Preventive Effect of *Helicobacter pylori* Treatment on Gastric Cancer Incidence and Mortality: A Korean Population Study

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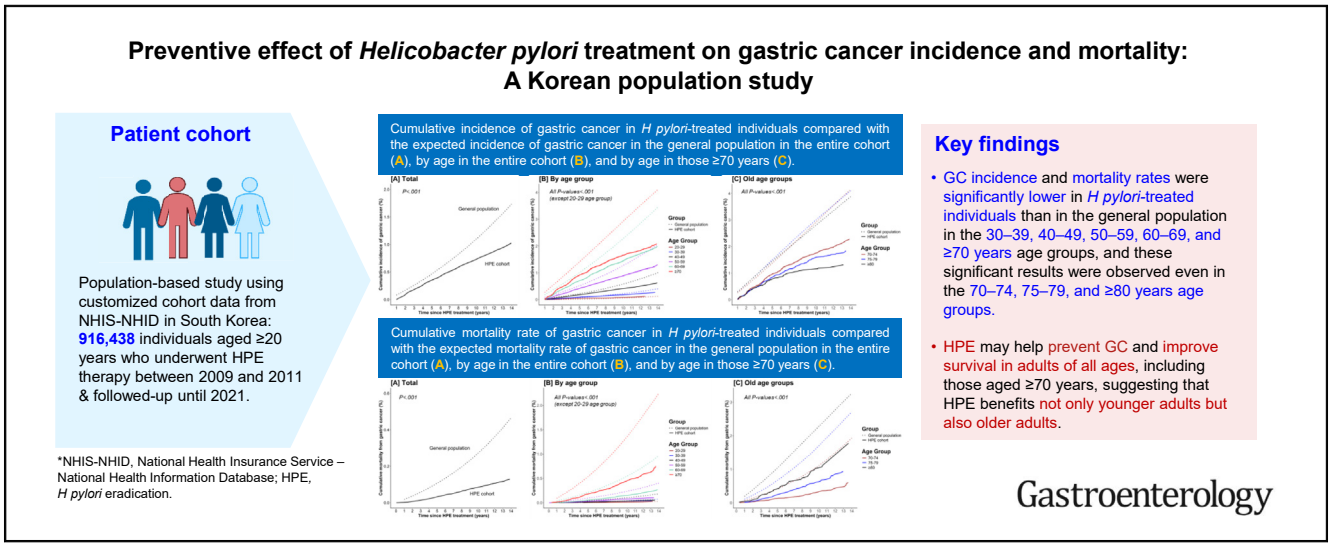

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BACKGROUND & AIMS: *Helicobacter pylori* (*H pylori*) infection is a major risk factor for gastric cancer (GC); however, whether *H pylori* eradication (HPE) benefits the older population remains unclear. We compared GC incidence and mortality between *H pylori*-treated individuals and the general population, stratified by age. **METHODS:** We conducted a population-based study in South Korea involving 916,438 individuals aged ≥20 years who underwent HPE therapy between 2009 and 2011, with follow-up until 2021. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) for GC were calculated, comparing *H pylori*-treated individuals with the general population. **RESULTS:** The mean follow-up period was 12.4 ± 1.1 years. GC incidence and mortality rates were significantly lower in *H pylori*-treated individuals than in the general population across all age-groups (30–39, 40–49, 50–59, 60–69, and ≥70 years), except for the 20 to 29 years age-group. Notably, in the 70 to 74, 75 to 79, and ≥80 years age-groups, GC incidence and mortality in *H pylori*-treated individuals remained significantly lower. The SIRs for these groups were 0.56 (95% confidence interval [CI], 0.52–0.61), 0.48 (95% CI, 0.42–0.54), and 0.36 (95% CI, 0.28–0.46), respectively, and the SMRs were 0.30 (95% CI, 0.25–0.35), 0.38 (95% CI, 0.31–0.47), and 0.43 (95% CI, 0.30–0.59), respectively. **CONCLUSIONS:** HPE may help prevent GC and improve survival in adults of all ages, including those aged ≥70 years. These findings suggest that HPE benefits not only younger adults but also older adults. HPE treatment is preferable at a younger age, but older age may not be a limiting factor for the treatment

Keywords: Eradication; *Helicobacter pylori*; Stomach Cancer; Prevention; Age.

Gastric cancer (GC) was the fifth most frequently diagnosed cancer in 2022, with 968,350 new cases,[1] and the fifth leading cause of cancer deaths, with 659,853

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Abbreviations used in this paper: **CI, confidence interval; GC, gastric cancer; *H pylori*, *Helicobacter pylori*; HPE, *Helicobacter pylori* eradication; ICD-10, International Classification of Diseases 10th Edition; IM, intestinal metaplasia; NHIS-NHID, National Health Insurance Service-National Health Information Database; PPI, proton pump inhibitor; RCT, randomized controlled trial; SIR, standardized incidence ratio; SMR, standardized mortality ratio.**

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deaths.[1] The high prevalence of *Helicobacter pylori* (*H pylori*) infection in East Asia has contributed to the highest incidence of GC in this region. Although its incidence is generally decreasing, GC is expected to have a high incidence, mortality rate, and disease burden for the next several decades because of the aging population, especially in East Asia, including Korea.[2,3]

H pylori infection is a major risk factor for GC, driving persistent active inflammation in the stomach.[4] *H pylori*-associated gastric carcinogenesis is a prolonged process with a series of histologic stages: chronic gastritis, atrophic gastritis, intestinal metaplasia (IM), dysplastic mucosa, and ultimately, cancer.[4] Recent meta-analyses have demonstrated that *H pylori* eradication (HPE) effectively reduces GC incidence.[5,6] However, successful eradication may lose its preventive effect once advanced preneoplastic changes of the gastric mucosa are present ("point of no return"),[7,8] highlighting the importance of early intervention before IM develops.[9] Consequently, the Maastricht VI/Florence Consensus Report published in 2022 states that the magnitude of the benefit of HPE decreases with age.[9]

Although it is best to receive HPE treatment at a younger age, a significant number of *H pylori*-infected individuals are older adults, often with atrophic gastritis or IM. *H pylori* infection typically occurs at a young age[10,11]; however, *H pylori*-associated GC progress over decades. Consequently, the prevalence of precancerous gastric lesions increases with age, and GC is typically diagnosed in older adults. A Thai study found that atrophic gastritis and IM prevalence increased from 28% and 9% in those <50 years to 43% and 30% in those >60 years.[12] Similarly, a Korean study reported that 62% of patients with GC were diagnosed at ≥60 years and 33% at ≥70 years.[13] To effectively reduce GC incidence, prevention strategies for the older population with high incidence need to be set up in parallel to strategies for the younger population.

