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Association Between *Helicobacter pylori* and Gastrointestinal Symptoms in Children

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KEY WORDS
Helicobacter pylori, signs and symptoms, digestive, meta-analysis, review

ABBREVIATIONS
GI— gastrointestinal
RAP—recurrent abdominal pain
OR— odds ratio
CI— confidence interval
UAP— unspecified abdominal pain
SRAP—short-term recurrent abdominal pain
GP— general practitioner

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abstract

OBJECTIVE: Recurrent abdominal pain (RAP) and other gastrointestinal (GI) symptoms are common complaints among children. The role of *Helicobacter pylori* in the cause of these complaints remains controversial. Nevertheless, there is an increasing pressure on primary care clinicians to screen for *H pylori* infection in symptomatic children. We systematically reviewed the published evidence for an association between *H pylori* infection and GI symptoms in children.

METHODS: Medline and Embase databases up to July 2009 were searched to identify studies that evaluated the association between *H pylori* and GI symptoms in children aged up to 18 years. When studies reported on abdominal pain without additional definition, thus not fulfilling Apley's criteria, we grouped these outcomes as unspecified abdominal pain (UAP). Methodologic quality was scored by using a standardized list of criteria, and crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and pooled.

RESULTS: Thirty-eight studies met our inclusion criteria: 23 case-control studies, 14 cross-sectional studies, and 1 prospective cohort study. The overall methodologic quality was low. Pooled ORs for the association between RAP and *H pylori* infection in children were 1.21 (95% CI: 0.82–1.78) in 12 case-control studies and 1.00 (95% CI: 0.76–1.31) in 7 cross-sectional studies. Meta-analysis of the association between UAP and *H pylori* infection in 6 hospital-based studies resulted in a pooled OR of 2.87 (95% CI: 1.62–5.09) compared with 0.99 (95% CI: 0.46–2.11) in 5 population-based studies. Two of 3 studies concerning epigastric pain reported a statistically significant positive association with *H pylori* infection.

CONCLUSIONS: We found no association between RAP and *H pylori* infection in children and conflicting evidence for an association between epigastric pain and *H pylori* infection. We found evidence for an association between UAP but could not confirm this finding in children seen in primary care. *Pediatrics* 2010;125:e651–e669

Helicobacter pylori is 1 of the most common bacterial pathogens in humans and affects ~50% of the world's population.[1] The prevalence of *H pylori* infection varies greatly between developing countries and developed countries (respectively, 90% vs 40% at the age of 40),[1] and infection is mainly acquired in early childhood.[2] In adults, *H pylori* infection is associated with conditions such as chronic active gastritis and peptic ulcer disease,[1] and *H pylori* has been confirmed as the most important risk factor for noncardia gastric adenocarcinomas and gastric mucosa-associated lymphoid tissue lymphomas.[3] Despite this knowledge, the natural history of *H pylori* infection in children, such as the mode of acquisition and signs of infection, is poorly understood.

Guidelines on screening for *H pylori* in children contradict. Recommendations vary from no need to screen children with gastrointestinal (GI) symptoms[4] and no need to screen children with recurrent abdominal pain (RAP)[5] to all children with upper GI symptoms should be tested for *H pylori* infection (Maastricht III).[6] These recommendations are based on the lack of proof that infection with *H pylori* is a significant cause of GI symptoms.

In addition, nowadays, a lot of diagnostic tests for *H pylori* are available. Some of them, such as the 13C-urea breath test, detection of *H pylori* antigen in stool, and detection of specific antibodies in serum,[7] are suitable for use in primary care. Thus, this increased availability is likely to result in increased number of children to be tested. This emphasizes the need for up-to-date guidelines with indications for investigating and treating children for *H pylori* infection.

Good-quality studies, preferably summarized in a systematic review, form the basis for evidence-based screening guidelines. Previous reviews[8,9] regarding this topic were limited to the association between *H pylori* and specific symptoms, such as RAP. Because of the limitations of previous systematic reviews and the several studies published after the publication of these analyses, we performed a new systematic literature review to review systematically the extent and the quality of the current published evidence for a relationship between GI symptoms and *H pylori* infection in children.

METHODS

To identify relevant publications, we performed a Medline database search from 1966 to July 27, 2009, by using the following key words: "*Helicobacter pylori*," "*Campylobacter pylori*," "abdominal pain," and "dyspepsia." A search strategy for follow-up studies recommended by Altman[10] was added. The Embase database was searched from 1980 to July 27, 2009; the search strategy for Medline was adapted for Embase with the assistance of a librarian (Appendix 1). To identify additional potentially relevant publications, we hand searched the reference lists of included studies, of published review articles, and of articles written by experts in the field. No language restriction was used.

Study Selection

We limited our search to studies that compared children who did have symptoms with children who did not have symptoms. All abstracts of identified articles were screened for eligibility, and decisions regarding inclusion of studies were made independently by 2 reviewers (L.A.A.S. and M.B.M. or Y.vL.). We used 4 criteria to select relevant studies: (1) the study had a case-control, cross-sectional, or prospective cohort design; (2) 1 of its aims was to evaluate the association between *H pylori* infection and GI symptoms; (3) the study group included children aged 0 to 18 years; and (4) at least 30 children were included and separately analyzed. Because of an increased risk for acquiring an *H pylori* infection, studies concerning exclusively children with relevant comorbidity such as mental disabilities, immunodeficient disorders, and diabetes were excluded.

Interobserver reliability of the eligibility screening was calculated with Cohen's κ.[11] Any disagreements between both reviewers were resolved through consensus or by arbitration of a third person (M.B.M. or Y.vL.). Full-text articles of all selected titles were retrieved or in case the abstract gave insufficient information on the inclusion criteria. When an included study or the data of a study were not available, first authors were contacted.

Quality Assessment

To rate the risk for bias of the included studies, we scored 9 identical methodologic criteria with 1 additional criterion for case-control/cross-sectional studies and 2 additional criteria for prospective cohort studies (Appendix 2). The criteria were adapted from Altman,[10] Lievense et al,[12] Hayden et al,[13] and the STROBE Statement[14] and were modified to cover the topic of this review. Criteria could be answered with "yes (+)," "no (−)." or "don't know (?)." One point was given to a criterion answered with "yes," and no points were given when answered with "no" or "don't know." Equal weights were applied to all items, resulting in a maximum score of 10 points for case-control/cross-sectional studies and 11 points for prospective cohort studies. Low risk for bias was defined as a score of $\geq$7 points. Two reviewers scored all included articles independently (L.A.A.S. and M.B.M.). Interobserver variability was calculated with Cohen's κ. In case of disagreement between both reviewers, a third reviewer (Y.vL.) made the final decision.

Data Extraction and Analysis

Two reviewers performed data extraction on a structured list independently. Extracted data included demographics, description of the study population, inclusion and exclusion criteria, baseline characteristics, type of symptoms analyzed, diagnostic tests used, and outcome data. As a measure for the association between GI symptoms and *H pylori*, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each symptom on the basis of unadjusted data presented in individual studies.

Data analysis was performed by using Review Manager 5.0 (RevMan). The weight given to each study was based on the inverse of the variance. Heterogeneity was quantified by Z^2 and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A value of 0% indicates no heterogeneity. When statistically significant heterogeneity ($P < .05$) was observed, the results of the random-effects model are presented. When there was statistically significant heterogeneity in outcomes across studies, subgroup analyses according to the level of risk for bias and different geographic locations (ie, low-prevalence areas [Western countries, United States, Canada] versus high-prevalence areas [Mediterranean, African, and Asian countries]) were performed. In addition, the effect of outliers on the results was evaluated.

