16 252 infection rate in men; however, there remains no consensus regarding these biases.^{36 37 38} Our
17
18 253 present study included participants of an unequal number of each sex. This was one reason
19
20
21 254 why we conducted separate analyses for each sex. A recent study showed that employees in
22
23
24 255 a large company are in better health than those in a small one.³⁹ As the target group of this
25
26 256 study were employees of a large company, there is the possibility of such bias. Heterogeneity
27
28
29 257 of age gaps between age groups and limitation of the target ages may have weakened analyses,
30
31
32 258 especially in younger age groups. However, the present study targeted all health insurance
33
34 259 society members working in a large company operating throughout Japan, and therefore, we
35
36
37 260 were able to include subjects from various age groups and regions throughout Japan. Second,
38
39
40 261 the history of *H. pylori* eradication may have influenced our findings. In 2008, T company
41
42 262 health insurance society performed serum *H. pylori* antibody screening tests for all its
43
44
45 263 members. Therefore, there may have been a higher proportion of post-eradication cases in
46
47
48 264 our study than in the general population. We attempted to reduce the influence of eradication
49
50
51 265 treatment by classifying patients who underwent eradication treatment as infected. However,
52
53 266 history information acquired through a self-reported questionnaire could have contained
54
55
56
57
58
59
60

1
2
3
4
5 267 inaccuracies, including recall bias.⁴⁰ In the 35-year-old analysis, we could not obtain
6
7
8 268 information regarding previous eradication treatment of the participants. We hence analyzed
9
10 269 the data based on the assumption that the rate of eradication treatment among participants in
11
12
13 270 the 35-year-old analysis was low, due to their younger age, and therefore would not
14
15
16 271 significantly affect the infection rate. The health insurance society collected and reported, as
17
18 272 part of their health services, that the rate of 35-year-old participants who had previously
19
20
21 273 undergone eradication treatment (both men and women) was 0.9%, 2.1%, and 1.4% in 2018,
22
23
24 274 2019, and 2020, respectively. Although this supports our assumption, it indicates the
25
26 275 possibility of errors of 1%–2 % from eradication treatment in the infection rates of the 35-
27
28
29 276 year-old analysis. In addition, previous medical history; medications; and measurement
30
31
32 277 biases, including test characteristics and threshold application in the test (including high-
33
34 278 negative issues), could have influenced our results.^{41 42} The limitations mentioned above may
35
36
37 279 hinder the generalization of our findings to the Japanese general population.
38
39
40 280

41
42 281 However, the present study collected data of 35-year-olds from 2009 to 2018, and data also
43
44
45 282 of various age groups from 2018, and this information was analyzed using a robust statistical
46
47
48 283 method called joinpoint analysis, demonstrating important findings for considering future *H.*
49
50 284 *pylori* eradication therapy targets.
51
52

53 285
54
55
56
57
58
59
60

286 **CONCLUSION**

287 Our study showed a constant decreasing time-trend in the infection rate of *H. pylori* among
288 35-year-old workers in Japan from 2008 to 2018 ⁴³. This time-trend indicates that the
289 infection rate of *H. pylori* may continue to decrease in the future. Trends in the infection rate
290 by age in 2018 indicated the possibility of a slowing down of the rate of decrease in the
291 prevalence of *H. pylori* in Japan. In populations with few *H. pylori*-positive individuals, the
292 efficiency of measures to routinely test for antibodies is low, and therefore, it would be
293 difficult to rely solely on the *H. pylori* test and treatment strategy to achieve gastric cancer
294 prevention. We believe that the data regarding changes in the prevalence of *H. pylori* over
295 the years observed in Japan could be useful for other countries with a high incidence of *H.*
296 *pylori* infection, in planning future eradication strategies.

297

298 **Acknowledgments**

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

302

303 **Footnotes**

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

1
2
3
4
5 305 Hirayama contributed to the study design and performed general supervision of the whole
6
7
8 306 study. JO, Y Harada, and T Toi assisted in conducting the study, interpreting the results, and
9
10
11 307 revising the manuscript. KK and TK contributed to data collection and provided advice and
12
13 308 opinions from an expert perspective. TT contributed to data analysis and revising the
14
15
16 309 manuscript from statistical and public health perspectives. All authors read and approved the
17
18 310 final manuscript.

