Asymptomatic *Helicobacter pylori* Infection and Iron Deficiency are Not Associated With Decreased Growth Among Alaska Native Children Aged 7–11 Years

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Abstract

Introduction: Alaska Native children have high *Helicobacter pylori* infection and iron deficiency prevalences, and their average height-for-age is lower than US reference populations. During a clinical trial to determine the impact of *H. pylori* treatment on iron deficiency, we evaluated the effects of *H. pylori* infection and treatment on growth.

Materials and Methods: We measured height and weight for children aged 7–11 years in western Alaska using village-based measuring devices. *H. pylori* infection was determined by urea breath test and iron deficiency using serum ferritin. Children with *H. pylori* infection and iron deficiency entered the treatment phase and received iron alone or iron plus triple therapy for *H. pylori*. Follow-up evaluations occurred at 2, 8, and 14 months. We evaluated the association between baseline *H. pylori* infection and growth; among children in the treatment phase, we also assessed the effect of *H. pylori* resolution on growth.

Results: At baseline, 566 (87.1%) of 650 children were infected with *H. pylori*. Neither height and weight, nor body mass index differed by *H. pylori* infection status. Of 189 children in the treatment phase, 20 (10.6%) were uninfected at all three follow-up periods, and 54 (28.6%) were uninfected for one or two periods. Compared with continuously infected children, children in these two groups had little evidence of improvements in any of the measured growth outcomes.

Conclusions: *H. pylori* infection is not related to growth among Alaska Native children aged 7–11 years. Growth deficiency should not be considered an indication for *H. pylori* therapy.

Helicobacter pylori colonizes the human stomach and can cause gastritis, peptic ulceration, and is linked to gastric cancer [1,2]. The epidemiology of *H. pylori* infection among Alaska Natives is similar to that in developing nations, where the prevalence is high and infection occurs at an early age [3,4]. The seroprevalence of *H. pylori* among Alaska Natives reaches 78% by age 10–14 years and has been associated with low serum ferritin levels [5,6].

Compared to US reference populations, Alaska Natives are shorter and heavier for almost all ages [7–11]. Current hypotheses for the difference in growth among Alaska Natives include genetic differences based on adaptation to the arctic environment, nutritional deficiencies such as inadequate vitamin D, or increased incidence of chronic infection. To our knowledge, no studies have been conducted to determine whether the high prevalence of *H. pylori* infection among Alaska Native children explains any of the variation of this growth pattern.

We conducted a household-randomized clinical trial of the effects of treatment and resolution of asymptomatic *H. pylori* infection on iron deficiency [12]. Because we measured the heights and weights of children, this study also provided the opportunity to evaluate the association between asymptomatic *H. pylori* infection and height,

weight, and body mass index (BMI) among rural Alaska Native children aged 7–11 years.

Previous studies have evaluated the effects of *H. pylori* infection on children's growth [13–21]. Despite this, we believed an evaluation of our data would be a useful contribution to the literature. The earlier studies reported conflicting results, including effects on height alone, weight alone, or no effect at all [13–21]. Many were limited by small sample sizes or did not control for socioeconomic status, and no studies have evaluated whether successful treatment of *H. pylori* infection affects subsequent growth. The parent study for the current evaluation was large, population-based, and conducted in 10 separate villages. The study also involved a relatively long follow-up period and was conducted in a population with high prevalences of *H. pylori* infection and iron deficiency similar to much of the developing world's pediatric population.

Methods

Study Population

We conducted the study in 10 villages in western Alaska, an area with high iron deficiency and *H. pylori* infection prevalences [5,6,22]. We selected the eight most populous villages in the Yukon-Kuskokwim Delta and the two most populous in the Bristol Bay area (other than the two population hubs, which we believed were not representative of the remainder of the region). The year 2000 populations of these 10 villages ranged from 471 to 1014 persons, all predominantly Alaska Natives [23]. During the study period, none of the villages was accessible by road. Most did not have public water or sewage systems connected to individual residences, and health care at all locations was delivered by village health aides.

