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Effects of Anti-*Helicobacter pylori* Therapy on Incidence of Autoimmune Diseases, Including Inflammatory Bowel Diseases

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Abstract

Background & Aims: *Helicobacter pylori* induces immune tolerance and is associated with a lower risk for immune-mediated disorders, such as autoimmune and inflammatory bowel diseases (IBD). We aimed to determine the effects of treatment for *H pylori* infection on the incidence of autoimmune disease and IBD.

Methods: We collected data from the National Health Insurance Research Database in Taiwan on patients younger than 18 years old without a prior diagnosis of autoimmune disease or IBD. Patients with peptic ulcer disease (PUD) with treatment of *H pylori* infection (PUD+HPRx), PUD without *H pylori* treatment (PUD–HPRx), a urinary tract infection (UTI) treated with cephalosporin, or without PUD (controls) were matched for age, sex, insurance, and Charlson's comorbidity index score.

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AUTHOR CONTRIBUTIONS:

K.D.L. and G.F.C. performed most of the data collection and analyses with assistance from M.E., S.B., H.G., and S.Y.O. J.Y.K. and D.C.W. jointly designed, interpreted, and analyzed all of the data from the experiments, and contributed to the writing of the manuscript. A.K.W. provided critical comments to data interpretation and analyses.

DISCLOSURES:

The authors have no conflict of interest to disclose.

Results: Of the 1 million patients we collected data from in 2005, we included 79,181 patients in the study. We compared the effects of treatment for *H pylori* infection on the risk of autoimmunity or IBD and found that PUD+HPRx has the highest adjusted hazard risk (aHR) for autoimmunity or IBD (aHR, 2.36), compared to PUD–HPRx (aHR, 1.91) or UTI (aHRs, 1.71) (P<.001). The increased risk of autoimmune disease was not completely accounted for by antibiotic therapy alone, because PUD+HPRx had a higher aHR than UTI (P<.001). A small but significant increase in mortality was observed in the PUD+HPRx cohort (aHR, 1.11; P=.001).

Conclusion: In an analysis of data from the National Health Insurance Research Database in Taiwan, we found that treatment for *H pylori* infection is associated with a significant increase in the risk for autoimmune disease, including IBD.

Keywords

eradication; autoimmunity; immune response; bacteria

INTRODUCTION

Nearly half of the world's population is colonized by *Helicobacter pylori*. Approximately 10–15% of the infected individuals will go on to develop gastroduodenal ulcers, and <3% will develop gastric cancer[1]. Universal vaccination has been proposed[2], and yet the negative impact of eradicating *H pylori* in the 85–90% of otherwise asymptomatic individuals has not been evaluated. Its existence in the stomach of Otzi the Iceman's 5000-year-old mummified remains indicates their coexistence since the beginning of human civilization[3]. This has led to the emerging idea of a Human-*H pylori* symbiosis. There is growing evidence that *H pylori* is a protective factor against chronic immune-mediated disorders such as asthma[4–6], rheumatoid arthritis[7], and inflammatory bowel disease (IBD)[8–11]. There is little epidemiological evidence, however, to suggest that treatment of *H pylori* is associated with increased incidence of immune-mediated disorders such as autoimmune diseases (AD) and IBD.

It has been hypothesized that this protection includes the induction of intestinal IL-10 and IL-18-mediated regulatory T cell (Treg) responses [12, 13]. The ability of *H pylori* to persist in humans has been attributed to several bacterial factors that dampen host immune responses. These include VacA, CagA, *H pylori* LPS, and other unidentified secreted factors[14–16]. Rad et al. recently demonstrated that *H pylori*-infected individuals expressed higher levels of Foxp3, a regular T cell marker, and that the depletion of Tregs resulted in a higher degree of gastric inflammation and reduced bacterial colonization[17]. In fact, it has previously been shown that peripheral memory T cells are less proliferative in *H pylori*-infected individuals compared to uninfected controls[18]. In that same study, it was found that the inhibitory effect was due to the presence of suppressive T cells in infected individuals. This raises the possibility of circulating regulatory T cells in *H pylori*-infected host which may play a protective role against AD and IBD.

Several regions around the world are reporting a rising incidence of immune-mediated and allergic diseases[19]. Coincidentally, this occurs during the period of post-*H pylori* discovery and there is growing concern that increased testing and treatment of *H pylori* may have

contributed to these rising incidences. While a number of host factors have been implicated including obesity, westernization of diet, changes in the hygiene and gut microbiota[20], it is important to better understand the relationship between *H pylori* treatment and the risk of developing immune-mediated disorders in order to better inform health care providers, authors of practice guidelines, and global health policymakers on the potential negative impact of global *H pylori* eradication.

One of the challenges of conducting a study looking at the impact of *H pylori* treatment on the risks of developing AD and IBD is the relatively low prevalence of AD in regions with high rates of *H pylori* infection and the requirement of a large sample size to draw meaningful conclusions. In this study, we utilized the National Health Insurance Research (NHIR) Database of Taiwan, where the prevalence of *H pylori* approaches 80% [21], in order to determine the impact of *H pylori* therapy on the risk of developing AD and IBD.