19
20
21 311
22
23 312 **Funding:** This research received no specific grant from any funding agency in the public,
24
25
26 313 commercial, or not-for-profit sectors.

27
28
29 314
30
31 315 **Competing interests:** None declared.

32
33
34 316
35
36 317 **Patient consent for publication:** Not required.

37
38
39 318
40
41
42 319 **Ethics approval:** The institutional review boards of Tokyo Medical University (T2019-
43
44
45 320 0044)

46
47
48 321
49
50 322 **Provenance and peer review:** Not commissioned; externally peer-reviewed.

51
52
53 323
54
55
56
57
58
59
60

324 **Data sharing statement:** Data is available in a public, open access repository.⁴³

325

326

327 REFERENCES

- 328 1. Wang F, Meng W, Wang B, et al. Helicobacter pylori-induced gastric inflammation and
329 gastric cancer. *Cancer Lett* 2014;345(2):196-202. doi: 10.1016/j.canlet.2013.08.016
330 [published Online First: 2013/08/29]
- 331 2. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal
332 anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*
333 2002;359(9300):14-22. doi: 10.1016/s0140-6736(02)07273-2 [published Online
334 First: 2002/01/26]
- 335 3. Eck M, Schmausser B, Haas R, et al. MALT-type lymphoma of the stomach is associated
336 with Helicobacter pylori strains expressing the CagA protein. *Gastroenterology*
337 1997;112(5):1482-6. doi: 10.1016/s0016-5085(97)70028-3 [published Online First:
338 1997/05/01]
- 339 4. Sasazuki S, Inoue M, Iwasaki M, et al. Effect of Helicobacter pylori infection combined
340 with CagA and pepsinogen status on gastric cancer development among Japanese
341 men and women: a nested case-control study. *Cancer Epidemiol Biomarkers Prev*
342 2006;15(7):1341-7. doi: 10.1158/1055-9965.EPI-05-0901 [published Online First:

1
2
3
4
5 343 2006/07/13]
6

7
8 344 5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes,
9
10 345 Liver Flukes and *Helicobacter pylori*. Lyon (FR): International Agency for Research
11
12
13 346 on Cancer 1994.

14
15
16 347 6. IARC *Helicobacter pylori* Working Group. *Helicobacter pylori* Eradication as a Strategy
17
18 348 for Preventing Gastric Cancer: International Agency for Research on Cancer 2014.

19
20
21 349 7. Ford AC, Forman D, Hunt RH, et al. *Helicobacter pylori* eradication therapy to prevent
22
23 350 gastric cancer in healthy asymptomatic infected individuals: systematic review and
24
25
26 351 meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174. doi:
27
28
29 352 10.1136/bmj.g3174

30
31 353 8. Center for Cancer Control and Information Services, National Cancer Center. CANCER
32
33 354 STATISTICS IN JAPAN '19 [updated 17 April 2020. Available from:
34
35
36 355 https://ganjoho.jp/en/professional/statistics/brochure/2019_en.html accessed 22 Dec
37
38
39 356 2020.

40
41
42 357 9. Matsuo T, Ito M, Takata S, et al. Low prevalence of *Helicobacter pylori*-negative gastric
43
44 358 cancer among Japanese. *Helicobacter* 2011;16(6):415-9. doi: 10.1111/j.1523-
45
46
47 359 5378.2011.00889.x [published Online First: 2011/11/09]

48
49
50 360 10. Peleteiro B, Bastos A, Ferro A, et al. Prevalence of *Helicobacter pylori* infection
51
52
53 361 worldwide: a systematic review of studies with national coverage. *Dig Dis Sci*

