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Helicobacter pylori and lung function, asthma, atopy and allergic disease—A population-based cross-sectional study in adults

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Background Exposure to microbes may result in the polarization of the immune system and a decrease in the risk of asthma and associated allergic disease, whilst exposure to *Helicobacter pylori* has been hypothesized to increase the risk of obstructive airways disease. We tested the hypotheses that exposure to *H. pylori* reduces the risk of asthma and allergic disease and is associated with a decrease in lung function.

Methods Data were collected on allergic disease symptoms, forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), bronchial reactivity, allergen skin sensitization, serum IgE and *H. pylori* serological status in 2437 randomly selected adults.

Results Individuals with serological evidence of exposure to *H. pylori* had lower lung function, FEV_1 being lower by 53 ml (95% CI 1–106) and FVC 83 ml (95% CI 20–145) lower in the cross-sectional analysis. These differences ceased to be statistically significant after adjustment for height or socio-economic status. There was no association between *H. pylori* serological status and measures of asthma or atopy in the cross-sectional analysis, and there was no significant association between *H. pylori* serological status and decline in FEV_1 and FVC over 9 years.

Conclusion Although *H. pylori* exposure may be associated with lower cross-sectional FEV_1 and FVC, this association was not independent of height or socio-economic status. There was no association between *H. pylori* exposure and either chronic obstructive pulmonary disease (COPD), measures of allergic disease or decline in lung function.

Keywords *Helicobacter pylori*, lung function, asthma, atopy, COPD

Introduction

Helicobacter pylori is a bacterium that colonizes the gastric mucosa, typically before the age of 5 years.[1] The prevalence of *H. pylori* infection varies from over 70% in developing countries to <40% in developed countries,[2] and in the United Kingdom a cohort effect is seen, with the odds of being seropositive decreasing by 26% per decade of birth.[3] Chronic obstructive pulmonary disease (COPD) is common and has a prevalence of 7–23% in adults.[4] It is characterized by low lung function with a reduction in the Forced

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Expiratory Volume in 1 s (FEV_1)/Forced Vital Capacity (FCV) ratio, and this in turn results in an increase in both morbidity and mortality.[5] Adult lung function is a consequence of both the peak lung growth attained by the third decade,[6] and the subsequent rate of decline in lung function that occurs throughout subsequent adult life. Infection with *H. pylori* is associated with reduced growth in children[7] and thus may negatively impact on lung development.[8] The chronic inflammatory host response observed with *H. pylori* infection has been considered to be a potential risk factor for accelerated decline in lung function[9] which may also result in lower lung function. Whilst the most important risk factor for COPD is cigarette smoking, if infection with *H. pylori* is contributing to the risk of COPD, this would provide a rationale to consider using novel therapeutic interventions that target this response. The need for larger prospective studies of the association between *H pylori* infection and both symptoms of bronchitis and lung function was identified in a recent review.[10]

Helicobacter pylori infection may also modify the risk of allergic disease. The hygiene hypothesis proposes that increased exposure to microbes in early life may be protective against asthma and associated allergic diseases.[11] Over the same time period that infection with *H. pylori* has been decreasing in prevalence, the prevalence of both asthma and atopy have increased, and *H. pylori* thus constitutes an attractive candidate bacterium that may explain some of this change in allergic disease. The presence of the *cagA*$^+$ strain of *H pylori* was recently reported to be associated with a 21% decrease in the risk of ever having had asthma, and a similar protective effect was also seen for rhinitis.[12] However, other investigators have failed to report a significant difference in levels of *H. pylori* antibodies in studies of atopy,[13,14] asthma[15–17] or wheeze.[18]

To date, there are no longitudinal studies of the impact of infection with *H. pylori* on respiratory disease. We have used data from a longitudinal community-based study to investigate associations between *H. pylori* infection and lung function, asthma and allergic diseases.

Methods

Participants

In 1991, 7016 adults aged 18–70 years were identified by systematic sampling from a random point in the local electoral register.

