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Association Between *Helicobacter pylori* and Mortality in the NHANES III Study

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Abstract

Objective—Persistent colonization by *Helicobacter pylori*, and especially by *cagA*-positive strains, has been related to several health outcomes with effects in opposite directions. Thus, it is important to evaluate its influence on both total and category-specific mortality.

Design—We conducted prospective cohort analyses in a nationally representative sample of 9895 participants enrolled in the National Health and Nutrition Examination Survey III (NHANES III) to assess the association of *H. pylori* status with all-cause and cause-specific mortality. Analyses for the association of *H. pylori cagA* positivity with mortality were conducted in 7,384 subjects with data on *H. pylori cagA* status.

Results—In older individuals (> 40.6 years of age), *H. pylori* was not associated with all-cause mortality (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.84–1.18). There was an inverse association of *H. pylori* status with stroke mortality (HR, 0.67; 95% CI, 0.44–1.08), and the inverse association was stronger for *H. pylori cagA* positivity, with the HR of 0.45 (95% CI, 0.27–0.75). *H. pylori* also was strongly positively related to gastric cancer mortality. After we adjusted p-values using the Benjamini–Hochberg false discovery rate (FDR) method to account for multiple comparisons, these associations remained, and *H. pylori* status was not related to other outcomes..

Conclusion—Our findings suggest that *H. pylori* has a mixed role in human health, but is not a major risk factor for all-cause mortality.

Keywords

Epidemiology; Cohort studies; Mortality; Cardiovascular disease; *Helicobacter pylori*

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INTRODUCTION

The gastric bacterium *Helicobacter pylori* has long been present in humans.[1] In the 30 years since the discovery of *H. pylori* in the human stomach, there has been substantial evidence linking gastric colonization of *H. pylori* to increased risks of gastric adenocarcinoma,[2–3] peptic ulcer disease,[4] and lymphoma.[5] In recent decades, *H. pylori* acquisition in industrialized countries has been diminishing with each succeeding generation,[6] and this birth cohort phenomenon parallels a decreasing incidence of gastric cancer[7] and an increasing incidence of esophageal adenocarcinoma and related diseases (GE-Junction adenocarcinomas). Several studies suggest an inverse association between *H. pylori* colonization and risk of GE-Junction adenocarcinomas.[8–11] In addition, *H. pylori* colonization has been linked with reduced risks of asthma and allergy,[12–13] and the risks of cardiovascular diseases[14–17] and lung cancer[18–23] are uncertain, although studies vary in size and design. Since *H. pylori* has been related to risks of a variety of health outcomes, it is important to evaluate its influence on both total mortality and category-specific mortality.

H. pylori is acquired almost exclusively in childhood and usually persists for life unless antimicrobial therapy is given.[24–25] Antibodies to *H. pylori* measured in serum are considered as valid measures for long-term colonization.[26–29] When present, *H. pylori* is the dominant species colonizing the human stomach,[30–31] and is intimately linked to gastric physiology,[32] especially the *cagA*-positive strains that inject *H. pylori* products into epithelial cells.[33] Antibody responses to the CagA protein permit detection of such *cag*-positive strains,[34] which are more interactive with host cells than are *cag*-negative strains,[21, 32] and are associated with higher risk for gastric cancer [35] and peptic ulcer disease, lower risk of esophageal reflux and sequelae [8–9, 36–37], as well as lower risk of childhood-onset asthma[12.8–10, 12–13, 36–37] However, few studies have evaluated the association of *H. pylori cag* positivity with all-cause and cause-specific mortality in healthy individuals.

We conducted prospective cohort analyses in a nationally representative sample of 9,895 participants in National Health and Nutrition Examination Survey III (NHANES III), with status of *H. pylori* colonization including status of *cagA* strains measured at the time of enrollment in 1988–1991 and mortality data with follow-up of nearly 20 years. The goal of our study was to examine the prospective relationship of *H. pylori* colonization with all-cause and cause-specific mortality, focusing on health outcomes that have been previously related to *H. pylori*.

MATERIAL AND METHODS

Study population

NHANES III, the seventh health examination survey performed in the United States beginning in 1960,[38] was conducted from October 1988 through October 1994 in two phases, each of which comprised a national probability sample. In NHANES III, 39695 persons were studied; of those, 17464 were sampled at the first phase. The first phase was conducted from October 18, 1988, through October 24, 1991, at 44 locations. All interviewed persons were invited to the mobile examination center for a medical examination. The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention. All participants gave written informed consent.

