

DR. SOO ICK CHO (Orcid ID : 0000-0003-3414-9869)

DR. HANJAE LEE (Orcid ID : 0000-0002-4455-8001)

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Title: Inverse association between *Helicobacter pylori* infection and atopic, skin, and autoimmune diseases: A nationwide population-based study in South Korea

Short title: *Helicobacter pylori* and extra-intestinal disorders

Soo Ick Cho, MD, PhD^{1*}, Hanjae Lee, MD^{1*}, Min-Suk Yang, MD, PhD², Soo-Jeong Cho, MD, PhD³, Dong Hun Lee, MD, PhD¹

¹Department of Dermatology, Seoul National University College of Medicine, Seoul, South Korea

²Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea

³Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

*These authors contributed equally to this manuscript.

Corresponding author:

Dong Hun Lee, MD, PhD,

Department of Dermatology, Seoul National University Hospital,

101 Daehak-ro, Jongro-gu, Seoul, Korea

Tel: +82-2-2072-4916

Fax: +82-2-742-7344

E-mail: ivymed27@snu.ac.kr

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To the Editor:

Helicobacter pylori is a highly prevalent gastric bacterium associated with disorders such as gastric ulcer and gastric cancer.¹ However, its role in extra-gastric disorders remains unclear. This study aimed to investigate the association between *H. pylori* and common atopic, skin, and autoimmune disorders.

A nationwide population-based cross-sectional study was performed using the Korean insurance claims database. We identified all patients who underwent any diagnostic test for *H. pylori* infection between January and December 2018 as the Korean insurance system has been covering *H. pylori*-induced gastritis since 2018. Subsequently, we used the prescription claims records to identify the patients who received either triple [proton-pump inhibitor (PPI), clarithromycin, and amoxicillin] or quadruple (PPI, bismuth, metronidazole, and tetracycline) therapy, which is exclusively prescribed to patients with *H. pylori* infection, as per the treatment guidelines in Korea.² Patients with existing claims records of either of the two pharmacological combinations until March 2019 were defined as *H. pylori*-positive, and patients who did not undergo treatment were defined as *H. pylori*-negative from amongst the patients who underwent diagnostic tests for *H. pylori* in 2018. The detailed study methodology, and inclusion and exclusion criteria are described in the online supplementary methods and Tables S1-S3. A total of 128,599 patients were identified as *H. pylori*-positive from amongst 395,492 eligible patients, and the remaining patients (n = 266,893) were categorized into the *H. pylori*-negative group (Table 1 and Figure S1). The odds ratios of atopic (allergic rhinitis, asthma, and atopic dermatitis), skin (alopecia areata, contact dermatitis, psoriasis, rosacea, seborrheic dermatitis, urticaria, and vitiligo), and autoimmune diseases (ankylosing spondylitis, Behcet's disease, Crohn's disease, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, type 1 diabetes, and ulcerative colitis) were calculated.

Atopic disorders were confirmed to have a significant inverse association with *H. pylori* infection. Moreover, contact dermatitis, rosacea, seborrheic dermatitis, urticaria, and vitiligo exhibited a significant inverse association with *H. pylori* infection (Table 2). The ten autoimmune disorders, except Graves' disease, showed a significant inverse association with *H. pylori* infection (Table 2). A subgroup analysis of the target diseases was also conducted based on the sex and age groups, adjusted for different sets of confounders, and the overall trend remained the same (Table S4).

Our large-scale population-based study confirmed the inverse association between atopic disorders and *H. pylori* infection, which was consistent with previous studies' results.³ Also, an overall inverse association was established between *H. pylori* infection and common skin and autoimmune diseases. In previous studies, the inverse relationship between *H. pylori* and atopic disorders was mainly attributed to the hygiene hypothesis; *H. pylori* could induce sufficient immune tolerance, lowering the prevalence of atopic and autoimmune diseases.⁴ The potential molecular mechanism underlying the *H. pylori*-induced hygiene effect was also demonstrated in a recent study, wherein *H. pylori* exposure caused a greater regulatory T cell response mediated by dendritic cells.⁵

Among the seven skin disorders, urticaria, rosacea, seborrheic dermatitis, contact dermatitis, and vitiligo had a significant inverse association with *H. pylori*. *H. pylori* eradication has been supported by several dermatological studies, especially those focusing on chronic urticaria and rosacea.⁶ However, the inverse association between *H. pylori* and both urticaria and rosacea in our study suggest that *H. pylori* infection is an unlikely etiology of these skin disorders.

Except for Graves' disease, all autoimmune disorders had a significant inverse association with *H. pylori* infection. The hygiene hypothesis has been mainly applied to T helper type 2 cell-mediated allergic disorders. However, the interleukin-10 dependent counter-regulatory effect induced by chronic microbial infection also reportedly inhibits T helper type 2 cell-mediated autoimmune diseases.⁷ This broader counter-regulatory model may explain the overall lower prevalence of autoimmune diseases in *H. pylori*-positive patients. However, the exact molecular mechanism underlying the effect of *H. pylori* infection on immune regulatory disorders remains unknown. It is unclear whether patients predisposed to the target diseases are less likely to be infected by *H. pylori* or vice versa. The upregulation of the overall immune response in patients with an autoimmune diathesis might lead to lower survival of the *H. pylori* bacteria.

