# Association between *Helicobacter pylori* Infection and Stroke: A Meta-analysis of Prospective Observational Studies

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*Background:* Some studies have suggested an association between *Helicobacter pylori* infection and the risk of stroke, but the relationship remains controversial. The aim of this study was to obtain a more comprehensive estimate of *H. pylori* on the risk of stroke by performing a meta-analysis. *Methods:* A computerized search of PubMed, EMBASE, and the Cochrane library (including CENTRAL) up to February 2014 was performed to identify eligible studies. Prospective studies reported that a multivariate-adjusted estimate for the association between *H. pylori* and stroke were included. A random-effects model was used to calculate the overall combined risk. *Results:* Ten prospective observational studies (6 cohort studies, 4 nested case–control, or case–cohort studies within cohort studies) were included in the meta-analysis. The overall combined odds ratio for *H.* infection and stroke was .96 (95% confidence interval, .78-1.14). Similar results were yielded in patients with cytotoxin-associated gene-A seropositive strains. The combined estimates were robust across sensitivity analyses and had no observed publication bias. *Conclusions:* In conclusion, our formal meta-analysis indicated no strong association between *H. pylori* infection and stroke, neither in those with cytotoxin-associated gene-A–positive infection. We believe that future epidemiologic studies of *H. pylori* and stroke are unlikely to be fruitful. **Key Words:** *Helicobacter pylori*—stroke—prospective study—meta-analysis.


## Introduction

Stroke is the second leading cause of death and serious disability worldwide.[1] It causes a significant public health burden. According to estimates, about 795,000 Americans experience a new or recurrent stroke annually—on average, 1 stroke for every 40 individuals.[2] The conventional risk factors, which manifest as hypertension, diabetes mellitus, smoking, obesity, serum lipids, and family history, do not fully account for all the cases, especially young subjects, and often do not have any of these factors.[3] It is, therefore, important to identify additional, treatable causes of stroke that could lead to more effective prevention. There has been increasing evidence that, in addition to established risk factors, markers of inflammation and chronic infectious diseases, including *Helicobacter pylori* infection, may be linked to stroke and other ischemic disease.[4-6]

*Helicobacter pylori* is a gram-negative bacterium infecting 50% of the world's population.[7] However, in some

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N.-H.L. and M.Y. conceived and designed the experiments. M.Y., Z.Y., and C.X. analyzed the data. M.Y. and N.-H.L. wrote the article. M.Y., Y.-B.Z., and Z.Y. performed the literature search and the data extraction. All authors saw and approved the final version of the manuscript.

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regions and countries of the world, more than 80% of the populations are infected.[8] *Helicobacter pylori* infection results in chronic gastritis, ulcers, stomach cancer, and many extra-gastrointestinal conditions. It has been suggested that the production of excessive amounts of pro-inflammatory factors and cross-mimicry between *H. pylori* and host antigens may contribute to the development of gastric mucosal damage and extra-digestive manifestations associated with *H. pylori* infection.[9-11] During the past decades, many epidemiologic studies have focused on the association between *H. pylori* infection and the risk of stroke.[12-14] However, the role of *H. pylori* in stroke is still controversial.[15-17]

Previous meta-analyses have shown a significantly increased risk for stroke in *H. pylori*–infected individuals, especially in those infected with cytotoxin-associated gene A (CagA)–positive strains.[18,19] But the data from these included by these meta-analyses were limited to case–control studies, in which selective bias and insufficient cofounding from risk factors remained an alternative explanation for significant association between *H. pylori* and stroke. Additionally, several recent population-based cohort studies yielded contrasting results.[20-22] To obtain a more comprehensive estimate of the putative influence of the *H. pylori* on stroke, we conducted a meta-analysis of prospective studies to determine the association between *H. pylori* and stroke.

## Materials and Methods

### *Literature Search*

A systematic search of PubMed, EMBASE, and the Cochrane library (including CENTRAL) was performed to identify potentially relevant publications from the date of database origination through February 2014. The following key words were used in our search strategies: "helicobacter pylori," "*H. pylori*," "helicobacter," or "hp" and "stroke," "brain ischemic," "transient brain ischemia," "cerebral arterial accident," "non-ischemic stroke," "ischemic stroke," "cerebrovascular accident," "intracranial artery disease," or "cardiovascular disease." The search was restricted to human studies. No language restrictions were set. In addition, the reference lists of all retrieved articles, and in reviews and abstracts from recent conferences, were manually searched. When the same or similar patient cohort was included in several publications, only the most recent or informative report was selected for analysis.

### *Study Selection*

Studies were initially selected based on their titles and abstracts. Two reviewers (M.Y. and Y.-B.Z) independently screened all abstracts to determine whether the studies met the inclusion criteria. Differences were resolved by a third investigator (Z.Y.). Studies were considered eligible if they met the following criteria: (1) the design was a prospective study; (2) the study population was patients with *H. pylori* infection; (3) reported quantitative estimates of the multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for fatal or nonfatal stroke associated with *H. pylori*; hazard ratio (HR)/relative risk were considered equivalent to OR. The prospective nested case–control studies or case–cohort studies within cohort studies were also included for the meta-analysis because of their advantages comparable with cohort studies in verifying a causal relationship. Studies were excluded if (1) the study design was retrospective, (2) unadjusted estimates were reported, and (3) studied the association in patients with diabetes, nephropathy, etc.

### *Data Abstraction and Quality Assessment*

To ensure homogeneity in data gathering and entry, the data extraction was conducted by 2 experienced investigators working independently (M.Y. and Y.-B.Z). A third investigator (Z.Y.) was called on to resolve any differences, and complete consensus was reached for all the main variables to be assessed in the analysis. Data were recorded as follows: the first author's last name (year of publication), country, study design, setting, size of the cohort, mean age, follow-up time, assessment of *H. pylori* and stroke, number of cases, cofounding covariates, and results. The Newcastle–Ottawa Scale was used to assess the methodologic quality of studies.[23] In this scale, observational studies were scored across 3 categories: selection (4 questions) and comparability (2 questions) of study groups and ascertainment of the outcome of interest (3 questions). An item scored 1 if the study met the demands; otherwise, a score of 0 was given for that item. The final score ranged from 0 to 9 for each study (recorded in Table 1), with higher scores indicating better methodology. We defined studies of high or low quality based on the median overall score among all studies.

### *Statistical Analyses*

OR with 95% CI were used as a common measure of the association between *H. pylori* and risk of stroke across studies. Taking both within-study and between-study variabilities into account, we used a random-effects model to combine outcome data (expressed as ORs and 95% CIs).[24] Heterogeneity was assessed by the $I^2$ statistic, a quantitative measure of inconsistency across studies.[25] To explore possible explanations for heterogeneity, we conducted stratified analyses by CagA situation, study design, setting, pathogen species studied, and study quality. We also assessed the influence of individual studies on the combined risk estimate by sequentially excluding 1 study in each turn to test the robustness of the main results. Potential publication bias was examined by Begg test and Egger test.[26,27] A trim and fill analysis was performed to identify and correct asymmetry of the