

# *Helicobacter pylori* infection is not associated with failure to thrive: a case control study

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**Purpose:** The long-term impact of *Helicobacter pylori* infection is complex, and concerns about the need for eradication exist. We conducted this case control study to investigate the association between *H. pylori* infection and failure to thrive (FTT).

**Patients and methods:** From January 2009 to December 2011, 53 children with FTT group and matched children with the same sex and age and similar socioeconomic status without FTT (control group) were enrolled. A questionnaire was administered to the parents/guardian, and a <sup>13</sup>C-urea breath test was performed to detect *H. pylori* infection.

**Results:** We found that the total prevalence of *H. pylori* infection was 29.2% and that there was no association between FTT and *H. pylori* infection (FTT group: 32%; control group: 26.4%;  $P=0.67$ ). Short stature was more common in the FTT group and abdominal pain in the control group (FTT group: 37.7%; control group: 11.3%;  $P=0.003$ ). In a comparison between the *H. pylori*-positive and -negative groups, abdominal pain (87.1% vs 64%;  $P=0.032$ ) and the frequency of endoscopy (74.2% vs 32%;  $P<0.001$ ) were significantly more common in the *H. pylori*-positive group.

**Conclusion:** We found that children with *H. pylori* infection are at an increased risk for abdominal pain and that FTT is not associated with *H. pylori* infection. The decision for eradication should be evaluated carefully and individualized.

**Keywords:** *Helicobacter pylori*, <sup>13</sup>C-urea breath test, failure to thrive, growth retardation, children

## Introduction

*Helicobacter pylori* infection is one of the most common causes of chronic infection and is associated with a variety of disorders. The prevalence of *H. pylori* infection ranges from approximately 10% to 90% and is influenced by country, age, socioeconomic background, nutritional status, urbanization, and hygiene.<sup>1-4</sup> While its prevalence appears to be declining in developed countries, it remains a major problem in developing nations.<sup>4</sup> The transmission pathway remains highly controversial and has not yet been definitively elucidated. Infection among family members is common, and the oral-oral route seems to be the most probable transmission pathway. Moreover, risk factors for infection are associated with a lower socioeconomic status, including overcrowding, unhygienic conditions, sharing beds during childhood, and a low maternal educational level.<sup>5,6</sup>

*H. pylori* infection is associated with several disorders, but the impact of infection is a subject of debate. In general, gastric infection with *H. pylori* is a risk factor for the development of chronic gastritis, peptic ulcers, gastric adenocarcinoma, short stature, and iron deficiency anemia (IDA).<sup>7-11</sup> *H. pylori* infection is also associated with a number of extragastric disorders, such as eye, skin, respiratory, and psychiatric disorders.<sup>7,12-15</sup>

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However, *H. pylori* infection may be beneficial for several diseases, such as asthma, obesity, and inflammatory bowel disease.<sup>16–19</sup> The role and pathophysiology of *H. pylori* remain poorly understood, and knowledge regarding infection continues to advance. Therefore, it is necessary to weigh the pros and cons of the need to screen and treat *H. pylori* infection. In addition, the impact of *H. pylori* infection on childhood growth and development is also controversial. Some studies suggest that gastric infection with *H. pylori* is associated with suboptimal nutrition and delayed growth during childhood. Although some studies have suggested that *H. pylori* infection affects growth,<sup>20</sup> others disagree.<sup>21,22</sup>

To describe the clinical features of *H. pylori* infection and assess its role in the development of childhood malnutrition and growth retardation, we conducted this case control study. Specifically, we investigated the association between the weight-for-age of children and *H. pylori* infection in a randomly selected population of children with similar diets and socioeconomic backgrounds in Taiwan.

## Patients and methods

### Study design and population

This prospective case control study, approved by the Committee for Clinical Investigation at MacKay Memorial Hospital, was conducted from January 2009 to December 2011 (approval no: MMHIS639). Children aged 4–18 years with failure to thrive (FTT) were enrolled in our study. FTT was defined as unsatisfactory body weight-for-age (less than 15th percentile) per the recommendations of National Center for Health Statistics and previous studies.<sup>23</sup> After a detailed explanation of the study, written informed consent was obtained from the children (whenever possible) and their parents. Children unable to perform the <sup>13</sup>C-urea breath test (<sup>13</sup>C-UBT) were excluded. We also obtained information regarding age, sex, family income, overcrowding (ie, ratio of total residents per household to the number of rooms and number of persons per bed), type of water consumed, mother's education, and breast-feeding. Once a child with FTT was enrolled in our study group, a matched child with the same age, sex, and similar socioeconomic status without FTT was assigned to the control group. One of the authors conducted the interviews, collected breath samples, and recorded the children's height and weight. The <sup>13</sup>C-UBT was performed in both groups to detect *H. pylori* infection, and the clinical manifestations, as well as the laboratory tests, were analyzed. Complete blood tests and biochemistry tests were performed and endoscopy done in some children with refractory abdominal pain. The need for an endoscopy

depended on the clinical symptoms, treatment responses, and the judgment of pediatric gastrointestinal specialists.