Data collection

The data collection is described in detail elsewhere.[19] In brief, trained interviewers collected data on the participants including socio-economic group using the UK Registrar General's classification of 1990 (based on the highest value for the individual and their partner). Data were collected on symptoms of wheeze and hayfever, FEV_1, FVC, bronchial reactivity; and allergen skin sensitization and serum IgE and *H. pylori* serological status (using the Siemens Immulite 2000 assay—a solid-phase, chemiluminescent IgG assay in 2006).

Data analysis

The initial analyses were cross-sectional using the 1991 data. All analyses compared individuals with positive *H. pylori* serology with those with negative serology. We analysed the cross-sectional association between serum *H. pylori* and FEV_1 and FVC in a multiple linear regression analysis with adjustment for *a priori* confounding factors of age, sex, age squared, smoking status in 1991 and total of cigarette pack years smoked. The effect of height and social-economic status were explored separately as these may be associated with both *H. pylori* exposure and lung function.[8] The potential effect modification of gender, smoking status and decade of birth on the association between *H. pylori* exposure and lung function were also explored. Logistic regression was used to assess the association of a positive *H. pylori* serological assay with COPD as defined by the Global Initiative for Chronic Lung Disease spirometric criteria ($FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted value), hyper-reactivity to methacholine, symptoms of wheeze in the past 12 months, self-reported chronic bronchitis, hayfever, a physician diagnosis of asthma and atopy defined by the presence of a positive skin prick test. All logistic regression analyses were adjusted for age, sex, BMI, dietary magnesium intake, serum CRP in quintiles and smoking status in 1991 as a priori confounding exposures, whilst the analysis using PD_{20}, asthma and wheeze were also adjusted for FEV_1, and the skin prick test analysis of atopy was adjusted for vitamin E intake.

The subsequent longitudinal analysis of the 1991 and 2000 datasets used the change in residual values to permit adjustment for smoking status and total smoking history. Predicted FEV_1 values were modelled for each sex in non-smoking, non-asthmatic, non-wheezing individuals with terms for age, height, age-squared and age–height interactions. Individual FEV_1 values were expressed as the residual difference from the predicted value, and these values were used to create a single value of change in the residual by subtracting the 1991 residual from the 2000 residual. The effect of a positive serology for *H. pylori* on change in residual value of FEV_1 was modelled independently using multiple linear regression adjusting for smoking status and smoking pack years in 1991.

The analyses were carried out STATA version nine (Stata Corporation, College Station, TX, USA).

Results

In 1991, 2633 individuals provided complete data, representing 48–59% of those eligible to participate[19]

Table 1 Baseline characteristics of study population in 1991

	Total	Provided blood for *H. pylori*	*H. pylori* seropositive	*H. pylori* seronegative
Number of participants	2633	2437	643	1732
Males, *N* (%)	1312 (50)	1216 (50)	341 (53)	841 (49)
Age mean in years (SD)	44.4 (13.6)	44.6 (13.5)	51.3 (12.3)	42 (13)
Mean height, m (SD)	1.68 (0.1)	1.68 (0.1)	1.67 (0.1)	1.68 (0.1)
Mean body mass index (kg/m^2)	25.5 (4.0)	25.5 (4.0)	26.0 (4.0)	25.3 (4.0)
	N = 2614	*N* = 2420	*N* = 639	*N* = 1719
Smoking status, *N* (%)				
Never	1306 (50)	1197 (49)	256 (40)	916 (53)
Ex	730 (28)	682 (28)	212 (33)	452 (26)
Current	597 (23)	558 (23)	175 (27)	364 (21)
Mean FEV_1 – L (SD)	3.19 (0.92)	3.18 (0.93)	2.87 (0.90)	3.30 (0.91)
Mean FVC – L (SD)	3.94 (1.07)	3.94 (1.08)	3.64 (1.06)	4.05 (1.06)
Wheeze in the past 12 months (%)	632 (24)	592 (24)	177 (27)	397 (23)
Hayfever (%)	669 (25)	612 (25)	143 (22)	455 (26)
Chronic bronchitis[a] (%)	354 (13)	330 (14)	107 (17)	208 (12)
Physician diagnosed asthma (%)	236 (9)	221 (9)	62 (9)	151 (9)
Atopy[b] (%)	801 (30)	735 (30)	162 (25)	552 (32)
Bronchial hyper-reactivity (%)				
Negative	2101 (80)	1946 (80)	484 (75)	1418 (82)
Positive	314 (12)	293 (12)	81 (13)	202 (12)
Not tested	218 (8)	198 (8)	78 (12)	112 (6)
Median serum CRP, mg/l (IQR)	–	1.14 (0.55–2.42)	1.47 (0.71–3.47)	1.05 (0.51–2.14)
		N=2423	*N*=642	*N*=1719
Mean log IgE, IU/ml (SD)	–	1.44 (0.74)	1.45 (0.75)	1.44 (0.73)
		N = 2434	*N* = 643	*N* = 1729
***Helicobacter pylori* serology**				
Negative	–	1732 (71)	–	–
Indeterminate	–	62 (3)	–	–
Positive	–	643 (26)	–	–