MATERIALS AND METHODS

Database

This retrospective cohort study was performed using the NHIR database which was established in 1996 by the Bureau of National Health Insurance of the Department of Health and covered 99% of the 23 million residents of Taiwan and is contracted with 97% of Taiwanese hospitals and clinics. The NHIR database includes data for inpatient and ambulatory expenditures as well as orders and prescriptions dispensed at contracted pharmacies. A longitudinal database was created using a random sample of 1 million subjects in the NHIR year 2005 database and the reimbursement data from January 1, 2000 to December 31, 2010 of the eligible study subjects were included for analysis. The rationale for creating this longitudinal database is to allow a 5-year window in both directions to analyze the long-term impact of *H pylori* therapy on AD including IBD.

Study design

We first selected study subjects >18 years of age with or without peptic ulcer disease (PUD) identified by the International Classification of Disease (ICD)-9 codes: 531 (gastric ulcer), 532 (duodenal ulcer), and 533 (nonspecific peptic ulcer). The algorithm to identify cases from ICD-9 codes was largely similar to that used by Bernstein et al. [22] and Kappelman et al. [23]; subjects with three or more outpatient ICD-9 codes were included for further analysis. Four cohorts were created: 1) subjects without PUD (Non-PUD), 2) subjects without PUD but were treated with first-generation cephalosporin antibiotics for urinary tract infection (UTI), 3) subjects with PUD without anti-*H pylori* treatment (PUD-HPRx), and 4) PUD subjects with *H pylori* treatment (PUD+HPRx). Subjects were considered to have received *H pylori* treatment if they were given a course of either triple or quadruple therapy for more than 7 days. *H pylori* testing results for diagnosis or treatment eradication are not available in the NHRI database. Subjects in the PUD-HPRx, UTI, or Non-PUD groups were matched to PUD+HPRx using propensity methods by age, gender, insurance range, and Charlson's comorbidity index score (CCIS). Subjects selected in one group will be excluded from the database and will not be selected in the other groups. There were apparent differences

between the cohorts on age, insurance range, and Charlson's comorbidity index scores after matching largely due to fewer subjects in the UTI group.

Study sample

These autoimmune diseases (AD) were defined by diagnosis of ICD-9 code of Lupus Erythematosus (ICD-9: 710.0), Systemic Sclerosis (ICD-9:710.1), Rheumatoid Arthritis (ICD-9: 714.30 – 714.33), Polymyositis (ICD-9:710.4), Dermatomyositis (ICD-9:710.3), Vasculitis (ICD-9: 446.0, 446.2, 446.4, 446.5, 443.1, 446.7, 446.1), Pemphigus (ICD-9: 694.4), Sicca Syndrome (ICD9: 710.2), Crohn's Disease (ICD-9: 555.x), and Chronic Ulcerative Colitis (ICD-9: 556.x). A diagnosis of UTI is identified by ICD-9 codes of 590.10–590.11, 590.80, 590.81, 590.9, 590.3, 590.00, 590.01, 590.2, 595.0–595.9, and 599.0. Only ambulatory patients who received cephalosporin were included in the UTI cohort. It is worth noting that AD including IBD are considered "Catastrophic Illnesses" which required additional review by NHRI clinical staff and approval was based on clinical data including clinical labs, radiological reports, and medication history. The person-years of follow-up were estimated from the index date plus 2-year lag time to the date of diagnosis of AD including IBD. We excluded 41,457 subjects with AD diagnosis within 2 years of receiving *H pylori* therapy (index date) to allow a 2-year lag time (e.g., patients treated with *H pylori* therapy after 2008 were excluded from the analysis). We also excluded the initial 2 years of follow-up from Non-PUD controls to avoid survival time bias. The index date is defined as the date when PUD or UTI was diagnosed and 2002 for controls. Subjects with incomplete demographical data (e.g., loss to follow-up, or withdrawal from the insurance system) (n=17,064) were also excluded from the study (Figure 1). The follow-up period begins after *H pylori* therapy (index date) plus 2-year lag time and ends on December 31, 2010. There are small differences in follow-up time between the groups with the shortest follow-up time in the PUD+HPRx group consistent with a higher rate of AD and IBD in that group.

Statistical Analysis

We analyzed the distribution of risk factors for the four study cohorts (PUD+HPRx, PUD-HPRx, UTI, and Non-PUD) by ANOVA test, chi-squared test or Fisher's exact test. Cox proportional hazards regression analyses were performed to determine the crude and adjusted hazard risk (aHR) after adjustment for age, gender, comorbidities, CCIS score, and NSAIDs or antiplatelet agent (Table 2, *Model i*). A competing risk model was also performed to determine the risk of AD incidence (Table 2, *Model ii*) and mortality (Table 3). Kaplan–Meier curves estimated the probability of AD onset or mortality and the log-rank test analyzed the differences between groups. Statistical analyses were performed using SAS 9.3 software (SAS Institute, Inc., Cary, NC). Statistical significance was set at $p< 0.05$.

RESULTS

Higher cumulative hazard risk of AD and IBD in PUD+HPRx individuals compared to PUD-HPRx, UTI, or Non-PUD subjects.

To gain further insight into the risk of developing AD including IBD by treating *H pylori,* we compared the new incidence of AD and IBD patients with PUD diagnosed by EGD who

received *H pylori* therapy (PUD+HPRx) or never received *H pylori* therapy (PUD-HPRx) with patients without PUD (Non-PUD) or UTI treated with cephalosporin (adjusted for age, gender, insurance, CCIS, and medication) (Figure 1). The patient characteristics are shown in Table 1. The average age was 49.45±16.6 with 51.6% male in Non-PUD controls, 46.52±16.9 with 51.0% male in UTI group, 49.49±16.7 with 51.7% male in PUD-HPRx group, and 49.54±16.6 with 51.7% male in PUD+HPRx group.

