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# Original papers

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# *Helicobacter pylori* infection increases subsequent ischemic stroke risk: a nationwide population-based retrospective cohort study

W.-S. HUANG[1,2]*, C.-H. TSENG[1,2]*, C.-L. LIN[3], C.-H. TSAI[1,2] and C.-H. KAO[2,4]

*From the [1]Department of Neurology, China Medical University Hospital, [2]Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, [3]Management Office for Health Data, China Medical University Hospital and [4]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan*

*Address correspondence to Dr C.-H. Kao, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2 Yuh-Der Road, Taichung 404, Taiwan. email: d10040@mail.cmuh.org.tw*

**W.-S. Huang and C.-H. Tseng equally contributed to this work.*

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## Summary

**Background and purpose:** The association of *Helicobacter pylori* infection (*HP*-I) with ischemic stroke (IS) incidence has been studied, but conflicting results have been reported. The purpose of this study was to investigate the association between chronic *HP*-I and the risk of acute IS by using data from the Taiwan National Health Insurance Research Database.
**Methods:** We identified17 332 patients with *HP*-I and 69 328 randomly selected age- and gender-matched controls from 1 January 2000 to 31 December 2010. Both cohorts were followed up until the occurrence of IS or until censored. The Cox proportional hazards model was used for assessing the association of *HP*-I with IS.
**Results:** Compared with the control cohort, patients diagnosed with *HP*-I exhibited a higher incidence rate of IS (14.8 vs. 8.45 per 1000 person years) and a hazard ratio (HR) of 1.52 (95% confidence interval [CI] = 1.40–1.65). The HRs for IS were 1.49 (1.37–1.62) in patients diagnosed with *HP*-I who had one admission, increasing to 2.26 (1.71–1.98) for those who had two or more admissions when adjusted for age, sex and comorbidities ($P$ for trend < 0.0001). In addition, we observed a significantly positive association between nonembolic IS and increased admissions ($P$ for trend < 0.0001) but negative association with embolic IS.
**Conclusion:** Chronic *HP*-I is significantly associated with an increased risk of IS, particularly nonembolic IS. Anti-*HP* therapy may be beneficial to IS prevention.

## Introduction

*Helicobacter pylori* (*HP*) is a gram-negative, spiral-shaped microaerophilic bacterium. *HP* may be a lifelong bacterial infection of the gastric mucosa that is primarily acquired during childhood. *HP* infection (*HP*-I) is a widespread infection in humans, and its prevalence is positively correlated with population age.[1–3] The seroprevalence of *HP*-I was

positively observed in ~50% of the world's population, and the results indicated higher numbers of *HP*-I in developing than in developed countries.[4] Large proportions of Asian populations, particularly the Chinese, Japanese, and Korean populations, are infected with *HP*.[2,3]

*HP*-I can cause various diseases, such as chronic gastritis, peptic ulcers and gastric cancer.[1,5] In addition, *HP* has been associated both epidemiologically and pathogenetically with coronary atherosclerosis,[6] but data on the relationship between chronic *HP*-I and ischemic stroke (IS) are conflicting.[7–12]

Stroke is the leading cause of death and disability for both men and women worldwide, and IS is the most common type of stroke.[13–16] Identifying potential risk factors is an effective method for preventing IS. The traditional risk factors for IS do not explain every clinical and epidemiological feature of the disease. The purpose of our study was to assess the relation between chronic *HP*-I and the risk of acute IS by using data recorded from the National Health Insurance Research Database (NHIRD) of Taiwan.

# Materials and Methods

## Data sources

We used inpatient claims data from Taiwan's NHIRD, which were provided by the National Health Research Institutes from 1996 to 2010. The Taiwanese government launched the National Health Insurance (NHI) program in March 1995 and ~99% of the 23.74 million people in Taiwan were covered by the end of 2009.[17] The NHIRD is derived from the NHI program established by the Bureau of National Health Insurance. The *International Classification of Diseases*, 9th Revision, *Clinical Modification* (ICD-9-CM) was used to determine health status. In addition, this study was approved by the Institutional Review Board of China Medical University in Central Taiwan (CMU-REC-101-012).

## Study patients

We identified 17 332 patients with newly diagnosed *HP*-I (ICD-9-CM code: 041.86) in the inpatient claims data of the NHIRD in 2000–2010 as the *HP*-I cohort, and the *HP*-I diagnosis date was used as the index date. We excluded patients with history of stroke before the index date and those for which information on age or gender was missing. Four study patients in the comparison cohort for every patient diagnosed with *HP*-I were randomly selected from the insured people without a history of *HP*-I or stroke, and then frequency-matched for age (±5 years), gender and index year. The *HP*-I cohort comprised 17 332 patients and the control cohort comprised 69 328 patients.

