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Final adult height of children with inflammatory bowel disease is predicted by parental height and patient minimum height Z-score

Jessica J. Lee, MD,

Division of Gastroenterology and Nutrition, Children's Hospital Boston

Johanna C. Escher, MD,

Department of Pediatric Gastroenterology, Erasmus MC- Sophia Children's Hospital, Rotterdam, the Netherlands

Melissa J. Shuman, BA,

Division of Gastroenterology and Nutrition, Children's Hospital Boston

Peter W. Forbes, MA,

Clinical Research Program, Children's Hospital Boston

Luçan C. Delemarre, MD,

Division of Gastroenterology and Nutrition, Children's Hospital Boston

Brian W. Harr, MD,

Division of Gastroenterology and Nutrition, Children's Hospital Boston

Marjan Kruijer, MD,

Division of Gastroenterology and Nutrition, Children's Hospital Boston

Marlous Moret, MD,

Division of Gastroenterology and Nutrition, Children's Hospital Boston

Sophie Allende-Richter, MD, and

Division of Gastroenterology and Nutrition, Children's Hospital Boston

Richard J. Grand, MD

Division of Gastroenterology and Nutrition, and Clinical and Translational Study Unit, Children's Hospital Boston

Abstract

Background—This study was designed to elucidate contribution of parental height to the stature of children with inflammatory bowel disease (IBD), who often exhibit growth impairment. Accordingly, we compared patients' final adult heights and target heights based on measured parental heights, and examined predictors of final adult height in pediatric IBD patients.

Methods—We prospectively analyzed growth of 295 patients diagnosed between ages 1 and 18 (211 Crohn's disease, 84 ulcerative colitis) and their family members (283 mothers, 231 fathers, 55 siblings).

Results—Twenty-two percent had growth impairment (height for age Z-score < -1.64, equivalent to <5th percentile on growth curve) in more than one measurement since diagnosis; most growth-impaired patients had Crohn's disease (88% Crohn's disease vs. 12% ulcerative colitis). Parents of

the growth-impaired group had lower mean height Z-scores compared to parents of non-growth impaired patients (-0.67 vs. 0.02 for mothers ($p<0.001$); -0.31 vs. 0.22 for fathers ($p=0.002$)). For 108 patients who reached adult heights and had available parental heights, the growth-impaired group continued to demonstrate lower adult height Z-scores (-1.38 vs. 0.07; $p<0.001$). Adult heights were within 1 SD of target heights even for the growth-impaired group. Only 11.3% remained persistently growth impaired in adulthood. Multivariate regression analysis demonstrated lower parental height and minimum patient height Z-score as significant predictors of lower final adult height in IBD.

Conclusions—Parental height is a powerful determinant of linear growth even in the presence of chronic inflammation, and should be an integral part of the evaluation of growth in IBD children.

Keywords

growth retardation; Crohn's disease; ulcerative colitis; pediatric

Introduction

Current assessment of linear growth in children with inflammatory bowel disease (IBD) utilizes growth curves based on heights of the general population. This measure fails to track individual growth patterns or potential in the context of mid-parental height or target height. Mid-parental height is defined as the mean of the heights of a child's mother and father, whereas target height is mid-parental height adjusted for the child's gender.¹ Linear growth impairment, seen in 15-40% of patients with pediatric-onset disease, is one of the major complications of IBD and poses a significant challenge to quality of life.² Growth impairment may precede clinical evidence of IBD, often by years,³ and stunting into adulthood may persist.^{4, 5} Patients with Crohn's disease (CD) are at least twice as likely to have growth failure as those with ulcerative colitis (UC).⁶ Impairment of growth in IBD has been attributed to nutritional, hormonal, and disease-related factors, and successful treatment of active disease may result in normalization of growth. Thus, uncontrolled inflammation has been thought to be the main cause of growth failure in children with IBD.⁶ Indeed, pro-inflammatory cytokines have been implicated in the mechanism of growth suppression.^{7, 8} However, there are conflicting data on growth after surgical removal of diseased bowel, suggesting that inflammation alone cannot explain persistent growth impairment.⁹⁻¹³ The effects of growth hormone on linear growth are not consistent,¹⁴ and the role of corticosteroid use in growth impairment is controversial since 60% of patients show growth delays before corticosteroid therapy, and 80% show a reversal of growth failure after treatment initiation.⁶ Most importantly, response to aggressive nutritional therapy and medication is heterogeneous, suggesting that pre-determined growth pattern may play a role in final adult heights of IBD patients.⁶

