中文題目：消化性潰瘍合併幽門螺旋桿菌感染無法降低成人氣喘之發生

英文題目：Peptic ulcer disease with *Helicobacter pylori* infection does not protect against adult asthma

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Background: Asthma is characterized by lung inflammation, airway hyper-responsiveness, and airway obstruction. Increased hygiene and T helper 1/T helper 2 (Th1/Th2) response polarization have been suggested as factors leading to increased asthma rates worldwide. Microbial-derived stimuli can potentially influence the pathogenesis of allergic diseases. Several studies have disclosed an inverse correlation between childhood-onset asthma and allergic disorder incidence and human gastric *H. pylori* infection. Whether the relationship between *H. pylori* infection and asthma patients in Taiwan and in developed countries, which are lower *H. pylori* prevalence areas, is different warrants further exploration. To investigate a possible relationship between these diseases, we analyzed *H. pylori* infection in patients aged 20-50 years with peptic ulcer disease, and grouped them as asthma and non-asthma patients based on insurance claims between the years 2000 and 2008 that were recorded in the Taiwan National Health Insurance (NHI) database. The main outcome of interest is to determine whether the *H. pylori* infection rate is lower for adult asthma patients

after contracting peptic ulcer disease.

Materials and Methods: A retrospective cohort study was conducted from January 1, 2000 to December 31, 2008 based on ambulatory care and inpatient discharge records. Patients aged 20-50 years were enrolled. The peptic ulcers were defined by gastric ulcer (ICD-9-CM: 531), duodenal ulcer (ICD-9-CM: 532), and nonspecific peptic ulcer (ICD-9-CM: 533). All of the diagnosed peptic ulcers after endoscopic confirmation and concurrent *H. pylori* tests, during this period, were selected as the study cohort. Patients with *H. pylori* infection were defined as those who received triple or quadruple therapy during the same outpatient visit or during the same inpatient discharge record. The duration of therapy was between 7 and 14 days. Patients without *H. pylori* infection were defined as those who took only PPIs or H_2-blockers for a minimum of 3 consecutive months after gastroscopy and *H. pylori* diagnostic tests.

Definition of asthma: Asthma patients were identified according to the code ICD-9-CM: 493 over a 9-year period, appearing once in the inpatient records or 3 or more times in ambulatory care claims. To be defined as a non-asthma patient, a person cannot have the code ICD-9-CM: 490-494, and 496 in his or her inpatient records or in the ambulatory care claims. Only patients aged 20-50 years were enrolled. The final sample included 2,894 *H. pylori*-positive patients and 522 *H. pylori*-negative patients. We compared peptic ulcer patients in both asthma and non-asthma groups with different ages, sex, aspirin use, NSAIDs

use, COX-2 specific inhibitors use, peptic ulcer history, DM, hypertension, CHF, CAD, CVD, COPD, GERD, EE, liver cirrhosis, and CKD, to analyze the effects of these factors on *H. pylori* infection.

Statistical analysis: A logistic regression model was used to calculate the odds ratio (OR) and a 95% confidence interval (CI) to determine whether asthma is an independent factor of lower *H. pylori* rates infection in peptic ulcer disease. Variables in this model included age, sex, asthma, aspirin use, NSAIDs use, COX-2 specific inhibitors use, peptic ulcer history, DM, hypertension, CHF, CAD, CVD, COPD, GERD, EE, liver cirrhosis, and CKD. All statistical analyses were performed using an SAS statistical package.

Results: Data were gathered for 2,894 *H. pylori*-positive patients and 522 *H. pylori*-negative patients. Table 1 shows the demographic data, including age (divided as 20 years-34 years and 35 years-50 years), sex, asthma, aspirin use, NSAIDs use, COX-2 specific inhibitors use, peptic ulcer history, DM, hypertension, CHF, CAD, CVD, COPD, GERD, EE, liver cirrhosis, and CKD. Table 2 shows the characteristics of *H. pylori* infection rate among asthma and non-asthma patients aged 20-50 years with peptic ulcer disease in the study population, including age, sex, aspirin use, NSAIDs use, COX-2 specific inhibitors use, peptic ulcer history, DM, hypertension, CHF, CAD, CVD, COPD, GERD, EE, liver cirrhosis, and CKD. Based on logistic regression analysis, Table 3 shows that asthma patients with peptic ulcer disease (OR=0.80, p=0.385) had similar *H. pylori* infection rates compared to non-asthma

patients with peptic ulcer disease.