Next, after multiple regression adjusted for age, gender, comorbidities, CCIS score, and medications, we found that the risk of AD including IBD was significantly higher for patients who received *H pylori* eradication therapy compared to those who did not receive the therapy ($p<0.001$, Figures 2a and 2b). Specifically, patients who received eradication therapy had higher risk of developing Lupus Erythematosus (aHR=4.41, 95% CI [2.12, 9.14], $p<0.001$), Rheumatoid Arthritis (aHR=2.44, 95% CI [2.01, 2.95], $p<0.001$), Vasculitis (aHR=3.10, 95% CI [1.32, 7.27], p=0.009), Sicca Syndrome (aHR= 3.15, 95% CI [2.57, 3.87], $p<0.001$), and IBD (aHR=2.15, 95% CI [1.88, 2.46], $p<0.001$) (Table 2, *Model i*). The incidence rates of AD and IBD were also significantly higher in PUD+HPRx cohort compared to PUD-HPRx, UTI, or Non=PUD control cohort (AD=11.299 vs. 9.902, 7.453, or 4.638 per 1,000 person-years; IBD=5.235 vs 3.662, 2.900, or 2.371 per 1,000 person-years, respectively, $p<0.05$). We also performed additional analyses using the competing risk model to adjust for competing risk of death (Table 2, *Model ii*). Similar results were observed compared to the Cox proportional hazards regression analysis (Table 2, *Model i*) in that PUD+HPRx cohorts had a higher aHR compared to Non-PUD controls (AD=1.34, 95% CI [1.27, 1.42]; IBD=1.13, 95% CI [1.06, 1.21], $p<0.001$). We did find that the UTI group had a lower aHR compared to Non-PUD controls using the competing risk model (UTI=0.87, 95% CI [0.80, 0.94], p=0.001) indicating antibiotic treatment might be associated with a lower risk of IBD.

Lower cumulative survival rate in PUD+HPRx individuals compared to PUD-HPRx, UTI, and Non-PUD control subjects.

During the follow-up period, we estimated the survival rate of PUD+HPRx cohort compared to PUD-HPRx, UTI, Non-PUD control groups. We performed multiple regression to adjust for age, gender, insurance range, comorbidities, CCIS score, and medications and competing risk analysis to adjust for competing risk of death. We observed a small but significantly lower survival rate in patients who have ever received *H pylori* therapy (aHR= 1.11, 95% CI [1.04, 1.18], p=0.001) compared to the other three cohorts (Figure 3, Table 3).

DISCUSSION

We found that PUD patients receiving *H pylori* treatment have a significant increase in the risk of developing AD and IBD compared to those never received *H pylori* treatment. The effect of antibiotic therapy on the risk of AD and IBD was assessed by adding a UTI cohort for comparison and the results showed that risk remained the highest in PUD+HPRx which supports the hypothesis that *H pylori* eradication may increase the risk of AD including IBD. There is also an increased risk of AD seen with UTI treatment using just one category of medication suggesting there may be an antibiotic effect which is consistent with published

literature[24]. However, using the competing risk model to adjust for competing risk of death, we found that UTI treatment with antibiotics was associated with a lower risk of IBD when compared to Non-PUD control group, an observation that was consistent with an observation made by Ng SC et al. in Asia-Pacific CD cohorts[25]. There is a small increase in mortality of those individuals that received *H pylori* treatment but the reason is unknown as the database does not include the cause of death. A similar finding of increased mortality with *H pylori* therapy was reported by Ma JL et al. studying a large cohort of individuals treated with anti-*H pylori* therapy in China[26]. Our data support the current practice of checking *H pylori* only in symptomatic patients as *H pylori* treatment is associated with an increased risk of AD including IBD particular in *H pylori* endemic regions.

The World Health Organization classifies *H pylori* as a type I carcinogen based on prior studies showing that infected individuals are at increased risk of developing gastric cancer[27, 28], however, the exact *H pylori* carcinogenic mechanisms remain unclear. Given that the majority of infected individuals will not develop *H pylori*-associated complications[1] and the emerging evidence that *H pylori* infection may provide protection against chronic immune-mediated disorders, physicians are caught in a conundrum how to manage asymptomatic patients that were incidentally found to have *H pylori* infection. Further research is needed to propel us toward precision medicine to better identify and treat only patients with high-risk profiles for *H pylori*-associated complications.

Recent epidemiological data have all shown an exponentially rising incidence of IBD in Asia Pacific regions[29]. Our study revealed a small but significant increase in patients who have received *H pylori* therapy suggesting that other factors may have a greater impact on the increasing incidence of IBD in these regions. Ng SC *et al.* have recently shown several risk factors associated with IBD in Asia[25]. These include breastfeeding for less than 12 months, Westernized diet, no childhood pets, and living in urbanized cities. Another possible explanation is that the host immunomodulatory effect of *H pylori* infection occurs early in life and eradication of *H pylori* in adults only has a modest impact on their risk of immune-mediated disorders. Arnold IC *et al.* demonstrated in a mouse model of allergic airway disease that *H pylori*'s protection against the development of the disease was most robust in mice infected neonatally and was abrogated by antibiotic eradication of *H pylori*[30]. Thus, the exponentially rising incidence of IBD in Asia may be a result of increasing *H pylori* eradication in the prior generation.

