Helicobacter pylori Colonization and its Effect on Asthma Development: A Systematic Review

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Abstract

Background: Previous epidemiologic studies have demonstrated an inverse association between childhood exposure to oral-fecal microbes, such as Helicobacter pylori, and the development of atopic conditions, such as asthma. Recent studies have also demonstrated immune modulating effects, specifically a decrease in the cytokine profile responsible for asthma, when mice were inoculated with H. pylori virulence factors. This systematic review looks at recent cross-sectional studies to determine if H. pylori colonization is associated with decreased asthma rates.

Methods: The medical literature search utilized MEDLINE (through Ovid and PubMed), Web of Science, and Evidence Based Medicine Review and found five case-control observational studies that clearly defined asthma and H. pylori diagnosis. Studies were critically appraised and assessed with GRADE criteria.

Results: Five retrospective case-control studies were used in this systematic review. The largest of these case-control studies (7663 participants) found a significant inverse relationship between CagA positive strains of H. pylori, a specific virulence factor, and the development of asthma before age 15 (OR=0.63 (0.43-0.93)). The study was repeated with 7412 participants the following year and found a strong inverse relationship between H. pylori and presence of asthma in children (OR=0.41 (0.24-0.69)) and onset of asthma before age 5 (OR=0.58 (0.38-0.88)). The smallest of these case-control studies (526 participants) found a significant inverse relationship between CagA positive strains of H. pylori and the development of asthma (OR=.57 (CI 0.36-0.89)). The Israeli study (6959 children) found a 1.8% increased prevalence of asthma in children without H. pylori. The United Kingdom study (3244 participants) found a suggested inverse relationship between H. pylori and asthma (OR=0.78 (0.59-1.05)).

Conclusion: The findings suggest that H. pylori and other oral-fecal microbe exposure at a young age may have an immune modulating effect which either delays and/or prevents the development of asthma. Future research is needed to determine whether H. pylori virulence factors may be utilized in medicine to prevent the development of asthma without causing pathology.

Keywords: H. pylori, asthma, atopy, atopic

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Helicobacter pylori Colonization and its Effect on Asthma Development: A Systematic Review

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Biography

Kelly Boeing is a native of Buffalo, NY. She attended the State University of New York at Geneseo where she majored in Sociology and minored in Anthropology. After completion of her undergraduate degree, she moved to California to complete an AmeriCorps term. She volunteered at Lifelong Medical Clinics during her term of service and was inspired to start pre-med requirements to provide medical access to low income and uninsured patients. While taking pre-med courses, she had various health care jobs in caregiving, nutrition education and public health throughout northern and southern California. She then moved to Portland, OR to study and pursue a career as a Physician Assistant. She hopes to take part in international medical trips in the future.
Abstract

**Background:** Previous epidemiologic studies have demonstrated an inverse association between childhood exposure to oral-fecal microbes, such as *Helicobacter pylori*, and the development of atopic conditions, such as asthma. Recent studies have also demonstrated immune modulating effects, specifically a decrease in the cytokine profile responsible for asthma, when mice were inoculated with *H. pylori* virulence factors. This systematic review looks at recent cross-sectional studies to determine if *H. pylori* colonization is associated with decreased asthma rates.

**Methods:** The medical literature search utilized MEDLINE (through Ovid and PubMed), Web of Science, and Evidence Based Medicine Review and found five case-control observational studies that clearly defined asthma and *H. pylori* diagnosis. Studies were critically appraised and assessed with GRADE criteria.

**Results:** Five retrospective case-control studies were used in this systematic review. The largest of these case-control studies (7663 participants) found a significant inverse relationship between CagA positive strains of *H. pylori*, a specific virulence factor, and the development of asthma before age 15 (OR=0.63 (0.43-0.93)). The study was repeated with 7412 participants the following year and found a strong inverse relationship between *H. pylori* and presence of asthma in children (OR=0.41 (0.24-0.69)) and onset of asthma before age 5 (OR=0.58 (0.38-0.88)). The smallest of these case-control studies (526 participants) found a significant inverse relationship between CagA positive strains of *H. pylori* and the development of asthma (OR=.57 (CI 0.36-0.89)). The Israeli study (6959 children) found a 1.8% increased prevalence of asthma in children without *H. pylori*. The United Kingdom study (3244 participants) found a suggested inverse relationship between *H. pylori* and asthma (OR=0.78 (0.59-1.05)).

**Conclusion:** The findings suggest that *H. pylori* and other oral-fecal microbe exposure at a young age may have an immune modulating effect which either delays and/or prevents the development of asthma. Future research is needed to determine whether *H. pylori* virulence factors may be utilized in medicine to prevent the development of asthma without causing pathology.

