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META-ANALYSIS

Helicobacter pylori infection and atopic diseases: Is there a relationship? A systematic review and meta-analysis

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Abstract

AIM: To review and conduct a meta-analysis of the existing literature on the relationship between *Helicobacter pylori* (*H. pylori*), atopy and allergic diseases.

METHODS: Studies published in English assessing the prevalence of atopy and/or allergic diseases in patients with *H. pylori* infection and the prevalence of *H. pylori* infection in patients with atopy and/or allergic diseases were identified through a MEDLINE search (1950-2014). Random-effect model was used for the meta-analysis.

RESULTS: Pooled results of case-control studies showed a significant inverse association of *H. pylori* infection with atopy/allergic disease or with exclusively atopy, but not with allergic disease, whereas pooled results of cross-sectional studies showed only a significant association between allergic disease and *H. pylori* infection.

CONCLUSION: There is some evidence of an inverse association between atopy/allergic diseases and *H. pylori* infection, although further studied are needed.

Key words: Atopy; Allergic diseases; *Helicobacter pylori*; Hygiene hypothesis; Infection

Core tip: As the hygiene hypothesis affirms, the most important factor connected with the large spreading of atopic disease is the decreased exposure to food born and oro-fecal infections, including *Helicobacter pylori* (*H. pylori*) infection, due to the improvement of hygienic condition occurred in developed countries. The aim of this article was to review and conduct a meta-analysis of the existing literature on the relationship between *H. pylori*, atopy and allergic diseases. There is some evidence of an inverse association between atopy/allergic diseases and *H. pylori* infection, although further studied are needed.

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INTRODUCTION

The International Study of Asthma and Allergy in Child-

hood phase three, estimated that the prevalence of asthma, rhino-conjunctivitis and eczema in 6-7-year-old children is 11.7%, 8.5% and 7.9%, respectively, and in 13-14-year-old subjects even higher (14.1%, 14.6% and 7.3%), confirming the significant impact of allergic diseases since childhood[1].

Today it is known that allergic diseases develop from the interaction between the host immune system and environmental factors[2]. The high geographical variability in the prevalence of these diseases suggests a decisive impact of the environmental factors (such as the geo-climatic and the socioeconomic ones) on their pathogenesis. Indeed, allergies are more common in the northern hemisphere, with respect to the southern one, as well as in developed countries than in developing ones[1]. The characteristic epidemiological trend of atopic diseases seems also to be linked to the environmental changes occurred in the last decades in industrialized countries: increase of outdoor and indoor pollution (combustion of fossil fuel, high volume of traffic, biomass combustion products, tobacco smoke), climate changes (warmer temperature that causes early spring), improvement of hygienic conditions (changes of exposure to microbiota)[3-6].

David Strachan, the founder of the historic hygiene hypothesis, is the first author who supposed that infections acquired in early childhood could prevent atopy. In the study published in 1989, he noticed that hay fever was inversely related to the number of children in the household and to the number of older children in families. He speculated that the declining of family size associated with the improvement of cleanliness had reduced the prevalence of cross infections in families, leading to a widespread of atopic disease, as occurred for hay fever[7]. Some years later, von Mutius *et al*[8] enlarged that hypothesis studying the prevalence of atopic sensitization (screened by skin prick tests) in two groups of people: children living in West Germany and children living in East Germany, with regard to the number of siblings. He observed that atopic sensitization was three times more prevalent in West Germany than in East Germany, because of a higher standard of living.

Nevertheless, many authors denied the hygiene hypothesis, considering gastrointestinal infections as triggers of allergic diseases, rather than protective factors: due to their capability in increasing the mucosal permeability, these infections could have facilitated the penetration of allergens and the loss of oral tolerance. Meanwhile, other authors supported the Strachan hypothesis, confirming that the decreased exposure to gastrointestinal infections occurred in developed countries could be inversely connected with the large spreading of atopic disease[9]. In recent years, it has been hypothesized an important role of *Helicobacter pylori* (*H. pylori*) infection in the host immune network arrangement and its influence on the development of allergic diseases. The exogenous infection and microbial substances including *H. pylori* infection may elicit a Th1-mediated immune response, which suppresses Th2 responses. The lack of adequate stimulation of the Th1 might result in an overactive Th2, which in turn lead to allergy[10]. Moreover, the acquisition of *H. pylori* may be of importance in the induction of regulatory T cells, which could effectively reduce the possibility of allergy[11]. The immune-modulatory properties that allow the bacteria to persist for decades in infected individuals in the face of a vigorous, yet ultimately non-protective, innate, and adaptive immune response may at the same time confer protection against allergies, asthma, and inflammatory bowel diseases. Experimental evidence from mouse models suggests that *H. pylori* has evolved to skew the adaptive immune response toward immune tolerance rather than immunity, which promotes persistent infection on the one hand, and inhibits autoaggressive and allergic T-cell responses on the other. Regulatory T-cells mediating peripheral immune tolerance have emerged as key cellular players in facilitating persistent infection as well as protection from allergies, in both observational studies in humans and experimental work in mice[12,13].

Although some clinical studies confirm an inverse association between *H. pylori* and asthma, some studies reported different results on asthma, other allergic diseases, and in general on atopy.

In the present article we provide a systematic review and meta-analysis of the existing literature on the relationship between *H. pylori,* atopy and allergic diseases, and we try to answer the question of whether there is evidence of an inverse relationship between the two conditions.

MATERIALS AND METHODS

Protocol

Before review and meta-analysis we developed a protocol, including eligibility criteria, search strategies, criteria for study selection, methods for extracting related data, and methods for assessing study quality and statistical methodology.

Eligibility criteria, information sources, search, and study selection

The association between atopy/allergic diseases and *H. pylori* infection was the focus of our search. The prevalence of atopy and/or allergic diseases in patients with *H. pylori* infection and the prevalence of *H. pylori* infection in patients with atopy and/or allergic diseases were our primary outcome measures. Atopy was defined by skin prick test reactivity, specific and total IgE; allergic diseases were defined in presence of a diagnosis of asthma, allergic rhinitis, rhino-conjunctivitis, atopic dermatitis, food allergy. Studies were identified by searching electronic databases and scanning reference lists of articles, and by consultation with experts in the field. This search was applied to the Medline database using PubMed by combining search terms for *H. pylori* infection with keywords for atopy and allergic diseases (atopy, atopic disease, allergy, allergic disease, asthma, allergic rhinitis, rhino-conjunctivitis, atopic dermatitis, eczema, food al-

lergy). All types of study design (*e.g.*, cross-sectional, cohort, case-control, and case series), except case reports, were considered for inclusion in this review. Search results were limited to human studies published in the English language, and providing sample size, odds ratios (OR), and their 95% confidence intervals or the information that help infer the results; no publication date or publication status restrictions were imposed. Eligibility assessment of studies was performed independently in an unblinded standardized manner by two reviewers (Drs Lionetti and Leonardi). Disagreements between reviewers were resolved by consensus. All studies described in this review were published between 1950 (start of Medline) and March 2014.

Data collection process

We developed a data extraction sheet (based on the Cochrane Consumers and Communication Review Group' s data extraction template)[14], pilot tested it on six randomly selected included studies, and refined it accordingly. Two authors (A.L. and M.T.G.) extracted the data from included studies, and one author (E.L.) checked the extracted data.

