Is *Helicobacter pylori* infection associated with Henoch-Schonlein purpura in Chinese children? a meta-analysis

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Background: **The prevalence of *Helicobacter pylori* (*H. pylori*) infection is high in China. It not only causes the damage of gastric epithelium, but also plays a potential pathogenic role in several extraintestinal diseases. Henoch-Schonlein purpura (HSP) is one of the most common vasculitis syndromes affecting children. Although its cause is unclear, HSP is often considered to be associated with infectious agents. This meta-analysis of previously published studies was conducted using a predefined protocol to evaluate the underlying association between *H. pylori* infection and HSP in Chinese children.**

Methods: **Predefined search strategy and inclusion criteria were set up to select studies reporting the prevalence of *H. pylori* infection among HSP children and control groups. Included studies were subjected to quality assessment and data extraction by two independent reviewers. The pooled odds ratio (OR) was calculated as the effect size via both traditional and cumulative meta-analysis. Heterogeneity was investigated by subgroup analysis, and the nonparametric "trim and fill" method was performed to adjust the overall estimate for the existence of publication bias.**

Results: **Ten eligible studies covering 749 HSP children and 560 controls were included for meta-analysis. Observational epidemiology studies clearly aimed at detecting the potential association between *H. pylori* infection and HSP with retrospective data collection from the children enrolled consecutively. Overall, 49.27% (369/749) of HSP children had evidence of *H. pylori* infection compared with 23.39% (131/560) of children in the control group. The pooled OR of *H. pylori* infection in HSP children (10 studies with 749 HSP children) was 3.80 [95% confidence interval (CI): 2.54-5.68, *P*<0.001], and the overall estimate from the cumulative meta-analysis confirmed the association with more narrow confidence interval (OR=3.35, 95% CI: 2.95-3.81). In HSP children mainly with abdominal manifestations (8 studies with 337 HSP children), the pooled OR was 4.62 (95% CI: 2.66-8.01, *P*<0.001). The adjusted pooled OR was 2.04 (95% CI: 1.48-2.82, *P*<0.001), determined by the nonparametric "trim-and-fill" method for eliminating the effect of publication bias. *H. pylori* eradication therapy (4 studies with 266 HSP children) was capable of reducing the recurrence of HSP (RR=0.38, 95% CI: 0.25-0.58, *P*<0.001). Although the subgroup analysis for heterogeneity suggested that diagnostic methods and geographical diversity might be account for the heterogeneity, statistical analysis of differences revealed no differences between subgroups, indicating their limited impact on the overall estimates.**

Conclusions: **These results suggest the necessity of screening *H. pylori* infection in HSP children, particularly in those with gastrointestinal manifestations in China. Eradication therapy may reduce the recurrence of HSP in children with *H. pylori* infection. However, further mechanistic and more clinical studies in different populations and regions are needed to confirm this association and the effect of eradication of *H. pylori* in HSP children.**

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Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative spiral, flagellated and microaerophilic bacterium, which colonizes human gastric mucosa as a significant factor involved in the pathogenesis

of various upper gastrointestinal diseases. Frequent clinical diagnosis tests for detecting *H. pylori* infection in children include rapid urea test (RUT), urea breath test (UBT), stool antigen test and serological test. Standard triple composed of proton pump inhibitors (PPI), clarithromycin and amoxicillin/metronidazole was recommended by the latest Maastricht Consensus for eradicating *H. pylori*.[1] Recently, researches have shown that *H. pylori* not only causes damages of gastric epithelium but also may play a potential pathogenic role in extraintestinal diseases via multiple mechanisms, mainly various immune responses.[2,3] However, except for unexplained iron deficiency anemia and idiopathic thrombocytopenic purpura, *H. pylori* infection has no proven role in other extraintestinal diseases.[1]

Henoch-Schonlein purpura (HSP), a type of acute leukocytoclastic vasculitis of small vessels which is characterized by IgA-deposits in vessel walls and renal mesangium, results in the lesions of many organs including the skin, kidney, gastrointestinal tract, and joint. Although its causes are complicated and unclear, infectious agents are often considered to be risk factors of HSP. For instance, because of positive throat cultures and the increase of anti-streptolysin O antibody titers in HSP children, group A β-hemolytic streptococcus has been implicated in the pathogenesis of HSP as the most extensively studied pathogen.[4,5]