Prior analyses of adult height in family and twin studies in the general population have shown that heritability of growth pattern ranges from 76-90%,¹⁵⁻¹⁸ and even under conditions of malnutrition heritability remains high.¹⁹ Hence, parental heights may be key determinants of final adult heights in pediatric IBD patients. Although there have been a number of studies of final adult heights of children with IBD, results have been inconclusive.^{5, 20-25} Majority of these studies did not compare observed final adult heights with target heights, and no prior study reported both measured final adult and target heights. The objectives of our study were to (1) compare observed final adult heights and target heights based on measured parental heights; and (2) determine predictors of final adult height in pediatric-onset IBD.

Patients and Methods

Patients

Two hundred ninety-five patients, 169 male and 126 female, who were diagnosed with CD or UC between the ages 1-18 were prospectively recruited from the Division of Gastroenterology from November 16, 2002 to November 25, 2008. We included both CD and UC patients in this prospective growth study as patients with UC can demonstrate growth impairment, albeit less commonly than those with CD. The Montreal classification²⁶ was used to describe disease location and behavior based on IBD type. In order to establish family growth phenotypes, biological parents (283mothers and 231 fathers) were also recruited. When available, heights from unaffected full siblings were measured.

Study design

This was a prospective cohort study investigating clinical characteristics related to linear growth impairment in pediatric-onset IBD. Patients and their family members were asked to participate in the study through invitation letters or in person anytime after IBD diagnosis.

Description of the study visit

Each research visit was conducted in the Clinical and Translational Study Unit (CTSU, formerly the General Clinical Research Center (GCRC)). Detailed demographic and clinical information was obtained from patients and their parents, and the medical record, including disease location and behavior, extraintestinal manifestations, present and past history of corticosteroid use, immunomodulator or biologic therapies (as yes/no dichotomous choice), history of corticosteroid dependence (defined as relapse within 30 days after treatment completion or relapse at dose reduction impeding discontinuation for more than one year), nutritional therapy (history of any formula supplementation), IBD-related surgical history, and family (immediate and extended) history of IBD. The lag-time was defined as number of months from onset of symptoms suggestive of IBD to definitive diagnosis. Parents and siblings completed a questionnaire to determine the presence/absence of symptoms suggestive of IBD (Supplemental Table 1 - generously provided by Bruce Sands, MD, Massachusetts General Hospital Crohn's and Colitis Center, Boston).

Height measurements

Patient, sibling, and parental heights were measured by 4 trained nursing staff in the CTSU using the same wall-mounted Holtain stadiometer on the day of study visit. All research nurses were trained in the Third National Health and Nutrition Examination Survey (NHANES III) Anthropometric Procedures and passed the competency test, which is reviewed yearly in the CTSU. To ensure accuracy, the Holtain stadiometer was calibrated at least once daily. All patients were instructed to stand looking straight ahead with the chin parallel to the floor, arms by the sides of the trunk with palms facing the thighs, and back of the head, scapulae, buttocks, and heels against the vertical backboard of the stadiometer. Heights were measured to the nearest 0.1 cm three times to ensure accuracy of measurements. If there was a discrepancy of more than 1.0 cm in one measurement, then the remaining two were averaged and recorded. If all measurements were within 1.0 cm of each other, the mean of three measurements was used. For patients, we also recorded retrospective heights measured during clinic visits from the beginning of their care at Children's Hospital Boston and prospectively recorded their adult heights if they had reached ≥ 18 years of age and demonstrated no further increase in linear growth over a minimum of 6 months (serving as a proxy for cessation of pubertal growth). Heights obtained during clinic visits were measured on a Holtain standing stadiometer identical to that used in the CTSU, and obtained by personnel trained in the correct use of the

instrument. The lowest measured height following diagnosis was recorded as minimum height for each patient from the retrospective and prospective height measurements. Heights were converted into standard deviation scores (Z-scores) using the National Center for Health Statistics reference values. For subjects or parents who were ≥ 18 years of age, heights were converted to the same Z-scores calculated for gender-matched persons who are 17.9 years of age.

