Association between *Helicobacter pylori* infection and delayed growth in children: A meta-analysis

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Abstract. *Helicobacter pylori (H. pylori)* infection is associated with extra-gastrointestinal diseases in children. The present study aimed to investigate the potential association between *H. pylori* infection and growth in children. The PubMed, Exerpta Medica dataBASE, Cochrane Library and Chinese Biomedical Literature Database databases were comprehensively searched for relevant publications dated between January 1st 1994 and January 1st 2019. Delayed childhood growth was defined according to the age-appropriate criteria in the World Health Organization Child Growth Charts (2006 edition). The odds ratios (ORs) and 95% CIs were pooled using the fixed-effects model and subgroup and sensitivity analyses were performed using Review Manager (version 5.3; Cochrane) and STATA (version 12.0; StataCorp LP) software. A total of 15 observational studies comprising 4,199 subjects were included in the present study. A higher frequency of delayed growth was observed in *H. pylori*-positive children compared with that in *H. pylori*-negative children (OR, 1.51; 95% CI, 1.28-1.78), particularly for linear growth (OR, 1.63; 95% CI, 1.32-2.00). The aforementioned association was only observed when *H. pylori* infection was detected using ^{13}C-urea breath tests (OR, 1.72; 95% CI, 1.22-2.40) or serum IgG antibodies targeted against *H. pylori* (OR, 1.81; 95% CI, 1.35-2.44).

H. pylori infection was also associated with delayed childhood growth in studies with a *H. pylori* prevalence of ≤30% (OR, 1.71; 95% CI, 1.31-2.23) or >30% but not >50% (OR, 1.43; 95% CI, 1.10-1.86). The association between infection and growth was only statistically significant in the cross-sectional (OR, 1.43; 95% CI, 1.18-1.73) and case-control (OR, 1.81; 95% CI, 1.23-2.67) studies. No significant heterogeneity among studies was identified in the present analysis. According to Begg's and Egger's linear regression methods for funnel plots and quantification assessments, no publication bias was identified. The trim and fill method further suggested that *H. pylori*-positive children were prone to delayed linear growth. Therefore, the present study suggested that preventing and detecting *H. pylori* infection in children may be critical to ensure normal growth and development during childhood.

Introduction

Helicobacter pylori (*H. pylori*) is a helical, gram-negative micro-aerobic bacterium that colonises the stomach (1). It is the major pathogen associated with gastritis, peptic ulcers and gastric cancer (2-4). Certain *H. pylori* genotypes are risk factors for gastric disease, e.g. the vacuolating toxin A-positive and cytotoxin-associated gene A-positive genotypes (5). *H. pylori*-positive children present with clinical manifestations that vary widely from *H. pylori*-positive adults, including iron deficiency anaemia (6). Furthermore, *H. pylori*-positive children display no adverse digestive system symptoms, except occasional abdominal pain or duodenal ulcers during late childhood. By contrast, *H. pylori*-positive adults are susceptible to various clinically significant diseases, including ulcers and cancer of the gastrointestinal system (7-10). It has been reported that successful eradication of *H. pylori* during childhood increases growth and restores serum acylated ghrelin levels in children (11). However, the European and North American Gastroenterology and Nutrition Society does not recommend the detection and treatment of *H. pylori* infection in children due to the low efficacy of the currently recommended *H. pylori* eradication therapy and the lack of broad availability of culture or molecular-based testing (12). Therefore, optimised vaccine strategies and a high-performance first-line treatment based on antimicrobial susceptibility profiles are urgently required for the efficient treatment of *H. pylori* infection in children (12-15).

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Abbreviations: H. pylori, Helicobacter pylori; OR, odds ratio

Key words: Helicobacter pylori, delayed growth, children, meta-analysis, observational study

A previous study reported a higher percentage of delayed growth, defined according to the World Health Organization (WHO) age-appropriate criteria (2006 edition) (16,17), in children infected with *H. pylori* compared with controls (18), while other studies have reported no effect of *H. pylori* infection on the growth of children (17-19). Thomas *et al* (19) reported that the effects of *H. pylori* colonisation on malnutrition and delayed growth during early infancy (age, 5-8 years) did not persist into late childhood. Conversely, Perri *et al* (20) and Fialho *et al* (21) reported an association between short stature and *H. pylori* infection in older children aged between 8 and 14 years. Furthermore, the effects of *H. pylori* infection on the growth and development of female children have been reported to be associated with puberty (22). Tasar *et al* (23) reported that *H. pylori* seroprevalence was higher in children with delayed growth compared with the control group. Therefore, the association between the *H. pylori* infection in childhood and delayed growth remains a topic of debate. Routine screening for *H. pylori* in children under 14 years of age is not recommended at present and the Fifth National *H. Pylori* Infection Consensus Report of China only recommended that children with peptic ulcers should undergo examination for *H. pylori* (24). As an intragastric infection that begins during infancy (25), the effective eradication of *H. pylori* in a paediatric population is critical (13). The meta-analysis performed in the present study comprehensively assessed all available published studies to determine the possible association between *H. pylori* infection and delayed growth during childhood.

Materials and methods

Literature search. The Meta-analyses of Observational Studies in Epidemiology and Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement guidelines were followed for the literature search in the present study (26,27). PubMed, Exerpta Medica dataBASE, Cochrane Library and the Chinese Biomedical Literature Database were searched for relevant literature using the following terms: 'Helicobacter pylori' [medical subject headings (MeSH) terms] or 'Helicobacter pylori' or 'H. pylori', and 'Growth Disorders' (MeSH Terms) or 'disorder, growth' or 'growth disorder', 'stunted growth' or 'growth, stunted' or 'stunting', 'thrive, failure to' or 'Failure to Thrive' (MeSH Terms), or 'growth retardation' or 'growth restriction'. Furthermore, the lists of references all the eligible studies were manually reviewed to identify additional studies.

Inclusion and exclusion criteria. Case-control, cohort and cross-sectional observational studies were included in the present study. All relevant full texts assessing the effect of *H. pylori* infection on delayed growth in children published between January 1st 1994 and January 1st 2019 were included in the present meta-analysis. Case reports, review articles, meta-analyses, duplicate reports, letters to the editor, commentaries, authors' replies and abstracts presented at conferences were excluded from the present study. Articles with insufficient data were also excluded from the present study after two reviewers performed an independent screening of the abstracts and full texts (SW and YD). Any disagreements were resolved by a third reviewer (LP).

Quality assessment. To ensure the quality of the meta-analysis, quality assessments of each of the included articles were performed. Quality evaluation of the case-control and cohort studies was performed using the Newcastle-Ottawa Scale (28). The methodological quality of the cross-sectional studies was evaluated using the 11-item checklist recommended by the Agency for Healthcare Research and Quality that was applied by a previous meta-analysis (29). Higher scores indicated higher quality articles; therefore, articles with a final score of ≥7 points were included in the present study (28,29).

Data extraction. The basic data were extracted from the studies by two reviewers (SW and YD) and included the following: First author, year of publication, country/continent, sample size, age and gender of participants, prevalence of *H. pylori* infection, study design, *H. pylori* detection method, type of delayed growth, definition of delayed growth and adjustment for confounders. Delayed growth was defined according to the WHO age-appropriate criteria (2006 edition) (16,17). The number of children with delayed growth and healthy participants in the *H. pylori*-positive and *H. pylori*-negative groups was also recorded.

Statistical analysis. The potential risk of delayed growth in children infected with *H. pylori* was evaluated using a fixed-effects model to estimate the odds ratio (OR) and 95% confidence intervals (CI). Statistical heterogeneity was assessed using the χ^2 test and I^2 index. P<0.10 and I^2>50% were considered to indicate statistically significant heterogeneity. I^2 values of 0-25, 26-50, 50-75 and >75% were considered to indicate no, low, medium and high heterogeneity, respectively (30).

Subgroup analyses were performed based on country/continent, *H. pylori* prevalance, study design, *H. pylori* detection method, type of delayed growth and confounder adjustment. Furthermore, sensitivity analyses were performed to assess whether removing any single study at a later stage affected the primary outcome of the meta-analysis performed in the present study. Begg's and Egger's linear regression were performed to assess publication bias, as evaluated by funnel plots. Finally, the credibility of the results was estimated using the trim and fill method (31). Data analyses were performed using Review Manager (version 5.3; Cochrane) and STATA (version 12.0; StataCorp LP) softwares.

Results

Baseline characteristics. Of the 488 records initially retrieved, 44 were duplicates and the remaining 444 articles were screened based on titles and abstracts, of which 390 irrelevant studies were excluded. An additional 38 studies were excluded due to insufficient data. Following quality assessment of the remaining 16 observational studies, a total of 15 studies with a quality assessment score of ≥7 (Tables I-III) were included in the present study (Fig. 1), including two cohort (18,32), eight cross-sectional (20,21,33-38) and five case-control (39-43) studies.

The included articles, published between January 1st 1994 and January 1st 2019, comprised 1,371 *H. pylori*-positive and 2,828 *H. pylori*-negative children. Delayed growth was reported in 454 (33.11%) *H. pylori*-positive children and 761

Table I. Quality assessment of cohort studies using the Newcastle-Ottawa quality assessment scale.

| Author (year) | Selection | | | | Comparability | Outcome | | | Score | (Refs.) |
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability of the cohorts on the basis of the design or analysis	Assessment of the outcome	Was follow-up long enough for outcomes to occur?	Adequacy of cohort follow-ups		
Raymond (1994)	+	+	+	no	+	+	+	+	7	(32)
Benavides-Ward (2018)	+	+	+	+	+	+	no	+	7	(18)

'+', one score.