Data items

Information was extracted from each included study on (1) setting, study design, characteristics of participants, including number, age, method of diagnosis of atopy and/or allergic disease, age at diagnosis; and (2) the presence of *H. pylori* infection, method of diagnosis, age at diagnosis.

Risk of bias

To ascertain the validity of the eligible studies, the study design, the size and representativeness of the study population (*i.e.*, the presence of selection bias), the validity of outcomes (risk of confounding or bias), and the quality of the statistical analysis were taken into account. We assessed the methodological quality of included studies in accordance with the guidelines of the Cochrane Consumers and Communication Review Group, adapted for the current review concerning observational non-intervention studies. In all cases, two authors (Drs Lionetti and Leonardi) independently assessed the quality of the studies included, with any disagreements resolved by discussion and consensus. Where necessary, study authors were contacted for additional information or for clarification of the study methods.

Statistical analysis

To assess the correlations between atopy/allergic disease and *H. pylori* infection we performed the meta-analysis by using meta-package of the R system. Random-effect model (DerSimonian and Laird) was used for the meta-analysis. Random effects analysis not only weights each study by its inverse variance but also includes the within- and between studies variances; it is more conservative than fixed-effects models, providing wider confidence intervals when there is between-study heterogeneity. We tested for heterogeneity in results across studies by using a Cochran Q statistic. Given the low test power, the significance level was defined as $P < 0.10$. The I^2 was used to quantify the extent of true heterogeneity. The significance of the pooled OR was determined by Z-test. A P value < 0.05 was considered to be statistically significant.

RESULTS

Table 1[15-25] and Table 2[26-35] show case-control and cross-sectional studies that, since 1997 up to now, have investigated the prevalence of *H. pylori* infection in atopic/allergic and non-atopic/non-allergic patients and the prevalence of atopy/allergic disease in *H. pylori* positive and *H. pylori* negative subjects, respectively.

Results of case-control studies

In 1999, Figura *et al*[15] tested for the first time the relationship between *H. pylori* infection and food allergy. Food allergy was defined by IgE to alimentary antigens, and *H. pylori* infection status was tested by serum anti *H. pylori* IgG and anti-CagA antibodies. This case-control study examined 38 patients with food allergy (cases) and 53 controls. Overall, 16 of 38 cases *vs* 26 of 53 controls were *H. pylori* seropositive (42.1% *vs* 48.3%; P = NS**)**. Otherwise, 24 of 38 cases, *vs* 15 of 53 of controls, expressed anti-CagA antibodies (62.5% *vs* 28%; $P < 0.05$). Therefore, the authors demonstrated the presence of no correlation between food allergy and anti-*H. pylori* antibodies, but a significant direct correlation between food allergy and anti-CagA antibodies.

In 2000, Matricardi *et al*[16] performed a case control, retrospective study to evaluate the association between atopy and several infections. The study was conducted among 240 atopic cases and 240 non-atopic controls from a sample of 1659 Italian cadets. The authors examined serology for some foodborne microbes (Toxoplasma gondii, *H. pylori* and hepatitis A virus) and for some airborne ones (measles, mumps, rubella, and chickenpox). The presence of atopy was evaluated by skin prick test and total and specific IgE. It was observed an inverse correlation between atopy and foodborne and orofecal microbes; conversely, the study excluded any association between atopy and airborne viruses. As regard to *H. pylori* colonization, although in non-atopic participants as compared with controls there was a lower prevalence of seropositivity, the difference observed was not statistically significant (18% *vs* 15%; P = NS). The explanation proposed by the authors was that an adequate exposure to foodborne and oro-fecal microbes acts on gut associated lymphoid tissue, enhancing T helper 1 immunity and preventing the development of atopy. Noteworthy, based on study's results this hypothesis was not applicable to *H. pylori* infection.

In the same year Bodner *et al*[17] published a case control study evaluating the correlation between childhood exposure to infections and the risk of adult onset of

Table 1 Summary of studies evaluating the prevalence of *Helicobacter pylori* infection in atopic/allergic (cases) and non-atopic/non-allergic subjects (controls) *n* (%)

Ref.	Location	Population	*H. pylori* measure	Definition of atopy/allergic disease	*H. pylori* +/ atopic-allergic	*H. pylori* +/non atopic-non allergic
Figura *et al*[15]	Italy	Adult	Anti-*H. pylori* IgG	Specific IgE to alimentary antigens	16 (42.1)	26 (48.3)
Figura *et al*[15]	Italy	Adult	Anti-*H. pylori* CagA IgG	Specific IgE to alimentary antigens	24 (65.5)	15 (28.0)
Matricardi *et al*[16]	Italy	Adult	Anti-*H. pylori* IgG	Positive skin prick test, total IgE and specific IgE	35 (15.0)	44 (18.0)
Bodner *et al*[17]	Scotland	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of wheezing or whistling in the chest)	49 (57.6)	93 (48.9)
Bodner *et al*[17]	Scotland	Adult	Anti-*H. pylori* IgG	Skin reactivity, total IgE and specific IgE	77 (51.3)	65 (52.0)
Tsang *et al*[18]	China	Adult	Anti-*H. pylori* IgG	Symptoms of asthma twice a week, FEV1 of 80% of predicted value or >, reversibility of greater than 15% with salbutamol, PC20 of less than 8 mg/mL histamine	43 (47.3)	37 (38.1)
Radon *et al*[19]	Germany	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of allergic symptoms) and specific IgE	18 (19.8)	50 (21.7)
Jun *et al*[20]	Japan	Adult	Anti-*H. pylori* IgG	Symptoms of asthma twice a week, FEV1 of 80% of predicted value or >, reversibility of greater than 15% with salbutamol, PC20 of less than 8 mg/mL histamine	27 (58.7)	26 (54.2)
Jun *et al*[20]	Japan	Adult	Anti-*H. pylori* CagA IgG	Symptoms of asthma twice a week, FEV1 of 80% of predicted value or >, reversibility of greater than 15% with salbutamol, PC20 of less than 8 mg/mL histamine	10 (21.7)	9 (18.8)
Janson *et al*[21]	Iceland, Sweden, Estonia	Adult	Anti-*H. pylori* IgG	Specific IgE to inhalant allergens	81 (24.8)	337 (36.6)
Shiotani *et al*[22]	Japan	Adult	Anti-*H. pylori* IgG	Questionnaires and direct interviews	42 (11.4)	72 (17.6)
Konturek *et al*[23]	Germany	Adult	C^{13}-urea breath test and anti- *H. pylori* CagA IgG	Clinical history, specific IgE, skin prick test, food challenge	14 (33.3)	8 (40.0)
Reibman *et al*[24]	Unites States	Adult	Anti H-pylori IgG and anti CagA IgG	Questionnaires (about any occurrence of asthma)	79 (24.8)	65 (31.3)
Holster *et al*[25]	Germany	Children	Anti-*H. pylori* IgG anti-H pylori CagA IgG	Questionnaires (about any occurrence of wheezing)	12 (5.9)	37 (10.9)
Holster *et al*[25]	Germany	Children	Anti-*H. pylori* IgG anti-*H. pylori* CagA IgG	Questionnaires (about any occurrence of allergic rhinitis)	25 (8.5)	24 (9.5)
Holster *et al*[25]	Germany	Children	Anti-*H. pylori* IgG anti-H pylori CagA IgG	Questionnaires (about any occurrence of atopic dermatitis)	21 (8.7)	28 (9.2)
Holster *et al*[25]	Germany	Children	Anti-*H. pylori* IgG anti-*H. pylori* CagA IgG	Questionnaires (about any physician diagnosis of asthma)	7 (7.1)	42 (9.4)