Hypothesis and Design

Previous studies evaluating the association of *H. pylori* on growth have found conflicting results. Thus, we arbitrarily used the null hypotheses that *H. pylori* infection would have no clinically relevant association with growth at baseline and that successful treatment of asymptomatic *H. pylori* infections would not improve growth over the 14-month evaluation period.

The current study used data collected during a randomized clinical trial evaluating the effect of *H. pylori* triple therapy on iron deficiency, and this primary study determined the study design. During December 2002 to January 2003, we screened 69% of the children aged 7–11 years in the study villages. All resident children who were not currently on iron therapy were invited to participate. Children with *H. pylori* infection and iron deficiency met enrollment criteria for the treatment phase of the trial. Those who enrolled were randomized to receive either 6 weeks of iron therapy or iron therapy plus 2 weeks of triple therapy for *H. pylori* (amoxicillin, clarithromycin, and lansoprazole); alternate therapies were available for children with drug allergies. Follow-up occurred at 2, 8, and 14 months after initial screening.

At each visit, children were administered a symptom questionnaire. Their height and weight were measured using locally available equipment, and were evaluated for *H. pylori*, serum ferritin, and peripheral hemoglobin status. At each evaluation, the study team measured heights and weights because these parameters were required for interpreting breath test results. Field evaluators were instructed to take the subject's shoes and heavy clothes off, to have the child stand as erect as possible with the legs straight, and – if possible using local equipment – to have the heels and head touching a vertical plane. At nine villages, children had weight measured using mechanical balance beam scales manufactured by Health-o-meter (Purvis, MS, USA) or Detecto (Webb City, MO, USA), and one village used a digital scale manufactured by Scale Tronix (White Plains, NY, USA). Height was measured in six villages with rods incorporated into the scales and in four villages with wall-mounted tape measures. None of the villages replaced their scales during the study period.

Laboratory Analysis

The ^{13}C-labelled urea breath test (Meretek: The Breath Test Company; Lafayette, CO, USA) was used to determine *H. pylori* status because of its high sensitivity and specificity and validation among pediatric populations [24–26] as well as adult Alaska Natives from western Alaska [27]. Additionally, unlike serology, it identifies active infection. This test has not been validated against the gold standard of upper endoscopy and biopsy among Alaska Native children. Infection was defined as a calculated urea hydrolysis rate of > 10 from the delta over baseline for $^{13}CO_2$ after adjusting for weight, height, and gender, based on the manufacturer's recommendation for pediatric patients [28,29]. Adjustment changed results for three of the total 1308 tests, all from positive to negative.

Iron deficiency was defined as a serum ferritin level of < 22.5 pmol/l (< 10 μg/l) based on radioimmunometric assay (ICN Pharmaceuticals Diagnostic Division, Orangeburg, NY, USA). Anemia was defined as a hemoglobin level < 115 g/l (< 11.5 g/dl) from a portable hemoglobinometer (HemoQue AB, Angelholm, Sweden) [30]. Secondary definitions of iron deficiency included serum iron < 4.5 μmol/l (25 μg/dl), and iron saturation < 15%. Because conclusions did not change based on these analyses, results are not presented. Iron deficiency anemia was

defined as meeting criteria for both iron deficiency and anemia.

Data Analysis

We used the NHANES III growth chart to calculate percentile values for height, weight, and BMI for each child [31]. Children with a height or weight 5 SD below or above the sample mean at baseline or follow-up were excluded since these values were viewed as probable data entry errors.

The primary study design allowed us to perform two types of analyses. First, we performed a cross-sectional analysis of data collected at baseline to determine if iron deficiency or *H. pylori* infection was associated with differences in height, weight, and BMI. This analysis included all children who received a baseline evaluation. Next, we conducted a longitudinal evaluation of the effect of changes in *H. pylori* and iron status on growth parameters over the 14-month course of the study among the children who entered the treatment phase. We limited the latter analysis to children who had valid laboratory and growth measurements at all three follow-up visits.