Table II. Quality assessment of cross-sectional studies according to the Agency for Healthcare Research and Quality.

Author (year)	Definition of the source of information	Inclusion and exclusion criteria for exposed and unexposed subjects	Time period used for patient recruitment	Whether or not the subjects are consecutive	Whether evaluators of subjective components of the study are masked to other aspects of the status of the participants	Description of any assessments undertaken for quality assurance purposes (forexample, test/re-test of primary outcome measurements)	Explanation of any patient exclusions from the analysis	Description of how confounding is assessed and/or controlled	Summary of patient response rates and completeness of data collection	Clarification of expected follow-up (if any) and the percentage of patients for which incomplete or follow-up data was obtained	Score	(Refs.)
Perri (1997)	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	Yes	No	8	(20)
Choe (2000)	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	Yes	No	8	(33)
Lin (2002)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	9	(34)
Fialho (2007)	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	Yes	No	8	(21)
Cherian (2009)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	8	(35)
Gulcan (2010)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	8	(36)
Mendoza (2014)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	8	(37)
Janjetic (2015)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	9	(38)

Table III. Quality assessment of case-control studies using the Newcastle-Ottawa quality assessment scale.

| Author (year) | Selection | | | | Comparability | Exposure | | | Score | (Refs.) |
	Is the case definition adequate?	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate		
Oderda (1998)	+	+	+	+	++	+	+	no	8	(39)
Cacciari (1999)	+	+	no	+	++	+	+	no	7	(40)
Buyukegebiz (2001)	+	+	+	+	++	+	+	no	8	(41)
Takahashi (2002)	+	+	no	+	++	+	+	no	7	(42)
Chiu (2017)	+	+	no	+	++	+	+	no	7	(43)

'+', 1 score; '++', 2 scores.

(26.91%) *H. pylori*-negative children. The major characteristics of the included studies are presented in Table IV.

Primary outcomes. The prevalence of delayed childhood growth in the *H. pylori*-positive group was significantly increased compared with that in the *H. pylori*-negative group (OR, 1.51; 95% CI, 1.28-1.78; P<0.00001), with no significant heterogeneity (χ^2=13.34; I^2=0%; $P_{Heterogeneity}$=0.50; Fig. 2). The results indicated that there was a positive association between *H. pylori* infection and delayed childhood growth.

Subgroup analyses
Country/continent. The 15 observational studies included in the present study consisted of participants from all five continents (Europe, America, Asia, Africa and Oceania). Participants from Europe (OR, 1.61; 95% CI, 1.11-2.35; Z=2.49; P=0.01; I^2=0%; $P_{Heterogeneity}$=0.80), America (OR, 1.50; 95% CI, 1.16-1.94; Z=3.06; P=0.002; I^2=2%; $P_{Heterogeneity}$=0.38) and Asia (OR, 1.66; 95% CI, 1.25-2.20; Z=3.49; P=0.0005; I^2=0%; $P_{Heterogeneity}$=0.59) displayed an association between *H. pylori* infection and delayed childhood growth; however, no association was observed in participants from Africa and Oceania (OR, 0.83; 95% CI, 0.44-1.56; Z=0.58; P=0.56; I^2=53%; $P_{Heterogeneity}$=0.14; Fig. 3).

Prevalence of H. pylori infection. The prevalence of *H. pylori* infection varied among the included studies, ranging from 9.17-81.87% (Table IV). Delayed growth in children among studies with a *H. pylori* prevalence of ≤30% (OR, 1.71; 95% CI, 1.31-2.23; Z=3.93; P<0.0001; I^2=0%; $P_{Heterogeneity}$=0.99) or >30 but ≤50% (OR, 1.43; 95% CI, 1.10-1.86; Z=2.64; P=0.008; I^2=34%; $P_{Heterogeneity}$=0.21) was associated with *H. pylori* infection, with no significant heterogeneity (χ^2=1.38; I^2=0%; $P_{Heterogeneity}$=0.50). However, there was no association between delayed growth and *H. pylori* infection in studies with a *H. pylori* prevalence prevalence of >50% (OR, 1.36; 95% CI, 0.97-1.90; Z=1.78; P=0.08; Fig. 4).

Study design. Of the three types of observational studies included in the present analysis, cross-sectional (OR, 1.43; 95% CI, 1.18-1.73; Z=3.68; P=0.0002) and case-control (OR, 1.81; 95% CI, 1.23-2.67; Z=3.00; P=0.003) studies displayed an association between *H. pylori* infection and delayed childhood growth. Cohort studies did not display any association between the two factors (OR, 1.64; 95% CI, 0.89-3.03; Z=1.58; P=0.11). The heterogeneity among the three subgroups was not significant (χ^2=1.24; I^2=0%; $P_{Heterogeneity}$=0.54; Fig. 5).

H. pylori detection method. In the studies using ^{13}C-urea breath tests (UBTs; OR, 1.72; 95% CI, 1.22-2.40; Z=3.14; P=0.002; I^2=0%; $P_{Heterogeneity}$=0.86) and serum IgG antibodies targeted against *H. pylori* (OR, 1.81; 95% CI, 1.35-2.44; Z=3.97; P<0.0001; I^2=0%; $P_{Heterogeneity}$=0.89) detection methods, an association between *H. pylori* infection and delayed childhood growth was detected. However, the studies using other detection methods did not display any association, including the rapid urease test (OR, 1.32; 95% CI, 0.90-1.94; Z=1.43; P=0.15; I^2=0%; $P_{Heterogeneity}$=0.88), monoclonal faecal antigen enzyme immunoassay testing (OR, 0.55; 95% CI, 0.24-1.25; Z=1.44; P=0.15), PCR amplification of the 23S ribosomal
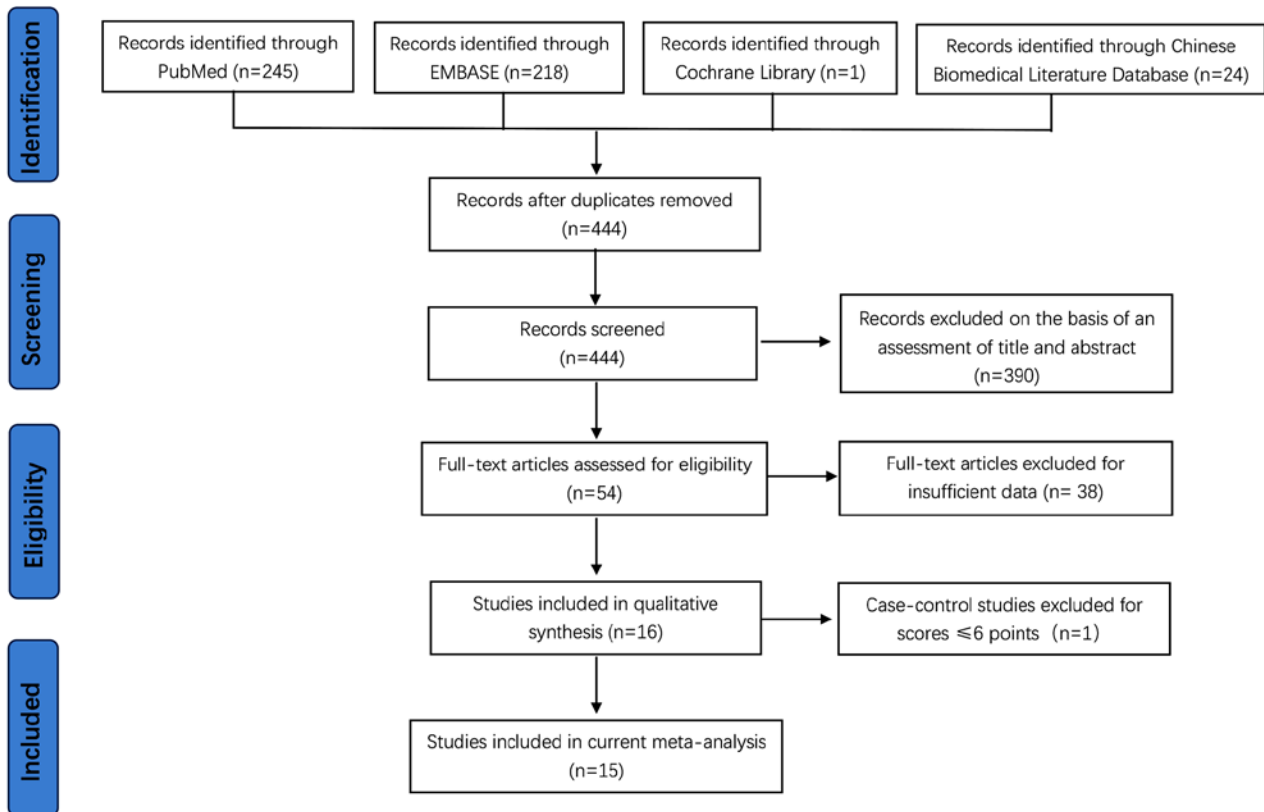
Figure 1. Flow diagram of the literature search conducted in the present study. EMBASE, Exerpta Medica data BASE.

RNA gene (OR, 3.08; 95% CI, 0.98-9.67; Z=1.92; P=0.05) or at least one of three positive examinations [^{13}C-UBT, antibodies to whole-cell *H. pylori* and cytotoxin-associated gene A (CagA) antigens; OR, 1.24; 95% CI, 0.86-1.79; Z=1.17; P=0.24; Fig. 6].