Discussion: Our study showed that adult asthma patients with peptic ulcer disease demonstrate similar *H. pylori* infection rates, compared to non-asthma patients with peptic ulcer disease. Our findings do not show that an inverse relationship between asthma patients with peptic ulcers and *H. pylori* infection exists in Taiwan (OR=0.80, p=0.385). Previous studies showed an inverse relationship between asthma patients with *H. pylori* infection. These studies enrolled childhood asthma and non-asthma patients, regardless of peptic ulcer status, and evaluated serum anti-*H. pylori* IgG antibody levels and C^{13} breath tests to confirm *H. pylori* infection status. However, the risk factors in adult asthma may be much more heterogeneous than in childhood asthma. Adult asthma may be complicated by tobacco use and occupation. In addition, asthma in adults may be newly-onset, persistent from childhood, or exacerbated from childhood asthma. Chen et al found an inverse association in those who had asthma before the age of 15 years, with no association with those with adult-onset asthma.

Strachan proposed the hygiene hypothesis in which an unhygienic environment may educate the immune system and protect against the development of allergic disease. *H. pylori*, which induces Th1 directed immune response, increases gastric mucosa inflammation and atrophy. *H. pylori* infection may protect against asthma, which is related to Th2 and Th17 directed immune response, because it can alter the polarized Th1/Th2 response. *H.*

pylori infection leads to regulatory T cells inducing CD4+CD25+ T cells. These cells express the transcription factor forkhead box P3 that suppresses T cell function, including Th2 directed immune response. Th-1-driven primarily asymptomatic gastritis is suggested as a major link to allergy protection in childhood. According to the hygiene hypothesis, a Th-1 status was previously established in infected, but asymptomatic individuals.

In summary, our study indicates that there is no different *H. pylori* infection rate in adult asthma and non-asthma patients with peptic ulcer disease. The effect of *H. pylori* may be less important in adulthood asthma.

Conclusion: Our data show peptic ulcer disease with concurrent *H. pylori* infection does not protect against adult asthma.

Table 1: Baseline characteristics of *H. pylori* infection among patients aged 20-50 years with peptic ulcer disease in the study population

Variables	HP (+)		HP (-)		*p* value
	N=2,894	%	N=522	%	
Age					0.210
20-34	786	86.00	128	14.00	
35-50	2,108	84.25	394	15.75	
Sex					<0.001
Male	1,743	86.72	267	13.28	
Female	1,151	81.86	255	18.14	
Asthma	74	77.89	21	22.11	0.061
Medication					
Aspirin	37	80.43	9	19.57	0.416
NSAIDs or COX-2 inhibitors	67	72.04	26	27.96	<0.001
Peptic ulcer history	128	79.01	34	20.99	0.039
Co-morbidities					
DM	114	83.21	23	16.79	0.617
Hypertension	195	78.31	54	21.69	0.004
CHF	5	62.50	3	37.50	0.110
CAD	64	80.00	16	20.00	0.235
CVD	23	82.14	5	17.86	0.704
COPD	158	74.53	54	25.47	<0.001
GERD or EE	16	84.21	3	15.79	0.969
Liver cirrhosis	32	76.19	10	23.81	0.122
CKD	59	75.64	19	24.36	0.024

NSAIDs: non-steroidal anti-inflammatory drugs. COX-2 inhibitors: cyclooxygenase-2 specific inhibitors. DM: diabetes mellitus, CHF: congestive heart failure, CAD: coronary artery disease, CVD: cerebral vascular disease, COPD: chronic obstructive pulmonary disease, GERD: gastro-esophageal reflux disease, EE: erosive esophagitis, CKD: chronic kidney disease.

HP (+): *Helicobacter pylori* infection, HP (-): no *Helicobacter pylori* infection, N: number.