Data analysis was performed using SAS version 8.0 statistical software (SAS Institute, Cary, NC, USA) proc generalized linear model (GLM) procedure to construct general linear models. Because the number of participants per household was low (mean 1.2 participants per household) and the number of households large (455 households assessed for eligibility; 181 households randomized in the treatment phase), it was not necessary to adjust for household in statistical models or limit analysis to only one participant per household.

For the baseline analysis, we constructed separate models for six dependent variables: height in centimeters, height percentile score, weight in kilograms, weight percentile score, BMI, and BMI percentile score. We constructed univariate models for the independent variables sex, age, village, *H. pylori* infection status, and iron deficiency status. We also constructed multivariable models with all five independent variables entered at the same time, plus an interaction term between *H. pylori* infection and iron deficiency status. For multivariable models, we obtained means and 95% confidence intervals of each dependent variable for each category of *H. pylori* infection and iron deficiency status following adjustment for age, sex, and village using least square means methodology [32]. After all models were constructed, we ran a second series of models in which we substituted iron deficiency anemia for iron deficiency.

For the longitudinal evaluation, we constructed separate models evaluating the change over the 14-month study period in the six growth variables. We constructed univariate and multivariate models using a similar methodology as the baseline models, including the addition of an interaction term between *H. pylori* infection and iron deficiency status. We entered *H. pylori* infection and iron deficiency status into the models as the number of the three follow-up periods each child was free of infection or had a normal ferritin, respectively, expressed as three levels: 0 periods, 1–2 periods, or 3 periods. We collapsed one and two periods into a single category because the number of children infected for a single period was small. We obtained the differences in our dependent variables between categories of *H. pylori* and iron deficiency status (each relative to no periods of improvement and adjusted for sex, age, and village) using differences in least square means. We were unable to construct models to assess the effects of improvements in anemia on growth because the subset of subjects in the longitudinal study that were anemic was small relative to the number of variables included in the multivariable models. For the same reason, we were unable to run models on the subset of children who were either shorter or lighter than their peers at baseline.

Males and females may have different ages at which peak growth occurs, particularly during adolescence. To evaluate this possibility, we stratified all multivariate models by sex. Because associations did not differ substantially from those obtained by including sex in the multivariable models, these results are not presented.

Power calculations were performed retrospectively because sample size was predetermined by the parent study. For all calculations, we used observed sample sizes and variances. For baseline data, we evaluated the power to detect a 2-cm (power, 0.95) or 1.5-cm (power, 0.62) difference in height and a 2-kg (power, 0.80) and 1.5-kg (power, 0.50) difference in weight between *H. pylori* infection groups. For the longitudinal study, we evaluated the power to detect a 1-cm (power, > 0.99) and 2-cm (power, > 0.99) difference in height and a 2-kg (power, > 0.99) and 1-kg (power, 0.87) difference in weight and assumed that all three *H. pylori* groups would have different means. Power was 0.99 for a 1 cm difference in height and 0.87 for a 1 kg difference in weight. All calculations were performed on adjusted models using the SAS Power Macro for general linear models [33].

Ethical Issues

The Institutional Review Boards of the Centers for Disease Control and Prevention and the Alaska Area Health Research Board approved the primary study and the current subanalysis. The Yukon-Kuskokwim Regional Health Corporation Review Board and the village or tribal councils of the 10 study villages also approved the primary study. Children provided written assent for participation,

Table 1 Baseline characteristics of study populations during cross-sectional and longitudinal studies of the growth effects of *Helicobacter pylori* infection and iron deficiency among Alaska Native children aged 7–11 years; Alaska pediatric iron deficiency and *H. pylori* treatment trial, 2002–2004