H. pylori: *Helicobacter pylori*.

wheezing and atopy. Atopy was tested by skin reactivity, specific and total IgE; wheezing was defined based on a questionnaire evaluating clinical symptoms (asthma or cough and phlegm for as much as three month per year in association with wheeze). *H. pylori* infection was diagnosed by specific IgG antibodies. The authors reached data about 319 subjects aged 39-40 years (102 cases and 217 controls), originally identified when they were 10-14 years old. *H. pylori* positivity was demonstrated in 77 of 150 atopic subjects *vs* 65 of non-atopic, and in 49 of 85 subject with wheezing *vs* 93 of 190 non-wheezers (51.3% *vs* 52%, and 57.6% *vs* 48.9%; P = NS) . Therefore, the observed rate of *H. pylori* seropositivity was similar in atopic and non-atopic subjects and in wheezers and non-wheezers, denying any association between childhood infections and adult onset of atopy and allergic disorders.

Tsang *et al*[18] further investigated *H. pylori* seroprevalence in asthmatic and healthy subjects. A total of 90 patients with stable asthma (cases) and 97 healthy subjects (controls) were recruited. The diagnosis of asthma was made according to the American Thoracic Society Guidelines. *H. pylori* seroprevalence was determined by serum IgG. The results were the following: 43 asthmatic and 37 controls were seropositive (47.3% *vs* 38.1%; P = NS). The study demonstrated that there were no significant differences in the *H. pylori* specific IgG levels between controls and study group. Otherwise, among asthmatic patients, there were no differences in FEV1 and duration of symptoms between *H. pylori* positive subjects and negative ones.

In 2004 Radon *et al*[19] studied a population of 321 young adults living in a rural town of Northern Germany, with the aim to investigate the influence of the so-called "farming related factors" (starting age of regular contacts with animal stables, entry age to kindergarten and school, raw uncooked farm milk consumption at

Table 2 Summary of studies evaluating the prevalence of atopy/allergic disorders in *Helicobacter pylori* positive (cases) and *Helicobacter pylori* negative (controls) subjects *n* (%)

Ref.	Location	Population	*H. pylori* measure	Definition of atopy/Allergic disease	Atopy-Allergic disorders/*H. pylori* +	Atopy-Allergic disorders/*H. pylori* -
Kosunen *et al*[26]	Finland	Adult	Anti-*H. pylori* IgG, IgA	Specific IgE antibodies (against birch, timothy pollen, cat and dog epitelium allergens) in 1973	16 (10.9)	20 (11.2)
Kosunen *et al*[26]	Finland	Adult	Anti-*H. pylori* IgG, IgA	Specific IgE antibodies (against birch, timothy pollen, cat and dog epitelium allergens) in 1994	3 (5.1)	54 (20.8)
Linneberg *et al*[27]	Denmark	Adult	Anti-*H. pylori* IgG	Specific IgE (at least 6 allergens: birch, grass, mug, wort, dog, cat, mite)	75 (27.5)	323 (39.2)
Linneberg *et al*[27]	Denmark	Adult	Anti-*H. pylori* IgG	Questionnaires (about any symptoms of allergic rhinitis)	48 (17.7)	236 (28.7)
Cullinan *et al*[28]	United Kingdom	Adults	Anti-*H. pylori* IgG	Skin prick tests to extracts of Dermatophagoides pteronyssinus, cat fur or grass pollen	53 (35.0)	278 (37.0)
McCune *et al*[29]	England	Adult	C^{13}-urea breath test	Self-reported use of any appropriate medications for asthma, rhinitis and eczema, as surrogate markers of these diseases	85 (7.9)	235 (10.9)
Jarvis *et al*[30]	United Kingdom	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of wheezing)	60 (28.9)	165 (27.2)
Jarvis *et al*[30]	United Kingdom	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of walking with cough)	62 (30.0)	190 (31.0)
Jarvis *et al*[30]	United Kingdom	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of hay fever or nasal allergies)	60 (28.9)	181 (29.6)
Jarvis *et al*[30]	United Kingdom	Adult	Anti-*H. pylori* IgG	Specific IgE (to any of five allergens: house dust mite, cat, grass, Cladoporum and birch)	83 (39.9)	230 (37.6)
Chen *et al*[31]	United States	Adult	Anti-*H. pylori* IgG and anti- *H. pylori* CagA IgG	Self-reported asthma (current)	169 (4.5)	196 (5.0)
Chen *et al*[31]	United States	Adult	Anti-*H. pylori* IgG and anti- *H. pylori* CagA IgG	Self-reported asthma (lifetime)	229 (6.1)	296 (7.5)
Chen *et al*[31]	United States	Adult	Anti-*H. pylori* IgG and anti-*H. pylori* CagA IgG	Specific IgE for Ragweed	204 (33.0)	741 (6.7)
Chen *et al*[32]	United States	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of asthma)	267 (10.2)	679 (14.2)
Chen *et al*[32]	United States	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of dermatitis, eczema or rash)	234 (8.9)	514 (10.7)
Chen *et al*[32]	United States	Adult	Anti-*H. pylori* IgG	Questionnaires (about any occurrence of wheezing)	275 (10.5)	653 (13.6)
Seiskari *et al*[33]	Russian Karelia	Children	Anti-*H. pylori* IgG	Specific IgE (for at least one allergen for birch, cat and egg albumin	9 (5.0)	8 (11.0)
Baccioglu *et al*[34]	Turkey	Adults	Microscopy on gastric tissue samples	Questionnaires (about any occurrence of doctor-diagnosed asthma)	8 (11.0)	5 (31.0)
Baccioglu *et al*[34]	Turkey	Adults	Microscopy on gastric tissue samples	Self-reported allergic rhinitis symptoms	45 (61.0)	11 (69.0)
Baccioglu *et al*[34]	Turkey	Adults	Microscopy on gastric tissue samples	Self-reported urticaria in the last two years	20 (27.0)	6 (38.0)
Baccioglu *et al*[34]	Turkey	Adults	Microscopy on gastric tissue samples	Self-reported food allergy symptoms	9 (12.0)	1 (6.0)
Baccioglu *et al*[34]	Turkey	Adults	Microscopy on gastric tissue samples	Skin prick test	20 (7.0)	4 (25.0)
Cam *et al*[35]	Turkey	School children	C^{13}-urea breath test	Questionnaires (about any occurrence of doctor diagnosed allergic rhinitis)	3 (6.4)	1 (3.7)
Cam *et al*[35]	Turkey	School children	C^{13}-urea breath test	Questionnaires (about any occurrence of doctor diagnosed asthma)	3 (6.4)	1 (3.7)
Cam *et al*[35]	Turkey	School children	C^{13}-urea breath test	Questionnaires (about any occurrence of doctor diagnosed atopic dermatitis)	4 (8.5)	1 (3.7)
Cam *et al*[35]	Turkey	School children	C^{13}-urea breath test	Skin prick test to extracts of five groups of aeroallergens (mites, molds, pollens, animal dander, insects)	15 (31.9)	13 (48.1)

