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Association between *Helicobacter pylori* and risk of childhood asthma: a meta-analysis of 18 observational studies

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Abstract

Objective: The association between *Helicobacter pylori* (*H. pylori*) and childhood asthma is unclear. Thus, the aim of this study was to explore the association between *H. pylori* and childhood asthma.

Methods： A literature search, study selection, and data extraction were performed independently and in duplicate. Data were analyzed using STATA software.

Results: Eighteen studies enrolling 17196 children were analyzed. All studies were of moderate-to-high quality. Four studies subcategorized *H. pylori* infection according to CagA status. Overall, there was a significant negative association between *H. pylori* and risk for childhood asthma (OR = 0.68; 95% CI, 0.54–0.87; P = 0.002), with no/marginal publication bias identified by the Egger's test and the Begg's test (P = 0.162 and P = 0.198, respectively). The observed inverse association persisted for CagA(+) strains of *H. pylori* (OR = 0.58; 95% CI, 0.35–0.96; P = 0.034) but not for CagA(-) strains (OR = 0.52; 95% CI, 0.12–2.28; P = 0.387). There was no significant difference between studies with respect to study design, participant age, geographical region, and method of measuring *H. pylori*.

Conclusion: The evidence suggests that *H. pylori* infection, particularly CagA(+) *H. pylori* infection, is inversely associated with the risk of childhood asthma.

Key Words: Helicobacter pylori; childhood asthma; meta-analysis; observational studies

1. Introduction

Asthma, characterized by reversible airflow obstruction and bronchospasm, is one of the most common chronic respiratory diseases in children, ranking among the top 20 conditions worldwide for disability-adjusted life years(1). An important contributor to the development of asthma is an imbalance between T helper 1 (Th1) and T helper 2 (Th2) responses; Th1 responses usually occur during infection, whereas Th2 responses induce production of cytokines that mediate allergy(2). Suppressive and regulatory mechanisms critical for preventing activation of harmful effector responses(3) affect the risk of asthma.

The 'hygiene hypothesis' postulates that the recent rise in the incidence of allergic disease is attributable to reduced exposure to certain microbes and infections during childhood; this view has gained widespread acceptance(4). The hygiene hypothesis of asthma signifies a shift from a Th1 response to a Th2 response; this is the main explanation for the increased prevalence of asthma in western countries, whereby improved hygiene reduces environmental stimulus of the Th1 response(5). *Helicobacter pylori* (*H. pylori*), a gram-negative bacterium that naturally colonizes the gastric mucosa, is usually acquired in early childhood; the bacterium often causes a chronic form of gastritis that remains mostly asymptomatic(6). Infection with *H. pylori* induces a stronger Th1 cellular immune response, which may counterbalance the pro-allergic Th2 response(7, 8). Thus, we speculate that *H. pylori* plays a role in modulating the risk of childhood asthma.

Previously, studies reported an inverse association between *H. pylori* infection and asthma in adults(9, 10). This association is stronger for more pathogenic strains of *H. pylori*, which express the virulence factor cytotoxin associated gene A (CagA)(7). CagA(+) strains usually co-express the most active form of the vacuolating cytotoxin A (VacA), which is important for induction of immunosuppressive regulatory T cell (Treg) responses(11). Three meta-analyses(12-14) of observational studies show a significant and inverse association between *H. pylori* infection and asthma. Most of the studies included in these meta-analyses were cross-sectional studies of adults. However, the association between *H. pylori* infection and asthma in children is heterogeneous, which is important because *H. pylori* is usually acquired in very early childhood(15), when the immune system is developing. In addition, since the last meta-analysis was published, six observational studies(16-21) of children have been published, although the results are conflicting (the results of one study(17) are different from those of the other five). Moreover, three of the six studies(18-20) were case-control studies, and one(21) was a cohort study, with a stronger quality of evidence. Therefore, we decided to undertake an up-to-date meta-analytic approach to investigate the association between *H. pylori* infection and risk of asthma in children. In addition, we examined whether the association between the risk of asthma for children with CagA(+) strain *H. pylori* differed from that in children with CagA(-) strain *H. pylori* .

2. Methods

2.1 Data sources and search strategy

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From study inception to August 31, 2020, two investigators (CYX and WDH) searched PubMed, Embase, and Web of Science independently to identify eligible studies. The following search terms were used: (*Helicobacter pylori* OR *H. pylori* OR *Campylobacter pylori*) AND (asthma OR asthmatic OR wheeze OR wheezing OR allergic asthma OR atopic asthma). In addition, the reference lists of the included studies were searched for eligible reports. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines(22).