Our study has several limitations. First, the diagnostic code of *H. pylori* alone was not sufficient to identify the study group, a problem that was also encountered by a previous *H. pylori* study conducted in another country.⁸ However, as the treatment of *H. pylori* infection requires specific combinations of exclusively prescribed drugs, we believe that the study population identified on the basis of prescription claims is highly reliable. Additionally, only patients who were diagnosed with peptic ulcer, an absolute indication for *H. pylori* treatment in South Korea, were included in the

study, and the validity of the study design was re-confirmed with our institutional data. Second, the confounding factors used for the adjustments were limited due to the claims-based study design; information on potential confounding factors such as family history, tobacco use, and alcohol consumption, as well as other genetic or environmental factors, is not stored in the Korean claims database. Third, the use of medication, especially steroids, or stress itself may cause more gastric symptoms in patients with allergic and/or autoimmune diseases, which might lead to selection bias with our study design. Finally, it should be noted that our cross-sectional study confirmed the inverse association but not causal relationship between *H. pylori* infection and the target diseases.

Despite some limitations, our study offers the first large-scale epidemiological investigation of *H. pylori* infection and its overall inverse association with common atopic, skin, and autoimmune disorders. Future studies are warranted to confirm our findings.

References

1. Mbulaiteye SM, Hisada M, El-Omar EM. Helicobacter Pylori associated global gastric cancer burden. *Front Biosci (Landmark Ed)*. 2009;14:1490-1504.
2. Kim SG, Jung HK, Lee HL, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. *J Gastroenterol Hepatol*. 2014;29(7):1371-1386.
3. Amberbir A, Medhin G, Abegaz WE, et al. Exposure to Helicobacter pylori infection in early childhood and the risk of allergic disease and atopic sensitization: a longitudinal birth cohort study. *Clin Exp Allergy*. 2014;44(4):563-571.
4. Cremonini F, Gasbarrini A. Atopy, Helicobacter pylori and the hygiene hypothesis. *Eur J Gastroenterol Hepatol*. 2003;15(6):635-636.
5. Oertli M, Sundquist M, Hitzler I, et al. DC-derived IL-18 drives Treg differentiation, murine Helicobacter pylori-specific immune tolerance, and asthma protection. *J Clin Invest*. 2012;122(3):1082-1096.
6. Kutlubay Z, Zara T, Engin B, et al. Helicobacter pylori infection and skin disorders. *Hong Kong Med J*. 2014;20(4):317-324.
7. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol*. 2001;1(1):69-75.
8. Egeberg A, Weinstock LB, Thyssen EP, Gislason GH, Thyssen JP. Rosacea and gastrointestinal disorders: a population-based cohort study. *Br J Dermatol*. 2017;176(1):100-106.

Tables

Table 1. General characteristics of the study population

	Helicobacter pylori-positive group (n = 128,599)	Helicobacter pylori-negative group (n = 266,893)	p-value
Sex			
Male	74,178 (57.7%)	142,789 (53.5%)	<0.001
Female	54,421 (42.3%)	124,104 (46.5%)	
Age (years)			
20-29	3,552 (2.8%)	12,701 (4.8%)	<0.001
30-39	11,296 (8.8%)	24,378 (9.1%)	
40-49	35,950 (28.0%)	58,915 (22.1%)	
50-59	40,240 (31.3%)	73,531 (27.5%)	
60-69	27,461 (21.3%)	63,290 (23.7%)	
70-79	10,100 (7.8%)	34,078 (12.8%)	
Income			
First quartile (Lowest)	28,723 (22.3%)	59,939 (22.5%)	<0.001
Second quartile (Medium lowest)	26,857 (20.9%)	54,080 (20.3%)	
Third quartile (Medium highest)	34,554 (26.9%)	69,133 (25.9%)	
Fourth quartile (Highest)	38,465 (29.9%)	83,741 (31.4%)	

Table 2. Association between patients with *Helicobacter pylori* infection and allergic, skin, and autoimmune disorders compared to the *Helicobacter pylori*-negative patients

Disorders	<i>H. pylori</i> -positive (n=128,599)	<i>H. pylori</i> -negative (n=266,893)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio [†] (95% CI)	p-value
Allergic diseases						
Allergic rhinitis	39,480 (30.70%)	90,262 (33.82%)	0.867 (0.855-0.879)	<0.001	0.910 (0.897-0.924)	<0.001
Asthma	5,047 (3.92%)	13,333 (5.00%)	0.777 (0.752-0.803)	<0.001	0.859 (0.830-0.888)	<0.001
Atopic dermatitis	1,170 (0.91%)	3,110 (1.17 %)	0.779 (0.728-0.833)	<0.001	0.857 (0.800-0.917)	<0.001
Skin diseases						
Alopecia areata	759 (0.59%)	1,596 (0.60%)	0.987 (0.905-1.076)	0.766	0.933 (0.855-1.018)	0.119
Contact dermatitis	17,454 (13.57%)	41,816 (15.67%)	0.845 (0.829-0.862)	<0.001	0.907 (0.890-0.925)	<0.001
Psoriasis	666 (0.52%)	1,444 (0.54%)	0.957 (0.873-1.049)	0.349	0.971 (0.885-1.066)	0.534
Rosacea	135 (0.10%)	385 (0.14%)	0.728 (0.598-0.885)	0.002	0.756 (0.620-0.921)	0.006