An obvious strength of this study is the large sample size that made testing our main hypothesis feasible. However, several limitations must be noted. First, there are general limitations of claims based data, such as data entry errors and underreporting of diagnoses. Second, since the database lacks *H pylori* testing results, the following assumptions were made: 1) most patients diagnosed with PUD in Taiwan would be tested for *H pylori*, and no treatment assumed no *H pylori* infection; and 2) since the prevalence of *H pylori* infection in those over 30 years of age is 54.7% in Taiwan[31], most of the patients without PUD are assumed to be *H pylori*-infected but not treated. Third, although we matched the study cohorts by age, gender, comorbidities, CCIS score, and medications, a generally acceptable method, it is not possible to fully account and correct for other potential confounders (e.g., smoking status, or diet) thus preventing causal inference from the observed associations.

Fourth, there were apparent differences between the cohorts on age, insurance range, and Charlson's comorbidity index scores after matching largely due to the subsequent inclusion of the UTI group which has a fewer number of cases. This is a potential confounding factor when interpreting the results comparing the risk of AD and IBD in the UTI group. Lastly, it is possible that our controls may have been treated before 2000 but this is unlikely to explain the significant increase in the risk of AD and IBD in the PUD+HPRx group. Further research using a large database with confirmed *H pylori* eradication is needed to verify our findings.

In the era of precision medicine, there is a need for further research to understand how to differentiate beneficial *H pylori* strains versus pathogenic strains and define the critical host factors which provide the "second hit" necessary for the development of gastroduodenal ulcers and malignancies. Meanwhile, the current recommendation of testing and treating only symptomatic patients or patients with a strong family history of gastric cancer[32] and not asymptomatic individuals should still be followed as treatment may increase the risk of AD and IBD. Our finding also demonstrates the importance of our resident gut microbes in modulating one's susceptibility to systemic immune-mediated disorders and the judicious use of antibiotics should continue to be emphasized in medical training to potentially limit the rapid rise of AD and IBD incidence.

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ABBREVIATIONS:

aHR	Adjusted hazard risk
AD	Autoimmune disease
CCIS	Charlson's comorbidity index score
IBD	Inflammatory bowel disease
ICD	International Classification of Disease
NHIR	National Health Insurance Research
NSAIDs	Nonsteroidal anti-inflammatory agents
PUD	Patients with peptic ulcer disease
PUD+HPRx	Patients with peptic ulcer disease and *H pylori* treatment
PUD-HPRx	Patients with peptic ulcer disease and without *H pylori* treatment
UTI	Patients with urinary tract infection and with antibiotic treatment
Treg	Regulatory T cell

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What You Need to Know

Background:

We aimed to determine the effects of treatment for *H pylori* infection on the incidence of autoimmune diseases and inflammatory bowel diseases.

Findings:

We collected data from the National Health Insurance Research Database in Taiwan and found that peptic ulcer disease with treatment of *H pylori* infection had the highest adjusted hazard risk for autoimmune and inflammatory bowel diseases (almost a 2.4-fold increase in risk), compared to peptic ulcer disease without treatment of *H pylori* infection or urinary tract infections treated with cephalosporin.

Implications for patient care:

Treatment for *H pylori* infection is associated with a significant increase in the risk for autoimmune and inflammatory bowels diseases.