[a]Chronic bronchitis defined as the presence of either a cough or phlegm in the morning for 3 months or more per year.
[b]Defined as a positive skin prick test $\geqslant$3 mm to *Dermatophagoides pteronyssinus*, grass pollen and cat fur subtracting the negative saline control.
IQR, interquartile range.

and of these 1346 (51%) were followed up and provided further data in 2000 (Table 1). The reasons for not subsequently participating were death (4%), moved away (7%), declined to participate (23%) and 15% of the initial sample population were uncontactable. Satisfactory lung function measures were unavailable in three individuals, and these were excluded from further analyses. Of those who participated in 1991, 93% gave a serum sample suitable for *H. pylori* analysis and these individuals were generally representative of the total study population. Serum HP status was significantly positively associated with C-reactive protein ($P < 0.001$) and body mass index ($P < 0.001$), and inversely associated with dietary magnesium intake ($P = 0.006$) and height ($P = 0.001$).

Cross-sectional analysis of serum *H. pylori* and atopy, bronchial hyper-reactivity and allergic disease

There was no association between *H. pylori* serological status and atopy as defined by a positive skin prick test, bronchial hyper-reactivity to methacholine, symptoms of chronic bronchitis, wheeze in the past 12 months; hayfever or asthma diagnosed by a physician (Table 2). There was also no association

Table 2 The effect of a positive *H. pylori* serological assay on risk of respiratory symptoms, allergic disease, atopy and bronchial hyper-reactivity in the Nottingham Lung Health Study population in 1991: a cross-sectional analysis

	Number of individuals	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)
Wheeze in the past 12 months[c]	Yes—574 No—1801	1.08 (0.86–1.35)	0.94 (0.74–1.19)
Chronic bronchitis[d]	Yes—315 No—2060	1.20 (0.92–1.57)	1.00 (0.75–1.33)
Self-reported hayfever	Yes—598 No—1777	0.94 (0.75–1.18)	1.00 (0.79–1.26)
Doctor diagnosed asthma[c]	Yes—213 No—2162	1.11 (0.80–1.56)	1.09 (0.77–1.54)
Atopy[e]	Yes—714 No—1661	0.94 (0.76–1.17)	0.92 (0.74–1.15)
Bronchial hyper-reactivity[c,f]	Yes—283 No—1902	1.11 (0.82–1.51)	1.07 (0.79–1.47)

[a]Adjusted for age.
[b]All analyses adjusted for age, sex, serum C-reactive protein (in quintiles), smoking status in 1991, smoking pack years, dietary magnesium intake and body mass index in 1991.
[c]Analysis also adjusted for FEV_1.
[d]Defined as the presence of either a cough or phlegm in the morning for 3 months or more per year.
[e]Defined as a positive skin prick test $\geqslant 3$ mm to *Dermatophagoides pteronyssinus*, grass pollen and cat fur subtracting the negative saline control, analysis also adjusted for vitamin E intake.
[f]Defined as a $PD_{20} \leqslant 12.25$ μmol.

between log IgE and positive *H. pylori* serological status (0.03 IU/ml, 95% CI −0.04 to +0.10) after adjusting for age, sex and vitamin E intake.