2.2 Study selection

CYX and WDH scrutinized the identified articles for inclusion and in-depth examination. Any discrepancies were resolved by discussion. The inclusion criteria were as follows: (1) cohort, cross-sectional, or case-control study design; (2) evaluating the association between *H. pylori* infection and the risk of asthma or wheeze in children; (3) reporting sample sizes, ORs, and 95% CI, or other information that may help to infer the results; (4) Confirmation of H.pylori infection by the ^{13}C-urea breath test(^{13}C-UBT), mucosal biopsy, enzyme-linked immunosorbent assay (ELISA), stool antigen test, and stool DNA test. At least one positive test result was considered as confirmation of infection; (5) Confirmation of asthma according to the criteria published by the Global Initiative for Asthma, national asthma education and prevention program, physician diagnosis, the self-reported information provided in response to questionnaires about previous asthma diagnosis or the occurrence of associated clinical symptoms. Clinical trials, reviews, letters, editorials, and commentaries were excluded, as were studies conducted on adults and those not conducted on humans.

2.3 Data extraction and quality assessment

CYX and WDH conducted data extraction and quality assessment independently, and any disagreements were resolved by discussion with ZX. The following information was extracted from each eligible study: the first author's surname, year of publication, country, study design, study participants, age, gender, method of *H. pylori* detection, criteria for asthma diagnosis, research content, type of control, and adjusted covariates. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies(23). Study quality was then divided into three grades: low (0–3 stars), moderate (4–6 stars), and high (7–9 stars). The 11-item checklist, which was recommended by the Agency for Healthcare Research and Quality (AHRQ), was used to assess the quality of cross-sectional studies(24). An item would be scored "0" if the answer was "No" or "Unclear", and "1" if the answer was "Yes". A total score of 0 to 3 was assessed as low quality, 4 to 7 as moderate quality, and 8 to 11 as high quality.

2.4 Statistical analyses

In the present meta-analysis, OR and 95% CI were used as the effect size to assess the association between asthma risk and *H. pylori* infection. The P-value of the Z test for overall effect ($P < 0.05$)

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was considered significant. The Cochran Q test and I^2 statistic were introduced to assess heterogeneity across studies. Both fixed-effects and random-effects pooled estimates were performed, but the random-effects model was employed by pooling references if a substantial level of heterogeneity was detected ($I^2 > 50\%$). To explore the sources of heterogeneity in terms of participant characteristics, subgroup analyses were conducted, stratified according to study design, age, study location, economic conditions, research content, and different methods of *H. pylori* testing. Meta-regression analysis and several sensitivity analyses were performed to test the robustness of the results via various exclusions. Publication bias was estimated using Begg's test and Egger's test. All statistical tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using STATA 16.0 (STATA Corporation, College Station, TX, USA).

3. Results

3.1 Study characteristics

Initially, 2266 records were identified from different databases. After applying the selection criteria, 18 original papers (including 17196 children) were identified: 12 cross-sectional studies(16, 17, 25-34) (including two studies reporting cross-sectional results from cohorts(25, 26)), three case-control studies(18-20), and three prospective cohort studies(21, 35, 36) (Figure 1). The main characteristics of the included studies are presented in Table 1. The papers were published between May 27, 2000 and July 7, 2020, and were carried out in 11 different countries and regions; eight articles(19-21, 25-27, 33, 34) were from developed countries and ten (16-18, 28-32, 35, 36) were from developing countries or regions. Only one study(27) involved participants aged 3–19 years; the other participants were all aged less than or equal to 18 years; only two studies(16, 28) involved participants aged <3 years. With respect to the method of *H. pylori* measurement, ten studies(16, 17, 20, 21, 25-29, 34) used an enzyme-linked immunosorbent assay (ELISA; serum), three30, 33, 35) used the ^{13}C-urea breath test, four(20, 26, 32, 34) used the *H. pylori* surface CagA protein test, and five used other methods. All exposure assessments and outcome definitions met the inclusion criteria. The longest period of follow-up for the cohorts was 16 years(21). According to the NOS and AHRQ, the methodological quality of 13 studies(16, 18, 20, 25-29, 31, 33-36) was high, whereas that of five studies(17, 19, 21, 30, 32) was moderate (Supplementary material and Tables 1–3).

3.2 Overall analysis

The overall results of this meta-analysis revealed a significant negative association between *H. pylori* infection and the risk of childhood asthma (OR = 0.68; 95% CI, 0.54–0.87; P = 0.002; $I^2 = 63.6\%$; P = 0.000 using the random model; Figure 2). This suggests that *H. pylori* infection protects against childhood asthma. Due to high heterogeneity, we conducted a sensitivity analysis, an analysis of publication bias, a meta-regression analysis, and subgroup analysis based on various study characteristics and clinical factors.