### Height and weight measurement

One of the authors recorded the standing height (cm) and weight (kg) for each subject. Standard deviation (SD) scores and the percentile values for weight and height were calculated for each child according to the National Center for Health Statistics (NCHS) standardized values for Taiwan.<sup>23</sup> Children with a weight-for-age below the 15th percentile value were defined as FTT, and children with a height-for-age below the 15th percentile value were defined as having short stature.

### <sup>13</sup>C-UBT

The <sup>13</sup>C-UBT was performed after a fasting period of 6 h. After providing an initial breath sample, the children received a 100 mL glass of orange juice containing 50 mg <sup>13</sup>C-urea (for those less than 30 kg) or 75 mg of <sup>13</sup>C of urea (for those more than 30 kg). A second breath sample was collected 30 min later. The samples were analyzed with an infrared spectrometer (IRIS; Wagner Isotope Analysen Technik, Bremen, Germany). The results were considered positive when the delta over baseline (DOB) was 4.0.<sup>5,24</sup>

### Statistical analyses

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 15 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the  $\chi^2$  test and the Fisher's exact test. Continuous variables were compared using the Student's *t*-test. A multivariate logistic regression model was used to assess the independent effect of *H. pylori* status and the percentile for weight.  $P < 0.05$  was considered statistically significant. Variables with  $P$ -values  $< 0.25$  were included in the logistic regression model, such as short stature and abdominal pain. Odds ratio (OR) and 95% confidence intervals (CIs) were used as an estimate of the risk. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate the fit of the models. The nutritional status was scored using the EPINUT program (EpiInfo, version 6; CDC, Atlanta, GA, USA).

### Results

About 106 children were enrolled in our study ( $n=53$  in the FTT group and  $n=53$  in the control group). Of these, 64 (60.4%) were boys, and the mean age was  $11 \pm 3.74$  years. The overall prevalence of *H. pylori* infection was 29.2%, with 32% in the FTT group and 26.4% in the control group, but this difference was not statistically significant

( $P=0.67$ ) (Table 1). Short stature was found to be more common in children with FTT (37.7% vs 11.3%;  $P=0.003$ ), but the frequency of abdominal pain was lower (56.6% vs 84.9%;  $P=0.003$ ). Myopia was reported in six children in the control group, but none in the FTT group. Endoscopy was performed in 47 (44.3%) children, and gastritis/gastric ulcer was the most common finding (40, 85.1%). In a comparison between the *H. pylori*-positive and -negative groups, the children with *H. pylori* infection were found to be older and predominantly male (Table 2). In addition, abdominal pain (87.1% vs 64%;  $P=0.032$ ) and the frequency of endoscopy (74.2% vs 32%;  $P<0.001$ ) were significantly more common in the *H. pylori*-positive group. Our findings indicate that *H. pylori* infection was not associated with FTT in this case control study. Furthermore, FTT was associated with short stature, while children with *H. pylori* infection were at a higher risk for developing abdominal pain.

## Discussion

Infection with *H. pylori* is common, and the disease burden is substantial. The prevalence of *H. pylori* infection differs according to country, ethnicity, age, socioeconomic background, nutritional status, urbanization, public hygiene, and

**Table 1** Characteristics of the FTT and control groups

Clinical characteristics	Overall (n=106)	FTT group (n=53)	Control group (n=53)	P-value
Age, years	11±3.74	11±3.76	11±3.76	>0.99
Male, n (%)	64 (60.4)	32 (60.4)	32 (60.4)	
HP infection, n (%)	31 (29.2)	17 (32.0)	14 (26.4)	0.67
Short stature, n (%)	26 (24.5)	20 (37.7)	6 (11.3)	0.003*
Clinical symptoms				
Abd pain, n (%)	75 (70.8)	30 (56.6)	45 (84.9)	0.003*
Constipation, n (%)	27 (25.5)	13 (24.5)	14 (26.4)	>0.99
GERD, n (%)	26 (24.5)	10 (18.9)	16 (30.2)	0.26
Associated diseases				
Asthma	11 (10.4)	4 (7.5)	7 (13.2)	0.52
Allergic rhinitis	21 (19.8)	8 (15.1)	13 (24.5)	0.33
Myopia	6 (5.7)	0 (0)	6 (11.3)	0.036*
ADHD	14 (13.2)	6 (11.3)	8 (15.1)	0.77
Laboratory tests				
IDA	15 (22.7)	6 (22.2)	9 (23.1)	0.83
PES	47 (44.3)	18 (34.0)	29 (54.7)	0.05
EU	11 (23.4)	4 (22.2)	7 (24.1)	0.84
GU	40 (85.1)	15 (83.3)	25 (86.2)	0.88
DU	32 (68.1)	12 (66.7)	20 (69.0)	0.87

**Notes:** For categorical variables, the results are expressed as number (%), and for continuous variables, the results are expressed as mean ± standard deviation. A  $P$ -value  $<0.05$  was considered statistically significant between FTT and control groups and indicated by an asterisk (\*).

