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Long-Term Effects of Clearing *Helicobacter pylori* on Growth in School-Age Children

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Abstract

Background—A new *H. pylori* infection affects growth velocity negatively, and clearing the infection produces a small significant rebound, but it is not known whether height and weight in children are impacted over the long term.

Methods—We investigated 295 school-age children followed in two cohorts, one treated (150) and one untreated (145), from 2004 for 3.7 years with 1105 child-years of observation. Follow-up intervals were 3 months for anthropometry measurements and 6 months for *H. pylori* status ascertained by urea breath test. Height in centimeters and weight in kilograms were analyzed using growth models.

Results—A multivariate mixed model that adjusted for age, sex, father's education and number of siblings found no significant differences in height or weight at baseline by *H. pylori* status. The same model showed a significant impact of clearing *H. pylori* across time, with increasing significant differences in average height and weight as the follow-up progressed.

Conclusions—Children who were always negative or who cleared the infection grew significantly faster than those who stayed positive after adjusting for other covariates. This study suggests that school age children's growth benefits from being treated for *H. pylori* infection.

Keywords

Helicobacter pylori; height; weight; growth velocity

Introduction

Helicobacter pylori infection has been recognized as one of the most common chronic bacterial infections in humans with prevalences varying around 20% in European studies, ~60% in South America and ~50% among Asian populations on average.¹ Most children are colonized in early childhood, and in a substantial number of cases the infection will last many years unless the child is treated with appropriate antibiotics.¹

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H. pylori infection has been implicated as a causal link for chronic gastritis, gastric and duodenal ulcers and gastric cancer.²⁻³ It may produce partial loss of the gastric acid barrier among children and this may result in chronic diarrhea, malnutrition due to impaired nutrient absorption, direct nutrient losses, or increased metabolic requirements.⁴ The infection has also been reported to be associated in children with iron deficiency⁵ and the retardation of growth.⁶

An apparent negative impact of *H. pylori* infection on growth velocity or height has been documented in cohort studies in infants^{6,7,8} and school age children⁹, as well in several well designed cross-sectional studies^{10,11,12}. Although the amount and quality of the evidence seems to support the association of *H. pylori* infection and growth, it is not known whether attained height and weight in children will be impacted over the long term.

The objective of this study is to investigate the long term effect on height and weight of acquiring or clearing *H. pylori* infection in school-age children.

Methods

Subjects and Design

Two cohorts of school-age children were recruited in separate rural communities in the Andean region of Nariño, Colombia and followed for an average of 3.7 years. One of the cohorts was offered anti-helicobacter treatment. The two communities were similar in size, demography and socioeconomic status. Details on the history of the communities and the cohorts can be found elsewhere.⁹ In short, at baseline, children from both communities were tested for *H. pylori* infection and measured for height and weight. Study staff interviewed the child's primary caretaker, using a structured questionnaire to record information on demographics, household composition, and general socioeconomic and hygiene-related factors. Follow-up began at 6 months post baseline and occurred at 3-month intervals thereafter. At each follow-up visit, the children's height and weight were measured in duplicate using the procedure recommended in Lohman's anthropometric standardization reference manual.¹³ Fresh stool specimens were collected from the children for ova and parasite examination. Every six months, children were tested for *H. pylori* status with the ¹³C-urea breath test.¹⁴

Children who tested positive for *H. pylori* at baseline from the treated cohort received directly supervised treatment with lansoprazole (30 mg/kg/day for children <30Kg, 60 mg/kg/day for children ≥30kg), amoxicillin (50 mg/kg/day), metronidazole (30 mg/kg/day), and bismuth (262 mg/day) for 14 days. Study staff administered the medications twice daily either at the health care center or the child's home. Treated children were given an additional breath test around 3 months post treatment. Those whose treatment failed were re-treated once as soon as practicable. Written informed parental consent was obtained in accordance with the standards of the Vanderbilt University review board and the research ethics committee of the Universidad del Valle.