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3.3 Sensitivity analysis and publication bias

To evaluate the robustness of the pooled results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary estimate. The results revealed that no one study had a significant impact on overall effect-size estimates for childhood asthma (Supplementary material and Figure 1). Visual inspection of the funnel plot showed little asymmetry (Supplementary material and Figure 2). The Egger's and Begg's tests revealed no evidence of publication bias (P = 0.162 for the Egger's test and P = 0.198 for the Begg's test). Thus, there was no evidence of publication bias.

3.4 Subgroup analysis and meta-regression analysis

Due to significant between-study heterogeneity, we conducted a meta-regression and a series of subgroup analyses according to study design, geographical location, economic conditions, patient age, research content, and method of *H. pylori* measurement. Subgroup analysis revealed that the majority of strata showed an inverse association between *H. pylori* and the risk of childhood asthma. Subgroup analysis by study design reduced heterogeneity significantly in the cohort study subgroup (I^2 = 3.6%), but it remained high in the cross-sectional study subgroup (I^2 = 66.6%) and case-control study subgroup (I^2 = 66.1%). Subgroup analysis according to *H. pylori* measurement method led to a significant decrease in heterogeneity in the ^{13}C-urea breath test subgroup (I^2 = 0.0%) and stool antigen test subgroup (I^2 = 0.0%); however, heterogeneity remained high in the *H. pylori*-IgG ELISA subgroup (I^2 = 70.0%). Subgroup analysis by region led to a significant reduction in heterogeneity in the Africa subgroup (I^2 = 0.0%), but it remained high in the Asia (I^2 = 54.6%) and Europe (I^2 = 81.4%) subgroups. Subgroup analysis by different research content resulted in a significant reduction in heterogeneity in studies screening for asthma in *H. pylori*-positive or -negative participants (I^2 = 41.0%), but it remained high in studies screening for *H. pylori* infection in asthma and non-asthma (control groups) (I^2 = 71.6%). Subgroup analysis by age and economic condition did not alter heterogeneity. However, there was no significant difference between subgroups after meta-regression analysis, indicating that these clinical factors did not contribute to heterogeneity (Table 2).

3.5 CagA status in relation to risk of asthma

Three studies used both *H. pylori*-IgG ELISA and CagA protein ELISA as *H. pylori* tests, whereas one study used only the CagA protein ELISA test. There was a significant negative association in CagA(+) individuals (OR = 0.58; 95% CI, 0.35–0.96; P = 0.034; I^2 = 0.0%; P = 0.401 for the fixed model; Figure 3); however, there was no association between CagA(-) *H. pylori* infection and risk of childhood asthma (OR = 0.52; 95% CI, 0.12–2.28; P = 0.387; I^2 = 88.7%; P = 0.000 for the random model; Figure 3). Thus, we conclude that CagA(+) *H. pylori* infection plays a more important role in reducing the risk of childhood asthma.

4. Discussion

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The present meta-analysis provides evidence supporting an inverse association between *H. pylori* infection and the risk of childhood asthma. Previously published meta-analyses(12-14) on the relationship between *H. pylori* infection and asthma attempted to establish this relationship, but the present study is the first meta-analysis limited to children. There is growing awareness that many chronic adult diseases (including asthma) are associated with the negative impact of respiratory infections or environmental exposure during early childhood(37). In addition, adult-onset asthma can be triggered by more heterogeneous causes (such as occupational exposure, tobacco, and air pollution); thus *H. pylori* infection may play an important role in childhood asthma(38).

The inverse association between *H. pylori* infection and the risk of childhood asthma is more significant for CagA(+) strains. CagA(+) stains, which contribute to most *H. pylori* infections, interact more strongly with the host immune system than CagA(-) strains(39). Previously, there was no meta-analysis that confirmed the relationship between CagA(+) *H. pylori* infection and the risk of childhood asthma. The present study is the first to identify an inverse association between CagA(+) *H. pylori* infection and asthma risk compared with CagA(-) IgG antibody(+) *H. pylori* infection in children. In addition, in this study, we attempted to divide patients into two subgroups according to research content: screening for *H. pylori* in patients with asthma and a control group, and screening for asthma in *H. pylori*-positive and negative groups. Although most of the included studies were cross-sectional studies, the evidence for causal inference is weak. However, we attempted the subgroup analysis because we think that different research content may affect the results. On one hand, the positive rate of *H. pylori* in asthmatic children was low, which is related mainly to the medication used by asthmatic patients; indeed, previous studies show a positive correlation between asthma drug prescription and antibiotic prescription(40). On the other hand, the incidence of asthma in H. pylori-positive children ($P = 0.004$) was low, as was the heterogeneity ($I^2 = 41.0\%$), suggesting strongly that *H. pylori* protects against childhood asthma. However, the underlying mechanisms are more complex.