## Measurement

The demographic factors in this study were gender and age. Age was categorized into four groups: ⩽35, 36–50, 51–65, and >65 years. We considered diabetes (ICD-9-CM code: 250), hypertension (ICD-9-CM codes: 401-405), hyperlipidemia (ICD-9-CM code: 272), congestive heart failure (CHF; ICD-9-CM codes: 398.91, 402, 404.01, 404.03, 404.10, 404.11, 404.13, 404.91, 404.93 and 428), coronary artery disease (CAD; ICD-9-CM codes: 410-414), atrial fibrillation (AF; ICD-9-CM code: 427.31), chronic obstructive pulmonary disease (COPD; ICD-9-CM code:491, 492 and 496) and asthma (ICD-9-CM code:493, 494) to be comorbidities that were potential confounders for the association of *HP*-I with IS.

The endpoints were the first diagnosis date of IS (ICD-9-CM codes: 433–438), death and loss to follow-up, and 31 December 2010. The IS cases were grouped into embolic IS (ICD-9-CM code: 434.11) and nonembolic IS (ICD-9-CM codes: 433–438; except embolic IS, ICD-9-CM 434.11).

## Statistical analysis

Proportions were calculated for the study patients for categorical variables including gender, age and comorbidity. The *t* test was used for the continuous variables and the chi-square test was used for the categorical variables. The incidence rates of IS were calculated by dividing the number of newly diagnosed cases by the number of person years. The number of person years was calculated by summing the number of years from the entry date to the endpoint determined according to the incidence of stroke, death, loss to follow-up and the end of follow-up. We used the Kaplan–Meier (K-M) estimation method to depict the survival curves of nonembolic IS for patients diagnosed with and those not diagnosed with *HP*-I. We then used the log-rank test to evaluate whether the K-M curves differed. The Cox proportional hazard regression and 95% confidence interval (CI) were used to estimate the independent effect of *HP*-I by adjusting for gender, sex and comorbidity. Statistical significance was considered to be $P < 0.05$ in all analyses. SAS version 9.3 was used for the statistical analyses.

## Results

Table 1 shows the baseline demographic factors and comorbidity of the study patients according to *HP*-I status. The distributions of gender and age were the same for both cohorts. Compared with the participants without *HP*-I, patients with *HP*-I exhibited a higher prevalence of diabetes (17.6% vs. 11.7%), hypertension (26.5% vs. 10.2%), hyperlipidemia (8.7% vs. 2.4%), CHF (11.0% vs. 4.3%), CAD (12.0% vs. 5.3%), AF (1.8% vs. 0.9%), COPD (7.22% vs. 2.78%) and asthma (5.19% vs. 1.86%).

**Table 1** Demographic characteristics and comorbidity in patient with and without *HP*-I

| Variable | *HP*-I | | *P*-value |
|---|---|---|---|
| | No *N*=69,328 | Yes *N*=17,332 | |
| Sex | *N* (%) | *N* (%) | |
| Female | 26016 (37.5) | 6504 (37.5) | 0.99 |
| Male | 43312 (62.5) | 10828 (62.5) | |
| Age, mean (SD) | 57.0 (16.9) | 57.4 (16.8) | 0.006[#] |
| Stratified age | | | |
| ⩽35 | 7420 (10.7) | 1855 (10.7) | 0.99 |
| 36–50 | 16608 (24.0) | 4152 (24.0) | |
| 51–65 | 20256 (29.2) | 5064 (29.2) | |
| 65+ | 25044 (36.1) | 6261 (36.1) | |
| Comorbidity | | | |
| Diabetes | 8108 (11.7) | 3046 (17.6) | <0.0001 |
| Hypertension | 7063 (10.2) | 4598 (26.5) | <0.0001 |
| Hyperlipidemia | 1680 (2.42) | 1507 (8.69) | <0.0001 |
| CHF | 2891 (4.31) | 1909 (11.0) | <0.0001 |
| CAD | 3682 (5.31) | 2078 (12.0) | <0.0001 |
| AF | 651 (0.94) | 316 (1.82) | <0.0001 |
| COPD | 1929 (2.78) | 1251 (7.22) | <0.0001 |
| Asthma | 1291 (1.86) | 899 (5.19) | <0.0001 |

Chi-square test; [#]Two-sample *T*-test.