Increasing evidences suggested that HSP might be associated with *H. pylori* infection. The first reported case was a 21-year-old woman with HSP and active chronic gastritis and *H. pylori* infection identified by ^{13}C-urea breath test and gastroscope. *H. pylori* eradication promoted disappearance of clinical symptoms of HSP in this woman.[6] When four adult cases were reported,[6-9] two similar HSP children with *H. pylori* infection were also reported in 1997[10] and 2008,[11] respectively. Furthermore, *H. pylori* infection has been discovered in IgA nephropathy which shared similarities with HSP.[12] *H. pylori* infection is acquired during childhood, when HSP is also a common disease with obvious clinical manifestations including abdominal pain and gastrointestinal bleeding. Therefore, *H. pylori* infection may be related to HSP, especially abdominal HSP.

As one of the most frequent bacterial infections around the world, the prevalence of *H. pylori* ranges from 20% to 80%.[13] Because of the lower socioeconomic status and poor sanitary environment, the prevalence of *H. pylori* infection is about 41% in children aged from 3 to 12 years old in China.[14] Importantly, the selective colonization of *H. pylori* mainly occurs in childhood and once established, can persist lifelong if untreated. While few infected-individuals will progress to upper gastrointestinal diseases, the majority coexisting with *H. pylori* have no relevant clinical consequences. Furthermore, as a genetically diverse organism,[15] *H. pylori* isolates of Chinese are different from those of Westerners.[16-18] Consequently, we conducted a meta-analysis of previously published studies to investigate the underlying association between *H. pylori* infection and HSP in Chinese children and whether the eradication is able to provide a favorable prognosis in HSP children with *H. pylori* infection.

Methods

Search strategy

We searched the following databases using such MeSH headings as "*Helicobacter pylori*", "Purpura, Schoenlein-Henoch" and non-MeSH words "*Helicobacter pylori* infection", and "Henoch Schonlein purpura": Medline, EMBASE, Chinese Biomedical Literautre Database (CBM), Chinese National Knowledge Infrastructure (CNKI) database, Google Scholar, and the Cochrane Library. From the initial searching results, we restricted the studies on children or adolescents. Studies with full text manuscripts and meeting abstracts were included. The titles and abstracts of the search papers were screened for potential inclusion.

Study selection

To avoid selection bias, inclusion criteria were established before screening. Studies meeting the following criteria were included in the meta-analysis. Two independent reviewers were involved in the selection. Discrepancies were resolved by discussion and consultation with other reviewers.

Inclusion criteria: 1) observational epidemiology studies in Chinese children; 2) HSP diagnosis with the description of typical palpable purpuric eruption and at least one additional criterion including diffuse abdominal pain, arthritis or arthralgia and renal involvement (hematuria or proteinuria); 3) description of the diagnostic method of *H. pylori* infection; 4) studies containing normal controls comparable with HSP children in age, sex and birth place; 4) data sufficient to estimate *H. pylori* infection rates and OR or RR in both HSP children and controls.

Exclusion criteria: 1) case reports, reviews, commentaries and studies on the pathogenesis of HSP or *H. pylori*; 2) part of the data obtained from HSP adults or non-Chinese children; 3) studies in HSP children with defined causes or other complications.

Data extraction and assessment of study quality

Two independent reviewers extracted the following information from selected studies: 1) authors, titles

of articles, year of publication, and journals; 2) study design; 3) inclusion and exclusion criteria; 4) diagnosis methods of *H. pylori* infection; 5) criteria by which HSP patients and controls were selected; 6) number of patients with HSP and abdominal HSP, number of children in the control group; 7) number of *H. pylori*-positive in the HSP and control groups; 8) number of HSP patients who accepted routine treatment combined with eradication therapy after diagnosis of *H. pylori* infection, number of HSP patients who only accepted routine treatment after diagnosis of *H. pylori* infection; 9) number of HSP patients with recurrence after combined treatment; 10) regimens of eradication therapy; 11) time of follow-up after eradication therapy.

The quality of this study was assessed under the guidance of the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[19] and Methodological Index for Non-Randomized Studies (MINORS).[20] The following criteria were used to assess the quality of each study: 1) study design; 2) diagnostic method of *H. pylori*; 3) whether there were descriptions of the diagnosis of HSP; 4) enrollment of HSP patients and controls; 5) whether *H. pylori* infection rate was taken as the primary or secondary outcome of the study; 6) time of follow-up.