Evidence supporting a possible protective role for *H. pylori* in asthma is provided by studies in animal models(41). In this regard, the bacterium has the ability to re-program dendritic cells (DCs) toward a tolerance-promoting phenotype, thereby inducing production of regulatory Forkhead box P3 (Foxp3+) T lymphocytes that protect against atopy(42). By contrast, studies in *H. pylori*-infected mice show that DC depletion down-regulates Tregs and improves airway inflammation(43). In addition, urease produced by the bacterium activates NOD-like receptor family protein 3 (NLRP3), a component of the cytoplasmic inflammasome in DCs, which stimulates the Toll-like receptor 2 (TLR2)/NLRP3/interleukin-18 (IL-18) axis, a well-known pathway that protects against asthma(44). Additionally, the immune response mediated by Th1 versus Th2 cells may explain the balance between *H. pylori* infection and atopy. The bacterium may elicit a Th1-dependent immune response over a Th2 response(45), resulting in high levels of tumor necrosis factor alpha in the gastric mucosa(46). This could prevent the development of Th2-mediated responses, thereby driving onset of allergic disease. From this perspective, *H. pylori* neutrophil-activating protein (HP-NAP) elicits IL-12 and IL-23 production *in vitro* via agonistic interaction with toll-like receptor 2, and promotes Th1 polarization of allergen-specific T cell responses. Indeed, in a murine model, administration of HP-NAP reduced eosinophilia and immunoglobulin E (IgE) and Th2 cytokine levels in bronchoalveolar lavage fluid(47). Similarly, in an ovalbumin-induced allergic asthma animal model,

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HP-NAP reduced IL-4 and IL-13 levels (two mediators of atopic response), as well as that of total IgE(48). Of note, IgE concentrations were significantly lower when individuals were infected with CagA(+) strains(49). In other studies, the number of mucosal Treg cells increased dramatically(50), and CagA translocation induced IL-12 production upon CagA(+) *H. pylori* colonization(51), which could explain the stronger inverse association between CagA(+) strains and the risk of asthma.

When the data were stratified according to geographical location, the inverse association was even higher in studies from Africa. The global incidence of asthma and allergic reactions is different in different countries, likely due to genetic and environmental contributors(52). However, the association of interest did not differ across studies according to economic conditions or participant age (≥3 years or ＜3 years). In the present analysis, we identified five different methods for measuring *H. pylori* infection, but only one study(31) used endoscopy plus biopsy from gastric mucosa, which is the definitive diagnostic method for *H. pylori* infection; however, the method is invasive and uncomfortable. The other methods are not very accurate and could be subject to error. Therefore, future studies should use more accurate diagnostic tests to assess the relationship between childhood asthma and *H. pylori* infection.

Although this study combined the most comprehensive and updated findings from the literature, it has some limitations. First, the primary studies are mostly cross-sectional. Randomized clinical trials are not feasible, and prospective cohort studies are limited, which compromises the establishment of a causal relationship between *H. pylori* infection and the risk of childhood asthma. Second, the results should be interpreted with care because of the limited number of studies and small sample sizes reported in some studies. Third, we could not do the subgroup analysis for different asthma diagnosis criteria to reduce heterogeneity, because 9 of inclued studies were diagnosed with asthma based on the doctor's experience. Fourth, subgroup analyses of other confounding factors such as the crowding index, exposure to cigarette smoke, and a family history of asthma were not conducted due to lack of information in the primary literature. Moreover, in the present analysis, only four studies detected CagA(+) strains, which show stronger evidence of protection.

5. Conclusion

In summary, this present meta-analysis suggests an inverse association between *H. pylori* infection and the risk of childhood asthma, particularly in cases of infection by CagA(+) strains. The emerging data support the hypothesis that *H. pylori* infection could be a critical target for prevention or management of childhood asthma. However, more prospective cohort studies are needed to obtain solid evidence.