When in studies the term RAP was used, we considered it conform Apley's criteria,[15] when there was a reference to Apley or the definition used by the authors was almost similar in time spectrum to the definition proposed by Apley (ie, at least 3 discrete episodes of abdominal pain of sufficient severity to interrupt normal daily activities or performance over a period of not less than 3 months). When studies reported on "unspecified abdominal pain," "abdominal pain," "symptomatic patients," or "GI-referral patients" in relation to *H pylori* infection and thus not fulfilling Apley's criteria, we grouped these outcomes as unspecified abdominal pain (UAP).

RESULTS

In total, 1120 potentially relevant abstracts were identified. After removing duplicates, we were left with 880 unique abstracts. After screening all abstracts, 39 publications met our inclusion criteria and none of the exclusion criteria.[16–54] By searching the reference lists of previous review articles and included studies, we identified 1 additional study.[55] The interobserver agreement of the overall eligibility was $\kappa = 0.826$.

One study could not be retrieved and thus could not be included in our analysis.[49] After reading full-text articles, we excluded another article because the study population did not include children who were aged 0 to 18 years.[50] Finally, 38 articles were reviewed: 23 case-control studies,[16–35,53,54] 14 cross-sectional studies,[36–47,51,52] and 1 prospective cohort study.[48] Of 23 included case-control studies, 19 were hospital based[16,17,19–21,23–35,55], 3 were population-based,[18,53,54] and 1 was primary care based.[22] All cross-sectional studies were population based,[36–42,44–47,51,55] except for 1 that included children in whom infection was successfully eradicated previously.[43] The only included prospective cohort study was population based.[48]

Results of the Methodologic Quality Assessment

The 2 reviewers (L.A.A.S. and M.B.M.) initially agreed on 89.5% of all quality items scored. The interobserver agreement of the assessment of risk for bias was high ($\kappa = 0.789$).

Mean score of risk for bias of all 38 included studies was 6.03, ranging from 3.00 to 10.00. The mean quality score of case-control studies and cross-sectional studies separately was 5.35 (range: 3.00–10.00) vs 6.93 (range: 5.00–9.00), respectively. This difference was mainly caused by the lack of equal assessment of GI symptoms for both case patients and control subjects in 19 of 23 case-control studies, whereas all 14 cross-sectional studies used equal symptom assessment. Furthermore, 12 case-control studies did not draw case patients and control subjects from a population at the same risk for exposure, whereas the studied populations of all cross-sectional studies did. The only prospective cohort study scored 9 of 11 points.

In total 8 case-control studies,[17–19,22,28,29,30,53] 7 cross-sectional studies,[36,37,39,41,45,46,52] and the prospective cohort study[48] were categorized as having low risk for bias. The most prevalent shortcomings of case-control and cross-sectional studies were a lack of blinded assessment of GI symptoms and *H pylori* infection ($n = 31$), no use of multivariate analysis ($n = 27$), and that prognostic factors were not comparable at baseline and no correction for these factors was applied in the analysis ($n = 29$).

Prevalence of *H pylori*

The prevalence of *H pylori* in population-based cross-sectional studies ranged from 9.4% to 56.6% with a mean prevalence of 28.0% (SD: 16.2%). The prevalence in high-prevalence areas ($n = 8$) ranged from 15.8%[47] to 56.6%[36] with a mean prevalence of 37.0%. The prevalence in low-prevalence areas ($n = 6$) ranged from 9.4%[41] to 28.9%,[42] with a mean prevalence of 16.1%. The effect of different tests on the prevalence of *H pylori* could not be evaluated because a large diversity of (combinations of) diagnostic tests for *H pylori*

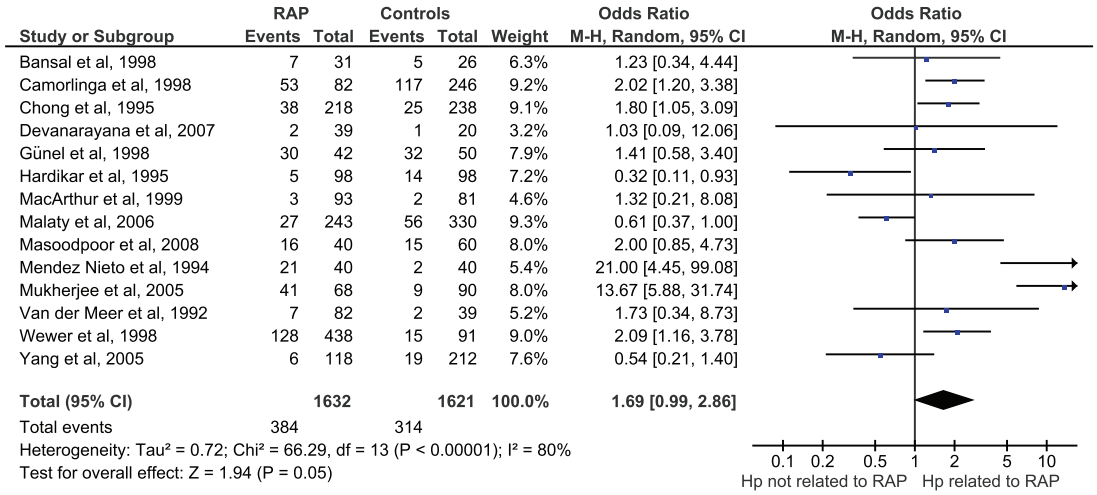

FIGURE 1
Meta-analysis of case-control studies concerning RAP related to *H pylori* infection. Events indicates number children with *H pylori* infection.

with different cutoff points were used, although the vast majority of studies included serology testing.

RAP and *H pylori*

Fourteen case-control studies, involving 3253 participants, reported on the relationship between RAP and *H pylori* infection in children.* Six had low risk for bias[17,18,22,26,30,53] and 8 had high risk for bias.[23,25,31–34,54,55] Figure 1 presents the meta-analysis of the OR of an *H pylori* infection given the presence of RAP. Because of statistically significant heterogeneity ($P < .00001$), the random-effects model is presented. The pooled OR for all case-control studies was 1.69 (95% CI: 0.99–2.86).

When we excluded the 2 outlier studies of Mendez Nieto et al[32] and Mukherjee et al.[34] the pooled OR became 1.21 (95% CI: 0.82–1.78), but statistical heterogeneity remained significant. In all additional analyses, the aforementioned outliers remained excluded. Evaluation of heterogeneity explained some of it but did not alter the estimated effect size.

Ten cross-sectional studies, involving 3980 participants, reported on the relation between RAP and *H pylori*. Four had low risk for bias[36,37,39,45] and 6 high risk.[38,42–44,47,51] However, the study of Ertem et al,[44] reporting an OR of 1.33, could not be pooled due to missing the pooled OR for the remaining studies was 1.69 (95% CI: 0.83–3.44; random effects-model; $P < .00001$; Fig 2). The studies of Leandro Liberato et al[47] and Telmesani[51] explained statistical heterogeneity; excluding these outliers resulted in a pooled OR of 1.00 (95% CI: 0.76–1.31; fixed model; $P = .60$). In additional analyses, these outliers remained excluded.

The pooled OR for the 4 studies with low risk for bias was 0.95 (95% CI: 0.66–1.37; fixed model; $P = .24$). The relationship between RAP and *H pylori* infection was not influenced by risk for bias, setting, or geographic location. Two case-control studies[22,30] and 2 cross-sectional studies[37,46] concerning RAP reported ORs adjusted for confounders (Tables 1 and 2) ; however, all adjusted ORs are comparable to the pooled unadjusted ORs presented and remained nonsignificant.

