Helicobacter pylori Colonization Is Inversely Associated with Childhood Asthma

Yu Chen[1,2,3] and Martin J. Blaser[3,4,5]

Departments of [1]Environmental Medicine, [3]Medicine, and [4]Microbiology, School of Medicine, and [2]Cancer Institute, New York University, and [5]Department of Veterans Affairs Medical Center, New York, New York

Background. Asthma, a serious health problem worldwide, is becoming more common. Colonization with *Helicobacter pylori,* a major human indigenous (commensal) microbe, during early life may be relevant to the risk of childhood asthma.

Methods. We conducted cross-sectional analyses, using data from 7412 participants in the National Health and Nutrition Examination Survey (NHANES) 1999–2000, to assess the association between *H. pylori* and childhood asthma.

Results. *H. pylori* seropositivity was inversely associated with onset of asthma before 5 years of age and current asthma in children aged 3–13 years. Among participants 3–19 years of age, the presence of *H. pylori* was inversely related to ever having had asthma (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.45–1.06), and the inverse association with onset of asthma before 5 years of age was stronger (OR, 0.58; 95% CI, 0.38–0.88). Among participants 3–13 years of age, *H. pylori* positivity was significantly inversely associated with current asthma (OR, 0.41; 95% CI, 0.24–0.69). *H. pylori* seropositivity also was inversely related to recent wheezing, allergic rhinitis, and dermatitis, eczema, or rash.

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

In developed countries, asthma, especially childhood asthma, has been becoming more prevalent in recent decades [1]. There has been a particular increase in the number of children with allergic asthma, which is manifested by the constellation of asthma, allergic rhinitis, eczema, and skin sensitization [2]. A rapid change in disease incidence is occurring in broad parts of the world and strongly indicates that a widespread environmental perturbation is involved in the causation of asthma. 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, thereby 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 that coexist with humans and have the ability to regulate and balance the development of the immune system in humans [4]. This explanation is attractive because the composition and stability of the endogenous microbe population have been changing and because the conservation of the constituents of our microbiota is greater than that of exogenous organisms [5]. The impact of an internal change may be more profound than the consequences of most external exposures, especially if the change involves 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

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Reprints or correspondence: Dr. Martin J. Blaser, Dept. of Medicine, New York University School of Medicine, 550 First Ave., OBV A-606, New York, NY 10016 (Martin.Blaser@med.nyu.edu).

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concept of microecologic change is particularly important now that we are entering the seventh decade of widespread antibiotic use [8].

Helicobacter pylori has appeared in the stomach of humans at least since the initial migration of our ancestors from 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 prevalent in nearly all 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, where it injects bacterial constituents into epithelial cells [14]. *H. pylori*–positive persons have lymphoid cells, including helper and regulatory T cells, in the gastric lamina propria, and these cell populations are essentially absent in *H. pylori*–negative persons [15, 16]. Despite its close, nearly universal association with humans that dates back millennia, the prevalence of *H. pylori* positivity has been decreasing at an astonishing rate in developed countries [17, 18], a trend that began early during the 20th century and probably accelerated after the advent of antibiotics. Monotherapies with several commonly used classes of antibiotics lead to *H. pylori* eradication rates of 10%–50% [19].

We postulated an inverse relationship between the presence of *H. pylori* and both asthma and atopic conditions in children. We tested this hypothesis by analyzing data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000.

SUBJECTS, METHODS, AND MATERIALS

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 US population. Beginning in 1999, the 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]. NHANES 1999–2000 is the first phase of 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 teenagers.

Variable Definitions

Demographic characteristics, asthma, allergic rhinitis, and allergy symptoms. Information on demographic characteristics and medical history of asthma, allergic rhinitis, and allergy symptoms was collected using in-person interviews [20]. Participants were asked whether they had ever received a diagnosis of asthma from a physician and whether they had had an asthma attack, dermatitis, eczema, rash, or wheezing in the past year. Participants' ages were recorded as integers. Interviews for participants ≤15 years of age were conducted with a proxy respondent who was a family member ≥18 years of age. Participants ≤19 years of age also were asked about the age at which asthma was first diagnosed and whether they had had hay fever in the past year.

The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (Atlanta, GA). All participants or their proxy respondents gave written informed consent.