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Table 1. Characteristics of included studies

Author,year, Country	Study design	Cases /total	Age year	H. Pylori measurement	Asthma definition	Research content	Type of controls	OR (95% CI)	Adjusted confounders	Quality of study
Fouda, 2017, Egypt	Cross-sectional	90/180	1-17	H. pylori-IgG ELISA	GINA, 2012	Screening H. pylori in asthma and control group	Non-atopic, non-asthmatic healthy children	UN	Social class，Crowding index，frequency of antibiotic courses, Gastrooesophageal reflux symptoms,Total serum IgE	High
Khamechian, 2015, Iran	Cross-sectional	36/264	5-18	Undergoing endoscopy biopsy	GINA,2010 questionnaire	Screening asthma in H. pylori and control group	Participants without asthma diagnosis	UN	Gender,age,family history	High
Holster,2012, Netherlands	Cross-sectional	98/545	7-9	H. pylori-IgG ELISA	Physician diagnosis	Screening H. pylori in asthma and control group	Participants without asthma diagnosis	0.87 (0.37-2.08)	Sex, race, exposure to indoor smoking, breastfeeding, and education of parents	High

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Chen, 2008, USA	Cross-sectional	507/3327	3-19	H. pylori-IgG ELISA	Physician diagnosis	Screening asthma in H. pylori and control group	Participants without asthma diagnosis	0.69 (0.45–1.06)	Race-ethnicity, country of birth, age, sex, body mass index, smoking status , and education level	High
Annagur, 2007, Turkey	Cross-sectional	79/115	5-15	H. pylori-IgG ELISA	GINA, 2006	Screening H. pylori in asthma and control group	Non-atopic healthy children	1.69 (0.57-5.69)	UN	High
Karimi, 2013, Iran	Cross-sectional	98/196	6-12	^{13}C-urea breath test	Physician diagnosis	Screening H. pylori in asthma and control group	Healthy individuals	0.73 (0.34-1.55)	Age, sex, duration of asthma , severity and control status of the disease	Moderate
Nasiri, 2019, Iran	Cross-sectional	50/100	5-15	H. pylori-IgG ELISA	Confirmed by spirometry	Screening H. pylori in asthma and control group	Children without allergic disorders	0.45 (0.12-1.62)	Gender,living place,exposure to cigarette smoke	Moderate
Youseficha ijan, 2016, Iran	Cross-sectional	104/208	5-12	CagA protein-IgG ELISA	GINA, 2012	Screening H. pylori in asthma and control group	Age-matched healthy children	UN	Age,gender,residence	Moderate

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Zevit, 2012, Israel	Cross-sectional	578/6959	5-18	^{13}C-urea breath test	Physician diagnosis	Screening asthma in H. pylori and control group	Participants without asthma diagnosis	0.79 (0.66-0.94)	Age,gender,urban residence,socioeconomic Status,ethnicity	High
Corrado, 2000, Italy	Cross-sectional	30/60	4-11	H. pylori-IgG and CagA protein-IgG ELISA	Symptoms suggesting asthma	Screening H. pylori in asthma and control group	Patients with atopic dermatitis without gastrointestinal disease or asthma	UN	UN	High
Jaber, 2006, Saudi Arabia	Cross-sectional	220/763	1-10	H. pylori-IgG ELISA	Physician diagnosis	Screening H. pylori in asthma and control group	Participants without asthma, and other chronic diseases	0.84 (0.56-1.24)	Age,ethnicity	High
Hollander, 2016, Netherlands	Cross-sectional	198/3062	5-7	H. pylori-IgG and CagA protein-IgG ELISA	Physician diagnosis	Screening H. pylori in asthma and control group	Participants without asthma diagnosis	1.75 (1.07-2.87)	Maternal age, race, educational level, history of asthma or atopy, parity, keeping pets, smoking during pregnancy	High

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Elias, 2020, Israel	Case-control	75/235	5-17	H. pylori-IgG and CagA protein-IgG ELISA	GINA, 2019	Screening H. pylori in asthma and control group	Children without asthma/respiratory disease	0.51 (0.28-0.94)	Age, sex, parental schooling years, the number of siblings, monthly family income, and parental smoking habits	High
Tsigalou, 2019, Greece	Case-control	27/81	4-13	Stool antigen test	Physician diagnosis	Screening H. pylori in asthma and control group	Age-sex-matched non-asthmatic children	0.10 (0.04-0.31)	Age,gender,disease duration	Moderate
Karakulluk cu, 2017, Turkey	Case-control	92/180	3-8	Stool H. pylori DNA test	NAEPP Guidelines 2007	Screening H. pylori in asthma and control group	Age-sex matched healthy children	0.79 (0.72-0.88)	Sex,family history	High
Cam, 2009, Turkey	Cohort	5/74	9-18	^{13}C-urea breath test	Physician diagnosis	Screening asthma in H. pylori and control group	Participants without asthma diagnosis	UN	UN	High
Amberbir, 2011, Ethiopia	Cohort	80/616	3	Stool antigen test	Questionnaire of Asthma in Children	Screening asthma in H. pylori and control group	Participants without asthma diagnosis	0.80 (0.46-1.38)	Gender,older siblings,Paracetamol use	High

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Melby, 2020, Norway	Cohort	30/195	16	H. pylori-IgG ELISA	Physician diagnosis	Screening asthma in H. pylori and control group	Participants without asthma diagnosis	UN	UN	Moderate

UN unknown, *H. pylori Helicobacter pylori*, IgG immunoglobulin G, ELISA enzyme-linked immunosorbent assay, DNA deoxyribonucleic acid, GINA global initiative for asthma, NAEPP national asthma education and prevention program.