UAP and *H pylori*

Six hospital-based case-control studies[16,19,21,24,28,35] that included 3142 participants reported on the association between UAP and *H pylori* infection. Two studies with low risk for bias[19,28] and 4 with high risk[16,21,24,35] had a pooled OR of 2.87 (95% CI: 1.62–5.09; random-effects model; $P = .0001$; Fig 3). In the studies with low risk for bias only, the pooled OR was 1.66 (95% CI: 1.21–2.28; fixed model; $P = .23$). Pooling the 4 studies with high risk for bias resulted in a pooled OR of 4.69 (95% CI: 3.35–6.57; fixed model; $P = .36$).

Five population-based cross-sectional studies[36,37,39,41,52] that included 3251 participants and reported on UAP in children who were seen in primary care all had low risk for bias. The pooled OR was 0.99 (95% CI: 0.46–2.11; random-effects model; $P < .00001$; Fig 4).

Three studies, 1 hospital-based case-control study[16] and 2 population-based cross-sectional studies,[37,52] adjusted for confounders (Tables 1 and 2). The adjusted ORs were comparable to the pooled ORs presented.

Epigastric Pain and *H pylori*

Epigastric pain was evaluated in 2 case-control studies[18,20] and 1 cross-sectional study.[43] Because of the diversity of outcome definitions, we were not able to pool data. The population-based case-control study of Yang et al[18] had low risk for bias and included

*Refs 17, 18, 22, 23, 25, 26, 30–34, and 53–55.

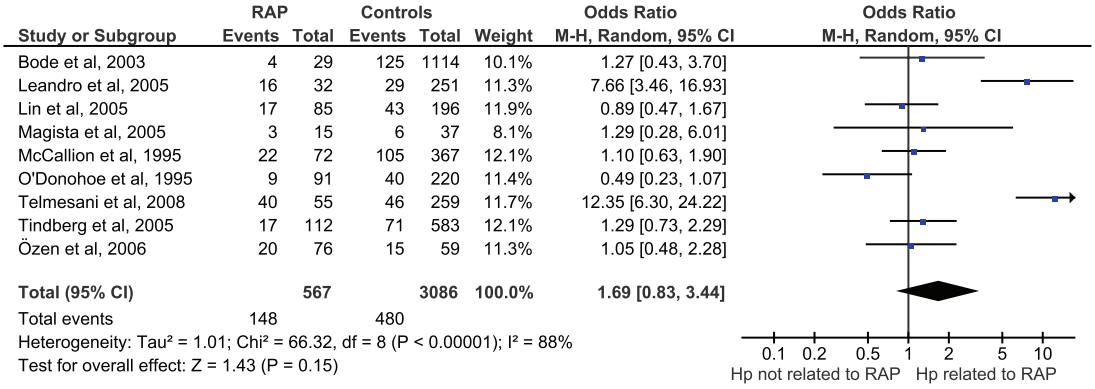

FIGURE 2
Meta-analysis of cross-sectional studies concerning RAP related to *H pylori* infection. Events indicates number children with *H pylori* infection.

253 participants. They reported on short-term recurrent abdominal pain (SRAP): abdominal pain that met Apley's criteria[15] but with a shorter duration in a range from 2 weeks to 3 months. The prevalence of *H pylori* infection was higher in children with SRAP than in healthy control subjects (OR: 3.4 [95% CI: 1.6–7.2]). They further assessed whether specific clinical presentations were associated with *H pylori* infection in the children with SRAP or RAP. Children who presented with abdominal pain in the epigastric area had a significantly higher prevalence of *H pylori* infection when they had SRAP but not when they had RAP; the OR could not be calculated with the available data.

The hospital-based case-control study of Ng et al[20] had high risk for bias. The study, which included 1088 participants, reported an OR of 2.03 (95% CI: 1.35–3.06) given the presence of epigastric pain. The OR of the 1 hospital-based cross-sectional study with high risk for bias[43] was 3.2 (95% CI: 0.77–13.35).

Diarrhea and *H pylori*

Two case-control studies[18,27] and 3 population-based cross-sectional studies[36,39,40] reported outcomes on the association between diarrhea and *H pylori* infection in children. One case-control study[18] and 2 cross-sectional studies[36,39] had low risk for bias. All studies that reported on diarrhea, except for the 1 by Bode et al,[39] were performed in high-prevalence areas. The pooled OR in case-control studies that included 365 participants, 1 of which was population based[18] and 1 of which was hospital based,[27] was 0.95 (95% CI: 0.47–1.90; fixed model; $P = .32$). In the cross-sectional studies that included 999 participants, the pooled OR was 0.70 (95% CI: 0.13–3.96; random-effects model; $P = .01$).

Vomiting and *H pylori*

Three population-based cross-sectional studies, all of which were at low risk for bias, included 2054 participants and investigated the association between vomiting and *H pylori* infection[36,39,52]; the pooled OR was 1.05 (95% CI: 0.40–2.75; random-effects model; $P = .0002$). Two studies[36,52] were performed in high-prevalence areas, and 1 study[39] was performed in low-prevalence areas.

Other Symptoms and *H pylori*

Several studies reported on various other GI symptoms, such as periumbilical pain,[18] flatus,[18] constipation,[18,37] nausea,[43] loose stools,[37] postprandial fullness,[18,43] halitosis,[43] dyspepsia,[29,36] and regurgitation,[37] but none of these symptoms was associated with *H pylori* infection.

The only prospective cohort study with a follow-up period from 6 months to 11 years[48] included 305 participants and had low risk for bias. The authors concluded that UAP during childhood was reported more often in children with *H pylori* seropositivity at some point during the study than for seronegative children (adjusted OR: 2.2 [95% CI: 1.0–4.4). Children who were seropositive at some point during the study more often reported RAP at 11 years of age than did seronegative children, but the difference was not statistically significant (OR adjusted for gender: 2.0 [95% CI: 0.8–4.6) (Table 3). Spontaneous clearance of *H pylori* infection was reported in 80% of previously infected children at the end of the study.

DISCUSSION

We found evidence for an association between UAP (ie, patients with abdominal pain, symptoms, or GI referral) and *H pylori* infection in referred children (pooled OR: 2.87 [95% CI: 1.62–5.09) but could not confirm this finding in children who were seen in primary care (pooled OR: 0.99 [95% CI: 0.46–2.11). Two studies[16,37] adjusted for known risk factors for *H pylori*, but this did not change this results. In addition, we found conflicting evidence for an