H. pylori status

Antibodies to *H. pylori* were measured in 1993 on 6–19 year old examinees from phase 1 (1988–1991) of the survey using an enzyme-linked immunoassay (ELISA) (Pylori Stat, Whittaker Bioproducts, Walkersville, MD) on surplus serum samples.[39] Examinees 20 years

and older from phase 1 were tested for *H. pylori* IgG antibodies in 1996 using the *H. pylori* IgG ELISA (Wampole Laboratories, Cranbury, NJ).[40] For examinees 20 years and older, in addition to determining whether *H. pylori* IgG was present, anti-CagA IgG also was measured on surplus sera, using a method developed and standardized by Vanderbilt University, as described.[34] As numerous tests were conducted before the testing, *H. pylori* status surplus serum was not available from all of the participants. Of the 13,714 individuals aged 6 and above enrolled in Phase I, 10,168 have data on *H. pylori* status, of which 9,966 tested positive or negative, and 202 had equivocal results. Of the 9,488 individuals aged 20 and above enrolled in Phase I, 7,384 had data on *H. pylori cagA* status. All data collected for the NHANES are kept in strict confidence. Results of some tests, which did not include serological testing of *H. pylori* status, had been communicated to the participants [41]. All three tests used the exact same methodology which was developed in the laboratory of one of the authors (MJB) in the 1980s[42].

Participants aged 6 and older with data on *H. pylori* IgG antibodies were classified as *H. pylori*-positive or *H. pylori*-negative. For participants 20 years and older, on the basis of *H. pylori* and *cagA* results, participants were classified into three groups: *H. pylori*-positive and *cagA*-positive, *H. pylori*-positive and *cagA*-negative, and both *H. pylori* and *cagA* negative, as described.[43] The *H. pylori*-positive and *cagA*-positive group included all persons with a positive *cagA* assay, regardless of the results of the *H. pylori* assay, based on the utility of the CagA antigen to detect true-positive responses in culture-positive persons in the face of negative or equivocal values in the *H. pylori* serologic assay.[44] By definition, all persons in the *H. pylori*-negative group had negative CagA assays.

Among individuals aged 6 years and above who were included in phase I of the NHANES III, 9,966 subjects were found either clearly positive or clearly negative for *H. pylori*. We excluded 68 adults > 17 years old with missing BMI and 3 participants not eligible for mortality follow-up (in the restricted data only). The final study population for association between *H. pylori* and mortality included 9895 subjects, over 147796 person-years of observation. Among participants ≥ 20 years old, *cagA* was tested for 7384 subjects. We excluded 28 adults with missing BMI and 3 participants not eligible for mortality follow-up. The final study population for association between *cagA* positivity and mortality included 7,354 subjects, over 105930 person-years of observation.

Mortality in NHANES III

The updated NHANES III Linked Mortality Restricted-use File was used for the present study. Compared with public-use linked mortality files, the restricted-use file includes detailed mortality information for all eligible survey participants including children, as well as more precise and detailed age and follow-up information critical for age-specific analyses[45]. The data provided mortality follow-up data from the date of NHANES III survey participation (1988–1994) through December 31, 2006.[46] Vital status and cause of death assignment were based on probabilistic matching of NHANES III with the National Death Index (NDI) death certificate records. Cause of death was determined based on the underlying cause listed on the death certificates. The linking of NHANES III and NDI records was conducted by probabilistic matching, similar to the standard methodology offered by the NDI. Details have been presented elsewhere[47]. Briefly, National Center for Health Statistics (NCHS) conducted a new calibration study to establish the cut-off scores for determining whether an NDI match is considered a true match or a false match using the information on social security number, name, birth date, sex, race, state of residence and birth, and marital status. NCHS reviewed a subset of death certificates to verify whether the NHANES III and NDI record match was correct. Of the selected 2544 death certificates that were reviewed, 2521 were considered “true” matches by the probabilistic matching process (assumed deceased), and 23 were considered alive. Among the 2,521 assigned decedents,

98.8% were confirmed deceased after death certificate review[47]. Among the 23 persons assumed to be alive, 3 were found to be deceased[47]. We used the *International Classification of Diseases, Ninth Revision* (*ICD-9*) to classify deaths that occurred from 1988 through 1998 and the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*) for deaths that occurred from 1999 through 2006 (eTable 1). Data collection for NHANES III was approved by the NCHS Research Ethics Review Board. Analysis of deidentified data from the survey is exempt from the federal regulations for the protection of human research participants. Analysis of restricted data through the NCHS Research Data Center also has been approved by the NCHS Ethics Review Board.