Statistical Analysis

Height and weight were considered outcome measurements. The exposure of interest, *H. pylori* status, was evaluated each time a breath test was done. Because both outcomes are age-dependent, estimates were adjusted for non-linear relationship with age at each measurement. Visit number was used as a proxy for time elapsed since baseline, and was not completely collinear with age, since the visits did not occur precisely on schedule. We assessed socio-environmental factors to control confounding by poverty-related determinants of *H. pylori* prevalence and growth. These include presence of protozoa or intestinal parasites, modeled as time-dependent, and factors that did not change over time

(ascertained at baseline): sex, community of residence, mother's and father's education, number of siblings, time at current address, residential stability, type of housing, number of people in the house, number of rooms in the house, and household density (people/rooms).

Outcomes were evaluated with growth models that used non-linear (age) and linear random and fixed covariates such as gender in a mixed model. These models account for the intra-person variability accrued by multiple measurements on the same child. Separate growth models were constructed for height and weight. The coefficient for the *H. pylori* exposure depicts its overall effect *at any point in time*. An interaction term was built for each visit, so that the coefficient (log-odds) of the interaction between the exposure and each visit measures the size of the effect at each point in time where measurements were taken.

For ease of explanation, marginals (average means) in the appropriate measurement scale for the best fitting growth models for height and weight were obtained, after adjusting for non-linear age, sex and a set of significant covariates for each model. All statistical analysis were carried out using STATA® version 11.

Results

Baseline characteristics of children by cohort appear in SDC 1 (table). Three hundred and nineteen children enrolled in the study and were followed for an average length of 3.7 years (median 3.7, range 0.5-3.8). The intervention (treated) cohort included 162 children (53%) who received anti-helicobacter treatment. In total, 24 children were lost to follow up (12 per group) for a rate of 7.5% over the period of observation or 2.1% per year. Two hundred and ninety five children had measurements and complete data at visit 14, for an average of 43.6 months per subject with a maximum of 45.9 months. Baseline visits occurred between August and October 2004 and the last visit used for this analysis occurred in June 2008.

At the first breath test measurement, 78.7% of 319 children tested positive for *H. pylori*. There were no significant differences in *H. pylori* status by sex, but positive children were significantly older on average than negative children, with mean ages of 6.4 years (95% CI 5.62 - 6.23) for positive and 5.9 years (95% CI 6.25 - 6.57) for negative children. The treated cohort had 9% lower *H. pylori* infection prevalence (see Table, SDC 1), but no other factors were found to be associated with infection status at baseline in a multivariate logistic model.

At the post-treatment breath test measurement, in the treated cohort 72.7% (112/154, 95% CI 65.7 - 79.8%) tested negative for *H. pylori*. The percentage of those who remained uninfected declined slowly but significantly (χ^2 test, $p < 0.001$), to 66% (101/153, 95% CI 58.5% - 73.5%) at visit 8 and 52.7% (79/150, 95% CI 44.6 - 60.7%) at the last visit. In the untreated cohort, the proportion uninfected declined slowly but non-significantly from 16% (25/156, 95% CI 10.5 - 22.2%) at baseline to 10.3% (15/145, 95% CI 5.3 - 15.3%) at the last visit.

Height

At the baseline visit, after adjusting for age and sex, cohort membership, father's education, number of siblings and presence of helminths/protozoa in the stool, there was no significant difference in average height between children who had a negative breath test (n=68) compared to those who tested positive (n=251).

At baseline, according to the same multivariate model, each additional year of father's education increased the children's average height by 0.26 cm (95% CI 0.105 - 0.418) in both treated and untreated cohorts. By the same token, each additional sibling reduced the

children's average height by 0.63 cm (95% CI 0.302 - 0.965). At the end of observation period, children from the treated cohort were 2.98 cm (95% CI 2.04 - 3.94) taller on the average than children from the untreated cohort after adjusting for all of the key baseline variables.

Helminths presence at baseline was included in the same model, and it reduced non-significantly ($p = 0.061$) by -1.33 cm 95% CI 0.06 - 2.73 the average baseline height of any child. Protozoa were not significantly associated with height.

