

Inverse Associations of *Helicobacter pylori* With Asthma and Allergy

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Background: Acquisition of *Helicobacter pylori*, which predominantly occurs before age 10 years, may reduce risks of asthma and allergy.

Methods: We evaluated the associations of *H pylori* status with history of asthma and allergy and with skin sensitization using data from 7663 adults in the Third National Health and Nutrition Examination Survey. Adjusted odds ratios (ORs) for currently and ever having asthma, allergic rhinitis, allergy symptoms in the previous year, and allergen-specific skin sensitization were computed comparing participants seropositive for *cagA*⁻ or *cagA*⁺ strains of *H pylori* with those without *H pylori*.

Results: The presence of *cagA*⁺ *H pylori* strains was inversely related to ever having asthma (OR, 0.79; 95% confidence interval [CI], 0.63-0.99), and the inverse association of *cagA* positivity with childhood-onset (age

≤15 years) asthma was stronger (OR, 0.63; 95% CI, 0.43-0.93) than that with adult-onset asthma (OR, 0.97; 95% CI, 0.72-1.32). Colonization with *H pylori*, especially with a *cagA*⁺ strain, was inversely associated with currently (OR, 0.77; 95% CI, 0.62-0.96) or ever (OR, 0.77; 95% CI, 0.62-0.94) having a diagnosis of allergic rhinitis, especially for childhood onset (OR, 0.55; 95% CI, 0.37-0.82). Consistent inverse associations were found between *H pylori* colonization and the presence of allergy symptoms in the previous year and sensitization to pollens and molds.

Conclusion: These observations support the hypothesis that childhood acquisition of *H pylori* is associated with reduced risks of asthma and allergy.

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ASTHMA AND RELATED ALLERGIC disorders are becoming more common in the Western world.¹ The rapid increase in their incidence must reflect changing environmental exposures, but these remain largely undefined, despite active investigation.¹ Some asthma cases are related to gastroesophageal reflux disease (GERD)²⁻⁴; GERD and its sequelae, Barrett esophagus and adenocarcinoma of the esophagus, also have been rising in incidence, a phenomenon occurring later in life but with secular trends similar to those for asthma.⁴

The gastric bacterium *Helicobacter pylori* is present in all human populations and is so ancient that its genetic variations can be used to trace migrations during the past 100 000 years.^{5,6} In developing countries, virtually all adults harbor *H pylori*, but the prevalence is much lower in industrialized nations.⁷ This difference is due to a birth cohort phenomenon in which *H pylori* acquisition in industrialized countries has been diminishing with each succeeding generation, at least for the past 60 years.⁷ Since, when present, *H pylori* is the dominant species colonizing the stomach⁸ and is intimately linked to gastric

physiology,⁹ especially the *cagA*⁺ strains that inject *H pylori* products into epithelial cells,¹⁰ this disappearance across the population represents a fundamental change in human microecology.⁹

Colonization with *H pylori* is associated with adenocarcinoma of the distal stomach and peptic ulcer disease.¹¹⁻¹³ In contrast, a substantial body of work¹⁴⁻²⁰ now shows an inverse relationship between the presence of *H pylori*, especially *cagA*⁺ strains, and GERD and its sequelae. These observations suggest that *H pylori* presence in the stomach protects against GERD and, therefore, could protect against GERD-related asthma. Using data from the Third National Health and Nutrition Examination Survey (NHANES III),²¹ herein we address the hypothesis that *H pylori* acquisition, which predominantly occurs before age 10 years,²²⁻²⁴ is associated with reduced subsequent risks of asthma and allergy.