Cross-sectional analysis of serum *H. pylori* and lung function

Individuals with serological evidence of exposure to *H. pylori* had lower lung function with a decrease in FEV_1 of 53 ml (95% CI 1–106) and a decrease in FVC of 83 ml (95% CI 20–145) in the cross-sectional analysis (Table 3). However, after adjustment for either height or social class the size of these associations were reduced and the confidence intervals included zero.

After adjustment for height and stratification for gender, effect modification ($P < 0.001$) was seen for the association between positive serology for *H. pylori* and FEV_1 in men (−40 ml; 95% CI −118 to +38) compared with women (+35 ml; 95% CI −18 to +87). Similar effect modification by gender of the association between *H. pylori* with lung function was also seen for FVC ($P = 0.001$). Complex effect modification by decade of birth on the association between *H. pylori* exposure and lung function were observed ($P = 0.002$–0.215), with no apparent trend seen.

There were 128 individuals with COPD. There was no association between a positive serological assay for *H. pylori* and a diagnosis of COPD with an odds ratio of 0.92 (95% CI 0.61–1.39).

Longitudinal analysis of serum *H. pylori* seropositivity and decline in lung function

Helicobacter pylori serological status had no effect on the decline in lung function over 9 years. Those with a positive *H. pylori* serological assay in 1991 had an increased loss of FEV_1 of 17 ml (95% CI −26 to +60) compared with those who were seronegative. There was no evidence of effect modification of the association between decline in lung function and *H. pylori* serological status by gender or smoking status on decline in lung function.

Discussion

This is the first study to investigate the association between exposure to *H. pylori* and objective measures of asthma, atopy and lung function both cross-sectionally and longitudinally using a randomly selected population with detailed outcome measurements and longitudinal follow up data. In the cross-sectional analysis, those who had a positive *H. pylori* serology had a decrease in FEV_1 of −53 ml and a decrease in FVC of −83 ml compared with those with negative *H. pylori* serology. These differences did not persist after adjustment for socio-economic status or height. We were unable to identify an association between positive *H. pylori* serological status and either COPD, asthma, allergic disease or atopy cross-sectionally or decline in lung function.

Strengths and limitations of our data

The strengths of this dataset are the randomly selected population of over 2000 individuals from the electoral register of a Local Authority Area in Nottingham, which is likely to be a representative sample of the general population. We had detailed phenotypic data on outcomes associated with allergic

Table 3 The effect of a positive *H. pylori* serological assay on lung function in the Nottingham Lung Health Study population in 1991: a cross-sectional analysis

