

# Eradication of *Helicobacter Pylori* May Be Associated With the Incidence of Alzheimer's Disease in Diabetes Mellitus Patients

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## Research

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# Abstract

*Introduction:* Alzheimer's disease (AD) is the most common form of dementia. Eradication of *Helicobacter pylori* (*H. pylori*) could affect the incidence and progression of many diseases; however, there are limited studies of the association between *H. pylori* eradication and AD outcome. We utilized the National Health Insurance Research Database (NHIRD) of Taiwan to determine the relationship between *H. pylori* eradication and AD in a diabetes mellitus (DM) population.

*Methods:* We collected data from the NHIRD and the Diabetes Mellitus Health Database in Taiwan of patients without a prior diagnosis of AD. We specified three cohorts: patients with (1) peptic ulcer disease (PUD) but no *H. pylori* treatment, without DM (PUD-HPRx in GP); (2) PUD and DM, but no *H. pylori* eradication therapy (PUD-HPRx in DM); (3) PUD and DM, with *H. pylori* eradication therapy (PUD+HPRx in DM). All cohorts were matched according to age, sex, Charlson Comorbidity Index score, and comorbidities.

*Results:* Data were collected from 2000 to 2010, and 157,231 patients were enrolled in total. We compared the effects of treatment for *H. pylori* infection on the incidence and mortality of AD. The patients with DM who received *H. pylori* eradication therapy had a higher incidence of AD than the general population (adjusted hazard ratio of incidence [aHR], 1.088). Subgroup analysis showed that the risk of AD was higher in the younger patients who received *H. pylori* eradication therapy as compared with those who did not (aHR for younger than 45 years, 1.071; aHR of age 45-54 years, 1.089; aHR of age 55-64 years, 1.079) However, a lower mortality rate was observed in the PUD+HPRx in DM group (aHR, 0.945, compared with PUD-HPRx in DM;  $P < 0.001$ ).

*Conclusion:* In this study, we demonstrated that DM patients who underwent treatment for eradication of *H. pylori* had a higher incidence of AD, especially younger patients. Nevertheless, there was a lower mortality rate in patients who received *H. pylori* treatment. Further study is needed to clarify the interrelated roles of AD and eradication therapy for *H. pylori*.

## Introduction

Alzheimer's disease (AD), also known as "senile dementia" or "cognitive disorder", is a progressive, age-influenced neurodegenerative disease. It is the most common form of dementia, especially in industrialized countries, and affects approximately 30 million people around the world with a continuous rising trend.(1, 2) AD is characterized by progressive impairments in diverse behavioral and cognitive functions that exert a prominent impact on AD patients, their families, and society. The pathophysiology of AD is complex, and has not yet been fully elucidated. AD can display an early or late onset depending upon the genome, diet and lifestyle of the patient.(3) Currently, identified risk factors of AD include age, sex, plasma homocysteine level, and genetic factors such as apolipoprotein E allele  $\epsilon 4$ .(4) Several studies have shown an association between infection and AD, including HSV-1, chlamydia pneumonia, and spirochetes.(5, 6) Nonetheless, the significant heterogeneity of AD-related risk factors, etiologies, and

neuropathologic processes makes the development of new therapeutic strategies to slow disease progression especially challenging.(7)

*Helicobacter pylori* (*H. pylori*) is a gram-negative, spiral-shaped pathogenic bacterium that inhabits the gastrointestinal system in more than 50% of adults. It can cause chronic gastritis, peptic ulcer disease and gastric malignancies in humans.(8) In recent years, numerous studies have emphasized the relationships between *H. pylori* infection and the pathogenesis of extra-gastrointestinal disorders, such as coronary heart disease(9) and cerebrovascular disease.(10) Eradication of *H. pylori* using a proton pump inhibitor and antibiotics could lower the incidence and progression of many diseases, such as gastrointestinal tract malignancies (11) and even coronary heart disease.(12)