METHODS

STUDY POPULATION

The NHANES III, the seventh health examination survey performed in the United States since 1960,²¹ was conducted between October 18,

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Table 1. Distribution of Demographic and Lifestyle Factors by *Helicobacter pylori* Status

Factor	<i>H pylori</i> ⁻ (n = 3943)	<i>H pylori</i> ⁺ <i>cagA</i> ⁻ (n = 1445)	<i>H pylori</i> ⁺ <i>cagA</i> ⁺ (n = 2275)
Male sex, %	47.1	52.9	53.1
Age, mean (SD), y	42.6 (19.1)	54.6 (19.3)	50.7 (19.1)
Educational attainment			
Mean (SD), y	11.9 (3.3)	9.9 (4.1)	9.6 (4.1)
Unknown, No.	25	10	17
Race/ethnicity, %			
Non-Hispanic white	55.9	47.3	24.4
Non-Hispanic black	21.8	16.2	35.5
Mexican-American	19.4	34.1	35.7
Other	2.9	2.5	4.4
Country of birth			
United States, %	87.2	75.6	71.8
Mexico, %	8.1	18.4	19.6
Other, %	4.7	6.0	8.7
Unknown, No.	2	1	4
Region of the United States, %			
Northeast	15.4	8.8	12.9
Midwest	23.8	16.6	16.8
South	34.7	45.6	39.9
West	26.0	29.0	30.4
Body mass index*			
Mean (SD)	26.2 (5.59)	27.1 (5.46)	27.1 (5.48)
Unknown, No.	9	7	12
Cigarette smoking, %			
Nonsmokers	48.6	44.8	47.6
Past smokers	23.8	29.7	25.2
Current smokers	27.6	25.5	27.2

*Calculated as weight in kilograms divided by height in meters squared.

1988, and October 15, 1994, in 2 phases, each of which comprised a national probability sample. In the NHANES III, 39 695 persons were studied; of those, 10 120 were adults (≥ 17 years old) sampled during the first phase (October 18, 1988, to October 24, 1991). All interviewed persons were invited to undergo a medical examination. The survey protocol was approved by the institutional review board of the Centers for Disease Control and Prevention. All the participants gave written informed consent.

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.²¹ Participants were asked whether they had ever been diagnosed as having asthma or hay fever by a physician, the age they were first diagnosed, and whether they continued to have asthma or hay fever. They also were asked about allergy symptoms in the previous year (including wheezing; whistle in chest; wheezy/whistling chest sounds; stuffy, itchy, or runny nose; and watery, itchy eyes) that were unrelated to the common cold and about potential exposures that elicited allergic symptoms.

H PYLORI STATUS

Examinees 20 years and older from phase 1 were tested for *H pylori* IgG antibodies in 1996 using the *H pylori* IgG enzyme-linked immunosorbent assay (Wampole Laboratories, Cranbury, NJ) and the CagA IgG enzyme-linked immunosorbent assay developed and standardized at Vanderbilt University, as

described elsewhere.²⁵ On the basis of *H pylori* and *cagA* results, patients were classified into 3 groups: *H pylori* positive and *cagA* positive, *H pylori* positive and *cagA* negative, and *H pylori* negative and *cagA* negative, as described elsewhere.²⁶ The *H pylori*⁺ *cagA*⁺ group included all persons with a positive *cagA* assay regardless of the results of the *H pylori* assay, based on the utility of the CagA antigen to detect true-positive responses in culture-positive persons in the face of negative or equivocal values in the *H pylori* serologic assay.²⁷ By definition, all persons in the *H pylori*⁻ group had negative CagA assays.

POSITIVITY ON ALLERGY SKIN TESTING

Allergy skin tests included evaluation of immediate hypersensitivity reactions to 10 licensed, commercially available, Food and Drug Administration–approved, standardized allergens.²¹ Prick-puncture allergy skin tests to the 10 allergens and positive (histamine) and negative (glycerinated diluent) controls were administered to a random half-sample of the 20- to 59-year-old adults, following a standard allergy testing protocol.²¹ Hypersensitivity reactions were evaluated 15 minutes after administering the allergens on an examinee's forearms; the length and width of each wheal and flare induced were measured. A skin test panel was considered valid if there was at least 1 mm of difference between the wheal diameters of the positive and negative controls.²⁸ An allergen-specific skin test response was considered positive if the skin test was valid, and the differences in the wheal's length and width for the allergen-specific test with the negative control were 3 mm or greater.

