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Original Article

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Association of *Helicobacter pylori* Infection with Pediatric Asthma in Palestine

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ABSTRACT

Purpose: Significant debate exists on the association between *Helicobacter pylori* infection and childhood asthma. We aimed to explore this association in a cohort of children in Palestine while estimating the prevalence of *H. pylori* in this population.
Methods: We conducted a prospective case-control study among children aged 6–15 years in Palestine, including 44 asthma cases diagnosed by pediatric pulmonologists and 99 age-matched healthy controls recruited through cluster sampling from schools. *H. pylori* status was determined using a stool antigen test. Asthma severity was assessed using the International Study of Asthma and Allergies in Childhood questionnaire. Data on recent antibiotic use, which could affect *H. pylori* status, were collected for both groups. Multiple logistic regression analyzed the association between *H. pylori* and asthma, adjusting for age and sex. The chi-square test assessed the impact of antibiotic use on *H. pylori* status.
Results: The prevalence of *H. pylori* infection in the study population was 45%. Children with asthma had a lower prevalence of *H. pylori* infection compared to healthy controls (32% vs. 51%, adjusted odds ratios, 0.46; 95% confidence interval, 0.22–0.99; p=0.04). Antibiotic use in the past month or year did not significantly impact *H. pylori* status. Among children with asthma, *H. pylori* infection rates did not vary by asthma severity (p=0.05).
Conclusion: *H. pylori* infection is associated with a reduced risk of asthma in children, suggesting a potential protective role. Further prospective cohort studies are warranted to clarify the mechanisms underlying this association.

Keywords: *Helicobacter pylori*; Asthma; Child

INTRODUCTION

Asthma is the most common chronic disease in children and the leading cause of emergency department visits [1]. The hallmarks of asthma are airflow obstruction, bronchial hyperresponsiveness, and airway inflammation [2]. Asthma prevalence has dramatically increased in the last decade [3]. According to the most recent data from the Centers for

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Conflict of Interest
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Disease Control and Prevention, the overall prevalence of childhood asthma in the United States of America in 2020 was 5.8% [4]. Despite the lack of recent data on asthma prevalence in Palestine, the available data from International Study of Asthma and Allergies in Childhood (ISAAC) III in 2003 showed a prevalence of 9.6% [5].

Helicobacter pylori is a gram-negative bacteria that affects about 50% of the world's population, with a prevalence ranging from 20% in developed countries to 80% in developing countries [6]. Its transmission is associated with low socioeconomic status, poor sanitary conditions, and crowded areas [7]. For decades, researchers in the *H. pylori* field aimed to understand the pathologic traits related to long-standing inflammation, including duodenal ulcer (in 1–10% of infected patients), mucosa-associated lymphoid tissue lymphoma (0.01%), and gastric carcinoma (0.1–3%) [6]. A large body of evidence currently suggests strong immunomodulatory and protective properties of *H. pylori*. Since it is reported that *H. pylori* migrated with the first humans about 60,000 years ago from East Africa and spread worldwide [8], this intimate co-existence between *H. pylori* and its human host provides a context for mutual benefits.

Many epidemiological studies have linked *H. pylori* infection to extra-gastrointestinal diseases, including idiopathic thrombocytopenic purpura, unexplained iron deficiency anemia [9], Sjögren syndrome [10], and nephropathy [11]. On the other hand, many studies suggest potential beneficial effects of *H. pylori* infection due to the inverse relationship to childhood atopy. The increased incidence of allergic and autoimmune diseases in the past decades and a concomitant decrease in infectious diseases support this association. This trend can be attributed to improved socioeconomic status, better sanitary conditions, and the increasing use of antibiotics and vaccination [12]. The original concept stems from the hygiene hypothesis Strachan formulated in 1989 [13]. It postulates that exposure to infectious agents in early childhood may confer protection against allergic diseases.