Table 2 shows the incidence rates and HRs for IS according to *HP*-I status. Overall, the incidence of IS was higher in the *HP*-I cohort than in the control cohort (14.8 vs. 8.45 per 1000 person years), with an HR of 1.52 (95% CI = 1.40–1.65) when adjusting for age, gender and comorbidity. Furthermore, patients with *HP*-I were 0.93 times more likely to develop embolic IS (95% CI = 0.45–1.91) and were 1.53 times more likely to develop nonembolic IS (95% CI = 1.41–1.67) than the control patients after adjusting for age, sex and comorbidities. The sex-specific *HP*-I cohort to non-*HP*-I cohort relative risk of IS were significant for both men (HR = 1.45, 95% CI = 1.31–1.61) and women (adjusted HR = 1.65, 95% CI = 1.44–1.89).

Table 3 shows the unadjusted and multivariate adjusted HRs for nonembolic IS according to *HP*-I status and stratified according to the number of admissions. Compared with patients without *HP*-I, the HRs for IS were 1.49 (95% CI = 1.37–1.62) in *HP*-infected patients who had one admission, increasing to 2.26 (95% CI = 1.71–2.98) for those who had two or more admissions when adjusted for age, sex and comorbidities. In addition, we observed a significantly positive association between nonembolic IS and increased admissions (*P* for trend < 0.0001).

Table 4 shows the unadjusted and multivariate adjusted HRs for nonembolic IS associated with *HP*-I and covariates. In the multivariate analysis, the HRs for nonembolic IS were higher in patients aged 36–50 years, 51–65 years and >65 years than in those aged ⩽35 years (HR = 4.27, 95% CI = 2.47–7.39 for those aged 36–50 years; HR = 11.3, 95% CI = 6.62–19.2 for those aged 51–65 years;

**Table 2** The risk of IS compared to study subjects without *HP*-I in Cox proportional hazard regression

| Variables | *HP*-I | | | | Compared to non-HPI | |
|---|---|---|---|---|---|---|
| | No | | Yes | | | |
| | Stroke Event | Stroke Rate[#] | Stroke Event | Stroke Rate[#] | Crude HR* (95% CI) | Adjusted HR[†] (95% CI) |
| All | 2103 | 8.45 | 837 | 14.8 | 1.76(1.68, 1.83)*** | 1.52(1.40, 1.65)*** |
| Subtype | | | | | | |
| Embolic IS | 35 | 0.14 | 10 | 0.18 | 1.26(1.18, 1.35)*** | 0.93(0.45, 1.91) |
| Nonembolic IS | 2068 | 8.31 | 827 | 14.7 | 1.76(1.69, 1.84)*** | 1.53(1.41, 1.67)*** |
| Sex | | | | | | |
| Male | 1381 | 8.75 | 506 | 14.2 | 1.63(1.54, 1.72)*** | 1.45(1.31, 1.61)*** |
| Female | 722 | 7.94 | 331 | 15.9 | 2.00(1.87, 2.14)*** | 1.65(1.44, 1.89)*** |

Rate[#], incidence rate per 1000 person-years; crude HR*, relative HR; adjusted HR[†], multivariable analysis including age, sex and comorbidities of diabetes, hypertension, hyperlipidemia, CHF, CAD, AF, COPD and asthma; *$P<0.05$, **$P<0.01$, ***$P<0.001$.

**Table 3** Cox model estimated HRs of stroke in relation to number of admissions visits due to *HP*-I

| | Stroke | Compared to non-HPI | |
|---|---|---|---|
| | No. of Cases | Crude HR* (95% CI) | Adjusted HR† (95% CI) |
| Ischemic stoke | | | |
| Number of admissions | | | |
| 0 (Noninfected *H. pylori*) | 2103 | 1 (Reference) | 1 (Reference) |
| 1 | 785 | 1.72 (1.58, 1.86)*** | 1.49 (1.37, 1.62)*** |
| ⩾2 | 52 | 2.65 (2.01, 3.49)*** | 2.26 (1.71, 2.98)*** |
| *P* for trend | | | *P*<0.0001 |
| Embolic IS | | | |
| Number of admissions | | | |
| 0 (Noninfected *H. pylori*) | 35 | 1 (Reference) | 1 (Reference) |
| 1 | 10 | 1.30(0.65, 2.63) | 0.97(0.47, 2.00) |
| ⩾2 | 0 | | |
| *P* for trend | | | *P* =0.72 |
| Nonembolic IS | | | |
| Number of admissions | | | |
| 0 (Noninfected *H. pylori*) | 2068 | 1 (Reference) | 1 (Reference) |
| 1 | 775 | 1.72 (1.59, 1.87)*** | 1.50 (1.38, 1.64)*** |
| ⩾2 | 52 | 2.69 (2.05, 3.55)*** | 2.31 (1.75, 3.05)*** |
| *P* for trend | | | *P*<0.0001 |

Crude HR*, relative HR; adjusted HRs†, adjusted for age, sex and comorbidities of diabetes, hypertension, hyperlipidemia, CHF, CAD, AF, COPD and asthma; *$P<0.05$, **$P<0.01$, ***$P<0.001$.