Measures of delayed growth. H. pylori infection was associated with the incidence of delayed growth when the primary outcome was height (OR, 1.63; 95% CI, 1.32-2.00; Z=4.57; P<0.00001; I^2=0%; P$_{Heterogeneity}$=0.72), which suggested that delayed linear growth was associated with *H. pylori* infection. *H. pylori* infection was also associated with delayed growth when height and weight were collectively analysed as the primary outcome (OR, 1.33; 95% CI, 1.00-1.75; Z=1.99; P=0.05; I^2=33%; P$_{Heterogeneity}$=0.19). No association was observed when the height, weight and mid-upper arm circumference were collectively analysed as the primary outcome (OR, 1.39; 95% CI, 0.52-3.74; Z=0.66; P=0.51) and no heterogeneity was identified among these subgroup analyses (χ^2=1.34; I^2=0%; P$_{Heterogeneity}$=0.51; Fig. 7).

Confounder adjustment. Subgroup analyses were performed based on confounder adjustment; four studies were adjusted for potential confounders and the pooled OR was 1.32 (95% CI, 1.02-1.70; Z=2.12; P=0.03) with no significant heterogeneity (I^2=52%; P$_{Heterogeneity}$=0.10). The pooled unadjusted OR value was 1.67 (95% CI, 1.34-2.07; Z=4.63; P<0.00001) for the remaining 11 studies, with no significant heterogeneity (I^2=0%; P$_{Heterogeneity}$=0.88). Therefore, the results suggested that *H. pylori* infection was associated with delayed childhood

growth, regardless of the adjustment for potential confounders (Fig. 8).

Sensitivity analysis. Following the omission of one study at a time, the pooled OR values of the remaining studies ranged from 1.47-1.58 with insignificant heterogeneity (I^2=0-2%; P$_{Heterogeneity}$>0.10), and the upper and lower thresholds of the 95% CI were >1, indicating that none of the results were significantly altered by the removal of one article from the meta-analysis (P$_{Remainders' effect}$<0.0001; Table V; Fig. 9).

Publication bias. The funnel plot analysis suggested that there may be a certain amount of publication bias, since the included studies were not distributed completely symmetrically in the funnel plots (Fig. 10A). To investigate the potential publication bias, the included studies were evaluated using the Begg's and Egger's linear regression tests. No significant publication bias was detected using Begg's (P>|z|=0.113) or Egger's (P>|t|=0.257) linear regression analyses (Fig. 10B). Furthermore, adjustment of the funnel plots by the trim and fill method did not alter the results and a statistically significant association between *H. pylori* infection and delayed childhood growth was still observed (P<0.0001), indicating that the results were stable and credible (Fig. 10C).

Discussion

To the best of our knowledge, the present study was the first to investigate the association between *H. pylori* infection and delayed childhood growth. Following searching and

Table IV. Baseline characteristics of the included studies.

Author (year)	Country, continent	Study design	Sample size	Age (years)	Males/female	Detection method	Type of delayed growth	Delayed growth group (*H. pylori* +/-)	Control group (*H. pylori* +/-)	*H. pylori* prevalence (%)	Definition of delayed growth	Quality score	(Refs.)
Raymond (1994)	France, Europe	Cohort	151	0-16	N/A	Rapid urease test	Height and weight	21/17	56/57	50.99	Absence of growth hormone deficit	7	(32)
Perri (1997)	Italy, Europe	Cross-Sectional	216	3-14	N/A	13C-UBT	Height	8/13	41/154	22.69	Below the 25th centile value for height	8	(20)
Oderda (1998)	Italy, Europe	Case-control	268	5-13	170/98	Serum *H. pylori* IgG antibodies	Height	27/107	18/116	16.79	Below the 3rd centile value of height	8	(39)
Cacciari (1999)	Italy, Europe	Case-control	338	2-16	169/169	Serum *H. pylori* IgG antibodies	Height	18/138	13/169	9.17	Stature below the 3rd percentile for the corresponding age	7	(40)
Choe (2000)	Korea, Asia	Cross-sectional	375	10-15	205/170	Serum *H. pylori* IgG antibodies	Height and weight	18/63	45/249	16.80	Below the 25th centile values for height or weight	8	(33)
Buyukgebiz (2001)	Turkey, Asia	Case-control	56	Mean 14.53±1.12	N/A	Serum *H. pylori* IgG antibodies	Height and weight	16/8	12/20	50.00	Stature below parental height, retarded bone age (>2 SD below chronological age) and height velocity <25th percentile	8	(41)
Takahashi (2002)	Japan, Asia	Case-control	88	1-16	57/31	Serum *H. pylori* IgG antibodies	Height	6/35	3/44	10.23	Height of 1.5-2.0 SD or more below the mean height for age	7	(42)
Lin (2002)	China, Asia	Cross-sectional	356	2-7	206/150	Serum *H. pylori* IgG antibodies	Height	34/111	30/181	17.98	Below the 25th centile value for height	9	(34)
Fialho (2007)	Brazil, South America	Cross-sectional	353	0.5-14	180/173	13C-UBT	Height	122/75	75/81	55.81	Below the 25th centile for height	8	(21)

Table IV. Continued.

Author (year)	Country, continent	Study design	Sample size	Age (years)	Males/female	Detection method	Type of delayed growth	Delayed growth group (H. pylori +/-)	Control group (H. pylori +/-)	H. pylori prevalence (%)	Definition of delayed growth	Quality score	(Refs.)
Cherian (2009)	Sudan, Burundi and Liberia, Africa	Cross-sectional	182	Mean 8.0±4.3	93/89	MFAT MUAC	Weight, height and	32/11	117/22	81.87	Z-score <1.64 SD below normal (correlating to <5th centile)	8	(35)
Gulcan (2010)	Turkey, Asia	Cross-sectional	490	6-15	229/261	Rapid urease test	Height and weight	51/45	180/214	47.14	Height and BMI SDS below the 5th percentile	8	(36)
Mendoza (2014)	Mexico, North America	Cross-Sectional	641	6-13	N/A	At least one of three tests with positive results[a]	Height	66/95	172/308	37.13	Z-score of height for age <-1 SD	8	(37)
Janjetic (2015)	Argentina, South America	Cross-Sectional	525	4-16	233/292	^{13}C-UBT	Height and weight	6/13	126/380	25.14	Height, weight or BMI-for-age below the 3rd SD	9	(38)
Chiu (2017)	Australia, Oceania	Case-control	106	4-18	64/42	^{13}C-UBT	Height and weight	9/17	22/58	29.25	Height or weight-for-age below the 15th percentile value	7	(43)
Benavides-Ward (2018)	Peru, South America	Cohort	56	6-12	29/27	PCR amplification of the 23S rRNA gene	Height	20/13	7/14	48.21	2.2 SD below the Z-score of height-for-age	7	(18)

[a]^{13}C-UBT, antibodies against H. pylori whole-cell and CagA antigens. H. pylori, Helicobacter pylori; UBT, urea breath test; IgG, immunoglobulin G; MFAT, monoclonal faecal antigen enzyme immunoassay testing; MUAC, mid-upper arm circumferences; BMI, body mass index; SDS, standard deviation score; rRNA, ribosomal RNA; CagA, cytotoxin-associated gene A.

Study or Subgroup	H.pylori positive Events	Total	H.pylori negative Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year	Odds Ratio M-H, Fixed, 95% CI
Raymond et al.	21	77	17	74	5.5%	1.26 [0.60, 2.63]	1994	
Perri et al.	8	49	13	167	2.2%	2.31 [0.90, 5.95]	1997	
Oderda et al.	27	45	107	223	6.3%	1.63 [0.85, 3.12]	1998	
Cacciari et al.	18	31	138	307	4.6%	1.70 [0.80, 3.58]	1999	
Choe et al.	18	63	63	312	6.6%	1.58 [0.86, 2.92]	2000	
Buyukgebiz et al.	16	28	8	28	1.5%	3.33 [1.10, 10.12]	2001	
Takahashi et al.	6	9	35	79	1.0%	2.51 [0.59, 10.78]	2002	
Lin et al.	34	64	111	292	8.2%	1.85 [1.07, 3.19]	2002	
Fialho et al.	122	197	75	156	13.9%	1.76 [1.15, 2.69]	2007	
Cherian et al.	32	149	11	33	6.2%	0.55 [0.24, 1.25]	2009	
Gulcan et al.	51	231	45	259	14.4%	1.35 [0.86, 2.11]	2010	
Mendoza et al.	66	238	95	403	22.3%	1.24 [0.86, 1.79]	2014	
Janjetic et al.	6	132	13	393	2.7%	1.39 [0.52, 3.74]	2015	
Chiu et al.	9	31	17	75	3.1%	1.40 [0.54, 3.59]	2017	
Benavides et al.	20	27	13	27	1.5%	3.08 [0.98, 9.67]	2018	
Total (95% CI)		1371		2828	100.0%	1.51 [1.28, 1.78]		
Total events	454		761					