	N	FEV_1 (ml) (95% CIs)			FVC (ml) (95% CIs)		
Stratified by	2344	Basic model[a] −53 (−106 to −1)	Basic model plus SEC[b] −38 (−91 to +16)	Basic model plus height −6 (−53 to +42)	Basic model[a] −83 (−145 to −20)	Basic model plus SEC[b] −62 (−125 to +2)	Basic model plus height −21 (−76 to +34)
Smoking status							
Never	1155	−128 (−206 to −51)	−107 (−187 to −28)	−62 (−131 to +8)	−152 (−243 to −61)	−128 (−223 to −33)	−64 (−144 to +16)
Ex	655	+23 (−72 to +119)	+33 (−64 to +130)	+55 (−34 to +145)	+21 (−94 to +136)	+33 (−84 to +150)	+65 (−40 to +170)
Current	534	−20 (−130 to +89)	−23 (−133 to +88)	+19 (−79 to +117)	−96 (−222 to +30)	−89 (−218 to +40)	−49 (−160 to +63)
		$P = 0.164$ (interaction)	$P = 0.256$ (interaction)	$P = 0.257$ (interaction)	$P = 0.203$ (interaction)	$P = 0.218$ (interaction)	$P = 0.285$ (interaction)
Gender							
Male	1178	−74 (−159 to +12)	−56 (−141 to +28)	−40 (−118 to +38)	−104 (−203 to −5)	−84 (−184 to +16)	−60 (−148 to +28)
Female	1180	−24 (−83 to +35)	−24 (−86 to +37)	+35 (−18 to +87)	−50 (−123 to +22)	−42 (−119 to +34)	+25 (−38 to +89)
		$P = 0.003$ (interaction)	$P = 0.003$ (interaction)	$P < 0.001$ (interaction)	$P = 0.011$ (interaction)	$P = 0.007$ (interaction)	$P = 0.001$ (interaction)
Decade of birth							
1920s	316	−15 (−147 to +117)	+23 (−112 to +159)	+46 (−84 to +176)	−40 (−196 to +116)	−3 (−164 to +159)	+44 (−107 to +195)
1930s	457	−175 (−282 to −68)	−163 (−273 to −53)	−135 (−232 to −38)	−228 (−357 to −99)	−203 (−336 to −71)	−177 (−293 to −62)
1940s	579	+20 (−77 to +117)	+15 (−84 to +114)	+40 (−48 to +128)	−6 (−121 to +109)	−5 (−122 to +113)	+22 (−79 to +123)
1950s	545	+15 (−96 to +126)	+23 (−89 to +135)	+62 (−35 to +159)	+1 (−131 to +134)	+16 (−119 to +151)	+68 (−41 to +177)
1960s	333	−91 (−298 to +115)	−80 (−304 to +144)	−41 (−215 to +133)	−74 (−314 to +166)	−60 (−321 to +202)	−18 (−224 to +187)
1970s	114	+15 (−406 to +436)	+38 (−440 to +516)	+298 (−87 to +682)	−30 (−508 to +449)	+32 (−577 to +641)	+402 (+22 to +782)
		$P = 0.025$ (interaction)	$P = 0.215$ (interaction)	$P = 0.002$ (interaction)	$P = 0.037$ (interaction)	$P = 0.037$ (interaction)	$P = 0.004$ (interaction)

[a]Basic model using FEV_1 adjusted for sex, age, age squared, smoking status (categorical), smoking pack years, diagnosis of asthma, magnesium intake, CRP (quintiles) and body mass index.
[b]SEC, socio-economic status using 1990 UK Registrar-General categories.

disease including the objective measure of bronchial reactivity, serum IgE and skin prick testing as well as self-reported symptoms of wheeze and diagnoses of asthma and hayfever. The initial response rate was estimated to range from 48% to 59% of those eligible to participate,[19] so we cannot exclude the possibility of response bias impacting on our observations. Whilst the response rate of 51% for the follow up study was potentially biased by survival, non-migration and motivation to participate, our data suggest that the participants in 2000 were broadly similar to the original population in terms of diet, smoking history, initial lung function and history of respiratory disease.[20] Another strength of this study was the availability of archived serum from 1991, and that over 90% of those who participated provided serum suitable for *H. pylori* serological analysis, thus minimizing bias. Our use of an IgG assay to ascertain prior exposure to *H. pylori* has a reported sensitivity of 91% and a specificity of 100%.[21] Although no data are specifically available on the stability of *H. pylori* serology over a 15-year period, storage of the cohort's serum samples at −80°C and testing the assays in a standardized manner by the same individual permits optimized the accuracy of our *H. pylori* serological analyses and should ensure that the bias is not introduced as a consequence of the analytical process. The fact that the prevalence of *H. pylori* infection of 26% in our population was comparable to other estimates from the United Kingdom[22] in the early 1990s suggests that our *H. pylori* serological analyses are valid. However, the serological data is unable to distinguish between current and prior infection with *H. pylori* which limits interpretation of the associations observed.

We opportunistically used the available data from our population to test two hypotheses; firstly that prior *H. pylori* exposure would result in a reduction in lung function as measured by FEV_1 and FVC; and secondly that exposure to *H. pylori* would reduce allergic disease including bronchial reactivity and atopy as measured by both skin prick test and serum IgE. These will be considered separately below.