- 1
2
3
4
5 362 2014;59(8):1698-709. doi: 10.1007/s10620-014-3063-0 [published Online First:
6
7
8 363 2014/02/25]
- 9
10 364 11. Tsuda M, Asaka M, Kato M, et al. Effect on *Helicobacter pylori* eradication therapy
11
12
13 365 against gastric cancer in Japan. *Helicobacter* 2017;22(5) doi: 10.1111/hel.12415
14
15 366 [published Online First: 2017/08/05]
- 16
17
18 367 12. Wang C, Nishiyama T, Kikuchi S, et al. Changing trends in the prevalence of *H. pylori*
19
20
21 368 infection in Japan (1908-2003): a systematic review and meta-regression analysis of
22
23 369 170,752 individuals. *Sci Rep* 2017;7(1):15491. doi: 10.1038/s41598-017-15490-7
24
25
26 370 [published Online First: 2017/11/16]
- 27
28
29 371 13. Inoue M. Changing epidemiology of *Helicobacter pylori* in Japan. *Gastric Cancer*
30
31 372 2017;20(Suppl 1):3-7. doi: 10.1007/s10120-016-0658-5 [published Online First:
32
33 373 2016/10/21]
- 34
35
36 374 14. Watanabe M, Ito H, Hosono S, et al. Declining trends in prevalence of *Helicobacter pylori*
37
38
39 375 infection by birth-year in a Japanese population. *Cancer Sci* 2015;106(12):1738-43.
40
41 376 doi: 10.1111/cas.12821 [published Online First: 2015/09/24]
- 42
43
44 377 15. Carmack SW, Genta RM. *Helicobacter pylori* seroprevalence in symptomatic veterans: a
45
46
47 378 study of 7310 patients over 11 years. *Helicobacter* 2009;14(4):298-302. doi:
48
49 379 10.1111/j.1523-5378.2009.00693.x
- 50
51
52 380 16. den Hoed CM, Vila AJ, Holster IL, et al. *Helicobacter pylori* and the birth cohort effect:
53
54
55
56
57
58
59
60

- 1
2
3
4
5 381 evidence for stabilized colonization rates in childhood. *Helicobacter* 2011;16(5):405-
6
7
8 382 9. doi: 10.1111/j.1523-5378.2011.00854.x [published Online First: 2011/09/20]
9
10 383 17. Komatsu Y, Sugiyama T, Asaka M. Helicobacter pylori kansenshingan ni okeru
11
12 384 nihonjinkabu wo siyou sita ELISA kit " E-plate eiken H.pylori koutai" no yuyousei
13
14 385 no kentou [Study of effectiveness of E-plate eiken which is ELAISA kit using
15
16 386 Japanese strain in diagnose of Helicobacter pylori infection]. *The Journal of Clinical*
17
18 387 *Laboratory Instruments and Reagents* 2001;24(5):331-35.
19
20
21 388 18. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with
22
23 389 applications to cancer rates. *Stat Med* 2000;19(3):335-51. doi: 10.1002/(sici)1097-
24
25 390 0258(20000215)19:3<335::aid-sim336>3.0.co;2-z [published Online First:
26
27 391 2000/01/29]
28
29
30 392 19. Joinpoint Regression Program [program]. Version 4.9.0.0 version: Statistical
31
32 393 Methodology and Applications Branch, Surveillance Research Program, National
33
34 394 Cancer Institute., March 2021.
35
36
37 395 20. Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health
38
39 396 Research Involving Human Subjects 2015 [Available from:
40
41 397 [https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf)
42
43 398 [Daijinkanboukouseikagakuka/0000080278.pdf](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf) accessed 6 Dec 2020.
44
45
46 399 21. Kusano C, Gotoda T, Ishikawa H, et al. The administrative project of Helicobacter pylori
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5 400 infection screening among junior high school students in an area of Japan with a high
6
7
8 401 incidence of gastric cancer. *Gastric Cancer* 2017;20(Suppl 1):16-19. doi:
9
10 402 10.1007/s10120-017-0688-7 [published Online First: 2017/01/18]
11
12
13 403 22. Honma H, Nakayama Y, Kato S, et al. Clinical features of Helicobacter pylori antibody-
14
15 404 positive junior high school students in Nagano Prefecture, Japan. *Helicobacter*
16
17 405 2018:e12559. doi: 10.1111/hel.12559 [published Online First: 2018/12/06]
18
19
20
21 406 23. Nakayama Y, Lin Y, Hongo M, et al. Helicobacter pylori infection and its related factors
22
23 407 in junior high school students in Nagano Prefecture, Japan. *Helicobacter* 2017;22(2)
24
25 408 doi: 10.1111/hel.12363 [published Online First: 2016/10/28]
26
27
28
29 409 24. Kakiuchi T, Matsuo M, Endo H, et al. A Helicobacter pylori screening and treatment
30
31 410 program to eliminate gastric cancer among junior high school students in Saga
32
33 411 Prefecture: a preliminary report. *J Gastroenterol* 2019 doi: 10.1007/s00535-019-
34
35 412 01559-9 [published Online First: 2019/02/17]
36
37
38
39 413 25. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and Helicobacter pylori. *J*
40
41 414 *Infect Dis* 1993;168(1):219-21. doi: 10.1093/infdis/168.1.219
42
43
44
45 415 26. O'Ryan ML, Lucero Y, Rabello M, et al. Persistent and transient Helicobacter pylori
46
47 416 infections in early childhood. *Clin Infect Dis* 2015;61(2):211-8. doi:
48
49 417 10.1093/cid/civ256
50
51
52
53 418 27. Ueda M, Kikuchi S, Kasugai T, et al. Helicobacter pylori risk associated with childhood
54
55
56
57
58
59
60