STATISTICAL ANALYSIS

We included 7663 participants with valid answers on asthma history and valid serologic testing for *H pylori*. Analysis of skin reactivity was conducted in a subsample (n=2385) of these participants who underwent allergy skin testing. We first described distributions of demographics, smoking status, body mass index, and outcomes of interest in the 3 groups with respect to *H pylori* status (*H pylori*⁺ *cagA*⁺, *H pylori*⁺ *cagA*⁻, and *H pylori*⁻). Unconditional logistic regression models were conducted to estimate adjusted odds ratios (ORs) for asthma and allergy symptoms and ORs for allergy skin reactivity. Multivariate analysis excluded participants with unknown information on any of the covariates. We did not use sampling weights in the analysis for the following reasons: (1) for the present analysis, the internal validity, that is, the relationships of *H pylori* status with asthma and allergy, is considered to be more important than generalization to the total US population; (2) representative population estimates were not needed; and (3) parameter estimators can vary considerably when the weights are highly variable, especially when a few individuals have very large sample weights.^{29,30}

All ORs were adjusted for sex, race/ethnicity, age, smoking status, body mass index, and educational attainment. A separate analysis was conducted to additionally adjust for country of birth and region in the United States; the ORs did not change appreciably, and, therefore, the results are not shown. Stratified analysis was conducted based on the median age (43 years) in the overall study population. Age also was adjusted in the stratified analysis by age to control for potential confounding due to differences in age strata. The statistical significance of interaction was determined based on *P* values of the cross-product terms of *H pylori* status with age. Participants who ever had asthma or allergic rhinitis were divided into those with childhood onset (age at onset ≤ 15 years) and those with older onset (> 15 years) for comparison with participants who never had asthma or allergic rhinitis. Sensitivity analysis conducted using age 12 or 18 years as the cutoff point yielded results similar to using age 15 years

Table 2. Association of *Helicobacter pylori* Status With Asthma

Participants' <i>H pylori</i> / <i>CagA</i> Status	Asthma Status									
	Never, No.	Current		Ever						
		No.	OR (95% CI)*	Overall		Age at Onset ≤15 y†		Age at Onset >15 y†		
			No.	OR (95% CI)*	No.	OR (95% CI)*	No.	OR (95% CI)*	No.	OR (95% CI)*
All										
-/-	3613	196	1 [Reference]	296	1 [Reference]	149	1 [Reference]	129	1 [Reference]	
+/-	1330	64	0.91 (0.67-1.23)	98	0.94 (0.73-1.20)	34	0.97 (0.65-1.45)	57	0.95 (0.68-1.33)	
+/+	2115	105	0.94 (0.72-1.23)	131	0.79 (0.63-0.99)	38	0.63 (0.43-0.93)	86	0.97 (0.72-1.32)	
Age <43 y, median										
-/-	2117	112	1 [Reference]	167	1 [Reference]	NA	NA	NA	NA	
+/-	427	17	0.84 (0.49-1.44)	23	0.75 (0.47-1.20)	NA	NA	NA	NA	
+/+	882	29	0.68 (0.43-1.07)	40	0.63 (0.43-0.93)	NA	NA	NA	NA	
Age ≥43 y, median										
-/-	1496	84	1 [Reference]	129	1 [Reference]	NA	NA	NA	NA	
+/-	903	47	0.98 (0.67-1.42)	75	1.07 (0.79-1.45)	NA	NA	NA	NA	
+/+	1233	76	1.14 (0.81-1.61)	91	0.92 (0.68-1.23)	NA	NA	NA	NA	
Interaction <i>P</i> value of <i>H pylori</i> ⁻ <i>cagA</i> ⁻ and age	NA		.50		.14		NA		NA	
Interaction <i>P</i> value of <i>cagA</i> ⁺ and age	NA		.02		.04		NA		NA	

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

*All ORs were adjusted for race/ethnicity, age, sex, body mass index, smoking status, and educational attainment.