The Maastricht VI/Florence consensus report suggests that it is never too late to eradicate *H pylori* for GC prevention and that older age is not a limiting factor.[9] However, more data are needed to support the preventive effect of HPE in older individuals. If the effect of HPE therapy is confirmed in the older population, the next consideration would be whether HPE therapy has a beneficial impact on survival in older adults, particularly in very old individuals, such as those aged ≥80 years.

We conducted this study to determine whether HPE therapy could reduce the risk of GC and associated mortality in adults of all ages, including older adults. Using a large population-based cohort of individuals treated for *H pylori* in South Korea, we compared their age-stratified incidence and mortality rates of GC with those of the general population.

Material and Methods

Study Design and Settings

The study population comprised all individuals in South Korea who received HPE therapy between January 1, 2009, and December 31, 2011. Data were extracted from a customized retrospective cohort using The National Health Insurance Service-National Health Information Database (NHIS-NHID). The NHIS is a mandatory health insurance system covering the entire Korean population, and the NHIS-NHID includes demographics, health care use, and national health screening results of the entire Korean population.[14] Medical records from January 1, 2002, until the start of HPE treatment in 2009 to 2011 were also obtained and used as the washout period. The Ewha Womans University Mokdong Hospital Institutional Review Board approved the study (EUMC 2023-07-004). Informed consent was waived because the NHIS-NHID was constructed using anonymized data. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Study Population

H pylori-treated individuals were defined as those prescribed proton pump inhibitor (PPI) + amoxicillin + clarithromycin, PPI + metronidazole + tetracycline/bismuth, or PPI + amoxicillin + levofloxacin/rifabutin. We identified all individuals aged ≥20 years who received their first HPE prescription between 2009 and 2011. Indications for HPE were categorized based on Korean guidelines and included peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, immune thrombocytopenic purpura, and *H pylori*-associated gastritis, using the International Classification of Diseases 10th Edition (ICD-10) code.[15,16]

We used data obtained during the washout period to exclude patients with a history of GC (n = 7791), gastric adenoma (n = 13,740), or gastrectomy (n = 188). To ensure the study included only patients who received their first HPE treatment, those with a history of HPE treatment during the washout period were also excluded (n = 84,862). In addition, we excluded patients who developed GC within 12 months after the first HPE prescription to eliminate potentially prevalent GC cases (n = 3874). The final study population comprised 916,438 individuals (Figure 1).

Outcomes

The primary outcomes of this study were GC incidence and mortality in the HPE cohort compared with the expected GC incidence and mortality in the general population. GC incidence in the HPE cohort was defined as the combination of the ICD-10 code for GC (C16) and the catastrophic illness code for cancer.[17] The catastrophic illness code is related to the cost-sharing of out-of-pocket expenses for diseases with a high financial burden in South Korea, including cancer; thereby improving the accuracy of GC ascertainment.[17,18] In the HPE cohort, GC-related death was defined using the cause of death information provided by the Statistics Korea.[19] The incidence and mortality rates of GC in the general population were obtained from data published by the Korea Central Cancer Registry[20] and the Korean Statistical Information Service.[21] The rates by 5-year age-group (from age-group 20–24 to ≥80 years) and by sex, from 2009 to 2021, were obtained for the analysis. The follow-up time for both outcomes was ascertained as the duration up to December 31, 2021. A previous study has reported a high concordance rate between GC incidence defined by the combination of the ICD-10 and catastrophic illness codes and that reported by the Korea Central Cancer Registry (90.8% in 2009, 91.0% in 2012, and 91.8% in 2013).[18]

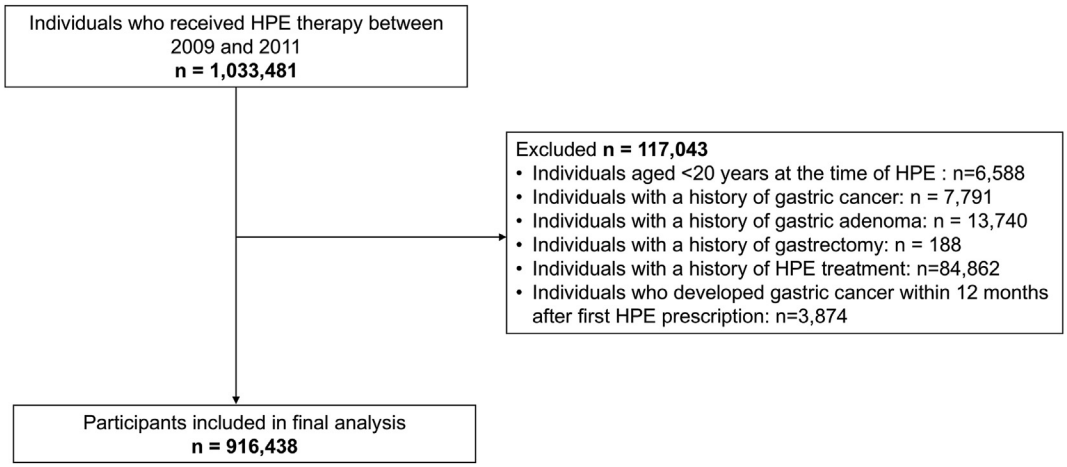

Figure 1. Flowchart of the study population selection.

Statistical Analysis

Follow-up time was calculated as the time from the date of the first HPE prescription to the date of GC incidence/mortality or December 31, 2021. Person-years at risk of GC were calculated for each individual. Results were reported for the total population, by sex, and by the following age-groups: 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years. Further analyses were performed for the 70 to 74, 75 to 79, and ≥80 years age-groups. The age-groups were based on the age at the time of HPE.