**Keywords:** *H. pylori*, asthma, atopy, atopic
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Table I: Grading of Recommendations Assessment, Development and Evaluation (GRADE), Characteristics of Reviewed Studies

Table II: Summary of Findings

List of Abbreviations

BMI………………………………………………………………………………………………..Body Mass Index
CagA……………………………………………………………………………Cytotoxin Associated Gene A
CHS……………………………………………………………………………….Clalit Health Services
CI………………………………………………………………………………………………Confidence Interval
ELISA………………………………………………………………………..Enzyme-linked immunosorbent assay
GEE………………………………………………………………………………..Generalized Estimating Equation
GERD…………………………………………………………………………..Gastroesophageal Reflux Disease
GRADE………………Grading of Recommendations Assessment, Development and Evaluation
HP-NAP……………………………………..Helicobacter pylori Neutrophil Activating Protein
MALT………………………………………………………………………….Mucosa-Associated Lymphoid Tissue
NHANES………………………………National Health and Nutrition Examination Survey
OR………………………………………………………………………………………..Odds Ratio
RCT………………………………………………………………………………Randomized Controlled Trial
Th………………………………………………………………………………………..T helper cells
**Helicobacter pylori Colonization and its Effect on Asthma Development:**

A Systematic Review

**BACKGROUND**

Asthma is a common chronic medical condition that affects both children and adults worldwide. Its prevalence is increasing among all ages, sexes and races. From 2001-2009, the prevalence of asthma increased from 7.3% to 8.2%, a 12.3% increase. Between the years of 1980 and 1994, the prevalence of asthma in children aged 4 to 15 increased by 74%, and among children younger than 4, the prevalence increased by 160%. As of 2011, 14% of children under 17 had a past medical diagnosis of asthma, and 10% of children aged 17 and under had a current asthma diagnosis. Asthma has a significant impact on an individual’s quality of life, and places a huge economic burden on society due to missed work days and hospital admissions. The pathophysiology of asthma is better understood than the rapid increase in rates worldwide, which is quite contested and most likely multifactorial.

One theory for the rise in atopic conditions, such as asthma, is the hygiene hypothesis. The British scientist Strachan, in 1989, was the first to formally study this when he looked for a correlation between improved living conditions in England and increased prevalence of allergies and respiratory asthma. He commented, “Over the past century declining family size, improvements in household amenities, and high standards of personal cleanliness have reduced the opportunity for cross infection in young families. This may have resulted in more widespread clinical expression of atopic disease.” The idea he brought forth was later labeled the “hygiene hypothesis”, which states, “…exposure to microbes (both pathogenic and commensal) early in life prevents the later development of allergic diseases.”
The hygiene hypothesis was further supported in 1990 when *H. pylori* and other microbes obtained via the oral-fecal route were studied in relation to atopy in young male Italian cadets.\(^7\) The results indicated that there was a statistically significant inverse relationship between exposure to two or more microbes obtained via the oral-fecal route and the development of atopic conditions. Highly contagious airborne viruses, such as measles and mumps, did not have an inverse relationship with atopic conditions. The authors suggested that microbes obtained via the oral-fecal route are often representative of hygiene in general, and a less hygienic environment in childhood that exposes individuals to oral-fecal microbes decreases the likelihood of developing atopic conditions. The authors suggested the explanation that bacteria passing through the GI tract may be necessary to activate gut associated lymphoid tissue, with some immune-modulating effects seen later in life.\(^7\)

*Helicobacter pylori*, a gram negative, motile, spiral, urease-positive bacteria transmitted amongst humans via the oral-fecal route,\(^8\) has interested scientists because it has colonized humans for thousands of years.\(^9\) Based on research by Linz et al,\(^9\) *H. pylori* was present when humans migrated from East Africa around 58 000 years ago, and researchers believe *H. pylori* also colonized individuals for many years prior to this migration. *H. pylori* is unique in that it colonizes individuals at a very young age and is often present for the remainder of the host’s life, unless specific triple antimicrobial therapy is utilized.\(^10\) *H. pylori* has a unique ability to mutate.\(^10\) Due to this ability, *H. pylori* has been able to inhabit humans all over the world, from birth until death.\(^11\) Mutations have also made it more difficult to treat, as there is growing resistance to clarithromycin.\(^12\) The ability to mutate has lead to the evolution of different virulence factors. One factor that has been studied specifically is the Cytotoxin associated gene A (CagA), which is a bacterial oncoprotein that is injected by *H. pylori* into epithelial cells of the gastric mucosa and is well known for its association
with peptic ulcer disease.\textsuperscript{13} CagA also has been shown to have the strongest immune modulating effects, decreasing the cytokine profile responsible for atopic conditions.\textsuperscript{10}

Without specific testing methods for \textit{H. pylori} available worldwide, colonization rates vary depending on the study. Some studies report a colonization rate up to 100\% in developing countries compared to a colonization of less than 10\% in the United States.\textsuperscript{14} According to the WHO, there is approximately a 70\% colonization rate in developing countries and 10-30\% in developed countries.\textsuperscript{15} The decline in colonization rates is attributed to antibiotics as well as a general improvement in sanitary conditions in developed countries.\textsuperscript{16}