†A total of 32 participants who ever had asthma but with an unknown age at onset were excluded from the analysis.

(data not shown). All analyses were conducted using a software program (SAS 9.1.3; SAS Institute Inc, Cary, NC).

RESULTS

H PYLORI STATUS IN THE STUDY POPULATION

In the 7663 participants, *H pylori* status varied in relation to demographic and lifestyle factors, reflecting well-recognized trends.³¹ Participants in the *H pylori*-positive groups (*H pylori*⁺*cagA*⁻ and *H pylori*⁺*cagA*⁺) were more likely to be men, older, and born in Mexico compared with participants in the *H pylori*⁻ group (**Table 1**). Participants in the *H pylori*⁺*cagA*⁺ group were more likely to be non-Hispanic blacks compared with those in the *H pylori*⁺*cagA*⁻ and *H pylori*⁻ groups.

ASSOCIATION OF *H PYLORI* STATUS WITH ASTHMA

There was no overall association between the presence of either a *cagA*⁻ or a *cagA*⁺ strain of *H pylori* and current asthma status (**Table 2**). However, the association between colonization with *H pylori*⁺*cagA*⁺ strains and current asthma differed by age (interaction *P* = .02); *H pylori*⁺*cagA*⁺ strains were inversely related to current asthma in younger participants (OR, 0.68; 95% confidence interval [CI], 0.43-1.07), although the estimate was not significant (*P* = .09). Participants colonized with *H pylori*⁺*cagA*⁺ strains were less likely to have ever been diagnosed as having asthma compared with those without *H pylori* (OR, 0.79; 95% CI, 0.63-0.99). Colonization with a *cagA*⁺ *H pylori* strain was inversely associated with ever having had asthma only in younger

participants (age <43 years; interaction *P* = .04); this inverse association was consistent with the inverse association of childhood onset of asthma (age ≤15 years) and *cagA*⁺ status (OR, 0.63; 95% CI, 0.43-0.93).

ASSOCIATION OF *H PYLORI* STATUS WITH ALLERGIC RHINITIS

Current allergic rhinitis status and ever having had allergic rhinitis diagnosed were inversely associated with the presence of *H pylori*, especially *cagA*⁺ strains (**Table 3**). Inverse associations between *H pylori* presence and current allergic rhinitis diagnosis were more significant in younger than in older participants (interaction *P* = .06 and .07 for *cagA*⁻ and *cagA*⁺ strains, respectively). Similarly, inverse associations between *H pylori* presence and ever having had allergic rhinitis diagnosed also were more significant in younger participants. The presence of *H pylori*, especially *cagA*⁺ strains, was inversely associated with childhood-onset allergic rhinitis (OR, 0.68; 95% CI, 0.44-1.05 and OR, 0.55; 95% CI, 0.37-0.82 for *cagA*⁻ and *cagA*⁺ strains, respectively).

ASSOCIATION OF *H PYLORI* STATUS WITH ALLERGY SYMPTOMS AND SOURCES

Colonization with either a *cagA*⁺ or a *cagA*⁻ strain of *H pylori* was inversely associated with having had 1 of a group of specified allergy symptoms in the previous 12 months (**Table 4**). The associations of *H pylori*⁺*cagA*⁻ and *cagA*⁺ status with allergy were not significantly different (*P* = .83) and were apparent only in younger adults. The interaction *P* values indicate that the association of *H pylori* (either *cagA*⁻ [*P* = .04] or *cagA*⁺

