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Helicobacter pylori colonization is inversely associated with childhood asthma

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Abstract

Background—Asthma, a serious health problem worldwide, is growing more common. The colonization of *Helicobacter pylori*, a major human indigenous (commensal) microbe that is present early in life may be relevant to childhood asthma risk.

Methods—We conducted cross-sectional analyses using data from 7,412 participants in the National Health and Nutrition Survey (NHANES) 1999–2000 to assess the association between *H. pylori* and childhood asthma.

Results—*H. pylori* seropositivity was inversely associated with early-onset asthma (onset age < 5 years) and current asthma in children 3–13 years. Among participants 3–19 years of age, the presence of *H. pylori* was inversely related to ever having asthma (OR = 0.69; 95% CI = 0.45–1.06), and the inverse association with early childhood-onset (<age 5) asthma was stronger (OR = 0.58; 95% CI = 0.38–0.88). Among participants 3–13 years of age, *H. pylori* was significantly inversely associated with current status of asthma (OR = 0.41; 95% CI = 0.24–0.69). *H. pylori* also was inversely related to having recently had wheezing, allergic rhinitis, and dermatitis, eczema, or rash.

Conclusions—This study is the first to report an inverse association of *H. pylori* with asthma in children. The findings indicate new directions for research and asthma prevention.

Keywords

Helicobacter pylori; epidemiology; asthma; cross-sectional study

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Introduction

In developed countries throughout the world, asthma, especially childhood asthma, has been becoming more prevalent in recent decades [1]. There has been a particular increase in children with allergic asthma, manifested by the constellation of asthma, allergic rhinitis, eczema, and skin sensitization [2]. A rapid change in disease incidence occurring in broad parts of the world strongly indicates that a widespread environmental perturbation is involved in the causation. One explanation for this phenomenon has been termed the 'hygiene hypothesis', which considers that humans are more prone to allergic disorders because of a lifestyle that may be too 'clean' [3]. The underlying hypothesis is that an antigenically rich environment may be essential for normal immune maturation, preventing allergy and asthma.

Attention has focused on exogenous exposure to environmental microbes and antigens, but no obvious candidate has emerged. The hygiene hypothesis has expanded to include exposure to several types of microorganisms and parasites, with which humans have coexisted that regulate and balance immune system development [4]. This explanation is attractive because our endogenous microbes have been changing and there is greater conservation of the constituents of our microbiota than of exogenous exposures [5]. The impact of an internal change may be more profound than the consequences of most external exposures, especially if involving microbiota that are persistent colonizers of humans [6]. Infections involving the gastrointestinal tract may be particularly relevant to this mechanism because gut-associated lymphoid tissue is critical for maturation of mucosal immunity [7]. The concept of microecologic change is particularly important now that we are entering the seventh decade of widespread antibiotic usage [8].

Helicobacter pylori has been carried in the stomach of humans at least since our ancestors last left Africa (>58,000 years ago) [9], is present in all surveyed human populations, is usually acquired within the first few years of life [10] and carried through most or all of life (if not removed by antibiotic treatment) [11], and has been nearly universal in adult populations [12]. When present, *H. pylori* is the single dominant member of the gastric microbiota [13], and has an intimate relationship with the gastric mucosa, involving its injection of bacterial constituents into epithelial cells [14]; *H. pylori*+ persons have lymphoid cells in the gastric lamina propria, including helper and regulatory T-cells, cell populations that are essentially absent in *H. pylori*-negative persons [15;16]. Despite its close, nearly universal association with humans, dating back millennia, *H. pylori* has been disappearing at an astonishing rate in developed countries [17;18], a trend that began in the early 20th century, and probably has accelerated since the advent of antibiotics. Monotherapies with several commonly used classes of antibiotics lead to *H. pylori* eradication rates between 10 and 50% [19].

We postulated an inverse relationship of the presence of *H. pylori* with asthma and atopic conditions in children. We tested this hypothesis using data from the NHANES 1999–2000 study.