We applied the method described by Finkelstein et al,[22] known as the 1-sample log-rank test, to estimate the standardized incidence ratio (SIR) and standardized mortality ratio (SMR) of GC. For the general population, mean GC incidence and mortality rates by 5-year age-group and sex from 2009 to 2021 were used. Each individual in our HPE cohort was matched by age and sex to the general population, and the probability of observing GC incidence/death cases during the same follow-up period in the matched general population was calculated. We then compared the observed incidence and mortality of GC in our HPE cohort with the expected incidence and mortality in the matched general population. The SIR and SMR were estimated as the ratio of observed-to-expected GC incidence/death cases, with 95% confidence intervals (CIs). The 1-sample log-rank test was used to compare cumulative incidence/mortality between the HPE cohort and the general population. As a sensitivity analysis, we estimated SIR and SMR, excluding GC cases diagnosed within 1 and 3 months after the first HPE prescription.

All reported *P* values were 2-sided, with a type I error ($\alpha < .05$) considered significant. Analyses of SIR/SMR and the 1-sample log-rank test were conducted using the R *OneSampleLogRankTest* package with R 4.2.2 software (R Foundation for Statistical Computing). Other analyses were performed using SAS 9.4 statistical software (SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics of the Study Population

The baseline characteristics of the study population are presented in Table 1. The mean age of the study participants at the time of eradication therapy was 49.5 ± 12.2 years, and 57.2% were men. The mean follow-up period was 12.4 ± 1.1 years (median, 12.5 years; interquartile range, 11.7–13.2 years). The 2009 Korean *H pylori* treatment guidelines,[15] applicable during our study period, recommended only standard triple therapy as the first-line treatment. Accordingly, most participants were prescribed standard triple therapy (98.7%), whereas a small proportion received bismuth quadruple therapy (1.1%) or therapy containing levofloxacin or rifabutin (0.2%). The most common indications for HPE therapy were *H pylori*-associated gastritis (45.7%), gastric ulcer (30.7%), and duodenal ulcer (17.1%).

Gastric Cancer Risk in Helicobacter pylori-Treated Individuals Compared With the General Population by Age and Sex

Table 2 presents a comparison of GC incidence in our cohort, stratified by age at HPE, with the expected incidence in the general population. In all age-groups except for the 20 to 29 years age-group, the GC incidence was significantly lower in *H pylori*-treated individuals than in the general population. The SIRs of GC in the 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70-years age-groups receiving HPE therapy were 0.72 (95% CI, 0.65–0.80), 0.65 (95% CI, 0.61–0.68), 0.65 (95% CI, 0.63–0.68), 0.60 (95% CI, 0.58–0.62), and 0.52 (95% CI, 0.49–0.56), respectively (all $P < .001$). Sex-stratified analyses showed that GC incidence in *H pylori*-treated individuals was significantly lower than in the general population across all age-groups, except in men aged 20 to 29 years and in women aged 20 to 29 and 30 to 39 years. Sensitivity analyses for GC incidence, excluding GC cases diagnosed within 1 and 3 months after the first HPE prescription, yielded comparable results (Supplementary Tables 1 and 2).

Figure 2*A* illustrates the cumulative GC incidence in the entire HPE cohort compared with the expected GC incidence in the general population, and Figure 2*B* presents the results stratified by age. The cumulative incidence of GC was significantly lower in *H pylori*-treated individuals than in the general population, both in the entire HPE cohort ($P < .001$)

Table 1. Baseline Characteristics of *Helicobacter pylori*-Treated Individuals

Characteristics	Data value (N = 916,438)
Age at eradication therapy, mean ± SD, *y*	49.5 ± 12.2
Male sex	524,187 (57.2)
Duration of follow-up, y	
Mean ± SD	12.4 ± 1.1
Median (IQR)	12.5 (11.7–13.2)
Eradication therapy regimen	
PPI + amoxicillin + clarithromycin	904,215 (98.7)
PPI + metronidazole + tetracycline/bismuth	10,360 (1.1)
PPI + amoxicillin + levofloxacin/rifabutin	1863 (0.2)
Charlson Comorbidity Index	
0	88,838 (9.7)
1	442,734 (48.3)
2	228,983 (25.0)
≥3	155,883 (17.0)
Indications for *H pylori* treatment	
Gastric ulcer	281,679 (30.7)
Duodenal ulcer	156,982 (17.1)
Both gastric and duodenal ulcer	33,957 (3.7)
Unclassified peptic ulcer	25,217 (2.8)
Gastric mucosa-associated lymphoid tissue lymphoma	93 (0.0)
Immune thrombocytopenic purpura	80 (0.0)
H pylori-associated gastritis	418,430 (45.7)

NOTE. Data are presented as n (%) or as indicated otherwise. IQR, interquartile range; SD, standard deviation.

and in all age-groups (all $P < .001$), except for the 20 to 29 years age-group.

Gastric Cancer Mortality in Helicobacter pylori-Treated Individuals Compared With the General Population by Age and Sex

Table 3 presents a comparison of GC mortality in our cohort, stratified by age at HPE, with the expected mortality in the general population. The findings for GC mortality by age were consistent with those for GC incidence. In all age-groups except the 20 to 29 years age-group, the GC mortality rate was significantly lower in *H pylori*-treated individuals than in the general population. The SMRs in the 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years age-groups receiving HPE therapy were 0.64 (95% CI, 0.48–0.83), 0.31 (95% CI, 0.26–0.37), 0.29 (95% CI, 0.25–0.33), 0.28 (95% CI, 0.25–0.32), and 0.34 (95% CI, 0.30–0.38), respectively (all $P < .001$). Sex-stratified analyses showed that GC mortality in *H pylori*-treated individuals was significantly lower than that in the general population across all age-groups, except for the 20 to 29 years age-group in men and the 20 to 29 and 30 to 39 years age-groups in women. Sensitivity analyses for GC mortality, excluding GC cases diagnosed within 1 and 3 months after the first HPE prescription, yielded comparable results (Supplementary Tables 3 and 4).

Figure 3*A* illustrates the cumulative GC mortality in the entire HPE cohort compared with the expected GC mortality in the general population, and Figure 3*B* presents the results stratified by age. The cumulative GC mortality was significantly lower in *H pylori*-treated individuals than in the general population, both in the entire HPE cohort ($P < .001$) and in all age-groups (all $P < .001$), except for the 20 to 29 years age-group.