Seborrheic dermatitis	2,783 (2.16%)	6,600 (2.47%)	0.872 (0.834-0.912)	<0.001	0.915 (0.874-0.957)	<0.001
Urticaria	6,548 (5.09%)	15,821 (5.93%)	0.851 (0.827-0.877)	<0.001	0.893 (0.867-0.920)	<0.001
Vitiligo	176 (0.14%)	468 (0.18%)	0.780 (0.656-0.928)	0.005	0.830 (0.697-0.989)	0.037
Autoimmune diseases						
Ankylosing spondylitis	151 (0.12%)	435 (0.16%)	0.720 (0.599-0.867)	0.001	0.707 (0.586-0.852)	<0.001
Behcet's disease	74 (0.06%)	225 (0.08%)	0.683 (0.525-0.888)	0.004	0.691 (0.530-0.901)	0.006
Crohn's disease	32 (0.02%)	197 (0.07%)	0.337 (0.232-0.490)	<0.001	0.356 (0.245-0.519)	<0.001
Graves' disease	386 (0.30%)	891 (0.33%)	0.899 (0.797-1.013)	0.080	0.910 (0.806-1.026)	0.124
Hashimoto's thyroiditis	394 (0.31%)	1,042 (0.39%)	0.784 (0.698-0.881)	<0.001	0.845 (0.752-0.951)	0.005
Rheumatoid arthritis	1,338 (1.04%)	3,893 (1.46%)	0.711 (0.667-0.756)	<0.001	0.783 (0.735-0.834)	<0.001

Sjogren's syndrome	71 (0.06%)	237 (0.09%)	0.622 (0.477-0.810)	<0.001	0.689 (0.528-0.900)	0.006
Systemic lupus erythematosus	47 (0.04%)	220 (0.08%)	0.443 (0.323-0.607)	<0.001	0.472 (0.344-0.648)	<0.001
Type 1 diabetes	373 (0.29%)	1,071 (0.40%)	0.722 (0.642-0.813)	<0.001	0.787 (0.699-0.887)	<0.001
Ulcerative colitis	98 (0.08%)	533 (0.20%)	0.381 (0.307-0.473)	<0.001	0.378 (0.304-0.469)	<0.001

†Adjusted for age, sex, income, and residence; the residential districts used in the adjustment process were divided into the capital and major provinces of South Korea.

CI, confidence interval

Supporting Information

Article type: Letter to the Editor

Title: Inverse association between *Helicobacter pylori* infection and atopic, skin, and autoimmune diseases: A nationwide population-based study in South Korea

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Soo Ick Cho, MD, PhD^{1*}, Hanjae Lee, MD^{1*}, Min-Suk Yang, MD, PhD², Soo-Jeong Cho, MD, PhD³, Dong Hun Lee, MD, PhD¹

¹Department of Dermatology, Seoul National University Hospital, Seoul, South Korea.

²Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea

³Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea.

*These authors contributed equally to this manuscript.

Supplementary method

Data sources

In South Korea, the National Health Insurance system covers around 97% of Korean residents, and the Medical Aid Program covers the rest of the population.¹ National Health Insurance Service (NHIS) that provides the claims data covered by both the insurance programs offers almost all medical claims records of the South Korean population since 2002. The dataset includes diagnosis codes (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes), prescriptions for drugs, claims for procedures, and general demographic information, such as sex, birth year, income, and place of residence.²

This study was approved by the Institutional Review Board of Seoul National University Hospital with a waiver for informed consent (IRB No. 2003-101-1109 and IRB No. 2011-050-1171). All claims data provided by the NHIS (No. NHIS-2020-2-109) were deidentified.

Identification of the study population

The NHIS database includes insurance claims for diagnostic tests but not the results of the tests. Also, the insurance coverage of the treatment of *H. pylori* infection in South Korea requires a diagnostic code of either peptic ulcer, MALT lymphoma, early gastric cancer, or idiopathic thrombocytopenic purpura, but not necessarily *H. pylori* infection itself. Therefore, to correctly identify the study population, we adopted multiple steps, incorporating prescription data for drugs, in addition to diagnosis codes and claims for diagnostic tests.

First, as the Korean insurance system covered *H. pylori*-induced gastritis since 2018, we identified all the patients who received any direct or indirect diagnostic test for *H. pylori* infection from January to December 2018. Then, we used the prescribed drug claims records to identify the patients who received either a triple (proton-pump inhibitor [PPI], clarithromycin, and amoxicillin) or quadruple (PPI, bismuth, metronidazole, and tetracycline) therapy, which is exclusively prescribed to patients with *H. pylori* infection, as per the guidelines for the treatment of *H. pylori* infection in Korea.³ Among patients who received a diagnostic test for *H. pylori* in 2018, those who had the claims record of either of the two combinations of drugs until March 2019 were defined as *H. pylori*-positive, and patients who did not receive the treatment were defined as *H. pylori*-negative. We hypothesized that the patients who were identified as positive for *H. pylori* would have received the treatment for *H. pylori*, while the patients who did not receive the treatment would be *H. pylori*-negative. To ensure that our hypothesis did not result in high false negativity and did not overestimate the *H. pylori*-negative control group, we included only the patients diagnosed with peptic ulcer in our study as it is an absolute indication for *H. pylori* treatment, which is covered by the Korean insurance. We also validated our inclusion criteria with the data from our own institution of consecutive patients from January to December 2018 and found a positive predictive value of 100% and a negative predictive value of 90.3% (Table S1). For the lists of diagnosis codes of the target disorders, diagnostic procedure codes, and prescribed drug codes that were used in the study, see Tables S2.