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Table 2 Subgroup analyses and metaregression analysis of the association of *Helicobacter pylori* infection and the risk of childhood asthma.

	No. of study	Pooled effect estimate	p value	Assessment of heterogeneity		Metaregression P value
Subgroup analyses		OR(95% CI)		I^2(%)	P value	
Study design						0.819
Cross-sectional	12	0.76(0.58-0.98)	0.037	66.6%	0.001	
Case–control	3	0.25(0.06-0.97)	0.046	66.1%	0.053	
Cohort	3	0.60(0.34-1.08)	0.091	3.60%	0.355	
Region						0.615
Asia	10	0.73(0.53-1.00)	0.051	54.6%	0.019	
Europe	5	0.44(0.14-1.33)	0.144	81.4%	0.000	
America	1	0.80(0.63-1.01)	0.060	NA	NA	
Africa	2	0.51(0.34-0.76)	0.001	0.0%	0.480	
Economic condition						0.578
Developing country	10	0.68(0.46-1.00)	0.051	58.0%	0.011	
Developed country	8	0.70(0.50-0.98)	0.040	70.7%	0.001	
Age						0.534
≥ 3 years	16	0.69(0.52-0.91)	0.009	65.4%	0.000	
Contain <3years	2	0.63(0.33-1.20)	0.157	67.9%	0.078	
H. pylori measurement method						0.378
H. pylori-IgG ELISA	10	0.76(0.52-1.10)	0.145	70.0%	0.000	
Undergoing endoscopy biopsy	1	0.29(0.13-0.67)	0.004	NA	NA	
^{13}C-urea breath test	3	0.79(0.67-0.94)	0.006	0.0%	0.607	
Stool antigen test	2	0.53(0.33-0.85)	0.008	0.0%	0.364	
Stool H. pylori DNA test	1	0.02(0.00-0.35)	0.007	NA	NA	
Research content						0.907
Screening H. pylori	12	0.66(0.43-1.01)	0.056	71.6%	0.000	
Screening asthma	6	0.70(0.55-0.89)	0.004	41.0%	0.132	

NA not available, *H. pylori Helicobacter pylori*, IgG immunoglobulin G, ELISA enzyme-linked immunosorbent assay, DNA deoxyribonucleic acid.

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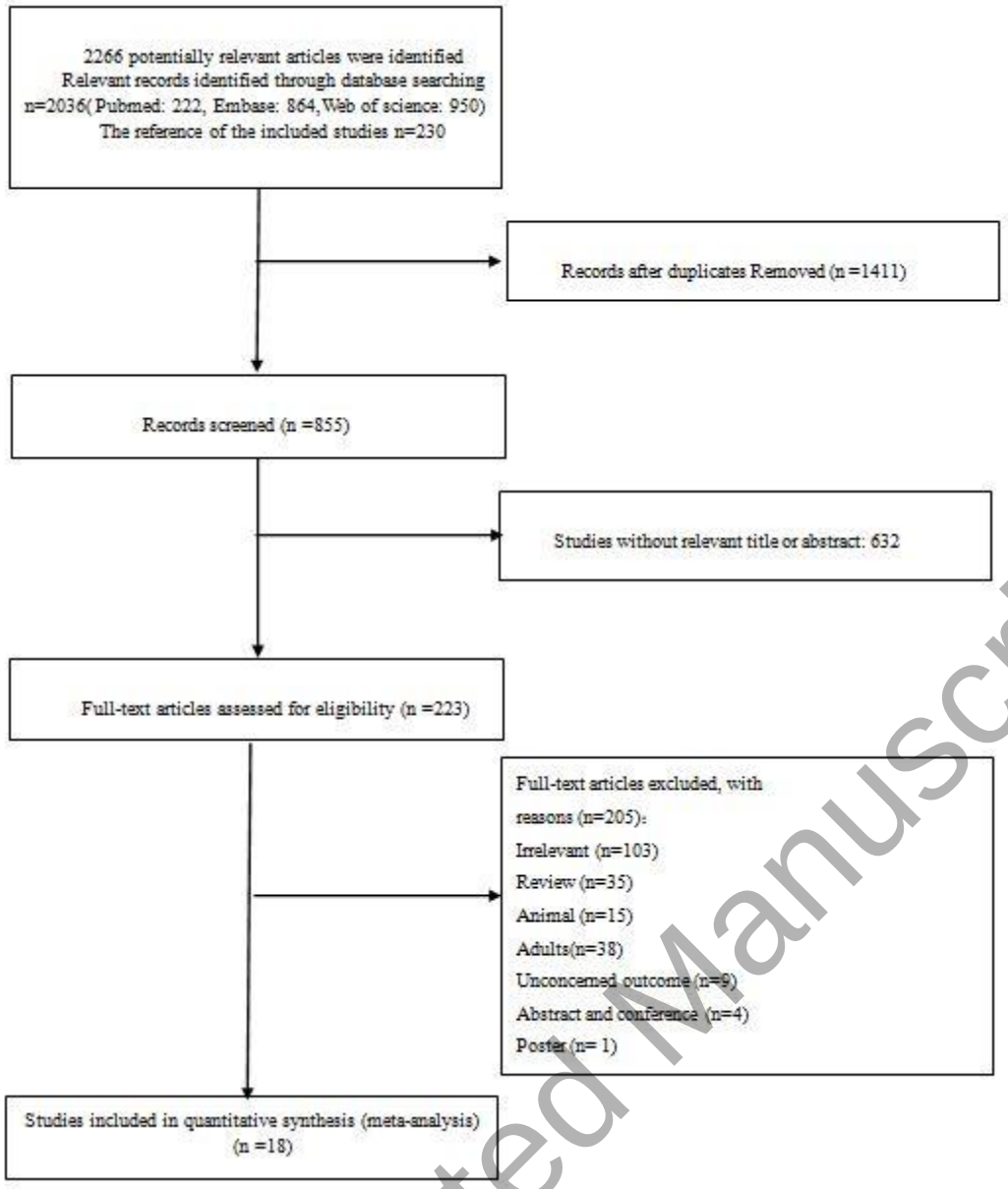