Statistical analysis

Outcomes of eligible studies were analyzed by Reviewer Manager Version 5.0 and STATA version 10.0. Pooled odds ratio (OR) or relative risk (RR) with 95% confidence interval (CI) was used to describe the ratio of the probability of *H. pylori* infection in HSP children versus the control group. Because of the limited sample size which would lead to exaggerated estimates, traditional meta-analysis and cumulative meta-analysis on the basis of sample sizes were performed simultaneously. Heterogeneity between compared studies was tested using the Chi-square test and considered significant at $P<0.1$. If heterogeneity existed, the following approaches were adopted for explanation and solution: (1) meta-analysis using the random effects model; (2) subgroup analysis for potential impact factor; and (3) sensitivity analysis by eliminating potentially biased studies.[21] Analysis with a funnel plot, Begg's test was performed to examine the publication bias. The nonparametric "trim and fill" procedure[22] was performed for further assessment of the possible effect of publication bias and adjustment of pooled OR by conservatively imputing hypothetical negative unpublished studies to mirror the positive studies. The results of crude and adjusted analysis are both considered in estimating the overall effect.

Results

Search and selection results

The initial search yielded 272 potentially studies. After removing duplicates and irrelevant studies, 74 articles were retained. A total of 34 full-text articles were reviewed in detail. Twenty-one studies without control group and 3 duplicated studies were excluded (Fig. 1). Finally, 10 eligible studies involving 749 HSP children and 560 controls were included for meta-analysis.

Study characteristics

The characteristics and quality assessment of each observational epidemiology study are summarized in Table 1[23-32] and Table 2[23-32] respectively. All the studies clearly aimed at detecting the underlying association

Table 1. Characteristics of the included studies

Ref.	District	Study design	HSP diagnosis	Control inclusion	Age of HSP/ control (y) (SD)	Sex of HSP/ control (male/ female) (*n*)	Total (*n*)	Control (*n*)	HSP (*n*)	Gastro-intestinal HSP (*n*)	Eradication therapy (time)	Treatment regimen
Wang YL[23] 2004	Northern China	Case-control	Clinical manifestation	Health examination	8/-	21/14 -	65	30	35	30	Yes (2 wk)	OAM
Zhang WY[24] 2004	Southern China	Case-control	Clinical manifestation	Health examination	6.9/7.25	38/22 36/24	120	60	60	-	No	-
Lv X[25] 2005	Eastern China	Case-control	Clinical manifestation	Health examination	8.5/-	19/15 -	62	28	34	11	No	-
Li H[26] 2006	Central China	Case-control	Clinical manifestation	Health examination	5-15/-	78/72 -	270	120	150	90	Yes (2wk)	OCA
Wang BH[27] 2007	Central China	Case-control	Not stated	Health examination	7.7/-	23/13 -	98	30	68	36	Yes (2 wk)	OCA
Yuan JM[28] 2007	Central China	Case-control	Clinical manifestation	Random sampling from school	9.7/10	117/69 83/67	336	150	186	118	Yes (1 wk)	OCM
Li YH[29] 2008	Southwestern China	Case-control	Clinical manifestation	Health examination	4-11/-	-/-	69	30	39	-	Yes (2 wk)	OCA
Li J[30] 2008	Northern China	Case-control	Clinical manifestation	Health examination	6.8 (2.7)/ 6.6 (2.6)	35/25 24/18	102	42	60	40	Yes (2 wk)	OCA
Xia XM[31] 2008	Eastern China	Case-control	Clinical manifestation	Outpatients with abdominal pain	9.5/-	25/12 -	67	30	37	37	No	-
Gao XL[32] 2009	Southwestern China	Case-control	Clinical manifestation	Health examination	9.09 (2.49)/-	35/16 -	120	40	80	51	No	-

O: omeprazole; C: clarithromycin; A: amoxicillin; M: metronidazole; HSP: Henoch-Schonlein purpura.