Gastric Cancer Risk and Mortality in Helicobacter pylori-Treated Individuals Aged ≥70 Years Compared With the General Population

We stratified *H pylori*-treated individuals aged ≥70 years into 3 age-groups of 70 to 74, 75 to 79, and ≥80 years and compared their GC incidence and mortality rates with those of the general population (Table 4). In all 3 groups, GC incidence was significantly lower in *H pylori*-treated individuals than in the general population. The SIRs of GC in the 70 to 74, 75 to 79, and ≥80 years age-groups were 0.56 (95% CIs, 0.52–0.61), 0.48 (95% CIs, 0.42–0.54), and 0.36 (95% CIs, 0.28–0.46), respectively (all $P < .001$).

Similarly, GC mortality was significantly lower in *H pylori*-treated individuals than in the general population across all age-groups. The SMRs of GC in the 70 to 74, 75 to 79, and ≥80 years age-groups were 0.30 (95% CIs, 0.25–0.35), 0.38 (95% CIs, 0.31–0.47), and 0.43 (95% CIs, 0.30–0.59), respectively (all $P < .001$). In all 3 age-groups, the cumulative incidence (Figure 2*C*) and cumulative mortality (Figure 3*C*) of GC were significantly lower in *H pylori*-treated individuals than in the general population (all $P < .001$).

Discussion

This is the first and largest population-based study to evaluate the effect of HPE on GC risk and mortality in a highly aged population. In this study, we found that *H pylori*-treated individuals had lower GC incidence and mortality than the general population across all age-groups, except those in their 20s. Notably, even when HPE therapy was administered to individuals aged 70 to 74, 75 to 79, and ≥80 years, the incidence and mortality rates of GC remained lower than those in the general population. These results suggest that HPE therapy may help prevent GC development and reduce mortality, not only in younger individuals but also in older individuals. Our findings suggest that there may be no need to impose an age limit on HPE treatment and that even individuals aged ≥80 years could benefit from active HPE treatment if they are able to tolerate antibiotics. However, our results should not be misinterpreted to mean that delaying eradication until older age could be beneficial. Although HPE treatment may remain effective in older adults, administering treatment at a younger age is preferable.

In 2011, the prevalence of *H pylori* infection in the Korean general population aged 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years was 26%, 42%, 53%,

Table 2. Gastric Cancer Incidence in *Helicobacter pylori*-Treated Individuals Compared With the General Population by Age and Sex

Variables	Individuals (n)	Person-years	Observed (n)	Expected (n)	SIR (95% CI)	*P* value
Total	916,438	29,254,203	8321	13,428	0.62 (0.61–0.63)	<.001
By age-group, *y*						
20–29	45,571	572,783	52	44	1.17 (0.88–1.54)	.283
30–39	140,501	1,757,111	335	464	0.72 (0.65–0.80)	<.001
40–49	275,152	3,417,910	1465	2278	0.65 (0.61–0.68)	<.001
50–59	259,074	3,204,987	2916	4462	0.65 (0.63–0.68)	<.001
60–69	140,554	1,739,974	2498	4167	0.60 (0.58–0.62)	<.001
≥70	55,586	686,155	1055	2012	0.52 (0.49–0.56)	<.001
By sex						
Male	6058	6,496,364	6058	10,251	0.59 (0.58–0.61)	<.001
Female	2263	4,882,556	2263	3177	0.71 (0.68–0.74)	<.001
By sex and age-group, *y*						
Male						
20–29	25,025	314,256	22	23	0.97 (0.61–1.47)	.990
30–39	89,056	1,112,598	196	320	0.61 (0.53–0.71)	<.001
40–49	162,027	2,009,915	1045	1724	0.61 (0.57–0.64)	<.001
50–59	142,543	1,758,798	2208	3497	0.63 (0.61–0.66)	<.001
60–69	77,428	954,988	1880	3236	0.58 (0.55–0.61)	<.001
≥70	28,108	345,808	707	1451	0.49 (0.45–0.52)	<.001
Female						
20–29	20,546	258,527	30	22	1.39 (0.94–1.98)	.101
30–39	51,445	644,513	139	144	0.96 (0.81–1.14)	.708
40–49	113,125	1,407,994	420	554	0.76 (0.69–0.83)	<.001
50–59	116,531	1,446,189	708	965	0.73 (0.68–0.79)	<.001
60–69	63,126	784,986	618	931	0.66 (0.61–0.72)	<.001
≥70	27,478	340,347	348	562	0.62 (0.56–0.69)	<.001

61%, 62%, and 59%, respectively.[23] Conversely, a significant proportion of the general population may not have *H pylori* infection and thus may be at low risk of developing GC. Nonetheless, our study showed that individuals treated for *H pylori* had a lower risk of developing GC than the general population, emphasizing the importance of HPE. Notably, despite the relatively higher proportion of uninfected individuals in the younger general population (58% in the 30–39 age-group), *H pylori*-infected individuals aged 30 to 39 years who received HPE therapy had significantly lower GC incidence and mortality rates than the age-matched general population.

These results underscore the need for HPE treatment at a younger age. In our study, the effect of HPE therapy was insignificant in the 20 to 29 years age-group, likely because the proportion of uninfected individuals in the age-matched general population was relatively high (74%) and the follow-up period did not extend until the age of high GC incidence. If the comparison had been made with *H pylori*-infected individuals who did not receive HPE therapy and the follow-up period had been sufficiently extended to 20 to 30 years or more, the effect of HPE therapy on GC prevention might have been confirmed in the 20 to 29 age-group as well.

The effectiveness of HPE therapy in preventing GC has become more evident as new studies evaluating the impact of HPE therapy on GC risk with long-term follow-up have been published.[5,6] A 2020 meta-analysis including 7 randomized controlled trials (RCTs) demonstrated that healthy individuals who received HPE treatment had a 46% reduced risk of developing GC (relative risk, 0.54; 95% CI, 0.40–0.72) and a 39% reduced risk of death from GC (relative risk, 0.61; 95% CI, 0.40–0.92) compared with those who did not receive HPE treatment.[5] However, this meta-analysis did not provide sufficient information on the effectiveness of HPE therapy in older individuals, because the mean age of participants in the 7 RCTs was 42 to 53 years (range, 20–75 years).

Some meta-analyses have demonstrated that HPE therapy can improve gastric atrophy but not IM.[7,8] Successful eradication significantly impacts gastric inflammation; however, the effect may be less pronounced when there are more advanced architectural changes in the mucosa. Given concern that there may be a "point of no return" for HPE treatment, there is no doubt that the treatment should be performed as early as possible. However, a significant number of patients with *H pylori* are older individuals who did not receive HPE treatment in their youth and already have structural changes in the gastric mucosa.