TABLE 1 Study Characteristics of Included Case-Control Studies

Source	Setting, Place, Country, Period	Case Patients	Control Subjects	Diagnostic Test Used for Determination of *H pylori* Infection (Cutoff Point)	OR (95% CI)	Quality Score
Daugule et al,[16] 2007	Diagnostic Centre of Riga, Latvia, 1998–2000	40 consecutive children with indication for upper GI endoscopy, age range 8–12 y, 39% male	55 asymptomatic children who visited their doctor for general checkup or minor health problems, aged 7–12, 55% male	Cases: RUT and/or culture positive Controls: 13C-UBT	UAP: 1.80 (0.62–5.14) (adjusted for age)	4
Malaty et al,[17] 2006	Pediatric Gastroenterology Clinic Texas Children's Hospital and 6 primary care pediatric clinics, Houston, TX, Jun 2001–Dec 2002	243 consecutive children referred with abdominal pain, age range 3–18 y, 40% male; excluded: children with chronic illness/other medical conditions	330 asymptomatic children attending 13 licensed child care centers in Houston, TX, aged 3–18 y, 45% male	Cases: 13C-UBT Controls: 13C-UBT (increase of 13C abundance of 10 μg of urea hydrolyzed per min)	RAP: 0.61 (9.37–1.00)	7
Yang et al,[18] 2005	Elementary school and associated preschool kindergarten, Tainan, Taiwan	178 children who fulfilled the criteria of RAP or SRAP (RAP during 2 wk–3 mo); age range 4–12 y, mean: 9.2 y, 52% male	212 age- and gender-matched, asymptomatic children from the same school	Cases: ELISA Controls: ELISA (absorbance index of >0.14)	RAP: 0.54 (0.21–1.40) SRAP: 3.39 (1.60–7.17)	7
Chong et al,[19] 2003	12 children's hospitals or medical centers throughout the United States, Jun 1996–Dec 1997	373 symptomatic GI referral children evaluated in a GI clinic for abdominal pain and vomiting, age range: 1–18 y, mean: 10.1 y, 48% male; excluded: children with intake of antibiotics, histamine-2 blockers, or proton pump inhibitors 1 mo before entering the study	618 children seen in a clinical setting, who required blood drawing as part of standard clinical management, without GI complaints age range: 2 mo–18 y, mean age: 7.7 y, 56% male	Cases: EIA Controls: EIA	Referred (symptomatic): 1.77 (1.27–2.47)	8
Ng et al,[20] 2003	National University Hospital, Singapore, Republic of Singapore	489 consecutive patients with epigastric pain; outpatient referrals to pediatric GI clinic, mean age: 8.5 ± 3.3 y, 46% male; excluded: children who used antibiotics within 4 wk of the study	599 schoolchildren participating in a seroepidemiologic survey of Dengue in the eastern part of Singapore, mean age: 9.0 ± 0.5 y	Cases: ELISA Controls: ELISA (2 SD above value for histology-confirmed negative sera)	Epigastric pain (spiral): 2.03 (1.35–3.06)	5
Plebani et al,[21] 1999	Pediatric Department, Padua University Hospital, Italy	183 consecutive symptomatic children who underwent upper GI endoscopy, age range: 1–16y, 43% male	921 randomly selected from those present at the second-degree schools of Padua, age range: 11–14 y, 53% male	Cases: at least histology positive Controls: anti–Hp-IgG	UAP: 4.98 (3.03–8.16)	3
MacArthur et al,[22] 1999	6 primary care pediatricians, Toronto, Canada	100 children presenting with RAP, age range: 5–15 y, mean: 9.0 ± 2.7 y, 37% male; excluded: children with concurrent disease, suspected organic disease, aged <5 y, or had used bismuth in the previous month	100 healthy children undergoing a routine checkup or vaccination, mean age: 10.0 ± 3.2 y, 57% male	Cases: serology and/or 13C-UBT Controls: serology and/or 13C-UBT	RAP: 0.65 (0.08–2.56) (adjustment not mentioned)	10
Günel et al,[23] 1998	Departments of Pediatric Surgery and Pediatrics, Konya, Turkey, during 12-mo period	42 children with RAP, age range 9–15 y, mean: 9.4 ± 3.2 y; excluded: if organic cause for RAP (eg, peptic disease, IBD, enzyme deficiencies) was found	50 healthy children attending routine day surgery, mean age: 9.65 ± 3.15 y	Cases: IgG antibody test Controls: IgG antibody test	RAP: 1.41 (0.58–3.40)	3
Blümel et al,[24] 1998	Kinderspital der Stadt Wien, Austria	31 children presenting with chronic abdominal pain >4 wk with negative stool culture, normal blood counts, and normal abdominal echo, age range: 6–14 y, mean: 10.51 y, 52% male	31 age- and nationality- matched asymptomatic children who were undergoing elective/acute surgery or outpatient children who received treatment for noninfectious diseases, mean age: 10.5 y	Cases: Hp IgG-AK (>3 SD above the mean of all negative tests) Controls: Hp IgG-AK	UAP: 2.52 (0.90–7.02)	5

TABLE 1 Continued

Source	Setting, Place, Country, Period	Case Patients	Control Subjects	Diagnostic Test Used for Determination of *H pylori* Infection (Cutoff Point)	OR (95% CI)	Quality Score
Bansal et al,[25] 1998	Kalawati Children Hospital, Division of Pediatric Gastroenterology and Nutrition, New Delhi, India	72 children referred with complaints of RAP; no organic cause was found after stool and urine examinations and a psychological evaluation; age range: 3–12 y, 55% male	26 age- and gender-matched children with complaints other than those related to the GI tract, age range: 3–14 y	Cases: RUT and/or histology positive Controls: serology (Hp-IgG >20 U/mL)	RAP: 1.23 (0.34–4.44)	3
Wewer et al,[26] 1998	Hvidovre Hospital, University of Copenhagen, Denmark	450 children with RAP with no other obvious causes of RAP, age range 3.1–17.0 y, mean: 9.0 y, 40% male	93 children admitted for minor elective surgery, otherwise in good health and did not suffer from GI complaints, age range: 3–15 y, mean age: 6.3 y, 82% male	Cases: ELISA (>200 EU) and Western blot positive Controls: ELISA and Western blot positive	RAP (Western blot): 2.36 (1.14–4.87) RAP (ELISA): 2.09 (1.16–3.78)	7
Kehrt et al,[27] 1997	Health Center, Tipitapa, Nicaragua, Sep 1993–Dec 1993	59 children with persistent diarrhea recruited from the URO of the health center with no history of antibiotic use in the previous month, age range: 2–56 mo, 53% male	64 randomly selected age-matched asymptomatic children referred from pediatricians of the center, age range: 1–65 mo, 41% male	Cases: 13C-UBT (13C/12C ratio at 60 min ≥3‰ over baseline) Controls: 13C-UBT	Persistent diarrhea: 0.75 (0.32–1.74)	6
Ozturk et al,[28] 1996	Day Surgery Clinic, Hacettepe University Children's Hospital, Ankara, Turkey, Mar 1993–Jun 1993	29 children who had GI symptoms and reported to the day surgery clinic, the latter for minor outpatient surgical procedures of non-GI origin, age range: 1–17, 59% male; excluded: children who used antibiotics, Bismuth-containing compounds, NSAIDs, or antacids during preceding 2 mo	32 children without GI symptoms who reported to the day surgery clinic, the latter for minor outpatient surgical of non-GI origin, age range: 1–17 y, 81% male	Cases: at least 2 of 4 following tests positive: serology, RUT, histology, bacterial culture Controls: at least 2 of 4 following tests positive: serology, RUT, histology, bacterial culture	UAP: 0.93 (0.34–2.55)	7
Gurakan et al,[29] 1996	Pediatric Gastroenterology Unit, Ankara, Turkey, Nov 1993–May 1994	59 children referred for evaluation of epigastric or periumbilical pain and/or nausea, vomiting, or regurgitation for at least 1 mo, age range: 5–17 y, mean: 11.1 ± 3.4, 53% male; excluded: use of antibiotics, H2-antagonists, Bismuth-salt 1 mo before serologic examination	48 children who were seen in the outpatient clinics for non-GI complaints, age range: 5–17 y, mean age: 10.73 ± 3.63, 50% male	Cases: serology (IgG >2 SD above the mean of all negative titers: OD units at 450 nm) Controls: serology	Dyspepsia: 1.55 (0.72–3.34)	6
Hardikar et al,[30] 1996	RAP Clinic at Royal Children's Hospital, Melbourne, Australia, Feb 1990–Feb 1991	111 children between 5 and 12 y who had RAP and had not been seen previously by a pediatrician or subspecialist, mean age: 8.5 ± 2.1 y, 33% male	103 consecutive children between 5 and 12 y attending day surgery unit for common surgical disorders, otherwise in good health and without GI symptoms, mean age: 7.7 ± 2.1 y, 74% male	Cases: IgG antibody test (8 U of anti-Hp IgG/mL) Controls: IgG antibody test	RAP: 0.21 (0.05–0.85) (adjusted for gender, age, and parental ethnicity and occupation)	7
Chong et al,[31] 1995	GI Disease Outpatient Clinic, J Whitcomb, Riley Hospital for Children, Indiana University, IN, Jan 1991–Dec 1993	218 children who fulfilled criteria of RAP and were seen in the GI disease outpatient clinic (RAP group), age range: 3–18 y, mean age: 9.5 y, 49% male	238 children, not fulfilling criteria of RAP, who were seen in the GI disease outpatient clinic (non-RAP group) age range: 3–18 y, mean age: 9.8 y, 55% male	Cases: serology Controls: serology	RAP: 1.80 (1.05–3.10)	5
Mendez Nieto et al,[32] 1994	Gastroenterology Department, National Pediatric Institute of Mexico, Jan–Jun 1993	40 children referred for recurrent abdominal pain, age range 5–18 y, mean age: 10.3 y	40 healthy children without GI complaints	Cases: histology and rapid urease test Controls: ELISA (OD of 2 SD of the mean of healthy children)	RAP: 21.00 (4.45–99.08)	3