H. pylori *status.* Of the 8969 participants aged ≥3 years enrolled in NHANES 1999–2000 [20], *H. pylori* status had been determined in 7493 (84%), using the Wampole ELISA. For each specimen, an immune status ratio (ISR) was calculated by dividing the optical density of the specimen by the mean optical density of the cutoff controls. Specimens were considered negative for *H. pylori* if the ISR was 0–0.90 and positive for *H. pylori* if the ISR was >0.90, as described in previous studies [21].

Herpes simplex virus type 1 (HSV-1) and* Toxoplasma *serum antibody status. In NHANES 1999–2000, serum specimens from examinees aged 14–49 were tested for antibody to HSV-1, as described elsewhere [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 were asked whether they had taken a medication in the past month for which they needed a prescription. The medication's complete name as it appeared on the container was compared with drug names in the prescription medication database. Data were coded using the standard generic ingredient code and therapeutic drug class codes assigned in the Food and Drug Administration's National Drug Code Directory. We extracted data on the use of corticosteroids and antibiotics, including tetracyclines, quinolones, macrolides, penicillins, cephalosporins, amoxicillin, and antimycobacterials. Penicillins and cephalosporins were considered β-lactam antibiotics.

Statistical Analyses

Analyses of descriptive statistics were first conducted to compare the distributions of sociodemographic and lifestyle variables on the basis of *H. pylori* status, using *t* tests (for continuous variables) and χ^2 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, education level, race-ethnicity, and country of

The figure is available in its entirety in the online edition of the *Journal of Infectious Diseases*.

Figure 1. Age-specific prevalence of *Helicobacter pylori* positivity among men and women in the National Health and Nutrition Examination Survey (NHANES) III Phase I (1988–1991) and NHANES 1999–2000, by age and year of birth. Prevalence data for participants ⩽19 years of age were not available in NHANES III. For consistency, we did not consider the *H. pylori cagA* IgG ELISA results in NHANES III and participants with an immune status ratio 0.91–1.09 in NHANES 1999–2000.

birth. A total of 81 subjects with missing data for any of the covariate variables were excluded from the analyses. The analyses were conducted for all participants and for 3327 participants <20 years old. In addition, we tested for multiplicative interaction between age and *H. pylori* status with respect to the risk of ever having had asthma, current asthma, and having had allergic rhinitis in the past year among participants <20 years old. The statistical significance of interaction was determined by calculation of *P* values of the cross-product term of *H. pylori* status and age in the model.

We further adjusted the ORs for antibiotic use and corticosteroid use in the past month, household income, medical insurance status, and housing type. In addition, analyses were conducted for participants aged 14–49 years, for whom data on HSV-1 and *Toxoplasma* serum antibody status were available, and participants aged 6–49 and 6–14 years, for whom data on *Toxoplasma* serum antibody status only 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) and accounted 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.

Table 1. Demographic characteristics and lifestyle factors, according to *Helicobacter pylori* status, among participants in the National Health and Nutrition Survey, 1999–2000.

	Overall, by *H. pylori* status			Age of 3–19 years, by *H. pylori* status		
Variable	Negative (n = 4787)	Positive (n = 2625)	P[a]	Negative (n = 2577)	Positive (n = 750)	P[a]
Male sex	48.9	49.4	.76	51.7	57.2	.15
Age, mean ± SD, years	34.0 ± 0.35	45.0 ± 0.51	<.01	11.1 ± 0.14	12.9 ± 0.29	<.01
Educational level						
Less than high school	37.4	46.4	<.01	91.7	94.1	.07
High school diploma	19.4	24.3		4.4	4.4	
More than high school	43.2	29.3		3.9	1.4	
Race-ethnicity						
Hispanic						
Mexican American	5.3	13.7	<.01	9.8	23.9	<.01
Other	6.0	14.2		7.8	11.0	
Non-Hispanic						
White	76.0	46.5		63.3	24.0	
Black	8.4	19.4		12.1	33.9	
Other, including multiracial	4.4	6.2		7.0	7.1	
Birthplace						
US state or Washington, DC	91.4	69.5	<.01	94.4	77.4	<.01
Mexico	1.5	8.1		1.3	7.6	
Elsewhere	7.1	22.3		4.3	14.8	
Body mass index,[b] mean ± SD	25.7 ± 0.14	27.4 ± 0.19	<.01	20.2 ± 0.14	21.8 ± 0.35	<.01
Cigarette smoking						
Nonsmoker	44.1	43.9	<.01	21.8	27.8	<.01
Past smoker	21.5	23.9		13.5	18.5	
Current smoker	18.9	28.2		11.0	16.0	
Unknown (<12 years old)	15.5	3.9		53.9	37.6	
Antibiotic use in past month	7.2	5.8	.17	8.7	6.4	.29
Corticosteroid use in past month	7.0	7.2	.88	2.8	1.8	.24

NOTE. Data are percentage of participants, unless otherwise indicated.

