



The effect of *Helicobacter pylori* infection on the decline of lung function in a health screening population

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Background: Although *Helicobacter pylori* (*H. pylori*) infection has long been associated with many extra-gastric diseases, its long-term effects on declining lung function and the development of chronic obstructive pulmonary disease (COPD) remains controversial.

Methods: We conducted a retrospective study in a health screening population (Gene-Environment of Interaction and Phenotype Cohort at Seoul National University Gangnam Health Center in Korea) recruited from 2004 to 2015. The annual decline rates of lung function and the risk for COPD were compared to the seropositivity for *H. pylori*. We also assessed the impact of the *H. pylori* eradication treatment on lung function.

Results: Among 3,619 subjects, 1,849 subjects (51.1%) tested positive for *H. pylori*-specific IgG. In the first year, 95 (2.6%) patients were diagnosed with COPD. However, there was no difference in seropositivity for *H. pylori* in patients with COPD compared to non-COPD subjects ($P=0.756$). There was no significant difference in the incidence of COPD between the seronegative (2.2%) and the seropositive group (2.0%; $P=0.728$) even during the follow-up period. The decline rates of the mean FVC and FEV₁ were not different between the seronegative and seropositive group (35.38 vs. 34.34 mL/year for FVC, $P=0.389$; 39.23 vs. 37.49 mL/year for FEV₁, $P=0.086$). The eradication treatment for *H. pylori* did not affect the decline rates of mean FVC and FEV₁.

Conclusions: Infection or eradication treatment of *H. pylori* was not associated with the decline of lung function or COPD progression in this general population health screening. As a result, *H. pylori* may not be a significant contributor to deteriorating lung function.

Keywords: *Helicobacter pylori* (*H. pylori*); chronic obstructive pulmonary disease (COPD); spirometry

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Introduction

Helicobacter pylori (*H. pylori*) is the leading cause of several gastric diseases, including superficial gastritis, peptic ulcer

disease, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. Since reports indicated that *H. pylori* infection was associated with coronary heart

disease (1), subsequent epidemiological studies also associated *H. pylori* infection with extra-gastric diseases, such as cardiovascular, neurologic, hematologic, allergic, metabolic, and other diseases (2-4).

However, the relationship between chronic obstructive pulmonary disease (COPD) and *H. pylori* infection remains controversial. A previous study demonstrated that patients with chronic bronchitis tested significantly higher for *H. pylori* seropositivity than controls (83.3% vs. 60%; $P=0.007$) (5). Additionally, the rate of *H. pylori* seropositivity was reported to be higher in patients with COPD than in controls (54.7% of 58 patients with COPD, 23.5% of 17 controls ($P=0.026$)) (6).

Recently, large epidemiological studies have shown an association between *H. pylori* seropositivity and COPD. Specifically, previous findings revealed that *H. pylori* IgG levels correlated with the severity of COPD (7). Conversely, a population-based cross-sectional study reported no association between *H. pylori* exposure and COPD, measures of allergic disease, or decline in lung function (8). These results support our previous study of a population with high *H. pylori* infection rates that demonstrated no relationship between COPD and *H. pylori* seropositivity (9). However, a meta-analysis that consisted of 16 studies suggested that *H. pylori* infection was associated with an increased risk of COPD [odds ratio (OR) 2.07, 95% CI: 1.81–2.36, $P=0.05$] (10).

Since *H. pylori* infection rates vary by geographic area, age, and ethnicity, we conducted a large-scale longitudinal data analysis in Korea where *H. pylori* infection is prevalent. Herein we investigated the relationship between *H. pylori* infection and the rate of lung function decline, including the risk for COPD. In addition, we evaluated the impacts of medical eradication of *H. pylori* on lung function decline and the risk of COPD to further clarify the relationships.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/apm-20-850>).