The patients were excluded based on the following criteria: (1) patients who died during the observation period, from January 2018 to March 2019; (2) patients with incomplete health insurance information; (3) patients who had a record of gastric cancer from January 2015 to March 2019; (4) patients with records of previous *H. pylori* eradication therapy from January 2015 to the date they received a diagnostic test for *H. pylori*; (5) patients aged < 19 years or > 80 years; and (6) patients who did not have the diagnostic code for peptic ulcer. While the overall positive rate of *H. pylori* was slightly lower as compared to that reported in the literature, we found a correlation in the *H. pylori*-positive rates based on residential districts in South Korea among this study and previous studies that reported seropositive rates of *H. pylori* in the South Korean population (Table S3).^{4,5}

Study outcome

We defined cases of allergic diseases (allergic rhinitis, asthma, atopic dermatitis), skin diseases (alopecia areata, contact dermatitis, psoriasis, rosacea, seborrheic dermatitis, urticaria, and vitiligo), and autoimmune diseases (ankylosing spondylitis, Behcet's disease, Crohn's disease, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, type 1 diabetes, and ulcerative colitis) based on relevant ICD-10 codes (Table S2).

A patient was regarded as having the target disease if there were three or more outpatient claims records with a relevant diagnosis code as the principal diagnosis, or more than one inpatient claims records with a relevant code as either the principal or secondary diagnosis, within 3 years before the date of the diagnostic test for *H. pylori* was undertaken.

Statistical analysis

Categorical variables were compared using Chi-squared test. Pearson correlation analysis was conducted to determine the correlation between two variables. Multivariable logistic regression with adjustment for confounders, including age, sex, income, and residence, was performed to explore the association between *H. pylori* infection and various disease outcomes. P-value of < 0.05 was considered statistically significant. All statistical tests were performed with SAS Enterprise 7.15 (SAS Institute; Cary, NC) or R statistical software version 3.63 (R Foundation for Statistical Computing, Vienna, Austria).

Table S1. Validation of the inclusion criteria based on Seoul National University Hospital retrospective data from 2018.

Study criteria	H. pylori-positive		H.pylori-negative	
Positive	True positive	10	False positive	0
Negative	False negative	3	True negative	28

Negative predictive value: 90.3%

Table S2. The lists of ICD-10 codes for the target diseases, diagnostic tests for *H. pylori*, and prescribed drugs for *H. pylori* eradication therapy

Disease	ICD-10 code
Allergic rhinitis	J30.x
Asthma	J45.x, J46.x
Atopic dermatitis	L20.x
Alopecia areata	L63.x
Contact dermatitis	L23.5
Psoriasis	L40.x
Rosacea	L71.x
Seborrheic dermatitis	L21.x
Urticaria ^a	L50.x
Vitiligo	L80.x
Ankylosing spondylitis	M45.0
Behcet's disease	L35.2
Crohn's disease	K50.x
Graves' disease	E05.0
Hashimoto's thyroiditis	E06.3
Rheumatoid arthritis	M05.x, M06.x
Sjogren's syndrome	L35.0
Systemic lupus erythematosus	L32.x
Type 1 diabetes	E10.x
Ulcerative colitis	K51.x
Gastric cancer	C16.x
Peptic ulcer	K25.x, K26.x, K27.x
Diagnostic test	Procedure code
CLO Test (Urease Test); endoscopic	B4151, D5892
<i>Helicobacter pylori</i> bacterial culture; endoscopic	B4152, D5893
Warthin-Starry Silver stain; endoscopic	B4153, D5891
<i>Helicobacter pylori</i> ELISA	B4155
Urea breath test	B4156, D5896
<i>Helicobacter pylori</i> stool antigen test	B4157, D5895, D5899
<i>Helicobacter pylori</i> antibody test	D5894, D5898
<i>Helicobacter pylori</i> clarithromycin resistance test	D5897
Drug	Prescription code
Pantoprazole	208801ATE, 208802ATE, 519201ATE, 519202ATE, 519203ATE, 656701ATE
Omeprazole	204401ACE, 204401ATE, 204402ATE, 204403ATE
Lansoprazole	181301ACE, 181301ATD, 181302ACE, 181302ATD, 181302ATE
Esomeprazole	367201ACH, 367201ATB, 367202ACH, 367202ATB, 498001ACH, 498002ACH, 509901ACH, 509902ACH
Rabeprazole	222201ATE, 222202ATE
Dexlansoprazole	621901ACR, 621902ACR
Amoxicillin	108101ACH, 108103ACH, 310500ATB, 310600ATB, 310700ATB, 380000ATB, 440100ATB, 462000ATB, 467200ATB, 467300ATB, 467400ATB, 467600ATB, 467300ASS, 467400ASS
Clarithromycin	134901ATB, 134904ATB, 134904ATR
Metronidazole	194101ATB
Bismuth	244802ATB, 271800ATB, 631800ATB, 457003ATB
Tetracycline	207403ACH, 236701ACH

^aBased on the ICD-10 codes, it is not possible to differentiate between acute and chronic urticaria. However, considering our inclusion criterion of the presence of three or more outpatient claims records with a relevant diagnostic code within three years, the enrolled patients are more likely to have chronic urticaria than acute urticaria.