Heterogeneity: Chi² = 13.34, df = 14 (P = 0.50); I² = 0%
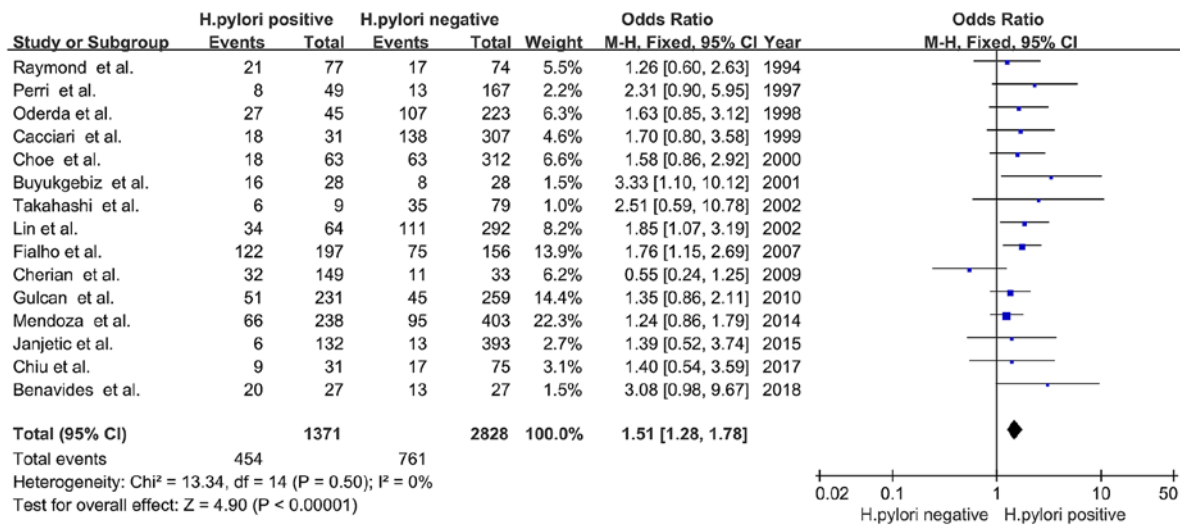Test for overall effect: Z = 4.90 (P < 0.00001)

Figure 2. Forest plots of the meta-analysis of the association between *H. pylori* infection and delayed childhood growth. The blue squares represent the OR value, whilst black diamonds represent the combined results of the included studies. *H. pylori*, *Helicobacter pylori*; df, degrees of freedom; M-H, Mantel-Haentzel.

Study or Subgroup	H.pylori positive Events	Total	H.pylori negative Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Europe								
Raymond et al.	21	77	17	74	5.5%	1.26 [0.60, 2.63]	1994	
Perri et al.	8	49	13	167	2.2%	2.31 [0.90, 5.95]	1997	
Oderda et al.	27	45	107	223	6.3%	1.63 [0.85, 3.12]	1998	
Cacciari et al.	18	31	138	307	4.6%	1.70 [0.80, 3.58]	1999	
Subtotal (95% CI)		202		771	18.6%	1.61 [1.11, 2.35]		
Total events	74		275					
Heterogeneity: Chi² = 1.01, df = 3 (P = 0.80); I² = 0%								
Test for overall effect: Z = 2.49 (P = 0.01)								
1.2.2 America								
Fialho et al.	122	197	75	156	13.9%	1.76 [1.15, 2.69]	2007	
Mendoza et al.	66	238	95	403	22.3%	1.24 [0.86, 1.79]	2014	
Janjetic et al.	6	132	13	393	2.7%	1.39 [0.52, 3.74]	2015	
Benavides et al.	20	27	13	27	1.5%	3.08 [0.98, 9.67]	2018	
Subtotal (95% CI)		594		979	40.4%	1.50 [1.16, 1.94]		
Total events	214		196					
Heterogeneity: Chi² = 3.07, df = 3 (P = 0.38); I² = 2%								
Test for overall effect: Z = 3.06 (P = 0.002)								
1.2.5 Asia								
Choe et al.	18	63	63	312	6.6%	1.58 [0.86, 2.92]	2000	
Buyukgebiz et al.	16	28	8	28	1.5%	3.33 [1.10, 10.12]	2001	
Takahashi et al.	6	9	35	79	1.0%	2.51 [0.59, 10.78]	2002	
Lin et al.	34	64	111	292	8.2%	1.85 [1.07, 3.19]	2002	
Gulcan et al.	51	231	45	259	14.4%	1.35 [0.86, 2.11]	2010	
Subtotal (95% CI)		395		970	31.8%	1.66 [1.25, 2.20]		
Total events	125		262					
Heterogeneity: Chi² = 2.84, df = 4 (P = 0.59); I² = 0%								
Test for overall effect: Z = 3.49 (P = 0.0005)								
1.2.6 Other states #								
Cherian et al.	32	149	11	33	6.2%	0.55 [0.24, 1.25]	2009	
Chiu et al.	9	31	17	75	3.1%	1.40 [0.54, 3.59]	2017	
Subtotal (95% CI)		180		108	9.3%	0.83 [0.44, 1.56]		
Total events	41		28					
Heterogeneity: Chi² = 2.15, df = 1 (P = 0.14); I² = 53%								
Test for overall effect: Z = 0.58 (P = 0.56)								
Total (95% CI)		1371		2828	100.0%	1.51 [1.28, 1.78]		
Total events	454		761					

Heterogeneity: Chi² = 13.34, df = 14 (P = 0.50); I² = 0%
Test for overall effect: Z = 4.90 (P < 0.00001)
Test for subgroup differences: Chi² = 4.02, df = 3 (P = 0.26), I² = 25.3%

Figure 3. Forest plots of subgroup analysis based on country/continent. The blue squares represent the OR value, whilst black diamonds represent the combined results of the included studies. #, Africa and Oceania; *H. pylori*, *Helicobacter pylori*; df, degrees of freedom; M-H, Mantel-Haentzel.

screening, low-quality studies (23) were excluded and fifteen observational studies involving 4,199 children were used for the meta-analysis performed in the present study. The likelihood of delayed childhood growth was significantly
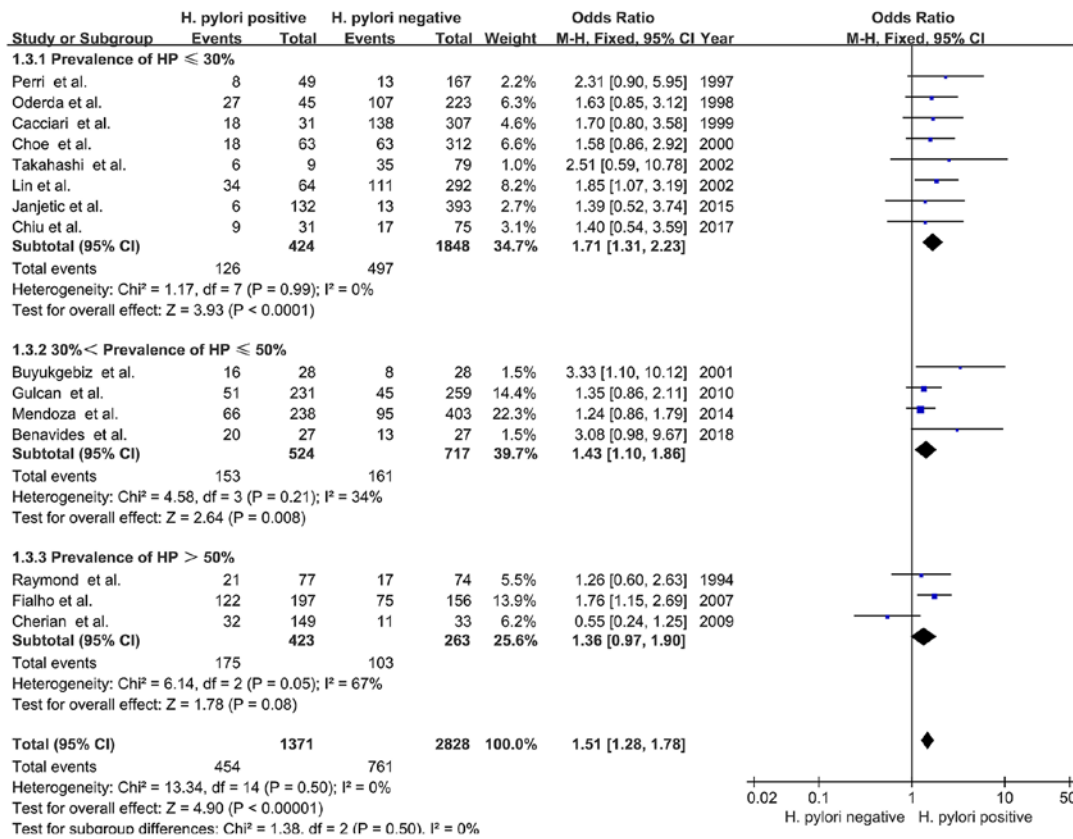
Figure 4. Forest plots of subgroup analysis based on prevalence of *H. pylori*. The blue squares represent the OR value, whilst black diamonds represent the combined results of the included studies. *H. pylori*, *Helicobacter pylori*; df, degrees of freedom; M-H, Mantel-Haentzel.