		Cross-sectional study (n = 650)	Longitudinal study (n = 189)
Demographics			
Age, years	Mean	9.5	9.6
	Range	7.0–11.9	7.0–11.9
	Standard deviation	1.4	1.4
Male sex	n (%)	314 (48%)	93 (49%)
Region	Bristol Bay, n (%)	107 (17%)	26 (14%)
	Y-K Delta, n (%)	543 (83.5%)	163 (86.2%)
Laboratory			
H. pylori positive	n (%)	566 (87%)	189 (100%)
Ferritin (pmol/l)	Mean (range)	30.6 (3.0–178.7)	13.8 (3.0–22.5)
	Standard deviation	21.1	5.3
	Low ferritin[a], n (%)	253 (39%)	189 (100%)
	Missing data, n (%)	2 (0.3%)	0 (0%)
Hemoglobin (g/l)	Mean (range)	122 (82–145)	121 (82–143)
	Standard dev	8.0	8.4
	Anemia[b], n (%)	102 (16%)	45 (24%)
	Missing data, n (%)	5 (0.8%)	0 (0%)
Symptoms			
Abdominal pain	Present, n (%)	52 (8.0%)	15 (8.0%)
	Missing data, n (%)	3 (0.5%)	0 (0%)
Blood in stool	Present, n (%)	3 (0.5%)	1 (0.5%)
	Missing data, n (%)	2 (0.3%)	0 (0%)
Dyspepsia	Present, n (%)	18 (2.8%)	4 (2.1%)
	Missing data, n (%)	2 (0.3%)	1 (0.5%)
Vomiting	Present, n (%)	13 (2.0%)	2 (1.6%)
	Missing, n (%)	1 (0.2%)	0 (0%)
Growth			
Height (cm)	Mean (range)	133.3 (109.9, 163.1)	133.7 (111.8, 156.8)
	Standard deviation	9.4	9.4
Height percentile	Mean (range)	39 (0, 99)	38 (0, 99)
	Standard deviation	26.4	25.0
Weight (kg)	Mean (range)	34.6 (19.5, 68.0)	34.3 (21.6, 68.0)
	Standard deviation	8.9	8.2
Weight percentile	Mean (range)	62 (0, 99)	65 (0, 99)
	Standard deviation	25.8	24.9
Body mass index	Mean (range)	19.2 (11.9, 38.9)	18.9 (12.9, 32.6)
(BMI, kg/m^2)	Standard deviation	3.3	2.7
BMI percentile	Mean (range)	74 (0, 99)	74 (0, 99)
	Standard deviation	20.3	19.4

[a]< 22.5 pmol/l (10 µg/l).
[b]< 115 g/l (11.5 g/dl).

and their parents or guardians provided written informed consent.

Results

Baseline Data

We initially screened 690 children in the 10 study villages. We excluded 10 (1.4%) children aged > 11 or < 7 years, and eight (1.2%) with heights or weights outside five standard deviations of the sample mean. We were unable to obtain *H. pylori* specimen results for 22 (3.2%) because the urea breath test bags leaked. A total of 650 (94%) children remained in the study.

The median age at baseline was 9.5 years, and 48% of study participants were male (Table 1). The prevalences of *H. pylori* infection, iron deficiency, and anemia were 87, 39, and 16%, respectively. Gastrointestinal symptoms were uncommon.

During univariate analysis, neither *H. pylori* infection nor iron deficiency was significantly associated with height,

Table 2A During a cross-sectional study among Alaska Native children aged 7–11 years, the unadjusted and adjusted[a] means[b] of growth parameters by *Helicobacter pylori* infection status; Alaska pediatric iron deficiency and *H. pylori* treatment trial, 2002–2004