Once it was isolated by Australian scientists Marshall and Warren in 1982,\textsuperscript{17} \textit{H. pylori} has been commonly thought of as pathogenic and eradicated due to its correlation with gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma. According to the WHO,\textsuperscript{15} \textit{H. pylori} is a class I carcinogen and is strongly correlated with gastric cancer, the second leading cause of cancer death worldwide, and the seventh leading cause of cancer death in the United States.\textsuperscript{18} The decline in U.S. gastric cancer rates is often attributed to the decreased prevalence of \textit{H. pylori}.\textsuperscript{15} More recent research, however, questions the previous assumption that \textit{H. pylori} is strictly pathogenic. Mutualism is demonstrated in epidemiologic studies revealing an inverse relationship between \textit{H. pylori} and the development of gastroesophageal reflux disease (GERD), along with its complications, including Barrett’s esophagus, and esophageal adenocarcinoma.\textsuperscript{19} Esophageal adenocarcinoma is the sixth most common cause of cancer death worldwide,\textsuperscript{20} and continues to increase in frequency in the United States.\textsuperscript{10} The most likely explanation for this inverse relationship is the fact that \textit{H. pylori} reduces acid secretion by causing pangastritis.\textsuperscript{21} \textit{H. pylori} is also inversely associated with atopic conditions,\textsuperscript{22} which this systematic review will further explore.
Amidst the numerous contrasting epidemiologic studies that demonstrate both mutualism and parasitism between *H. pylori* and humans, the majority of those colonized with *H. pylori* are actually asymptomatic, and the bacteria never cause any pathology.\textsuperscript{14} Even if *H. pylori* does not cause disease, it does lead to a specific immune response in all humans. Dendritic cells are antigen presenting cells found throughout the GI tract that activate a specific subset of helper T cells (Th), either Th1, Th2, Th17 or Regulatory T cells (Treg cells), when exposed to bacteria such as *H. pylori*.\textsuperscript{23} Th1 responds to intracellular organisms and activates macrophages, Th2 responds primarily to parasitic infections and is also responsible for atopy, Th17 responds to extracellular bacteria and fungi, and Treg cells regulate and attenuate the immune response of the other 3 helper T cell subsets.\textsuperscript{23} *H. pylori* primarily activates a Th1 response, leading to the accumulation of leukocytes in the gastric mucosa,\textsuperscript{21} decreases the Th2 response, which is responsible for asthma, and increases production of Treg cells.\textsuperscript{10}

Studies have shown that the immune system may be more modifiable at a younger age.\textsuperscript{24} In a recent study conducted by Oertli et al., mice infected with *H. pylori* had decreased bronchial hyperresponsiveness and increased production of Treg cells.\textsuperscript{24} The authors noted that the increase in Treg cells enables *H. pylori* to persist for many years in humans and inadvertently shifts the cytokine profile to a Th1 dominant pathway, decreasing the likelihood of asthma development.\textsuperscript{10} Oertli et al. noted that “…*H. pylori* possesses the distinct ability to reprogram DCs toward a tolerogenic phenotype in vitro and in vivo, a process that ensures persistence of the bacteria in the host and may cross-protect against chronic inflammatory and autoimmune diseases.”\textsuperscript{24} These findings were most evident in mice younger than 7 days, possibly suggesting the immune system is more modifiable at a younger age.\textsuperscript{24} A similar study attempted to inject mice with the neutrophil activating protein of *H. pylori* (HP-NAP) without colonizing the mice with *H. pylori*.\textsuperscript{25} The results demonstrated that those
mice given HP-NAP had decreased airway and serum eosinophilia and decreased bronchial inflammation compared with the control group. In addition, those injected with HP-NAP had a predominant Th1 response as noted by the cytokines released and a decreased Th2 response as is seen in asthma.\textsuperscript{26}

These laboratory studies suggest that infection with \textit{H. pylori} or its virulence factors may have an impact on immune system development and/or function. At least in mouse studies, \textit{H. pylori} shifts the immune response from a Th2 response, responsible for asthma, to a Th1 response and decreases bronchial inflammation. This systematic review attempts to determine if lower rates of asthma exist amongst those colonized with \textit{H. pylori}.

**METHODS**

The search for medical literature used MEDLINE (through Ovid and PubMed), Web of Science, and Evidence Based Medicine Review using the keywords ‘asthma’ and ‘\textit{H. pylori}’. All relevant studies were reviewed that were in the English language and were not published prior to 2000. Exclusion criteria included a population studied less than 200 (n<200), unclear asthma diagnosis methods, and addressing “atopy” in general, without distinguishing allergic rhinitis, for example, from asthma. Studies were excluded if they did not specify methods for testing \textit{H. pylori} or if the methods of testing are not common in the United States. After applying the exclusion criteria, 5 retrospective case-control studies were included in this systematic review. The studies were critically appraised and then evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the GRADE Working Group.\textsuperscript{27}
RESULTS

A total of 142 studies were screened. After the exclusion criteria were applied and duplicates were removed, 5 retrospective case-control studies were identified as appropriate.

Reibman et al

In this retrospective case-control study, the authors hypothesized that *H. pylori* serostatus would be inversely related to the presence of asthma. Adults with and without asthma were recruited to participate in the New York University/ Bellevue Asthma Registry in New York City. Participants had to be between 18 and 65 and have less than a 10 pack-year smoking history. They were excluded if they had unstable cardiac disease, uncontrolled hypertension, lung disease other than asthma or neuromuscular disease. Initially, 573 participants were given an internationally recognized asthma questionnaire and were evaluated by a clinician with experience in asthma. Twelve people were excluded due to unclear asthma diagnosis. Age of asthma diagnosis was a self reported age and was not obtained from previous medical records. Serum anti-*H. pylori* IgG antibody levels were tested using Enzyme-linked immunosorbent assay (ELISA). CagA status was also tested using ELISA. Thirty-five individuals were excluded due to inadequate serum samples. After the above patients were excluded, there were 526 subjects left in the study, 318 with asthma and 208 controls.