Statistical analyses

We used Cox proportional regression models to estimate hazard ratios for all-cause and cause-specific mortality comparing subjects who were *H. pylori*-positive, *H. pylori*-positive/*cagA*-positive, *H. pylori*-positive/*cagA*-negative, with persons of *H. pylori*-negative status. We selected diseases that have been *a priori* associated with *H. pylori* in the literature; no other outcomes were examined. The assumption of proportional hazards was examined by testing the cross-product terms between covariate variables and log function of survival time, and P values for all the terms were >0.10. Analyses comparing *H. pylori*-positive with *H. pylori*-negative were conducted in participants aged 6 years or older, using the data on *H. pylori* status. Analyses comparing subjects who were *H. pylori*-positive/*cagA*-positive or *H. pylori*-positive/*cagA*-negative with *H. pylori*-negative subjects were conducted in participants ≥ 20 years old. Potential confounding variables included sex, race-ethnicity, age, smoking status (for subjects > 17 years old), body mass index (for subjects > 17 years old), and educational attainment. Additional adjustment for health insurance status, income, poverty/income ratio, and history of hypertension and diabetes also was conducted. Multivariate analyses were not conducted for rare outcomes to avoid over-specification of the models. Sensitivity analyses were conducted excluding deaths in the first 5 years of follow-up.

Since most (94%) of the deaths occurred after the age of 40 years in the NHANES III, we focused analyses in older individuals (> 40.6 years, which was the median age of the *H. pylori*-negative subjects in the population). Analyses also were conducted in the overall and younger study populations separately. The number of younger subjects who died below age 40.6 from gastrointestinal cancers was already limited (five persons) and therefore we conducted subgroup analyses only for older subjects. All analyses included sample weights that account for the unequal probabilities of selection and nonresponse in the NHANES III, and variance calculations incorporated the sample weights that account for the complex sample design, as specified in prior NHANES publications [48] and similar to studies using mortality data from NHANES III [49–51]. All significance tests were two-sided using $P < 0.05$ as the level of statistical significance. Although in the present study, p-values from the various models were not independent and the work was hypothesis-oriented, we also adjusted p-values using the Benjamini–Hochberg false discovery rate (FDR) method to account for multiple comparisons.[52] FDR adjustment was conducted using PROC MULTTEST statement in SAS 9.2 (SAS Institute, Inc., Cary, North Carolina). All other analyses were conducted using commercially available software (SUDAAN, version 10.0; Research Triangle Institute, Research Triangle Park, North Carolina) and were conducted in the National Center for Health Statistics Research Data Center at Baruch College, City University of New York due to confidentiality requirements for the restricted-use linked mortality files.

RESULTS

H. pylori status in NHANES III

Table 1 shows the distributions of subjects in relation to *H. pylori* status by demographic and chronic disease risk factors in the overall study population, including those with data on *H. pylori cagA* status. Subjects who were *H. pylori*-positive or *H. pylori*-positive/*cagA*-positive were more likely to be older, have lower educational attainment, have larger household size, and have higher body mass index, than *H. pylori*-negative or *H. pylori*-negative/*cagA*-negative subjects.[12] Subjects of race-ethnicity other than non-Hispanic White, and those who had a history of diabetes or hypertension were more likely to be *H. pylori*-positive or *H. pylori*-positive/*cagA*-positive. There was no apparent association of *H. pylori* positivity with sex and smoking status.

H. pylori status and all-cause mortality and common causes of death in older subjects

Because most (94%) deaths were observed in older subjects, we conducted analyses focusing on these individuals. Table 2 shows analyses of findings pertaining to subjects > 40.6 years old, the median of age of the overall study population who were *H. pylori*-negative. There was no association of either *H. pylori*-positivity or *cagA*-positivity with all-cause mortality in the population. The HRs for all-cause mortality in relation to *H. pylori* were all around 1.0. An inverse but not statistically significant association was observed for cardiovascular disease mortality in relation to *H. pylori*-positivity and *cagA* positivity, with an HR of 0.89 (95% CI, 0.71–1.11), and 0.85 (95% CI, 0.67–1.04), respectively. The HR for stroke mortality was 0.69 (95% CI, 0.44–1.08) comparing subjects who were *H. pylori*-positive with those who were *H. pylori*-negative. Subjects who were *H. pylori*-positive/*cagA*-positive were 55% significantly less likely to die from stroke (HR, 0.45; 95% CI, 0.27–0.76) than those who were *H. pylori*-negative/*cagA*-negative.