There is a tremendous controversy among the observational epidemiological studies regarding the association between asthma and *H. pylori* infection. While several meta-analyses provided evidence of a lower rate of *H. pylori* infection in patients with asthma [14], others could not prove such an association [15]. This discrepancy can be attributed to different *H. pylori* detection methods, and diverse study populations in which the prevalence of *H. pylori* is significantly variable. The prevalence of *H. pylori* infection in Palestine, a low-middle income country [16], is expected to be high, but no previous studies reported that. This study aims to assess *H. pylori* prevalence and investigate its association with pediatric asthma in the Palestinian population. In this case-control study, we used a monoclonal stool antigen test to examine the association of the *H. pylori* infection; the independent variable, with the asthma status; the dependent variable. We hypothesized that *H. pylori* infection is inversely associated with asthma in children.

MATERIALS AND METHODS

Study population

This prospective case-control study was conducted from March 2019 to July 2021 among children aged 6-15 years in Palestine. The study included 44 children diagnosed with asthma, recruited from pulmonary clinics across various cities. Asthma diagnoses were made by pediatric pulmonologists and confirmed by spirometry testing, and patients were enrolled regardless of the timing of their diagnosis. The control group consisted of 99 age-matched

healthy children, recruited through cluster sampling from various schools. Children with chronic diseases, including chronic respiratory conditions like cystic fibrosis and primary ciliary dyskinesia, were excluded from the study.

Power analysis and sample size determination

The sample size was determined to detect a significant negative association between Helicobacter pylori infection and childhood asthma, aiming for an odds ratio between 0.5 and 0.7, indicating a reduced risk of asthma in children with *H. pylori* infection. Assuming a two-sided significance level of 0.05 and a power of 0.80, we calculated that 44 asthma cases and 99 controls would provide sufficient power. This sample size ensures an adequate number of events per variable for logistic regression, meeting the requirement of at least 10 events per predictor variable. This allows adjustment for key confounders such as age and sex, while maintaining the stability of the model.

Variable definitions

In this study, the primary dependent variable was asthma status. Therefore, we split the study population into two categories: children with asthma (cases) and children without asthma (controls). The primary independent variable was having *H. pylori* infection, which was assessed via a rapid antigen test using stool samples to report a qualitative result (positive vs. negative). We also used the core questionnaire for the ISAAC [17] as a standardized tool to assess the severity of asthma.

Recruitment of children with asthma was through multiple pediatric pulmonary clinics in Ramallah, Jerusalem, Bethlehem, and Hebron. For all patients, the diagnosis was made by pediatric pulmonologists based on symptoms and spirometry results. We excluded cases with asthma concomitant with another respiratory disease like cystic fibrosis. After the clinic visit, a research team member interviewed the family in a quiet and private place to explain the study protocol and obtain consent for the children who met the study criteria. The children gave a stool sample either on the same day of the clinic visit, if possible, or at a later day at their convenience, making sure the lab receives the sample in less than one hour.

During the interview, parents completed the ISAAC questionnaire to assess the severity of asthma symptoms and exacerbations. We used specific questions in the core questionnaire to categorize asthma into severe and non-severe. We defined severe asthma as having ≥4 attacks of wheezing per year, or ≥1 night per week, sleep disturbances from wheezing or wheezing affecting speech in the past 12 months [18]. We also collected more data to compare the background characteristics of children in both groups and to examine the association between past use of antibiotics and *H. pylori* status to account for coincident elimination. This included a history of asthma in first-degree relatives, the age of onset of asthma symptoms, whether the child used antibiotics within the last month and the frequency of antibiotic use within the previous 12 months.

Recruitment of age-matched healthy controls was done from primary schools in the same cities where the cases were recruited. The first step was to get the school principals' approval after explaining the study's Institutional Review Board-approved protocol. The school principals then selected random groups of children from different classes and communicated directly with the parents to gain their consent over the phone. When the parents agreed to participate, a written consent form was obtained from the parents. Samples were obtained at families'/children's convenience. Afterward, we arranged a phone interview with the family

to discuss and answer the ISAAC core questionnaire, which was used to ensure the children were healthy and didn't have undiagnosed asthma.