Figure 5. Forest plots of subgroup analysis based on study design. The blue squares represent the OR value, whilst black diamonds represent the combined results of the included studies. *H. pylori*, *Helicobacter pylori*; df, degrees of freedom; M-H, Mantel-Haentzel.
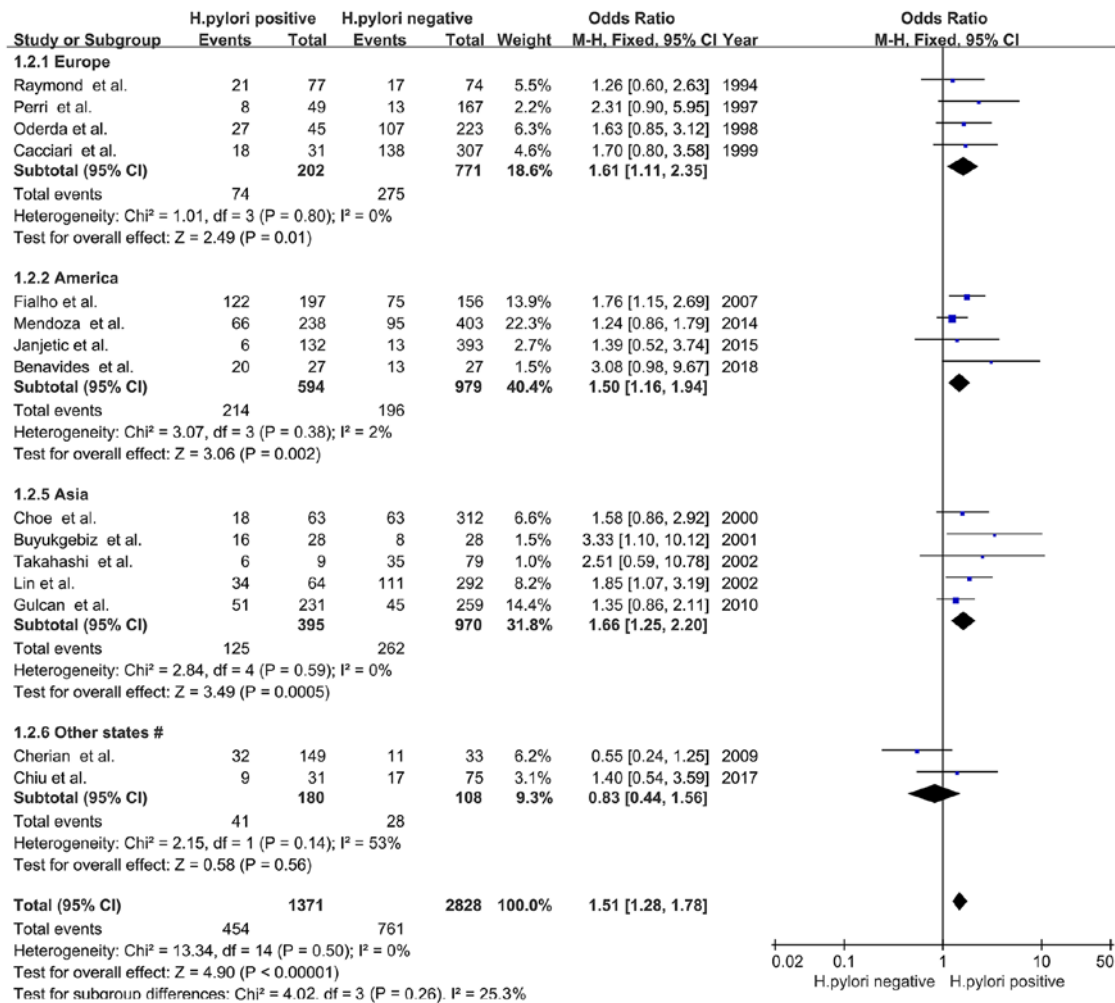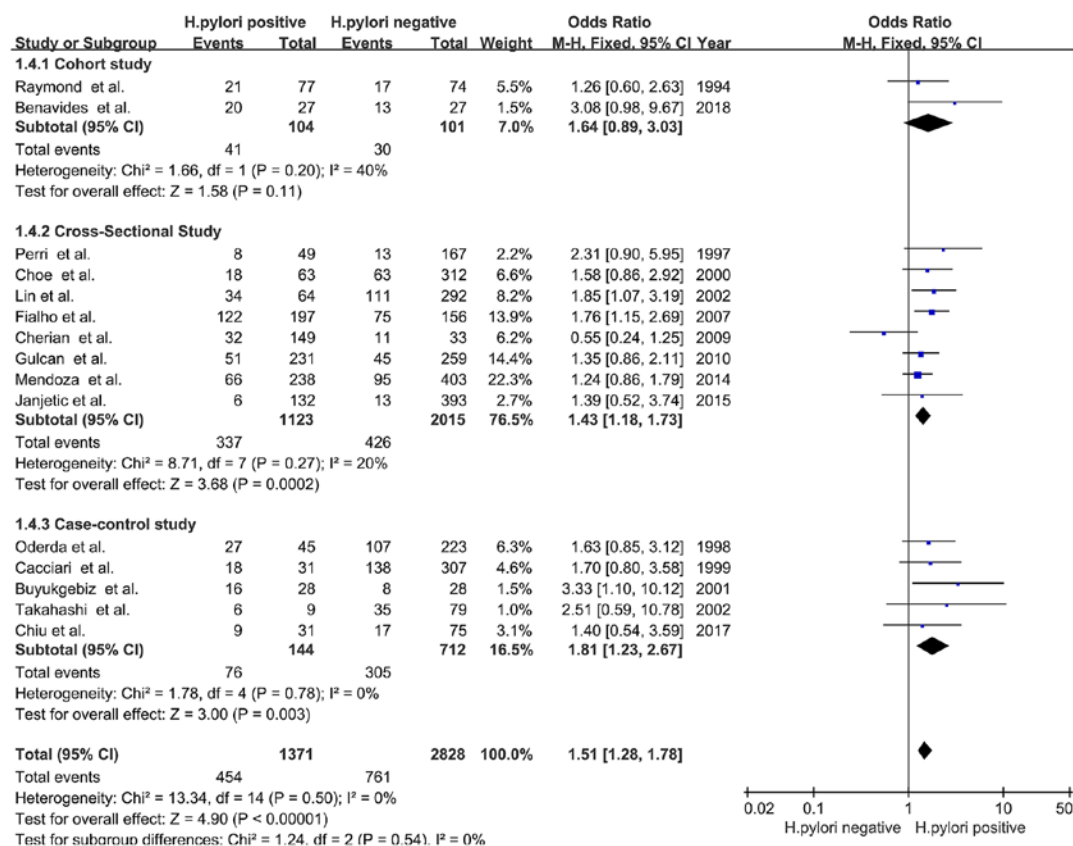
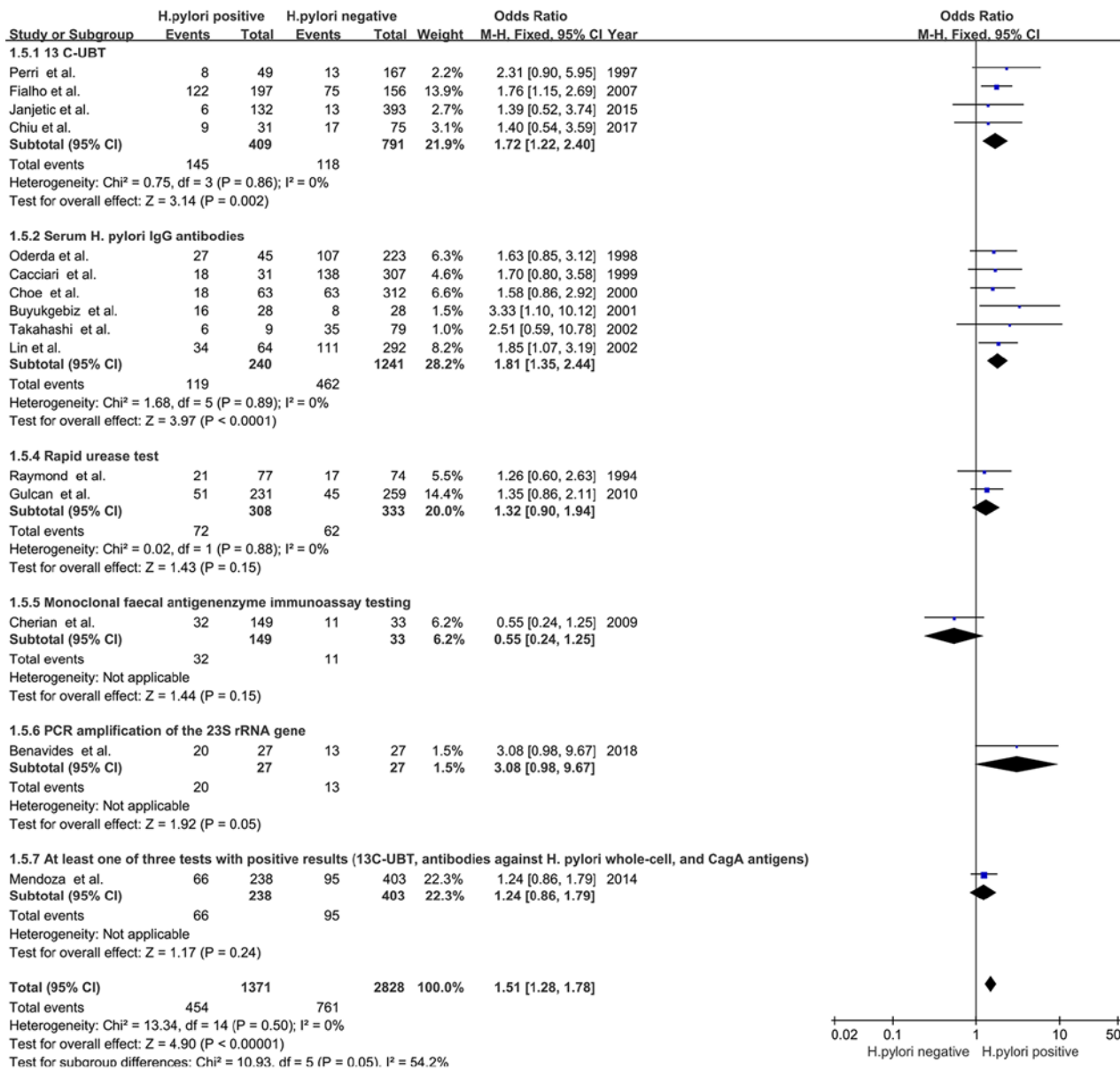| Study or Subgroup	H.pylori positive Events	Total	H.pylori negative Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.5.1 13 C-UBT							
Perri et al.	8	49	13	167	2.2%	2.31 [0.90, 5.95]	1997
Fialho et al.	122	197	75	156	13.9%	1.76 [1.15, 2.69]	2007
Janjetic et al.	6	132	13	393	2.7%	1.39 [0.52, 3.74]	2015
Chiu et al.	9	31	17	75	3.1%	1.40 [0.54, 3.59]	2017
Subtotal (95% CI)		409		791	21.9%	1.72 [1.22, 2.40]	
Total events	145		118				
Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%							
Test for overall effect: Z = 3.14 (P = 0.002)							
1.5.2 Serum H. pylori IgG antibodies							
Oderda et al.	27	45	107	223	6.3%	1.63 [0.85, 3.12]	1998
Cacciari et al.	18	31	138	307	4.6%	1.70 [0.80, 3.58]	1999
Choe et al.	18	63	63	312	6.6%	1.58 [0.86, 2.92]	2000
Buyukgebiz et al.	16	28	8	28	1.5%	3.33 [1.10, 10.12]	2001
Takahashi et al.	6	9	35	79	1.0%	2.51 [0.59, 10.78]	2002
Lin et al.	34	64	111	292	8.2%	1.85 [1.07, 3.19]	2002
Subtotal (95% CI)		240		1241	28.2%	1.81 [1.35, 2.44]	
Total events	119		462				
Heterogeneity: Chi² = 1.68, df = 5 (P = 0.89); I² = 0%							
Test for overall effect: Z = 3.97 (P < 0.0001)							
1.5.4 Rapid urease test							
Raymond et al.	21	77	17	74	5.5%	1.26 [0.60, 2.63]	1994
Gulcan et al.	51	231	45	259	14.4%	1.35 [0.86, 2.11]	2010
Subtotal (95% CI)		308		333	20.0%	1.32 [0.90, 1.94]	
Total events	72		62				
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%							
Test for overall effect: Z = 1.43 (P = 0.15)							
1.5.5 Monoclonal faecal antigenenzyme immunoassay testing							
Cherian et al.	32	149	11	33	6.2%	0.55 [0.24, 1.25]	2009
Subtotal (95% CI)		149		33	6.2%	0.55 [0.24, 1.25]	
Total events	32		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
1.5.6 PCR amplification of the 23S rRNA gene							
Benavides et al.	20	27	13	27	1.5%	3.08 [0.98, 9.67]	2018
Subtotal (95% CI)		27		27	1.5%	3.08 [0.98, 9.67]	
Total events	20		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.92 (P = 0.05)							
1.5.7 At least one of three tests with positive results (13C-UBT, antibodies against H. pylori whole-cell, and CagA antigens)							
Mendoza et al.	66	238	95	403	22.3%	1.24 [0.86, 1.79]	2014
Subtotal (95% CI)		238		403	22.3%	1.24 [0.86, 1.79]	
Total events	66		95				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.17 (P = 0.24)							
Total (95% CI)		1371		2828	100.0%	1.51 [1.28, 1.78]	
Total events	454		761				
Heterogeneity: Chi² = 13.34, df = 14 (P = 0.50); I² = 0%							
Test for overall effect: Z = 4.90 (P < 0.00001)							
Test for subgroup differences: Chi² = 10.93, df = 5 (P = 0.05), I² = 54.2%							