Whether HPE is beneficial for this older population remains unclear; however, recent research findings may provide some insights. Several recent studies have shown that

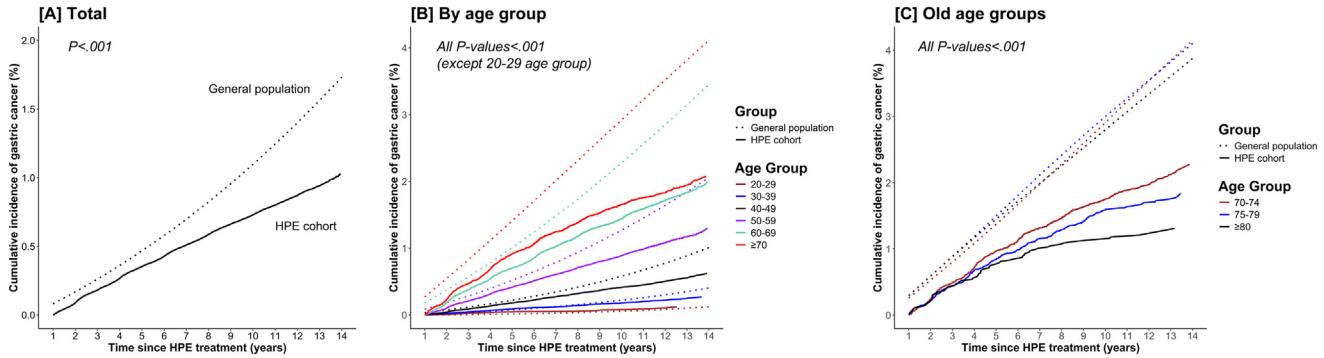

Figure 2. Cumulative incidence of GC in *H pylori*-treated individuals compared with the expected incidence of GC in the (*A*) general population in the entire cohort, (*B*) by age in the entire cohort, and (*C*) by age in those aged ≥70 years. *P* values in *B* and *C* are from log-rank tests comparing those treated for *H pylori* with the general population and were significant in all age-groups (all $P < .001$) except for the 20 to 29 years group.

HPE therapy can prevent the progression of IM or even reverse it.[24–27] Moreover, several RCTs have reported that HPE therapy reduces the risk of metachronous GC in patients undergoing endoscopic resection of early GC, who likely have concurrent preneoplastic lesions in the remaining stomach.[27–29] These recent findings, along with our findings, suggest that HPE therapy administered later in life may still reduce the risk of GC.

When HPE therapy is administered to older adults, concerns may arise that high rates of antibiotic resistance in this population could reduce its effectiveness.[30] However, a recent study of European populations found no clinically relevant differences in effectiveness between older (≥60 years) and younger groups (18–59 years) for the most frequently prescribed HPE regimens.[31] Furthermore, the incidence of antibiotic-related adverse events was

Table 3. Gastric Cancer Mortality in *Helicobacter pylori*-Treated Individuals Compared With the General Population by Age and Sex

Variables	Individuals (n)	Person-years	Observed (n)	Expected (n)	SMR (95% CI)	*P* value
Total	916,438	11,424,029	987	3154	0.31 (0.29–0.33)	<.001
By age-group, *y*						
20–29	45,571	573,053	10	10	1.00 (0.48–1.83)	1.000
30–39	140,501	1,758,760	54	85	0.64 (0.48–0.83)	<.001
40–49	275,152	3,425,652	125	407	0.31 (0.26–0.37)	<.001
50–59	259,074	3,220,797	240	827	0.29 (0.25–0.33)	<.001
60–69	140,554	1,753,982	286	1019	0.28 (0.25–0.32)	<.001
≥70	55,586	691,785	272	806	0.34 (0.30–0.38)	<.001
By sex						
Male	524,187	6,529,234	715	2412	0.30 (0.28–0.32)	<.001
Female	392,251	4,894,795	272	742	0.37 (0.32–0.41)	<.001
By sex and age-group, *y*						
Male						
20–29	25,025	314,387	2	5	0.44 (0.05–1.58)	.331
30–39	89,056	1,113,591	26	53	0.49 (0.32–0.72)	<.001
40–49	162,027	2,015,405	85	303	0.28 (0.22–0.35)	<.001
50–59	142,543	1,770,758	185	671	0.28 (0.24–0.32)	<.001
60–69	77,428	965,418	241	814	0.30 (0.26–0.34)	<.001
≥70	28,108	349,676	176	567	0.31 (0.27–0.36)	<.001
Female						
20–29	20,546	258,666	8	5	1.46 (0.63–2.88)	.375
30–39	51,445	645,169	28	31	0.89 (0.59–1.29)	.628
40–49	113,125	1,410,247	40	104	0.39 (0.28–0.53)	<.001
50–59	116,531	1,450,040	55	157	0.35 (0.26–0.46)	<.001
60–69	63,126	788,564	45	204	0.22 (0.16–0.29)	<.001
≥70	27,478	342,109	96	240	0.40 (0.32–0.49)	<.001

Table 4. Incidence and Mortality Rates of Gastric Cancer in *Helicobacter pylori*-Treated Individuals Aged ≥70 Years Compared With the General Population by Age and Sex

Variable	Individuals (n)	Incidence of GC					Mortality of GC				
		Person-years	Observed (n)	Expected (n)	SIR (95% CI)	*P* value	Person-years	Observed (n)	Expected (n)	SMR (95% CI)	*P* value
By age, *y*											
70–74	36,521	450,556	750	1328	0.56 (0.52–0.61)	<.001	454,819	143	480	0.30 (0.25–0.35)	<.001
75–79	13,909	171,861	241	507	0.48 (0.42–0.54)	<.001	172,994	90	236	0.38 (0.31–0.47)	<.001
≥80	5156	63,738	64	177	0.36 (0.28–0.46)	<.001	63,972	39	91	0.43 (0.30–0.59)	<.001
By sex and age, *y*											
Male											
70–74	18,914	232,580	507	976	0.52 (0.48–0.57)	<.001	235,533	97	349	0.28 (0.23–0.34)	<.001
75–79	6812	83,838	159	356	0.45 (0.38–0.52)	<.001	84,562	60	159	0.38 (0.29–0.49)	<.001
≥80	2382	29,390	41	119	0.34 (0.25–0.47)	<.001	29,581	19	58	0.32 (0.20–0.51)	<.001
Female											
70–74	17,607	217,976	243	353	0.69 (0.61–0.78)	<.001	219,285	46	130	0.35 (0.26–0.47)	<.001
75–79	7097	88,023	82	151	0.54 (0.43–0.67)	<.001	88,432	30	77	0.39 (0.26–0.56)	<.001
≥80	2774	34,348	23	58	0.40 (0.25–0.60)	<.001	34,391	20	33	0.61 (0.37–0.95)	.024

significantly lower in the older group.[31] These findings suggest that the efficacy and safety of HPE therapy may not be reduced in older adults.