Laboratory method

Stool samples were obtained from cases and controls and tested for *H. pylori* stool antigen (ALL TEST- REF IHP-602H). This rapid chromatographic immunoassay was selected for its favorable low cost and non-invasive nature. The test uses monoclonal antibodies to detect *H. pylori* antigens in human stool specimens. It has a relative sensitivity >99.9% (95% confidence interval [CI], 97.0–100%), a relative specificity of 98.4% (95% CI, 94.2–99.8%), and an accuracy of 99.1% (95% CI, 96.8–99.9%). Processing of the sample and interpretation of the results were done following the manufacturer's instructions.

Statistical analysis

We used Microsoft Office Excel to organize and store data, and we used IBM SPSS Statistics for Windows, Version 28.0 (IBM Co.) for conducting descriptive analysis and association tests.

We used multiple logistic regression analysis to examine the association between *H. pylori* test results and asthma status, adjusting for age and sex as potential confounders. We used the Chi-square test for independence to explore the association between categorical variables among children's background characteristics and assess the effect of antibiotic use. We also used Independent-Samples Mann-Whitney U-test and Independent Sample *t*-test for continuous variables normally distributed and skewed, respectively. A *p*-value <0.05 was considered significant.

Ethical approval

The Institutional Review Board approved the study protocol at Al-Quds University (Ref No: 171/REC/2021). A written consent form was obtained from the parents.

RESULTS

Overall, the prevalence of *H. pylori* infection in our study was 45%. We enrolled 44 asthma cases and 99 healthy controls. Fifty-one percent (50/99) of the controls tested positive for *H. pylori* stool antigen, while only 32% of the cases tested positive (**Fig. 1**).

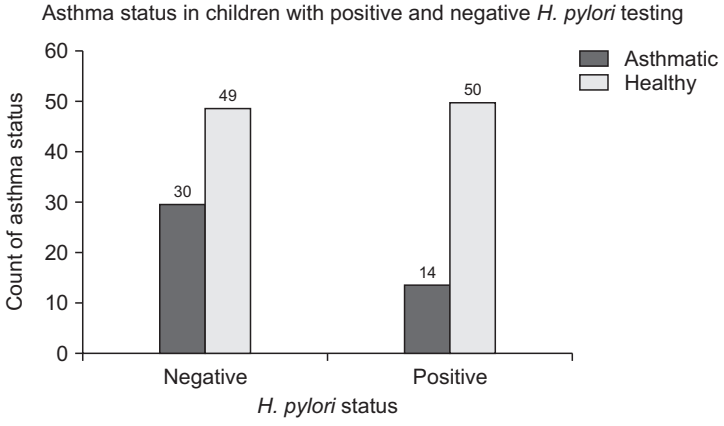

Fig. 1. Prevalence of asthma among children who have vs. do not have *H. pylori*.
H. pylori: Helicobacter pylori.

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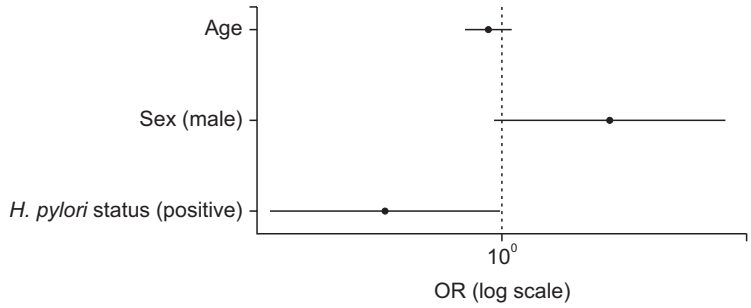

Fig. 2. Forest plot of adjusted OR for asthma status. This plot displays the adjusted OR for asthma status associated with *H. pylori* infection, gender, and age. The OR for *H. pylori* positive status is 0.46 (95% CI: 0.22-0.99), suggesting a significantly lower risk of asthma in children with *H. pylori* infection. The OR for males is 2.04 (95% CI: 0.95-4.36), indicating a potential trend toward higher asthma risk in males, though this is not statistically significant as the confidence interval crosses 1. Age has an OR of 0.92 (95% CI: 0.79-1.07), showing no significant association with asthma in this model. The vertical gray line at OR=1 represents no effect.
OR: odds ratio, CI: confidence interval.