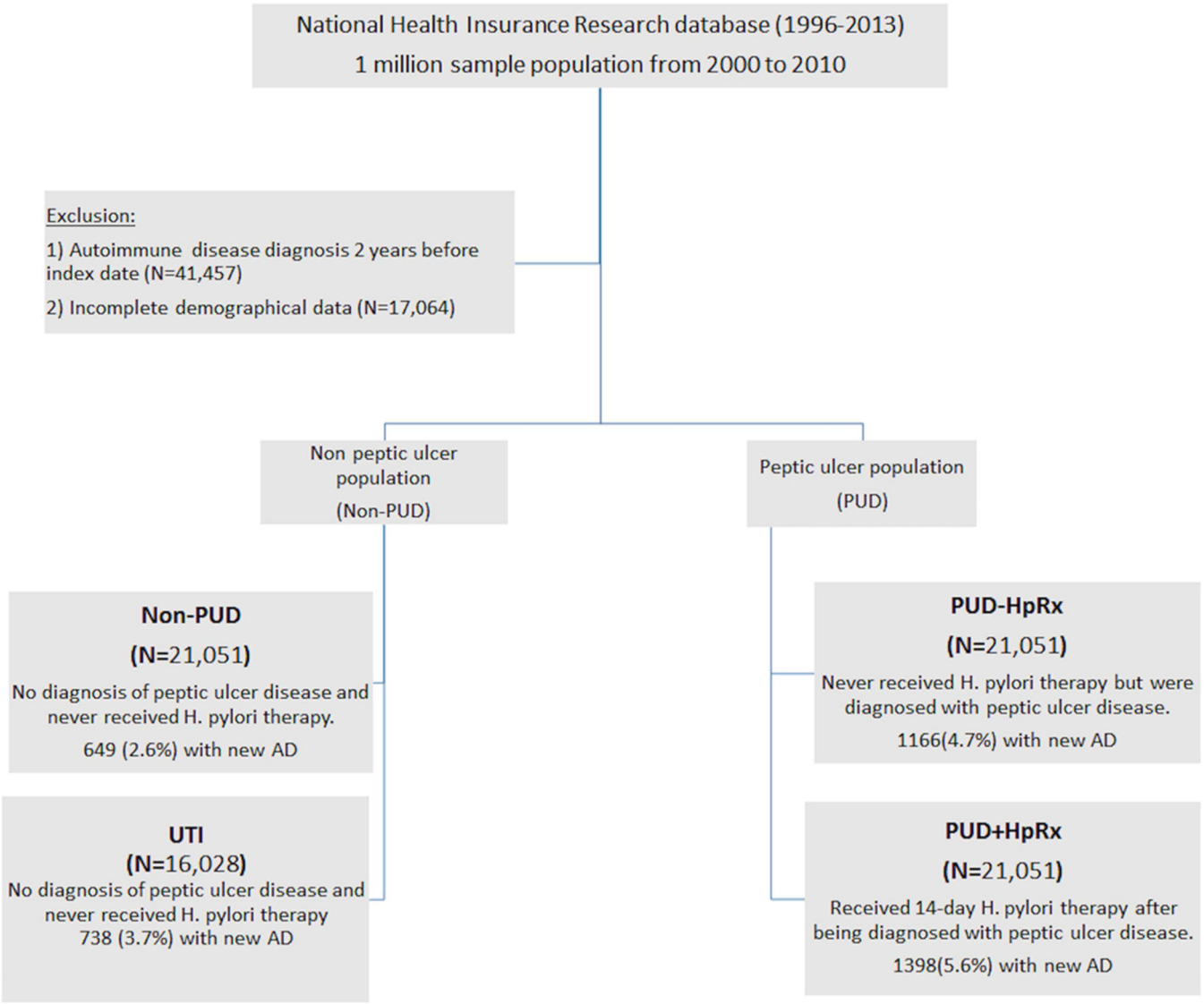

Figure 1.
Study design flow chart.

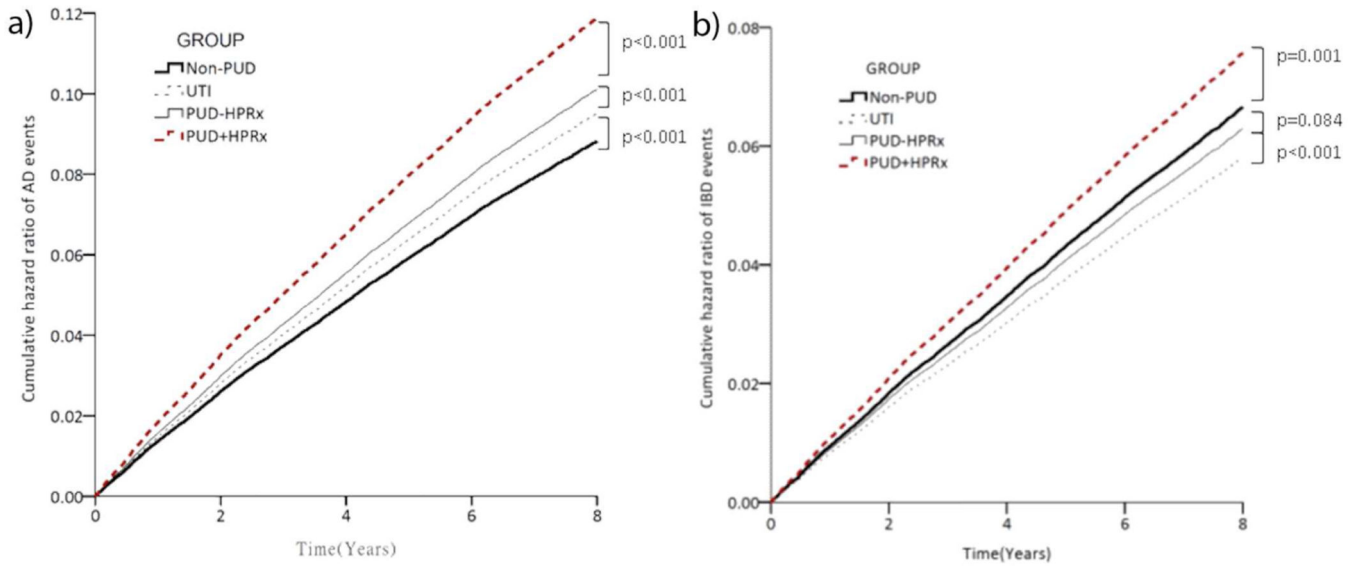

Figure 2. Higher adjusted hazard risk of AD and IBD in PUD+HPRx individuals compared to PUD-HPRx, UTI, or Non-PUD control subjects.

Kaplan–Meier curves estimated the probability of new-onset AD (**a**) and IBD (**b**) events, and the log-rank test was used for statistical analysis. A competing risk model was used to adjust for competing risk of death.