Table 3. Association of *Helicobacter pylori* Status With Allergic Rhinitis

Participants' <i>H pylori</i> / <i>CagA</i> Status	Allergic Rhinitis Status								
	Never, No.	Ever							
		Current		Overall		Age at Onset ≤15 y†		Age at Onset >15 y†	
		No.	OR (95% CI)*	No.	OR (95% CI)*	No.	OR (95% CI)*	No.	OR (95% CI)*
All									
-/-	3469	380	1 [Reference]	439	1 [Reference]	201	1 [Reference]	211	1 [Reference]
+/-	1313	95	0.81 (0.63-1.03)	115	0.82 (0.65-1.03)	26	0.68 (0.44-1.05)	84	0.97 (0.74-1.28)
+/+	2082	141	0.77 (0.62-0.96)	163	0.77 (0.62-0.94)	34	0.55 (0.37-0.82)	118	0.91 (0.70-1.17)
Age <43 y, median									
-/-	2032	225	1 [Reference]	252	1 [Reference]	NA	NA	NA	NA
+/-	424	22	0.59 (0.37-0.94)	26	0.63 (0.41-0.96)	NA	NA	NA	NA
+/+	866	48	0.65 (0.46-0.93)	56	0.69 (0.50-0.96)	NA	NA	NA	NA
Age ≥43 y, median									
-/-	1437	155	1 [Reference]	187	1 [Reference]	NA	NA	NA	NA
+/-	889	73	0.95 (0.71-1.29)	89	0.94 (0.71-1.23)	NA	NA	NA	NA
+/+	1216	93	0.87 (0.65-1.16)	107	0.82 (0.63-1.08)	NA	NA	NA	NA
Interaction <i>P</i> value of <i>H pylori</i> ⁺ <i>cagA</i> ⁺ and age	NA		.06		.07		NA		NA
Interaction <i>P</i> value of <i>cagA</i> ⁺ and age	NA		.07		.15		NA		NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

*All ORs were adjusted for race/ethnicity, age, sex, body mass index, smoking status, and educational attainment.

†A total of 43 participants who ever had allergic rhinitis but with an unknown age at onset were excluded from the analysis.

Table 4. Association of *Helicobacter pylori* Status With Allergy Symptoms*

Participants' <i>H pylori</i> / <i>CagA</i> Status	Participants With Allergy Symptoms, No.		OR (95% CI)†
	No	Yes	
All			
-/-	1511	2398	1 [Reference]
+/-	654	774	0.84 (0.74-0.96)
+/+	1085	1161	0.87 (0.78-0.98)
Age <43 y, median			
-/-	852	1432	1 [Reference]
+/-	220	230	0.82 (0.66-1.02)
+/+	490	432	0.80 (0.67-0.95)
Age ≥43 y, median			
-/-	659	966	1 [Reference]
+/-	434	544	0.91 (0.77-1.07)
+/+	595	729	0.99 (0.84-1.16)
Interaction <i>P</i> value of <i>H pylori</i> ⁺ <i>cagA</i> ⁺ and age			.04
Interaction <i>P</i> value of <i>cagA</i> ⁺ and age			<.01

Abbreviations: CI, confidence interval; OR, odds ratio.

*Allergy symptoms were defined as having any of the following in the previous 12 months: wheezing, whistling in the chest; stuffy, itchy, or runny nose; and watery or itchy eyes.

†All ORs were adjusted for race/ethnicity, age, sex, body mass index, smoking status, and educational attainment.

[*P* = .01]) with allergy differs significantly based on age. Analysis of individual allergy symptoms consistently showed significantly stronger inverse associations in younger participants (interaction *P* < .01). Among par-