Figure 1. Flowchart of selection of studies for inclusion in meta-analysis.

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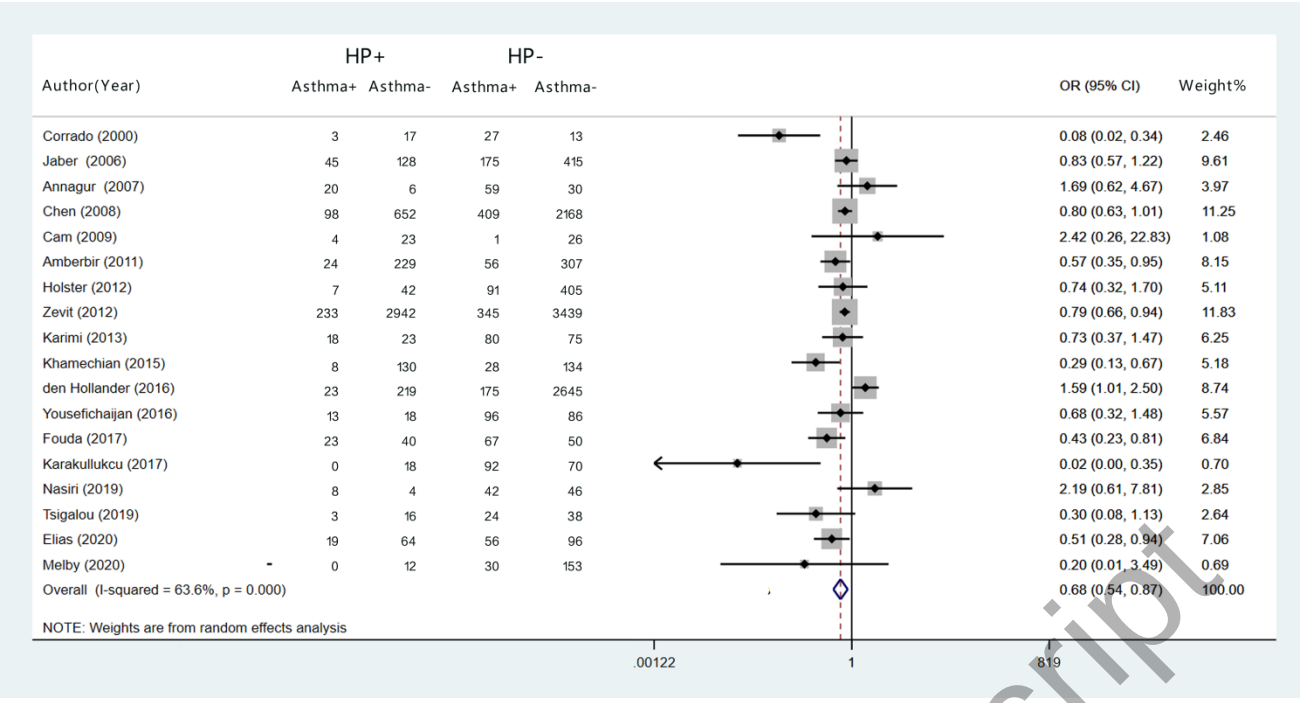


Figure 2. Forest plot of the association between Helicobacter pylori and the risk of childhood asthma.