Methods

Patients and data

We conducted this retrospective cohort study using the Gene-Environment of Interaction and phenotype (GENIE) data. The GENIE cohort consisted of participants who had visited Seoul National University Gangnam Center in South Korea for health checkups, agreed to participate in

genetic studies, and donated blood samples (11).

Data were obtained from 2004 to 2015 in adults at least 40 years old, and the clinical information was collected including age, sex, height, weight, comorbidities, smoking status, spirometric and laboratory data, and esophagogastroduodenoscopy (EGD) results. Spirometry and *H. pylori*-specific IgG concentrations were measured annually for up to 12 years. Smoking-related variables were obtained by questionnaire. Patients who had undergone at least one *H. pylori* IgG test and who had spirometry for more than two years were included in the study. We excluded patients who were diagnosed with lung cancer during the follow-up period or who underwent pulmonary resection. Spirometry was performed according to the standard guidelines of the American thoracic society (12).

H. pylori-specific IgG concentrations were measured using two different tests depending on the study year. A commercially available enzyme-linked immunosorbent assay (RADIM, Pomezia-Rome, Italy) was used according to the manufacturer's protocol prior to April 2013. We included only positive (≥ 30 U/mL) or negative (< 15 U/mL) results in this analysis excluding equivocal results (15–30 U/mL). *H. pylori*-specific IgG concentrations were measured with HPG kits (Immulite 2000 Chemiluminescent Microparticle Immuno Assay SIEMENS, UK) from April 2013 until the end of the study. *H. pylori* IgG levels higher than 1.10 IU/mL were regarded as positive, and values that ranged from 0 to 0.9 IU/mL were considered negative in the Immulite 2000 assay. We defined a recently infected person as a subject whose *H. pylori*-specific IgG value changed from negative to positive during the follow-up period.

Outcome measures

Using the baseline *H. pylori*-specific IgG concentrations, we determined whether *H. pylori* seropositivity was associated with the incidence or development of COPD. COPD was defined as a prebronchodilator FEV₁/forced vital capacity (FVC) ratio of < 0.7 . We also compared the annual FEV₁ or FVC reduction rates of seropositive and seronegative subjects.

Moreover, the difference in the rate of decline in pulmonary function of seropositive patients was evaluated by stratifying the patients into two groups: (I) the *H. pylori*-treated group and (II) the non-treated group. The treated group included the patients who completed the course of eradication regimen drugs such as a proton pump inhibitor (PPI), clarithromycin, and amoxicillin.

A subject whose *H. pylori*-specific Ig G value changed from negative to positive during the follow-up period was defined as a recently infected person.

Statistical analysis

Data are presented as the mean \pm standard deviations (SDs) for continuous, normally distributed variables or medians with interquartile ranges (IQRs) for non-normally distributed variables. Categorical variables were analyzed using the chi-square test, and a *t*-test was used to compare the differences between normally distributed, continuous data. $P < 0.05$ (two-tailed) was considered statistically significant. A random intercept and random slope model were used to estimate the annual lung function decline. The data were adjusted for multiple covariates, including age, sex, height, and smoking pack-year. We performed statistical analyses using STATA software version 15.0 (StataCorp, College Station, TX, USA).

Ethical statement

The present study was approved by the Institutional review board (IRB No. H-1804-028-934) and was in accordance with the 1964 and later modifications of the Helsinki declaration (as revised in 2013) on the use of human subjects for research. Written informed consent was obtained from the patient before GENIE cohort registration.

Results

A total of 3,843 patients were followed-up for 2–12 years (median follow-up, 7 years; IQR, 5–9). Among these participants, 224 subjects (5.83%) were excluded due to equivocal *H. pylori* IgG tests. Therefore, we included 3,619 subjects in our analysis. The baseline characteristics of the study subjects are presented in *Table 1*. The mean age of patients was 48.57 years; 2,226 (61.5%) were men, and 602 (16.7%) were current smokers. The mean FEV₁ was 3.13 \pm 0.66 L (104.2% of the predicted value), and the mean FVC was 3.86 \pm 0.82 L (96.66% of the predicted value). Further, 1,849 (51.1%) patients were seropositive, and 1,770 (48.9%) were seronegative according to the first serology test.