H. pylori: *Helicobacter pylori*.

school entry age), as well as the role of markers of infections (Toxoplasma gondii and *H. pylori*), in the development of atopy. The presence of atopy was defined by the detection of serum specific IgE against a panel of 7 aeroallergens (birch pollen, mixed-grass pollen, mugwort pollen, dog dander, cat dander, Cladosporium herbarum, Dermatophagoides pteronyssinus). The presence of exposure to farming environment was evaluated by questionnaires, while *H. pylori* status was studied by searching serum *H. pylori* IgG antibodies. The study showed that the farming related factors were more frequent in non-atopic patients than in atopic ones, but only the early contact (< 7 years) with animal stables showed a significant inverse association with atopy (OR = 1.70, OR =0.51, OR = 0.58, respectively for the three factors). The presence of *H. pylori* infection was detected in 50/230 of non-atopic subjects and in 18/91 (21.7% *vs* 19.8%; *P* = NS) of atopic ones. Basing on these data, the authors concluded that neither the markers of infection nor farming related factors (with the exception of early contact with animals) showed a statistically significant inverse association with atopy, even though both of them were more frequent in non-atopic subjects than atopic ones.

Another study that contrasts the *hygienist theory* was published in 2005 by Jun *et al*[20]. It was a case control study evaluating three groups of subjects: 46 mild asthmatic non-smoker adults (cases), 48 patients with peptic ulcer (cases) and 48 healthy individuals (controls). The authors tested patients of each group for anti-*H. pylori* IgG antibodies and anti-*H. pylori* CagA IgG antibodies. It was observed no significant difference in both anti-*H. pylori* IgG seropositivity and anti-*H. pylori* CagA IgG seropositivity between the asthmatic patients and the controls.

In 2007, Janson *et al*[21] investigated the correlation between fooborn/orofecal and airborn/contact infection and atopy, allergic asthma and allergic rhinitis. The study population was composed by 1249 Icelandic, Sweden and Estonian adult subjects who participated in European Community Respiratory Health Survey (ERCHS) Ⅰ, conducted from 1999 to 1994, and ERCHS Ⅱ, of 1999-2000. The detection of specific IgE against Dermatophagoides pteronyssinus, timothy grass, Cladosporium herbarum and cat was used as the definition of allergy sensitization; atopy was defined as being sensitized to any of these allergens. Atopic asthma and rhinitis were defined as the association of atopy with symptoms of asthma and rhinitis respectively. Fooborn/orofecal infections included *H. pylori*, hepatitis A virus (HAV) and Toxoplasma gondii; airborn/contact infections were Herpes Simplex Virus 1, Ebstain Barr Virus, Chlamydia pneumonia, and Cytomegalovirus. The infection status was tested by specific IgG. The study showed that 81 of 327 atopic subjects and 337 of 922 non-atopic ones were *H. pylori* seropositive (24.8% *vs* 36.6%; *P* < 0.01). The data supported the hypothesis that *H. pylori* has a protective effect against atopy. It was observed also an inverse correlation between *H. pylori* and allergic asthma and rhinitis, even if no numeral data were reported in the text. Compared to previous studies, the current one added four important findings: (1) both foodborn/orofecal and airborn/contact infections had a protective effect on development of atopy; (2) there was no correlation between HAV and atopy; (3) the risk of development of atopy increased with increasing number of infection; and (4) there was no correlation between infection seroprevalence and total IgE.

In 2008, Shiotani *et al*[22] through an observational, cross sectional study evaluated the relationship between *H. pylori* and allergic disease. The presence of allergic manifestations (such as pruritus of skin or eyes, nasal discharge, cough and dyspnoea) was determined through questionnaires and direct interviews in a total of 1953 Japanese students. The presence of *H. pylori* infection was detected by dosing serum IgG in 777 patients (including 369 with allergic disease and 408 controls). The infection was detected in 42 subjects of allergic group and in 72 of the control group (11.4% *vs* 17.6%; *P* = 0.01). The significant negative association was demonstrated in the whole sample and in men, but not in women, underlining a gender difference in the negative association that could suggest a different immune response to *H. pylori* in women rather than in men.

In 2008 Konturek *et al*[23] investigated the relationship between *H. pylori* infection and food allergy. The authors studied 42 patients with food allergy and 20 controls (case-control-study). Food allergy was tested by clinical history, skin prick tests, RAST, double blind placebo-controlled food challenge and determinations of cells specific markers of allergy, such as plasma histamine, urinary N-tele-methyl-histamine, plasma tryptase and serum eosinophilic cationic proteins (ECP). *H. pylori* infection was tested by ^{13}C-Urea Breath Test. They observed that food allergy patients had significant lower *H. pylori* infection prevalence than healthy controls (33.3% *vs* 40%; *P* < 0.05). The authors proposed also an explanation for this phenomenon: *H. pylori* infection reduces serum level of some inflammatory mediators, such as ECP and mast cell tryptases, leading to an ameliorating effect of *H. pylori* on the allergic reactions in the gastrointestinal mucosa.

In the same year, Reibman *et al*[24] performed a case-control study about the association between asthma and *H. pylori* status. Asthma cases (*n* = 318) and controls (*n* = 208) were recruited to participate in the New York University/Bellevue Asthma Registry in New York City. Subjects were defined as "asthmatics" basing on their response to questions derived from validates questionnaires used for international studies of asthma. Measurements of total serum IgE, allergen specific IgE for allergens were also performed. Serum IgG antibodies to *H. pylori* and the immunodominant CagA were measured. The authors identified a trend towards an inverse association between *H. pylori* and asthma, that became significant when they examined individuals who carried CagA+ *H. pylori* strains . Moreover, the authors did not

detect an effect of *H. pylori* serostatus on total IgE or the presence of atopy in the studied population.

Finally, in 2012, Holster *et al*[25] published a study about the association between the prevalence of anti-*H. pylori* IgG antibodies and anti-CagA antibodies and the prevalence of allergic diseases in a sample of 545 Dutch children aged 8 years. Among children with wheezing (n = 204), 12 were *H. pylori* positive *vs* 37 among those without wheezing (n = 341) (5.9% *vs* 10.9%; P = 0.05). Otherwise, no significant differences in *H. pylori* prevalence were found between children with or without allergic rhinitis, atopic dermatitis, physician diagnosed asthma (8.9% *vs* 9.5%; 8.7% *vs* 9.2%; 7.1% *vs* 9.4%; P = NS). Therefore, he found a quite inverse association between *H. pylori* and wheezing, but no associations between *H. pylori* and allergic rhinitis, atopic dermatitis or asthma.

For each case-control study mentioned, the OR of atopy and allergic diseases associated with the presence of *H. pylori* was estimated. Overall, the meta-analysis shows that the pooled OR of developing atopy/allergic diseases in *H. pylori* positive patients was 0.8 (P = 0.02) (Figure 1A), the OR of developing exclusively atopy was 0.8 (P = 0.03) (Figure 1B), and the OR of developing exclusively allergic diseases was 0.9 (P = 0.2) (Figure 1C).