To date, few studies have focused on the effectiveness of HPE therapy in older populations. A Chinese RCT comparing the 15-year effect of HPE therapy between the HPE and placebo groups, involving 2258 participants infected with *H pylori*, revealed that HPE therapy was associated with a significant reduction in GC incidence (odds ratio, 0.36; 95% CI, 0.17–0.79) and GC mortality (hazard ratio, 0.26; 95% CI, 0.09–0.79) in the 55 to 71 years age-group.[32] However, this study did not assess the effect of HPE in the individuals aged ≥72 years.

Similar to our study, a study in Hong Kong analyzed the SIR of GC in 73,237 individuals treated for *H pylori* compared with the general population. This study classified *H pylori*-treated individuals into <40, 40 to 59, and ≥60 years age-groups and found that those aged ≥60 years had a significantly lower risk of GC than the general population (SIR, 0.82; 95% CI, 0.69–0.97).[33] However, their study did not evaluate the effectiveness of HPE in individuals much older than 60 years, such as those aged 70 or ≥80 years, and included only 27,423 individuals aged ≥60 years. Furthermore, that study did not confirm the effectiveness of HPE in those aged <40 years.

In contrast, our study involved 916,438 individuals treated for *H pylori*, enabling analysis of a sufficient number of individuals in each age-group (30–39, n = 140,501; 40–49, n = 275,152; 50–59, n = 259,074; 60–69, n = 140,554; and ≥70 years, n = 55,586). Moreover, the follow-up period in our study was much longer than that in the Hong Kong study (median, 12.5 vs 7.6 years). These strengths of our study allowed us to confirm the GC prevention effect of HPE therapy in younger age-groups, such as those in their 30s and 40s.

An additional strength of our study is the analysis of GC mortality and the inclusion of an adequate washout period, which was at least 7 years, spanning from 2002 to the time of HPE prescription (2009–2011). This allowed us to exclude individuals with a history of GC, gastric adenoma, or prior HPE treatment, enabling a more accurate evaluation of the preventative effect of HPE against GC.

Interestingly, in our study, the effect of HPE was stronger on GC mortality than on GC incidence. Although explaining the exact reason for this is difficult, HPE may play a role in improving the prognosis of GC by inhibiting further malignant changes, even in patients who have already developed GC. Some studies support this possibility. A recent Chinese study demonstrated the significant survival benefits of *H pylori* treatment after radical gastrectomy in patients with GC who had *H pylori* infection.[34]

A Korean study also revealed that patients who underwent subtotal gastrectomy for GC had statistically significant benefits in the successfully eradicated group compared with the eradication failure/untreated group in overall survival, GC-specific survival, and GC recurrence rates.[35] In particular, this study reported that the benefit of HPE was relatively higher in advanced GC than in early GC. Based on these studies and ours, intensive screening and treatment

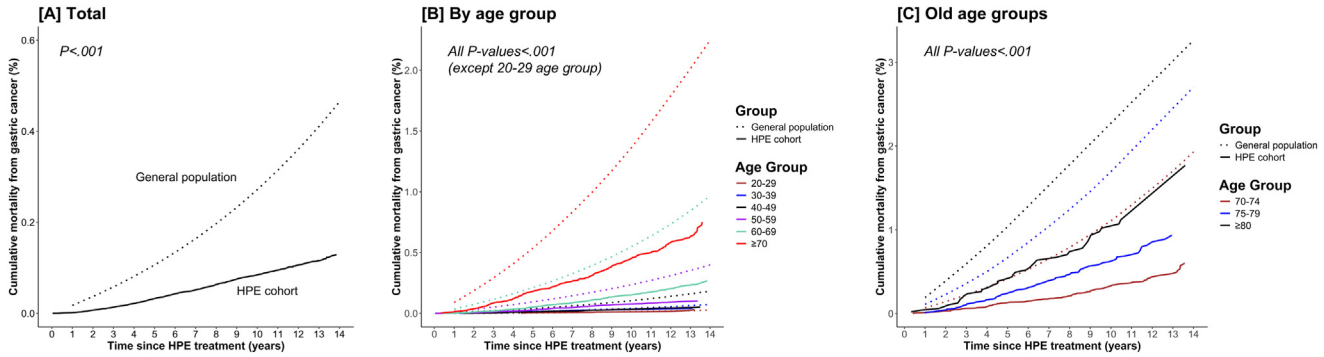

Figure 3. Cumulative mortality rate of GC in *H pylori*-treated individuals compared with the expected mortality rate of GC in the (*A*) general population in the entire cohort, (*B*) by age in the entire cohort, and (*C*) by age in those aged ≥70 years. The *P* values in *B* and *C* were from log-rank tests comparing those treated with *H pylori* with the general population and were significant in all age-groups (all $P < .001$), except for the 20 to 29 years group.

for *H pylori* may be necessary not only for patients undergoing endoscopic resection for early GC but also for patients undergoing surgical treatment for advanced GC.

Another interesting finding of our study is that HPE appeared to be more beneficial in men (SIR, 0.59) than in women (SIR, 0.71). We analyzed *P* heterogeneity to test for significant differences in SIR values between men and women. The *P* heterogeneity for SIR was <.001, indicating a significant difference in GC incidence by sex. The reasons for this sex difference are unclear, but hormonal differences between men and women may have played a role. Estrogen in women has been reported to exert a protective effect on GC by protecting the mucous epithelium or suppressing oncogene expression.[36,37] This protective effect of female hormones may have relatively attenuated the impact of HPE on GC in women compared with men.

Our study has some limitations. First, we compared the incidence and mortality of GC in *H pylori*-treated individuals with that in the general population, including those with and without *H pylori* infection, because we could not identify *H pylori*-infected individuals from the claims data. However, if *H pylori*-treated individuals had been compared with *H pylori*-infected individuals who did not receive HPE therapy, the effect of HPE therapy in preventing GC would have been greater.