TABLE 1 Continued

Source	Setting, Place, Country, Period	Case Patients	Control Subjects	Diagnostic Test Used for Determination of *H pylori* Infection (Cutoff Point)	OR (95% CI)	Quality Score
van der Meer et al,[33] 1992	Academic Hospital Maastricht, Netherlands, during 6-mo period	82 children between 5.5 and 12.0 y, with at least a 6-mo period of RAP of unknown origin, attacks of pain varying in severity, duration, and frequency, sometimes accompanied by vegetative symptoms such as paleness, nausea, or vomiting, mean age: 10.8 y, 34% male	39 preoperative children or children attending the outpatient clinics for other than GI diseases, mean age: 6.6 y, 64% male	Cases: ELISA (1.40 OD units) Controls: ELISA	RAP: 1.70 (0.34–8.73)	4
Mukherjee et al,[34] 2005	Outpatient Department of a teaching hospital, Punjab, India	68 children >3 y of age attending the outpatient department of a teaching hospital because of RAP with no obvious cause of pain, age range: 3–12 y, 52% male	90 normal control subjects, age range: 3–12 y, 74% male	Cases: IgG antibody test Controls: IgG antibody test	RAP: 13.67 (5.88–31.70)	5
Sedlackova et al,[35] 2003	Hospital in Morvia, Czech Republic, 1994–1999	829 children between 2 and 18 y, who were referred for GI endoscopy because of RAP and/or dyspepsia	205 Age-, gender-, and SES-matched children attending the hospital in Morvia for other reasons than GI complaints	Cases: serology Controls: serology	Unspecified (symptomatic): 6.20	4
Camorlinga et al,[55] 1998	National Medical Center of the Instituto Mexicano del Seguro Royal, Mexico City, Mexico, Jan 1995–Sep 1996	82 consecutive children seeking medical attention because of RAP, age range: 1–17 y, mean age infected cases: 9.1 ± 3.9 y, 42% male; excluded: children who received antibiotics, H2 blockers, or proton pump inhibitors during the previous 30 d	246 age- and gender-matched, asymptomatic patients selected using a master sampling frame based on general population census data, age range: 2–17 y, mean age infected controls: 10.6 ± 3.7 y, 35% male	Cases: ELISA (mean value >3 SD of the OD of 30 uninfected patients) Controls: ELISA	RAP: 2.02 (1.20–3.38)	3
Masoodpoor et al,[53] 2008	Guidance schools in Rafsanjan City, Iran, Jan 2006–Jan 2007	40 children fulfilling criteria of RAP, attending the guidance school, mean age: 12.7 ± 1.0 y, 50% male; excluded: children who received antibiotic treatment, H2 blockers, or proton pump inhibitors before entering study	60 randomly selected, age-, school-, and gender-matched healthy children who had no clinical manifestations of RAP and were normal on physical examination, mean age: 12.9 ± 1.1 y, 50% male	Cases: HpSA ELISA stool antigen test (an absorbance at 450/630 of ≥0.120) Controls: HpSA ELISA stool antigen test	RAP: 2.00 (0.85–4.73)	7
Devanarayana et al,[54] 2007	School in Gampaha District of Sri Lanka	55 children identified as fulfilling criteria of RAP were recruited during a school survey, mean age: 7.9 ± 3 y, age range: 5–15 y, 41% male; excluded: children who received antibiotics, acid suppression, or anti–*H pylori* therapy within 3 mo before inclusion	20 healthy children recruited from the same area, mean age: 9.0 ± 2.7 y, age range: 5–15 y, 50% male	Cases: Microwell-based EIA that detected *H pylori* antigens in stool (absorbance value ≥190)Controls: antigens in stool	RAP: 1.03 (0.09–12.00)	4

RUT indicates rapid urease test; 13C-UBT, 13C-urea breath test; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; SES, socioeconomic status; IBD, irritable bowel syndrome; URO, oral rehydration unit; NSAID, nonsteroidal anti-inflammatory drug; OD, optic density.

