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ORIGINAL ARTICLE

Helicobacter pylori infection increases the risk of adult-onset asthma: a nationwide cohort study

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Abstract *Helicobacter pylori* infection (HPI) appears to reduce risk of childhood-onset asthma, but the relationship between HPI and adult-onset asthma is inconclusive. This study explored the potential association between HPI and risk of adult-onset asthma. We conducted a national insurance retrospective cohort study using the longitudinal health insurance database (LHID 2000) in Taiwan. We enrolled the HPI group consisting of 1664 patients with HPI diagnosis between 2000 and 2007, and the non-HPI group consisting of 6,656 age- and sex-matched subjects without HPI. All study participants had been followed up from index date to the diagnostic date of asthma, withdrawal from the National Health Insurance program, or the end of 2011, which came first. We analyzed risk of adult-onset asthma with respect to sex, age, and comorbidities by using Cox models. Cigarette smoking status, which could not be obtained from the program, was adjusted indirectly by considering chronic obstructive pulmonary diseases in our statistical models because the disease is related to heavy smoking. After adjustment for sex, age, and comorbidities, HPI was significantly associated with an increased 1.38-fold risk of adult-onset asthma. Moreover, among people without comorbidities, the 1.85-fold risk of adult-onset asthma remained higher for the HPI population compared with the non-HPI population. In this study, patients with HPI exhibited a significantly higher risk of adult-onset asthma than did the subjects without HPI.

Abbreviations

HPI	*Helicobacter pylori* infection
NHIRD	National Health Insurance Research Database
NHI	National Health Insurance
LHID2000	Registry for the Longitudinal Health Insurance Database 2000

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ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
AC	Allergic conjunctivitis
AR	Allergic rhinitis
AD	Atopic dermatitis
COPD	Chronic obstructive pulmonary disease
GERD	Gastroesophageal reflux disease
SD	Standard deviation
HR	Hazard ratio
CI	Confidence interval

Introduction

Helicobacter pylori is a gastric pathogen responsible for the development of peptic ulcers [1], gastric adenocarcinoma [2], and primary gastric lymphoma [3]. The prevalence of *H. pylori* infection (HPI) varies from 10%–20% to 80%–90% in developed and developing countries respectively [4, 5]. Most people acquire HPI in their early lives [6, 7]. The colonization and chronic inflammatory response elicited by HPI are known to induce many extra-gastric diseases, including coronary artery disease [8, 9], metabolic syndrome [8, 9], and dementia [9, 10]. However, HPI has also been determined to reduce the risk of allergic diseases [11–13] and childhood-onset asthma [12, 13].

A predisposition for asthma, characterized by chronic inflammation of the airway [14, 15], is attributable to multiple factors, including genetic features, socioeconomic status, smoking, obesity, environmental factors, and allergens [14–16]. The disease affects more than 300 million persons globally and causes approximately 250,000 annual deaths [16]. In the United States, the number of people with asthma has increased by 2.9% annually, rising from 20.3 million persons to 25.7 million persons in one decade [17]. In Taiwan, asthma increased its prevalence from 5.07% to 11.9% over two decades [18, 19]. Late life-onset asthma differs from early life-onset asthma, because it is probably non-atopic and is accompanied by a prompt decrease in lung function [15, 20, 21]. Although the incidence of adult-onset asthma is much lower than that of childhood-onset asthma [17, 22], it has significantly increased in the past decades [23–25].

Several reports have claimed that HPI can diminish the risk of childhood-onset asthma [12, 26]; however, the influence of HPI on adult-onset asthma remains elusive [11, 27]. Although some studies have documented an inverse association of HPI and adult-onset asthma [28–30], others have failed to attain similar conclusions [31–33]. Previous research regarding the correlation between HPI and adult-onset asthma has been restricted to cross-sectional studies [29, 30, 33] and small case–control studies [28, 31, 32]. A large population-based cohort study may help to elucidate the possible link between HPI and adult-onset asthma. Therefore, we designed a national insurance retrospective cohort study by using data from the Taiwan National Health Insurance Research Database (NHIRD) to determine the association between HPI and the risk of adult-onset asthma.