Second, the incidence and mortality rates of GC according to the success or failure of HPE therapy were not analyzed; such an analysis could have been performed by defining eradication failure as a retreatment prescription. However, considering that ∼20% of patients were lost to follow-up or refused retreatment after first-line treatment,[38] we deemed it inaccurate to equate retreatment prescriptions as eradication failure and, therefore, did not conduct an analysis on this. A meta-analysis of 29 RCTs on standard triple therapy in Korea showed a pooled eradication success rate of ∼80%.[39] On the basis of this meta-analysis, the treatment failure rate in our HPE cohort can be estimated at ∼20%. Nevertheless, our HPE cohort had a lower incidence of GC than the general population. If our cohort had included only successfully eradicated patients, the effect of HPE would have been greater.

Third, although *H pylori* infection is more strongly associated with noncardiac GC,[40] analyses based on GC location were not performed because this information was not available in the claims data. For the same reason, analyses by GC stage could not be performed.

Fourth, our HPE cohort may have benefited not only from HPE treatment itself but also from endoscopic screening, reducing GC incidence and mortality. To assess the impact of GC screening on outcomes, we compared the GC screening rates of our HPE cohort obtained from the NHIS-NHID with those of the general population reported in previously published studies.[41,42] Consequently, the average GC screening rate over the 10 years from 2012 to 2021 was slightly higher in our HPE cohort than in the general population (63.1% vs 58.1%, respectively). However, because the GC screening rate differed by only 5%, it is reasonable to attribute the reduction in GC incidence and mortality in our HPE cohort to the effect of HPE rather than the effect of endoscopy.

Fifth, because our cohort consisted of patients who visited a physician and received treatment, selection bias may exist. To rule out the possibility that the estimated effect on GC incidence is due to selection bias, we calculated SIRs for thyroid, breast, and prostate cancers, which are known to be affected by overdiagnosis related to health care use.[43,44] The SIRs of thyroid, prostate, and breast cancers in our HPE cohort were 1.00 (95% CIs, 0.98–1.02), 0.98 (95% CIs, 0.96–1.01), and 1.03 (95% CIs, 1.01–1.06), respectively. These SIRs, being very close to 1, support the conclusion that the reduced GC incidence and mortality in our HPE cohort were related to HPE treatment rather than a selection effect.

Finally, because our study was conducted in South Korea, where the prevalence of *H pylori* infection and GC is high, caution is necessary when applying our results to other regions.

Conclusion

In conclusion, individuals treated for *H pylori* had significantly lower GC incidence and mortality rates than the general population in the 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years age-groups. Furthermore, very old individuals aged ≥80 years who received HPE therapy also

had significantly lower GC incidence and mortality rates than the general population. HPE may help prevent GC and improve survival in adults of all ages, including older adults, suggesting that HPE is beneficial not only for younger adults but also for older adults. Eradicating *H pylori* at a younger age is preferable; however, there may be no need to impose an age limit on HPE treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2025.03.036.

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Conflicts of interest
The authors disclose no conflicts.

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Data Availability
All data relevant to the study are included in the article.

Supplementary Table 1. Sensitivity Analysis for Gastric Cancer Incidence in *Helicobacter pylori*-Treated Individuals Compared With the General Population by Age and Sex After Excluding Gastric Cancer Cases Diagnosed Within 1 Month After the First *Helicobacter pylori* Eradication Prescription

	Individuals		Observed	Expected		
Variable	(n)	Person-years	(n)	(n)	SIR (95% CI)	*P* value
Total	918,009	11,379,523	9892	13,429	0.74 (0.72–0.75)	<.001
By age-group, *y*						
20–29	45,582	572,787	63	44	1.42 (1.09–1.82)	.010
30–39	140,566	1,757,140	400	464	0.86 (0.78–0.95)	.003
40–49	275,396	3,418,002	1709	2278	0.75 (0.71–0.79)	<.001
50–59	259,539	3,205,168	3381	4462	0.76 (0.73–0.78)	<.001
60–69	141,021	1,740,151	2965	4168	0.71 (0.69–0.74)	<.001
≥70	55,905	686,275	1374	2013	0.68 (0.65–0.72)	<.001
By sex						
Male	525,309	6,496,788	7180	10,251	0.70 (0.68–0.72)	<.001
Female	392,700	4,882,735	2712	3177	0.85 (0.82–0.89)	<.001
By sex and age-group, *y*						
Male						
20–29	25,029	314,257	26	23	1.14 (0.75–1.68)	.545
30–39	89,103	1,112,618	243	320	0.76 (0.67–0.86)	<.001
40–49	162,182	2,009,976	1200	1724	0.70 (0.66–0.74)	<.001
50–59	142,904	1,758,938	2569	3497	0.73 (0.71–0.76)	<.001
60–69	77,782	955,115	2234	3237	0.69 (0.66–0.72)	<.001
≥70	28,309	345,885	908	1451	0.63 (0.59–0.67)	<.001
Female						
20–29	20,553	258,530	37	22	1.71 (1.21–2.36)	.003
30–39	51,463	644,522	157	144	1.09 (0.93–1.27)	.304
40–49	113,214	1,408,026	509	554	0.92 (0.84–1.00)	.055
50–59	116,635	1,446,230	812	965	0.84 (0.78–0.90)	<.001
60–69	63,239	785,036	731	931	0.79 (0.73–0.84)	<.001
≥70	27,596	340,390	466	562	0.83 (0.76–0.91)	<.001

Supplementary Table 2. Sensitivity Analysis for Gastric Cancer Incidence in *Helicobacter pylori*-Treated Individuals Compared With the General Population by Age and Sex After Excluding Gastric Cancer Cases Diagnosed Within 3 Months After the First *Helicobacter pylori* Eradication Prescription