The growth-impaired phenotype was defined as height for age Z-score < -1.64 (equivalent to $< 5^{\text{th}}$ percentile on growth curve) in more than one measurement since diagnosis. Target height (cm) - ie, mid-parental height adjusted for the child's gender - was calculated using the following formulas:²⁷

Male: $[\text{paternal height (cm)} + (\text{maternal height (cm)} + 13)]/2$

Female: $[\text{maternal height (cm)} + (\text{paternal height (cm)} - 13)]/2$

Statistical analysis

Two-sample *t*-tests, Wilcoxon rank sum tests, χ^2 and Fisher's exact tests were used to assess differences in demographic and clinical characteristics of the study groups. Mean follow-up time was calculated by subtracting date of visit from date of diagnosis. Mean height measurements of patients and family members were compared based on patients' growth status using two-sample *t*-tests. For the 108 patients who reached adult height and also had available measured parental heights, linear regression analyses were performed to determine predictors of final adult stature. A forward variable selection method was used in the multivariate analysis.

Data were collected and stored in Microsoft Access 1997. Statistical analyses were performed using the SPSS Statistics Version 17.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as *p*-values less than 0.05.

Ethical Considerations

The Committee on Clinical Investigation (CCI) at Children's Hospital Boston approved the study protocol. Prior to enrollment into the study, informed consent was obtained from subjects who were at least 18 years old, and assent and parental consent were obtained from subjects who were 8-17 years old.

Results

Demographic and clinical characteristics of pediatric-onset IBD

Table 1 summarizes demographic and clinical characteristics of the study patients. Mean age of 295 patients at enrollment was 13.9 ± 3.9 , with a slight male preponderance. Twenty-two percent (65/295) of patients met the criterion for growth impairment using height Z-score < -1.64 in more than one measurement following diagnosis. Growth impairment was significantly more prevalent in CD than UC patients. More growth-impaired patients received immunosuppressive (6-MP or methotrexate) or biologic (infliximab, adalimumab, or certolizumab) therapy and supplemental nutrition compared to non-growth impaired individuals. The mean follow-up duration was 2.3 years from the time of diagnosis. Montreal classification²⁶ at the time of study enrollment revealed predominantly ileocolonic disease with or without upper GI involvement (75.8%), and non-stricturing and non-penetrating disease behavior (58.8%) for CD, and extensive involvement for UC (73.8%). Two mothers in the growth-impaired group had IBD (1 CD and 1 UC), and 17 mothers in the non-growth impaired group had IBD (6 CD and 11 UC); 3 fathers in the growth-

impaired group had IBD (2 CD and 1 UC), and 9 fathers in the non-growth impaired group had IBD (5 CD and 4 UC).

Height measurements of children with IBD

As demonstrated in Figure 1, mean height Z-scores of children with IBD were left-shifted (-0.46 ± 1.0) compared to the normal distribution curve ($p < 0.001$). When stratified by growth group, mean height Z-scores of growth-impaired and non-growth impaired groups were -1.76 ± 0.5 , and -0.09 ± 0.8 , respectively (Figure 2). Mean minimum height Z-score obtained from patients from the time of diagnosis was -2.39 ± 0.6 for the growth-impaired group, and -0.37 ± 0.8 ($p < 0.001$) for the non-growth impaired group.

Height measurements of family members

Parental height Z-scores were normally distributed (Figure 3). Mothers' mean height Z-score was -0.13 ± 1.0 , and fathers' mean height Z-score was 0.11 ± 1.0 . However, parents of growth-impaired patients had significantly lower height Z-scores than parents of the non-growth impaired group (Table 2). Actual measured heights are shown in Supplemental Table 2. Unaffected sibling mean height Z-scores were also lower for the growth-impaired group compared to the non-growth impaired group (-1.55 ± 1.0 ($n = 12$) vs. 0.04 ± 1.0 ($n = 43$), $p < 0.001$).

Target and final adult heights of children with IBD

Mean target height Z-scores were calculated for 46 growth-impaired patients and 176 non-growth impaired patients using measured parental height. Target height Z-scores were significantly lower for patients with, compared to those without, growth impairment (Table 3).