Table S3. Correlation in the *H. pylori*-positive rates with previous studies based on residence^a

Residence	Helicobacter positive group (n = 128,599)	Helicobacter negative group (n = 266,893)	Positive rate	Reported positive rate in previous studies	
				Lee et al. ⁴	Lim et al. ⁵
Seoul	22,053 (17.1%)	49,660 (18.6%)	30.8%	47.4%	38.8%
Gyeonggi	36,704 (28.5%)	79,978 (30.0%)	31.5%	44.6%	40.6%

Gangwon-do	2,648 (2.1%)	6,272 (2.4%)	29.7%	49.1%	46.8%
Chungcheong	12,469 (9.7%)	23,993 (9.0%)	34.2%	59.2%	47.4%
Kyungsang	36,879 (28.7%)	75,839 (28.4%)	32.7%	55.1%	49.1%
Cholla	16,407 (12.8%)	28,233 (10.6%)	36.8%	59.5%	54.5%
Jeju	1,439 (1.1%)	2,918 (1.1%)	33.0%	54.4%	56.3%

Correlation between our study and study from Lee et al.; correlation (pearson): 0.836 (p = 0.019)

Correlation between our study and study from Lim et al.; correlation (pearson): 0.635 (p = 0.126)

Correlation between studies from Lee et al. and Lim et al.; correlation (pearson): 0.750 (p = 0.052)

^aThe residential data of each patient was provided by the NHIS database, and the residential districts used in the adjustment process were divided into Seoul (the capital of South Korea) and six major provinces ('doh' in Korean) of South Korea.

Figure S1. Flow diagram of the study population

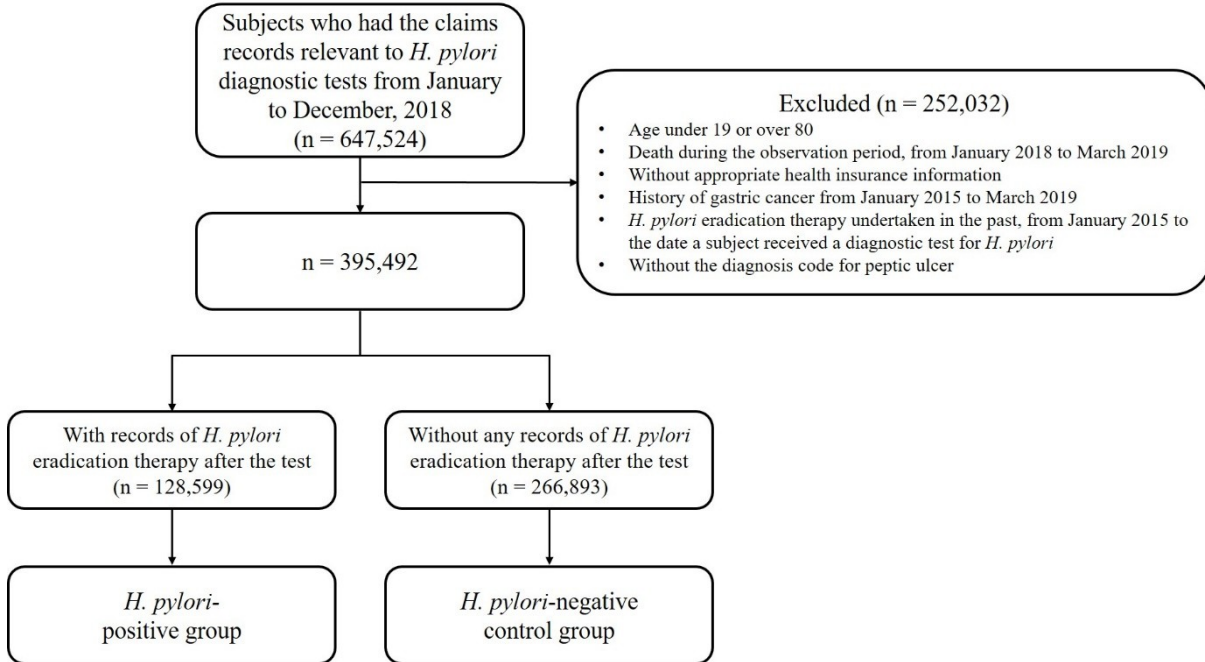


Table S4. Subgroup analysis of association between patients with *H. pylori* infection and allergic, skin, and autoimmune disorders compared to *H. pylori* negative patients.