Previously, one small-group case-control study identified an association between *H. pylori* and AD.(13) One hypothesis is that *H. pylori* might access the brain, mainly via the oral-nasal-olfactory pathway or the circulation, by circulating monocytes (infected with *H. pylori* due to defective autophagy) through a disrupted blood-brain barrier (BBB).(14) However, there are limited reports and evidence of associations between *H. pylori* eradication and the outcome of AD. Some of the greatest challenges include the relatively low prevalence of AD in regions with high rates of *H. pylori* infection and the requirement for a large sample size in order to draw meaningful conclusions. Therefore, in this study, we utilized the National Health Insurance Research Database (NHIRD) of Taiwan, a country in which the prevalence of *H. pylori* approaches 80%,(15) in order to determine the relationship between *H. pylori* eradication and Alzheimer's disease, and analyzed the outcome in a diabetes mellitus (DM) population.

## Material And Methods

### Data Acquisition

Since March 1995, the Taiwan National Health Insurance (NHI) has covered ambulatory care, outpatient care, dental services, hospital inpatient care, and drug prescriptions. It insured more than 96% of the whole population of 23 million in 2000, rising to 99% by the end of 2004. We also collected data from a subgroup database, the Longitudinal Health Insurance Database (LHID 2010), which details anonymized reimbursement claims data for medical research and includes 1-million randomly-selected individuals from the NHIRD from January 2000 to December 2010. We further collected data from the Diabetes Mellitus Health Database (to identify the DM cohort) from January 2000 to December 2015, DM being identified according to Ninth Revision of the International Classification of Diseases (ICD-9) code 250, and patients with  $\geq 3$  outpatient department follow-up visits or at least one hospitalization were included. The rationale for creating this longitudinal database was to allow a 5-year window in both directions in order to analyze the long-term impact of *H. pylori* treatment on AD in the general population and DM patients.

### Study Design

We selected peptic ulcer disease (PUD) patients over 18 years of age identified by ICD-9 codes 531 (gastric ulcer), 532 (duodenal ulcer), and 533 (nonspecific peptic ulcer). Then, we specified three cohorts, as follows: (1) patients with PUD but no *H. pylori* treatment, without DM (PUD-HPRx in GP); (2) patients with PUD and DM, but no *H. pylori* eradication therapy (PUD-HPRx in DM); and (3) patients with PUD and DM who had received *H. pylori* eradication treatment (PUD + HPRx in DM). The definition of patients who had received *H. pylori* treatment was that they were given a course of either triple or quadruple therapy (proton pump inhibitor or H2 receptor blocker, plus clarithromycin or metronidazole, plus amoxicillin or tetracycline, with or without bismuth)(16) for more than 7 days, rather than a negative result of an *H. pylori* test, due to the latter not being available in the NHIRD. The three groups were matched using the propensity-score method by age, gender, Charlson Comorbidity Index score (CCIS), comorbidities, and medications for underlying diseases. Subjects who were selected into one group were excluded from the database and were not selected in the other groups. After matching, there were apparent differences between the cohorts in terms of age (especially those under 35 years); comorbidities of hyperlipidemia, myocardial infarction, and chronic kidney disease (CKD); and the percentage of patients receiving antiplatelet drugs.

## Study Sample

Diagnosis of AD was defined by ICD-9 code 331.0, with  $\geq 3$  months of AD-related medical treatment including cholinesterase inhibitors such as Donepezil, Galantamine or Rivastigmine. The person-years of follow-up were estimated from the index date plus a 2-year lag time to the date of diagnosis of AD. We excluded any first date of an AD-defined event prior to the index date. Subjects with incomplete demographic data (e.g., lost to follow-up, withdrawal from the insurance system, or erroneous information) were also excluded from the study. The follow-up period began after *H. pylori* therapy (index date) plus a 2-year lag time, and ended on December 31, 2010.