Helicobacter pylori exposure and FEV_1 and FVC

To our knowledge this is the first large epidemiological study to assess the impact of *H. pylori* exposure on lung function as measured by FEV_1 and FVC. We observed that individuals with serological evidence of *H. pylori* exposure have a lower lung function as measured by FEV_1 and FVC, and that this association disappeared after statistical adjustment for either socio-economic status or height. The most likely interpretation for these data is that the unadjusted association between prior *H. pylori* infection and lung function is confounded by exposures associated with socio-economic status or height. A more speculative explanation is that infection with *H. pylori* or other associated exposures associated with a less affluent socio-economic status[2] reduces growth in general and of the lungs in particular.[7,8] In 2000, Davey-Smith suggested that the inverse association between height and stomach cancer may be mediated by *H. pylori* infection in childhood, and our data are consistent with the hypothesis that that *H. pylori* infection in early life may also contribute to the inverse association between height and cardio-respiratory mortality that these authors reported in the same paper.[23]

Helicobacter pylori exposure and chronic bronchitis

Although serological evidence of *H. pylori* exposure has been demonstrated in previous studies to be higher in those with chronic bronchitis[24–27] this was not replicated in our dataset. This may be a consequence of our study using a community-based sample with data permitting adjustment for multiple confounding factors.

Helicobacter pylori exposure and allergic disease

The hygiene hypothesis proposes that an increased exposure to microbes may be protective against allergic diseases such as asthma.[11] This may be a consequence of the development of a immune phenotype that is less susceptible to develop allergic disease after exposure to chronic infections with microbes that humans have evolved with over time.[28] Thus it may be hypothesized that infection with a bacterium that commonly colonizes individuals in early life such as *H. pylori* reduces the risk of allergic disease. This is consistent with data reported by Herbarth, who observed that children aged 6 years old with evidence of *H. pylori* colonization as detected by a urea breath test had a 63% reduction in physician diagnosed eczema.[29] Using data from the Third National Health and Nutrition Examination Survey, Chen reported that individuals who had serological evidence of *H. pylori* infection had no increased risk of asthma or rhinitis, although those who were seropositive for the more virulent $cagA^+$ strains of *H. pylori* had a 21% decrease in the risk of ever having had asthma, and a similar protective association was also seen for rhinitis and for skin sensitization due to moulds and pollens.[12] These authors also demonstrated that infection with either $cagA^+$ or $cagA^-$ strains of *H. pylori* was associated with a reduction in allergy symptoms, and that these associations were generally present in younger individuals, although no association was seen for self-reported wheeze in the total population. The associations with *H. pylori* serology and allergic disease are generally similar to ours, although we did not have serological data to explore the associations between individual $cagA^{+/-}$ strains and *H. pylori* infection, but only data on total exposure. We are unable to make direct comparisons with the composite measure of allergy symptoms presented by Chen but our data on the association

of *H. pylori* seropositivity with self-reported wheeze or hayfever similarly demonstrates no association. Other studies have also reported no association between *H. pylori* positive serological status with asthma[14–17] or wheeze.[18]

Atopy is associated with allergic disease, and it has been demonstrated in a population-based case–control study from Finland that individuals who are seronegative for *H. pylori* have odds ratios that vary from 1.6 to 2.3 for being atopic as defined by a positive skin prick test to one of 22 allergen extracts.[30] Similar results were observed in a second case–control study from northern Europe.[31] *Helicobacter pylori* seropositivity has been estimated to potentially account for 32% of the difference in atopy between Finland and Russia,[32] whilst a significantly lower prevalence of atopic disease was seen in those with higher levels of markers of poor hygiene,[14] although no association was reported for *H. pylori*. We also did not see any association of atopy as determined by skin prick testing or total serum IgE with *H. pylori* positive serological status using a more limited definition of atopy compared with that used in Finland.[30]

In summary, we have demonstrated that serological evidence of *H. pylori* exposure is associated with lower FEV_1 and FVC in a cross-sectional analysis, and that this association is confounded by exposures associated with socio-economic status or height. There was no association between *H. pylori* seropositivity with COPD, measures of asthma, atopy and allergic disease.

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Conflict of interest: None declared.

KEY MESSAGES

- There is no association between exposure to *H. pylori* and measures of asthma and allergic disease.
- *Helicobacter pylori* exposure may be associated with lower cross-sectional FEV_1 and FVC, but this association was not independent of height or socio-economic status.

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