Table 2: Characteristics of *H. pylori* infection rate among asthma and non-asthma patients aged 20-50 years with peptic ulcer disease in the study population

Variables	Asthma				Non-Asthma				*p* value
	HP (+)		HP (-)		HP (+)		HP (-)		
	N=74	%	N=21	%	N=2,820	%	N=501	%	
Age									
20-34	12	80.00	3	20.00	774	86.10	125	13.90	0.454
35-50	62	77.50	18	22.50	2,046	84.48	376	15.52	0.092
Sex									
Male	34	82.93	7	17.07	1,709	86.80	260	13.20	0.470
Female	40	74.07	14	25.93	1,111	82.17	241	17.83	0.130
Medication									
Aspirin	3	100.00	0	0.00	34	79.07	9	20.93	0.377
NSAIDs or COX-2 inhibitors	5	83.33	1	16.67	62	71.26	25	28.74	0.524
Peptic ulcer history	3	75.00	1	25.00	125	79.11	33	20.89	0.842
Co-morbidities									
DM	7	87.50	1	12.50	107	82.95	22	17.05	0.738
Hypertension	11	78.57	3	21.43	184	78.30	51	21.70	0.981
CHF	0	0.00	0	0.00	5	62.50	3	37.50	-
CAD	4	80.00	1	20.00	60	80.00	15	20.00	1.000
CVD	2	100.00	0	0.00	21	80.77	5	19.23	0.494
COPD	16	61.54	10	38.46	142	76.34	44	23.66	0.105

GERD & EE	2	100.00	0	0.00	14	82.35	3	17.65	0.517
Liver cirrhosis	1	50.00	1	50.00	31	77.50	9	22.50	0.373
CKD	3	60.00	2	40.00	56	76.71	17	23.29	0.400

NSAIDs: non-steroidal anti-inflammatory drugs. COX-2 inhibitors: cyclooxygenase-2 specific inhibitors. DM: diabetes mellitus, CHF: congestive heart failure, CAD: coronary artery disease, CVD: cerebral vascular disease, COPD: chronic obstructive pulmonary disease, GERD: gastro-esophageal reflux disease, EE: erosive esophagitis, CKD: chronic kidney disease.

HP (+): *Helicobacter pylori* infection, HP (-): no *Helicobacter pylori* infection, N: number.

Table 3: Logistic regression model for prediction of *H. pylori* in patients aged 20-50 years with peptic ulcer disease in the study population

Variables	Total		
	Odds ratios	95% CI	*p*-value
Age			
20-34 versus 35-50	0.97	0.77-1.20	0.752
Sex			
Male versus female	1.42	1.18-1.72	<0.001
Asthma			
Yes versus no	0.80	0.48-1.33	0.385
Aspirin			
User versus non-user	0.94	0.41-2.16	0.880
NSAIDs or COX-2 inhibitors			
User versus non-user	0.54	0.33-0.87	0.011
Peptic ulcer history			
Yes versus No	0.67	0.45-0.99	0.045
DM			
Yes versus No	1.15	0.70-1.88	0.592
Hypertension			
Yes versus No	0.73	0.51-1.05	0.088
CHF			
Yes versus No	0.51	0.12-2.26	0.377
CAD			
Yes versus No	0.92	0.49-1.71	0.786
CVD			
Yes versus No	1.25	0.45-3.49	0.672
COPD			
Yes versus No	0.57	0.41-0.80	0.001
GERD or EE			
Yes versus No	1.22	0.35-4.29	0.754
Liver cirrhosis			
Yes versus No	0.64	0.30-1.34	0.238
CKD			
Yes versus No	0.65	0.37-1.13	0.123

NSAIDs: non-steroidal anti-inflammatory drugs. COX-2 inhibitors: cyclooxygenase-2 specific

inhibitors. DM: diabetes mellitus, CHF: congestive heart failure, CAD: coronary artery disease, CVD: cerebral vascular disease, COPD: chronic obstructive pulmonary disease, GERD: gastro-esophageal reflux disease, EE: erosive esophagitis, CKD: chronic kidney disease. CI: confidence interval.