Participants were diverse in respect to race and gender. They were not completely homogenous in respect to prognostic factors. Participants in this study who had asthma were more likely to be low income (yearly income <15,000) and more likely to be Hispanic. They were also more likely to be atopic and have higher levels of IgE. All participants lived in an urban setting. Follow-up was complete.
Statistically significant results indicated that CagA seropositivity was inversely associated with asthma development in an urban setting (OR=.57 (CI 0.36-0.89)), and CagA positive strains of *H. pylori* were also associated with a later age at onset of asthma when compared to those without CagA seropositivity. The OR for those *H. pylori* positive and CagA negative was 1.23 (CI 0.74-2.03), and after adjustments was 0.74 (CI 0.41-1.3), suggesting an inverse relationship between *H. pylori* positivity/CagA negativity and asthma, without reaching statistical significance (p=0.39). The Odds Ratio (OR) was given before and after using generalized estimating equation (GEE) multiple logistic regression analysis. GEE multiple logistic regression analysis adjusted for age, race, Hispanic ethnicity, income, and the genetic relatedness among the subjects.28

The secondary outcome of this study was to determine if *H. pylori* status was associated with a later age at onset of asthma. The average age at onset was 19 for those *H. pylori* positive and CagA negative, the average age at onset was 21 for those CagA positive, and the average age at onset was 11 among those *H. pylori* negative. After GEE was used to adjust for potential confounders, there was a statistically significant association between those participants positive for CagA and later age at asthma diagnosis (p=0.02). An association was noted between *H. pylori* positive/CagA negative serology and a later age of asthma diagnosis, but this was not statistically significant.28

**Chen et al, 2007**

This retrospective case-control study22 hypothesized that childhood acquisition of *H. pylori* is associated with reduced risks of asthma and allergy. To test this hypothesis, the authors used the third National Health and Nutrition Examination Survey (NHANES) III, which consisted of data
collected between 1988 and 1994. NHANES selects a representative sample of adults and children to assess the greater health and nutritional status of the United States population. There were 10,120 adults sampled during the first phase of the trial. Information of asthma history was obtained with an in person interview. Participants were specifically asked if they were ever diagnosed with asthma and the age at which they were diagnosed. They were also asked about wheezing symptoms in the last year. The individuals were all 20 years and older. *H. pylori* was detected with ELISA. The CagA strain of *H. pylori* was also detected with ELISA. Of the 10,120 original candidates, 2,457 were excluded due to missing information, unclear asthma status or inadequate serology sample, and 7,663 were included in the analysis. In the analysis, individuals were separated based on whether they were diagnosed with asthma before the age of fifteen or after age fifteen.²²

Participants included in the study, due to its design and large population size, were quite heterogeneous. Individuals born in Mexico, older individuals and men were more likely to be colonized with *H. pylori*. Follow up was complete.²²

The authors concluded that the results support the hypothesis that childhood colonization of *H. pylori* is associated with reduced risks of asthma and allergy. There was a statistically significant inverse relationship between positive CagA serology and ever having had asthma in all age groups (OR=0.79 (CI 0.63-0.99)) and between positive CagA serology and the diagnosis of asthma before the age of 15 (OR=0.63 (0.43-0.93)), but not for diagnosis of asthma after the age of 15. The results were then broken down by age, into those participants older than 43 and younger than 43. There was a strong inverse relationship between CagA positive strains and current asthma diagnosis (OR=0.68 (0.43-1.07)) or past asthma diagnosis (OR=0.63 (0.43-0.93)) in participants younger than 43, but this was not the case for participants older than 43. There was also suggested but not statistically significant inverse correlation between *H. pylori* positive/CagA negative strains and current or past...
asthma diagnosis. The ORs were adjusted using unconditional logistic regression models to adjust for sex, race, ethnicity, age, smoking status, BMI, education status, and country of birth. Since the ORs did not change very much with the adjustments, the study made use of the non-adjusted ORs.22

Chen et al, 2008

In this retrospective case-control study,31 data was acquired from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2000 in order to determine if H. pylori colonization in early life decreases the risk of developing childhood asthma. There were 8969 individuals 3 years and older enrolled in the NHANES between 1999 and 2000, and of these, H. pylori status was obtained in 7493. There was missing data for 81 subjects, so 7412 individuals were left with known H. pylori status. There were 3327 individuals included in the study who were between the ages of 3 and 19. H. pylori was detected using the Wampole ELISA. The asthma history and age at diagnosis were obtained with in person interviews. Those participants who were 19 and younger were also asked at what age they were diagnosed with asthma.31

The participants were representative of the United States population and quite diverse. Those positive for H. pylori were more likely to be older, Hispanic, to have been born in a country outside of the United States, and to have a lower education level. H. pylori colonization rates in children younger than 10 was 5.4%, and among all age groups, the colonization rate was 25.8%. Follow up was complete.31

The authors concluded that H. pylori colonization was inversely correlated with asthma in children. Among children aged 3-13, there was a statistically significant inverse relationship between positive H. pylori status and current asthma, with the OR being 0.41 (CI 0.24-0.69). Among children
aged 3-19, there was a statistically significant inverse relationship between positive *H. pylori* status and the development of asthma before the age of 5, with the OR being .58 (CI 0.38-0.88). For children aged 3-19, there was a suggested inverse relationship between positive *H. pylori* status and ever having had asthma (OR=0.69 (CI 0.45-1.06)). Among all individuals included in the study, including children and adults, there was a suggested inverse relationship between positive *H. pylori* status and ever having had asthma (OR=0.89 (CI 0.68-1.16)). There was a statistically significant inverse relationship between positive *H. pylori* status and wheezing in the past year (OR=0.73 (0.57-0.94)). The above ORs were statistically adjusted for age, sex, BMI, smoking status, education level, race/ethnicity, and country of birth. The OR was also adjusted for antibiotic use in the last month, income, medical insurance status and housing type. The analysis was performed using SAS 9.1.4 proc survey procedures.