- 1
2
3
4
5 419 home environment. *Cancer Sci* 2003;94(10):914-8. doi: 10.1111/j.1349-
6
7
8 420 7006.2003.tb01375.x [published Online First: 2003/10/15]
9
10 421 28. JAPAN WATER WORKS ASSOCIATION. Water Supply in Japan 2017 [Available
11
12
13 422 from: http://www.jwwa.or.jp/jigyoku/kaigai_file/2017WaterSupplyInJapan.pdf
14
15 423 accessed Dec 22 2020.
16
17
18 424 29. Ministry of Health, Labour and Welfare. General Welfare and Labour Japan [Available
19
20
21 425 from: <https://www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf> accessed 1st Oct 2020.
22
23
24 426 30. Council JBF. Seisan Tokei [Production statistics] Japan [Available from:
25
26 427 <https://www.baby-food.jp/link/ayumi-jikei.html> accessed 11 Dec 2020.
27
28
29 428 31. Hiroi S, Sugano K, Tanaka S, et al. Impact of health insurance coverage for *Helicobacter*
30
31 429 *pylori* gastritis on the trends in eradication therapy in Japan: retrospective
32
33
34 430 observational study and simulation study based on real-world data. *BMJ Open*
35
36
37 431 2017;7(7):e015855. doi: 10.1136/bmjopen-2017-015855 [published Online First:
38
39
40 432 2017/08/02]
41
42
43 433 32. Kowada A. Cost-effectiveness of *Helicobacter pylori* screening followed by eradication
44
45 434 treatment for employees in Japan. *Epidemiol Infect* 2018;146(14):1834-40. doi:
46
47
48 435 10.1017/S095026881800208X [published Online First: 2018/07/31]
49
50
51 436 33. Kato S, Matsukura N, Tsukada K, et al. *Helicobacter pylori* infection-negative gastric
52
53 437 cancer in Japanese hospital patients: Incidence and pathological characteristics.
54
55
56
57
58
59
60