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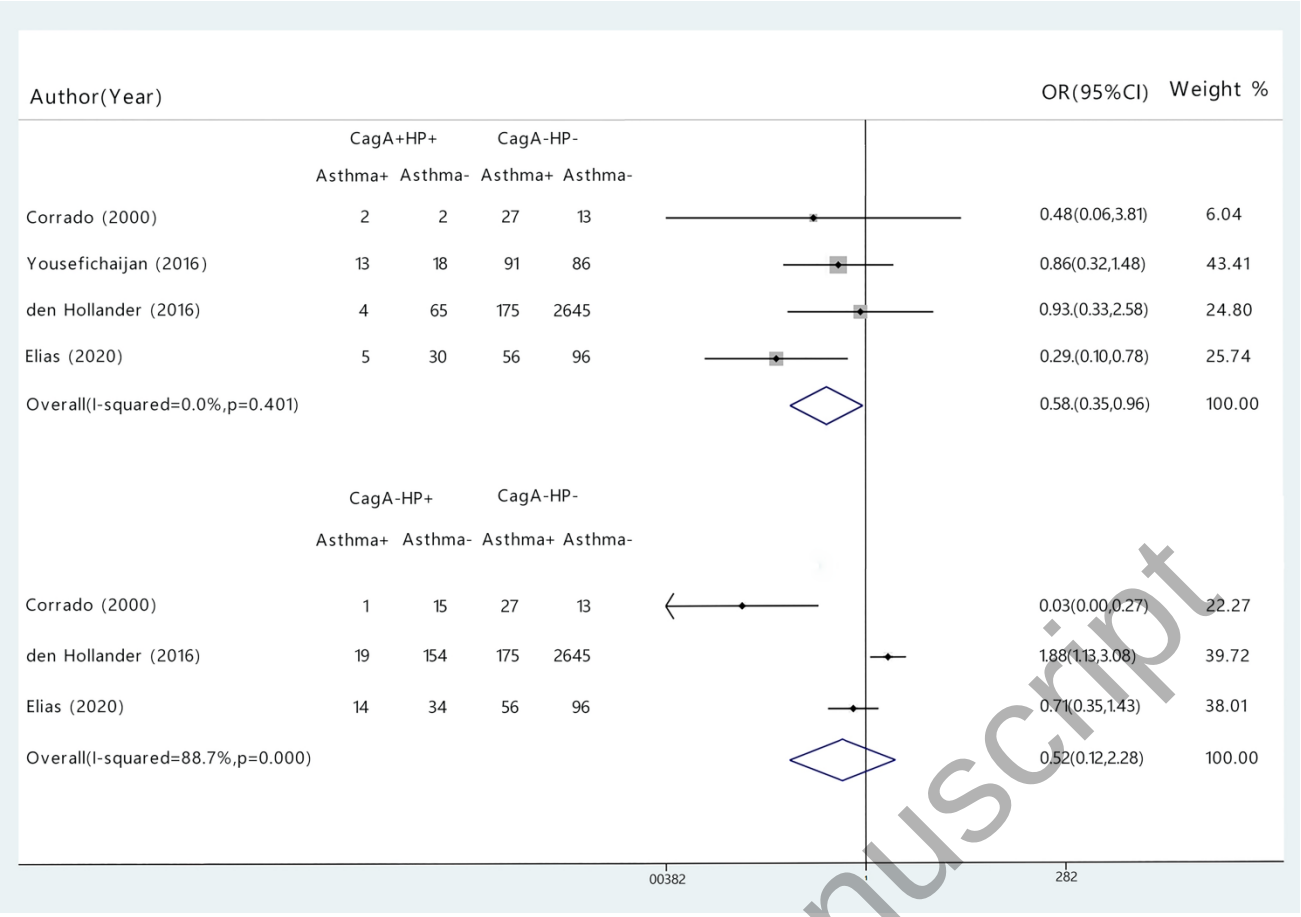


Figure 3. Forest plot of the association between CagA status and the risk of childhood asthma. CagA-HP-, negative for CagA and Helicobacter pylori; CagA+HP+, positive for CagA and Helicobacter pylor.

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