[a] Determined on the basis of χ^2 tests or t tests.

[b] Defined as the weight in kilograms divided by the height in meters squared.

Table 2. Association of *Helicobacter pylori* status with asthma, wheezing, dermatitis, and allergic rhinitis.

Outcome	*H. pylori* status		
	Negative (n = 4787)	Positive (n = 2625)	OR (95% CI)[a]
Asthma history			
None	4108	2358	. . .
Ever	679	267	0.89 (0.68–1.16)
⩾1 attack in past year	234	85	0.68 (0.44–1.05)
Dermatitis, eczema, or rash in past year			
No	3947	2356	. . .
Yes	514	234	0.73 (0.56–0.96)
Wheezing or whistling in chest in past 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)
Visited physician's office or hospital for wheezing or whistling	298	118	0.66 (0.45–0.95)
Limited usual activities because of wheezing	257	105	0.52 (0.36–0.75)
Speech limited to 1–2 words between breaths because of wheezing	110	53	0.51 (0.28–0.90)
Missed work or school because of wheezing or whistling	139	50	0.56 (0.31–0.99)

[a] Odds ratios (ORs) and 95% confidence intervals (CIs) correspond to the ratio of the odds of outcome in *H. pylori* positivity versus the odds of outcome in *H. pylori* negativity. Analyses were adjusted for race-ethnicity, country of birth, age, sex, body mass index, smoking status (for participants >12 years old), and education level (for participants >12 years old). Participants ⩽12 years old were considered to be nonsmokers and in a separate category for education level.

RESULTS

The median age of the NHANES 1999–2000 study population was 25 years (the median age was 43 years for the NHANES III population); in total, the seroprevalence of *H. pylori* was 25.8%, with a lower prevalence in younger age groups (figure 1, which appears only in the electronic edition of the *Journal*). For children aged <10 years who were born in the 1990s, only 5.4% tested positive for *H. pylori*. A clear birth-cohort effect with a decreasing prevalence was seen for persons born early in the 20th century, consistent with findings from previous studies [12, 17, 18]. For all 7412 participants and the 3327 participants <20 years old in this analysis, *H. pylori* positivity was associated with older age, lower education level, race-ethnicity other than non-Hispanic white, and foreign country of birth, which reflects known relationships between *H. pylori* status and 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 ⩾1 asthma attack in the past year (table 2). There was a significant inverse association between *H. pylori* positivity and having had dermatitis, rash, and eczema in the past year (OR, 0.73; 95% confidence interval [CI], 0.56–0.96). Wheezing, one of the most characteristic manifestations of asthma, was consistently inversely related to *H. pylori* positivity (table 2).

Because our past studies involving adults [24, 25] indicated that the inverse association with *H. pylori* positivity was more pronounced for asthma that began earlier in life, we evaluated attributes of childhood asthma. We focused the analyses on 3327 subjects aged ⩽19 years for whom information on allergic rhinitis in the year before the survey, current asthma status, and age at asthma onset were available (table 3). *H. pylori* positivity was significantly inversely related to having had allergic rhinitis in the past year. The overall association between *H. pylori* status and current asthma or ever having had asthma was not statistically significant. There was a strong inverse association between *H. pylori* positivity and onset of asthma before 5 years of age (OR, 0.58; 95% CI, 0.38–0.88). Because wheezing during early life may not necessarily represent asthma, we also estimated the OR for asthma after exclusion of participants <2 years old from the analysis. The inverse association remained significant (table 3). We further examined the associations between *H. pylori* status and both asthma and allergic rhinitis in analyses stratified by age. Subjects younger than the median age (i.e., those aged 3–13 years) showed strong inverse associations between *H. pylori* positivity and current asthma, ever having had asthma, and having had allergic rhinitis in the past year (table 3). There was a statistically significant difference in the relationship between *H. pylori* positivity and current asthma (P = .03) and having had allergic rhinitis in the past year (P = .02), according to age.

Table 3. Association between *Helicobacter pylori* status and both asthma and allergic rhinitis in participants 3–19 years of age.