**Table 4** Cox model with HRs and 95% CIs of non-embolic IS associated with *HP*-I and covariates

| Variable | Crude* | | Adjusted† | |
|---|---|---|---|---|
| | HR | (95% CI) | HR | (95% CI) |
| Stratify age | | | | |
| ⩽35 | 1.00 | (Reference) | 1.00 | (Reference) |
| 36–50 | 4.45 | (2.57, 7.71)*** | 4.27 | (2.47, 7.39)*** |
| 51–65 | 13.0 | (7.66, 22.2)*** | 11.3 | (6.62, 19.2)*** |
| 65+ | 52.0 | (30.8, 87.9)*** | 37.4 | (22.1, 63.4)*** |
| Sex | | | | |
| Male | 1.04 | (0.97, 1.13) | | |
| Female | 1.00 | (Reference) | 1.00 | (Reference) |
| Baseline comorbidities (yes vs. no) | | | | |
| *HP*-I | 1.76 | (1.63, 1.91)*** | 1.48 | (1.37, 1.61)*** |
| Diabetes | 2.82 | (2.59, 3.06)*** | 1.54 | (1.41, 1.68)*** |
| Hypertension | 4.18 | (3.88, 4.52)*** | 1.63 | (1.48, 1.80)*** |
| Hyperlipidemia | 2.33 | (2.02, 2.68)*** | 1.03 | (0.89, 1.20) |
| CHF | 4.33 | (3.93, 4.77)*** | 1.20 | (1.06, 1.35)** |
| CAD | 3.43 | (3.12, 3.78)*** | 1.15 | (1.02, 1.28)* |
| AF | 4.33 | (3.54, 5.30)*** | 1.36 | (1.10, 1.67)** |
| COPD | 3.90 | (3.46, 4.39)*** | 1.44 | (1.26, 1.64)*** |
| Asthma | 2.74 | (2.34, 3.21)*** | 1.05 | (0.89, 1.24) |

Crude HR*, relative HR; †adjusted HR, multivariable analysis including for stratify age, and comorbidities of diabetes, hypertension, hyperlipidemia, CHF, CAD, AF, COPD and asthma. *$P<0.05$, **$P<0.01$, ***$P<0.001$.

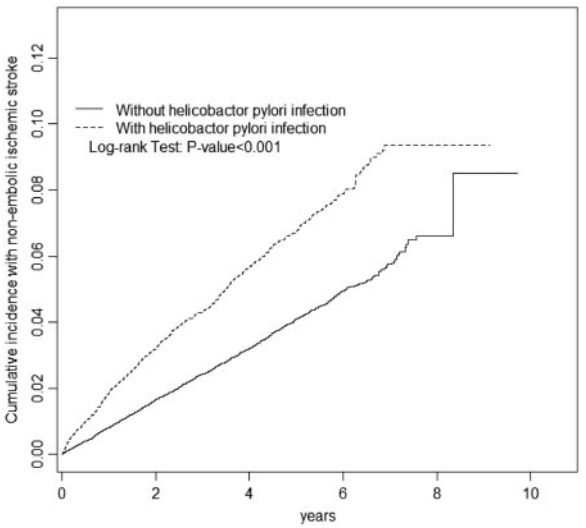


**Figure 1.** Cummulative incidence of nonembolic IS in patients with and without *HP*-I.

HR = 37.4, 95% CI = 22.1–63.4 for those aged > 65 years). Significant associations were observed between nonembolic IS and *HP*-I, diabetes, hypertension, CHF, CAD, AF and COPD, and the respective adjusted HRs were 1.54 (95% CI = 1.41–1.68), 1.63 (95% CI = 1.48–1.80), 1.20 (95% CI = 1.06–1.35), 1.15 (95% CI = 1.02–1.28), 1.36 (95% CI = 1.10–1.67) and 1.44 (95% CI = 1.26–1.64).

The cumulative incidence curves for nonembolic IS according to *HP*-I status are illustrated in Figure 1. We used the log-rank test to examine the cumulative incidence of nonembolic IS between the *HP*-I cohort and the control cohort. We determined that the cumulative incidence of nonembolic IS was significantly higher in patients with *HP*-I than in patients without *HP*-I ($P < 0.001$).