Target diseases	Unadjusted odds ratio	Adjusted odds ratio 1 [†]	Adjusted odds ratio 2 [‡]
Allergic rhinitis	0.867 (0.855-0.879)***	0.911 (0.898-0.924)***	0.910 (0.897-0.924)***
M	0.856 (0.839-0.873)***	0.895 (0.877-0.913)***	0.895 (0.876-0.913)***
F	0.917 (0.898-0.936)***	0.928 (0.909-0.947)***	0.928 (0.908-0.947)***
Young	0.799 (0.767-0.831)***	0.837 (0.803-0.873)***	0.834 (0.800-0.870)***
Middle	0.907 (0.890-0.925)***	0.925 (0.907-0.944)***	0.926 (0.908-0.945)***
Old	0.896 (0.874-0.919)***	0.917 (0.894-0.940)***	0.915 (0.892-0.939)***
Asthma	0.777 (0.752-0.803)***	0.866 (0.837-0.895)***	0.859 (0.830-0.888)***
M	0.713 (0.678-0.750)***	0.815 (0.775-0.858)***	0.807 (0.766-0.849)***
F	0.863 (0.825-0.901)***	0.907 (0.868-0.949)***	0.901 (0.862-0.943)***
Young	0.847 (0.748-0.959)**	0.866 (0.764-0.982)*	0.856 (0.755-0.971)*
Middle	0.818 (0.777-0.862)***	0.844 (0.801-0.889)***	0.838 (0.795-0.883)***
Old	0.838 (0.800-0.878)***	0.884 (0.843-0.926)***	0.876 (0.836-0.918)***
Atopic dermatitis	0.779 (0.728-0.833)***	0.852 (0.796-0.912)***	0.857 (0.800-0.917)***
M	0.720 (0.655-0.792)***	0.801 (0.727-0.881)***	0.802 (0.729-0.883)***
F	0.858 (0.780-0.945)**	0.909 (0.825-1.001)	0.917 (0.832-1.010)
Young	0.610 (0.510-0.730)***	0.680 (0.567-0.815)***	0.693 (0.577-0.831)***
Middle	0.855 (0.773-0.945)**	0.869 (0.785-0.961)**	0.876 (0.791-0.969)*
Old	0.869 (0.781-0.967)*	0.908 (0.815-1.011)	0.905 (0.812-1.008)
Alopecia areata	0.987 (0.905-1.076)	0.928 (0.851-1.013)	0.933 (0.855-1.018)
M	0.968 (0.863-1.085)	0.898 (0.800-1.007)	0.899 (0.801-1.009)
F	1.008 (0.882-1.151)	0.972 (0.850-1.111)	0.981 (0.858-1.122)
Young	0.937 (0.762-1.152)	0.893 (0.725-1.100)	0.898 (0.728-1.107)
Middle	0.938 (0.842-1.045)	0.926 (0.831-1.032)	0.933 (0.837-1.040)
Old	1.011 (0.821-1.244)	0.974 (0.790-1.199)	0.967 (0.785-1.192)
Contact dermatitis	0.845 (0.829-0.862)***	0.910 (0.892-0.927)***	0.907 (0.890-0.925)***
M	0.815 (0.793-0.837)***	0.888 (0.864-0.913)***	0.885 (0.861-0.910)***
F	0.903 (0.879-0.927)***	0.930 (0.905-0.956)***	0.929 (0.904-0.954)***