**Zevit et al.**

This was a retrospective case-control study of 6959 children between the ages of 5 and 18 conducted in Israel between 2007 and 2008 to determine if correlation exists between *H. pylori* colonization and decreased rates of asthma in children. The study obtained participants via the Clalit Health Services (CHS), which is a health organization that has medical records for 53% of the total population. *H. pylori* was diagnosed using a C-urea breath test for children aged 5-18. They reported that C-urea breath tests are less accurate in children younger than 5, so this age group was not included. Diagnosis of asthma was obtained from the electronic data warehouse of the CHS which included medical records from 2003-2008, and was further specified via a prescription for an asthma-specific medication.
Individuals were all living in Israel and in the CHS. There were 45.6% participants that tested positive for *H. pylori*, and 8.3% had a diagnosis of asthma. Those that tested positive for *H. pylori* were more likely to be from low income families. Those with asthma were more likely to be male and have resided in an urban area. Follow up was complete.\textsuperscript{32}

The authors concluded that there was an inverse correlation between *H. pylori* and pediatric asthma, and that *H. pylori* is an independent factor that protects against asthma. The results indicated that 7.3% of those who tested positive for *H. pylori* had asthma, whereas 9.1% of those who tested negative for *H. pylori* had asthma. This demonstrated a difference of 1.8%. There was a statistically significant inverse correlation between positive *H. pylori* status and asthma (0.82 (CI 0.69-0.98), \( p=0.032 \)). A stepwise multivariate regression model was used to determine the association between independent variables and current asthma diagnosis. Age, gender, socioeconomic status, ethnicity and type of residence were independent variables that had a statistically significant relationship with asthma.\textsuperscript{32}

\textbf{McCune et al}

This was a retrospective case-control study\textsuperscript{33} that took place in northeast Bristol amongst 26 203 people aged 20-59 and aimed to determine if *H. pylori* colonization decreases the risk of developing asthma. There were 10 537 individuals included in this study. These individuals were tested for *H. pylori* with a C-urea breath test. There were 1634 participants (15.5%) that tested positive for *H. pylori*. The study then randomly selected 3268 *H. pylori* negative individuals for the control group. From these participants, the study collected data about medication use, since the study assumed current asthma status if they were taking an inhaled corticosteroid or an inhaled oral
bronchodilator. Of these individuals, 1079 \( H. pylori \) positive subjects and 2165 \( H. pylori \) negative individuals provided complete information about their medications. Participants also answered a questionnaire about lifestyle, adult and childhood social background (number of children sharing a bedroom in childhood and what type of house they grew up in), GI symptoms and any other medications they were taking.\(^{33}\)

Participants were all between the ages of 20 and 59 and were all living in a specific geographic region of the United Kingdom. The authors noted that atopy was less common in older individuals and among participants that grew up in a lower socioeconomic status. Those individuals in the study that had attended daycare, had older siblings, and those that grew up in a lower social class were less likely to develop atopic conditions, such as asthma. Follow up was complete.\(^{33}\)

The results indicated a 30% reduction in the presence of eczema, allergic rhinitis and asthma in participants colonized with \( H. pylori \). When asthma was independently analyzed with \( H. pylori \), there was a suggested inverse relationship without reaching statistical significance. There was a suggested inverse relationship between positive \( H. pylori \) status and inhaler usage (OR=0.78 (CI 0.59-1.05), p=0.10). Initially, univariate analysis was used to analyze the data. This was followed by hierarchical logistical regression analysis for those factors that were significant in univariate analysis. Adjustments were made for gender, smoking status, and measures of socioeconomic status.\(^{33}\)

**DISCUSSION**

Asthma is a complex disorder with many possible proposed causes. The end result for all individuals affected regardless of the reason is a chronic disorder that has a significant impact on
quality of life. This systematic review specifically examines the role of *H. pylori* colonization and its effect on asthma development and hopes to clarify the question: Are there aspects of mutualism in *H. pylori*’s relationship with humans, or is this relationship strictly parasitic? Furthermore, can researchers isolate aspects of *H. pylori* to trigger immune modulating effects without causing pathology? These are all important avenues that should be explored if there is a consistent inverse relationship between *H. pylori* and atopic conditions such as asthma.

The findings in the above studies suggest that *H. pylori* exposure at a young age, especially the more virulent strain CagA, delays and/or prevents the development of atopic conditions such as asthma. Laboratory studies indicate that exposure to this microbe at a young age has significant immune modulating effects which increase Treg cell production and shift the immune reaction from a Th2 cytokine profile, responsible for atopic conditions, to a Th1 cytokine profile. The CagA strain was specifically studied in two of the five studies \(^\text{22,28}\) and was consistently inversely associated with asthma, which if it develops at all, develops at a later age. For the studies addressing *H. pylori* in general, an inverse relationship between *H. pylori* and asthma was implied without reaching statistical significance in three studies, \(^\text{22,28,33}\), whereas the inverse association between *H. pylori* and asthma was statistically significant in two of the studies. \(^\text{31,32}\) In all 5 studies, with or without statistical significance, the results were trending in the same general direction in support of the hygiene hypothesis.