Results of cross-sectional studies

In 2002, Kosunen *et al*[26] supported the hypothesis that *H. pylori* could counteract atopy. They determined the prevalence rate of specific IgE antibodies and anti-*H. pylori* antibodies in two cross sectional, adult-based serum samples, selected randomly from a Finnish population in 1973 (n = 326) and 1994 (n = 319). The data collected confirmed the already previously observed increasing trend of prevalence of allergic disorders and decreasing trend of *H. pylori* infection from 1973 to 1994. The results that mainly support the hygiene hypothesis were that the increase in the prevalence rate of IgE antibodies observed from 1973 to 1994 was limited to *H. pylori* seronegative subjects. Indeed, in 1994 the presence of specific IgE antibodies was detected in only 5% of *H. pylori* seropositive subjects and in more than 20% of the *H. pylori* seronegative ones.

One year later Linneberg *et al*[27] investigated the association between atopy and two different groups of foodborne and orofecal infections: HAV, *H. pylori* and Toxoplasma gondii on the one hand and Clostridium difficile, Campilobacter jejuni and Yersinia enterocolitica on the other hand. Microbes of the first group were markers of poor hygiene, whereas the second group were intestinal bacterial pathogens. The cross sectional study involved 1112 Danish subjects, among adolescents and adults. The authors define atopy as the positivity of specific IgE for at least one inhalant allergen and exposure to microbes as the positivity of specific IgG. The study demonstrated that different foodborne and orofecal infections differently conditioned the developing of atopy. HAV, *H. pylori* and Toxoplasma gondii infections were inversely related to atopy, whereas Clostridium difficile, Campilobacter jejuni and Yersinia enterocolitica were directly related to it. The authors suggested that the first ones induce chronic gastrointestinal infections that minimally modify intestinal microflora, but polarize immune response to the Th1 profile. Otherwise, intestinal bacterial pathogens induce changes of intestinal microflora and destruction of mucosal barrier, posing a threat for oral tolerance. The same study evaluated the relationship between allergic rhinitis and *H. pylori* infection, confirming a significant inverse association.

A cross-sectional study conducted by Cullinan *et al*[28] in 2003 tested the relationship between atopy and family size, a pattern that was plausibly assumed to reflect a protective effect of early infections. All females presenting for antenatal care at three general practices and all suitable partners were invited to enrol in this prospective study. At recruitment, 622 mothers and 542 fathers underwent skin-prick tests to several allergens. Mothers and fathers were defined as atopic if they had one or more positive reactions to skin tests to extracts of Dermatophagoides pteronyssinus, cat fur or grass pollen. Therefore, a questionnaire was administered to 583 out of the initially enrolled 622 mothers and to 480 of the initially enrolled 542 partners, with the aim to obtain information about any medical diagnoses of asthma, hay fever or eczema, the siblings number and ages of siblings and pet ownership before the age of five. Then, venous blood was collected from 896 of both mother and father and assayed for specific IgG antibodies to *H. pylori*, HAV and Toxocara canis. Finally, for each adult, contemporary general practice notes were scrutinised for details of infective illnesses and antibiotic prescriptions up to the age of 5 years. The study established that atopy was less common among those from larger families, especially with a higher number of brothers. The sibling effect was unexplained by evidence of infection with either HAV or *H. pylori*. Indeed, 53 of 151 *H. pylori* positive subjects were atopic *vs* 278 of 745 negative ones (35% *vs* 37%; P = 0.52). Although the current study replicates the finding that atopy was inversely associated with family size, this could not be explained by documentary or serological evidence of early infection. The findings lead to the suggestion that the sibling effect in atopy may not simply reflect protection by early infection.

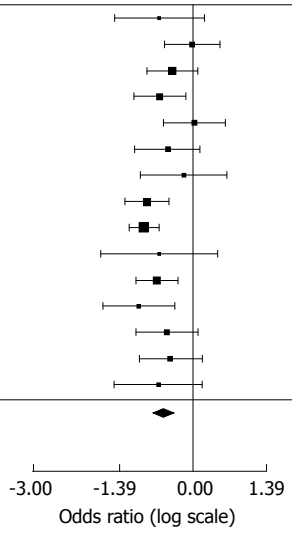
In 2003 McCune *et al*[29] developed a cross-sectional study about the prevalence of three allergic disorders (asthma, eczema and rhinitis) in 3244 subjects participating in a community-based, prospective, randomized, controlled trial of *H. pylori* eradication. The prevalence of these allergic disorders was measured by assessing the self-reported use of the medications commonly used in their treatment: inhaled corticosteroids, inhaled cromoglicate and inhaled (or oral) bronchodilators for asthma, oral antihistamines for allergic rhinitis and topical corticosteroids for eczema. These data were used as surrogate markers for the three cited conditions. The presence of active *H. pylori* infection was determined by the ^{13}C-urea breath test. The authors demonstrated that

A

Author(s) and year	Cases *H.pylori* +	Cases *H.pylori* -	Control *H.pylori* +	Control *H.pylori* -	Odds ratio (95%CI) (log scale)
Figura, 1999	16	22	26	27	-0.28 [-0.12, 0.56]
Bodner (1), 2000	49	36	93	97	0.35 [-0.17, 0.87]
Bodner (2), 2000	77	73	65	60	-0.03 [-0.50, 0.45]
Matricardi, 2000	35	205	44	196	-0.27 [-0.76, 0.21]
Tsang, 2000	43	47	37	60	0.39 [-0.19, 0.98]
Radon, 2004	18	73	50	180	-0.12 [-0.72, 0.48]
Jun (1), 2005	27	19	26	22	0.18 [-0.63, 1.00]
Shiotani, 2007	42	327	72	336	-0.51 [-0.92, -0.10]
Janson, 2007	81	246	337	585	-0.56 [-0.84, -0.27]
Konturek, 2008	14	28	8	12	-0.29 [-1.39, 0.81]
Reibman, 2008	79	239	65	143	-0.32 [-0.71, 0.07]
Holster (1), 2012	12	192	37	304	-0.67 [-1.34, 0.01]
Holster (2), 2012	25	269	24	227	-0.13 [-0.72, 0.46]
Holster (3), 2012	21	220	28	276	-0.06 [-0.65, 0.53]
Holster (4), 2012	7	91	42	405	-0.30 [-1.13, 0.53]
RE model					-0.20 [-0.38, -0.03]

Heterogeneity: Q (df = 14) = 20.3, P = 0.1; t^2: 0.04 (SE = 0.04), I^2: 36.0%, H^2: 1.5

Test for overall effect: Z = -2.2, P = 0.02

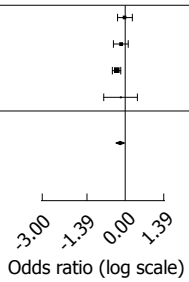


B

Author(s) and year	Cases *H.pylori* +	Cases *H.pylori* -	Control *H.pylori* +	Control *H.pylori* -	Odds ratio (95%CI) (log scale)
Bodner (2), 2000	77	73	65	60	-0.01 [-0.28, 0.25]
Matricardi, 2000	35	205	44	196	-0.15 [-0.42, 0.12]
Janson, 2007	81	246	337	585	-0.31 [-0.47, -0.15]
Konturek, 2008	14	28	8	12	-0.16 [-0.77, 0.45]
RE model					-0.19 [-0.35, -0.02]