## Discussion

Compared with the control cohort, patients diagnosed with *HP*-I exhibited a higher incidence rate of IS (14.8 vs. 8.45 per 1000 person years) and a hazard ratio (HR) of 1.52 (95% CI = 1.40–1.65, Table 2). The HRs for IS were 1.49 (1.37–1.62) in patients diagnosed with *HP*-I who had one admission, increasing to 2.26 (1.71–1.98) for those who had two or more admissions when adjusted for age, sex and comorbidities ($P$ for trend < 0.0001). In addition, we observed a significantly positive association between nonembolic IS and increased admissions ($P$ for trend < 0.0001, Table 3) but negative association with embolic IS.

The association of *HP*-I with the risk of IS has been widely studied since 1998[7]; however, it remains undetermined because conflicting results have been reported. A case–control study involving 145 cases and 160 controls by Heuschmann *et al.*[11] indicated that *HP* seropositivity is not associated with the risk of IS. However, after subgroup analyses, they determined that *HP* seropositivity is associated with a 3.31-fold risk of IS caused by small artery occlusion and a 0.21-fold risk of cardioembolic stroke. Similarly, a recent case–control study involving 150 Chinese patients and 131 controls indicated that *HP* seropositivity is not associated with the risk of IS and its subtypes.[12] Nevertheless, several studies have reported that chronic *HP*-I is positively associated with the risk of IS.[9–10,18,19] A case–control study involving 62 acute IS and 143 healthy controls by Sawayama *et al.*[9] suggested that *HP* seropositivity is significantly associated with an increased risk of IS, particularly that caused by small artery occlusion. A meta-analysis by Wang *et al.*[10] revealed that chronic *HP*-I is significantly associated with an increased risk of IS, particularly noncardioembolic IS. The positive association was also reported by two other studies.[18,19] The presence of specific *HP* DNA in human atherosclerotic plaques detected using a PCR were also reported.[20,21]

The mechanisms by which chronic *HP*-I increases the risk of IS are still not completely understood. Previous animal and epidemiological studies have indicated that chronic inflammation and autoimmune processes caused by chronic *HP*-I promote atherosclerosis and the incidence of atherosclerosis-related diseases, such as stroke and CAD.[22–24] Most inflammatory reactions have been attributed to cytokines, such as interleukins, which are responsible for the upregulation of adhesion molecules, recruitment and activation of leucocytes, promotion of leukocyte–endothelium interaction and conversion of the local endothelium to a prothrombotic state.[25] A higher value of plasma fibrinogen concentration was observed in *HP*-infected Cag A-positive stroke patients than in *HP*-negative controls, suggesting that plasma fibrinogen may play a role in IS.[8,26–28] Fibrinogen is an acute phase protein, and its level strongly corresponds with the process of atherogenesis. Fibrinogen seems to participate directly in the earlier phases of atherosclerotic plaque formation and arterial thrombosis. Moreover, fibrinogen is a vital component of acute and chronic inflammatory responses.[29,30]

The use of a nationwide population-based dataset that provides a sufficient sample size and statistical power to explore the link between *HP* and IS is a particular strength of this study. In addition, the patients in our study displayed a wide range of demographic characteristics, which enabled stratified analyses to be performed according to sex, age and comorbidities. Nevertheless, this study has limitations. First, the principal concern is the degree of

accuracy in coding the *HP*-I and IS. Second, detailed information, such as data on smoking habits, socioeconomic status, family history and Cag-A strains are not available in the NHIRD. All of these variables are possible risk factors for IS. To minimize confounding from smoking habit factors, we have included in the data analysis with smoking-related disorders such as CAD, COPD, and asthma for adjustment. The overall measured adjusted IS risk associated with changed little from the crude risk. In addition, <5% women are smoker in Taiwan, the IS risk associated with *HP*-I was greater for women than for men. Third, the database does not include body mass index information, so we excluded people with triple H (hypertension, hyperlipidemia, hyperglycemia (DM)) to reduce the influence of obesity as Triple H and obesity is highly correlated. We acknowledge that this is a limitation of the present study. Fourth, evidence derived from a cohort study is generally of a lower quality than that derived from randomized control trials. A cohort study design is subject to numerous biases regarding confounding adjustment. Despite our meticulous study design using adequate controls for confounding factors, bias may have occurred in unmeasured and unknown confounders.

## Conclusion

In summary, this study indicated that chronic *HP*-I is significantly associated with an increased risk of IS, particularly nonembolic IS. Anti-*HP* therapy may have a beneficial influence on IS prevention. An additional ideal prospective trial that examines the association of *HP*-I with IS, involving antibacterial and antiinflammatory therapy, may provide definitive proof.

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