Methods

Study population

The NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey uses a stratified, multistage probability design to select a representative sample of the civilian, noninstitutionalized U.S. population. Beginning in 1999, NHANES became a continuous annual survey of 5000 people rather than a periodic survey [20]. The data are released on public use data files every 2 years and

can be analyzed separately or together [20]. The 1999–2000 NHANES is the first phase of the NHANES IV. It is the most recent and the only release of this cross-sectional national survey that includes laboratory data on *H pylori* status in children and teens < 20 years old.

Variable definitions

Demographics, asthma, allergic rhinitis, and allergy symptoms—Information on demographics and medical history of asthma, allergic rhinitis, and allergy symptoms was collected using in-person interviews [20]. Participants were asked whether they had ever been diagnosed with asthma by a physician, and whether they had an asthma attack, dermatitis, eczema, rash, or wheezing in the prior year. Age of the participants was recorded as integers. Interviews for participants ≤ 15 years of age were conducted with a proxy respondent, a family member ≥ 18 years of age. Participants ≤ 19 years of age also were asked about the age at which they were first diagnosed with asthma, and whether they had hay fever in the prior year. 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—**Among all 8,969 participants aged ≥ 3 years enrolled in the NHANES 1999–2000 [20], *H. pylori* status had been determined in 7,493 participants (84%) using the Wampole enzyme-linked immunosorbent assay. For each specimen, an immune status ratio (ISR) was calculated by dividing the specimen optical density by the mean optical density of the cutoff controls. Specimens were considered negative if the ISR was 0– 0.90, and positive if the ISR was > 0.90, as in prior studies [21].

Herpes simplex I and Toxoplasma serum antibody status—In the NHANES 1999–2000, sera from examinees aged 14–49 were tested for antibody to Herpes simplex virus type 1 as described [22]. Toxoplasma serum IgG antibody status was measured for participants 6–49 years of age [23].

Antibiotic and corticosteroid use—During the household interview, participants are asked whether they had taken a medication in the past month for which they needed a prescription. The medication's complete name from the container was compared with the prescription medication database. Data were coded using the standard generic ingredient code and therapeutic drug class codes assigned based on FDA's National Drug Code Directory. We extracted data on the use of corticosteroid and antibiotic, including tetracyclines, quinolones, macrolides, penicillins, cephalosporins, amoxicillin, and antimycobacterials. Penicillins and cephalosporins were considered β-lactam antibiotics.

Statistical Methods

Descriptive analyses were first conducted to compare the distributions of sociodemographic and lifestyle variables by *H. pylori* status using T-tests (for continuous variables) and Chi-squared tests (for categorical variables). Age-specific *H. pylori* prevalence proportions were estimated using both NHANES III and NHANES 1999–2000 data.

We estimated odds ratios (ORs) associated with *H. pylori* positivity for asthma, wheezing (a characteristic symptom of asthma), and other atopic conditions including allergic rhinitis and dermatitis, eczema, or rash using unconditional logistic regression. The ORs were adjusted for age, sex, body mass index, smoking status, educational attainment, ethnic background, and country of birth. A total of 81 subjects with missing on any of the covariate variables were excluded from the analyses. The analyses were conducted in overall and in 3,327 participants < 20 years old. In addition, we tested multiplicative interaction between age and *H. pylori* status on risk of ever having asthma, current asthma status, and allergic

rhinitis status in participants < 20 years old. The statistical significance of interaction was determined based on p-values of the cross-product term of *H. pylori* status with age in the model.

We further adjusted the ORs for antibiotic use and corticosteroid use in the prior month, household income, medical insurance status, and housing characteristics. In addition, analyses were conducted in participants aged 14–49, for whom data on Herpes simplex I and Toxoplasma serum antibody status were available, and participants aged 6–49 and 6–14, for whom data on Toxoplasma serum antibody status were available, to assess the potential confounding effects of these infections.

All analyses were conducted using SAS 9.1.4 proc survey procedures (SAS Institute, Inc., Cary, NC), accounting for the complex sampling design in NHANES. Sampling errors were estimated using the primary sampling units and strata provided in the data set. Sampling weights were used to adjust for nonresponse bias and the oversampling in NHANES.