H. pylori infection and prevalence of COPD

The initial spirometry revealed that a total of 95 (2.6%)

patients had COPD; however, the prevalence of COPD did not differ according to the seropositivity for *H. pylori* (2.5% in seropositive group *vs.* 2.7% in seronegative group; $P=0.756$). Although 76 patients (2.1%) were newly diagnosed with COPD during the total observation period, there were no significant differences in the development of COPD between the seropositive group (37 patients, 2.0%) and the seronegative group (39 patients, 2.2%) ($P=0.728$).

The impact of *H. pylori* infection on the rate of decline in lung function

When comparing the annual decline rates of the mean FVC and FEV₁ according to the seropositivity of *H. pylori*, we found no significant difference in the annual decline rate of the mean FVC between the two groups (35.38 \pm 0.90 mL/year for seronegative group *vs.* 34.34 \pm 0.81 mL/year for seropositive group, $P=0.389$) (*Table 2*, *Figure 1*) or in the annual decline rate of the mean FEV₁ (39.23 \pm 0.75 mL/year in seronegative group *vs.* 37.49 \pm 0.68 mL/year in the seropositive group, $P=0.086$). To minimize the limitation of *H. pylori*-specific IgG in identifying recent infection, we also performed subgroup analyses in 143 patients with recent seroconversion to seropositive status during the observation period. Nevertheless, there were no differences in the mean FVC (40.05 \pm 2.54 mL/year) or FEV₁ (34.62 \pm 3.13 mL/year) rates of decline (*Table 3*).

The impact of eradication on the decline of lung function

A total of 460 of the 1,849 seropositive patients (24.9%) received antibiotics and PPI for *H. pylori* eradication therapy. The annual mean FVC decline rate (34.51 \pm 1.41 mL/year) did not significantly differ from that of subjects without eradication treatment (34.26 \pm 0.99 mL/per year, $P=0.603$) (*Table 4*). Also, there was no significant difference in the annual decline rate of FEV₁ between the two groups (37.29 \pm 1.15 mL/year for *H. pylori* treated group *vs.* 37.37 \pm 0.81 mL/year for the group without *H. pylori* treatment ($P=0.954$) (*Figure 2*).

Discussion

This large-scaled longitudinal analysis demonstrated that *H. pylori* infection did not affect the annual decline rates of FEV₁ or FVC, and infection was not associated with the incidence of COPD. Although several reports indicate that *H. pylori* infection increases the risk of COPD, the present study, in

Table 1 Baseline characteristics of study population

Characteristics	<i>H. pylori</i> sero-negative group (n=1,770)	<i>H. pylori</i> sero-positive group (n=1,849)	P
Age (year), mean ± SE	48.26 (±6.54)	48.87 (±6.37)	0.004
Sex (male), n (%)	1,029 (58.1)	1,197 (64.7)	<0.001
Body mass index (kg/m ²), mean ± SE	23.32 (±2.83)	23.61 (±2.77)	0.002
Height (cm), mean ± SE	165.94 (±7.87)	166.49 (±7.75)	0.034
Smoking status			0.140
Ex-smoker, n (%)	545 (30.9)	633 (34.3)	
Current smoker, n (%)	295 (16.7)	307 (16.6)	
Smoking amount (pack-year), mean ± SE	9.12 (±14.03)	10.08 (±15.08)	
Lung function, mean ± SE			
FEV ₁ , L	3.11 (±0.67)	3.16 (±0.66)	0.021
FEV ₁ , % predicted	104.06 (±12.56)	104.45 (±12.97)	0.352
FVC, L	3.82 (±0.82)	3.90 (±0.82)	0.003
FVC, % predicted	96.32 (±10.80)	96.99 (±10.90)	0.065
FEV ₁ /FVC, %	81.80 (±6.5)	81.41 (±6.48)	0.067
COPD, n (%)	48 (2.7)	47 (2.5)	0.756
Follow-up period, mean year	5.69 (±0.06)	6.28 (±0.06)	<0.001
WBC, mean ± SE	5,286 (±35.9)	5,658 (±35.0)	<0.001
Eosinophil count/μL	153 (±3.42)	155 (±3.44)	0.7160
Neutrophil count/μL	3,043 (±28.8)	3,272 (±28.6)	<0.001
CRP (mg/dL), mean ± SE	0.11 (±0.272)	0.098 (±0.177)	0.1772