Logistic regression analysis was conducted to examine the association between *H. pylori* infection and asthma status, adjusting for age and gender (**Fig. 2**). The model revealed that children with positive *H. pylori* status had a significantly lower likelihood of having asthma compared to those with negative *H. pylori* status, with an adjusted odds ratio (OR) of 0.46 (95% CI, 0.22–0.99; p=0.04). Although gender showed a trend toward increased asthma risk in males (OR, 2.04; 95% CI, 0.95–4.36; p=0.067), this finding was not statistically significant. Age was also not significantly associated with asthma status (OR, 0.92; 95% CI, 0.79–1.07; p=0.27). The model fit, as indicated by the Nagelkerke R^2 value of 0.086, suggests that the predictors explained approximately 8.6% of the variance in asthma status. Overall, these results support a significant negative association between *H. pylori* infection and asthma in children.

Among the characteristics of cases and controls (**Table 1**), having asthma in first-degree relatives was more frequent in patients than in controls (p<0.001). There was no statistically significant association between the background characteristics of children who tested positive versus negative for *H. pylori* antigen (**Table 2**).

Table 1. Characteristics of children with (cases) and without asthma (controls)

Associated factor	Number of healthy Participants (%) (n=99)	Number of participants having asthma (%) (n=44)	*p*-value*
Age (yr)	9 (4)	9 (3)	0.29
Sex			
Female	48 (48.5)	14 (31.8)	0.06
Male	51 (51.5)	30 (68.2)	
Asthma in a first-degree relative			<0.001
Yes	38 (38.4)	34 (77.3)	
No	61 (61.6)	10 (22.7)	
Maternal education y	12 (4)	12 (3.5)	0.18
Paternal education y	12 (6)	12 (2.75)	0.04
Household monthly income			0.08
Above average	5 (5.1)	7 (15.9)	
Below average	28 (28.3)	9 (20.5)	
Around average	66 (66.7)	28 (63.9)	

Values are presented as median (interquartile range) or number (%).
*Chi-Square test and Independent-Samples Mann-Whitney U-test.

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Table 2. Characteristics of children with *H. pylori* positivity and negativity

Associated factor	*H. pylori* positive (n=64)	*H. pylori* negative (n=79)	*p*-value*
Age (yr)	9.5 (3.5)	9 (4)	0.78
Sex			
Female	29 (45.3)	33 (41.8)	0.67
Male	35 (54.7)	46 (58.2)	
Asthma in a first-degree relative			0.35
Yes	35 (54.7)	37 (46.8)	
No	29 (45.3)	42 (53.2)	
Maternal education y	12 (5.25)	12 (4)	0.79
Parental education y	12 (4)	12 (4)	0.71
Household monthly income			0.31
Above average	5 (7.8)	7 (8.9)	
Below average	21 (32.8)	17 (21.5)	
Around average	38 (59.4)	55 (69.6)	

Values are presented as median (interquartile range) or number (%).
H. pylori: Helicobacter pylori.
*Chi-Square test and Independent-Samples Mann-Whitney U-test.

Among children with asthma, 32 cases had severe asthma, and 12 had non-severe asthma. The symptoms' severity according to the ISAAC questionnaire is summarized in **Table 3**. The severity of asthma was defined as having four or more wheezing attacks per year, or ≥one night per week, sleep disturbances from wheezing or wheezing affecting speech in the past 12 months [18]. There was no significant association between the severity of asthma and *H. pylori* test results (Chi-square test for independence, $\chi 2=5.834$, df=2, n=143, $p=0.05$. Among children with asthma, there was no significant association between the average age of asthma onset and *H. pylori* status (independent-samples *t*-test, t(39)=1.245, $p=0.11$, two-tailed).