Materials and methods

Data sources

This study population cohort was established based on the longitudinal health insurance database (LHID 2000), which is one of the National Health Insurance Research Database (NHIRD) of Taiwan. The Taiwan government began the universal National Health Insurance (NHI) program in March 1995 to provide comprehensive health care for all residents of Taiwan. By the end of 2014, the NHI program comprised nearly 99% of the Taiwanese population. The NHIRD contains 1 million beneficiaries' comprehensive demographic data, which includes sex and date of birth, and outpatient and inpatient information, which included dates of clinical visits, diagnostic codes, and details of prescriptions. Diseases were coded on the basis of the International Classification of Disease Diagnoses, Ninth Revision, Clinical Modification (ICD-9-CM). All claims data in the NHIRD are released by the National Health Insurance Administration for research and are managed by the National Health Research Institutes. For the safety and privacy of the insured people, the insured people identity information was encrypted in the NHIRD. This study was approved by the China Medical University ethical review committee (CMUH104-REC2–115).

Study population

We identified 2051 patients with newly diagnosed HPI (ICD9-CM 041.86) during 2000–2007 as the potential study group. The date of HPI diagnosis was considered the index date for this group. To increase the validity of HPI diagnoses, we selected patients who used outpatient services at least twice or were hospitalized at least once as an inpatient. We excluded patients aged younger than 20 years ($n = 38$) and those with a history of previously diagnosed asthma (ICD-9-CM 493) ($n = 349$) from the HPI group. For each HPI patient, four insured subjects without HPI were randomly selected from subjects in the LHID2000 to form the non-HPI group and frequency-matched according to sex, 5-year age interval, and index year by using the same inclusion criteria as that of the HPI group. The index day and month were randomly assigned to the non-HPI group members, and the index year was assigned as the same year as that of the corresponding HPI group member. A total of 1664 patients with HPI and 6656 subjects without HPI were included in the data analysis.

Demographic variables comprised sex and stratified age groups, which involved in aged 20–39, 40–59, and 60 years or over. Comorbidities potentially associated with asthma were identified before the index date, including diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401–405), allergic conjunctivitis (AC, ICD-9-CM 372.05, 372.10, 372.14), allergic rhinitis (AR, ICD-9-CM 477), atopic dermatitis (AD, ICD-9-CM 691.8), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490–496), and gastroesophageal reflux disease (GERD; ICD-9-CM 530.11 and 530.81).

The principal outcome was asthma (ICD9-CM 493). Both groups were followed from the index data to the date of asthma diagnosis, withdrawal from the NHI program, or the end of 2011, which came first.

Statistical analysis

The difference in the distribution of categorical variables (such as sex, age group, and comorbidity) between the HPI and non-HPI groups were analyzed by Chi-square (χ^2) test. The *t*-test was used to estimate the statistical difference of continuous age between the two groups, and the mean age and standard deviation (SD) were presented. Incidence density rates of asthma were calculated for both groups stratified by sex, age, and comorbidities. The incidence density rates of asthma were calculated by dividing the number of new asthma diagnoses by the person-years at risk in both groups. A Kaplan–Meier estimate was used to depict the incidence proportion of asthma between those with and without HPI, and the log-rank test was used to evaluate the differences between the two. We assessed the hazard ratios (HRs) and 95% confidence intervals (CIs) of asthma to estimate the independent effect of HPI after adjustment for sex, age, and each comorbidity (including diabetes, hyperlipidemia, hypertension, AC, AR, AD, COPD, and GERD) in a Cox model.

All statistical analyses were performed by SAS 9.3 statistical package (SAS Institute, Cary, NC, USA). The Kaplan–Meier curves were constructed using R software (R Foundation for Statistical Computing, Vienna, Austria). All statistical thresholds were established as p value <0.05 in two-tailed tests.

Results

We identified 1664 patients with newly diagnosed HPI between 2000 and 2007, and 6656 sex- and age-matched subjects without HPI (Table 1). Patients with HPI had a higher prevalence of pre-existing comorbidities of diabetes, hyperlipidemia, hypertension, AC, AR, COPD, and GERD (Table 1). The incidence proportion of asthma was considerably higher in the HPI group than it was in the non-HPI group (log–rank test; $p < 0.001$; Fig. 1). During a mean follow-up period of 3.59 years, 101 patients were diagnosed with asthma in the HPI group, with an incidence proportion of 11.9 per 1,000 person-years, and 251 subjects were diagnosed with asthma in the non-HPI population, with a person–time incidence rate of 7.07 per 1,000 person-years (Table 2). A Cox model showed that those patients with HPI had a considerably higher risk of asthma than did the subjects without HPI after adjustment for sex, age, and comorbidities (adjusted HR = 1.38, 95% CI = 1.09–1.75). A multivariate analysis showed that female sex (adjusted HR = 1.29, 95% CI = 1.04–1.59), age group of 45+ years (adjusted HR = 1.52, 95% CI = 1.15–2.01), AR (adjusted HR = 1.43, 95% CI = 1.11–1.84), AD (adjusted HR = 1.69, 95% CI = 1.05–2.73), and COPD (adjusted HR = 2.96, 95% CI = 2.30–3.80) were significantly associated with an increasing risk of asthma.