Heterogeneity: Q (df = 3) = 3.8, P = 0.3; t^2: 0.00 (SE = 0.02), I^2: 35.15%, H^2: 1.5

Test for overall effect: Z = -2.2084, P = 0.03



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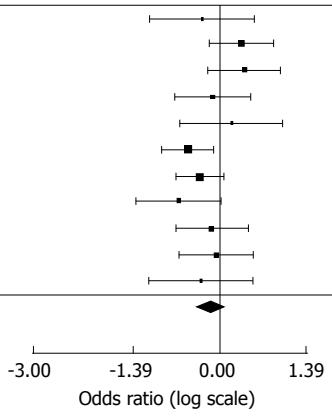
Author(s) and year	Cases *H.pylori* +	Cases *H.pylori* -	Control *H.pylori* +	Control *H.pylori* -	Odds ratio (95%CI) (log scale)
Figura, 1999	16	22	26	27	-0.28 [-1.12, 0.56]
Bodner (1), 2000	49	36	93	97	0.35 [-0.17, 0.87]
Tsang, 2000	43	47	37	60	0.39 [-0.19, 0.98]
Radon, 2004	18	73	50	180	-0.12 [-0.72, 0.48]
Jun (1), 2005	27	19	26	22	0.18 [-0.63, 1.00]
Shiotani, 2007	42	327	72	336	-0.51 [-0.92, -0.10]
Reibman, 2008	79	239	65	143	-0.32 [-0.71, 0.07]
Holster (1), 2012	12	192	37	304	-0.67 [-1.34, 0.01]
Holster (2), 2012	25	269	24	227	-0.13 [-0.72, 0.46]
Holster (3), 2012	21	220	28	276	-0.06 [-0.65, 0.53]
Holster (4), 2012	7	91	42	405	-0.30 [-1.13, 0.53]
RE model					-0.14 [-0.36, 0.07]

Heterogeneity: Q (df = 10) = 13.9, P = 0.2; t^2: 0.04 (SE = 0.06), I^2: 32.57%, H^2: 1.48

Test for overall effect: Z = -1.3113, P = 0.2



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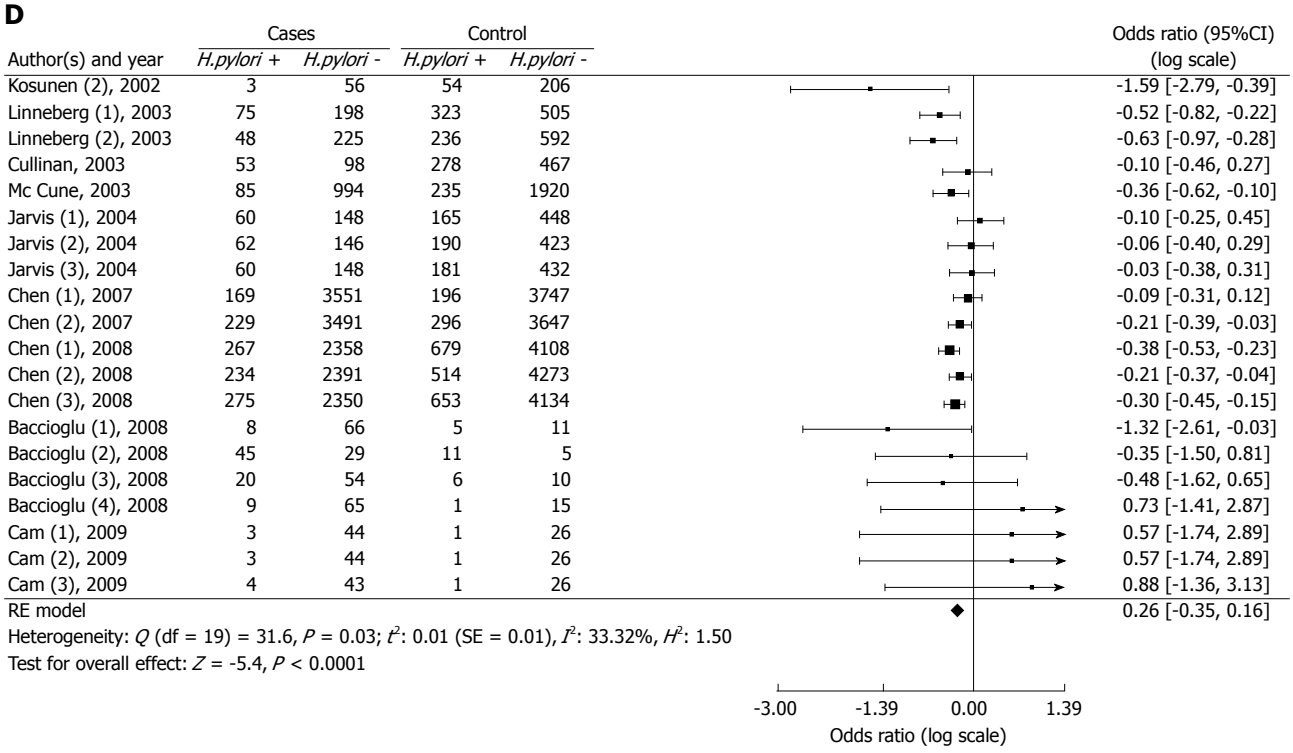

Figure 1 Meta-analysis of case-control studies. A: Concerning atopy/allergic diseases and *Helicobacter pylori* (*H. pylori*) infection; B: Concerning atopy and *H. pylori* infection; C: concerning allergic diseases and *H. pylori* infection; D: Concerning allergic diseases and *H. pylori* infection.

85 of 1079 *H. pylori* positive subjects *vs* 235 of 2155 *H. pylori* negative ones had ever used any of that medications (7.9% *vs* 10.9%; $P = 0.007$). Therefore, the authors concluded that *H. pylori* infection was negatively associated with asthma, rhinitis and eczema considered together. Nevertheless, for each individual allergic disorder, the data were not quite large enough to reach statistical significance.

In 2004, Jarvis *et al*[30] published a study that reported no association between atopy/allergic diseases and *H. pylori* infection. He tested a sample of 1211 individuals, selected randomly from 15000 young adults, aged from 20 to 44 years and living in East Anglia. Allergic symptoms of asthma, hay fever and wheezing were investigated through questionnaires, the atopic status was determined by total IgE and specific IgE values to five of the more common allergens (dust mite, cat, grass, Cladosporium and birch), and *H. pylori* positivity was tested by specific IgG levels. It was observed that the prevalence of symptoms of hay fever and wheeze were the same in *H. pylori* seropositive and seronegative participants. Otherwise, it was observed a negative association between *H. pylori* and grass sensitization, although it no reached statistical significance. The incomplete results (only 841 of 1211 samples were tested for *H. pylori*), an increased cut off of IgE for allergy sensitization and an undetailed definition of hay fever may be the reasons because the study lacked statistical significance.