Due to the nature of retrospective case-control studies, a relationship between exposure and prognosis can be implied, but it is difficult to assess the degree of causation and/or prevention. This stands as one important limitation, and because of this, all studies initially started as low quality evidence according to GRADE. Another limitation is inconsistency amongst the studies in detecting *H. pylori*. The C-urea breath test was used in two of the above studies. It has a sensitivity of 88-95%
and specificity of 95-100%, which made false negatives more likely.\textsuperscript{34} Three of the above studies\textsuperscript{22,28,31} used serology, specifically detecting anti-\textit{H. pylori} IgG antibodies. This method has a sensitivity of 90-100%, and a specificity of between 76-96%, which made false positives more likely.\textsuperscript{35} Consistency of \textit{H. pylori} detection would make comparison of the studies easier.

There were some common limitations seen throughout all of the studies. Firstly, none of the studies independently assessed for GERD. In epidemiologic studies, \textit{H. pylori} has been inversely associated with GERD, and GERD can be a trigger for asthma. Therefore, this could potentially contribute to the inverse relationship between \textit{H. pylori} and asthma. Secondly, children with asthma are more prone to respiratory infections, and because of this, tend to receive more antibiotics at a younger age. Therefore, it is possible that antibiotics given for other infections may inadvertently clear \textit{H. pylori} colonization, making it appear that those people without \textit{H. pylori} colonization are more likely to have asthma. Without accurate medical records, which only one study utilized, this would be difficult to ascertain.

In the retrospective case-control by Reibman et al,\textsuperscript{28} the authors concluded that in an urban setting, CagA positive strains of \textit{H. pylori} are inversely related to asthma. CagA positive strains of \textit{H. pylori} are also associated with a later age at onset of asthma when compared to those without \textit{H. pylori}. Specific limitations in this study included the fact that age of asthma diagnosis was self-reported, adding recall bias, there was no one in the study younger than eighteen years old, and the study results were not broken down by age. Since this was an observational study, it started off as a low quality study according to GRADE. Even though age of asthma diagnosis may have been affected by recall bias, this was not a primary outcome in the study, so the study was not downgraded for this. The study remained low quality evidence according to GRADE. The results of this low quality study echo the results of the other studies.
In this retrospective case-control study by Chen et al in 2007, there was an inverse relationship between *H. pylori* and current or past asthma diagnosis in participants younger than 43, and this inverse relationship was more pronounced with CagA strains of *H. pylori*. There was also a strong inverse relationship between CagA strains of *H. pylori* and the development of asthma before the age of 15. The advantage of this study was the very large sample size representative of the United States population. The limitations of this study included the fact that the diagnosis of asthma and age of diagnosis were self reported, and that the study did not include anyone younger than 20. Participants did not know their *H. pylori* status at the time of the interview, so this should not have influenced their responses. Since this was a cross sectional study, it also started off at a low quality according to GRADE. After analyzing the study according to GRADE, it was neither upgraded nor downgraded, leaving this study as low quality evidence. The results of this low quality study also echo the results of the other studies. As stated best by Chen et al, “The present observations also are consistent with the ‘hygiene hypothesis’ that microbial infections during early childhood may prevent or diminish atopic sensitization and asthma.”

In 2008, Chen et al did a second retrospective case control study to further examine asthma prevalence in children and *H. pylori* status, and it was found that there was a strong inverse association between positive *H. pylori* status and current asthma status in children between the ages of 3 and 13, and a strong inverse association between positive *H. pylori* serology and onset of asthma in children younger than 5. This was the first study to report a statistically significant inverse association between positive *H. pylori* status and asthma in children, especially early onset asthma (less than 5 years old). The study had a very large sample size representative of the population of the United States. Specific limitations of study include the fact that CagA status was not assessed, which was included in 2007 study, asthma diagnosis was obtained via interviews only, so participants in
theory could have lied about the diagnosis, or they could have been completely unaware that they were diagnosed if the diagnosis occurred at a young age. Participants were unaware of their H. pylori status at the time of the interview, so this should not have influenced their answers. Those positive for H. pylori were more likely to be smokers, which if anything, would downplay the relationship between H. pylori and asthma, as mentioned by the authors. The study was neither downgraded nor upgraded, and according to GRADE, remains a low quality study. This study also echoes the results of the other studies in this systematic review.

In the retrospective case-control study by Zevit et al., the study found that children not colonized by H. pylori had a 1.8% increased risk of developing asthma, which would translate into a significant number of children in the United States, with approximately 10% of children having the diagnosis of asthma. The authors concluded, “the priming toward atopy is likely [an] early phenomenon.” The study had a large sample size of 6959, all of whom were children. The study had excellent objective approaches to assess H. pylori status and asthma, including the C-urea breath test for H. pylori and medical records for the asthma diagnosis supported by the appropriate medication. The limitations included the fact that no participants were younger than 5, CagA status was not assessed, and the participants were all living in Israel, which is important to remember if directly applying this to patients in the United States. Also, the C-urea breath test was ordered only for those with clinical indications for it, and it was not ordered randomly for all individuals in this medical records system. Due to the nature of the study being an observational case-control study, it started off as a low quality study according to GRADE and was neither upgraded nor downgraded, so it remains a low quality study but supports the results common to all of the studies.