Adult heights were obtained from 37 growth-impaired patients and 104 non-growth impaired patients at a mean age of 19.8 years, and the calculated mean Z-score was -0.39 ± 1.1 (range -3.60 to 2.97). As shown in Table 2, the growth-impaired group had lower final adult height compared to the non-growth impaired group, but only 11.3% (16 out of 141 patients who reached adult heights) remained persistently growth-impaired with height Z-scores < -1.64 . Details of actual measured heights are shown in Supplemental Table 2.

Among all patients, 108 reached adult heights and also had available parental heights. The growth-impaired group demonstrated persistently lower adult heights (Table 4). Non-growth impaired male patients reached their exact mean target height of 177.0 cm, whereas non-growth impaired female patients had a mean final height 1.9 cm less than their target height. Growth-impaired male patients had a mean final height that was 5.2 cm less than their target height, and growth-impaired female patients had a mean final height that was 3.4 cm less than their target height.

Predictors of final adult stature for patients with pediatric-onset IBD

As demonstrated in Table 5, univariate regression analyses demonstrated that a family history of IBD, minimum height Z-score since diagnosis, mother's height, and father's height were significant factors in determining final adult height. When target height was adjusted in the univariate regression analyses, only the patient's minimum height Z-score remained significant in predicting final adult height. Multivariate regression analysis continued to demonstrate personal history of lower minimum height Z-score and lower parental heights as the strongest predictors of lower final adult heights in patients with IBD. None of the other disease-related factors was found to be a significant predictor of final adult height in our patients. Although male gender approached near significance in the univariate analysis ($p = 0.05$), it lost significant in the multivariate analysis (Table 5).

Characteristics of persistently growth-impaired patients

We compared 16 patients with final adult height Z-score <-1.64 to the 65 overall growth-impaired patients previously described in Table 1. Statistical analysis of differences was not performed due to small sample size, but overall these 16 patients were similar to the growth-impaired group in Table 1 (Supplemental Table 3). None of the mothers with persistently growth-impaired children had IBD, and only one father in this group had a diagnosis of CD. Parental height Z-scores were lower for persistently growth-impaired individuals compared to the overall growth-impaired group.

Discussion

This study demonstrates the impact of parental heights on final heights of patients with pediatric-onset IBD. Children with lower mean height Z-scores were found to have shorter parents and siblings, and final adult stature appeared to be significantly correlated with parental heights. As the data show, prevalence of growth impairment in children with IBD (22% in our study) has not changed over the past 16 years, despite advances in medical and nutritional therapies, as Motil et al. reported it to be 23% in 1993 using the same diagnostic criteria.⁶ Furthermore, a recent study suggests that growth delay persists in many children with CD despite improved disease activity and the frequent use of immunomodulators and biologics.²⁸ Thus, advances in therapy have not appreciably affected the prevalence of growth impairment. Parental heights and final adult heights were not reported in the above study, but one might wonder whether patients who did not respond to immunomodulators and biologics and continued to have suboptimal linear growth were actually children from shorter-statured families. Our study indicates that parental heights powerfully affect adult heights even for children with IBD whose height Z-scores have been consistently <-1.64 . This strong genetic influence on final height is further supported by the fact that unaffected siblings of growth-impaired patients were also shorter than siblings of non-growth impaired patients.

This is the first study to examine measured heights of parents and unaffected siblings under the same conditions as patients, allowing accurate calculation of linear growth characteristics. Although there have been prior studies of adult and target heights, the majority of height data were obtained by report or measured by patients at home; therefore they were not as accurate as heights measured by appropriately trained staff.^{20, 25} Sawczenko et al. reported that growth retardation is not related to parental height since the mean mid-parental height and paternal and maternal heights were the same as in the general population.²⁵ We observed similar findings in the present study when height measurements of all parents were combined. However, when we compared parental heights based on patients' growth status, the parents of growth-impaired patients were markedly shorter than the parents of non-growth impaired patients.