between *H. pylori* infection and HSP with retrospective data collection from the children enrolled consecutively. In the included studies, abdominal pain and gastrointestinal bleeding were the most frequent primary clinical symptoms in HSP children. To identify *H. pylori* infection, serum anti-*H. pylori* IgG detected by ELISA was used in 7 studies,[23,25-30] UBT was used in 4 studies,[24,27,29,31] RUT on biopsies was used in 3 studies.[26,27,29] However, only 3 studies[26,28,30] detected *H. pylori* infection via combined diagnostic tests, which was considered to be the golden standard.[33] Additional PPI-based triple antibiotics therapy after *H. pylori* diagnosis was applied in several studies,[23,26-30] in which only 4 studies[26,29,30,31] divided *H. pylori*-positive HSP children into two matched groups in order to assess the eradication effect on the HSP children. No special therapy of HSP was given to one group, and the other group was treated with *H. pylori* eradication therapy in addition to the routine therapy of HSP. The follow-up activities after treatment were mentioned only in 4 studies.[23,26,27,30] The prevalence of *H. pylori* infection in HSP children ranged from 20% to 70% (Table 3). Overall, 49.27% (369/749) of HSP children had evidence of infection with *H. pylori* comparing to 23.39% (131/560) of children in the control group.

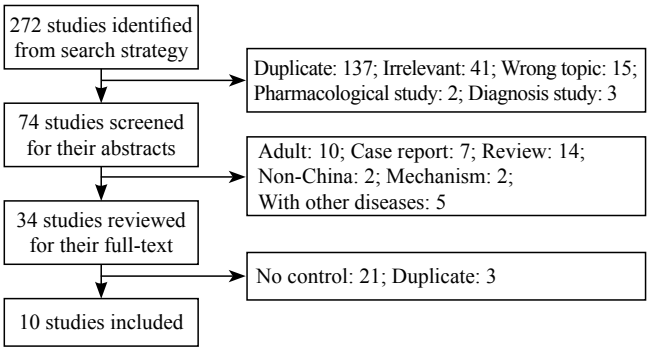

Fig. 1. Flow diagram for selection of studies.

Summary estimates

The Chi-square test for heterogeneity (χ^2=16.61,

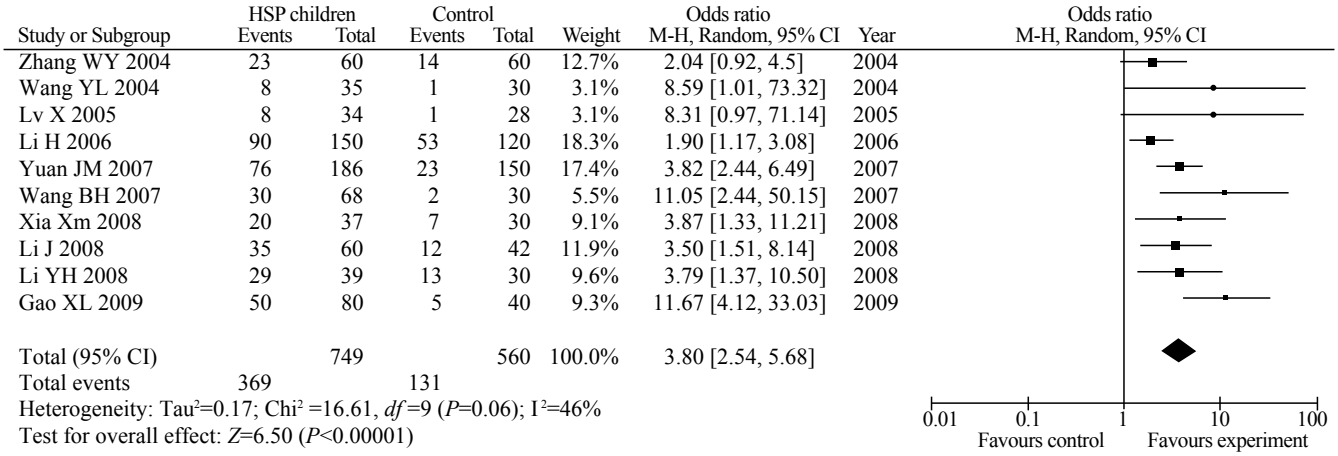

Fig. 2. Forest plot of prevalence (rectangles), 95% confidence interval (CI) (horizontal line), and pooled prevalence rate (diamonds) of *H.pylori* infection in children with Henoch-Schonlein purpura (HSP) versus controls. M-H, Random: Mantel-Haenszel heterogeneity random effects model.