The HR for lung cancer mortality was 0.61 (95% CI, 0.35–1.05) comparing *H. pylori*-positive with *H. pylori*-negative persons. A significant inverse association between *H. pylori cagA*-positivity and lung cancer mortality was observed in these older subjects. The HRs were 0.67 (0.35–1.29) and 0.55 (0.31–0.98) comparing *H. pylori*-positive/*cagA*-negative subjects and *H. pylori*-positive/*cagA*-positive subjects, respectively, with *H. pylori*-negative/*cagA*-negative subjects.

After adjustment for FDR, the association of *H. pylori*-positive/*cagA*-positive with stroke mortality remained significant (FDR-adjusted p = 0.045). However, the adjusted p-value for the association between *H. pylori*-positive/*cagA*-positive and lung cancer mortality was no longer significant (FDR-adjusted p = 0.21) (eTable 3).

There was no overall association of *H. pylori* status with all-cause mortality, overall cancer mortality, overall gastrointestinal cancer mortality, or respiratory disease mortality. Additional adjustment for health insurance status, family income, and poverty index did not change the effect estimates appreciably (data not shown). For instance, the HRs for stroke were 0.98 (95% CI, 0.57–1.70) and 0.43 (95% CI, 0.25–0.73) comparing *H. pylori*-positive/*cagA*-negative and *H. pylori*-positive/*cagA*-positive, respectively, with *H. pylori*-negative/*cagA*-negative, and the HRs for lung cancer were 0.65 (0.34–1.25) and 0.49 (0.27–0.89) comparing *H. pylori*-positive/*cagA*-negative and *H. pylori*-positive/*cagA*-positive, respectively, with *H. pylori*-negative/*cagA*-negative. Additional adjustment for hypertension status at baseline also did not change the effect estimates appreciably (data not shown). For instance, the HRs for stroke was 1.03 (0.59–1.81) and 0.46 (0.28–0.77) comparing *H. pylori*-positive/*cagA*-negative and *H. pylori*- positive/*cagA*-positive, respectively, with *H. pylori*-negative/*cagA*-negative. Sensitivity analyses excluding deaths in the first 5 years generated similar results (data not shown). For instance, after excluding deaths in the first 5 years, the

HRs for stroke were 1.11 (0.60–2.07) and 0.47 (0.26–0.87) comparing *H. pylori*-positive/*cagA*-negative and *H. pylori*-positive/*cagA*-positive, respectively, with *H. pylori*-negative/*cagA*-negative, and the HRs for lung cancer were 0.65 (0.30–1.40) and 0.50 (0.26–0.99) comparing *H. pylori*-positive/*cagA*-negative and *H. pylori*-positive/*cagA*-positive, respectively, with *H. pylori*-negative/*cagA*-negative. All of the observed associations were similar in the overall study population (eTable 2). Because of the relatively small number of deaths observed in younger subjects, many effect estimates were not reliable (data not shown).

H. pylori status and gastrointestinal cancer mortality

Since the associations between *H. pylori* and the risk of gastrointestinal cancer have been investigated extensively in prior studies, we assessed the effects of *H. pylori* colonization on mortality due to selected gastrointestinal cancers in older individuals (Table 3). There was a strongly positive association between *H. pylori*-positivity and gastric cancer mortality, and positive associations of similar magnitude were observed for subjects who were *H. pylori*-positive/*cagA*-negative or *H. pylori*-positive/*cagA*-positive compared to those who were *H. pylori*-negative/*cagA*-negative. For pancreatic cancer, the inverse association was stronger for *cagA*-negative strains (HR, 0.21; 95% CI, 0.05–0.91). However, the numbers of deaths for these outcomes were limited. All of the observed associations were similar in the overall study population (eTable 2). After adjustment for FDR, the association of *H. pylori*-positivity, *H. pylori*-positive/*cagA*-negative, and *H. pylori*-positive with gastric cancer mortality remained significant (FDR-adjusted p = 0.045). All other associations were not statistically significant (eTable 3). Models for rare outcomes excluding deaths in the first 5 years did not converge due to limited sample size.

DISCUSSION

Since *H. pylori* has been present in humans for at least 58000 years,[1] and has been rapidly declining from human populations during the past century,[6],28 an important question is whether its presence affects human health in the aggregate. In the present study, *H. pylori* status was not related to overall all-cause mortality. *H pylori* was associated with an increased risk of death due to gastric cancer, but with reduced risks of deaths due to stroke and lung cancer.