The sex-stratified analyses demonstrated that the person–time incidence rates of asthma between the two (women and men) with HPI were 14.1 and 10.3 per 1000 person-years, which were further apart than those for subjects without HPI (7.89 and 6.52 per 1,000 person-years, separately; Table 3). Moreover, female patients with HPI were at a greater risk of asthma than were those without HPI (adjusted HR = 1.51, 95% CI = 1.06–2.16). The age-stratified analyses indicated that the incidence proportion of asthma increased with age in both groups. Moreover, the patients with existing HPI had a considerably higher risk for asthma than those without HPI in the stratified age group of 20–44 years (adjusted HR = 2.28, 95% CI = 1.41–3.70). Regardless of the comorbidity status, the patients with HPI had an increasing risk of asthma than those without HPI, as follows: 1) no comorbidity population: adjusted HR had been 1.85 (95% CI = 1.09–3.13), and 2) existing comorbidity population: adjusted HR was 1.50 (95% CI = 1.16–1.94).

Discussion

This national insurance retrospective cohort study demonstrated that those with HPI revealed an increasing risk, 1.38-fold, of developing adult-onset asthma when comparing the differences between subjects with HPI and without HPI after adjusting for several classical risk factors. Several studies [28–30] have reported an inverse association between HPI and asthma based on the 'hygiene hypothesis' [34]. However, Sheikh et al. postulated that this model may be an oversimplification because it has yielded several conflicting results [35]. For example, the incidence rate of childhood-onset asthma and prevalence of HPI were reported to be low in Malaysia [36]. Therefore, Lee et al. posited that HPI is only an indicator of poor hygiene, rather than as a protection factor against asthma [36]. This theory failed to predict the link between HPI and adult-onset asthma, as indicated by the results of our study.

HPI leads to the secretion of T-helper 1 lymphocyte-dominated immune cytokines, and reduces the risk of childhood-onset asthma by inhibiting the T-helper 2 (Th2) lymphocyte-associated immune response [27, 37, 38].

Table 1 Baseline demographic factors and comorbidity of patients according to *Helicobacter pylori* infection status

Characteristics	Non-HPI group (*n* = 6,656)		HPI group (*n*= 1,664)		*P*-value
	N	%	*N*	%	
Sex					> 0.99
Women	2,688	40.4	672	40.4	
Men	3,968	59.6	992	59.6	
Age, years					> 0.99
20–39	1,580	23.7	395	23.7	
40–59	3,184	47.8	796	47.8	
≥ 60	1,892	28.4	473	28.4	
Mean (SD)†	51.6	(15.4)	51.9	(15.3)	0.50
Comorbidity					
Diabetes	711	10.7	240	14.4	<0.001
Hyperlipidemia	1437	21.6	500	30.1	<0.001
Hypertension	1916	28.8	605	36.4	<0.001
AC	1417	21.3	467	28.1	<0.001
AR	906	13.6	322	19.4	<0.001
AD	167	2.51	44	2.64	0.82
COPD	634	9.53	263	15.8	<0.001
GERD	124	1.86	188	11.3	<0.001

Abbreviations: HPI, *Helicobacter pylori* infection; SD, standard deviation; AC, allergic conjunctivitis; AR, allergic rhinitis; AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease

† Student's *t*-test

Unlike childhood-onset asthma, adult-onset asthma is more likely to be classified as non-Th2 asthma [39]. Therefore, the influence of HPI on the development of adult-onset asthma might be quite different from that on childhood-onset asthma.

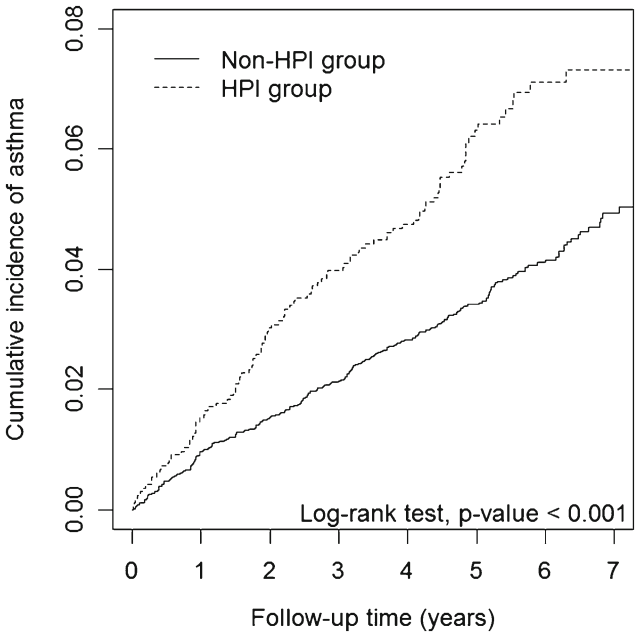

Fig. 1 Cumulative incidence curves of asthma for groups with and without *Helicobacter pylori* infection (HPI)

This may explain the discrepancy between our findings and the findings of previous studies on the relationship between HPI and childhood-onset asthma.