Results

The NHANES 1999–2000 study population median age was 25 years (compared with 43 years for NHANES III); in total, *H. pylori* seroprevalence was 25.8%, with lower prevalence in younger age groups (Supplemental Fig 1). For children under 10 who were born in the 1990's, only 5.4% were positive. A clear birth cohort effect with declining prevalence was seen for persons born early in the 20th century, consistent with 7prior studies [12;17;18]. Among the overall 7,412 and the 3,327 participants < 20 years old in this analysis, *H. pylori* positivity was associated with older age, lower educational attainment, race-ethnicity other than non-Hispanic white, and foreign country of birth, reflecting known relationships with demographic and lifestyle factors (Table 1).

Overall, there was a trend toward an inverse association between *H. pylori* positivity and ever having had asthma, and having had an asthma episode in the prior year (Table 2). There was a significant inverse association with dermatitis, rash, and eczema in the prior year (OR = 0.73, 95% CI: 0.56–0.96). Wheezing, one of the most characteristic manifestations of asthma, was consistently inversely related to *H. pylori* (Table 2).

Because our prior studies in adults [24;25] indicated that the inverse association with *H. pylori* was more pronounced for asthma with onset earlier in life, we now evaluated attributes of childhood asthma. We focused the analyses on the 3,327 subjects ≤ 19 years old for whom information on allergic rhinitis in the year prior to the survey, current asthma status, and age of asthma onset were available (Table 3). *H. pylori* was significantly inversely related to allergic rhinitis in the prior year. The overall association between *H. pylori* and current or lifetime status of asthma was not statistically significant. There was a strong inverse association of *H. pylori* with early-onset asthma (≤ 5 years old; OR = 0.58 95% CI: 0.38–0.88). Since early life wheezing may not necessarily represent asthma, we also estimated OR for asthma excluding participants younger than 2 years old. The inverse association remained significant (Table 3). We further examined the associations of *H. pylori* status with asthma and allergic rhinitis in stratified analyses by age. Subjects below the median age (3–13 years) in this group showed strong inverse associations of *H. pylori* with current asthma and ever having had asthma, as well as with allergic rhinitis in the prior year (Table 3). There was a statistically significant difference in the relationship of *H. pylori* with current asthma status (p=0.03) and allergic rhinitis in the prior year (p=0.02) by age. *H. pylori* also was significantly inversely related to ever having had asthma in those who also had allergic rhinitis among the overall 3–19 year age group, and both the 3–13 and 14–19 age groups.

Additional statistical control for antibiotic use and corticosteroid use in the prior month, household income, medical insurance status, and housing characteristics did not appreciably change effect estimates (Supplemental Table 1). Analyses restricted to participants at a low level of household income (< $35,000), with no medical access, or whose home was a rental also did not suggest differences in the directions of the associations (data not shown). There was no evidence that the inverse associations of *H. pylori* with asthma and atopic conditions were due to Herpes simplex I and Toxoplasma infectious status (Supplemental Table 2). In addition, Herpes simplex I and Toxoplasma infectious status were not associated with asthma and atopic conditions in the analyses (data not shown).

Discussion

In this large study of a nationally representative population, we found inverse associations between *H. pylori*-positivity and asthma, allergic rhinitis, and atopic conditions. To our knowledge, this study is the first to report the inverse association in children.

Previous studies of the association between *H. pylori* status and asthma risk generate conflicting findings [7]. These studies were mostly small-scale, conducted in adults, and also did not address the modifying roles of age. Recently, we found an inverse association of *H. pylori* with asthma, especially early-onset asthma, as well as allergic rhinitis, and skin sensitization in 7,663 participants ≥ 20 years enrolled in 1988– 1991 in the National Health and Nutrition Survey III (NHANES III) [26], for whom data on asthma history and *H. pylori* status, including *cagA* status, was available [26]. In that study, the inverse associations were most strong for the *cagA+ H. pylori* strains, which are the most interactive with humans [6;14]. A prior case-control study conducted by our group in an urban (New York City) population also showed parallel results [25]. However, data on *H. pylori* for participants < 20 years were not available in these prior analyses.