TABLE 2 Study Characteristics of Included Cross-Sectional Studies

Source	Setting, Place, Country, Period	Study Population	Diagnostic Test Used for Determination of *H pylori* Infection (Cutoff Point)	*N* (Prevalence)	OR (95% CI)	Quality Score
Özen et al,[36] 2006	Preschools and schools, Turkey, 2004	136 children who participated in a previous study (Ertem et al), mean age: 13.45 ± 1.90 y, range: 8–17 y, 47% male	13C-UBT (a change in the 13C value over baseline of >5 ‰)	136 (56.6%)	RAP: 1.05 (0.48–2.28) UAP: 0.49 (0.17–1.38) Vomiting/diarrhea: 1.80 (0.68–4.74) Dyspepsia: 1.06 (0.44–2.51)	9
Tindberg et al,[37] 2005	11 local public schools in Stockholm, Sweden, Jan 1998	695 children, between 10 and 12 y, attending 1 of the participating local public schools, mean age: 11.2 ± 1.0 y, range: 9–13 y, 48% male	Positive if ELISA (>0.22 OD value) positive and at least 1 of 2 of the following tests was positive: immunoblot (CagA >116 kDa, VacA >89 kDa), 13C-UBT	695 (16.1%)	RAP: 1.00 (0.50–2.10) UAP: 0.50 (0.30–0.80) Regurgitation: 0.50 (0.30–0.90) Constipation: 0.70 (0.40–1.50) Weekly AP: 1.50 (0.70–3.30) Loose stools: 0.90 (0.50–1.60) (adjusted for age, gender, SES, family size, and immigrant background)	8
Lin et al,[38] 2005	1 primary school, Danshuei, Taipei, Taiwan, 2003	289 randomly selected grades 1 to 6 primary school students who volunteered for blood-tests for *H pylori* IgG and anti–hepatitis A antibody, mean age: 9.21, 51% male	ELISA	289 (21.5%)	RAP: 0.89 (0.47–1.67)	6
Bode et al,[39] 1998	Schools in Ulm, Southern Germany, 1996	945 preschool children, aged 5–8, who were examined for school fitness by the Public Health Service, mean age: 5.84 y, range: 5–8 y, 50% male; excluded: children who received antibiotic treatment within the last 4 wk	13C-UBT (difference between baseline 13CO2/12CO2 ratio and 30 min ratio >5‰)	945 (13.7%)	UAP: 0.48 (0.33–0.72) Vomiting: 0.45 (0.29–0.72) Diarrhea: 0.31 (0.20–0.48)	8
Rahman et al,[40] 1998	Periurban community adjacent to the capital city of Bangladesh, Jan–Oct 1993	151 children who were free from systemic infection causing diarrhea, respiratory infection, and other infections at time of enrollment, mean age Hp pos: 8.9 ± 7.0 mo, Hp neg: 9.9 ± 6.7, range: 1–23 mo, 50% male	13C-UBT (the excess over baseline value of 13CO2 was expressed as parts per thousand (Δ %); a cutoff point of 5 in the ratio was regarded as positive)	151 (45.0%)	Diarrhea: (after 1 mo): 0.91 (0.20–4.22) Diarrhea (after 6 mo): 1.08 (0.56–2.09)	6
Grimm et al,[41] 2003	Schools in Aschaffenburg and surroundings, Germany, school year 1997/1998	540 schoolchildren, aged 7–9, 11–15, and 16–20, who voluntarily took part, age range: 7–20 y, 46% male	13C-UBT (the DOB values were elevated above 3.5‰)	540 Prevalence = 9.4	UAP: 5.43 (2.64–11.13)	7
McCallion et al,[42] 1995	Royal Belfast Hospital for Sick Children, Ireland, during 6-mo period	439 children attending for routine day surgery, mean age: 7.3 y, range: 4–13 y	ELISA	439 (28.9%)	RAP: 1.10 (0.63–1.90)	6
Magista et al,[43] 2005	Department of Pediatric Gastroenterology, University of Bari, Italy, 1998–2000	52 children in whom infection was successfully eradicated previously, mean age: 12 y, range: 4.9–19.0 y, 52% male	Positive when all 3 tests were positive: 13C-UBT (change of 3.5 per thousand or more related to baseline signal), RUT, and histology	52 (28.8%)	Epigastric pain: 3.20 (0.77–13.35) Nausea: 4.38 (0.65–29.40) RAP: 1.29 (0.28–6.01) Halitosis: (4.28 (0.65–29.40) Postprandial fullness: 1.27 (0.21–7.79)	6

TABLE 2 Continued

Source	Setting, Place, Country, Period	Study Population	Diagnostic Test Used for Determination of *H pylori* Infection (Cutoff Point)	*N* (Prevalence)	OR (95% CI)	Quality Score
Ertem et al,[44] 2003	Preschools and schools, Turkey	327 preschool and school-aged healthy children, mean age: 8.2 ± 2.1 y, range: 3–12 y, 52% male; excluded: children who received oral or parenteral antibiotics within 4 wk before the investigation	13C-UBT (a change in the 13C value over baseline of >5‰)	327 (49.5%)	RAP: 1.33 (95% CI could not be calculated)	5
O'Donohoe et al,[45] 1995	7 schools in 1 central London District, England	640 state school and private school children who voluntarily participated, mean age: 9.15 y, range: 4–13 y, 60% male	IgG ELISA (10 U/mL)	640 (16.7%)	RAP: 0.49 (0.23–1.07)	7
Bode et al,[46] 2003	Schools in Ulm, Erbach, and Ehingen, south Germany, Jan–Jul 1997	1143 preschool children aged 5–8 y who were to attend first grade and underwent an school fitness examination by the Public Health Service, mean age: 5.88 y, range: 5–8 y, 49% male; excluded: children who used antibiotics within the past 4 wk	13C-UBT (a change of the 13C value over baseline of >5‰)	1143 (11.3%)	RAP: 1.60 (0.50–5.55) (adjusted for nationality, single-parent household, history of peptic ulcers of parents, and history of GI disorders of parents)	8
Leandro et al,[47] 2005	Health care center, Foral de Navarra, Spain, Jan 2003–Mar 2004	Random sample of children aged 1–14 y, visiting a regular health care program, mean age: 6.89 ± 4.25 y, 50.7% male; excluded: antibiotics in past month, previous eradication therapy for *H pylori*, chronic disease	EIA for fecal *H pylori* antigen; at 450 nm positive at DO >0.160, negative at DO <0.140	284 (15.8% overall) 1–3 y: 8.4% 4–9 y: 13.9% 10–14 y: 24% ($P < .05$)	RAP: 7.66 (3.46–16.93)	6
Telmesani,[51] 2008	Boys' school in Makkah City, Makkah Region, Western Saudi Arabia	314 boys, 103 of whom in intermediate level and 211 of whom in secondary level, age range: 12–18 y, 100% male; excluded: recent use of antibiotics or allergy toward the test material	14C-UBT (results calculated using grades 0, not infected; 1, borderline; 2, infected; borderline results required a repeat test)	314 (27.4%)	RAP: 12.35 (6.30–24.22)	6
Siai et al,[52] 2008	Schools in the Cap-Bon region, Nabeul Governorship, Tunesia	1055 randomly selected (1st, 10th, 20th, etc) first-grade primary school children belonging to the recruitment populations of 13 health care centers' databases, 813 children of 6 y, 242 children of 7 y, 49.9% male	IgG ELISA	1055 (51.4%)	UAP: 1.45 (1.01–2.50) (adjusted for household members >5, bottle weaning >18 mo plate/bed-sharing, SES, abdominal pain, vomiting) Vomiting: 1.63 (1.04–2.54)	9

ELISA indicates enzyme-linked immunosorbent assay; OD, optic density; DOB, delta over baseline.

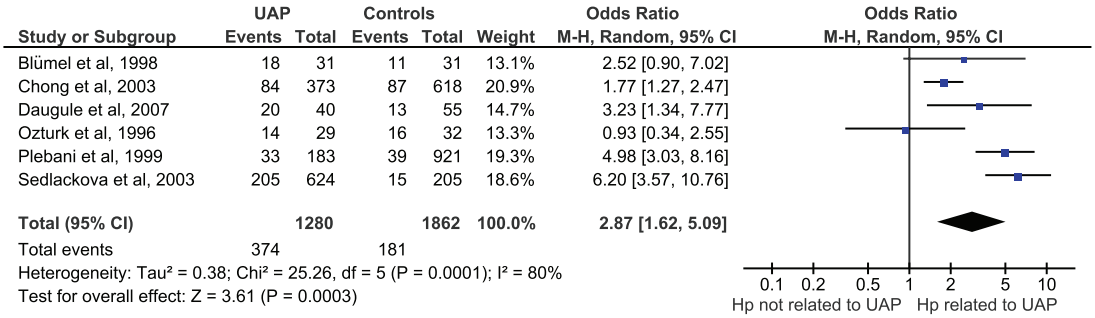

FIGURE 3
Meta-analysis of case-control studies concerning UAP related to *H pylori* infection. Events indicates number children with *H pylori* infection.