The pathophysiological mechanisms of adult-onset asthma are largely uninvestigated. The possible predisposing factors for the developing asthma in late life have been recognized, such as environmental exposure, existing morbidity, psychological problems [15], and microbial infection [40]. A significant increase of Proteobacteria, including *Haemophilus*, *Moraxella*, and *Neisseria* species, was observed in the bronchi of both children and adults with asthma [41]. *H. pylori*, a member of Proteobacteria, was also determined to be associated with adult-onset asthma in this study. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have been found to induce the pathogenesis of asthma, apparently, in a dose-dependent manner. A low level of *M. pneumoniae* infection enhanced the expression of the Th2 cytokines and vice-versa [42]. Similar situations have also been observed in people with lipopolysaccharide stimulation [43] and *C. pneumoniae* infection [44]. The development of adult-onset asthma might be the consequence of long-term exposure to *H. pylori* acquired early in life, as observed in *M. pneumoniae* and *C. pneumoniae* infections.

Several comorbidities were identified as associated with the development of adult-onset asthma in this study. COPD was associated with the highest risk (HR = 2.96), followed by AD (HR = 1.69), and AR (HR = 1.43), indicating that these

Table 2 Cox model measured Hazard ratios and 95% confidence intervals of asthma associated with *Helicobacter pylori* infection and covariates

Characteristics	Event no.	IR	HR (95% CI)	
			Univariate	Multivariate†
HPI				
No	251	7.07	1.00	1.00
Yes	101	11.9	1.67 (1.33–2.11)***	1.38 (1.09–1.75)**
Sex				
Women	161	9.09	1.25 (1.01–1.54)*	1.29 (1.04–1.59)*
Men	191	7.26	1.00	1.00
Age, years				
20–44	76	4.75	1.00	1.00
≥ 45	276	9.86	1.76 (1.51–2.05)***	1.52 (1.15–2.01)**
Comorbidity				
– Diabetes				
No	292	7.42	1.00	1.00
Yes	60	12.9	1.72 (1.31–2.28)***	1.08 (0.78–1.50)
– Hyperlipidemia				
No	228	6.7	1.00	1.00
Yes	124	12.4	1.85 (1.49–2.30)***	1.21 (0.94–1.55)
– Hypertension				
No	200	6.38	1.00	1.00
Yes	152	12.0	1.87 (1.52–2.31)***	1.15 (0.90–1.47)
– AC				
No	248	7.23	1.00	1.00
Yes	104	10.7	1.47 (1.17–1.85)***	1.01 (0.80–1.29)
– AR				
No	263	6.99	1.00	1.00
Yes	89	14.0	1.99 (1.56–2.53)***	1.43 (1.11–1.84)**
– AD				
No	334	7.78	1.00	1.00
Yes	18	17.0	2.17 (1.35–3.48)**	1.69 (1.05–2.73)*
– COPD				
No	245	6.18	1.00	1.00
Yes	107	24.6	3.97 (3.17–4.99)***	2.96 (2.30–3.80)***
– GERD				
No	331	7.78	1.00	1.00
Yes	21	14.4	1.81 (1.17–2.82)**	1.15 (0.73–1.82)

Abbreviations: IR, incidence density rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval; HPI, *Helicobacter pylori* infection; AC, allergic conjunctivitis; AR, allergic rhinitis; AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease

† Multivariate Cox proportional hazards regression model including HPI, sex, age, diabetes, hyperlipidemia, hypertension, AC, AR, AD, COPD, and GERD

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

comorbidities increase the risk of adult-onset asthma in patients with HPI (Table 2). While COPD and adult-onset asthma have similar characteristics and predisposing factors [45], it is not surprising that COPD may reveal the increasing risk of late life-onset asthma. Our findings are consistent with previous studies that reported that AD [46] and AR [47] were associated with the development of adult-onset asthma.