Table 2. Quality assessment of the included studies

Ref.	*H. pylori* diagnosis (*n*)	HSP diagnosis	Study type	Enrollment of patients	Outcome	Follow-up time (mon)
Wang YL[23]	Anti-*H. pylori* IgG (65)	Stated	Retrospective	Consecutive	Primary	1
Zhang WY[24]	UBT (120)	Stated	Retrospective	Consecutive	Primary	0
Lv X[25]	Anti-*H. pylori* IgG (62)	Stated	Retrospective	Consecutive	Primary	0
Li H[26]	Anti-*H. pylori* IgG (270)					
	RUT(60)	Stated	Retrospective	Consecutive	Primary	6
Wang BH[27]	RUT (52)	Not stated	Retrospective	Consecutive	Primary	1
	UBT (98)					
	Anti-*H. pylori* IgG (98)					
Yuan JM[28]	Anti-*H. pylori* IgG (336)	Stated	Retrospective	Consecutive	Primary	0
Li YH[29]	Anti-*H. pylori* IgG (69)	Stated	Retrospective	Consecutive	Primary	0
	UBT (69)					
	RUT (69)					
Li J[30]	Anti-*H. pylori* IgG (102)	Stated	Retrospective	Consecutive	Primary	3-6
Xia XM[31]	UBT (67)	Stated	Retrospective	Consecutive	Primary	0
Gao XL[32]	*H. pylori*-antigen (120)	Stated	Retrospective	Consecutive	Primary	0

RUT: rapid urease test; UBT: urea breath test; IgG: immunoglobulin G; HSP: Henoch-Schonlein purpura.

P=0.06, I^2=46%) indicated that there was heterogeneity between the included studies. Thus the random effects model was more appropriate than fixed effects model for estimation. The pooled OR of *H. pylori* infection in HSP children compared with the control group was 3.80 (95% CI: 2.54-5.68, *P*<0.001) (Fig. 2). Accumulation of studies with sample size, the estimate decreased and the final pooled OR from the cumulative meta-analysis confirmed the association with more narrow confidence interval (OR=3.35, 95% CI: 2.95-3.81) (Fig. 3). Furthermore, the pooled OR of *H. pylori* infection in the HSP children mainly with abdominal manifestations (8 studies with 337 HSP children) was 4.62 (95% CI: 2.66-8.01, *P*<0.001), indicating that *H. pylori* infection was associated with HSP, particularly gastrointestinal HSP. Additional eradication therapy reduced the recurrence of HSP comparing with the routine treatment in HSP children with *H. pylori* infection (RR=0.38, 95% CI: 0.25-0.58, *P*<0.001) (Fig. 4).

Since heterogeneity and publication bias were demonstrated by the asymmetric Begg's funnel plot (*P*<0.01, Fig. 5), subgroup analysis and the nonparametric "trim-and-fill" method were used to explain the heterogeneity and adjust the effect estimate respectively. Thus studies were divided into three subgroups in terms of geographical distribution and *H. pylori* diagnosis involving anti-*H. pylori* IgG, UBT and combined diagnosis method. The ORs of anti-*H. pylori* IgG, UBT and combined diagnosis method were 4.09 (95% CI: 2.29-7.31, *P*<0.001), 2.56 (95% CI: 1.36-4.84, *P*=0.004)

Table 3. Prevalence of *H. pylori* infection among children presenting with Henoch-Schonlein purpura (HSP)

Ref.	*H. pylori*-positive in HSP children (positive/tested/enrolled) (%)	*H. pylori*-positive in control (positive/tested/enrolled) (%)
Wang YL[23]	22.86 (8/35/35)	3.33 (1/30/30)
Zhang WY[24]	38.33 (23/60/60)	23.33 (14/60/60)
Lv X[25]	23.53 (8/34/34)	3.57 (1/28/28)
Li H[26]	60.00 (90/150/150)	44.17 (53/120/120)
Wang BH[28]	44.12 (30/68/68)	6.67 (2/30/30)
Yuan JM[29]	40.86 (76/186/186)	15.33 (23/150/150)
Li YH[30]	74.36 (29/39/39)	43.33 (13/30/30)
Li J[31]	58.33 (35/60/60)	28.57 (12/42/42)
Xia XM[32]	54.05 (20/37/37)	23.33 (7/30/30)
Gao XL[34]	62.50 (50/80/80)	12.50 (5/40/40)