Variable		*H. pylori* negative (n = 84) Mean (95% CI)	*H. pylori* positive (n = 566) Mean (95% CI)	*p*-value
Height (cm)	Unadjusted	132.6 (130.6, 134.6)	133.4 (132.6, 134.2)	.48
	Adjusted	134.0 (132.7, 135.3)	133.4 (132.9, 133.9)	.43
Weight (kg)	Unadjusted	34.0 (32.1, 35.9)	34.7 (33.9, 35.4)	.53
	Adjusted	34.6 (33.0, 36.3)	34.9 (34.2, 35.5)	.49
BMI[c] (kg/m^2)	Unadjusted	19.1 (18.4, 19.8)	19.2 (19.0, 19.5)	.69
	Adjusted	19.1 (18.3, 19.8)	19.3 (19.0, 19.6)	.52
Height (%)	Unadjusted	43.0 (37.4, 48.7)	38.9 (36.7, 41.0)	.18
	Adjusted	42.1 (36.1, 48.1)	39.8 (37.5, 42.0)	.46
Weight (%)	Unadjusted	62.3 (56.8, 67.9)	61.9 (59.7, 64.0)	.89
	Adjusted	61.0 (55.0, 66.9)	63.1 (60.9, 65.4)	.49
BMI‡ (%)	Unadjusted	72.5 (68.1, 76.8)	74.8 (73.1, 76.4)	.34
	Adjusted	71.4 (66.7, 76.0)	75.4 (73.6, 77.2)	.11

[a]Adjusted for age, sex, and village of residence.
[b]Estimated means determined from least mean squares from general linear models.
[c]BMI, body mass index.

Table 2B During a cross-sectional study among Alaska Native children aged 7–11 years, the unadjusted and adjusted[a] means[b] of growth parameters by iron deficiency status[d]; Alaska pediatric iron deficiency and *Helicobacter pylori* treatment trial, 2002–2004

Variable		Iron deficient[d] (n = 253) Mean (95% CI)	Not iron deficient (n = 397) Mean (95% CI)	*p*-value
Height (cm)	Unadjusted	133.6 (132.5, 134.7)	133.2 (132.3, 134.2)	.63
	Adjusted	133.8 (132.8, 134.7)	133.7 (132.9, 134.4)	.82
Weight (kg)	Unadjusted	34.4 (33.2, 35.5)	35.0 (34.1, 35.9)	.38
	Adjusted	34.3 (33.1, 35.5)	35.2 (34.2, 36.2)	.16
BMI[c] (kg/m^2)	Unadjusted	19.0 (18.6, 19.4)	19.4 (19.1, 19.8)	.13
	Adjusted	19.0 (18.4, 19.5)	19.4 (19.0, 19.9)	.08
Height (%ile)	Unadjusted	39.1 (35.8, 42.3)	39.9 (37.3, 42.5)	.7
	Adjusted	41.1 (36.8, 45.4)	40.8 (37.3, 44.2)	.87
Weight (%ile)	Unadjusted	62.1 (59.0, 65.3)	62.3 (59.8, 64.8)	.94
	Adjusted	62.2 (58.0, 66.4)	61.9 (58.5, 65.3)	.89
BMI[c] (%ile)	Unadjusted	74.9 (72.4, 77.4)	74.5 (72.5, 76.5)	.79
	Adjusted	73.4 (70.2, 76.7)	73.3 (70.7, 76.0)	.95

[a]Adjusted for age, sex, and village of residence.
[b]Estimated means determined from least mean squares from general linear models.
[c]BMI, body mass index.
[d]Iron deficiency defined as serum ferritin < 22.5 pmol/l.

weight, BMI, height percentile score, weight percentile score, or BMI percentile score (Table 2A and 2B, unadjusted models). Similarly, iron deficiency anemia was not significantly associated with any of the growth parameters.

Adjusted means in multivariable models differed little from unadjusted means, indicating little confounding by sex, age, and village. Additionally, no significant interaction was obtained between iron deficiency anemia and *H. pylori* infection in any of the multivariable models, and iron deficiency anemia was not significantly associated with any of the growth parameters.