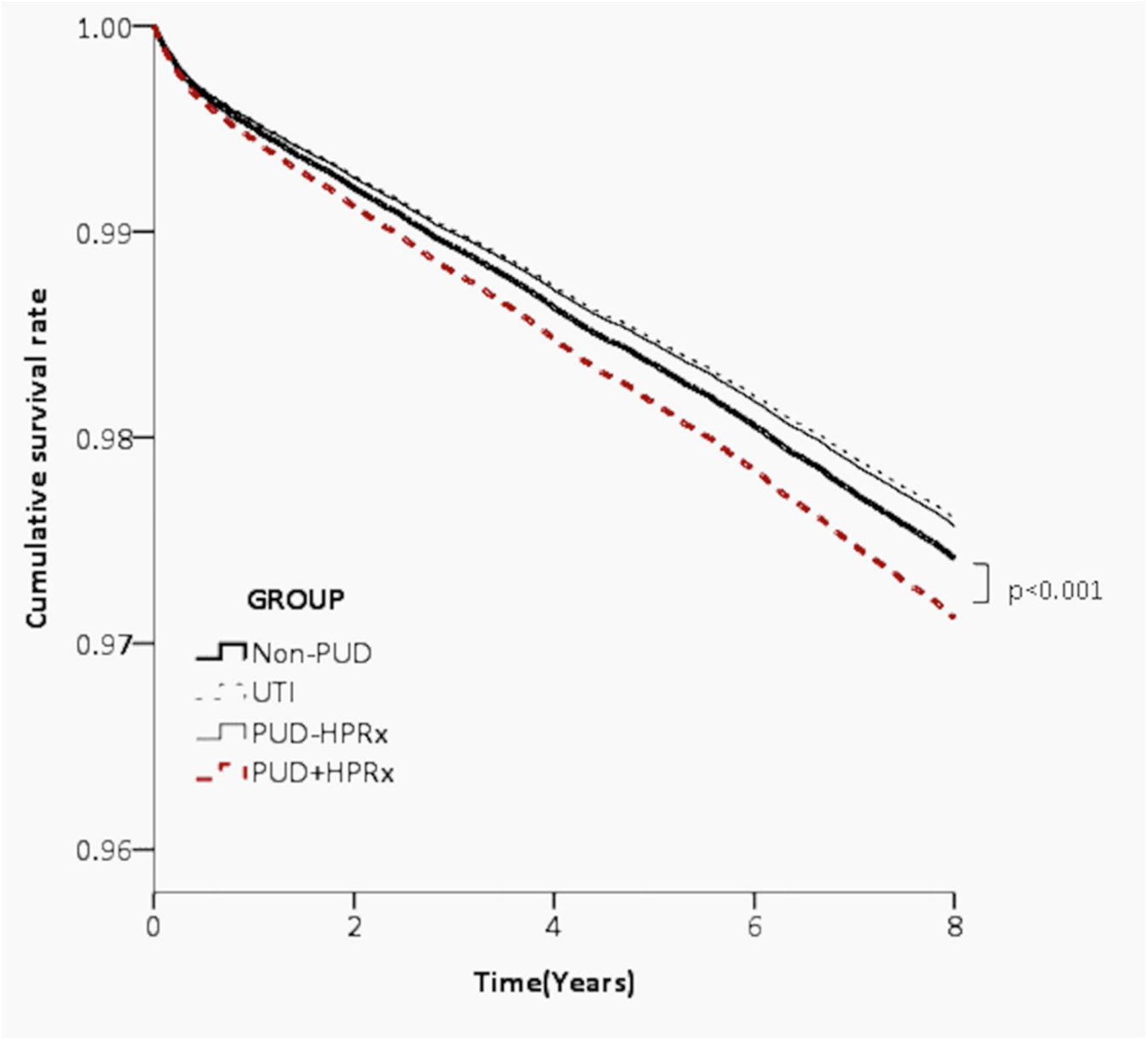

Figure 3. Lower cumulative survival rate in *PUD+HPRx individuals compared to PUD-HPRx, UTI, or Non-PUD control subjects*.

Kaplan–Meier curves estimated the probability of survival rate, and the log-rank test was used for statistical analysis. A competing risk model was used to adjust for competing risk of death.

Table 1.

Demographic prevalence of Non-PUD, UTI, and PUD population (N=79,181).