- 1
2
3
4
5 438 *Cancer Sci* 2007;98(6):790-94. doi: <https://doi.org/10.1111/j.1349->
6
7
8 439 7006.2007.00478.x
9
10
11 440 34. Yamamoto Y, Fujisaki J, Omae M, et al. Helicobacter pylori-negative gastric cancer:
12
13 441 characteristics and endoscopic findings. *Digestive endoscopy : official journal of the*
14
15 442 *Japan Gastroenterological Endoscopy Society* 2015;27(5):551-61. doi:
16
17 443 10.1111/den.12471 [published Online First: 2015/03/27]
18
19
20
21 444 35. Takita M, Ohata K, Inamoto R, et al. Endoscopic and histological features of Helicobacter
22
23 445 pylori-negative differentiated gastric adenocarcinoma arising in the antrum. *JGH*
24
25 446 *open : an open access journal of gastroenterology and hepatology* 2021;5(4):470-77.
26
27 447 doi: 10.1002/jgh3.12518 [published Online First: 2021/04/17]
28
29
30
31 448 36. Kheyre H, Morais S, Ferro A, et al. The occupational risk of Helicobacter pylori infection:
32
33 449 a systematic review. *Int Arch Occup Environ Health* 2018;91(6):657-74. doi:
34
35 450 10.1007/s00420-018-1315-6
36
37
38
39 451 37. Ueda J, Gosho M, Inui Y, et al. Prevalence of Helicobacter pylori infection by birth year
40
41 452 and geographic area in Japan. *Helicobacter* 2014;19(2):105-10. doi:
42
43 453 10.1111/hel.12110 [published Online First: 2014/02/11]
44
45
46
47 454 38. Ferro A, Morais S, Pelucchi C, et al. Sex differences in the prevalence of Helicobacter
48
49 455 pylori infection: an individual participant data pooled analysis (StoP Project). *Eur J*
50
51 456 *Gastroenterol Hepatol* 2019;31(5):593-98. doi: 10.1097/MEG.0000000000001389
52
53
54
55
56
57
58
59
60

1
2
3
4
5 457 [published Online First: 2019/03/07]
6

7
8 458 39. Kanamori S, Tsuji T, Takamiya T, et al. Size of company of the longest-held job and
9
10 459 mortality in older Japanese adults: A 6-year follow-up study from the Japan
11
12 Gerontological Evaluation Study. *J Occup Health* 2020;62(1):e12115. doi:
13 460 10.1002/1348-9585.12115 [published Online First: 2020/06/10]
14
15 461

16
17
18 462 40. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43(1):87-91.
19
20
21 463 doi: 10.1016/0895-4356(90)90060-3
22

23
24 464 41. Miftahussurur M, Yamaoka Y. Diagnostic Methods of Helicobacter pylori Infection for
25
26 465 Epidemiological Studies: Critical Importance of Indirect Test Validation. *BioMed*
27
28 *research international* 2016;2016:4819423. doi: 10.1155/2016/4819423 [published
29 466
30
31 467 Online First: 2016/02/24]
32
33

34 468 42. Inoue M, Sawada N, Goto A, et al. High-Negative Anti-Helicobacter pylori IgG Antibody
35
36
37 469 Titers and Long-Term Risk of Gastric Cancer: Results from a Large-Scale
38
39 470 Population-Based Cohort Study in Japan. *Cancer Epidemiol Biomarkers Prev*
40
41
42 471 2020;29(2):420-26. doi: 10.1158/1055-9965.EPI-19-0993 [published Online First:
43
44
45 472 2019/12/13]
46

47
48 473 [dataset] 43. Soichiro A. Data from: Changes in prevalence of Helicobacter pylori in Japan
49
50 474 from 2008 to 2018: a repeated cross-sectional study, figshare, July 13, 2022
51
52
53 475 <https://doi.org/10.6084/m9.figshare.14594571.v2>
54
55
56
57
58
59
60

1
2
3
4
5 476
6
7
8 477
9

10 478 **FIGURE LEGENDS**

11
12
13 479 **Figure 1**

14
15 480 *Numbers of participants*

16
17
18 481

19
20
21 482 Figure 1

22
23 483 *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The

24
25
26 484 2018 analysis: participants aged 35–65 years in 2018.

27
28
29 485

30
31
32 486

33
34 487 **Figure 2:**

35
36
37 488 *Infection rates of Helicobacter pylori at 35 years old from 2008 to 2018 (men: n = 7,586,*

38
39 489 *women: n= 1,739)*

40
41
42 490

43
44
45 491 Figure 2

46
47 492 *Note.* Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to

48
49
50 493 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51).