As expected, the greatest mortality in the studied population was that due to cardiovascular disease. The literature on the association between *H. pylori* and cardiovascular disease risk is not consistent, with reports of both positive[53–55] or null[56–60] associations. In a population-based case-control study in the Erlangen Stroke Project,[61] *H. pylori* was associated with lower risk of cardioembolic stroke (OR, 0.21; 95% CI, 0.06–0.71). More recently, a population-based German cohort of 9,953 older subjects showed a significant inverse association between *cagA* positivity and cardiovascular mortality (HR, 0.62; 95% CI, 0.41–0.94);[17] the association of *cagA*-positivity with myocardial infarction and stroke also was inverse (HR, 0.71, 0.59, respectively), but not statistically significant.[17] In the present study, we observed an insignificant reduced risk of cardiovascular disease mortality and a significant reduced risk of stroke mortality, comparing *H. pylori*-positive or *H. pylori*-positive/*cagA*-positive with *H. pylori*-negative/*cagA*-negative; all of the apparent association is with *cagA*-positive strains. While our findings indicate that *H. pylori* or *cagA* are not major risk factors for cardiovascular disease or mortality, it cannot be ruled out that *H. pylori* or specifically *cagA*-positive strains may be protective for stroke. Recent studies suggest that regulatory T-cells (T-reg cells) may be protective against stroke risk.[62–63] Persons with gastric *H. pylori* colonization have much more substantial gastric T-regulatory populations and higher gastric expression of T-reg-linked cytokines than *H. pylori*-negative persons.[64] The T-reg down-regulated immune system in *H. pylori* positive hosts may be less

damaging to aging blood vessels. *H. pylori*-associated inverse risk with asthma and allergies appear to be related to the induction of T-reg responses in animal models.[65–66] The strong positive association of *H. pylori* status with mortality due to gastric cancer (Table 3) was consistent with the literature.[2–3] The very high hazard ratios indicate that nearly all gastric fatal cancers in the US are *H. pylori*-related; the progressive decline in *H. pylori* prevalence thus may explain nearly all of the reduction in gastric cancer mortality over the past 80 years.[7] However, in the present study, there were no data on locations of the cancers and therefore we could not differentiate whether the association for gastric cancer could be due to cardia and/or non-cardia cancers. Although many studies show a heightened risk for CagA+ *H. pylori* strain with relation to gastric cancer, other studies have shown that both CagA+ and CagA- *H. pylori* strains are similarly associated with gastric cancer[2–3]. Prior case control studies documented an inverse association with mortality from esophageal cancer, especially for *cagA+* strains [8–10] , and a positive association with pancreatic cancer. Although we also observed an insignificant association with a consistent inverse direction for esophageal cancer, the numbers are limited, and studies with larger sample size and/or longer follow-up are needed.

Several case-control studies evaluated the association between *H. pylori* and lung cancer, with inconsistent findings and small sample sizes.[18–20,22–23] More recently, a prospective study in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort found no association between *H. pylori* and lung cancer;[21] however, the study population only included men who were smokers. In the present study, we found an overall inverse association between *H. pylori* and lung cancer in older subjects, a significant inverse association for *cagA*-positive strains, and a consistent trend for *cagA*-negative strains in older subjects. However, information on subtypes and histologic types of lung cancer was not available in NHANES mortality data to further investigate whether the association is due to a specific type of lung cancer. It should be noted that in the present study the adjusted p-value for the association between *H. pylori*-positive/*cagA*-positive and lung cancer mortality was no longer significant (FDR-adjusted p = 0.21). Future studies are needed to confirm or refute our findings on lung cancer.

There are strengths and limitations of our study. Our study included representative samples from the general population, comprehensive data on other risk factors, and objective follow-up data on mortality. However, the subjects were relatively young (median age 39 overall, and 40 among *H. pylori*-negative/*cagA*-negative subjects) at study entry, and therefore the numbers of deaths for uncommon cancers were limited. *H. pylori* testing was conducted on surplus serum samples from participants in certain age groups. Numerous tests were conducted on blood samples prior to the *H. pylori* testing and therefore surplus sera were not available for everyone. However, it is unlikely that *H. pylori* carriers who died during the follow-up were differentially excluded at the time of *H. pylori* testing (a necessary condition for a bias). Distributions of demographic and lifestyles are similar between subjects with and without *H. pylori* testing (data not shown), except that fewer Blacks (7% less) had surplus sera for *H. pylori* testing to be included in the study compared to other groups. The sampling weights that addressed the issues of oversampling and non-response may not account for the fact that many participants did not have surplus sera for *H. pylori* testing. However, we do not believe the external validity (generalizability) of the study results would be affected, as the association between *H. pylori* and mortality may not differ substantially by ethnic groups. Second, our results might have been influenced by death certificate errors, especially for non-cancer outcomes. Although some errors in the NHANES mortality linkage procedure are unavoidable, the process was conducted without the knowledge of the participants' health data. Studies that have examined the validity of the death certificate diagnosis of stroke have found a high specificity and a moderate sensitivity for the diagnosis.[67–68] Lower sensitivity or errors in the death certificate diagnosis of stroke would