	Non-PUD population				PUD population				
	* Non-PUD cohort (n=21,051)		UTI cohort (n=16,028)		** PUD-HPRx cohort (n=21,051)		*** PUD+HPRx cohort (n=21,051)		p value
Age									
<40	6727	(32.0)	6356	(39.7)	6723	(31.9)	6723	(31.9)	<0.001
40–59	8476	(40.3)	6137	(38.3)	8361	(39.7)	8361	(39.7)	
≧60	5848	(27.8)	3535	(22.1)	5967	(28.3)	5967	(28.3)	
Mean±SD	49.45	(16.6)	46.52	(16.9)	49.49	(16.7)	49.54	(16.6)	<0.001
Gender									
Female	10189	(48.4)	7846	(49.0)	10170	(48.3)	10170	(48.3)	0.582
Male	10862	(51.6)	8182	(51.0)	10881	(51.7)	10881	(51.7)	
Follow up (year)	6.29	(2.19)	6.09	(2.26)	6.03	(2.35)	5.88	(2.48)	<0.001
Insurance range									
<15,000	8541	(40.6)	6583	(41.1)	8676	(41.2)	8423	(40.0)	<0.001
15,000–29,999	6618	(31.4)	5761	(35.9)	7401	(35.2)	7848	(37.3)	
≧29,999	5892	(28.0)	3684	(23.0)	4974	(23.6)	4780	(22.7)	
Comorbidities									
Diabetes	3023	(14.4)	2189	(13.7)	3222	(15.3)	3496	(16.6)	<0.001
Hypertension	5562	(26.4)	3896	(24.3)	6590	(31.3)	6642	(31.6)	<0.001
Hyperlipidemia	3688	(17.5)	2656	(16.6)	4839	(23.0)	5091	(24.2)	<0.001
Myocardial infraction	1045	(5.0)	410	(2.6)	826	(3.9)	888	(4.2)	<0.001
Congestive heart failure	2147	(10.2)	1350	(8.4)	2589	(12.3)	2772	(13.2)	<0.001
Peripheral vascular disease	1167	(5.5)	750	(4.7)	1425	(6.8)	1571	(7.5)	<0.001
Cerebral vascular disease	4990	(23.7)	2966	(18.5)	5216	(24.8)	5261	(25.0)	<0.001
Dementia	1104	(5.2)	821	(5.1)	1290	(6.1)	1299	(6.2)	<0.001
Chronic kidney disease	4063	(19.3)	2568	(16.0)	4099	(19.5)	4408	(20.9)	<0.001
Cancer	3993	(19.0)	2405	(15.0)	3903	(18.5)	3994	(19.0)	<0.001
Charlson’s index score									
≦2	7822	(37.2)	7878	(49.2)	7823	(37.2)	7823	(37.2)	<0.001
3	3175	(15.1)	2598	(16.2)	3165	(15.0)	3165	(15.0)	<0.001
≧ 4	10054	(47.8)	5552	(34.6)	10063	(47.8)	10063	(47.8)	<0.001
Mean±SD	3.79	(3.0)	3.28	(2.8)	4.18	(3.1)	4.36	(3.3)	<0.001
Medication									
NSAIDs	1293	(6.1)	1407	(8.8)	2623	(12.5)	3375	(16.0)	<0.001
Antiplatelet agent	639	(3.0)	426	(2.7)	796	(3.8)	949	(4.5)	<0.001
Warfarin	70	(0.3)	38	(0.2)	56	(0.3)	57	(0.3)	0.340

* Non-PUD cohort: comparison cohort

** PUD-HPRx cohort: non-*H pylori* treatment cohort

*** PUD+HPRx cohort: *H pylori* treatment cohort

Table 2.

The adjusted hazard risk (aHR) of immune-mediated disorders, subtypes of autoimmune diseases among Non-PUD, UTI, and PUD population.

				Model i			Model ii		
	No. cases	**Per 1,000 PY**	**(%)**	**aHR**	**(95%CI)**	**p value**	**aHR**	**(95%CI)**	**p value**
Autoimmune Disorders									
Non-PUD cohort	614	4.638	(2.6)	Ref.	---		Ref.	---	
UTI cohort	728	7.453	(3.7)	1.71	(1.54 – 1.91)	<0.001	1.07	(1.00 – 1.15)	0.028
PUD-HPRx cohort	1154	9.092	(4.7)	1.91	(1.73 – 2.11)	<0.001	1.14	(1.08 – 1.21)	<0.001
PUD+HPRx cohort	1399	11.299	(5.6)	2.36	(2.14 – 2.59)	<0.001	1.34	(1.27 – 1.42)	<0.001
Lupus Erythematosus									
Non-PUD cohort	9	0.067	(0.0)	Ref.	---		Ref.	---	
UTI cohort	24	0.238	(0.1)	3.99	(1.85 – 8.63)	<0.001	0.81	(0.74 – 0.88)	<0.001
PUD-HPRx cohort	29	0.220	(0.1)	3.24	(1.53 – 6.86)	0.002	0.83	(0.77 – 0.90)	<0.001
PUD+HPRx cohort	39	0.299	(0.2)	4.41	(2.12 – 9.14)	<0.001	0.95	(0.88 – 1.02)	0.164
Systemic Sclerosis									
Non-PUD cohort	3	0.022	(0.0)	Ref.	---		Ref.	---	
UTI cohort	4	0.040	(0.0)	1.92	(0.42 – 8.69)	0.395	0.79	(0.72 – 0.87)	<0.001
PUD-HPRx cohort	5	0.038	(0.0)	1.54	(0.36 – 6.52)	0.554	0.82	(0.76 – 0.88)	<0.001
PUD+HPRx cohort	3	0.023	(0.0)	0.92	(0.18 – 4.67)	0.927	0.93	(0.86 – 1)	0.051
Rheumatoid Arthritis									
Non-PUD cohort	153	1.138	(0.7)	Ref.	---		Ref.	---	
UTI cohort	191	1.907	(1.0)	2.05	(1.65 – 2.54)	<0.001	0.92	(0.84 – 0.99)	0.044
PUD-HPRx cohort	348	2.664	(1.4)	2.29	(1.89 – 2.77)	<0.001	0.96	(0.90 – 1.03)	0.298
PUD+HPRx cohort	368	2.859	(1.5)	2.44	(2.01 – 2.95)	<0.001	1.06	(0.99 – 1.14)	0.054
Polymyositis									
Non-PUD cohort	6	0.044	(0.0)	Ref.	---		Ref.	---	
UTI cohort	10	0.099	(0.0)	2.55	(0.92 – 7.08)	0.072	2.55	(0.92 – 7.08)	0.072
PUD-HPRx cohort	10	0.076	(0.0)	1.74	(0.63 – 4.81)	0.283	1.74	(0.63 – 4.81)	0.283
PUD+HPRx cohort	12	0.092	(0.0)	2.16	(0.80 – 5.81)	0.125	2.16	(0.80 – 5.81)	0.125
Dermatomyositis									
Non-PUD cohort	7	0.052	(0.0)	Ref.	---		Ref.	---	
UTI cohort	6	0.059	(0.0)	1.33	(0.44 – 3.98)	0.611	0.79	(0.72 – 0.86)	<0.001
PUD-HPRx cohort	14	0.106	(0.1)	2.05	(0.82 – 5.10)	0.122	0.82	(0.76 – 0.89)	<0.001
PUD+HPRx cohort	12	0.092	(0.0)	1.79	(0.70 – 4.58)	0.222	0.93	(0.86 – 1.00)	0.064
Vasculitis									
Non-PUD cohort	7	0.052	(0.0)	Ref.	---		Ref.	---	
UTI cohort	10	0.099	(0.1)	1.91	(0.72 – 5.07)	0.189	0.79	(0.73 – 0.87)	<0.001
PUD-HPRx cohort	16	0.121	(0.1)	2.13	(0.87 – 5.20)	0.097	0.83	(0.77 – 0.89)	<0.001
PUD+HPRx cohort	24	0.184	(0.1)	3.10	(1.32 – 7.27)	0.009	0.94	(0.87 – 1.01)	0.099
Pemphigus									
Non-PUD cohort	5	0.037	(0.0)	Ref.	---		Ref.	---	