In 2007 and 2008, Chen *et al*[31,32] published two retrospective studies about the inverse association of *H. pylori* with asthma and allergy. Both of them were conducted using data of the Third National Health and Nutrition Examination (NHANES Ⅲ). The first one analysed the association between *H. pylori* positivity and allergic disease and atopy in 7663 participants aged ≥ 20 years enrolled in 1998-1991. Information about history of allergy (allergic rhinitis, asthma, wheezing, allergic symptoms, like itchy eyes, runt noose, *etc.*) was collected using in-person interviews; skin prick test were performed to define the presence of atopy. The *H. pylori* status was detected by IgG serum level and CagA enzyme-linked immunosorbent assay (ELISA). The study confirmed the inverse association of *H. pylori* infection and either atopy or allergic diseases. Moreover, it added two important considerations: (1) atopy and allergic diseases were inversely related to cagA+ *H. pylori* strains; and (2) the negative association between asthma and cagA status was stronger in child-onset asthma than in adult onset asthma. The inverse relationship between atopy/allergic diseases and cagA+ *H. pylori* strains is probably related to the more pronounced immune activation induced by cagA+ *H. pylori* strains, compared with the cagA-ones. The stronger association of atopy with child-onset asthma is consistent with the inverse trend of childhood onset of asthma (age < 15 years) and cagA+ status. Moreover, the heightened gastric atrophy induced by cagA+ strains, reducing the risk of gastro-esophageal reflux disease (*i.e.*, one of the causes of asthma), may explain the inverse association with asthma disease[31]. The second cross-sectional study was conducted using data from 7412 children-adult participants in the NHANES between 1999 and 2000. The study investigated only about

asthma, allergic rhinitis and allergic symptoms, using in-person interviews. The *H. pylori* status was determined using the ELISA for detecting specific IgG. This study showed a big cohort-effect, with a decreasing prevalence of *H. pylori* infection in people born early in the 20th century. The analysed data confirmed the inverse association between *H. pylori* and asthma: 267 of 2625 *H. pylori* positive subjects were asthmatic as compared to 679 of 4787 *H. pylori* negative ones. The significant inverse association was demonstrated also for other atopic disorders. Compared with the first Chen's study, this one included a younger population, providing an opportunity to test the inverse association between atopy and *H. pylori* infection in children. Then, by a stratified analysis among 3-19 years of age, it demonstrated that the inverse association with onset of asthma before 5 years was stronger[32].

In 2007, Seiskari *et al*[33] tested the hygiene hypothesis in two socio-economically and culturally different populations living in geographically adjacent areas: Russian Karelia and Finnish Karelia. Both the Russian Karelian study cohort and the Finnish study cohort comprised 266 school children. Atopic status was studied by levels of total IgE and allergen-specific IgE (for birch, cat and egg albumin). Microbial IgG antibodies were analysed against Enteroviruses (Coxsackievirus B4), HAV, *H. pylori* and Toxplasma gondii. The authors observed that the prevalence of microbial antibodies, as markers of microbial exposure and poor hygiene, was significantly higher in children in Russian Karelia than in children in Finnish Karelia. In line with this, atopic sensitization was significantly less common in Russian Karelian children than in Finnish ones. Moreover, the authors studied the correlation between the prevalence of allergic sensitisation and the prevalence of positive microbial serologies in both Russian and Finnish Karelia. In Russian Karelia 9 of 194 *H. pylori* positive were positive for at least one allergen-specific IgE, otherwise 8 of 72 *H. pylori* negative were allergen sensitized (5% *vs* 11%; $P = 0.04$), confirming an inverse correlation between atopy and *H. pylori* infection in Russian Karelia study population. In Finland, the number of *H. pylori* seropositive children was very low, which made it difficult to analyse their association with allergen-specific IgE.

In 2008 Baccioglu *et al*[34] investigated the correlation between *H. pylori* infection and atopy. Participants of the study were recruited among the outpatients who attended Kirikkale University Hospital (Turkey). A total of 90 subjects suffering dyspeptic symptoms were enrolled into the study. The presence of *H. pylori* infection was assessed in gastric mucosa tissue by microscopy. Skin prick tests against a large battery of inhalants and certain food allergens were performed with the aim to determine the population atopy status: atopy was defined as a positive result to at least one allergen. The presence of allergic symptoms was finally detected through questionnaires about any occurrence of doctor-diagnosed asthma, symptoms of allergic rhinitis, symptoms of food allergy and acute urticaria in the last two years. The study showed that the frequency of atopy was 20/74 *H. pylori* positive subjects and 4/16 *H. pylori* negative subjects (27% *vs* 25%, P = NS). The frequency of *H. pylori* infection in atopic and non-atopic patients was similar (83% in atopic group *vs* 81% in non-atopic group, P = NS). Finally, either in *H. pylori* positive or in negative subjects the occurrence of rhinitis, food allergy and urticaria was similar (61% *vs* 69%; 12% *vs* 6%; 27% *vs* 38%; P = NS). Although the diagnosis of asthma was significantly lower in the *H. pylori* positive group than in non-atopic one (11% *vs* 31%, $P < 0.05$) the authors concluded that the effect of asthma was insignificantly related to a lower risk of *H. pylori* infection (OR = 1.0; 95%CI: 0.1-18.9). Therefore, Baccioglu *et al* showed that *H. pylori* infection is not associated with atopic diseases at all. Therefore, they concluded that *H. pylori* eradication may not be assumed to have an effect on allergic inflammation.

In 2009 Cam *et al*[35] evaluated the relationship between atopy an *H. pylori* infection. The study group was recruited from a cohort of 327 healthy children evaluated and followed-up for 6 years to assess the natural history of *H. pylori* infection. 74 out of 136 healthy children who underwent ^{13}C-urea breath test were eligible and accepted to participate. All participants were evaluated by questionnaires about any occurrence of doctor diagnosed allergic rhinitis, asthma and atopic dermatitis; also skin-prick tests to extracts of five groups of aeroallergens (mites, molds, pollens, animal dander, insects) were performed: subjects who had at least one or more positive reaction to any of the tested antigens were considered atopic. The study demonstrated that the frequency of atopy was lower in *H. pylori*-infected group (31.9% *vs* 48.1%; $P = 0.22$), with respect to non-infected one, while the frequency of allergic symptoms was similar between infected and non-infected children.

For each cross-sectional study mentioned, the OR of atopy and allergic diseases associated with the presence of *H. pylori* was estimated. Overall, the meta-analysis shows that the pooled OR of *H. pylori* infection among patients with atopy/allergic diseases was 0.8 ($P = 0.3$) (Figure 2A), the OR among patients with atopy was 1.8 ($P = 0.8$) (Figure 2B), and the OR among patients with allergic diseases was 0.8 ($P < 0.0001$) (Figure 1D).

DISCUSSION

Several case control and cross-sectional studies have investigated the relationship between *H. pylori* infection and allergic diseases. Most of them have been conducted in industrialized countries (United States, Finland, Great Britain, Japan), where atopy is more common and the decreasing trend of *H. pylori* infection is effective.

Based on the literature review and meta-analysis we conclude that there is some evidence of an inverse association between atopy/allergic diseases and *H. pylori* infection, although further studied are needed.