51
52
53 494 There were no joinpoints. “*” in the graph legend indicates a significant difference in the

1
2
3
4
5 495 slope from zero at the alpha = 0.05 level.
6
7
8 496
9
10 497
11
12

13 498 **Figure 3**

14
15 499 *Infection rates of Helicobacter pylori according to age in 2018 (men: n = 9,580, women:*
16
17
18 500 *n=1,854)*

19
20
21 501
22
23 502 **Figure 3**

24
25
26 503 *Note.* Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67];
27
28 504 second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30];
29
30 505 second trend: 45–65 years [slope = 1.49]). “*” in the graph legend indicates a significant
31
32 506 difference in the slope from zero at the alpha = 0.05 level.
33
34
35
36

37 507

38
39 508
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

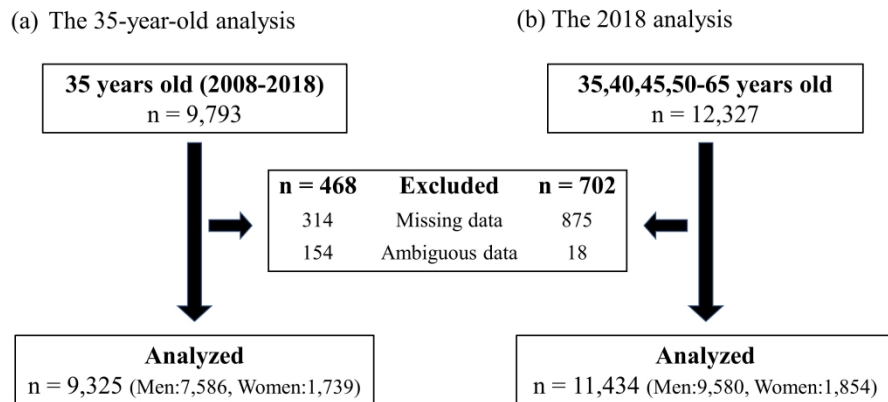


Figure 1: *Note.* (a) The 35-year-old analysis: participants aged 35 years from 2008 to 2018. (b) The 2018 analysis: participants aged 35–65 years in 2018.

338x190mm (300 x 300 DPI)

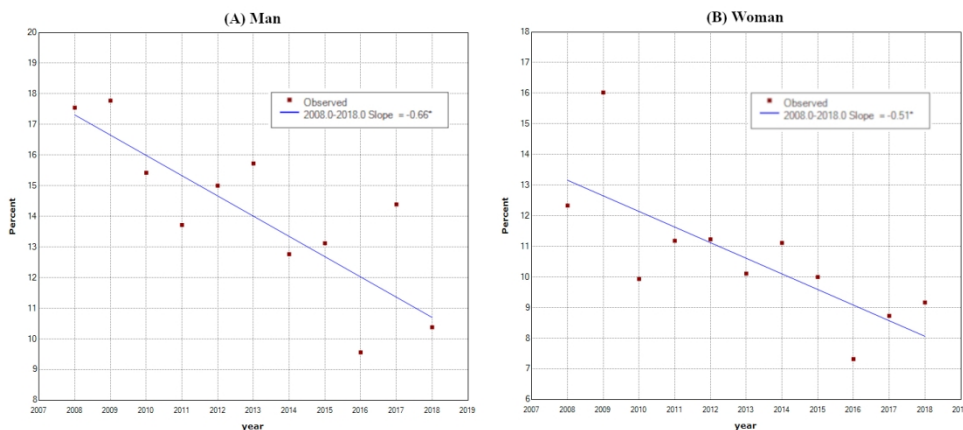


Figure 2: Note. Infection rates at 35 years linearly decreased by years. (A) men: 17.5% in 2008 to 10.1% in 2018 (slope: -0.65). (B) women: 12.3% in 2008 to 9.2% in 2018 (slope: -0.51). There were no joinpoints. "*" in the graph legend indicates a significant difference in the slope from zero at the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

32x14mm (1200 x 1200 DPI)