Young	0.806 (0.758-0.857)***	0.878 (0.825-0.935)***	0.877 (0.824-0.934)***
Middle	0.891 (0.867-0.915)***	0.914 (0.889-0.939)***	0.913 (0.888-0.939)***
Old	0.882 (0.856-0.910)***	0.912 (0.884-0.940)***	0.907 (0.879-0.935)***
Psoriasis	0.957 (0.873-1.049)	0.970 (0.884-1.064)	0.971 (0.885-1.066)
M	0.909 (0.810-1.020)	0.949 (0.845-1.065)	0.949 (0.845-1.066)
F	1.007 (0.864-1.175)	1.009 (0.864-1.178)	1.011 (0.866-1.181)
Young	0.772 (0.566-1.055)	0.752 (0.549-1.029)	0.751 (0.548-1.029)
Middle	1.085 (0.956-1.232)	1.079 (0.950-1.225)	1.086 (0.956-1.233)
Old	0.891 (0.765-1.038)	0.890 (0.764-1.036)	0.885 (0.759-1.031)
Rosacea	0.728 (0.598-0.885)**	0.748 (0.614-0.911)**	0.756 (0.620-0.921)**
M	0.680 (0.497-0.931)*	0.707 (0.516-0.968)*	0.721 (0.526-0.988)*
F	0.795 (0.619-1.023)	0.776 (0.603-0.999)*	0.780 (0.605-1.005)
Young	0.407 (0.193-0.861)	0.456 (0.215-0.966)*	0.452 (0.213-0.960)*
Middle	0.864 (0.674-1.109)	0.897 (0.699-1.150)	0.905 (0.705-1.161)
Old	0.591 (0.407-0.858)**	0.592 (0.408-0.860)**	0.605 (0.416-0.879)**
Seborrheic dermatitis	0.872 (0.834-0.912)***	0.921 (0.881-0.964)***	0.915 (0.874-0.957)***
M	0.855 (0.809-0.903)***	0.939 (0.889-0.992)*	0.932 (0.882-0.985)*
F	0.857 (0.793-0.927)***	0.887 (0.820-0.960)**	0.881 (0.814-0.953)**
Young	0.832 (0.720-0.961)*	0.854 (0.739-0.988)*	0.838 (0.724-0.971)*
Middle	0.956 (0.895-1.021)	0.952 (0.891-1.017)	0.949 (0.888-1.014)
Old	0.883 (0.824-0.945)***	0.905 (0.844-0.970)**	0.896 (0.836-0.961)**
Urticaria	0.851 (0.827-0.877)***	0.902 (0.875-0.929)***	0.893 (0.867-0.920)***
M	0.856 (0.820-0.893)***	0.917 (0.878-0.957)***	0.906 (0.868-0.946)***
F	0.872 (0.837-0.909)***	0.888 (0.852-0.926)***	0.881 (0.845-0.918)***
Young	0.826 (0.751-0.909)***	0.877 (0.796-0.966)**	0.827 (0.790-0.961)**
Middle	0.870 (0.834-0.908)***	0.890 (0.853-0.929)***	0.883 (0.846-0.921)***
Old	0.898 (0.857-0.941)***	0.922 (0.880-0.967)***	0.911 (0.869-0.955)***
Vitiligo	0.780 (0.656-0.928)**	0.831 (0.698-0.989)*	0.830 (0.697-0.989)*
M	0.721 (0.551-0.943)*	0.771 (0.588-1.011)	0.778 (0.593-1.020)
F	0.860 (0.686-1.079)	0.878 (0.699-1.102)	0.871 (0.693-1.095)
Young	1.025 (0.572-1.834)	1.000 (0.556-1.798)	0.994 (0.551-1.791)
Middle	0.790 (0.611-1.021)	0.816 (0.631-1.055)	0.821 (0.635-1.062)
Old	0.803 (0.620-1.041)	0.818 (0.630-1.061)	0.812 (0.626-1.054)
Ankylosing spondylitis	0.720 (0.599-0.867)***	0.710 (0.590-0.856)***	0.707 (0.586-0.852)***
M	0.732 (0.589-0.909)**	0.737 (0.593-0.917)**	0.732 (0.588-0.910)**
F	0.628 (0.438-0.899)*	0.643 (0.448-0.923)*	0.644 (0.448-0.925)*
Young	0.900 (0.553-1.467)	0.800 (0.490-1.307)	0.817 (0.499-1.336)
Middle	0.623 (0.479-0.812)***	0.605 (0.465-0.788)***	0.602 (0.462-0.785)***
Old	0.848 (0.624-1.154)	0.859 (0.631-1.169)	0.845 (0.620-1.151)
Behcet's disease	0.683 (0.525-0.888)**	0.684 (0.525-0.890)**	0.691 (0.530-0.901)**
M	0.594 (0.379-0.930)*	0.591 (0.377-0.926)*	0.590 (0.376-0.927)*
F	0.776 (0.561-1.073)	0.742 (0.536-1.027)	0.755 (0.544-1.046)
Young	0.714 (0.288-1.768)	0.779 (0.312-1.945)	0.751 (0.298-1.888)
Middle	0.624 (0.446-0.875)**	0.651 (0.464-0.912)*	0.663 (0.473-0.930)*
Old	0.750 (0.467-1.206)	0.732 (0.455-1.178)	0.736 (0.457-1.186)
Crohn's disease	0.337 (0.232-0.490)***	0.351 (0.241-0.510)***	0.356 (0.245-0.519)***
M	0.304 (0.192-0.481)***	0.318 (0.201-0.505)***	0.325 (0.205-0.516)***
F	0.392 (0.207-0.743)**	0.432 (0.227-0.823)*	0.434 (0.228-0.828)*
Young	0.105 (0.039-0.285)***	0.104 (0.038-0.282)***	0.108 (0.040-0.295)***
Middle	0.508 (0.305-0.847)**	0.500 (0.300-0.835)**	0.502 (0.301-0.838)**
Old	0.630 (0.304-1.306)	0.638 (0.307-1.324)	0.631 (0.303-1.313)
Graves' disease	0.899 (0.797-1.013)	0.912 (0.809-1.029)	0.910 (0.806-1.026)
M	0.759 (0.619-0.931)**	0.754 (0.615-0.926)**	0.750 (0.611-0.921)**
F	1.040 (0.897-1.205)	1.014 (0.874-1.176)	1.013 (0.873-1.176)
Young	0.877 (0.609-1.264)	0.873 (0.604-1.260)	0.879 (0.607-1.272)
Middle	0.918 (0.783-1.075)	0.948 (0.809-1.111)	0.944 (0.805-1.106)
Old	0.866 (0.699-1.073)	0.863 (0.697-1.070)	0.862 (0.695-1.069)
Hashimoto's thyroiditis	0.784 (0.698-0.881)***	0.835 (0.743-0.938)**	0.845 (0.752-0.951)**
M	0.732 (0.546-0.981)*	0.780 (0.581-1.047)	0.806 (0.600-1.083)
F	0.860 (0.758-0.977)*	0.846 (0.745-0.961)*	0.853 (0.751-0.969)*
Young	0.957 (0.667-1.372)	1.081 (0.752-1.554)	1.104 (0.766-1.591)
Middle	0.723 (0.615-0.850)***	0.773 (0.658-0.909)**	0.778 (0.662-0.916)**
Old	0.862 (0.713-1.041)	0.870 (0.720-1.052)	0.887 (0.733-1.072)
Rheumatoid arthritis	0.711 (0.667-0.756)***	0.791 (0.743-0.842)***	0.783 (0.735-0.834)***
M	0.659 (0.586-0.741)***	0.755 (0.671-0.850)***	0.746 (0.663-0.840)***
F	0.780 (0.725-0.840)***	0.806 (0.748-0.868)***	0.799 (0.741-0.861)***
Young	0.651 (0.451-0.939)*	0.672 (0.464-0.972)*	0.661 (0.456-0.958)*