Our study and previous reports [17, 25] found that women had a higher risk of developing asthma. There was a significantly higher incidence of asthma observed in adults aged between 20 and 44 years (Table 3). In patients aged more than 45 years, the incidence of asthma also increased in those with HPI compared with those without HPI. However, there was no significant difference between both the groups. Among people

Table 3 Incidence density rates and hazard ratios of asthma categorized according to *Helicobacter pylori* infection status stratified by sex, age, and comorbidity

	Non-HPI group			HPI group			Compared to non-HPI group	
							HR (95% CI)	
Characteristics	Event no.	Person-years	IR	Event no.	Person-years	IR	Crude	Adjusted‡
Sex								
Women	113	14,322	7.89	48	3395	14.1	1.78 (1.27–2.50)***	1.51 (1.06–2.16)*
Men	138	21,168	6.52	53	5124	10.3	1.59 (1.16–2.18)**	1.33 (0.96–1.84)
Age, years								
20–44	46	12,885	3.57	30	3123	9.61	2.69 (1.70–4.26)***	2.28 (1.41–3.70)***
≥ 45	205	22,605	9.07	71	5396	13.2	1.45 (1.11–1.90)**	1.17 (0.89–1.55)
Comorbidity status†								
No	61	16,268	3.75	18	2712	6.64	1.77 (1.04–2.99)*	1.85 (1.09–3.13)*
Yes	190	19,222	9.88	83	5808	14.3	1.44 (1.11–1.87)**	1.50 (1.16–1.94)**

Abbreviations: HPI, *Helicobacter pylori* infection; IR, incidence density rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval

† People with diabetes, hyperlipidemia, hypertension, AC, AR, AD, COPD, or GERD were classified into the comorbidity group

‡ Model mutually adjusted for sex, age, diabetes, hyperlipidemia, hypertension, AC, AR, AD, COPD, and GERD

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

without comorbidities, we observed an approximately 1.85-fold greater adult-onset asthma risk in patients with HPI than in the subjects without HPI. These findings illustrated that HPI is an independent predisposing factor for predicting the subsequent development of adult-onset asthma.

Smoking status, which could not be obtained from our database, is one of the most important predisposing factors for asthma. To overcome this limitation, we adjusted for cigarette smoking indirectly by considering COPD in our statistical models, because the disease is related to heavy cigarette smoking. In fact, the Taiwan government has conducted several projects for tobacco control, including the implementation of Tobacco Hazards Prevention Act, the collection of tobacco health and welfare surcharge, and the launch of the Outpatient Smoking Cessation Service. According to Taiwan Health Promotion Administration (http://tobacco.hpa.gov.tw/index.aspx), the rate of cigarette smoking has dropped in the past decades. However, the incidence of asthma has increased during the same period. Apart from smoking, fine-particulate air pollution [48] and chronic arsenic exposure [49] have also been documented to be associated with asthma. The absence of the influencing environmental factors and life-style habits of the studied population was an inherent weakness in NHIRD studies. To decrease the confounding factors of this study, we tried to enroll several variables into our analysis. We included several traditional metabolic syndrome comorbidities such as diabetes, hyperlipidemia, and hypertension to alter adjustment for the influence of clinical examination, such as body mass index. Furthermore, we adjusted for several comorbidities of atopic illnesses (including AC, AR, and AD) to reduce the hidden confounding effect in the present study as possible as we can. However, there were still several potential limitations. First, data on the HPI severity and the virulence factors of the *H. pylori* strains in our study were not available. Moreover, previous reports on the relationship between the virulence factors of *H. pylori* and asthma have enrolled relatively few patients. Second, the bias resulting from possible unknown confounders in a retrospective observation study might have affected our results despite our study being well designed.

The major strength of this study is the cohort study design with 7-year follow-up period. This enables us to clarify the risk of developing asthma in subjects with HPI. Furthermore, we carried out adjustment of several classical factors associated with asthma. We also validate the HPI diagnoses for selected patients who used outpatient services at least twice or were hospitalized at least once. All these could reinforce the results of our study.

Compliance with ethical standards

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Conflict of interest Miss Hsuan-Ju Chen has received salary from Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan. Dr. Shih-Ta Shang was supported by the Armed Forces Tao-Yuan General Hospital (AFTYGH-10501, AFTYGH-10616); Dr. Yung-Chih Wang was supported by Tri-Service General Hospital (TSGH-C104–117, TSGH-C105–112). The other authors declare that they have no conflict of interest.

Ethical approval The NHIRD comprises of encrypted and de-identified secondary data, only released to the research objectives. This study was reviewed and approved by the institutional review board committee of China Medical University (CMUH104-REC2–115), which waived requirements for informed consent due to the observational study.

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