Figure 6. Forest plots of subgroup analysis based on *H. pylori* detection method. The blue squares represent the OR value, whilst black diamonds represent the combined results of the included studies. *H. pylori*, *Helicobacter pylori*; df, degrees of freedom; M-H, Mantel-Haentzel; UBT, urea breath test; IgG, immunoglobulin G; rRNA, ribosomal RNA; CagA, cytotoxin-associated gene A.

increased in *H. pylori*-positive children compared with that in *H. pylori*-negative children. A series of further analyses indicated that the results of the present study were credible and stable.

Delayed growth is the most significant nutritional problem worldwide, which leads to long-term effects and may occur in utero (44). The present study suggested that *H. pylori* infection may be a potential risk factor for delayed childhood growth, particularly linear growth; however, the specific underlying mechanisms require further investigation. It remains elusive whether delayed childhood growth is due to the direct effects of *H. pylori*-induced inflammation or indirect effects of the infection, e.g. anorexia, abdominal pain, malabsorption or diarrhoea. Therefore, delayed growth may be due to direct as well as indirect effects of *H. pylori* infection (45). The clinical outcomes of *H. pylori* infection are affected by a number of

factors, including virulence, the host gastric mucosa and the environment (46).

Clinical symptoms of *H. pylori* infection vary between children and adults, with a lower incidence of gastroduodenal ulcers, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma in children (47,48). *H. pylori*-induced gastric inflammation is less severe in children compared with that in adults, due to the decreased gastric type 17 T-helper cell/interleukin-17 response in children, which is associated with increased activity of the mucosal regulatory T cells (48). Therefore, the extra-digestive manifestations of *H. pylori* colonisation in children, including iron deficiency anaemia (6), cognitive function (49), type I diabetes mellitus (50), Henoch-Schonlein purpura (51) and delayed growth, require constant medical attention. *H. pylori* infection has been reported in numerous studies as a risk factor for delayed childhood growth (18,20,21,23,34,37,41),
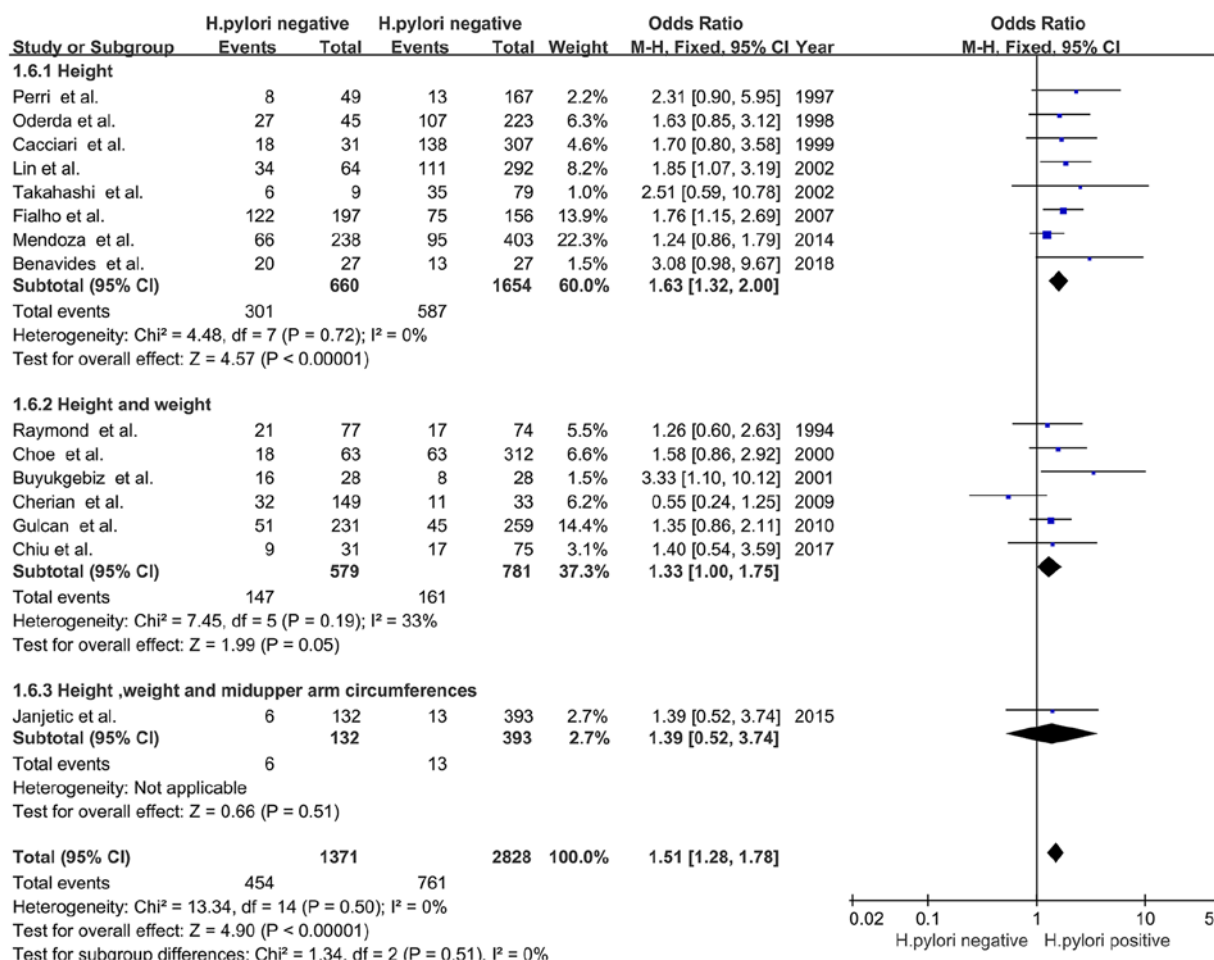
Study or Subgroup	H.pylori negative Events	Total	H.pylori negative Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.6.1 Height							
Perri et al.	8	49	13	167	2.2%	2.31 [0.90, 5.95]	1997
Oderda et al.	27	45	107	223	6.3%	1.63 [0.85, 3.12]	1998
Cacciari et al.	18	31	138	307	4.6%	1.70 [0.80, 3.58]	1999
Lin et al.	34	64	111	292	8.2%	1.85 [1.07, 3.19]	2002
Takahashi et al.	6	9	35	79	1.0%	2.51 [0.59, 10.78]	2002
Fialho et al.	122	197	75	156	13.9%	1.76 [1.15, 2.69]	2007
Mendoza et al.	66	238	95	403	22.3%	1.24 [0.86, 1.79]	2014
Benavides et al.	20	27	13	27	1.5%	3.08 [0.98, 9.67]	2018
Subtotal (95% CI)		660		1654	60.0%	1.63 [1.32, 2.00]	
Total events	301		587				
Heterogeneity: Chi² = 4.48, df = 7 (P = 0.72); I² = 0%							
Test for overall effect: Z = 4.57 (P < 0.00001)							
1.6.2 Height and weight							
Raymond et al.	21	77	17	74	5.5%	1.26 [0.60, 2.63]	1994
Choe et al.	18	63	63	312	6.6%	1.58 [0.86, 2.92]	2000
Buyukgebiz et al.	16	28	8	28	1.5%	3.33 [1.10, 10.12]	2001
Cherian et al.	32	149	11	33	6.2%	0.55 [0.24, 1.25]	2009
Gulcan et al.	51	231	45	259	14.4%	1.35 [0.86, 2.11]	2010
Chiu et al.	9	31	17	75	3.1%	1.40 [0.54, 3.59]	2017
Subtotal (95% CI)		579		781	37.3%	1.33 [1.00, 1.75]	
Total events	147		161				
Heterogeneity: Chi² = 7.45, df = 5 (P = 0.19); I² = 33%							
Test for overall effect: Z = 1.99 (P = 0.05)							
1.6.3 Height ,weight and midupper arm circumferences							
Janjetic et al.	6	132	13	393	2.7%	1.39 [0.52, 3.74]	2015
Subtotal (95% CI)		132		393	2.7%	1.39 [0.52, 3.74]	
Total events	6		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
Total (95% CI)		1371		2828	100.0%	1.51 [1.28, 1.78]	
Total events	454		761				
Heterogeneity: Chi² = 13.34, df = 14 (P = 0.50); I² = 0%							
Test for overall effect: Z = 4.90 (P < 0.00001)							
Test for subgroup differences: Chi² = 1.34, df = 2 (P = 0.51), I² = 0%							