There was no significant difference in the *H. pylori* status for both cases and controls between children who used antibiotics in the last month and those who did not. The lack

Table 3. Symptom severity in the past year

Symptom severity in the past year	Value (n=44)
Number of attacks of wheezing	
1–3	26 (59.1)
4–12	15 (34.1)
>12	3 (6.8)
Sleep disturbances	
Never	10 (22.7)
<Once a night per week	23 (52.3)
>Once a night per week	11 (25.0)
Speech disturbances	
Yes	25 (56.8)
No	19 (43.2)
Wheezing on exercise	
Yes	32 (72.7)
No	12 (27.3)
Nocturnal dry cough	
Yes	28 (63.6)
No	16 (36.4)
Rhinitis	
Present	19 (43.2)
Absent	25 (56.8)
Eczema	
Present	2 (4.5)
Absent	42 (95.5)

Values are presented as number (%).

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Table 4. Effect of antibiotic use last month vs. last year on the *H. pylori* test results

	H. pylori positive (n=64)	*H. pylori* negative (n=79)	*p*-value*
Use of antibiotic last month			0.74
Yes	21	28	
No	43	51	
Number of antibiotic courses within last year	2 (1.25)	2 (2)	0.46

Values are presented as number only or median (interquartile range).
H. pylori: Helicobacter pylori.
*Chi-Square test and Independent-Samples Mann-Whitney U-test.

of statistically significant association was also true when comparing both groups' median number of antibiotics used during the previous 12 months (**Table 4**).

DISCUSSION

The prevalence of *H. pylori* infection in our study was 45%. This is the first study assessing the prevalence of *H. pylori* in children in Palestine; It is higher than the 35% prevalence reported in children in Israel [19]. The variation in prevalence can be attributed to the difference in socioeconomic status and living conditions, such as household crowding that enhances intra-familial transmission [7]. Despite being completely asymptomatic, half of our healthy cohort were positive for *H. pylori* infection. We found that children with *H. pylori* infection are less likely to have asthma than those with negative *H. pylori* infection. Among the children with asthma, the status of *H. pylori* infection did not differ according to the severity of asthma.

The inverse association between asthma status and *H. pylori* infection cannot be merely interpreted as a causal effect. Exploring causation between an environmental factor and a disease requires checking multiple aspects, including temporality, biological gradient, plausibility, and consistency [20]. Temporality is highly relevant to deducing whether the *H. pylori* acquisition preceded the development of asthma. In our study, the average age of asthma onset was 4–5 years old, but we could not determine the age of *H. pylori* acquisition based on one point test. A previous study on children in Israel showed that infection is usually acquired during the first years of life, with an estimated median age of 18 months [19]. Once caught at pre-school age, the pathogen can persist at school age [21]. So, this may suggest that *H. pylori* infection may have been acquired earlier than asthma.

Past use of antibiotics has been associated with the coincident elimination of *H. pylori* [22] and is inversely associated with asthma in children [23]. Therefore, one may argue that the effect of antibiotics, commonly used in infections associated with asthma exacerbations, may play a role in eradicating *H. pylori* [22]. Thus, it can give an erroneous conclusion about this inverse association manifested by a lower rate of *H. pylori* infection in children with asthma compared to healthy children. We found no significant difference in the *H. pylori* status between children who used and did not use antibiotics in the previous month before the test. We also found no difference in the *H. pylori* status regardless of the number of antibiotic courses used during the last 12 months. These findings suggest that antibiotics use in children with asthma, presumably prescribed more frequently than in children without asthma [24], did not affect the *H. pylori* status in our study.

Based on the biological gradient, a causal relationship is more likely if the increasing severity of the cause has a stronger correlation with the effect according to the dose-response curve [20]. In our study, since the monoclonal stool antigen immunoassay is a qualitative test, we

could not assess the severity of *H. pylori* infection. However, it has been previously reported that the severity of gastric inflammation is associated with asthma status, where children who are seropositive for *H. pylori* with severe gastric inflammation are less likely to have asthma [25].

Several experimental studies found that the association between asthma and *H. pylori* is biologically plausible. The negative association is related to the immune response mechanism against *H. pylori* infection, which is determined by a balance between effector T cells (T_H1 and T_H17) and regulatory T cells. T_H1 and T_H17 responses are predominant in symptomatic patients, while the regulatory T cell response is reduced. Therefore, despite the adverse effect of inflammation, a strong response facilitates clearing the bacteria [26]. On the other hand, in asymptomatic carriers, especially in childhood (a period of immune tolerance), *H. pylori* induces tolerogenic dendritic cells, which favor the differentiation of regulatory T cells over the induction of effector T cells [27]. In this case, regulatory T cells predominate, which control effector T cell response and consequently enable persistent colonization while preventing severe inflammatory response and gastric pathology [28]. The markedly increased T regulatory cells and cytokines help control atopic immune disorders, including asthma.