Outcome	Age, *H. pylori* status[a]									
	3–19 years			3–13 years			14–19 years			
	Negative (n = 2577)	Positive (n = 750)	OR (95% CI)	Negative (n = 1491)	Positive (n = 298)	OR (95% CI)	Negative (n = 1086)	Positive (n = 452)	OR (95% CI)	P[b]
Allergic rhinitis in past year[c]										
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)	.02
Asthma history										
None	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)	.03
Ever, onset age[d]										
Overall	409	98	0.69 (0.45–1.06)	242	37	0.49 (0.30–0.80)	167	61	0.84 (0.46–1.55)	.15
<5 years	211	45	0.58 (0.38–0.88)	. . .	. . .	. . .	. . .	. . .	. . .	
2 to <5 years	103	16	0.32 (0.17–0.60)	. . .	. . .	. . .	. . .	. . .	. . .	
⩾5 years	194	51	0.78 (0.41–1.50)	. . .	. . .	. . .	. . .	. . .	. . .	
Allergic rhinitis in past year and ever having asthma	81	14	0.39 (0.20–0.75)	46	6	0.35 (0.12–1.00)	35	8	0.37 (0.16–0.89)	.99

NOTE. Allergic rhinitis in the past year, current asthma, and age at the 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 of age.

[a] Odds ratios (ORs) and 95% confidence intervals (CIs) correspond to the ratio of the odds of outcome in *H. pylori* positivity versus the odds of outcome in *H. pylori* negativity. Analyses were adjusted for race-ethnicity, country of birth, age, sex, body mass index, smoking status (for participants >12 years old), and education level (for participants >12 years old). Participants ⩽12 years old were considered nonsmokers and in a separate category for education level.

[b] Data indicate the interaction between *H. pylori* status and age on the risk of ⩾1 asthma attack, current asthma, and allergic rhinitis in past year.

[c] A total of 15 participants with an unknown allergic rhinitis status were excluded from analyses.

[d] Cut points were determined on the basis of the median onset age. Information on the age of onset was missing for 6 participants who had had ⩾1 asthma attack.

Table 4. Association between *Helicobacter pylori* status and both asthma and allergic rhinitis, with additional control for socioeconomic status.

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In the groups aged 3–19 years, 3–13 years, and 14–19 years, *H. pylori* positivity was also significantly inversely related to ever having had asthma for subjects who also had had allergic rhinitis.

Additional statistical control for antibiotic use and corticosteroid use in the past month, household income, medical insurance status, and housing type did not appreciably change effect estimates (table 4, which appears only in the electronic edition of the *Journal*). Analyses restricted to participants with a low level of household income (less than US$35,000 per year), 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 between *H. pylori* positivity and both asthma and atopic conditions were due to HSV-1 or *Toxoplasma* infections (table 5, which appears only in the electronic edition of the *Journal*). In addition, HSV-1 and *Toxoplasma* infections 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 associations in children.

Previous studies of the association between *H. pylori* status and asthma risk generated conflicting findings [7]. These studies were mostly small in scale, conducted in adults, and also did not address the modifying roles of age. Recently, we found an inverse association between *H. pylori* positivity and asthma, especially onset of asthma before 16 years of age, as well as allergic rhinitis, and skin sensitization in 7663 participants aged ⩾20 years enrolled in 1988–1991 in the 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*-positive *H. pylori* strains, which are the most interactive with humans [6, 14]. A previous case-control study conducted by our group in an urban population (i.e., New York City) also showed parallel results [25]. However, data on *H. pylori* status for participants aged <20 years were not available in these previous analyses.

Table 5. Association between *Helicobacter pylori* status and both asthma and allergic rhinitis, with additional control for herpes simplex type 1 and *Toxoplasma* serum antibody status.

The table is available in its entirety in the online edition of the *Journal of Infectious Diseases*.

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Figure 2. Use of any antibiotics and β-lactams only in the past month, as reported by 9965 participants in the National Health and Nutrition Examination Survey 1999–2000. All penicillins and cephalosporins were considered β-lactam antibiotics.