Table 2 The annual decline rate of lung function, adjusted by age, sex, height, and amount of smoking in pack-year

Lung function index	<i>H. pylori</i> sero-negative group (n=1,770)	<i>H. pylori</i> sero-positive group (n=1,849)	P
FEV ₁ , mL/year	-39.23 (±0.751)	-37.49 (±0.676)	0.086
FVC, mL/year	-35.38 (±0.896)	-34.34 (±0.807)	0.389

conjunction with our previous study, indicated that *H. pylori* infection was not associated with COPD (9). Additionally, the eradication of *H. pylori* did not affect the rate of decreased in lung function and the development of COPD.

This study presents some strengths compared with previous reports on the association between *H. pylori* infection and COPD. First, this was a large-scale population cohort study with a long follow-up period in a high prevalence area of *H. pylori* infection. Secondly, the study population, GINIE cohort, consisted of a health screening population and followed an organized system that resulted

in a low dropout rate. Numerous publications have already demonstrated the data quality of the study population. This suggests that the longitudinal data in this study may contain fewer biases such as the high drop-out rates seen in retrospective cohort studies. Furthermore, the effects of the eradication treatment of *H. pylori* infection were examined on main outcomes. To date, no studies have confirmed whether the rate of lung function is affected with *H. pylori* eradication.

As the prevalence of *H. pylori* infection varies by region, the effects of *H. pylori* infection on extra-gastric diseases

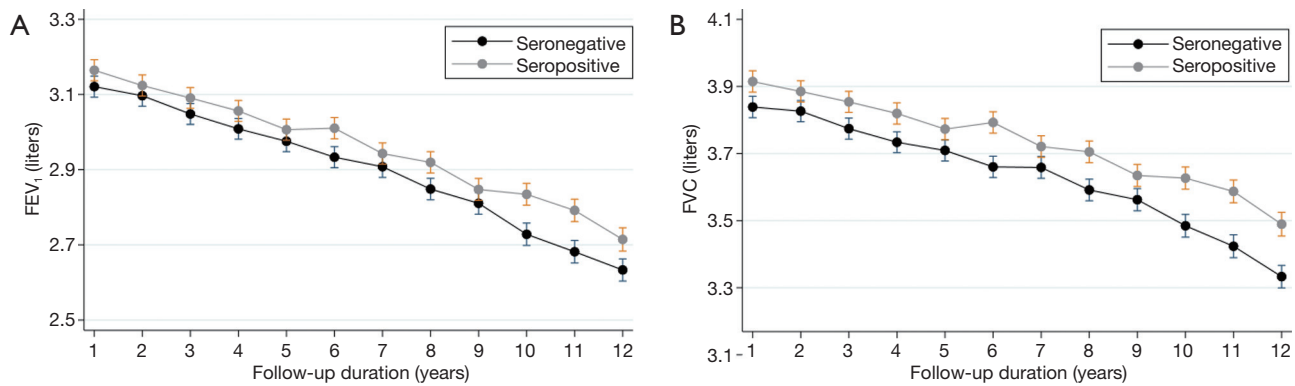


Figure 1 The annual rate of lung function decline. (A) Decline in FEV₁ for 12 years; 39.23±0.75 mL/year in seronegative group vs. 37.49±0.68 mL/year in the seropositive group, P=0.086. (B) Decline in FVC for 12 years; 35.38±0.90 mL/year for seronegative group vs. 34.34±0.81 mL/year for seropositive group, P=0.389.