The multivariate height-based growth model included the following variables: age and the square of age, sex, father's education, number of siblings, cohort, visit number, *H. pylori* status and the interaction between *H. pylori* status and visit number. Variables considered fixed, because they do not change over time, were sex, father's education, number of siblings and cohort type. Age and visit number are not collinear since the visits were not uniformly spaced over time. *H. pylori* status and presence of helminths/protozoa were considered random variables since they may be classified in a different category at each visit.

The changes over time in height were similar by gender, and the significant age and the square of age coefficients in the multivariate model correspond closely to the expected changes in the growth model for children. The coefficients for variables such as father's education (see Table, SDC 2), and number of siblings are very similar to those of the baseline model and have the same interpretation.

Supplemental Digital Content 2 (table) has the coefficients in centimeters for the difference in average height associated with *H. pylori* status at every visit except baseline (visit 0), which is used as a referent. Each coefficient depicts the difference in centimeters favoring *H. pylori* negative children as the visits accumulate. The differences in centimeters (coefficients) at each visit do not become statistically significant until visit 4, and they get notably and progressively larger as the children age.

Using the statistical model to obtain average heights at the corresponding age for each point in time we found that *H. pylori* negative and positive children had similar average heights of 108.9 cm (95% CI 108.4 - 109.4) and 109.3 (95% CI 108.7 - 109.7), respectively, at baseline. By the last visit, *H. pylori*-negative children had an average height of 130.5 cm (95% CI 129.9 - 131.1), more than a full centimeter taller than the average height of *H. pylori*-positive children of 129.4 cm (95% CI 128.8 - 129.8).

Another way of depicting the same changes is to use only the 295 children with complete data in a multivariate model and stratify them by *H. pylori* status and baseline and the last visit. Children who were always positive ($n=177$) accumulated from baseline to the last visit an average height difference of 19.8 cm (95% CI 19.4-20.2), while children who were negative at baseline and became positive ($n=24$) had an average height difference of 20.1 cm (95% CI 19.2-20.9). Those positive at baseline who cleared the infection ($n=55$) had an average height difference of 21.3 cm (95% CI 20.5-22.1) while children that were always negative ($n=39$) had an average height difference of 21.5 cm (95% CI 20.5-22.7). There were statistically significant differences between the first (always positive) and the last two groups (cleared the infection and always negative). Average heights for each group at baseline and last visit can be seen in Figure 1.

Weight

At the baseline visit, and after adjusting for age and sex, cohort, father's education, number of siblings and presence of helminths/protozoa in the stool there was no significant

difference in average weight between children who had a negative breath test (n=68) and those who tested positive (n=251).

At baseline, according to the same multivariate model, every additional year of the father's education increased the children's average weight by 0.14 kg 95% CI 0.06 - 0.22 in either cohort. By the same token, every additional sibling reduced the children's average weight by 0.27 kg (95% CI 0.10 - 0.46). The children from the treated cohort were 1.1 kg (95% CI 0.64 - 1.64) heavier on average than the children from the untreated cohort after adjusting for all of the key variables at baseline. There was a trend, though statistically non-significant (p=0.08), for the presence of helminths affecting the children's weight. Protozoa were not significantly associated with weight.

The multivariate weight-based growth model was identical to the height model and included the same variables: age and the square of age, sex, father's education, number of siblings, cohort, visit number, *H. pylori* status and the interaction between *H. pylori* status visit and number. The changes over time in weight were similar by gender, and the significant age and the square of age coefficients in the multivariate model correspond closely to the changes in the growth model. The coefficients for the fixed variables father's education (see Table, SDC 3), number of siblings and cohort type are very similar as those of the baseline model and have the same interpretation.

The changes in the coefficients of the multivariate weight model seen in SDC 3 (table) are nonetheless very different. The coefficients are smaller, for the most part, and not consistently negative through visit 11. A statistically significant detrimental effect of *H. pylori* on weight starts at visit 12 (-0.73 cm), and it remains negative, significant and increasing in size through visit 14.

Obtaining average means for variables that do not change over time and at the corresponding age for each point in time from the multivariate mixed model, we found that *H. pylori* negative and positive children had nearly identical average weights of 18.9 kg (95% CI 18.4 - 19.4) and 18.8 kg (95% CI 18.4 - 19.2), respectively, at baseline. By the last visit, *H. pylori*-negative children had an average weight of 28.6 kg (95% CI 28.2 - 29.0), nearly a full kilogram more than *H. pylori*-positive children, who had an average weight of 27.7 kg (95% CI 27.4 - 28.1).