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 with 43 in the NHANES III study). Although there was no ascertainment of *cagA* status in the present study, the inverse association between *H. pylori* presence and current asthma in children 3–13 years of age (OR, 0.41; 95% CI, 0.24–0.69) independently confirmed the past observation of a strong inverse association with onset of asthma before 16 years of age in adults [26]. Furthermore, stratified analysis among participants 3–19 years of age revealed that the inverse association with onset of asthma before 5 years of age 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, whereas 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 the absence of allergic rhinitis. 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., *cagA*-positive and -negative strains) 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 percentage (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 aged <10 years having received an antibiotic (a β-lactam antibiotic in 8.9% of cases) in the month before they were surveyed (figure 2, which appears only in the electronic edition of the *Journal*), similar to the extent of antibiotic use previously estimated on the basis of NHANES III data [28]. The high levels of such exposures in recent years could explain the progressive decrease in *H. pylori* seroprevalence, which now is <10% among native-born children in the United

States 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 for treatment of 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 education level and ethnic backgrounds, were controlled in this study and the study involving adults [26]. Additional statistical control for country of birth, household income, medical insurance status, and housing type did not appreciably change effect estimates (table 4). Other infectious agents that have been proposed to be relevant to the hygiene hypothesis and the risk of asthma include hepatitis A virus, HSV-1, and *Toxoplasma* organisms [30]. In our previous analysis of adults, the inverse associations between *H. pylori* positivity and both skin sensitization and the risk of asthma remained similar among persons who tested negative for serum antibody to hepatitis A virus [24]. Although information on hepatitis A virus antibody status was not available in NHANES 1999–2000, there was no evidence of confounding when analyses of the associations of *H. pylori* status with asthma, wheezing, dermatitis, and allergic rhinitis were additionally adjusted for HSV-1 and *Toxoplasma* serum antibody status (table 5). HSV-1 and *Toxoplasma* serum antibody status were not associated with any of the outcomes of interest. In a study comparing adults in Finland and Russia, of 22 microbes examined, *H. pylori* alone explained approximately half of the difference in the prevalence of atopy between the 2 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 a cross-sectional study design and self-reported health data. ELISA detects IgG antibodies to *H. pylori,* indicating current infection or infection in the recent past. The cross-sectional design could reflect possible problems of reverse causation. For example, asthmatics may more frequently receive antibiotics and corticosteroids that could reduce *H. pylori* prevalence, compared with nonasthmatics. The present study cannot entirely rule out this possibility. However, evidence in the literature is lacking about changes in the *H. pylori* status in asthmatics. Once acquired, *H. pylori* is carried through most or all of life; Kuipers et al. [11] 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. In the present study, among asthma cases, there was no association between time since onset and *H. pylori* positivity (data not shown). Statistical adjustment for the use of antibiotics and corticosteroids in the past month, as a proxy measure of frequent antibiotic use, did not change the effect estimates (table 4). In addition, the specificity of the inverse association with onset of asthma before 5 years of age and not with long-standing asthma seen in adults is an argument against that proposition. The use of self-reported data on asthma and atopic conditions also may have led to recall bias or measurement errors. Future studies involving 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 information on 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 increase 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 decrease in the prevalence of *H. pylori* positivity since 1930, and the rate of the decrease increased 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.

References

1. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med **2006**; 355:2226–35.
2. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax **1989**; 44:614–9.
3. Strachan DP. Hay fever, hygiene, and household size. BMJ **1989**; 299: 1259–60.
4. Gold DR, Wright R. Population disparities in asthma. Annu Rev Public Health **2005**; 26:89–113.
5. Blaser MJ. Who are we? Indigenous microbes and the ecology of human diseases. EMBO Rep **2006**; 7:956–60.
6. Blaser MJ, Atherton JC. *Helicobacter pylori* persistence: biology and disease. J Clin Invest **2004**; 113:321–33.
7. Matricardi PM, Rosmini F, Riondino S, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. BMJ **2000**; 320:412–7.
8. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. JAMA **2002**; 287:3096–102.
9. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. Nature **2007**; 445: 915–8.
10. Malaty HM, El Kasabany A, Graham DY, et al. Age at acquisition of *Helicobacter pylori* infection: a follow-up study from infancy to adulthood. Lancet **2002**; 359:931–5.