Longitudinal Study

Of the 237 children who met the enrollment criteria for the treatment phase, four (1.7%) were excluded for invalid heights or weights at baseline; 215 (91%) of the remaining 233 enrolled in the longitudinal study. Of 109 control and 106 intervention children, 103 (95%) and 94 (89%), respectively, were followed through 14 months among whom 103 control children (100%) and 86 intervention children (91%) had consistently valid height and weight measurements.

By definition, all children in the longitudinal study were iron deficient and *H. pylori*-infected. Seventy-three children (39%) were below the 25th percentile for height, and 22 (12%) were below the 25th percentile for weight. At baseline, age, sex, region of residence, growth parameters, and the prevalence of gastrointestinal symptoms were similar to the cross-sectional study population (Table 1).

Of the 189 children with valid heights and weights at all three follow-up periods, 20 (11%) were uninfected with

Table 3A During a longitudinal study among Alaska Native children aged 7–11 years, the unadjusted and adjusted[a] mean differences[b] of changes in growth parameters among children with continued *Helicobacter pylori* infection at three versus zero follow-up evaluations and one or two versus zero follow-up evaluations; Alaska pediatric iron deficiency and *H. pylori* treatment trial, 2002–2004. Follow-up evaluations occurred at 2, 8, and 14 months post-enrollment

		H. pylori negative at follow-up evaluations			
		3 versus 0 evaluations		1 or 2 versus 0 evaluations	
Dependent Variable		Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Change in height (cm)	Unadjusted	0.47 (–0.55, 1.49)	.36	0.03 (–0.67, 0.71)	.94
	Adjusted	0.65 (–0.40, 1.71)	.22	0.23 (–0.50, 0.95)	.53
Change in weight (kg)	Unadjusted	–0.35 (–1.70, 0.99)	.61	0.73 (–0.18, 1.65)	.12
	Adjusted	–0.02 (–1.44, 1.36)	.97	1.11 (0.16, 2.07)	.02
Change in BMI[c] (kg/m^2)	Unadjusted	–0.34 (–0.92, 0.23)	.24	0.38 (–0.01, 0.78)	.06
	Adjusted	–0.28 (–0.91, 0.33)	.35	0.46 (0.04, 0.89)	.04
Change in height percentile score	Unadjusted	1.91 (–3.37, 7.19)	.47	0.42 (–3.20, 4.04)	.85
	Adjusted	1.84 (–3.62, 7.29)	.65	0.43 (–3.36, 4.21)	.15
Change in weight percentile score	Unadjusted	–1.39 (–5.30, 2.51)	.48	0.84 (–1.84, 3.52)	.54
	Adjusted	–1.69 (–5.80, 2.40)	.41	1.89 (–0.98, 4.70)	.21
Change in BMI‡ percentile score	Unadjusted	–1.17 (–5.78, 3.44)	.62	1.07 (–2.08, 4.24)	.49
	Adjusted	–1.49 (–6.41, 3.44)	.55	2.00 (–1.42, 5.41)	.24

[a]Adjusted for age, sex, and village of residence.
[b]Estimated means determined from least mean squares from general linear models.
[c]BMI, body mass index.

H. pylori for all three periods, 54 (29%) were uninfected for one or two periods, and 115 (61%) remained infected for all three periods. Twenty-eight (15%) children had normal ferritin levels for all three periods, 129 (68%) had normal levels for one or two periods, and 32 (17%) had low ferritin levels for all three periods. The median gain in height for the study group was 7.6 cm (range: 1.3–14.0). The median gain in weight was 5.0 kg (range: 0.1–16.3). The median change in BMI was 0.7 kg/m^2 (range: 2.1–3.3).

During univariate analysis, the number of follow-up periods for which children were free from infection or had iron deficiency was not predictive of changes in any of the evaluated growth parameters (Table 3A, B unadjusted differences). In every multivariable model, the addition of an interaction term between *H. pylori* infection and low iron status did not statistically improve model fit and was omitted. After controlling for age, village of residence, and sex, we found that children free of infection for one or two study periods gained an additional average of 1.1 kg and 0.46 BMI units relative to children infected throughout the study (p = .02 and .04, respectively; Table 3A, adjusted differences). However, remaining free of infection for all three follow-up periods did not result in similar changes. For all other multivariable models, the adjusted mean differences in changes in growth parameters between groups defined by *H. pylori* infection and iron deficiency were small, not statistically significant, and differed little from unadjusted, univariate means (Table 3A and 3B).