Using again only the 295 children with complete data, we found that children who were always positive (n=177) accumulated from baseline to the last visit an average weight difference of 8.8 kg (95% CI 8.4 - 9.3), while children who were negative at baseline and became positive (n=24) had an average weight difference of 8.1 kg (95% CI 7.2 - 8.9). Those positive at baseline who cleared the infection (n=55) had an average weight difference of 10.1 kg (95% CI 9.3 - 10.7) while children that were always negative (39) had an average weight difference of 9.3 kg (95% CI 8.5 - 10.1). Average weights for each group at baseline and last visit can be seen in Figure 2.

Discussion

Our study on the long-term effect of clearing *H. pylori* infection among schoolchildren has shown that there was a steady comparative gain in height and weight after adjusting for other factors associated with reduced growth in our population.

The growth model provided a very good statistical fit to the non-linear relationship between age, sex and elapsed time in a multivariate mixed model. The coefficients for the interaction between *H. pylori* status and time (as marked by visit number), which estimate the effect on

height of clearing *H. pylori* infection over time, were noticeably consistent as they got progressively larger from visit to visit attaining their largest size at the last visit.

After nearly four years of observation and after adjusting for cohort effect and all other fixed and time-dependent covariates, we estimated that children at an average age of 10.1 years who were not infected with *H. pylori* were 1.1 cm taller on average compared to positive children of the same age. Children who were always *H. pylori* positive were 1.76 cm shorter by the end of the observation period than those who were always negative, and 1.45 cm shorter than those who cleared the infection, after adjusting for initial values and all other covariates.

Among the positive children from the untreated cohort with complete follow up, 95% remained positive throughout visit 14, while among children from the treated cohort who cleared the infection, 58% were still free of infection three years later.

The effect of being *H. pylori* negative on weight took longer to become apparent over the period of observation, mostly due to more variability, but after adjusting for all other fixed and time-dependent covariates, uninfected children at an average age of 10.1 years old were 0.85 Kg heavier on average compared to positive children of the same age. This difference in the effect over time can be attributed to the inherent added variability of weight when compared to height and to a greater lag in the effect. Children who became *H. pylori* positive during the observation period were 1.9 Kg lighter on average than those who cleared the infection, after adjusting for initial values and all other covariates.

Despite attaining a 73% clearance rate by the end of the first year among the treated children, recurrence/recrudescence of the infection made that percentage decline, but nonetheless the *H. pylori* negative children in the two cohorts accumulated 9038 months of follow up while free of the infection.

These findings are consistent with a prior cohort study ^{6,8} with a two year follow-up of preschool children in which a new *H. pylori* infection was linked to decreased height and weight.

Growth in children is complex and depends on many factors such as diet, socioeconomic status, and co-infections ¹⁵. We examined several socio-environmental factors as potential confounders, and identified the father's education and the number of siblings as significant confounders which do not appear to modify the effect of *H. pylori* on growth. There was a tendency for the time-dependent presence of helminths in the stool to impact negatively both height and weight, but our estimates were not statistically significant. No apparent association was found between presence of protozoa and growth.

It should be noted that the breath test is an objective measure of active infection status, as it detects the activity of *H. pylori* organisms currently colonizing the stomach, and has high sensitivity and specificity, thus the direct effect of a current, active infection can be appropriately estimated with our statistical model. Strengths of this study include the number of person-years of follow-up and the large number of measurements. A limitation of this study is the potential presence of residual confounding not accounted for statistical adjustment by cohort membership. Results can be generalized only to populations of school-age children with a moderate to high acquisition of infection caused by *H. pylori*.

This study showed a significant and durable effect of clearing *H. pylori* infection on increased height and weight. Although treatment is only recommended for certain indications, this study suggests that in terms of growth, school age children may benefit from being treated for *H. pylori* infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Average Height at baseline and last visit by *H. pylori* status

Figure 2.
Average Weight at baseline and last visit by *H. pylori* status