## Statistical Analysis

We analyzed the distribution of risk factors for the 3 study cohorts (PUD-HPRx in GP, PUD + HPRx in DM, PUD-HPRx in DM) by analysis of variance (ANOVA), the chi-square test, or Fisher's exact test. Cox proportional hazards regression analyses were performed to determine the crude and adjusted hazard ratios (aHRs) after adjustment for age, gender, comorbidities, CCIS, and nonsteroidal anti-inflammatory drugs or antiplatelet agents. A competing risk model was also performed to determine the risks of AD incidence and mortality. Kaplan–Meier curves were employed to estimate the probability of AD onset or mortality, and the log-rank test was used to analyze the differences between groups. Statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC, USA). Statistical significance was set at  $P < 0.05$ .

## Results

*Higher cumulative incidence of AD in PUD + HPRx in DM cohort as compared with PUD-HPRx in GP and younger DM patients*

To understand the impact on the development of AD of treatment for *H. pylori* and other underlying diseases (GP and DM), we first compared the new incidence of AD patients with PUD diagnosed by esophagogastroduodenoscopy who received *H. pylori* therapy (PUD + HPRx) or never received *H. pylori* therapy (PUD-HPRx) in patients with DM. Then, we compared these cohorts with patients diagnosed with PUD but without DM in order to reduce confounding factors of different incidences. The patient characteristics are shown in Table 1. The average age and gender balance was  $57.61 \pm 14.37$  years with 43.9% men in the PUD-HPRx in GP control group,  $57.35 \pm 13.73$  years with 43.32% men in the PUD + HPRx in DM group, and  $57.52 \pm 14.08$  years with 43.32% men in the PUD-HPRx in DM group.

Table 1  
Demographic and prevalence of PUD + HPRx and PUD-HPRx in DM and a general population.

<b>Post-PSM-Matching</b>				
	General Population	DM Population		
	PUD-HPRx	PUD + HPRx	PUD-HPRx	
N	52,114	52,564	52,564	p-value
Age, years (Mean ± SD)	57.61 (± 14.37)	57.35 (± 13.73)	57.52 (± 14.08)	0.0041
Age categories, years (N, %)				
< 35	2,787 (5.35%)	2,838 (5.40%)	2,837 (5.40%)	0.0108
35–44	6,279 (12.05%)	6,465 (12.30%)	6,462 (12.29%)	
45–54	12,762 (24.49%)	13,205 (25.12%)	13,205 (25.12%)	
55–64	13,062 (25.07%)	13,298 (25.30%)	13,300 (25.30%)	
65+	17,213 (33.04%)	16,758 (31.88%)	16,760 (31.88%)	
Gender (N, %)				
Female	29,229 (56.10%)	29,793 (56.68%)	29,792 (56.68%)	0.0922
Male	22,874 (43.90%)	22,771 (43.32%)	22,772 (43.32%)	
Comorbidities (N, %)				
Hypertension	22,958 (44.06%)	23,301 (44.33%)	23,300 (44.33%)	0.6087
Hyperlipidemia	19,739 (37.88%)	20,277 (38.58%)	20,277 (38.58%)	0.0296
Myocardial infarction	957 (1.84%)	834 (1.59%)	856 (1.63%)	0.0035
Congestive heart failure	2,329 (4.47%)	2,238 (4.26%)	2,295 (4.37%)	0.2433
Chronic kidney disease	3,144 (6.03%)	2,610 (4.97%)	2,789 (5.31%)	< .0001
Cancer	3,369 (6.47%)	3,367 (6.41%)	3,360 (6.39%)	0.874
Charlson's Index Score (Mean ± SD)	1.84 (± 1.63)	1.85 (± 1.60)	1.86 (± 1.65)	0.0926
Charlson's Index Categories (N, %)				