Middle	0.733 (0.666-0.807)***	0.777 (0.706-0.856)***	0.769 (0.698-0.847)***
Old	0.776 (0.713-0.845)***	0.809 (0.743-0.881)***	0.802 (0.736-0.874)***
Sjogren's syndrome	0.622 (0.477-0.810)***	0.684 (0.524-0.892)**	0.689 (0.528-0.900)**
M	0.770 (0.394-1.504)	0.916 (0.466-1.799)	0.926 (0.470-1.823)
F	0.650 (0.486-0.868)**	0.650 (0.486-0.870)**	0.656 (0.490-0.877)**
Young	2.081 (0.635-6.821)	2.024 (0.615-6.665)	2.167 (0.655-7.163)
Middle	0.596 (0.406-0.876)**	0.644 (0.439-0.946)*	0.658 (0.448-0.968)*
Old	0.623 (0.421-0.922)*	0.657 (0.443-0.973)*	0.651 (0.439-0.965)*
Systemic lupus erythematosus	0.443 (0.323-0.607)***	0.468 (0.341-0.641)***	0.472 (0.344-0.648)***
M	0.570 (0.259-1.255)	0.558 (0.252-1.233)	0.562 (0.254-1.246)
F	0.460 (0.326-0.650)***	0.453 (0.321-0.640)***	0.457 (0.323-0.646)***
Young	0.170 (0.053-0.548)**	0.203 (0.063-0.654)**	0.204 (0.063-0.661)**
Middle	0.386 (0.252-0.591)***	0.408 (0.267-0.625)***	0.412 (0.269-0.631)***
Old	0.791 (0.466-1.341)	0.803 (0.473-1.363)	0.809 (0.476-1.375)
Type 1 diabetes	0.722 (0.642-0.813)***	0.794 (0.705-0.894)***	0.787 (0.699-0.887)***
M	0.692 (0.595-0.804)***	0.764 (0.657-0.889)***	0.759 (0.652-0.883)***
F	0.754 (0.624-0.912)**	0.864 (0.698-1.024)	0.836 (0.690-1.013)
Young	1.036 (0.588-1.824)	1.037 (0.586-1.833)	0.993 (0.560-1.760)
Middle	0.740 (0.610-0.898)**	0.738 (0.608-0.895)**	0.734 (0.604-0.891)**
Old	0.790 (0.676-0.923)**	0.818 (0.700-0.956)*	0.811 (0.694-0.949)**
Ulcerative colitis	0.381 (0.307-0.473)***	0.380 (0.306-0.472)***	0.378 (0.304-0.469)***
M	0.392 (0.301-0.509)***	0.390 (0.299-0.507)***	0.387 (0.297-0.504)***
F	0.346 (0.237-0.505)***	0.363 (0.248-0.530)***	0.359 (0.246-0.526)***
Young	0.213 (0.112-0.406)***	0.209 (0.109-0.399)***	0.207 (0.108-0.396)***
Middle	0.411 (0.309-0.547)***	0.407 (0.305-0.541)***	0.407 (0.305-0.542)***
Old	0.454 (0.308-0.670)***	0.450 (0.305-0.663)***	0.439 (0.298-0.649)***

M, male; F, female; Young, 20-39 years old; Middle, 40-59 years old; Old, 60-79 years old

†adjusted for age and sex

‡adjusted for age, sex, income, and residence

p<0.001***, p<0.01**, p<0.05*

Supplementary reference

1. Cho S, Shin J-Y, Kim HJ, et al. Chasms in achievement of recommended diabetes care among geographic regions in Korea. J Korean Med Sci. 2019;34(31):e190.
2. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: Strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci. 2017;32(5):718-728.
3. Kim SG, Jung HK, Lee HL, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. J Gastroenterol Hepatol. 2014;29(7):1371-1386.
4. Lee JH, Choi KD, Jung H-Y, et al. Seroprevalence of Helicobacter pylori in Korea: A multicenter, nationwide study conducted in 2015 and 2016. Helicobacter. 2018;23:e12463-e12463.
5. Lim SH, Kim N, Kwon JW, et al. Trends in the seroprevalence of Helicobacter pylori infection and its putative eradication rate over 18 years in Korea: A cross-sectional nationwide multicenter study. Plos One. 2018;13:e0204762.