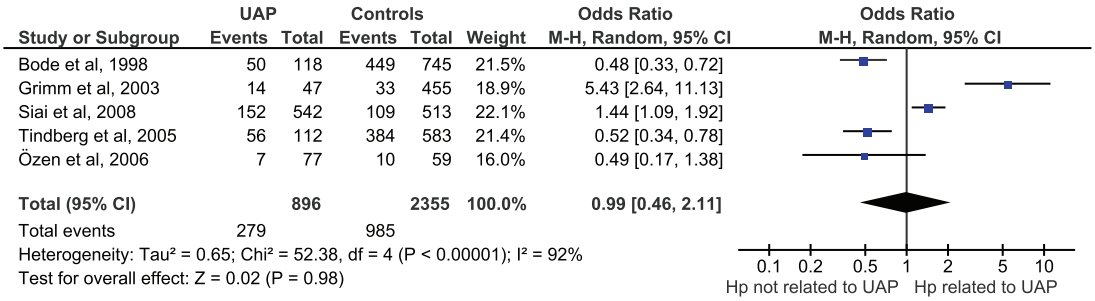

FIGURE 4
Meta-analysis of cross-sectional studies concerning UAP related to *H pylori* infection. Events indicates number children with *H pylori* infection.

TABLE 3 Study Characteristics of Included Prospective Cohort Study

Source	Setting, Place, Country, Period	Study Population	Diagnostic Test Used for Determination of *H pylori* Infection (Cutoff Point)	Patients Lost to Follow-up, %	OR (95% CI)	Quality Score
Tindberg et al,[48] 1999	Vaccine trial, Southern part of Sweden, Stockholm, 1984–1995	305 children, born in 1984, who participated in a pertussis vaccine trial, starting at 6 mo to 11 y; mean age at end of follow-up: 10.9 y (range: 10.5–12.3 y)	ELISA (0.360 [A405 nm]), measured at 6 mo, 8 mo, 10 mo, 18 mo, 2 y, 4 y, and 11 y	Blood samples from 6 to 18 mo of age and at least 1 additional serum sample drawn at 2, 4, or 11 y of age were available from 294 children; lost to follow-up: 11 (3.6%)	RAP (during last 6 mo): 2.0 (0.8–4.6) UAP (during childhood): 1.4 (0.7–2.9) UAP (last 6 mo): 2.2 (1.2–4.7)	9

ELISA indicates enzyme-linked immunosorbent assay.

association between epigastric pain and *H pylori* infection. In total, 2 of 3 studies showed a statistically significant association between epigastric pain and *H pylori* infection. This finding was independent of setting. Furthermore, there is strong evidence that RAP is not related to *H pylori*.

The European Pediatric Task Force[4] concluded in their guidelines on management of *H pylori* infection that, in children, *H pylori* infection is not related to GI symptoms. Our findings contradict this assumption but are in agreement with findings in adults, for whom dyspepsia is thought to be caused by *H pylori*. Our findings partially support the Consensus Report of The European *Helicobacter* Study Group; they reported that RAP is not an indication for a test-and-treat strategy for *H pylori* infection in children; however, children with upper GI symptoms should be tested after exclusion of other causes of the symptoms.[6]

The finding for an association between UAP and *H pylori* infection in referred children but not in children who were seen in primary care is in agreement with our finding of evidence that RAP and *H pylori* are not related. Abdominal pain in a child who sees a general practitioner (GP) has a different differential diagnosis than abdominal pain in a child who is seen in secondary care. Abdominal pain in primary care more often will be functional. In a setting where a symptom is dominantly related to functional disease, an association between the symptom and a low-prevalent disorder might be too weak to detect. In addition, a GP will

refer only children in whom he suspects underlying disease; therefore, in referred children, the same symptom is more likely to be related to a potential pathogen such as *H pylori*.

RAP as defined by Apley and Naish[15] is thought to be related to functional disease and should therefore theoretically preclude *H pylori*. We found no evidence for any relation between RAP by Apley and Naish and *H pylori* infection in children in both case-control studies (OR: 1.21 [95% CI: 0.82–1.78) and cross-sectional studies (OR: 1.00 [95% CI: 0.76–1.31). Subgroup analyses of RAP in different settings, high-quality studies, and different geographic locations did not alter this finding. In low-quality case-control studies, the association between RAP and *H pylori* was clinically and statistically significant (OR: 2.68 [95% CI: 1.47–4.89); however, we believe that this OR is overestimated because of a biased selection of control subjects. Whereas in 4 of 5 high-quality studies case patients and control subjects were drawn from a population at a comparable risk for exposure (ie, *H pylori* infection), this was not the case in all of the low-quality studies. The ORs suggest a selection of control subjects in whom not only GI symptoms but also *H pylori* infection was precluded. This might have seriously biased these outcomes.

After excluding the outlier studies of Leandro Liberato et al[47] and Telmesani,[51] the pooled OR of cross-sectional studies that evaluated the relation between RAP and *H pylori* was 1.00 (95% CI: 0.76–1.31). This finding underlines the absence of a relation between RAP and *H pylori* infection in children as found in the case-control studies. On the basis of the data presented, we could not explain the outlying results of the study of Leandro Liberato et al[47] and Telmesani.[51]

RAP is mainly defined by the duration of abdominal pain. We assume that selecting children with RAP is more than a selection that is based on duration of abdominal pain alone. Selection of children with RAP will implicitly comprise the belief of the primary care clinician that RAP in the long-term does not affect growth and that development of the child will be functional and that in referred children it will comprise the (negative) results of previous investigations. Because of these implicit selection criteria, we assume that the included children with RAP will be at high risk for functional disease. None of these selection mechanisms, however, was described in the studies on RAP that were included in this review. That duration of pain may preclude underlying disorders as a result of the aforementioned mechanisms is affirmed by the findings of Yang et al.[18] That population-based study reported a statistically significant association between SRAP (ie, abdominal pain that met the criteria of Apley and Naish[15] but with a shorter duration in range from 2 weeks to 3 months) in the epigastric region and *H pylori* infection.

To our knowledge, this is the first published review to investigate the association between GI symptoms in general and *H pylori* infection in children. The results of our review concerning RAP are consistent with 2 previous systematic reviews that reported no obvious association between RAP and *H pylori* infection in children.[8,9]

Although our literature search was comprehensive, some published and unpublished studies may have been missed. Also, some information pertinent to the review and collected by the reviewers may not have been provided in the journal article, although we contacted first authors to request missing data with variable success.

Cautious interpretation of pooled ORs is necessary because we found a large statistical and clinical heterogeneity between studies and an overall poor methodologic quality. Using a best evidence synthesis to summarize the data could overcome these problems, but limited data exist on best evidence syntheses for observational studies, and the possibility of misclassifying the results of studies with a small sample size is large.

We found that children who are referred to a gastroenterologist with UAP or pain in the epigastric region in general are at two- to threefold higher risk for *H pylori* infection than children without these symptoms. Because we are not aware of the criteria on which a GP decides to refer a child with abdominal pain to a pediatric gastroenterologist, a more specific clinical picture has yet to be established. Whether to screen systematically referred children with abdominal (epigastric) pain depends on effectiveness and adverse effects of eradication therapy. No optimal treatment has yet been defined.

To confirm, disclaim, or specify our findings on UAP and epigastric pain, additional research is necessary. If there is an association between these symptoms and *H pylori* infection, then treating and thus eradicating *H pylori* must lead to improvement or disappearance of symptoms. Randomized, placebo-controlled, double-blind trials with minimal loss to follow-up and standardized and validated outcome measures are needed. To our knowledge, no such trial has been published.

CONCLUSIONS

There is no association between RAP and *H pylori* infection in children; therefore, screening children with this classical symptom is not warranted, regardless of setting and geographic location. Furthermore, all other GI symptoms investigated in primary care–based or population-based studies, except for epigastric pain, were not associated with *H*

pylori infection in children; therefore, we postulate that as long as no typical clinical picture of a child with *H pylori* infection has been established and treatment effectiveness is not known, referral to a subspecialist for this matter is not recommended.