Post-PSM-Matching				
0	8,096 (15.54%)	8,072 (15.36%)	8,072 (15.36%)	0.2771
1–2	18,212 (34.95%)	18,200 (34.62%)	18,201 (34.63%)	
3	13,190 (25.32%)	13,248 (25.20%)	13,247 (25.20%)	
≥ 4	12,605 (24.19%)	13,044 (24.82%)	13,044 (24.82%)	
Medication (N, %)				
Antiplatelet agent	6,419 (12.32%)	7,479 (14.23%)	6,346 (12.07%)	< .0001

Next, after multiple regression analysis adjusted for age, gender, comorbidities, CCIS, and medications, we found that the patients with DM who received *H. pylori* eradication therapy had a higher incidence of AD than the general population (aHR of PUD + HPRx, 1.088; 95% confidence interval [CI], 1.011–1.166;  $P < 0.05$ ). However, we found that the risk of AD did not differ significantly in the patients who received *H. pylori* eradication therapy as compared with those who did not in the DM group (aHR, 1.060; 95% CI, 0.983–1.138) (Table 2). Nevertheless, subgroup analysis showed that the risk of AD was significantly higher in the patients who were aged under 65 years and received *H. pylori* eradication therapy as compared with those who did not in the DM group (aHR for younger than 45 years, 1.071; 95% [CI], 1.048–1.094;  $P < 0.05$ ; aHR of age 45–54 years, 1.089; 95% CI, 1.059–1.119;  $P < 0.05$ ; aHR of age 55–64 years, 1.079; 95% CI, 1.020–1.139;  $P < 0.05$ ) (Table 2, Fig. 1). Besides, DM patients who received *H. pylori* eradication therapy had a lower mortality rate. We identified a significantly lower mortality rate in the DM cohorts (aHR of PUD + HRPx, 0.945; 95% CI, 0.918–0.972;  $P < 0.001$ ) (Table 2).

Table 2  
Outcomes of AD among matched cohorts.

	General Population	DM Population		
	PUD-HPRx	PUD + HPRx	PUD-HPRx	P-value
N	52,103	52,564	52,564	
Two-year lag period				
Total follow-up person-years	352,545.79	379,124.83	365,014.85	
AD outcome (N, %)				
AD	3,207 (6.16%)	3,768 (7.17%)	3,503 (6.66%)	< 0.0001
Incidence rate ratio (95%CI)				
AD	ref.	1.088 (1.011,1.166)*	1.027 (0.956,1.098)	
AD	0.974 (0.906,1.042)	1.060 (0.983,1.138)	ref.	
Gender				
Female AD		1.010 (0.929,1.090)	ref.	
Male AD		0.972 (0.893,1.052)	ref.	
Age categories, years				
< 45		1.071 (1.048,1.097)*	ref.	
45–54		1.089 (1.059,1.119)*	ref.	
55–64		1.079 (1.02,1.139)*	ref.	
65+		1.028 (0.865,1.19)	ref.	
Charlson's Index Categories				
0		0.967 (0.899,1.035)	ref.	
1–2		1.010 (0.935,1.085)	ref.	

	General Population	DM Population	
3		0.987 (0.894,1.081)	ref.
≥ 4		0.987 (0.892,1.082)	ref.
All-cause mortality			
Total follow-up person-years	356,949.83	384,726.87	369,454.29
Mortality rate ratio (95%CI)			
Mortality	0.859(0.834,0.885)*	0.945 (0.918,0.972)*	ref.
*P-value < 0.05.			

## Discussion

In this study, we found that the patients with DM who received *H. pylori* eradication therapy had a higher incidence of AD than the general population after a 2-year follow-up period. In addition, the risk of AD was significantly higher in the younger patients who received *H. pylori* eradication therapy as compared with those who did not in the DM group. Despite the higher risk of developing AD, there was a lower mortality rate in the DM patients who received *H. pylori* eradication therapy.