Table 4. Subgroup analysis

Subgroup analysis	Studies	Subjects	OR	95% CI	Heterogeneity (chi^2)	*P**
H. pylori diagnosis method						
Anti-*H. pylori* IgG	6	955	4.09	2.29-7.31	12.51	0.03
UBT	2	187	2.56	1.36-4.84	0.89	0.35
Combined diagnosis method	2	167	5.60	1.99-15.74	5.70	0.24
Subgroup differences: *P*=0.37						
Geographical differences						
Eastern China	2	129	4.50	1.73-11.67	0.40	0.53
Northern China	2	167	4.13	1.90-8.98	0.60	0.44
Southern China	1	120	2.04	0.92-4.51	-	-
Central China	3	704	3.40	1.59-7.25	7.02	0.03
Southwestern China	2	189	6.62	2.19-20.00	2.31	0.13
Subgroup differences: *P*=0.49						

*: *P* value tested for heterogeneity of subgroups. UBT: urea breath test; OR: odds ratio; CI: confidence interval.

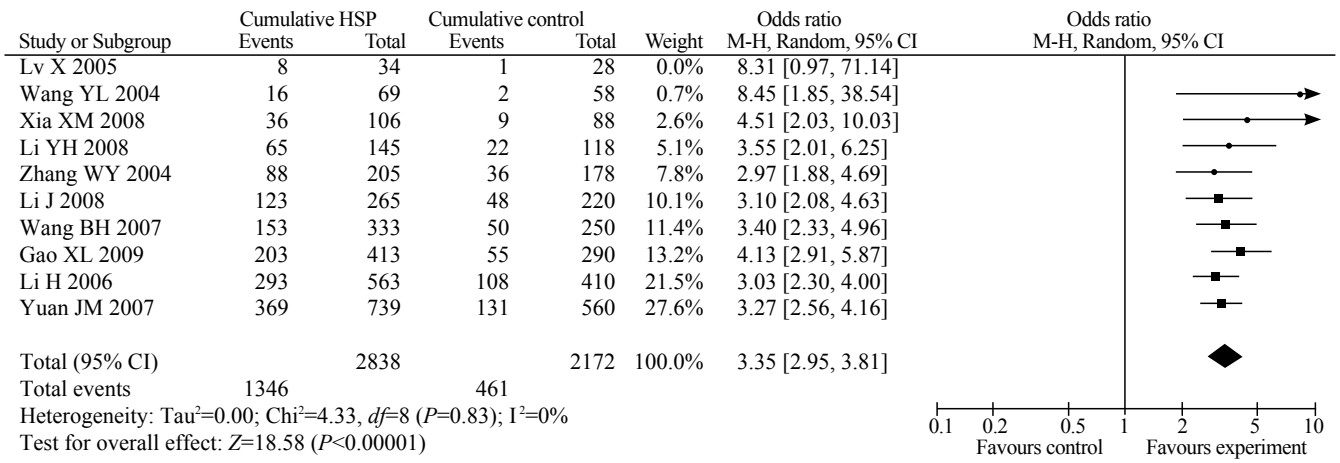

Fig. 3. Forest plot of prevalence (rectangles), 95% confidence interval (CI) (horizontal line), and pooled prevalence rate (diamonds) of *H. pylori* infection in children with Henoch-Schonlein purpura (HSP) *vs.* controls via cumulative meta-analysis based on sample size of studies. M-H, Random: Mantel-Haenszel heterogeneity random effects model.