be expected to be non-differential by *H. pylori* status and result in underestimation of the association. Third, the presence of *H. pylori* may merely be a marker for other important risk factors of disease. Although test results of *H. pylori* status were not communicated to the NHANES participants, since *H. pylori* may be eradicated collaterally after routine antibiotic treatment of co-existing illness presumed to have been infectious, its absence could reflect the loss of other bacteria. However, there is no evidence of a positive association between *H. pylori* and any specific bacterial infection that also is related to a reduced risk of lung cancer or stroke (positive confounding by other bacterial infection). The study findings also did not change appreciably with additional adjustments for other indicators of socioeconomic status. Nevertheless, because of the observational nature of this study, we cannot exclude the possibility of residual and unmeasured confounding. Lastly, we have no knowledge of whether *H. pylori* may have been lost or gained in the interval between ascertainment and mortality. However, from longitudinal studies of *H. pylori*-positive adults, we know that rates of "spontaneous" annual loss of the organism among those with established colonization are low.[29] Similarly, early childhood is the nearly exclusive time for colonization,[24–25] thus substantial later-in-life acquisitions are unlikely. Misclassification as a result of imperfect accuracy of the serological tests is likely to be non-differential (not related to the subsequent risk of death), which would bias the results towards no association.

In conclusion, our findings do not suggest that *H. pylori* colonization is a major risk factor for all-cause mortality. We observed an inverse association between *H. pylori* colonization and stroke mortality and a direct association with gastric cancer. While the associations observed need to be reexamined in future studies, our results provide further evidence that *H. pylori* has a mixed role in human health[69] and raise new possible protective effects of *H. pylori* colonization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	Confidence Interval
ELISA	enzyme-linked immunoassay
FDR	false discovery rate
H. pylori	*Helicobacter pylori*
HR	Hazard Ratio
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision

NHANES III	The National Health and Nutrition Examination Survey III
NCHS	National Center for Health Statistics
NDI	National Death Index

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SIGNIFICANCE OF THIS STUDY

What is already known about this subject?

- *H.pylori* colonization has been associated with increased risk of gastric cancer, and reduced risks of asthma and allergy.
- Previous studies on *H. pylori* colonization and risks of cardiovascular disease and lung cancer have yielded inconsistent findings.

What are the new findings?

- *H. pylori* status was not related to overall all-cause mortality.
- *H. pylori* colonization was associated with reduced risks of deaths due to stroke and increased risks of deaths due to gastric cancer. The data also suggest an inverse association with lung cancer.

How might it impact on clinical practice in the foreseeable future?

- These results suggest new possibly protective effects of *H. pylori* colonization.

Table 1

Baseline Demographic and Health-Related Characteristics of Study Subjects by *H pylori* Status in NHANES III

	Joint status of *H pylori* and *cagA* (n=7354)*					*H pylori* status (n=9895)*			
	No.	*H pylori*$^-$ *cagA*$^-$ (n =3124)	*H pylori*$^+$ *cagA*$^-$ (n = 1438)	*H pylori*$^+$ *cagA*$^+$ (n = 2792)	*P*†	No.	*H pylori*$^-$ (n = 5061)	*H pylori*$^+$ (n = 4834)	*P*†
Age, mean, y	7354	40.6	51.8	48.0	<0.01	9895	34.1	44.7	<0.01
Education, mean, y	7354	13.5	11.6	11.6		9895	11.1	11.9	<0.01
Gender‡									
Male	3694	59.7	15.0	25.4	0.42	4927	62.6	37.4	0.47
Female	3660	61.0	15.3	23.7		4968	63.8	36.2	
Race‡	3314	67.7	15.0	17.3	<0.01	4091	70.3	29.7	<0.01
Non-Hispanic White									
Non-Hispanic Black	1821	35.7	11.6	52.7		2455	42.0	58.0	
Mexican-American	1983	30.4	23.4	46.2		3008	39.0	61.0	
Other	236	33.6	16.8	49.5		341	40.2	59.8	
Body mass index, kg/m^2§									
<25	3067	65.0	13.5	21.4	<0.01	3033	65.6	34.4	<0.01
≥25.0	4287	56.1	16.6	27.3		4379	56.3	43.7	
Mean	7354	25.9	26.9	26.8	<0.01	7412	25.7	26.7	
Smoking status§									
Never	3419	59.8	15.4	24.8	0.88	3796	60.4	39.6	0.65
Past	1914	59.9	15.6	24.5		1940	60.1	39.9	
Current	2021	61.5	14.4	24.1		2116	62.0	38.0	
Household size‡									
<5	5584	62.0	15.4	22.6	<0.01	6691	64.0	36.0	0.06
≥5	1770	52.4	14.1	33.5		3204	60.5	39.5	
Mean	7354	3.1	3.0	3.3	<0.01	9895	3.4	3.4	
Diabetes history‡,§									
No	6747	60.9	14.8	24.3	<0.01	7242	61.4	38.6	<0.01