The first important finding of this study is that after 2 years of follow-up, the incidence of AD in patients with DM who received Helicobacter pylori eradication therapy was higher than that of the general population. In addition, compared with the untreated DM group, young patients who received *H. pylori* eradication therapy had a significantly higher risk of AD. Previous reports showed that *H. pylori* can induce systemic inflammation and increase homocysteine levels, contributing to worsening of AD.(17–19) However, the contribution of *H. pylori* to the neuro-inflammatory process in AD has not yet been confirmed or denied.(20) Seiler et al.(21) revealed that elevated levels of ammonia could be taken into account as a factor contributing to manifestations and the progression of AD. Also, existing evidence suggests that the accumulation of ammonia in the brain affects nerve function and may cause some neurological abnormalities.(22, 23) *H. pylori* obtains nutrition from food residues after travel of the meal from the stomach and drop of the acid to a minimum in a blink-like momentum protected by a shield of ammonia and leaving some scattered ammonia after it in the gastric lumen.(24) This scattered ammonia will stimulate the stomach wall to secrete acid to buffer the ammonia.(24, 25) This biological balance between the ammonia of *H. pylori* and gastric acid ensures a residual level of ammonia that could further account for a constant systemic serum ammonia level.(26, 27) However, under the influence of antibiotic treatment, H.pylori may be forced to migrate to the colon,(25, 28) where it will continue to produce

ammonia, causing a large accumulation that is toxic to the brain.(25, 28) One population-based study also found that eradication of *H. pylori* was associated with progression of dementia.(29)

Another important finding of this study was that the DM patients who received *H. pylori* eradication therapy had a lower mortality rate. One possible reason is that eradication of *H. pylori* could lower the incidence of related gastrointestinal tract malignancies.(11, 30) In addition, *H. pylori* may also confer a mortality risk to AD patients through its involvement in a variety of extradigestive vascular conditions, including ischemic heart disease(31, 32) and cerebrovascular disease.(10) Recently, *H. pylori* deoxyribonucleic acid (DNA) was consistently isolated from human carotid atherosclerotic plaques, providing further evidence of the relationship between *H. pylori* infection and atherosclerotic disease.(33) These conditions are the most common causes of death in AD patients.(34) Kountouras et al.(35) also reported that an *H. pylori* eradication regimen may improve the long-term survival rate of AD patients.

## Limitation

There were several limitations of this study. First, the results of tests showing eradication of *H. pylori* were not available. We instead obtained data from patient medical records, and patients documented as undergoing an *H. pylori* eradication regimen for more than 7 days were deemed to have received *H. pylori* treatment, but hard data showing successful *H. pylori* eradication did not exist. Second, although we matched the study cohorts by age, sex, comorbidities, CCIS, and medications, a generally acceptable method, it was not possible to fully account for and correct other potential confounders (e.g., diet, alcohol consumption), thus preventing causal inferences from being drawn from the observed associations. Third, we excluded a general population with PUD that received *H. pylori* eradication treatment, a cohort that consisted of fewer cases and was difficult to match with the other groups, which may have led to potential confounding bias. Finally, as per the general limitations that apply to retrospective data analyses, we were unable to correct data errors such as incorrect diagnoses or errors in data entry, and we were also unable to review patient medical records to double-check the accuracy of the data. Therefore, there may have been some unadjusted data in this cohort study.

In conclusion, the results of this study demonstrated that eradication of *H. pylori* in DM patients resulted in a higher incidence of AD, especially in the younger patients. Nevertheless, there was a lower mortality rate in the patients who received *H. pylori* treatment, even in light of the higher AD prevalence, in the DM group. Further longitudinal study is needed to clarify the interrelated roles of cognition, eradication therapy for *H. pylori* infection, and AD.

## Declarations

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**Authors' contributions:**

All authors participated in the conceptualization of this paper, participated in its writing, and approved the final manuscript.

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The authors declare that they have no competing interests

**Disclosure:**

We have no financial interest in the information contained in the manuscript.