Table 3 The annual decline rates of lung function in patients with positive seroconversion suggesting recent infection of *H. pylori*

Lung function index	Subjects with alleged <i>H. pylori</i> infection (n=1,849)	Subjects with newly positive seroconversion (n=143)	P
FEV ₁ , mL/year	-37.32 (±0.66)	-40.05 (±2.54)	0.300
FVC, mL/year	-34.36 (±0.81)	-34.62 (±3.13)	0.935

Table 4 The annual decline rates of lung function according to medical eradication for *H. pylori* during follow-up period among the patients with sero-positivity to *H. pylori* Ig G

Lung function index	Subjects treated for <i>H. pylori</i> (n=460)	Subjects without treatment for <i>H. pylori</i> (n=1,389)	P
FEV ₁ , mL/year	-37.29 (±1.15)	-37.37 (±0.81)	0.953
FVC, mL/year	-34.508 (±1.41)	-34.26 (±0.99)	0.886

are also expected to be variable. For example, the mean prevalence of *H. pylori* infection in the USA was 35% (range, 22–48%) between 1990 and 2006 with no increasing or decreasing infection rates over this time period (13). In this study, the prevalence of *H. pylori* infection was 51.1%, similar to previous studies conducted in Korea that reported a prevalence of *H. pylori* infection from 50 to 60% (14,15).

As for the physical characteristics of study population compared with previous reports (16–18), even though *H. pylori* seropositive group showed statistically higher values in age, BMI, and height, the absolute difference in each variable seems to be too small to suggest clinical significance in general population and some studies reported that the effect of *H. pylori* infection on height disappeared after a multivariate analysis (16,17,19,20). Male predominance

in the *H. pylori* seropositive group appeared in this study, similar to several large sample studies that have reported that men were more positive on serum or biopsies than women (21,22).

Currently, Sze *et al.* reported the most extensive study including patients with COPD in a lung health study (LHS) on the relationship between *H. pylori* seropositivity and COPD (7). With the observation over 11 years, they showed that the absolute FEV₁ value in seropositive patients was lower than that in seronegative patients even though the relationship disappeared when the FEV₁ (% predicted) value was used. The authors asserted that *H. pylori* infection was associated with reduced lung function related to the effects of the bacterium on lung growth earlier in life and systemic inflammation. Contrary to the report, our study