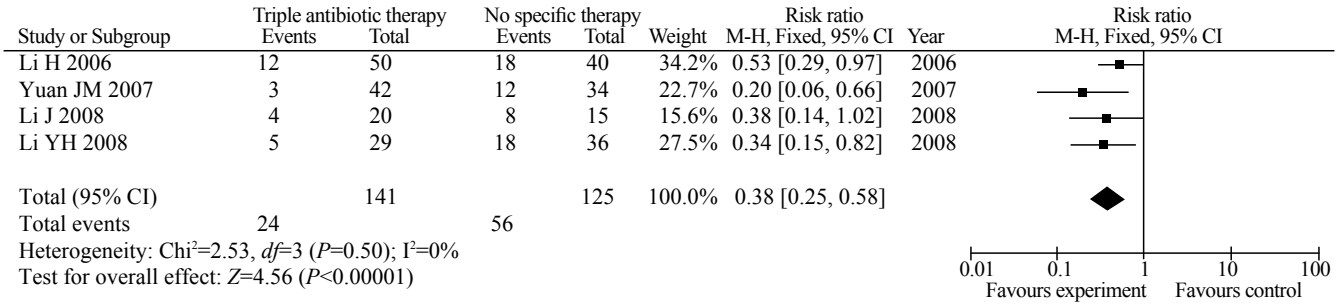

Fig. 4. Forest plot of treatment effect (rectangles), 95% confidence interval (CI) (horizontal line), and pooled eradication effect (diamonds) of *H. pylori* infection in children with Henoch-Schonlein purpura. M-H, Random: Mantel-Haenszel heterogeneity random effects model.

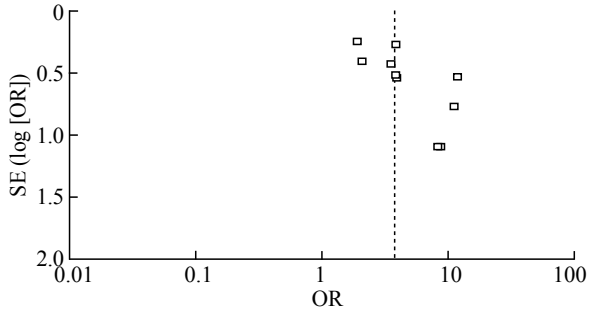

Fig. 5. Funnel plot analysis of included studies. The pseudo 95% CI is computed as part of the analysis that produces the funnel plot, and corresponds to the expected 95% CI for a given standard error (SE). OR: odds ratio.

and 5.60 (95% CI: 1.99-15.74, *P*=0.001), respectively. The ORs of studies from different regions of China are demonstrated in Table 4. Although there were significant heterogeneities in the subgroups of anti-*H. pylori* IgG, the ORs calculated from subgroups were consistent with the overall effect synthesized from all the included studies. However, the statistical test suggested no significant differences in subgroups of diagnosis methods (*P*=0.37) and subgroups of geographic areas (*P*=0.49). Visual inspection of the Begg's funnel plot revealed asymmetry. Nonparametric "trim-and-fill" method was used to mirror the positive studies that cause publication bias and adjust the result (adjusted pooled OR=2.043, 95% CI: 1.479-2.822, *P*<0.001). Post-adjustment OR confirmed the previous result that *H. pylori* infection was associated with HSP in Chinese children.

Discussion

Literature review identified 10 studies on the underlying association between *H. pylori* infection and HSP in Chinese children. The incidence of *H. pylori* infection was higher in the HSP children than in the controls. The overall estimate by traditional or cumulative meta-analysis suggested the possible relation of *H. pylori* infection to HSP, especially abdominal HSP. Results suggested that the PPI-based triple antibiotics therapy might improve the clinical manifestations and decrease recurrence of HSP.

Since synthetic results were affected by heterogeneity between studies, subgroup analysis was conducted to investigate the sources of heterogeneity. Diagnosis tests and geographical diversity were likely to account for the heterogeneity partly. Different *H. pylori* tests contribute to the variation of overall effects for their different sensitivities and specificities. Additionally, since the prevalence of *H. pylori* infection varied geographically, different regions were considered. Results from subgroup analysis were consistent with the previous estimates. However, statistical analysis revealed that no significant differences existed between subgroups, indicating their limited effect on the overall effects. Although the clinical and methodological diversity existed, with limited data, it failed to define the exact factors determining the heterogeneity between studies.

The publication bias was another factor affecting the estimate. There was no language restriction set up, but no non-Chinese studies were found on this issue. The problem of publication bias was anticipated when choosing Chinese children as our target population in this meta-analysis. Then, the nonparametric "trim-and-fill" method was applied to adjust the results. The adjusted estimate still suggested that the *H. pylori* infection might be a risk factor for HSP in Chinese children.