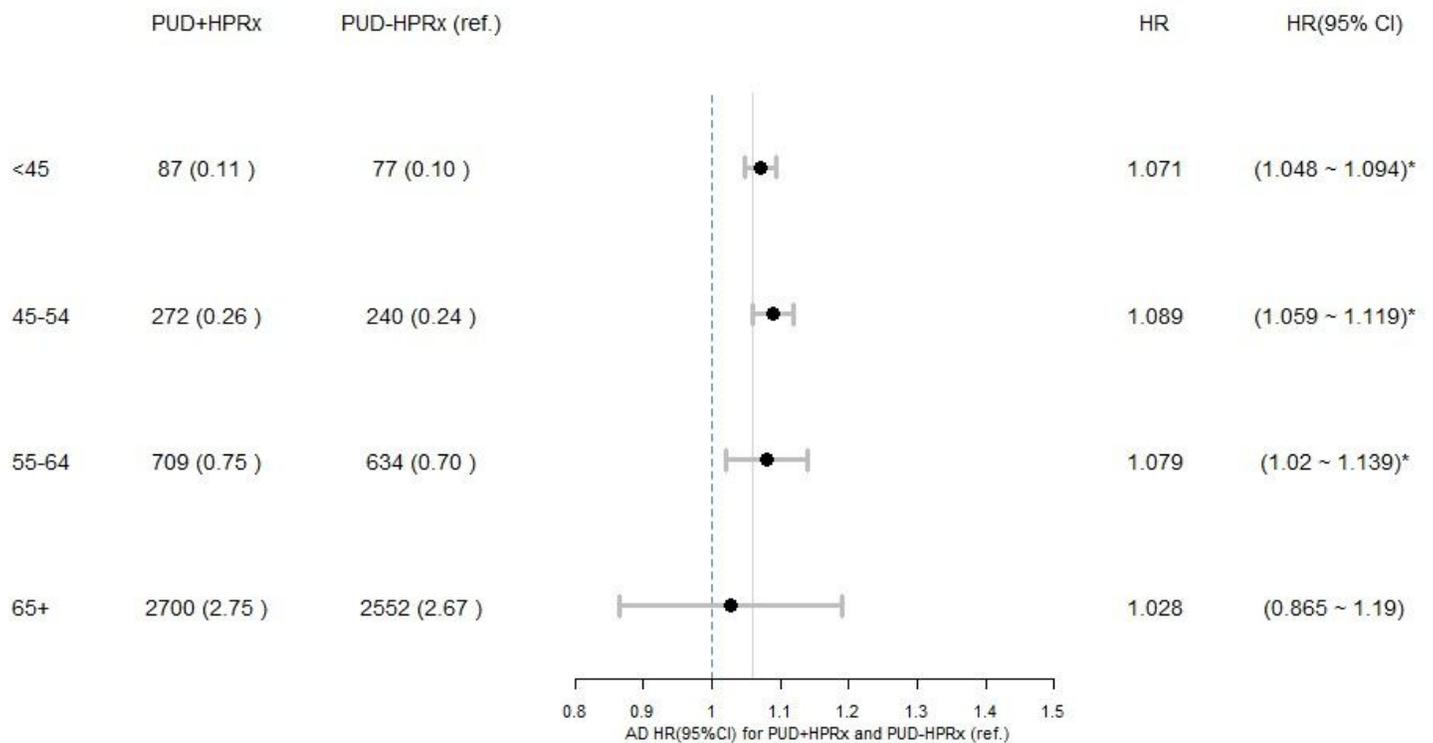
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## Figures



**Figure 1**

AD incidence Forest plot for PUD+HPRx and PUD-HPRx in DM groups. Subgroup analysis showed that the incidence of AD was significantly higher in the patients aged under 65 years who received H. pylori eradication therapy as compared with those who did not in the DM group (aHR for younger than 45 years, 1.071; 95% [CI], 1.048–1.094; P < 0.05; aHR of age 45-54 years, 1.089; 95% CI, 1.059–1.119; P < 0.05; aHR of age 55-64 years, 1.079; 95% CI, 1.020–1.139; P < 0.05).