Discussion

Among rural Alaska Native children aged 7–11 years, we found no association between growth outcomes and active *H. pylori* infection, low ferritin, or iron deficiency anemia. Among children who were iron deficient and *H. pylori*-infected at baseline, improvement in iron deficiency or resolution of *H. pylori* infection over a 14-month period did not result in consistent increases in growth relative to children who remained iron deficient or *H. pylori*-infected. Although we found greater increases in weight and BMI among children who were *H. pylori*-uninfected for one or two study periods compared with those who remained infected throughout the study, children uninfected for three study periods did not experience similar increases. The lack of dose–response suggests that these isolated findings resulted from a type 1 error rather than from a true biological effect [34].

Similar to our results, two previous cross-sectional studies found no association between growth and *H. pylori* infection [16,21]. Both studies were performed on different age groups than our study, one determined *H. pylori* infection by serology (which does not distinguish previous from active infection), one included only children with abdominal pain, and neither controlled for iron deficiency or socioeconomic status. Socioeconomic status has been associated with growth, *H. pylori* infection, and iron deficiency and thus might be an important confounding

Table 3B During a longitudinal study among Alaska Native children aged 7–11 years, the unadjusted and adjusted[a] mean differences[b] of changes in growth parameters at three follow-up evaluations (2, 8, and 14 months) by iron deficiency status[c]; Alaska pediatric iron deficiency and *H. pylori* treatment trial, 2002–2004

		Iron deficient at follow-up evaluations[c]			
		3 versus 0 evaluations		1 or 2 versus 0 evaluations	
Dependent variable		Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Change in height (cm)	Unadjusted	0.14 (–0.95, 1.23)	.81	0.13 (–0.71, 0.96)	.76
	Adjusted	–0.09 (–1.21, 1.04)	.88	–0.19 (–1.04, 0.67)	.66
Change in weight (kg)	Unadjusted	–0.51 (–1.96, 0.93)	.48	–0.29 (–1.39, 0.82)	.61
	Adjusted	–0.30 (–1.79, 1.18)	.68	–0.47 (–1.60, 0.66)	.41
Change in BMI[d] (kg/m^2)	Unadjusted	–0.20 (–0.82, 0.42)	.53	–0.19 (–0.66, 0.29)	.44
	Adjusted	–0.12 (–0.78, 0.54)	.71	–0.20 (–0.70, 0.31)	.43
Change in height percentile score	Unadjusted	0.91 (–4.74, 6.56)	.75	1.12 (–3.18, 5.44)	.62
	Adjusted	–0.69 (–6.54, 5.44)	.81	–0.17 (–4.62, 4.29)	.42
Change in weight percentile score	Unadjusted	–1.88 (–6.05, 2.29)	.37	–1.84 (–5.02, 1.35)	.26
	Adjusted	–1.38 (–5.77, 3.02)	.53	–2.10 (–5.44, 1.24)	.20
Change in BMI[d] percentile score	Unadjusted	–2.53 (–7.45, 2.39)	.31	–1.71 (–5.46, 2.04)	.37
	Adjusted	–1.65 (–6.94, 3.63)	.54	–1.41 (–5.43, 2.60)	.48

[a]Adjusted for age, sex, and village of residence.
[b]Estimated means determined from least mean squares from general linear models.
[c]Iron deficiency defined as serum ferritin < 22.5 pmol/l.
[d]BMI, body mass index.

variable [35–38]. A separate study among children aged 10–15 years that controlled for iron status found an association between *H. pylori* infection and decreased growth; however, decreased growth only occurred when iron deficiency anemia was present. This suggests that *H. pylori* infection and iron deficiency anemia may have a synergistic effect on growth, that iron deficiency anemia might be part of the causal pathway, or that only infection that is severe or prolonged enough to lead to iron deficiency anemia affects growth [15]. Additional cross-sectional and longitudinal studies have found associations between growth and *H. pylori* infection [13,14,17–20]. None of these studies controlled for iron deficiency and five had study populations with different age distributions than our population. Three of the studies did not employ a validated measure of active *H. pylori* infection or evaluated populations with low infection prevalence.