While the prevalence of *H. pylori* in children is high, its explicit role in the development of HSP remains unknown. Our study did not include any researches about the pathogenic mechanism of HSP caused by *H. pylori*. However, studies focusing on this aspect suggested that complicated immune responses might mediate the cross-talk between *H. pylori* infection and extragastrointestinal disease,[33,35] involving autoimmunity, proinflammatory substances and immune complex induced by molecular mimicry and cross-reactive antibodies.[36-38] The clinical features of HSP are a consequence of widespread leukocytoclastic

vasculitis with polymeric immunoglobulin A1 (pIgA1), C3 and certain fibrin deposited in vessel walls. Since *H. pylori* infection was also discovered in IgA nephropathy which shares several similarities with HSP for the high level of anti-Hp IgA antibodies and disposition of pIgA in glomerular,[12] it was speculated that increased serum IgA and cryoglobulins levels, decreased C3 levels caused by *H. pylori* infection would promote the formation of immune complexes and the occurrence of HSP.[39] However, there has been no proven evidence that whether *H. pylori*-induced immune response or the immune abnormalities was responsible for triggering the whole pathological process of HSP, since preceding or concomitant infections were common in patients with HSP. The *vac*A and *cag*A alleles which encode the most important virulence proteins VacA and CagA contribute to the differences between Chinese *H. pylori* isolates and those of Western countries via functional polymorphism. Because of the high toxigenicity of Chinese *H. pylori* strains, we hypothesized that VacA or CagA might play a potential role in the pathogenesis of HSP through a complicated and unknown mechanism. More intensive researches need to be performed in order to determine the pathological role of *H. pylori* in the HSP.

Our results suggested the importance of detecting *H. pylori* infection in HSP children particularly with serious gastrointestinal manifestation. The serologic antibody test as a convenient method to detect *H. pylori* infection was used in majority of included studies. Since the titers of IgG to *H. pylori* diminish slowly, indicating current or past infection, it fails to distinguish the timing of *H. pylori* infection in the development of HSP. UBT, with high sensitivity and specificity,[33] is a reliable method in both diagnosis of active *H. pylori* infection and confirmation of eradication. It may be a suitable noninvasive option in *H. pylori* diagnosis and follow-up activity in HSP children with *H. pylori*. Furthermore, objective parameters with uniform criteria including the clinical improvement (e.g., the reduction of HSP recurrence) should be established for comprehensive evaluation of eradication effect when treating HSP children with *H. pylori* infection. The negative-invert of anti-*H. pylori* antibodies and curative ratio of HSP should be applied simultaneously. The occurrence and severity of complications, such as renal disease, need to be considered in follow up activities.

In 2007, European Helicobacter Study Group consensus started to recommend the eradication of *H. pylori* in affected patients with extragastrointestinal diseases including unexplained iron deficiency anemia and idiopathic thrombocytopenic purpura.[1] Although the underlying association between *H. pylori* and HSP is still under investigation and it is not an indication of "test and treat strategy" for *H. pylori* infection in children, HSP children with serious gastrointestinal symptoms are necessary to be detected for *H. pylori* infection after exclusion of other causes and should be treated if they have the infection. Our result showed that the PPI-based triple antibiotics therapy might improve the clinical manifestations and decrease recurrence of HSP. However, the substantial effect of eradication therapy in HSP children with *H. pylori* infection need be confirmed by more randomized, double-blind, placebo-controlled studies.

The observational epidemiology studies included in this meta-analysis cannot be graded as high level of evidences with good methodological quality and homogeneity. In addition, because HSP is a type of immune disorder with complicated etiology, the possible association is not equal to the definite cause. Therefore, the limited strength of the association does not allow a reliable prediction of *H. pylori* infection in HSP children at an individual level. No included studies compared the rate of *H. pylori* infection in HSP children with the average prevalence of *H. pylori* in the same region and no data of the prevalence of *H. pylori* infection in each region were mentioned in all these studies. So the prevalence of *H. pylori* infection failed to be reflected overall in the selected areas of China, though the included studies were executed in different regions of China. Consequently, the association found in Chinese children requires further evaluation in different regions and population.

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Competing interest: We declare no potential conflicts of interest involved in this article.

Contributors: Xiong LJ is the first author of this article who was responsible for research design, data analysis, manuscript writing and revision. Tong Y and Wang ZL assisted in completing the analysis interpretation. Mao M had substantial contribution to conception and made final approval of the version to be published.

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