**Abbreviations:** HP, *Helicobacter pylori*; Abd pain, abdominal pain; GERD, gastroesophageal reflux disease; ADHD, attention deficit hyperactivity disorder; IDA, iron deficiency anemia; PES, endoscopy; EU, esophagitis/esophageal ulcer; GU, gastritis/gastric ulcer; DU, duodenitis/duodenal ulcer; FTT, failure to thrive.

**Table 2** Comparison between *Helicobacter pylori*-positive and -negative groups

Clinical characteristics	Overall (n=106)	HP (+) group (n=31)	HP (-) group (n=75)	P-value
Age, years	11±3.74	12.8±3.41	10.25±3.64	0.75
Male, n (%)	64 (60.4)	22 (71.0)	42 (56.0)	0.22
FTT, n (%)	53 (50.0)	17 (54.8)	36 (48.0)	0.67
Short stature, n (%)	26 (24.5)	9 (29.0)	17 (22.7)	0.67
Clinical symptoms				
Abd pain, n (%)	75 (70.8)	27 (87.1)	48 (64.0)	0.032*
Constipation, n (%)	27 (25.5)	8 (25.8)	19 (25.3)	0.85
GERD, n (%)	26 (24.5)	9 (29.0)	17 (22.7)	0.66
Associated diseases				
Asthma	11 (10.4)	2 (6.5)	9 (12.0)	0.62
Allergic rhinitis	21 (19.8)	4 (12.9)	17 (22.7)	0.38
Myopia	6 (5.7)	2 (6.5)	4 (5.3)	0.81
ADHD	14 (13.2)	2 (6.5)	12 (16.0)	0.31
Laboratory tests				
IDA	15 (22.7)	8 (25.8)	7 (9.3)	0.08
PES	47 (44.3)	23 (74.2)	24 (32.0)	<0.001*
EU	11 (23.4)	6 (26.0)	5 (20.8)	0.94
GU	40 (85.1)	21 (91.3)	19 (79.2)	0.45
DU	32 (68.1)	18 (78.3)	14 (58.3)	0.25

**Notes:** For categorical variables, the results are expressed as number (%), and for continuous variables, the results are expressed as mean ± standard deviation. A  $P$ -value  $<0.05$  was considered statistically significant between HP (+) and HP (-) groups and indicated by an asterisk (\*).

**Abbreviations:** HP, *Helicobacter pylori*; Abd pain, abdominal pain; FTT, failure to thrive; GERD, gastroesophageal reflux disease; ADHD, attention deficit hyperactivity disorder; IDA, iron deficiency anemia; PES, endoscopy; EU, esophagitis/esophageal ulcer; GU, gastritis/gastric ulcer; DU, duodenitis/duodenal ulcer.

diagnostic tools available.<sup>1-4</sup> As general public hygiene and sanitation improved, the infection rate has been decreasing.<sup>4</sup> Chi et al<sup>1</sup> reported that the *H. pylori* infection rate based on <sup>13</sup>C-UBT in a rural area in Taiwan was 54.7% in 2008. Mackay Memorial Hospital is a tertiary referral hospital in an urban area, and the prevalence of *H. pylori* infection in the current study was 29.2%. In addition, the different diagnostic methods used in each study also impact the prevalence. Endoscopic culture is the gold standard for diagnosis, but is not readily available for children.<sup>6,25</sup> A serum immunoglobulin G (IgG) test is relatively noninvasive and widely used but should be interpreted with caution.<sup>25</sup> Another study that measured *H. pylori* infection via serum IgG levels found that there was a prevalence of 15.1% in central, urban Taiwan in 2006.<sup>3</sup> In addition, a systematic review assessing the prevalence of *H. pylori* infection in the People's Republic of China and the US according to the serum IgG levels shows a weighted mean prevalence of 66% for Chinese rural populations and 47% for Chinese urban populations.<sup>4</sup> The weighted prevalence in the US from 1990 to 2006 was 35%.<sup>4</sup> <sup>13</sup>C-UBT is noninvasive, highly sensitive, and specific

and thus could be used to investigate epidemiological results and assess the efficacy of eradication therapy.<sup>24-26</sup> In general, *H. pylori* infection is common in both developed and developing countries and warrants our attention.