In the retrospective case-control study by McCune et al., results indicated that H. pylori colonization reduces the risk of developing atopic conditions in general, including asthma, eczema,
and allergic rhinitis. There was a suggested inverse relationship between positive *H. pylori* status and asthma, but it was not statistically significant. One advantage of the study was that C-urea breath tests were used to assess *H. pylori* status. One limitation of the study was the approach to asthma diagnosis, which was defined as the individual using an inhaled corticosteroid or short acting beta agonist. It is difficult to determine if this would underestimate or overestimate the number of people with asthma, since it is unknown how many people in this group were non-compliant, undiagnosed, or being treated with these medications for other pulmonary diseases. Other limitations included the fact that the study did not include individuals younger than 20, and the study did not address age at diagnosis or CagA status. Since it was an observational case-control study, it started off as low quality evidence according to GRADE. It was downgraded for its lack of specificity when assessing asthma diagnosis. Therefore, the study was downgraded to a very low quality study, and not able to be upgraded since it is difficult to determine if asthma diagnosis was underestimated or overestimated. The study, however, was well-designed and demonstrates support for the hygiene hypothesis in general.

The applicability of this data into clinical practice is ambiguous. As suggested in the above studies, *H. pylori* is clearly associated with decreased rates of asthma. However, there are pathologies that are also associated with *H. pylori*, and this systematic review does not imply that *H. pylori* is strictly beneficial or that individuals should be inoculated with *H. pylori*. There are several issues to consider when contemplating the application of the above data.

Firstly, at least half of the world’s population is colonized with *H. pylori* and many do not develop disease due to this colonization. Thus, the state of *H. pylori* colonization should not be immediately viewed as a pathologic state that warrants triple or quadruple antibiotic therapy. GERD
and atopic conditions may be less prevalent when individuals are colonized with *H. pylori*. Therefore, *H. pylori* should be treated if, and only if, it is causing disease.

Humans have been colonized with *H. pylori* for thousands of years, and the abolition of this microbe, and microbes in general, with increased usage of antibiotics may have significant effects on the symbiotic, potentially immune modulating relationship between microbes and humans. It is an important reminder that the common use of antibiotics can have unintended consequences. For example, if antibiotics are used for acute bronchitis in a young child, *H. pylori* may be eradicated, and the child may be more likely to develop asthma or other atopic conditions. Therefore, antibiotics should be used only when completely necessary in children.

*H. pylori* colonization, especially in the United States, is more prevalent in a specific subset of the population, notably immigrants, those from lower socioeconomic groups, and those children with multiple siblings, all factors that expose children to more microbes in general, not just *H. pylori*. Even if *H. pylori* is not directly responsible for reduced asthma, the above studies still provide evidence in support of the hygiene hypothesis. This research should call into question the common practice of feeding farm animals antibiotics as a preventive measure without an infection present. Anti-microbials are overused in the food supply and in people, which not only increases antibiotic resistance, but may also be partly responsible for the increased rates of asthma and other atopic conditions. Sterility is very important in certain settings, but exposure to microbes is also important in the developing immune system.
CONCLUSION

The reviewed studies show a correlation between exposure to *H. pylori* at a young age and decreased rates of asthma. This inverse correlation is strongest with CagA strains of *H. pylori*, the most virulent strain, and is strongest with asthma development in children under five, the age group that has the fastest increasing rate of asthma in the United States.

Randomized controlled trials provide the best opportunity to prove causation, but it would be unethical to inoculate individuals with *H. pylori*. Therefore, the ideal trial would study children and adults, break the results down by age, have provider diagnosed asthma, utilize medical records for age of asthma diagnosis, include testing for CagA, and use C-urea breath tests or even gastric biopsy, as these tests are more specific than serology. However, even if causation is proven, the issue remains complex since there are pathologies clearly associated with *H. pylori*. Future research is needed to determine if the protective effects of *H. pylori* exposure can be recreated without causing pathology.

As McCune et al stated, if bacterial infections such as *H. pylori* continue to be less common in developed countries, “…it may be desirable to try to develop other ways to prime the developing immune system so as to reduce the risk of atopy in later life.” Future research is needed to determine if the CagA oncoprotein or HP-NAP can be used to induce immune modulating effects and prevent asthma development without causing pathology. In addition, if a future vaccine is developed to prevent *H. pylori* colonization, it will be important to assess patients and evaluate their risk for the development of atopic conditions versus their risk of gastric cancer.
Even if a direct preventive relationship cannot be proven with case-control studies, it cannot be ruled out that *H. pylori* modulates the immune system in a way that is beneficial to humans, and this has important implications in a country with an asthma rate that continues to rise.
References