The present study included a younger study population, providing a unique opportunity to test the inverse association in children. The median age in this study was 25 years (compared to 43 in the NHANES III study). Although there was no ascertainment of *cagA* status in the present study, the inverse association between *H. pylori* and current asthma status in children (3–13 years of age, OR = 0.41; 95% CI = 0.24–0.69) independently confirms the prior observations of a strong inverse association with early-onset asthma (onset age ≤ 15 years) in adults [26]. Further, stratified analysis among participants 3–19 years of age reveals that the inverse association with early childhood-onset (<age 5) asthma was stronger (OR = 0.58; 95% CI = 0.38–0.88). It has been proposed that allergic rhinitis and allergic asthma are manifestations of the same disease entity [27]. In this way, persons with less severe disease express only rhinitis, while those with more severe disease express both rhinitis and asthma. This concept has been labeled "one airway, one disease [27]. Our analyses suggested that the association between *H. pylori* and asthma in the presence of allergic rhinitis was even stronger than in its absence. However, the sample size for this analysis was limited and the results will have to be confirmed in future studies. Taken together, findings from our analyses of data from NHANES III and NHANES 1999–2000 provide specificity of the association between *H. pylori* and asthma risk. Future studies are also needed to evaluate the associations between different *H. pylori* strains (e.g. based on *cagA status)* with asthma risk in children.

One hypothesis to explain the recent disappearance of *H. pylori* is that widespread use of antibiotics in children for treatment of a variety of infections (e.g. otitis media) [8] leads to the coincident elimination of *H. pylori* in a proportion (10–50% *per* treatment course) of children. In fact, the NHANES 1999–2000 population studied was strongly impacted by antibiotics, with 11.3% of the participants under the age of 10 years having received an

antibiotic in the month prior to their survey (8.9% having received a β-lactam antibiotic) (Supplemental Fig 2), similar to the extent of antibiotic use previously estimated based on NHANES III [28]. The high levels of such exposures in recent years could explain the progressive drop in *H. pylori* seroprevalence, which now is under 10% among native-born children in the US and other industrialized countries. Finding inverse associations between *H. pylori* status and childhood asthma also is consistent with evidence from prospective studies that antibiotic use in non-respiratory tract infections during the first year of life subsequently leads to an increased risk of childhood asthma [29].

H. pylori status could be a marker for other phenomena, such as other infections or better socioeconomic conditions. However, indicators of socioeconomic status, such as educational attainment and ethnic backgrounds were controlled in this and the study in adults [26]. Additional statistical control for country of birth, household income, medical insurance status, and housing characteristics did not appreciably change effect estimates (Supplemental Table 1). Other infectious agents that have been proposed to be relevant to the "hygiene hypothesis" and risk of asthma include Hepatitis A virus (HAV), Herpes simplex virus type I, and Toxoplasma [30]. In our previous analysis in adults, the inverse associations of *H. pylori* status with skin sensitization and risk of asthma remained similar in persons negative for serum antibody to HAV [24]. Although information on HAV antibody status was not available in NHANES 1999–2000, there was no evidence of confounding when the associations of *H. pylori* status with asthma, wheezing, dermatitis, and allergic rhinitis were additionally adjusted for Herpes simplex I and Toxoplasma serum antibody status (Supplemental Table 2). Herpes simplex I and Toxoplasma serum antibody status were not associated with any of the outcomes of interest. In a study comparing adults in Finland and Russia, among 22 microbes examined, *H. pylori* alone explained about half of the difference in atopy prevalence between the two populations [31]. Future large studies are needed to investigate the joint effect of these infections on asthma risk.

Potential limitations of the present study include the use of cross-sectional study design and self-report health data. The enzyme-linked immunosorbent assay (ELISA) detects IgG antibodies to *H. pylori*, indicating current or recent past infection. The crosssectional design could reflect possible problems of reverse causation. For example, asthmatics may more frequently receive antibiotics and corticosteroids that could reduce *H. pylori* prevalence, as compared to non-asthmatics. The present study can not entirely rule out this possibility. However, evidence in the literature is lacking about changes of *H. pylori* status in asthmatics. Once acquired, *H. pylori* is carried through most or all of life; Kuipers *et al*. have documented that *H. pylori* positivity converted in only 3 of 56 persons in the absence of specific antimicrobial therapy for unknown reasons over 11 years [11]. In the present study, among asthma cases, there was no association between time since onset and *H. pylori* positivity (data not shown). Statistical adjustment of the use of antibiotics and corticosteroids in the prior month, as a proxy measure of frequent use, did not change the effect estimates (Supplemental Table 1). In addition, the specificity of the inverse association with early-life onset asthma and not with long-standing asthma seen in adults is an argument against that proposition. The use of self-report data on asthma and atopic conditions also may have led to recall bias or measurement errors. Future studies in children should collect data on specific IgE concentrations in blood as well as from skin prick tests, to complement studies in adults [24;25]. However, it is not likely that participants would have reported their disease status differently according to *H. pylori* status because the latter was not known by them. Previous studies have suggested that self-reported asthma has acceptable validity and reliability [32–34].