11. Kuipers EJ, Pena AS, van Kamp G, et al. Seroconversion for *Helicobacter pylori*. Lancet **1993**; 342:328–31.
12. Taylor DN, Blaser MJ. The epidemiology of *Helicobacter pylori* infection. Epidemiol Rev **1991**; 13:42–59.
13. Bik EM, Eckburg PB, Gill SR, et al. Molecular analysis of the bacterial microbiota in the human stomach. Proc Natl Acad Sci U S A **2006**; 103: 732–7.
14. Odenbreit S, Puls J, Sedlmaier B, Gerland E, Fischer W, Haas R. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. Science **2000**; 287:1497–500.
15. Goll R, Gruber F, Olsen T, et al. *Helicobacter pylori* stimulates a mixed adaptive immune response with a strong T-regulatory component in human gastric mucosa. Helicobacter **2007**; 12:185–92.
16. Lundgren A, Stromberg E, Sjoling A, et al. Mucosal FOXP3-expressing $CD4^+$ CD25 high regulatory T cells in *Helicobacter pylori*–infected patients. Infect Immun **2005**; 73:523–31.
17. Perez-Perez GI, Salomaa A, Kosunen TU, et al. Evidence that $cagA^+$ *Helicobacter pylori* strains are disappearing more rapidly than $cagA^-$ strains. Gut **2002**; 50:295–8.
18. Banatvala N, Mayo K, Megraud F, Jennings R, Deeks JJ, Feldman RA. The cohort effect and *Helicobacter pylori*. J Infect Dis **1993**; 168:219–21.
19. Peterson WL, Graham DY, Marshall B, et al. Clarithromycin as monotherapy for eradication of *Helicobacter pylori:* a randomized, double-blind trial. Am J Gastroenterol **1993**; 88:1860–4.
20. National Center for Health Statistics (NCHS). NHANES 1999–2000 data files-data, docs, codebooks, SAS code. Hyattsville, MD: NCHS, **2005**.
21. Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and *Helicobacter pylori* infection in the United States. Am J Epidemiol **2006**; 163:127–34.
22. NHANES 1999–2000 Laboratory Files. Lab 09 Herpes I & II. Hyattsville, MD: National Center for Health Statistics, **2005**.
23. NHANES 1999–2000 Laboratory Files. Lab 17 *Cryptosporidum* and *Toxoplasma*. Hyattsville, MD: National Center for Health Statistics, **2005**.
24. Chen Y, Blaser MJ. Inverse associations of *Helicobacter pylori* with asthma and allergy. Arch Intern Med **2007**; 167:821–7.
25. Reibman J, Marmor M, Fernandez-Beros M, Rogers L, Perez-Perez GI, Blaser MJ. Asthma in an urban population is inversely associated with *Helicobacter pylori* status. In: Program and abstracts of the American Thoracic Society, May 2005.
26. National Center for Health Statistics (NCHS). Plan and operation of the Third National Health and Nutrition Examination Survey. 1988–94. Vital and Health Statistics. Series 1. No. 32. Hyattsville, MD: NCHS, **1994**.
27. Grossman J. One airway, one disease. Chest **1997**; 111(2 Suppl):11S–16S.
28. Spiro DM, Arnold DH, Barbone F. Association between antibiotic use and primary idiopathic intussusception. Arch Pediatr Adolesc Med **2003**; 157:54–9.
29. Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. Chest **2007**; 131:1753–9.
30. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. J Allergy Clin Immunol **2002**; 110:381–7.
31. von Hertzen LC, Laatikainen T, Makela MJ, et al. Infectious burden as a determinant of atopy—a comparison between adults in Finnish and Russian Karelia. Int Arch Allergy Immunol **2006**; 140:89–95.
32. Harlow SD, Linet MS. Agreement between questionnaire data and medical records: the evidence for accuracy of recall. Am J Epidemiol **1989**; 129:233–48.
33. Linet MS, Harlow SD, McLaughlin JK, McCaffrey LD. A comparison of interview data and medical records for previous medical conditions and surgery. J Clin Epidemiol **1989**; 42:1207–13.
34. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires: a literature review. Chest **1993**; 104: 600–8.
35. Parsonnet J, Blaser MJ, Perez-Perez GI, Hargrett-Bean N, Tauxe RV. Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. Gastroenterology **1992**; 102:41–6.
36. Cullen DJ, Collins BJ, Christiansen KJ, et al. When is *Helicobacter pylori* infection acquired? Gut **1993**; 34:1681–2.
37. Harvey RF, Spence RW, Lane JA, et al. Relationship between the birth cohort pattern of *Helicobacter pylori* infection and the epidemiology of duodenal ulcer. QJM **2002**; 95:519–25.
38. Blaser MJ, Kirschner D. The equilibria that allow bacterial persistence in human hosts. Nature **2007**; 449:843–9.