	Joint status of *H pylori* and *cagA* (n=7354)*					*H pylori* status (n=9895)*			
	No.	***H pylori*$^{-}$ *cagA*$^{-}$ (n =3124)**	***H pylori*$^{+}$ *cagA*$^{-}$ (n = 1438)**	***H pylori*$^{+}$ *cagA*$^{+}$ (n = 2792)**	***P*†**	**No.**	***H pylori*$^{-}$ (n = 5061)**	***H pylori*$^{+}$ (n = 4834)**	***P*†**
Yes	593	50.2	20.8	29.0		596	50.3	49.7	
missing	14	78.0	16.5	5.5		14	78.0	22.0	
High blood pressure history‡,§									
No	5314	62.5	13.5	24.0	<0.01	5776	63.1	36.9	<0.01
Yes	1967	54.2	20.2	25.6		1987	54.5	45.5	
missing	19	25.6	39.5	34.9		21	20.3	79.7	

*Data on *cagA* status were available for a total of 7354 subjects ≥ 20 years of age.

†*P* based on Chi-Square test or t-test. Subjects with missing values were excluded from test statistics.

‡Row percent estimates based on weighted stratified sample of NHANES III.

§These variables were available for individuals > 17 years of age.

Table 2

Risk of All-Cause, Cardiovascular Disease, Cancer, and Respiratory Disease Mortality in Relation to *H pylori* Status in NHANES III among Subjects ≥ 40.6 Years Old

	HR and 95% CI for total and cause-specific mortality by *H pylori*/*cagA* status			HR and 95% CI for total and cause-specific mortality by *H pylori* status	
	***H pylori*$^-$ *cagA*$^-$**	***H pylori*$^+$ *cagA*$^-$**	***H pylori*$^+$ *cagA*$^+$**	***H pylori*$^-$**	***H pylori*$^+$**
Follow-up person years	20469.9	12842.5	21838.7	20485.8	34681.3
All-cause mortality					
Deaths, No.	593	513	791	594	1304
Model 1 *	1.00 (ref)	1.13 (0.90–1.42)	1.04 (0.86–1.26)	1.00 (ref)	1.08 (0.90–1.29)
p-value		0.2928	0.6833		0.4144
Model 2 †	1.00 (ref)	1.03 (0.83–1.29)	0.97 (0.80–1.18)	1.00 (ref)	1.00 (0.84–1.18)
p-value		0.76	0.75		0.99
Cardiovascular disease					
Deaths, No.	274	241	330	274	571
Model 1 *	1.00 (ref)	1.01 (0.72–1.40)	0.89 (0.72–1.10)	1.00 (ref)	0.94 (0.75–1.18)
p-value		0.9617	0.2592		0.5668
Model 2 †	1.00 (ref)	0.96 (0.68–1.34)	0.83 (0.67–1.04)	1.00 (ref)	0.89 (0.71–1.11)
p-value		0.79	0.098		0.28
Ischemic heart disease					
Deaths, No.	169	138	190	169	328
Model 1 *	1.00 (ref)	0.98 (0.69–1.40)	0.94 (0.70–1.26)	1.00 (ref)	0.96 (0.73–1.25)
p-value		0.9277	0.6770		0.7530
Model 2 †	1.00 (ref)	0.94 (0.67–1.33)	0.91 (0.68–1.22)	1.00 (ref)	0.92 (0.72–1.19)
p-value		0.72	0.51		0.52
Stroke					
Deaths, No.	46	49	58	46	107
Model 1 *	1.00 (ref)	1.08 (0.61–1.90)	0.53 (0.32–0.88)	1.00 (ref)	0.76 (0.48–1.18)
p-value		0.78	0.02		0.21
Model 2 †	1.00 (ref)	1.05 (0.59–1.85)	0.45 (0.27–0.76)	1.00 (ref)	0.69 (0.44–1.08)

