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

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Received September 17, 2019; Accepted March 17, 2020

DOI: 10.3892/etm.2020.8654

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 13C-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).
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 $\chi^2$ test and $F$ index. $P<0.10$ and $F>50\%$ were considered to indicate statistically significant heterogeneity. $F$ values of 0-25, 26-50, 50-75 and >75% were considered to indicate low, medium and high heterogeneity, respectively (30).

Subgroup analyses were performed based on country/continent, *H. pylori* prevalence, 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 |
|---------------|-----------|---------------|---------|
| | Representativeness of the exposed cohort | Comparability of the cohorts on the basis of the design or analysis | Adequacy of cohort follow-ups | Score |
| | Selection of the non-exposed cohort | Assessment of the outcome | Was follow-up long enough for outcomes to occur? |
| | Ascertainment of exposure | | |
| | Demonstration that the outcome of interest was not present at the start of the study | |
| | | Adequacy of cohort follow-ups | |
| Raymond (1994) | + | + | + | 7 (32) |
| Benavides-Ward (2018) | + | + | + | 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 (for example, 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 |
|---------------|------------------------------------------|-------------------------------------------------|----------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------|
| 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                                                                                | Yes                                                                               | No                                                                | No                                                               | 8 (35)   |
| Gulc (2010)   | Yes                                      | Yes                                            | Yes                                   | Unclear                                 | Yes                                                                               | Yes                                                                              | Yes                                                                                | No                                                                | Yes                                                               | No                                                               | 8 (36)   |
| Mendoza (2014)| Yes                                      | Yes                                            | Yes                                   | Unclear                                 | Yes                                                                               | Yes                                                                              | No                                                                                 | No                                                                | Yes                                                               | No                                                               | 8 (37)   |
| Janjevic (2015)| Yes                                   | Yes                                            | Yes                                   | Unclear                                 | Yes                                                                               | Yes                                                                              | Yes                                                                                | Yes                                                                               | No                                                                | No                                                               | 9 (38)   |
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<0.0001), with no significant heterogeneity ($\chi^2=13.34; I^2=0\%$; $P_{\text{Heterogeneity}}=0.50$; 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; $Z=2.49$; $P=0.01$; $I^2=0\%$; $P_{\text{Heterogeneity}}=0.80$), America (OR, 1.50; 95% CI, 1.16-1.94; $Z=3.06$; $P=0.002$; $I^2=2\%$; $P_{\text{Heterogeneity}}=0.38$) and Asia (OR, 1.66; 95% CI, 1.25-2.20; $Z=3.49$; $P=0.0005$; $I^2=0\%$; $P_{\text{Heterogeneity}}=0.59$) 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; $Z=0.58$; $P=0.56$; $I^2=53\%$; $P_{\text{Heterogeneity}}=0.14$; 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; $Z=3.93$; $P<0.0001$; $I^2=0\%$; $P_{\text{Heterogeneity}}=0.99$) or >30 but ≤50% (OR, 1.43; 95% CI, 1.10-1.86; $Z=2.64$; $P=0.008$; $I^2=34\%$; $P_{\text{Heterogeneity}}=0.21$) was associated with *H. pylori* infection, with no significant heterogeneity ($\chi^2=1.38; I^2=0\%$; $P_{\text{Heterogeneity}}=0.50$). 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 ($\chi^2=1.24; I^2=0\%$; $P_{\text{Heterogeneity}}=0.54$; 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; $Z=3.14$; $P=0.002$; $I^2=0\%$; $P_{\text{Heterogeneity}}=0.86$) and serum IgG antibodies targeted against *H. pylori* (OR, 1.81; 95% CI, 1.35-2.44; $Z=3.97$; $P<0.0001$; $I^2=0\%$; $P_{\text{Heterogeneity}}=0.89$) 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; $Z=1.43$; $P=0.15$; $I^2=0\%$; $P_{\text{Heterogeneity}}=0.88$), 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