Furthermore we postulate that UAP in a hospital-based setting and epigastric pain in general might be associated with an (acute) *H pylori* infection. Data reporting on epigastric pain, however, were limited, so additional research to investigate this association is needed.

APPENDIX 1: SEARCH STRATEGIES

Medline search, 27th of July 2009 — 608 results

(epidemiologic-studies OR case-control OR cohort OR follow-up OR longitudinal OR prospective OR retrospective OR cross-sectional) AND (helicobacter pylori OR campylobacter) AND ("Signs and Symptoms, Digestive"[mesh] OR abdominal pain OR dyspepsia) AND (infant OR infant* OR child OR child* OR adolescent OR adolescen*)

Embase search, 27th of July 2009 — 512 results

(('epidemiologic studies'/exp OR 'epidemiologic studies') OR 'cross-sectional study' OR 'case control study' OR 'cohort analysis' OR ('follow up'/exp OR 'follow up') OR longitudinal OR prospective OR retrospective) AND (('helicobacter pylori'/exp OR 'helicobacter pylori') OR ('campylobacter'/exp OR 'campylobacter')) AND (('gastrointestinal symptom'/exp OR 'signs and symptoms, digestive') OR ('abdominal pain'/exp OR 'abdominal pain') OR ('dyspepsia'/exp OR 'dyspepsia')) AND (('infant'/exp OR 'infant') OR infant* OR ('child'/exp OR 'child') OR child* OR ('adolescent'/exp OR 'adolescent') OR adolescen*)

APPENDIX 2: EXPLANATION OF CRITERIA

Scored by:	**MB / YvL / LS / MM**

General
Article number:
Author:
Type of study: **Case control study / Cross-sectional study**

The criteria were adapted from Altman et al. (2001), Lievense et al. (2001), Hayden et al. (2006) and the STROBE Statement (2007) and were modified to cover the topic of this review.

	Criteria	**Score** ′+′=*1* ′-′ or ‘?′= 0
Study population	**1.** Study groups are clearly described (symptoms/no symptoms and duration/frequency of symptoms)	+ / - / ?
	2. Baseline study sample is described for key-characteristics	+ / - / ?
	3. Place of recruitment is clearly defined	+ / - / ?
Helicobacter pylori	**4.** Assessment of H. pylori was measured identically in both cases and controls	+ / - / ?
	5. Assessment of H. pylori diagnostics was blinded for knowledge of gastrointestinal symptoms and vice versa	+ / - / ?
Gastrointestinal symptoms	**6.** Assessment of gastrointestinal symptoms was equal for both cases and controls	+ / - / ?
Study design	**7.** Cases and controls drawn from a population at the same risk of exposure*	+ / - / ?
Analysis and data presentation	**8.** Data presentation: description of association (*see: explanation of criteria*) and measure of precision	+ / - / ?
	9. A multivariate model is used in the analysis	+ / - / ?
	10. Confounders are comparable at baseline, adjusted for in the analysis or study design	+ / - / ?
	Total Score (10 points maximum)	……

* *only applicable on case-control designed studies*

Explanation of criteria: Case control study/Cross-sectional study

Study population

1. Positive if the presence or absence of gastrointestinal symptoms in studied population, the duration/frequency of symptoms and the presence or absence of H. pylori at baseline are clearly described.

2. Positive if three out of five important key-characteristics are described for the baseline study sample:

a. Age (mean with standard deviation, CI or range)
b. Sex (percentage boys vs. girls)
c. Social Economic Status (SES)
d. Ethnicity
e. Use of antibiotics and anti-reflux medication

3. Positive if is described:

- what setting patients were recruited from (i.e general practice, hospital)
- what geographic location patients were recruited from

Helicobacter pylori

4. Positive if H. pylori infection was measured identically in the studied population

5. Positive if assessment of H. pylori diagnostics was blinded for knowledge of gastrointestinal symptoms and vice versa.

Gastrointestinal symptoms

6. Positive if assessment of gastrointestinal symptoms was equal for all cohort participants (for example by using a standard questionnaire or a detailed history).

Study design

7. Cases and controls drawn from a population at the same risk of exposure.

Analysis and data presentation

8. Positive if the association was expressed in percentages or means with SD, or in OR/RR with 95%-confidence interval.

9. Positive if a multivariate analysis model was used.

10. Positive if:

- Confounders are comparable at baseline

OR

- Most important confounders (at least two out of age, ethnicity and SES) were investigated and if necessary adjusted for with 95% confidence intervals.

Scored by:	MB / YvL / LS / MM

General	
Article number:	
Author:	
Type of study:	**Prospective cohort study**

The criteria were adapted from Lievense et al. (2001), Altman et al. (2001), Hayden et al. (2006) and the STROBE Statement (2007) and were modified to cover the topic of this review.

	Criteria	Score ′+′=1 ′-′ or ‘?′= 0
Study population	**1.** Study groups are clearly described (symptoms/no symptoms and duration/frequency of symptoms)	+ / - / ?
	2. Baseline study sample is described for key-characteristics	+ / - / ?
	3. Place of recruitment is clearly defined	+ / - / ?
Helicobacter pylori	**4.** Assessment of H. pylori was measured identically in all cohort participants	+ / - / ?
	5. Assessment of H. pylori diagnostics was blinded for knowledge of gastrointestinal symptoms and vice versa	+ / - / ?
Gastrointestinal symptoms	**6.** Assessment of gastrointestinal symptoms was equal for all cohort participants	+ / - / ?
Study design	**7.** Follow-up period ≥ 6 months*	+ / - / ?
	8. Is the loss to follow-up ≤ 20% and not different from patients not lost to follow-up *	+ / - / ?
Analysis and data presentation	**9.** Data presentation: description of association (*see: explanation of criteria*) and measure of precision	+ / - / ?
	10. A multivariate model is used in the analysis	+ / - / ?
	11. Confounders are comparable at baseline, adjusted for in the analysis or study design	+ / - / ?
	Total Score (11 points maximum)	…….

* *only applicable to cohort designed studies*

Explanation of criteria: Prospective cohort study

Study population

1. Positive if the presence or absence of gastrointestinal symptoms in studied population, the duration/frequency of symptoms and the presence or absence of H. pylori at baseline are clearly described.

2. Positive if three out of five important key-characteristics are described for the baseline study sample:

a. Age (mean with standard deviation, CI or range)
b. Sex (percentage boys vs. girls)
c. Social Economic Status (SES)
d. Ethnicity
e. Use of antibiotics and anti-reflux medication

3. Positive if is described:

- what setting patients were recruited from (i.e general practice, hospital)
- what geographic location patients were recruited from

Helicobacter pylori

4. Positive if H. pylori infection was measured identically in the studied population

5. Positive if assessment of H. pylori diagnostics was blinded for knowledge of gastrointestinal symptoms and vice versa.

Gastrointestinal symptoms

6. Positive if assessment of gastrointestinal symptoms was equal for all cohort participants (for example by using a standard questionnaire or a detailed history).

Study design

7. Positive if the follow-up period was ≥ 6 months.

8. Positive if the loss to follow-up was ≤ 20 % and not different from patients not lost to follow-up.

Analysis and data presentation

9. Positive if the association was expressed in percentages or means with SD, or in OR/RR with 95%-confidence interval.

10. Positive if a multivariate analysis model was used.

11. Positive if:

- Confounders are comparable at baseline

OR

- Most important confounders (at least two out of age, ethnicity and SES) were investigated and if necessary adjusted for with 95% confidence intervals.

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