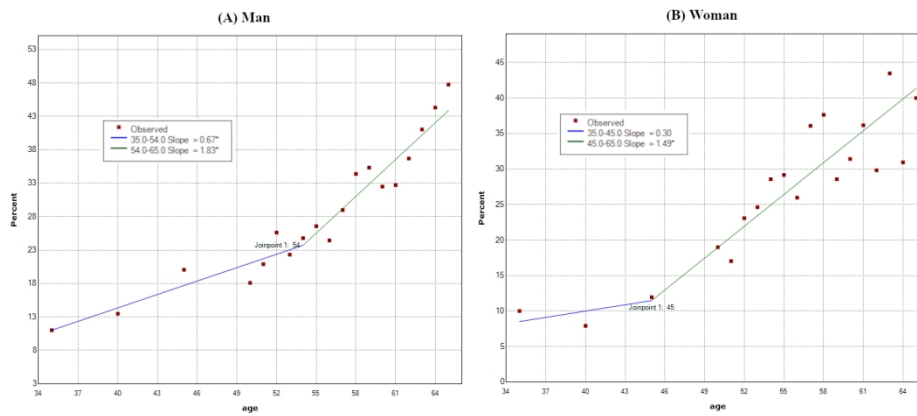


Figure 3: Note. Infection rates increased in two trends. (A) men: first trend: 35–54 years [slope = 0.67]; second trend: 54–65 years [slope = 1.83]. (B) female: first trend: 35–45 years [slope = 0.30]; second trend: 45–65 years [slope = 1.49]. “*” in the graph legend indicates a significant difference 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 sectional reporting guidelines, and cite them as:

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

			Page
		Reporting Item	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

1	Quantitative	#11	Explain how quantitative variables were handled in the	n/a
2				
3	variables		analyses. If applicable, describe which groupings were chosen,	
4				
5			and why	
6				
7				
8				
9	Statistical	#12a	Describe all statistical methods, including those used to control	7-8
10				
11	methods		for confounding	
12				
13				
14	Statistical	#12b	Describe any methods used to examine subgroups and	7-8
15				
16	methods		interactions	
17				
18				
19	Statistical	#12c	Explain how missing data were addressed	8
20				
21	methods			
22				
23				
24				
25	Statistical	#12d	If applicable, describe analytical methods taking account of	n/a
26				
27	methods		sampling strategy	
28				
29				
30	Statistical	#12e	Describe any sensitivity analyses	n/a
31				
32	methods			
33				
34				
35				
36	Results			
37				
38				
39	Participants	#13a	Report numbers of individuals at each stage of study—eg	9-10
40				
41			numbers potentially eligible, examined for eligibility, confirmed	
42				
43			eligible, included in the study, completing follow-up, and	
44				
45			analysed. Give information separately for for exposed and	
46				
47			unexposed groups if applicable.	
48				
49				
50				
51	Participants	#13b	Give reasons for non-participation at each stage	9
52				
53				
54	Participants	#13c	Consider use of a flow diagram	9
55				
56				
57	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	6, 14-15
58				
59				
60				

clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.

8	Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9-10
9				
10				
11				
12				
13	Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	9-10
14				
15				
16				
17				
18				
19				
20				
21	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
22				
23				
24				
25				
26				
27				
28				
29				
30				
31	Main results	#16b	Report category boundaries when continuous variables were categorized	n/a
32				
33				
34				
35				
36	Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
37				
38				
39				
40				
41				
42	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
43				
44				
45				
46				
47	Discussion			
48				
49				
50	Key results	#18	Summarise key results with reference to study objectives	10-12
51				
52				
53	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
54				
55				
56				
57				
58				
59				
60				

1	Interpretation	#20	Give a cautious overall interpretation considering objectives,	10-15
2			limitations, multiplicity of analyses, results from similar studies,	
3			and other relevant evidence.	
4				
5				
6				
7				
8				
9	Generalisability	#21	Discuss the generalisability (external validity) of the study	15
10			results	
11				
12				
13				
14	Other Information			
15				
16				
17	Funding	#22	Give the source of funding and the role of the funders for the	n/a
18			present study and, if applicable, for the original study on which	
19			the present article is based	
20				
21				
22				
23				
24				

25 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License
26 CC-BY. This checklist was completed on 20. September 2021 using <https://www.goodreports.org/>, a
27 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60