Figure 7. Forest plots of subgroup analysis based on types of delayed growth. *H. pylori*, *Helicobacter pylori*; df, degrees of freedom; M-H, Mantel-Haentzel.

and of note, Yang *et al* (11) reported that eradication of *H. pylori* infection promotes growth in children. A retrospective study indicated that the prevalence of childhood gastric cancer may be reduced by decreasing the prevalence of *H. pylori* infection in adolescents and children (15). However, Dehghani *et al* (52) suggested that *H. pylori* infection did not affect the calculated standard deviation score (height and body mass index) (52). Cherian *et al* (35), Janjetic *et al* (38), Chiu *et al* (43) and Choe *et al* (33) reported that childhood growth and puberty are affected by iron deficiency anaemia and *H. pylori* infection, rather than *H. pylori* infection alone. Ortiz-Princz *et al* (46) revealed that early identification and intervention of *H. pylori* infection during childhood prevents further serious complications during adulthood, which is consistent with the results of the present study.

In the present meta-analysis, the subgroup analyses demonstrated an association between *H. pylori* infection and childhood growth in European, American and Asian subjects, but not in African and Oceanian subjects. The association was also identified in studies with a *H. pylori* prevalence of ≤50%, but not in studies with a *H. pylori* prevalence of >50%. A potential explanation for these differences may be different *H. pylori* prevalence, as well as different environmental and nutritional factors in different countries and regions. Other factors associated with the high prevalence of *H. pylori* infection and delayed growth in children are linked to the

socio-economic development of the population, which is associated with limited health care resources, insufficient nutrition and a poor living environment, which may have influenced the results obtained (53-57).

Furthermore, only cross-sectional and case-control studies indicated that *H. pylori* infection was associated with delayed growth in children. An improvement in diet and living conditions during the long-term follow-up of cohort studies may impact the outcome. In addition, the ^{13}C-UBT and serum IgG antibodies targeted against *H. pylori* detection methods suggested that *H. pylori* infection was associated with delayed growth in children. Although ^{13}C-UBT effectively detects *H. pylori* infection (58), the detection method has a high rate of false-positives in children aged <6 years (59). A relevant study reported that detection of *H. pylori* using serum IgG antibodies displayed 88.4% sensitivity and 93.4% specificity compared with histology (60). Anti-*H. pylori* IgG and IgA antibody titers are higher in children with CagA-positive sera regardless of their age. Therefore, serum IgG or IgA antibodies are recommended for the detection of *H. pylori* in asymptomatic children aged <6 years (61). Non-invasive screening methods may be used for children aged >6 years based on different situations, while children with adverse gastrointestinal symptoms, including peptic ulcers and dyspepsia, should be evaluated by upper gastrointestinal endoscopy for the diagnosis of associated pathology (62). Consistent with the conclusion proposed
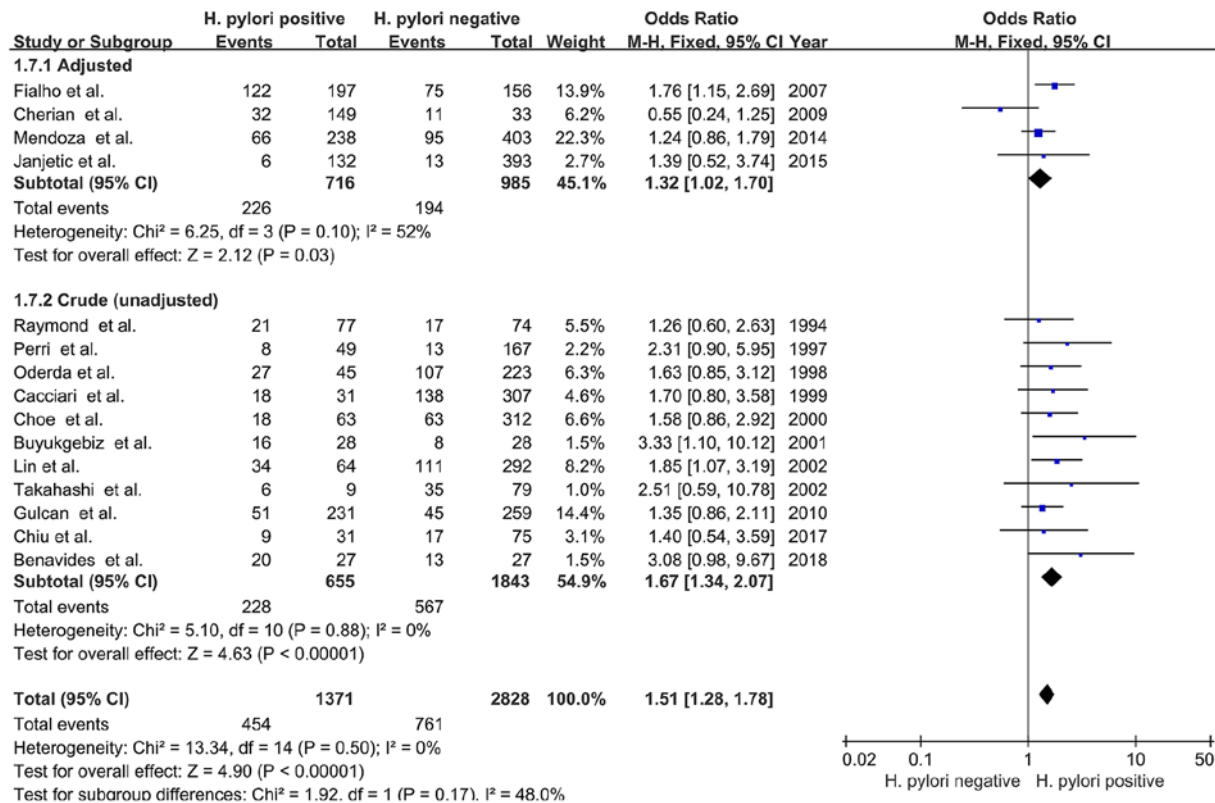
	H. pylori positive		H. pylori negative			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
1.7.1 Adjusted								
Fialho et al.	122	197	75	156	13.9%	1.76 [1.15, 2.69]	2007	
Cherian et al.	32	149	11	33	6.2%	0.55 [0.24, 1.25]	2009	
Mendoza et al.	66	238	95	403	22.3%	1.24 [0.86, 1.79]	2014	
Janjetic et al.	6	132	13	393	2.7%	1.39 [0.52, 3.74]	2015	
Subtotal (95% CI)		716		985	45.1%	1.32 [1.02, 1.70]		
Total events	226		194					
Heterogeneity: Chi² = 6.25, df = 3 (P = 0.10); I² = 52%								
Test for overall effect: Z = 2.12 (P = 0.03)								
1.7.2 Crude (unadjusted)								
Raymond et al.	21	77	17	74	5.5%	1.26 [0.60, 2.63]	1994	
Perri et al.	8	49	13	167	2.2%	2.31 [0.90, 5.95]	1997	
Oderda et al.	27	45	107	223	6.3%	1.63 [0.85, 3.12]	1998	
Cacciari et al.	18	31	138	307	4.6%	1.70 [0.80, 3.58]	1999	
Choe et al.	18	63	63	312	6.6%	1.58 [0.86, 2.92]	2000	
Buyukgebiz et al.	16	28	8	28	1.5%	3.33 [1.10, 10.12]	2001	
Lin et al.	34	64	111	292	8.2%	1.85 [1.07, 3.19]	2002	
Takahashi et al.	6	9	35	79	1.0%	2.51 [0.59, 10.78]	2002	
Gulcan et al.	51	231	45	259	14.4%	1.35 [0.86, 2.11]	2010	
Chiu et al.	9	31	17	75	3.1%	1.40 [0.54, 3.59]	2017	
Benavides et al.	20	27	13	27	1.5%	3.08 [0.98, 9.67]	2018	
Subtotal (95% CI)		655		1843	54.9%	1.67 [1.34, 2.07]		
Total events	228		567					
Heterogeneity: Chi² = 5.10, df = 10 (P = 0.88); I² = 0%								
Test for overall effect: Z = 4.63 (P < 0.00001)								
Total (95% CI)		1371		2828	100.0%	1.51 [1.28, 1.78]		
Total events	454		761					
Heterogeneity: Chi² = 13.34, df = 14 (P = 0.50); I² = 0%								
Test for overall effect: Z = 4.90 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 48.0%								