It is reassuring that the final adult height Z-scores are similar in our cohort (-0.39) to the United Kingdom (UK) cohort (-0.29) as the primary therapy for inducing remission is different: corticosteroids in the present cohort and enteral feeding in UK.²⁵ Our study also supports previous findings that corticosteroids as customarily used for treatment of IBD do not result in long-term growth impairment,^{22, 23} but our study was limited in that we did not have cumulative corticosteroid exposure measures for our patients. Since disease severity fluctuates throughout patients' lives and is frequently affected by various treatments, we used long-term assessments of disease severity, such as a history of IBD-related surgery or biologic therapy. Other measures such as erythrocyte sedimentation rate, C-reactive protein, serum albumin, Pediatric Crohn's Disease Activity Index (PCDAI),²⁹ or Pediatric Ulcerative Colitis Activity Index (PUCAI)³⁰ obtained at study visits varied in many patients such that their long-term value was mitigated. In our study, a history of IBD-related surgery did not

differ between the two growth groups and also did not significantly influence final height. Due to the relatively small sample size observed in each category of the Montreal classification, the association between disease location and growth impairment could not be analyzed with adequate power. Nevertheless, the distribution of disease characteristics in our cohort is very similar to that published by Van Limbergen et al.³¹

Growth impairment can be defined in many ways, and a decrease in growth velocity is a commonly accepted method against which to assess catch-up growth.⁶ We did not use reduction in growth velocity to define growth impairment, as growth velocity can vary significantly based on gender, age, and puberty. Growth velocity Z-scores cannot tease out temporary versus long-term growth velocity faltering, and seasonal variations in individual growth velocity can further affect calculation of true deficit in linear growth.³² In addition, catch-up growth is best defined as return to pre-morbid height.^{32, 33} Hence, we chose target height as the surrogate for pre-morbid height as it represents patient's genetic potential, and the difference between adult and target heights was used to determine whether patients ultimately achieved pre-morbid height percentiles. The majority of our patients reached their target heights, since the difference between adult and target heights was less than 1 SD even for the growth-impaired group (Table 4). Furthermore, only 16 out of 141 patients (11.3%) who reached adult heights remained growth-impaired with height Z-score of <-1.64. Hence, long-term growth impairment is uncommon in pediatric patients with IBD, and genetics appears to be the key determinant of growth in affected individuals.

One of the potential limitations of our study includes possible referral bias, reducing generalizability, as our institution is a tertiary care center. However, even in this setting, we have demonstrated that most children with IBD reach their target heights, including some of those who have the lowest height-for-age Z-scores. We invited all patients diagnosed with IBD to participate in the study, but it is possible that more parents with shorter children were willing to enroll into the study. However, it is unlikely that our data were significantly skewed by this potential bias since our primary outcome was the difference in adult and target heights of pediatric IBD patients irrespective of growth impairment status, and the prevalence of growth impairment in our study was no greater than previously reported.⁶ Another limitation is that we did not include bone age or pubertal staging in assessment of growth in our patients. Bone age is an important objective measure of growth delay during childhood, but unfortunately this was not available for many patients. Some prior studies have differentiated pubertal stages based on age,^{20, 25} but we chose not to use this method as puberty is often delayed in children with IBD. Since Tanner staging for our patients was performed by different gastroenterology providers and/or was missing, we decided not to include it in the analysis. Furthermore, timing of pubertal onset was not recorded for most of our patients, and as a result, we could not compare impact of pubertal timing on final heights. Nevertheless, target height integrates all other variables related to stature.

In conclusion, parental height is a powerful determinant of linear growth even in the presence of chronic inflammation. Accordingly, low parental height predicts reduced growth in pediatric patients with IBD, and current therapy has not appreciably affected the prevalence of growth impairment. Most IBD patients do not remain growth impaired in adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Mean height Z-score distribution of 295 children with inflammatory bowel disease demonstrates overall left shift compared to a normally distributed curve.

Figure 2. Comparison of mean height Z-scores of the growth-impaired (N = 65) and the non-growth impaired (N = 230) children with inflammatory bowel disease.

Figure 3. Mothers (N = 283) and fathers (N = 231) of all IBD patients demonstrated normally distributed height Z-scores.