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| Author (year) | 13C-urea breath test | Serum IgG antibodies | Rapid urease test | Monoclonal faecal antigen enzyme immunoassay testing | PCR amplification of the 23S ribosomal |
|---------------|----------------------|----------------------|------------------|---------------------------------------------------|-------------------------------------|
| Oderda (1998) | +                    | +                    | no               | +                                                 | no                                  |
| Oderda (1998) | +                    | +                    | +                | +                                                 | +                                  |
| Cacciari (1999) | +                    | +                    | no               | +                                                 | no                                  |
| Buyukegebiz (2001) | +                    | +                    | no               | +                                                 | no                                  |
| Takahashi (2002) | +                    | +                    | no               | +                                                 | no                                  |
| Chiu (2017) | +                    | +                    | no               | +                                                 | no                                  |
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 [13C-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; \( I^2=0\%\); \( P_{\text{Heterogeneity}}=0.72\)), 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; \( I^2=33\%\); \( P_{\text{Heterogeneity}}=0.19\)). 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 (\( \chi^2=1.34; I^2=0\%\); \( P_{\text{Heterogeneity}}=0.51\); 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 (\( I^2=52\%\); \( P_{\text{Heterogeneity}}=0.10\)). 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 (\( I^2=0\%\); \( P_{\text{Heterogeneity}}=0.88\)). 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 (\( I^2=0-2\%\); \( P_{\text{Heterogeneity}}<0.10\)), 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 (\( P_{\text{Remainders' effect}}<0.0001\); 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
| 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 | Definition of Quality (Ref.s.) |
|-------------------|----------------------------------------|----------------|-------------|-------------|--------------|--------------------------------------|------------------------|----------------------------------|------------------------------|-------------------------------|--------------------------|----------------|-------------------------------|
| 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                         | Statute 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 ±1.12  | N/A          | Serum H. pylori IgG antibodies       | Height and weight     | 16/8                            | 12/20                        | 50.00                        | Statute 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)                           |
| 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 score (Refs.) | Quality score (Refs.) |
|-----------------------|-------------------------------------|--------------|-------------|-------------|--------------|------------------|-----------------------|------------------------------------|----------------------------|------------------------|------------------------------------------|------------------------|
| Cherian (2009)        | Sudan, Burundi and Liberia, Africa  | Cross-sectional | 182         | Mean ±4.3   | 93/89        | MFAT            | Weight, height and  | 32/11                              | 117/22                    | 81.87                  | Z-score <1.64 (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 | 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      | ^13C-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        | ^13C-UBT         | Height and weight   | 9/17                               | 22/58                      | 29.25                  | Height or weight-for-age below the 15th percentile | 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)                 |

^13C-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.
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 \textit{H. pylori}. The blue squares represent the OR value, whilst black diamonds represent the combined results of the included studies. \textit{H. pylori}, \textit{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. \textit{H. pylori}, \textit{Helicobacter pylori}; df, degrees of freedom; M-H, Mantel-Haentzel.
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-Schönlein 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),

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**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.
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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 13C-UBT and serum IgG antibodies targeted against H. pylori detection methods suggested that H. pylori infection was associated with delayed growth in children. Although 13C-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

| Study of Subgroup | H. pylori negative | H. pylori positive | 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, 5.98] | 1997 |
| Oderda et al.     | 27                 | 45                 | 107                         | 223  | 6.3% | 1.83 [0.85, 3.12] | 1998 |
| Caciari et al.    | 18                 | 31                 | 138                         | 207  | 4.6% | 1.70 [0.80, 3.68] | 1999 |
| Lin et al.        | 34                 | 64                 | 111                         | 292  | 8.2% | 1.85 [1.07, 3.18] | 2002 |
| Takahashi et al.  | 6                  | 9                  | 35                          | 79   | 1.0% | 2.51 [0.59, 10.79] | 2007 |
| Fialho et al.     | 122                | 197                | 75                          | 156  | 13.9% | 1.76 [1.15, 2.69] | 2014 |
| Mendes et al.     | 66                 | 233                | 95                          | 403  | 22.3% | 1.24 [0.86, 1.79] | 2019 |
| Benavides et al.  | 20                 | 27                 | 13                          | 27   | 1.5% | 3.08 [0.88, 10.67] | 2016 |
| Subtotal (95% CI) | 669                |                    | 1594                        | 69.9% | 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 < 0.000001)

1.6.2 Height and weight

Raymond et al. | 21 | 77 | 17 | 74 | 5.5% | 1.28 [0.60, 2.63] | 1994 |
| Choe et al.    | 18 | 63 | 63 | 312| 6.6% | 1.58 [0.86, 2.92] | 2000 |
| Buyulgubic et al. | 16 | 28 | 8  | 28 | 1.5% | 3.33 [1.10, 10.12] | 2001 |
| Cheriyan et al.| 32 | 149| 11 | 33 | 6.2% | 0.55 [0.24, 1.29] | 2009 |
| Gutman et al.  | 31 | 231| 45 | 289| 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 [1.06, 1.75] |      |
| Total events   | 147|      | 101|      |      |      |      |

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 [0.62, 3.74] | 2015 |
| Subtotal (95% CI) | 132|      | 393| 2.7% | 1.39 [0.62, 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 < 0.000001)
Test for subgroups 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.
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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...
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 are needed. **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.
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.

Acknowledgements
Not applicable.

Funding
The present study was supported by the National Natural Science Foundation of China (grant no. 81770561), the Jiangsu Medical Leading Talent and Innovation Team (grant no. CXTDA2017033) and the Jiangsu Province ‘333’ Project (grant no. BRA2014332).

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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