That *H. pylori* could be protective against asthma is biologically plausible: there is a secular trend in which its disappearance coincides with the rise in asthma. Increases in the

prevalence of asthma of similar or even greater magnitude were reported from many countries during the second half of the 20th century [1]. There has been a sharp decline in *H. pylori* since 1930 and the decline accelerated after 1970 [35–37]. The loss of an endogenous highly interactive organism like *H. pylori* [6] would be predicted to have physiological consequences [38]. Indeed, its absence is associated with the loss of a metabolically active lymphoid compartment in the stomach [15;16]. This compartment, with both activator and regulatory T-cells, could be involved in setting the age-dependent threshold for allergic sensitization to environmental allergens; in its absence, we postulate a lowered threshold. Our findings suggest that *H. pylori* status is one of the measurable risk factors for asthma and atopic conditions in children. This epidemiologic observation points to the need for future prospective studies to delineate the underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Distribution of demographic and lifestyle factors by *H. pylori* status, NHANES 1999–2000

Demographic and lifestyle factor	Overall			Age 3–19		
	H. pylori- (n = 4787)	*H. pylori*$^{+}$ (n = 2625)	*p-value**	*H. pylori*- (n = 2577)	*H. pylori*$^{+}$ (n = 750)	*p-value**
Sex						
Men, %	48.9	49.4	0.76	51.7	57.2	0.15
Age						
Mean (SD), years	34.0 (0.35)	45.0 (0.51)	<0.01	11.1 (0.14)	12.9 (0.29)	<0.01
Educational attainment						
Less than high school	37.4	46.4	<0.01	91.7	94.1	0.07
High school diploma	19.4	24.3		4.4	4.4	
More than high shcool	43.2	29.3		3.9	1.4	
Race-ethnicity, column %						
Mexican American	5.3	13.7	<0.01	9.8	23.9	<0.01
Other Hispanic	6.0	14.2		7.8	11.0	
Non-Hispanic White	76.0	46.5		63.3	24.0	
Non-Hispanic Black	8.4	19.4		12.1	33.9	
Other Race – Including Multi-racial	4.4	6.2		7.0	7.1	
Country of birth, column %						
Born in 50 US States or Washington, DC	91.4	69.5	<0.01	94.4	77.4	<0.01
Mexico	1.5	8.1		1.3	7.6	
Elsewhere	7.1	22.3		4.3	14.8	
Body Mass Index						
Mean (SD)	25.7 (0.14)	27.4 (0.19)	<0.01	20.2 (0.14)	21.8 (0.35)	<0.01
Cigarettes smoking, column %						
Non-smokers	44.1	43.9	<0.01	21.8	27.8	<0.01
Past smokers	21.5	23.9		13.5	18.5	
Current smokers	18.9	28.2		11.0	16.0	
Unknown (< age of 12)	15.5	3.9		53.9	37.6	
Use of antibiotic in the prior month, column %	7.2	5.8	0.17	8.7	6.4	0.29

Demographic and lifestyle factor	Overall			Age 3–19		
	H. pylori- (n = 4787)	*H. pylori*+ (n = 2625)	*p-value* *	*H. pylori*- (n = 2577)	*H. pylori*+ (n = 750)	*p-value* *
Use of corticosteroid in the prior month, column %	7.0	7.2	0.88	2.8	1.8	0.24

* p-values were based on Chi-square test or T-test.