A bidirectional relationship known as the gut-lung axis further supports the complexity of this association. This axis represents a communication pathway where gut microbiota dysbiosis can influence lung health through immune modulation, potentially contributing to respiratory diseases like asthma. Mechanisms include micro-aspiration of gut bacteria and immune cell migration, affecting systemic immune responses [29]. Imbalances in specific gut bacteria, such as reduced *Bifidobacterium, Akkermansia,* and *Faecalibacterium*, alongside increased fungal species like *Candida* and *Rhodotorula*, are associated with heightened asthma risk in children [30]. Furthermore, asthma-related systemic inflammation can negatively affect gut health, highlighting the bidirectional impact of the gut-lung axis as a potential pathological marker in respiratory diseases [30].

Another feature that may support a causal relationship is the fact that different researchers found this association in different circumstances and study populations [20]. Although there is an apparent inconsistency in the literature regarding the association between asthma and *H. pylori* infection, many studies showed a negative association [22], while others failed to observe that association [31] or even found a positive one [32]. Different studies used different test arrays for *H. pylori* detection. Since the results of *H. pylori* detection methods in children may not be comparable to those used in adults, it may be confusing to select the best test for use in children [33]. Here, we used the monoclonal stool antigen test, which appears well-suited to young children. Commonly available kits that use monoclonal antibodies are reported to have better sensitivity and specificity than tests using polyclonal antibodies [34].

Most studies used the *H. pylori* IgG enzyme-linked immunosorbent assay (ELISA) or the ^{13}C-urea breath test to examine the association between *H. pylori* infection and asthma in children. Other methods like endoscopy biopsy or solid-phase chemiluminescent IgG assay were less commonly used in children. Poor specificity for the urea breath test is highlighted in infants and young children [35]. Serology, using ELISA, cannot give reliable information about current *H. pylori* infection, and has variable sensitivity in children based on the commercial kit used [36]. For these reasons, the inconsistency in finding an inverse association between asthma and *H. pylori* may be attributed to the various *H. pylori* detection methods used in different studies.

Concluding that a causal association exists between *H. pylori* infection and asthma is still challenging. Even if a protective role for *H. pylori* infection against asthma is confirmed, it should be balanced against the increased risk of developing peptic ulcer disease and gastric cancer. However, the chronic infection associated with *H. pylori* in children is rarely a cause of symptoms; and it has a minimal risk of developing a peptic ulcer or malignancy [7]. Taking these facts into consideration with the potential benefits of *H. pylori* infection in children supports the guidelines given by the European, North American, and Japanese Societies of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN, NASPGHAN, and JSPGHAN) that recommend against a "test and treat" strategy for *H. pylori* infection in children [37,38].

A strength of our study is that pediatric pulmonologists made the diagnosis of asthma, and the age limit was increased to 6 years to be able to obtain spirometry readings. All controls were age-matched healthy children without known acute or chronic diseases, which helped reduce confounders. We also selected the monoclonal stool antigen test as it is considered, along with immunoblot, the best non-invasive methods in children [33]. A limitation of this study is that the *H. pylori* stool antigen test was done at a single point in time; therefore, it was impossible to determine whether the infection preceded the onset of asthma. Additionally, a lot of data was collected through questionnaires and parental interviews, which creates the possibility of reporting bias.

In conclusion, our findings indicate that *H. pylori* infection is inversely associated with the rate of childhood asthma, which may suggest a protective role. Only randomized prospective trials can prove a causal relationship between *H. pylori* infection. However, they are not ethically feasible since *H. pylori* has been declared a carcinogen [39]. Future prospective cohort studies are needed to identify the nature of the protective mechanism and the timing of its effect on asthma sensitization.

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