While infection with *H. pylori* infection is common, the various effects of the disease are complex. It is associated with many disorders, and the strongest association is with chronic gastritis and peptic ulcers.<sup>7</sup> Our findings also support this association. In addition, patients with *H. pylori* infection have a higher risk of gastric adenocarcinoma.<sup>11,27</sup> Higher risk of colorectal neoplasia in patients with *H. pylori* infections is also reported.<sup>28</sup> The unfavorable influences of *H. pylori* include a short stature and IDA,<sup>29</sup> although these were not evident in our study. However, *H. pylori* infection does not always have negative consequences, and some effects may be beneficial. For example, a cross-sectional study revealed that adults younger than 40 years of age with an *H. pylori* infection had an inverse correlation with asthma (OR: 0.503).<sup>30</sup> The beneficial relationship between *H. pylori* infection and other atopic diseases, obesity, and inflammatory bowel disease has also been demonstrated.<sup>7,16,17,19,31</sup> Therefore, the decision to screen and eradicate infection with *H. pylori* should be individualized, and the pros and cons weighed. Growth and FTT are an important but complex issue, and thus, assessing the association between *H. pylori* infection and growth is highly complex. Some studies report that *H. pylori* may cause FTT, but the evidence is conflicting.<sup>20,22,32</sup> We have summarized the findings of some studies in Table 3.<sup>1,20,21,32-35</sup> The nature of the case control design could decrease these influencing factors. Our study reveals that there is no association between FTT and *H. pylori* infection. Therefore, physicians should not overtreat *H. pylori*-infected children with FTT.

We found that abdominal pain (87.1% vs 64%;  $P=0.032$ ) and the frequency of endoscopy (74.2% vs 32%;  $P<0.001$ ) were significantly more common in the *H. pylori*-positive group. There are concerns about whether endoscopy may

increase the risk of *H. pylori* infection. The <sup>13</sup>C-UBT was performed on children before undergoing endoscopy in our study; hence, the diagnosis of *H. pylori* was not affected by the endoscopy. Furthermore, Ribeiro et al<sup>36</sup> found the efficacy of endoscope disinfection was excellent. No detectable transmission of *H. pylori* was noted when sterilized biopsy forceps and stringent disinfection standards were employed.

## Limitations

Our study had some limitations. First, endoscopy was not routinely performed, and bacterial cultures were not obtained. According to the guidelines of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN); and other studies, culture-guided eradication contributes to successful treatment owing to the increase in drug resistance, and the regimen of eradication therapy is changing.<sup>6,37</sup> However, it is relatively invasive and is not readily available in children. Therefore, culture-guided treatment is not routinely used in children, and <sup>13</sup>C-UBT is a useful substitute to evaluate the response of eradication.<sup>7</sup> Second, assessing the association between *H. pylori* infection and growth is multifactorial and highly complex. The design of the case control study could minimize the influence of covariates, but the case number is still not adequate in the current study. Further large-scale case control study is warranted to consolidate the association between *H. pylori* infection and FTT.

## Conclusion

In conclusion, *H. pylori* infection is common, and its role and impact on growth remain controversial. The present study compared the *H. pylori* infection status in children with FTT and a matched control group. Our findings indicate that there is no association between FTT and *H. pylori* infection. Therefore, physicians should not overtreat *H. pylori*-infected

**Table 3** Studies investigating the association between *Helicobacter pylori* and FTT

Study	Country	Method	Prevalence of <i>H. pylori</i>	Associated with FTT?
Richter et al <sup>20</sup> (2001)	Germany	<sup>13</sup> C-UBT	Boys: 7.2% Girls: 6.1%	Yes for boys No for girls
Özçay et al <sup>21</sup> (2002)	Turkey	<sup>13</sup> C-UBT, histology	55.1%	No
Miller et al <sup>33</sup> (2003)	USA	Serum IgG antibodies	31.0%	No
Sood et al <sup>34</sup> (2005)	UK	<sup>13</sup> C-UBT	37.7%	Yes
Chi et al <sup>1</sup> (2009)	Taiwan	<sup>13</sup> C-UBT	54.7%	No
Kopáčová et al <sup>35</sup> (2014)	Czech Republic	<sup>13</sup> C-UBT	23.5%	No
Muhsen et al <sup>32</sup> (2015)	Israel	Stool antigen	53.0%	No
Current study	Taiwan	<sup>13</sup> C-UBT	29.2%	No

**Abbreviations:** <sup>13</sup>C-UBT, <sup>13</sup>C-urea breath test; FTT, failure to thrive; IgG, immunoglobulin G.



children with FTT. The decision for eradication should be evaluated carefully and individualized.

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## Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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