As with *H. pylori* infection, we did not find an effect of iron deficiency or iron deficiency anemia on growth. Previous work demonstrates that iron deficiency anemia is associated with poorer height and weight gain, and improvement of anemia through iron therapy can help restore normal growth [39–42]. However, these studies were limited to populations with high prevalences of protein or calorie malnutrition or intestinal parasitosis, or involved children during periods of maximum growth velocity (infancy and puberty). In contrast to these studies, and consistent with our results, Brazilian children aged 1–6 years with adequate nutrition had a low prevalence of decreased height (4.7%) and weight (2.6%) for age despite a high prevalence of iron deficiency anemia (69%) [43]. A second study found that nonanemic, iron-deficient Danish children treated with iron did not have substantial improvements in height and weight relative to those treated with placebo despite improvements in serum iron, total iron binding capacity, and mean cell volume [44].

Our study has limitations. We did not use standardized measuring tools that we knew to be well calibrated. Thus, absolute growth values should be interpreted with caution and comparisons with national standards should not be made. Nevertheless, we do not consider this issue to be a serious flaw. Our study evaluated relative differences in growth characteristics between groups of children defined by *H. pylori* or iron deficiency status rather than absolute measurements of individual persons. The same measuring devices were used at each village, measuring devices were not changed between study periods, and we controlled for differences in scale calibration between villages by adjusting for village of residence in all multivariable models. For these reasons, potential measurement inaccuracies were unlikely to have affected statistical hypothesis test results. In some settings, iron deficiency may be strongly associated with general malnutrition such that any association

between iron deficiency and growth may reflect the confounding effect of protein-energy deficiency. We do not believe that this was a substantial issue in our study since few children in Alaska have severe protein-energy malnutrition and previous nutritional studies have not found low iron intake among rural Alaska Natives; furthermore, this issue, even if it existed, would not explain our finding of no association between iron deficiency and baseline growth parameters.

Our follow-up period of 14 months was dictated by the primary hypothesis and may have been too short to identify relatively subtle growth effects occurring over a longer period. The lack of an association during cross-sectional analysis combined with results from the longitudinal analysis argues against a substantial effect. We did not assess socioeconomic status. However, relatively little variation exists in socioeconomic status among Alaska Natives from western Alaska, particularly within villages outside of the population hubs. The relatively homogeneous study population and adding village of residence to our multivariable models probably controlled for most of the potential effect of this variable. None of our study population had documented clinical symptoms related to *H. pylori* infection and, thus, we were unable to determine the growth effects of symptomatic *H. pylori* infections. Our analysis was limited to children aged 7–11 years at baseline and our results might not be valid for other ages, particularly older children undergoing a pubertal growth spurt. Lastly, *H. pylori* infection can occur at an early age in rural Alaska (> 40% by age 5 years), and we were unable to assess whether the infection duration was associated with delayed growth [5,6].

We found height and weight distributions similar to those found in previous studies of indigenous populations [7–11] and a relatively low height-for-age compared to US reference populations. Our results do not support a causal role for *H. pylori* infection or iron deficiency despite the high prevalence of both risk factors in our study population. Consequently, we find no evidence to recommend treatment for asymptomatic *H. pylori* infection to improve growth. Further work is needed to determine the growth effects of symptomatic *H. pylori* infections or infections that occur during the pubertal growth spurt among Alaska Natives and other populations with a high *H. pylori* prevalence.

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