4. Braman SS. The global burden of asthma. Chest. 2006;130:4S-12S.


## Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality Assessment</th>
<th>Quality</th>
<th>Importance</th>
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<tr>
<td>Reibman et. al. 2014</td>
<td>1</td>
<td>Observational study</td>
<td>No limitations</td>
<td>No inconsistency</td>
<td>No indirectness</td>
<td>No imprecision</td>
<td>None</td>
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<td>⊕⊕ΟΟ LOW</td>
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<tr>
<td>Effect of H. pylori colonization (CagA+ and CagA-) on the Development of Asthma; Age of asthma onset with and without H. pylori colonization</td>
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<td></td>
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<tr>
<td>Chen et. al., 2007</td>
<td>1</td>
<td>Observational study</td>
<td>No limitations</td>
<td>No inconsistency</td>
<td>No indirectness</td>
<td>No imprecision</td>
<td>None</td>
<td></td>
<td>⊕⊕ΟΟ LOW</td>
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<tr>
<td>Effect of H. pylori colonization (CagA+ and CagA-) on the Development of Asthma; Age of asthma onset with and without H. pylori colonization</td>
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<tr>
<td>Chen et. al., 2008</td>
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<td>No limitations</td>
<td>No inconsistency</td>
<td>No indirectness</td>
<td>No imprecision</td>
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<td>Effect of H. pylori colonization on the Development of Asthma; Age of asthma onset with and without H. pylori colonization</td>
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<tr>
<td>Zevit et. al. 2016</td>
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<td>Observational study</td>
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<td>No inconsistency</td>
<td>No indirectness</td>
<td>No imprecision</td>
<td>None</td>
<td></td>
<td>⊕ΟΟΟ LOW</td>
<td>CRITICAL</td>
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<tr>
<td>Effect of H. pylori colonization on the Development of Asthma</td>
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<tr>
<td>McCune et. al. 2018</td>
<td>1</td>
<td>Observational study</td>
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<td>No inconsistency</td>
<td>No indirectness</td>
<td>No imprecision</td>
<td>None</td>
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<td>⊕ΟΟΟ VERY LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>Effect of H. pylori colonization on the Development of Atopic Conditions (Asthma, Eczema, and Allergic Rhinitis)</td>
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</tbody>
</table>

1 Recall bias with age of asthma diagnosis, but this was a secondary outcome
2 Asthma was diagnosed based on medication prescribed rather than clinician diagnosis
Table II. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Control / Treatment</th>
<th>Ages of Participants</th>
<th>Method of asthma diagnosis/ method of H. pylori diagnosis</th>
<th>Odds Ratios</th>
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<tr>
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</tr>
<tr>
<td>H. pylori+ / CagA- serostatus and asthma</td>
<td></td>
<td></td>
<td></td>
<td>Crude OR</td>
<td>Adjusted OR (95% CI)</td>
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<tr>
<td>Reibman et al28</td>
<td>Retrospective Case Control Study</td>
<td>208 (no asthma) / 318 (asthma)</td>
<td>19-65</td>
<td>Questionnaire/ELISA¹</td>
<td>1.23 (0.74-2.03)</td>
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<tr>
<td>CagA+ and asthma</td>
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<td></td>
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<td>0.77 (0.50-1.18)</td>
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<tr>
<td>H. pylori+ / CagA+ serostatus and asthma</td>
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<td></td>
<td></td>
<td>Overall Asthma Status OR (95% CI)²</td>
<td>Age at onset of asthma &lt;15 OR (95% CI)³</td>
</tr>
<tr>
<td>Chen et al, 2007²²</td>
<td>Retrospective Case Control Study</td>
<td>3943 (Hp-) 1445 (Hp+ / CagA-) 2275 (Hp+ /CagA+)</td>
<td>20-59</td>
<td>Questionnaire/ELISA¹</td>
<td>0.79 (0.63-0.99)</td>
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<tr>
<td>H. pylori+ / CagA+ serostatus and asthma; age &lt;43</td>
<td></td>
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<td></td>
<td>Current Asthma Status OR (95% CI)⁴</td>
<td>Overall Asthma Status OR (95% CI)⁴</td>
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<td>0.68 (0.43-1.07)</td>
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<tr>
<td>H. pylori+ / CagA+ serostatus and asthma; age &gt;43</td>
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<td>1.14 (0.81-1.61)</td>
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<td>Age at Onset&lt;5 OR (95% CI)⁶</td>
<td>Age at Onset≥ 5 to &lt;5 OR (95% CI)⁶</td>
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<tr>
<td>Chen et al, 2008³¹</td>
<td>Retrospective Case Control Study</td>
<td>4787 (Hp-) 2625 (Hp+)</td>
<td>3+</td>
<td>Questionnaire/ELISA¹</td>
<td>0.58 (0.38-0.88)</td>
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<td>H. pylori+ serostatus and asthma; age 3-13</td>
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<td></td>
<td></td>
<td>OR (95% CI)⁸</td>
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<tr>
<td>H. pylori+ serostatus and asthma</td>
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<td>OR (95% CI)⁹</td>
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<tr>
<td>McCune et al³³</td>
<td>Retrospective Case Control Study</td>
<td>2165 (Hp-) 1079 (Hp+)</td>
<td>20-59</td>
<td>Atopic Medication/C-urea Breath Test</td>
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</tr>
</tbody>
</table>

Abbreviations: CI, Confidence interval; Hp Helicobacter pylori; ELISA Enzyme linked immunosorbent-assay

¹ Detected H. pylori and CagA status
² Adjusted for income and race via logistic regression
³ Multivariate analysis performed using GEE and adjusted for age (in years), education (in years), income, race (white, black, other) and Hispanic ethnicity
⁴ Adjusted for race/ethnicity, age, sex, body mass index, smoking status, and educational attainment
⁵ Cut points were determined on the basis of the median onset age
⁶ 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
⁷ Adjusted for socioeconomic status