Pooled results of case-control studies showed a significant inverse association of *H. pylori* infection with

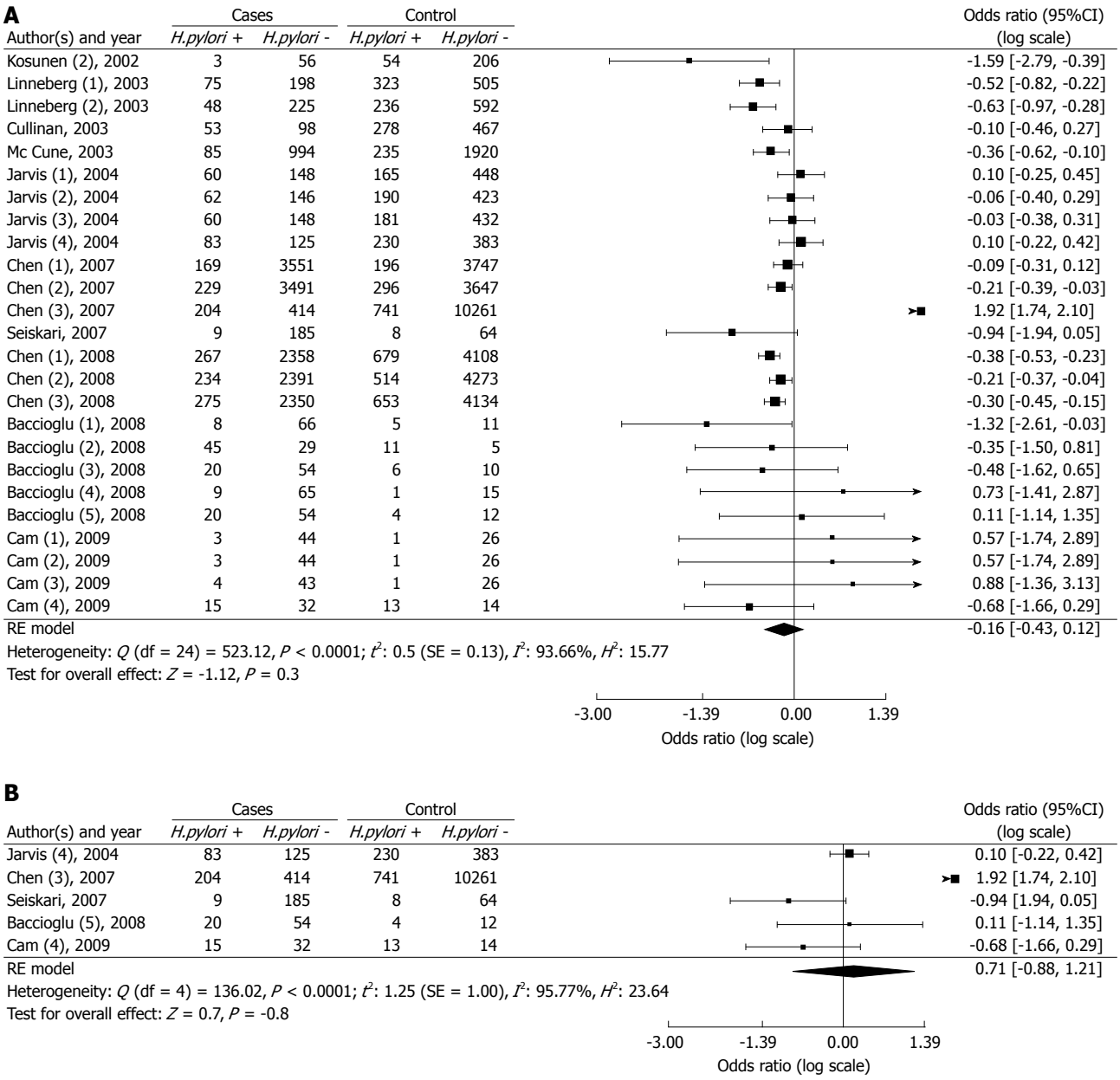

Figure 2 Meta-analysis of cross-sectional studies. A: Concerning atopy/allergic diseases and *Helicobacter pylori* (*H. pylori*) infection; B: Concerning atopy and *H. pylori* infection.

atopy/allergic disease or with exclusively atopy, but not with allergic disease, whereas pooled results of cross-sectional studies showed only a significant association between allergic disease and *H. pylori* infection. The discrepancy may be explained by the main limitations of the present review: (1) high statistical heterogeneity between studies; (2) most authors cluster heterogeneous conditions into one group of "allergic disorders", despite the fact that atopy and allergy are two different conditions, widely recognized to be heterogeneous entity with multiple underlying aetiologies; (3) many of studies tested *H. pylori* infection in serum samples of adult population, therefore it's impossible to determine the age of gastrointestinal colonization and specifically if it happened before the allergen sensitization. In fact, only if acquired early in life *H. pylori* infection can protect against allergies; (4) in included studies there are heterogeneous criteria for diagnosis of allergic disease and atopy (*e.g.*, in some studies asthma was diagnosed by physician tests, instead of by symptoms, so the number of children with a diagnosis of asthma was lower than the number of children with asthma diagnosed by symptoms); and (5) the major part of the studies uses screening for specific serum antibodies to diagnose *H. pylori* infection, that is not the recommended test for epidemiological studies, according to current guidelines[36].

Therefore, the question of an inverse relationship between allergy and *H. pylori* needs to be further investigated.

COMMENTS

Background

As the hygiene hypothesis affirms, the most important factor connected with the large spreading of atopic disease is the decreased exposure to food born and oro-fecal infections, including *Helicobacter pylori* (*H. pylori*) infection. Although some clinical studies confirm an inverse association between *H. pylori* and asthma, some studies reported different results on asthma, other allergic diseases, and in general on atopy.

Research frontiers

Further studies are needed to specifically address the role of *H. pylori* infection in the prevention of atopic disease especially in the paediatric population, differentiating atopy from allergic disorders, and using the recommended criteria for the diagnosis of *H. pylori* infection and atopic diseases.

Innovations and breakthroughs

Previous systematic reviews with meta-analysis have been performed to evaluate the relationship between asthma and *H. pylori* infection, showing a weak evidence for an inverse association both in children and in adults. In the present study we focused on the relationship between *H. pylori* infection and either atopy in general or all allergic disorders in detail (*i.e.*, asthma, rhinitis, atopic dermatitis, rhino-conjunctivitis, food allergy).

Applications

Based on the literature review and meta-analysis we conclude that there is some evidence of an inverse association between atopy/allergic diseases and *H. pylori* infection, although further studied are needed. This relationship might be of relevant importance in the perspective of the prevention of atopic disease. There are actually several reasons to refrain from treatment *H. pylori* infection in children, although it would be advisable to try to eradicate the infection, especially if early acquisition of the infection is confirmed to be a critical factor in assessing development of complications such as peptic ulceration or gastric cancers later in life. The confirmation of an inverse association between atopy/allergic diseases and *H. pylori* infection might in future alter the balance against the treatment.

Terminology

Atopy means a predisposition toward developing allergic hypersensitivity reactions. Atopy may have a hereditary component, although contact with the allergen must occur before the hypersensitivity reaction can develop. Allergy is a hypersensitivity disorder of the immune system that occurs when a person's immune system reacts to normally harmless substances in the environment.

Peer review

This is a very well written systematic review and meta-analysis paper concerning the relationship between *H. pylori* infection and atopic diseases. The authors give the extensive overview about the present outlook of the hygiene hypothesis, about the possible inverse association of *H. pylori* infection with allergic diseases. A very accurate analysis of the case-control as well as cross-sectional studies give a good overview about the evidences pro and contra the relationship between allergy and *H. pylori* infection which prevalence show the tendency to reduction with increasing prevalence of atopic diseases in developed and industrialized countries.

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