Figure 8. Forest plots of subgroup analysis based on confounders adjustment. The blue squares represent the OR value, whilst black diamonds represent the combined results of the included studies. *H. pylori*, *Helicobacter pylori*; df, degrees of freedom; M-H, Mantel-Haentzel.
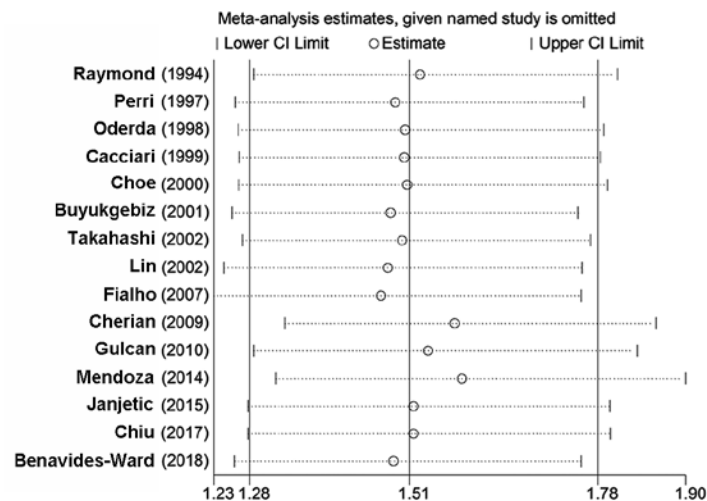
Figure 9. Sensitivity analysis of the association between *Helicobacter pylori* infection and delayed childhood growth.

by Chilengi *et al* (44), the subgroup analysis performed in the present study suggested that there was a significant association between *H. pylori* infection and delayed linear childhood growth, regardless of whether or not the potential confounders had been adjusted.

However, the present study had a number of limitations. First, although only medium- and high-quality studies were included, the 15 observational studies were of lower quality than randomized controlled trial which may have affected the objectivity of the major outcomes. Furthermore, delayed

childhood growth in the included studies was defined using different guidelines, resulting in different ranges of percentiles or 1-3 standard deviations. These criteria may have overlapped; therefore, they were not distinguished in the subgroup analyses. In addition, the age, growth rate and hormone levels of each group of children may have been different in each study, which may have further impacted the results of the present study. As another possible limitation, environmental factors, inter-individual differences and iron deficiency anaemia may also lead to malnutrition in children; therefore, management

Table V. Sensitivity analysis.

Author (year)	OR (95% CI)	Heterogeneity	Remainders' effect	(Refs.)
Raymond (1994)	1.52 (1.29-1.80)	I^2=1%; P=0.44	Z=4.89; P<0.00001	(32)
Perri (1997)	1.49 (1.26-1.76)	I^2=0%; P=0.49	Z=4.69; P<0.00001	(20)
Oderda (1998)	1.50 (1.27-1.78)	I^2=2%; P=0.43	Z=4.68; P<0.00001	(39)
Cacciari (1999)	1.50 (1.27-1.77)	I^2=2%; P=0.43	Z=4.71; P<0.00001	(40)
Choe (2000)	1.50 (1.27-1.78)	I^2=2%; P=0.42	Z=4.68; P<0.00001	(33)
Buyukgebiz (2001)	1.48 (1.25-1.75)	I^2=0%; P=0.58	Z=4.62; P<0.00001	(41)
Takahashi (2002)	1.50 (1.27-1.77)	I^2=0%; P=0.46	Z=4.78; P<0.00001	(42)
Lin (2002)	1.48 (1.24-1.76)	I^2=0%; P=0.47	Z=4.44; P<0.00001	(34)
Fialho (2007)	1.47 (1.23-1.75)	I^2=0%; P=0.47	Z=4.22; P<0.0001	(21)
Cherian (2009)	1.57 (1.33-1.86)	I^2=0%; P=0.89	Z=5.28; P<0.00001	(35)
Gulcan (2010)	1.53 (1.29-1.83)	I^2=0%; P=0.44	Z=4.75; P<0.00001	(36)
Mendoza (2014)	1.58 (1.32-1.90)	I^2=0%; P=0.44	Z=4.89; P<0.00001	(37)
Janjetic (2015)	1.51 (1.28-1.79)	I^2=2%; P=0.42	Z=4.85; P<0.00001	(38)
Chiu (2017)	1.51 (1.28-1.79)	I^2=2%; P=0.42	Z=4.85; P<0.00001	(43)
Benavides-Ward (2018)	1.48 (1.26-1.75)	I2=0%; P=0.54	Z=4.66; P<0.00001	(18)

OR, odds ratio.
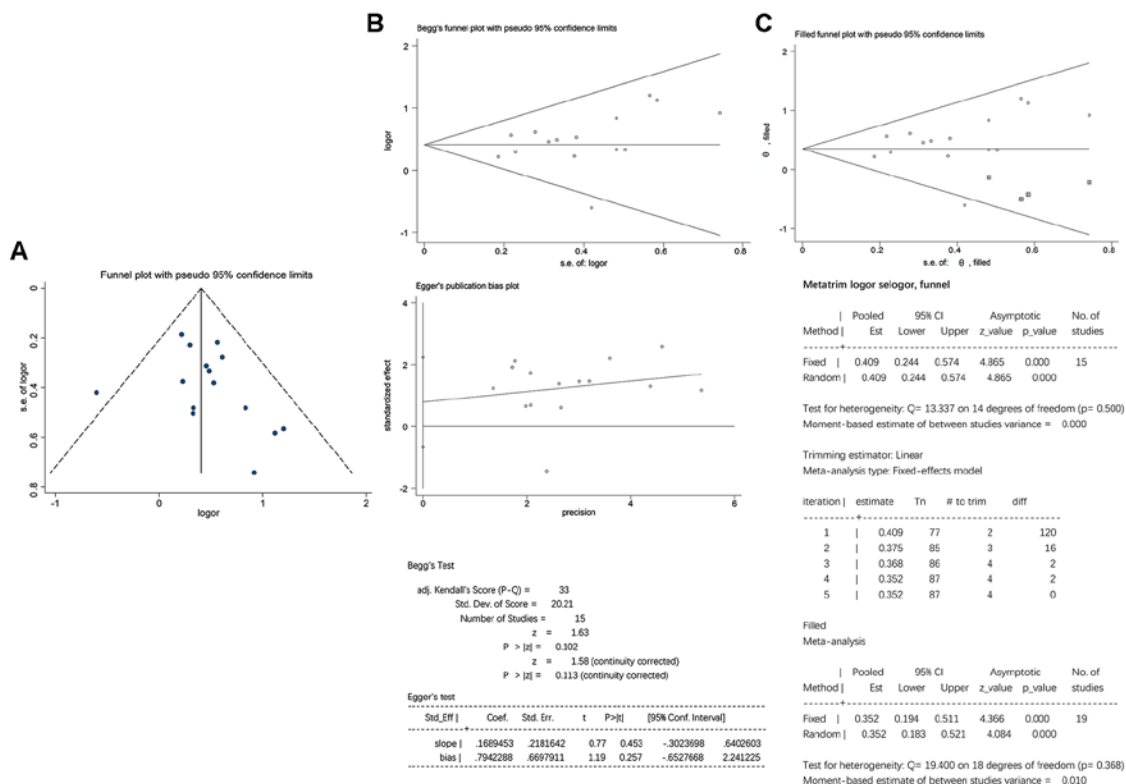
Figure 10. Evaluation of publication bias. (A) Funnel plots. (B) No significant publication bias was detected by Begg's (P>|z|=0.113) or Egger's (P>|t|=0.257) linear regression analyses. (C) Adjusted funnel plot using the trim and fill method. The data-points in squares indicate supplementary studies. OR, odds ratio; Std.Dev., standard deviation; P>|t|, 2-tailed P-value; Std_Eff, standard efficiency; Coef, coefficient; Std.Err./s.e., standard error; Conf Interval, confidence interval; adj, adjusted.

of the growth and development of *H. pylori*-positive children should fully consider these comprehensive factors. Finally, omission of relevant published or unpublished studies may have influenced the conclusions made in the present study.

In conclusion, the present study suggested that *H. pylori* infection increased the likelihood of delayed childhood growth, particularly linear growth. The results suggested that

children with delayed linear growth should be actively assessed and treated for *H. pylori* infection based on their antimicrobial susceptibility profile. Furthermore, it is necessary to establish a uniform standard definition for delayed childhood growth. Once diagnosed, the infection should be treated immediately to avoid further profound effects. Future extensive studies of vaccine strategies for the prevention of *H. pylori* infection

in children are required. Furthermore, future high-quality and well-designed studies should be performed to further investigate the results obtained in the present study.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

GZ and SW designed the study. SW and YD performed the literature search and extracted the data. LT, LP and XL analyzed the data. SW wrote the manuscript. All authors read and approved the final version of this manuscript.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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