TABLE 1
Demographic and clinical characteristics of pediatric-onset inflammatory bowel disease
by growth impairment status

	Growth-impaired (n = 65)	Non-growth impaired (n = 230)	p-value
Male gender, n (%)	37 (57)	132 (57)	0.95
Caucasian, n (%)	62 (95)	220 (96)	0.93
IBD type - CD, n (%)	57 (88)	154 (67)	0.001
UC, n (%)	8 (12)	76 (33)	
Age symptom onset, mean years (SD)	10.1 (3.5)	10.8 (3.8)	0.20
Age of diagnosis, mean years (SD)	10.9 (3.4)	11.3 (3.7)	0.36
Lag-time, mean months (SD)	7.9 (10.1)	6.7 (9.8)	0.38
Extraintestinal manifestation(s), n (%)	29 (45)	75 (33)	0.07
Corticosteroid therapy, n (%)	60 (92)	202 (88)	0.31
Immunosuppressive use, n (%)	59 (91)	159 (69)	<0.001
Biologic therapy, n (%)	25 (39)	55 (24)	0.02
History of steroid-dependence, n (%)	6 (9)	29 (13)	0.46
Nutrition therapy, n (%)	41 (63)	83 (36)	<0.001
History of surgery, n (%)	17 (26)	45 (20)	0.25
Family history of IBD, n (%)	38 (59)	124 (54)	0.52

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation

TABLE 2
Parental stature of growth-impaired and non-growth impaired children with IBD

	Growth-impaired		Non-growth impaired		p-value
	n	Z-score (SD)	n	Z-score (SD)	
Mother's mean height	61	-0.67 (0.9)	222	0.02 (1.0)	<0.001
Father's mean height	49	-0.31 (1.0)	182	0.22 (1.1)	0.002

SD, standard deviation

TABLE 3
Final adult height and target height Z-scores of the patients with pediatric-onset IBD

	Growth-impaired		Non-growth impaired		p-value
	n	Z-score (SD)	n	Z-score (SD)	
Mean final adult height	37	-1.34 (0.9)	104	-0.05 (1.0)	< 0.001
Mean target height	46	-0.65 (0.7)	176	0.08 (0.8)	< 0.001

SD, standard deviation

TABLE 4
Adult and target heights of IBD patients who have reached adulthood (N = 108)

Height measurement	Growth-impaired (n = 28)	Non-growth impaired (n = 80)	p-value
Mean target height, Z-score (SD)	-0.52 (0.8)	0.13 (0.8)	<0.001
Mean adult height, Z-score (SD)	-1.38 (1.0)	0.07 (1.0)	<0.001
Mean difference, Z-score (SD)	-0.86 (1.0)	-0.05 (0.7)	<0.001

SD, standard deviation

TABLE 5
Univariate and multivariate regression analyses to determine predictors of final adult height (n=108)

Predictor	Unadjusted univariate analyses β (SE), p-value	Univariate analyses adjusted for target height β (SE), p-value	Multivariate regression analysis β (SE), p-value
Male gender	0.22 (0.2), p=0.34	0.32 (0.2), p=0.05	
CD IBD type	0.04 (0.3), p=0.89	-0.06 (0.2), p=0.74	
Age at diagnosis	0.04 (0.04), p=0.25	0.04 (0.03), p=0.17	
Lag-time	-0.01 (0.01), p=0.43	0 (0.01), p=0.96	
Corticosteroid therapy	-0.57 (0.4), p=0.11	-0.34 (0.3), p=0.19	
Immunosuppressive use	-0.14 (0.3), p=0.63	-0.18 (0.2), p=0.38	
Biologic therapy	-0.01 (0.2), p=0.97	-0.14 (0.2), p=0.43	
Nutrition therapy	-0.23 (0.2), p=0.31	-0.19 (0.2), p=0.24	
History of surgery	0.14 (0.3), p=0.58	-0.05 (0.2), p=0.79	
Extraintestinal manifestation(s)	0.06 (0.2), p=0.80	0.14 (0.2), p=0.42	
Family history	-0.47 (0.2), p=0.03	-0.27 (0.2), p=0.10	
Minimum height Z-score	0.75 (0.05), p<0.001	0.60 (0.1), p<0.001	0.63 (0.06), p<0.001
Mother's height Z-score	0.58 (0.1), p<0.001	-	0.21 (0.06), p=0.001
Father's height Z-score	0.49 (0.09), p<0.001	-	0.17 (0.06), p=0.004
Target height Z-score	0.97 (0.1), p<0.001	-	

β , beta coefficient from linear regression models; SE, standard error; IBD, inflammatory bowel disease; CD, Crohn's disease