Table 2

Association of *H. pylori* status with asthma, wheezing, dermatitis, and allergic rhinitis

Outcome	*H. pylori* −	*H. pylori* +	OR (95% CI) for outcome associated with *H. pylori* positivity*
All	4787	2625	
Asthma			
Never had asthma	4108	2358	
Ever had asthma	679	267	0.89 (0.68–1.16)
Had an asthma episode in prior year	234	85	0.68 (0.44–1.05)
Dermatitis, eczema, rash in prior year			
No	3947	2356	
Yes	514	234	0.73 (0.56–0.96)
Wheezing or whistling in chest in prior year			
No	4126	2346	
Yes	653	275	0.73 (0.57–0.94)
Wheezing disturbed sleep	339	144	0.68 (0.48–0.96)
Chest sounded wheezy during exercise	315	126	0.63 (0.44–0.90)
Took medication for wheezing	315	123	0.66 (0.46–0.94)
Went to doctor’s office or hospital for wheezing or whistling	298	118	0.66 (0.45–0.95)
Limited usual activities, due to wheezing	257	105	0.52 (0.36–0.75)
Limited speech to one or two words between breaths, due to wheezing	110	53	0.51 (0.28–0.90)
Missed work or school, due to wheezing or whistling	139	50	0.56 (0.31–0.99)

*ORs and 95% Confidence Intervals (CI) were adjusted for race-ethnicity, country of birth, age, sex, BMI, smoking status (for participants > 12 years old), and educational attainment (for participants > 12 years old). Participants ≤ 12 years old were considered non-smokers and in a separate category for educational attainment. The reference group was *H. pylori*-negative persons.

Table 3

Association of *H. pylori* status with asthma and allergic rhinitis in participants 3–19 years of age ‡

Age group/Outcome	Age 3 – 19 *H. pylori* −	Age 3 – 19 *H. pylori* +	Age 3 – 19 OR (95% CI) for outcome associated with *H. pylori* positivity *	Age 3 – 13 *H. pylori* −	Age 3 – 13 *H. pylori* +	Age 3 – 13 OR (95% CI) for outcome associated with *H. pylori* positivity*	Age 14– 19 *H. pylori* −	Age 14– 19 *H. pylori* +	Age 14– 19 OR (95% CI) for outcome associated with *H. pylori* positivity *	P for interaction**
Total	2577	750		1491	298		1086	452		
Allergic rhinitis in prior year										
No	2289	687		1325	281		964	406		
Yes	275	62	0.60 (0.37–0.96)	156	18	0.31 (0.17–0.57)	119	44	0.88 (0.47–1.66)	0.02
Asthma										
Never	2168	652		1249	261		919	391		
Current	253	66	0.75 (0.44–1.27)	156	25	0.41 (0.24–0.69)	97	41	1.14 (0.56–2.32)	0.03
Ever	409	98	0.69 (0.45–1.06)	242	37	0.49 (0.30–0.80)	167	61	0.84 (0.46–1.55)	0.15
Ever, age at onset < 5 †	211	45	0.58 (0.38–0.88)							
Ever, age at onset 2–5 **	103	16	0.32 (0.17–0.60)							
Ever, age at onset ≥ 5 †	194	51	0.78 (0.41–1.50)							
Ever with allergic rhinitis in prior year	81	14	0.39 (0.20–0.75)	46	6	0.35 (0.12–1.00)	35	8	0.37 (0.16–0.89)	0.99

* ORs and 95% Confidence Intervals (CI) were adjusted for race-ethnicity, country of birth, age, sex, BMI, smoking status (for participants > 12 years old), and educational attainment (for participants > 12 years old). Participants ≤ 12 years old were considered non-smokers and in a separate category for educational attainment. The reference group was *H. pylori*-negative persons.

† Cut-point was determined based on median onset age. Information on age at onset was missing for 6 participants who had ever had asthma.

‡ Allergic rhinitis in the prior year, current status of asthma, and age at onset of asthma were ascertained only for participants ≤ 19 years of age. Stratified analysis was based on the median age (13 years) among participants ≤ 19 years. A total of 15 subjects with unknown allergic rhinitis status were excluded from the analyses of allergic rhinitis.

** P value for interaction between *H. pylori* status and age on the risk of ever having asthma, current asthma status, and allergic rhinitis in prior year.