ticipants younger than 43 years, those with *cagA*⁺ strains were less likely to have any wheezing, whistling in the chest (OR, 0.86; 95% CI, 0.66-1.13), stuffy, itchy, or runny nose (OR, 0.77; 95% CI, 0.64-0.91), or watery, itchy eyes (OR, 0.86; 95% CI, 0.71-1.03) in the previous year compared with those without *H pylori* (Appendix 1 [available at <http://homepages.nyu.edu/~chenyl6/Appendixes.pdf>]). We further evaluated the associations of *H pylori* status with allergy symptoms according to self-reported allergy sources. Compared with participants without *H pylori*, those with *cagA*⁺ strains were significantly or marginally significantly less likely to have allergy symptoms due to exposure to pollens (OR, 0.71; 95% CI, 0.71-0.95), animals (OR, 0.63; 95% CI, 0.43-0.88), or house dust (OR, 0.87; 95% CI, 0.73-1.04), especially younger adults (median age <43 years). There were no significant associations with exposures to the work environment, exercise, or cold air (Appendix 2 [available at <http://homepages.nyu.edu/~chenyl6/Appendixes.pdf>]).

ASSOCIATION OF *H PYLORI* STATUS WITH SKIN TEST RESULTS

We evaluated associations between *H pylori* status and allergen-specific skin sensitization in the subgroup of 2386 adults who had undergone allergy skin testing. Compared with participants with *H pylori*-negative status, participants with *H pylori*, especially with *cagA*⁺ strains, were less likely to have skin sensitization due to several pollens and molds, especially younger participants (**Table 5**). There were no significant associations of *H pylori* status with skin sensitization due to the tested indoor allergens and foods (Appendix 3 [available at <http://homepages.nyu.edu/~chenyl6/Appendixes.pdf>]).

Table 5. Association of *Helicobacter pylori* Status With Skin Sensitization Due to Pollens and Mold

Participants' <i>H pylori</i> / <i>cagA</i> Status	Ragweed*		Bermuda Grass*		Rye Grass*		White Oak*		Russian Thistle*		<i>Alternaria alternata</i> †	
	Yes/No, No.	OR (95% CI)‡	Yes/No, No.	OR (95% CI)‡	Yes/No, No.	OR (95% CI)‡	Yes/No, No.	OR (95% CI)‡	Yes/No, No.	OR (95% CI)‡	Yes/No, No.	OR (95% CI)‡
All												
-/-	414/1026	1 [Reference]	273/1165	1 [Reference]	419/1022	1 [Reference]	181/1256	1 [Reference]	199/1238	1 [Reference]	183/1255	1 [Reference]
+/-	74/278	0.77 (0.57-1.03)	47/305	0.81 (0.57-1.15)	81/271	0.87 (0.65-1.17)	29/322	0.82 (0.53-1.27)	44/308	0.97 (0.67-1.42)	25/325	0.68 (0.43-1.08)
+/+	130/463	0.73 (0.57-0.94)	88/503	0.85 (0.64-1.14)	126/466	0.73 (0.57-0.94)	52/541	0.84 (0.59-1.20)	58/535	0.69 (0.49-0.97)	46/546	0.69 (0.47-0.99)
Age <43 y, median												
-/-	358/774	1 [Reference]	242/888	1 [Reference]	358/774	1 [Reference]	162/967	1 [Reference]	174/955	1 [Reference]	161/969	1 [Reference]
+/-	45/159	0.63 (0.43-0.91)	34/170	0.82 (0.54-1.24)	56/148	0.87 (0.61-1.23)	19/184	0.73 (0.43-1.22)	29/175	0.91 (0.58-1.42)	18/185	0.63 (0.35-1.08)
+/+	100/294	0.71 (0.54-0.95)	62/330	0.75 (0.53-1.05)	94/299	0.69 (0.52-0.92)	36/358	0.71 (0.47-1.07)	42/352	0.63 (0.43-0.93)	37/156	0.65 (0.44-0.99)
Age ≥43 y, median												
-/-	56/252	1 [Reference]	31/277	1 [Reference]	61/248	1 [Reference]	19/289	1 [Reference]	25/283	1 [Reference]	22/286	1 [Reference]
+/-	29/119	1.06 (0.62-1.80)	13/135	0.82 (0.40-1.68)	25/123	0.84 (0.49-1.44)	10/138	1.19 (0.51-2.80)	15/133	1.15 (0.56-2.35)	7/140	0.87 (0.35-2.16)
+/+	30/169	0.71 (0.41-1.21)	26/173	1.28 (0.69-2.40)	32/167	0.82 (0.49-1.36)	16/183	1.45 (0.66-3.18)	16/183	0.90 (0.44-1.87)	9/190	0.69 (0.30-1.63)
Interaction <i>P</i> value of <i>H pylori</i> ⁺ <i>cagA</i> ⁺ and age	.05		.66		.88		.20		.39		.71	
Interaction <i>P</i> value of <i>cagA</i> ⁺ and age	.77		.04		.57		.05		.28		.94	