	Individuals		Observed	Expected		
Variable	(n)	Person-years	(n)	(n)	SIR (95% CI)	*P* value
Total	917,210	11,379,523	9093	13,429	0.68 (0.66–0.69)	<.001
By age-group, *y*						
20–29	45,578	572,787	59	44	1.33 (1.01–1.72)	.040
30–39	140,534	1,757,140	368	464	0.79 (0.71–0.88)	<.001
40–49	275,256	3,418,002	1569	2278	0.69 (0.66–0.72)	<.001
50–59	259,291	3,205,168	3133	4462	0.70 (0.68–0.73)	<.001
60–69	140,795	1,740,151	2739	4168	0.66 (0.63–0.68)	<.001
≥70	55,756	686,275	1225	2012	0.61 (0.58–0.64)	<.001
By sex						
Male	524,724	6,496,788	6595	10,251	0.64 (0.63–0.66)	<.001
Female	392,486	4,882,735	2498	3177	0.79 (0.76–0.82)	<.001
By sex and age-group, *y*						
Male						
20–29	25,026	314,257	23	23	1.01 (0.64–1.52)	1.000
30–39	89,079	1,112,618	219	320	0.68 (0.60–0.78)	<.001
40–49	162,095	2,009,976	1113	1724	0.65 (0.61–0.68)	<.001
50–59	142,712	1,758,938	2377	3497	0.68 (0.65–0.71)	<.001
60–69	77,597	955,115	2049	3237	0.63 (0.61–0.66)	<.001
≥70	28,215	345,885	814	1451	0.56 (0.52–0.60)	<.001
Female						
20–29	20,552	258,530	36	22	1.67 (1.17–2.31)	.006
30–39	51,455	644,522	149	144	1.03 (0.87–1.21)	.708
40–49	113,161	1,408,026	456	554	0.82 (0.75–0.90)	<.001
50–59	116,579	1,446,230	756	965	0.78 (0.73–0.84)	<.001
60–69	63,198	785,036	690	931	0.74 (0.69–0.80)	<.001
≥70	27,541	340,390	411	562	0.73 (0.66–0.81)	<.001

Supplementary Table 3. Sensitivity Analysis for Gastric Cancer Mortality in *Helicobacter pylori*-Treated Individuals Compared With the General Population by Age and Sex After Excluding Gastric Cancer Cases Diagnosed Within 1 Month After the First *Helicobacter pylori* Eradication Prescription

	Individuals		Observed	Expected		
Variable	(n)	Person-years	(n)	(n)	SMR (95% CI)	*P* value
Total	918,009	11,381,239	1233	3493	0.35 (0.33–0.37)	<.001
By age-group, *y*						
20–29	45,582	572,824	13	10	1.29 (0.69–2.20)	.433
30–39	140,566	1,757,315	77	85	0.91 (0.72–1.13)	.422
40–49	275,396	3,418,384	167	412	0.41 (0.35–0.47)	<.001
50–59	259,539	3,205,661	292	848	0.34 (0.31–0.39)	<.001
60–69	141,021	1,740,557	344	1098	0.31 (0.28–0.35)	<.001
≥70	55,905	686,497	340	1041	0.33 (0.29–0.36)	<.001
By sex						
Male	525,309	6,498,126	880	2692	0.33 (0.31–0.35)	<.001
Female	392,700	4,883,113	353	802	0.44 (0.40–0.49)	<.001
By sex and age-group, *y*						
Male						
20–29	25,029	314,264	4	5	0.87 (0.24–2.23)	1.000
30–39	89,103	1,112,714	45	54	0.84 (0.61–1.13)	.271
40–49	162,182	2,010,293	108	307	0.35 (0.29–0.42)	<.001
50–59	142,904	1,759,376	222	690	0.32 (0.28–0.37)	<.001
60–69	77,782	955,451	286	885	0.32 (0.29–0.36)	<.001
≥70	28,309	346,029	215	751	0.29 (0.25–0.33)	<.001
Female						
20–29	20,553	258,560	9	5	1.64 (0.75–3.11)	.210
30–39	51,463	644,601	32	31	1.02 (0.70–1.44)	.967
40–49	113,214	1,408,091	59	104	0.57 (0.43–0.73)	<.001
50–59	116,635	1,446,285	70	158	0.44 (0.34–0.56)	<.001
60–69	63,239	785,107	58	213	0.27 (0.21–0.35)	<.001
≥70	27,596	340,469	125	290	0.43 (0.36–0.51)	<.001

Supplementary Table 4. Sensitivity Analysis for Gastric Cancer Mortality in *Helicobacter pylori*-Treated Individuals Compared With the General Population by Age and Sex After Excluding Gastric Cancer Cases Diagnosed Within 3 Months After the First *Helicobacter pylori* Eradication Prescription

Age and sex	Individuals	Person-years	Observed, n	Expected, n	SMR (95% CI)	*P* value
Total	917,210	11,381,239	1127	3493	0.32 (0.30–0.34)	<.001
By age-group, *y*						
20–29	45,578	572,824	12	10	1.19 (0.61–2.08)	.626
30–39	140,534	1,757,315	65	85	0.77 (0.59–0.98)	.029
40–49	275,256	3,418,384	145	412	0.35 (0.30–0.41)	<.001
50–59	259,291	3,205,661	268	848	0.32 (0.28–0.36)	<.001
60–69	140,795	1,740,557	321	1098	0.29 (0.26–0.33)	<.001
≥70	55,756	686,497	316	1041	0.30 (0.27–0.34)	<.001
By sex						
Male	524,724	6,498,126	806	2692	0.30 (0.28–0.32)	<.001
Female	392,486	4,883,113	321	802	0.40 (0.36–0.45)	<.001
By sex and age-group, *y*						
Male						
20–29	25,026	314,264	3	5	0.65 (0.13–1.91)	.653
30–39	89,079	1,112,714	34	54	0.64 (0.44–0.89)	.006
40–49	162,095	2,010,293	96	307	0.31 (0.25–0.38)	<.001
50–59	142,712	1,759,376	205	690	0.30 (0.26–0.34)	<.001
60–69	77,597	955,451	268	885	0.30 (0.27–0.34)	<.001
≥70	28,215	346,029	200	751	0.27 (0.23–0.31)	<.001
Female						
20–29	20,552	258,560	9	5	1.64 (0.75–3.11)	.210
30–39	51,455	644,601	31	31	0.99 (0.67–1.40)	1.000
40–49	113,161	1,408,091	49	104	0.47 (0.35–0.62)	<.001
50–59	116,579	1,446,285	63	158	0.40 (0.31–0.51)	<.001
60–69	63,198	785,107	53	213	0.25 (0.19–0.33)	<.001
≥70	27,541	340,469	116	290	0.40 (0.33–0.48)	<.001