				Model i			Model ii		
	No. cases	**Per 1,000 PY**	**(%)**	**aHR**	**(95%CI)**	**p value**	**aHR**	**(95%CI)**	**p value**
UTI cohort	5	0.049	(0.0)	1.71	(0.48 – 5.98)	0.401	0.79	(0.72 – 0.87)	<0.001
PUD-HPRx cohort	5	0.038	(0.0)	0.93	(0.26 – 3.28)	0.918	0.82	(0.76 – 0.88)	<0.001
PUD+HPRx cohort	3	0.023	(0.0)	0.57	(0.13 – 2.44)	0.448	0.92	(0.86 – 0.99)	0.046
Sicca Syndrome									
Non-PUD cohort	123	0.913	(0.5)	Ref.	---		Ref.	---	
UTI cohort	227	2.268	(1.1)	2.60	(2.09 – 3.25)	<0.001	0.94	(0.86 – 1.02)	0.137
PUD-HPRx cohort	315	2.407	(1.4)	2.56	(2.08 – 3.16)	<0.001	0.95	(0.88 – 1.02)	0.163
PUD+HPRx cohort	385	2.989	(1.5)	3.15	(2.57 – 3.87)	<0.001	1.09	(1.02 – 1.17)	0.007
Inflammatory Bowel Disease									
Non-PUD cohort	317	2.371	(1.3)	Ref.	---		Ref.	---	
UTI cohort	289	2.900	(1.5)	1.22	(1.04 – 1.44)	0.012	0.87	(0.80 – 0.94)	0.001
PUD-HPRx cohort	476	3.662	(1.9)	1.52	(1.31 – 1.75)	<0.001	0.94	(0.88 – 1.00)	0.091
PUD+HPRx cohort	666	5.235	(2.7)	2.15	(1.88 – 2.46)	<0.001	1.13	(1.06 – 1.21)	<0.001
Crohn’s Disease									
Non-PUD cohort	291	2.175	(1.2)	Ref.	---		Ref.	---	
UTI cohort	278	2.787	(1.4)	1.28	(1.08 – 1.51)	0.003	1.28	(1.08 – 1.51)	0.003
PUD-HPRx cohort	452	3.474	(1.8)	1.57	(1.35 – 1.82)	<0.001	1.57	(1.35 – 1.82)	<0.001
PUD+HPRx cohort	618	4.848	(2.5)	2.17	(1.88 – 2.49)	<0.001	2.17	(1.88 – 2.49)	<0.001
Chronic Ulcerative Colitis									
Non-PUD cohort	28	0.207	(0.1)	Ref.	---		Ref.	---	
UTI cohort	12	0.119	(0.1)	0.62	(0.31 – 1.23)	0.175	0.78	(0.72 – 0.86)	<0.001
PUD-HPRx cohort	27	0.204	(0.1)	0.98	(0.58 – 1.68)	0.965	0.82	(0.76 – 0.89)	<0.001
PUD+HPRx cohort	53	0.407	(0.2)	1.97	(1.24 – 3.13)	0.004	0.94	(0.88 – 1.01)	0.143

Adjusted for age, gender, insurance range, comorbidities, CCIS score, and medication.

Non-PUD cohort: comparison cohort

PUD-HPRx cohort: non-*H pylori* treatment cohort

PUD+HPRx cohort: *H pylori* treatment cohort

Model i: Cox proportional hazards regression

Model ii: competing risk analysis

Table 3.

Mortality among Non-PUD population, UTI population and PUD population (N=79,181).

	No. Death	Cases/1,000 Person-years	aHR	(95%CI)	p value
Non-PUD cohort	2062	11.631		Ref.	
UTI cohort	1068	8.023	0.92	(0.85 – 0.99)	0.036
PUD-HPRx cohort	1894	10.865	0.93	(0.88 – 0.99)	0.047
PUD+HPRx cohort	2170	12.577	1.11	(1.04 – 1.18)	0.001

Adjusted for age, gender, insurance range, comorbidities, CCIS score, and medication.