Abbreviations: CI, confidence interval; OR, odds ratio.

*Pollen.

†Mold.

‡All ORs were adjusted for race/ethnicity, age, sex, body mass index, smoking status, and educational attainment.

COMMENT

Using the NHANES III database, we found that colonization with *cagA*⁺ strains of *H pylori* was inversely related to ever having had asthma, especially in younger adults and for asthma cases with onset during childhood. Colonization with *H pylori* also was inversely related to having had allergic rhinitis, allergy symptoms, and skin sensitization due to pollens and molds, especially in younger adults.

Consistent with the increasing prevalence of esophageal diseases as *H pylori* prevalence has been declining³² has come evidence of inverse associations between *H pylori* presence, especially *cagA*⁺ strains, and the risk of GERD and its sequelae.¹⁴⁻¹⁸ Because GERD can be asymptomatic,^{33,34} especially in childhood,³⁵ the extent of its increasing incidence may be underestimated. These trends and associations suggest the hypothesis that *H pylori*, especially *cagA*⁺ strains, could be protective against asthma, mediated in part by their protection against GERD, possibly due to heightened *cagA*⁻-induced gastric atrophy.³⁶ However, because the presence of GERD was not evaluated in NHANES III, and few participants reported taking prescription medicines for treating GERD, we did not directly evaluate whether the inverse association between asthma and *H pylori* is mediated via GERD. Future studies are needed.

The present observations also are consistent with the "hygiene hypothesis" that microbial infections during early childhood may prevent or diminish atopic sensitization and asthma.³⁷ In particular, inadequate microbial stimulation of gut-associated lymphoid tissue, a critical site for maturation of mucosal immunity,³⁸ may be relevant to

this mechanism. Consistent with the present findings, asthma and allergic rhinitis were less frequent in NHANES III participants seropositive for hepatitis A virus (HAV), *Toxoplasma gondii*, and herpes simplex virus 1 than in seronegative persons.³⁹ In Italian cadets, atopy was inversely related to infections (*T gondii* and HAV) transmitted through gastrointestinal routes but not to those with differing major transmission.⁴⁰

A few studies have reported no associations^{41,42} or weak inverse associations^{40,43-45} of *H pylori* colonization with asthma and allergy. However, some of these studies were not adequately powered to detect a moderate association, and they did not address the relationships regarding colonization of *H pylori cagA*⁺ strains. The findings from the present study confirm and extend a previous analysis (J. Reibman, MD, M. Marmor, PhD, M.-E. Fernandez-Beros, PhD, L. Rogers, MD, G. I. Perez-Perez, DSc, and M.J.B., unpublished data, 2006) of 318 asthmatic patients and 206 controls in New York in which a similar inverse association between colonization of *H pylori cagA*⁺ strains and risk of asthma was seen. One form of the hygiene hypothesis proposes that particular allergic conditions are increasing because of T_H1- and T_H2-type immune response imbalances due to modern lifestyles.^{37,46} Since T_H2 mediators suppress T_H1 responses and T_H1 mediators reciprocally inhibit T_H2 responses, these systems should be balanced in "health."⁴⁶ Evidence suggests that immune activation after the establishment of *H pylori* colonization is more pronounced with *cagA*⁺ strains,^{9,36,47} especially in children.^{48,49} One explanation for the present findings is that enhanced host cellular responses to *cagA*⁺ *H pylori* strains⁴⁸⁻⁵⁰ affect early life equilibria of T_H1- and T_H2-type immune responses, driving the induction of immunoregulatory lym-

phocytes that prevent immune hyperreactivity states, such as asthma and allergy.⁵¹ Future studies should examine this hypothesis.