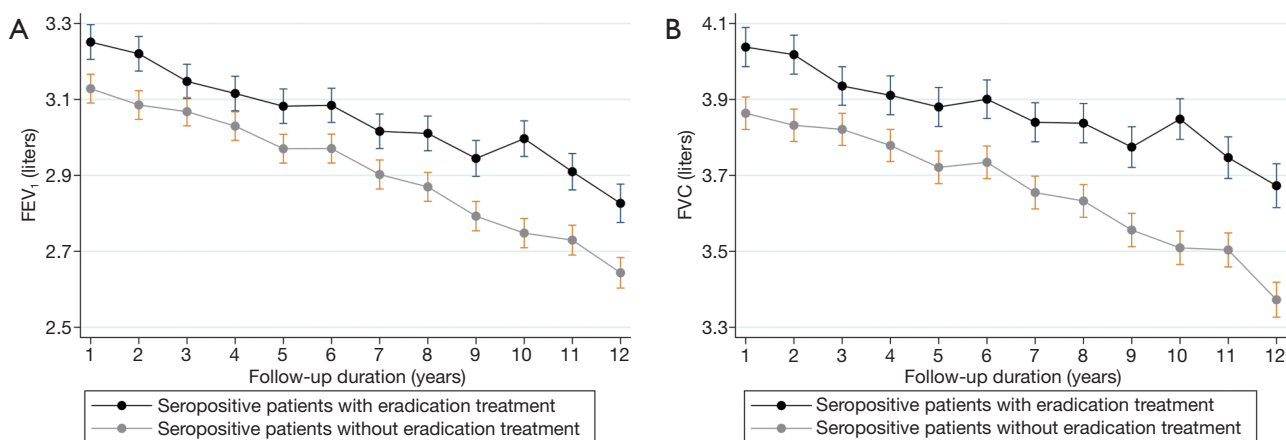


Figure 2 The annual decline rate of lung function depending on eradication of *H. pylori*. (A) Decline in FEV₁ for 12 years; 37.29±1.15 mL/year for *H. pylori* treated group vs. 37.37±0.81 mL/year for the group without *H. pylori* treatment (P=0.954). (B) Decline in FVC for 12 years; 34.51±1.41 mL/year for *H. pylori* treated group vs. 34.26±0.99 mL/year for the group without *H. pylori* treatment (P=0.603).

did not show any significant difference in the rate of lung function (both absolute value and % predicted value) in the seropositive population. Furthermore, although not statistically significant, a slower rate of decline in FEV₁ was observed in the seropositive group (P=0.08).

However, we should consider some different aspects in both studies. First, our study enrolled a healthier general population. The baseline lung function was higher in this population and only 2.6% of total subjects had COPD at the enrollment (mean FEV₁ 2.54 L, 83.87% predicted), while the analysis report of LHS targeted mild to moderate COPD patients (mean FEV₁ 2.80 L, 78% predicted) (7). Therefore, even the impacts of *H. pylori* infection may present, the influence on the total lung function may be limited or negligible in a healthier population than in established COPD. Another point is the difference in seropositivity in the study population. As shown in this study, the seropositivity of *H. pylori* was so prevalent that more than half of the population had a current or past infection of *H. pylori*, a rate much higher than the 18% reported in the LHS study.

The induction of systemic inflammation by *H. pylori* was proposed as the mechanism underlying the association between COPD and *H. pylori* infections. The infection can trigger a low-grade inflammatory state, including the type 1 helper immune response and suppression of the type 2 T helper cell immune response (23). This polarized T-helper cell response has explained the relatively low prevalence of asthma and the high prevalence of COPD in this seropositive population. In addition, recently, studies

are focusing on the effects of *H. pylori* on the intestinal microbiome (24). However, in a high prevalence area, the inflammation related to *H. pylori* may present such a weak or common signal that it may not be a major contributor to reduce lung function.

In this study, for the first time, we evaluated the effects of eradication of *H. pylori* on changes in lung function. However, the effect was not significant. This may suggest that the other factors including subsequent inflammation, are more critical rather than the initial *H. pylori* infection itself. However, as the main results were negative and the detailed inflammatory markers except CRP were not available in this study, further analysis and interpretation could not be performed.

Despite the interesting findings of this study, some limitations should also be considered. First, we considered the limitation of seropositivity in detecting current infection of *H. pylori* and the discrepancy with results using endoscopic biopsy samples (9,25). Unfortunately, endoscopic biopsy results of *H. pylori* were not available in the current study. Second, the study population may be relatively young to analyze more COPD patients considering that the prevalence of COPD increases with age (26) and other association studies (10,27).

Conclusions

In the present study using health screening general population, seropositivity defined infection or the eradication treatment of *H. pylori* were not associated with the decline of

lung function or progression to COPD. *H. pylori* infection may not be a significant factor contributing to deteriorating lung function.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/apm-20-850>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/apm-20-850>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-20-850>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was approved by the Institutional review board (IRB No. H-1804-028-934) and was in accordance with the 1964 and later modifications of the Helsinki declaration (as revised in 2013) on the use of human subjects for research. Written informed consent was obtained from the patient before GENIE cohort registration.

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