	HR and 95% CI for total and cause-specific mortality by *H pylori*/*cagA* status			HR and 95% CI for total and cause-specific mortality by *H pylori* status	
	***H pylori*⁻ *cagA*⁻**	***H pylori*⁺ *cagA*⁻**	***H pylori*⁺ *cagA*⁺**	***H pylori*⁻**	***H pylori*⁺**
p-value		0.8720	0.0041		0.1026
All Cancer					
Deaths, No.	143	106	182	143	288
Model 1 *	1.00 (ref)	1.04 (0.72–1.50)	0.96 (0.70–1.30)	1.00 (ref)	0.99 (0.76–1.29)
p-value		0.84	0.77		0.94
Model 2 †	1.00 (ref)	0.93 (0.65–1.33)	0.89 (0.67–1.17)	1.00 (ref)	0.91 (0.71–1.16)
p-value		0.69	0.39		0.43
Lung cancer					
Deaths, No.	50	32	48	50	80
Model 1 *	1.00 (ref)	0.80 (0.42–1.52)	0.63 (0.38–1.04)	1.00 (ref)	0.70 (0.42–1.16)
p-value		0.4798	0.0705		0.1626
Model 2 †	1.00 (ref)	0.67 (0.35–1.29)	0.55 (0.31–0.98)	1.00 (ref)	0.61 (0.35–1.05)
p-value		0.22	0.04		0.07
Gastrointestinal cancer					
Deaths, No.	25	25	49	25	74
Model 1 *	1.00 (ref)	0.98 (0.46–2.09)	1.54 (0.80–2.95)	1.00 (ref)	1.30 (0.72–2.32)
p-value		0.96	0.19		0.37
Model 2 †	1.00 (ref)	0.87 (0.41–1.87)	1.22 (0.58–2.59)	1.00 (ref)	1.07 (0.57–2.00)
p-value		0.71	0.58		0.82
Respiratory disease					
Deaths, No.	71	50	80	71	130
Model 1 *	1.00 (ref)	0.80 (0.54–1.19)	1.04 (0.67–1.63)	1.00 (ref)	0.94 (0.68–1.31)
p-value		0.26	0.85		0.72
Model 2 †	1.00 (ref)	0.70 (0.47–1.05)	1.02 (0.63–1.67)	1.00 (ref)	0.87 (0.61–1.26)
p-value		0.08	0.92		0.45

Abbreviations: HR, hazard ratio; CI, confidence interval.

* HRs were adjusted for age and sex.

[†] HRs were adjusted for age and sex, educational attainment (years), BMI (<25, >25, missing), race/ethnicity, and smoking status (never/past/current).

Table 3

Risk of mortality due to colorectal cancer, gastric cancer, esophageal cancer, and pancreatic cancer mortality (rare outcomes) in NHANES III in subjects ≥ 40.6 years old

	HR and 95% CI for total and cause-specific mortality by *H pylori*/*cagA* status			**HR and 95% CI for total and cause-specific mortality by *H pylori* status**	
	***H pylori* − *cagA* −**	***H pylori* + *cagA* −**	***H pylori* + *cagA* +**	***H pylori* −**	***H pylori* +**
Follow-up person years	20469.9	12842.6	21838.8	20485.8	34681.3
Colorectal cancer*					
Deaths (n)	11	11	20	11	31
Model 1[1]	1.0	0.59 (0.25–1.39)	1.46 (0.50–4.28)	1.0	1.08 (0.42–2.81)
		0.22	0.48		0.86
Gastric cancer*					
Deaths (n)	16 (total events)			16 (total events)	
Model 1[1]	1.0	40.37 (3.55–458.54)	41.41 (4.09–419.48)	1.0	40.95 (4.19–399.92)
		0.0045	0.0029		0.0026
Esophageal cancer*					
Deaths (n)	6 (total events)			6 (total events)	
Model 1[1]	1.0	0.44 (0.05–3.84)	0.24 (0.02–2.43)	1.0	0.33 (0.04–3.01)
		0.44	0.22		0.31
Pancreatic cancer*					
Deaths (n)	23 (total events)			8	15
Model 1[1]	1.0	0.21 (0.05–0.91)	0.95 (0.43–2.11)	1.0	0.63 (0.28–1.40)
		0.039	0.890		0.24

[1] HRs were adjusted for age and sex

* Total number of deaths was < 5 for at least one *H. pylori* category and therefore only the total numbers of evens were shown per NHANES publication restrictions.