The inverse relationships of *H pylori*, especially *cagA*⁺ strains, with asthma, allergic rhinitis, and allergies were more pronounced in younger (median age <43 years) than in older individuals. Similarly, *H pylori cagA* positivity was inversely associated with the onset of asthma and allergic rhinitis at age 15 years or earlier but not after (Tables 2 and 3). The specificity for younger but not older persons is consistent with a birth cohort phenomenon¹ and suggests that secular increases in asthma and atopy in children and young adults may reflect reduced exposures to microbes such as *H pylori*. Because the acquisition of many microbes has receded more than that of *H pylori*, the biological effects of *H pylori* may be easier to distinguish in younger persons. In 2 Finnish cross-sectional studies,⁵² the prevalence of allergen specific IgE increased between 1973 and 1994, mainly in *H pylori*-negative persons.

That *H pylori cagA*⁺ status was inversely related to the presence of allergic rhinitis, self-reported allergy symptoms, and skin sensitization suggests that the protection related to *H pylori* (especially *cagA*⁺ strains) may not be specific for asthma but extends to other allergic conditions. A recent study⁵³ of Russian adults also found that *H pylori* presence was inversely associated with atopy, consistent with the present findings. Skin sensitization examined in NHANES III also was inversely associated with HAV seropositivity.³⁹ For this reason, we performed additional analyses to evaluate the relationships of skin sensitization and risk of asthma with joint status of HAV and *H pylori* seropositivity. The inverse associations with *H pylori* status remained similar in persons negative for serum antibody to HAV (data not shown), suggesting the independent effect of *H pylori* colonization. The *H pylori cagA*⁺ strains were inversely associated with skin sensitization due to pollens and molds but not with other tested antigens. Skin sensitization may vary in an allergen-specific manner; increased domestic exposure to dust mite and cockroach may be more etiologically relevant⁵⁴ to sensitization to these allergens compared with *H pylori* status.

The present study and others collectively provide evidence that colonization with *H pylori*, especially *cagA*⁺ strains, may reduce risks of asthma and allergy. Although we conducted a cross-sectional analysis, we consider that the observed associations are not due to "reverse causation." *Helicobacter pylori* is acquired almost exclusively in childhood and usually persists for life unless antimicrobial therapy is given.^{55,56} Although *H pylori* acquisition age was not assessed in this study, in most cases it precedes the reported onsets of asthma, allergic rhinitis, and allergy.^{22,55} One issue is whether asthma or allergy would promote *H pylori* loss, for example, due to heightened antibiotic drug use. The stronger inverse associations between *H pylori* colonization and asthma and allergic rhinitis in younger adults provide evidence against the latter hypothesis since older persons should have had increased cumulative duration of asthma or atopy and exposure to medications (eg, antibiotics) compared with younger persons.

Treatment of *H pylori* was not evaluated in the NHANES III, and, therefore, some participants might have had previous treatment. However, no evidence has suggested that specific treatment to eradicate *H pylori* differs by affective status of asthma and allergy. Although laboratory-confirmed cases of asthma would be ideal for evaluating the putative association, errors in reporting history of asthma should not differ by *H pylori* status. These nondifferential misclassifications of outcome and exposure would, in general, bias toward the null, indicating that the true association may be greater.

In summary, these findings provide evidence that the continuing disappearance of *H pylori* in developed countries⁵⁶ is related to the increase in asthma and atopic disorders.⁵⁷ How the lack of *H pylori* might contribute to the pathogenesis of these disorders is not known but could relate to immunologic imbalance. Additional studies are needed to confirm these observations and to identify the mechanisms.

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