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### Authors

Gupta, Neera  
Lustig, Robert H  
Chao, Cewin  
[et al.](#)

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## Observational Study

**Thiopurines are negatively associated with anthropometric parameters in pediatric Crohn's disease**

Neera Gupta, Robert H Lustig, Cewin Chao, Eric Vittinghoff, Howard Andrews, Cheng-Shiun Leu

Neera Gupta, Division of Gastroenterology and Nutrition, Department of Pediatrics, Weill Cornell Medicine, New York, NY 10021, United States

Robert H Lustig, Division of Endocrinology, Department of Pediatrics, University of California, San Francisco, San Francisco, CA 94158, United States

Cewin Chao, Department of Nutrition and Food Services, University of California, San Francisco, San Francisco, CA 94143, United States

Eric Vittinghoff, Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA 94158, United States

Howard Andrews, Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY 10032, United States

Cheng-Shiun Leu, Department of Biostatistics, Columbia University Medical Center, New York, NY 10032, United States

ORCID number: Neera Gupta (0000-0002-9571-3913); Robert H Lustig (0000-0001-6983-2639); Cewin Chao (0000-0002-5711-926X); Eric Vittinghoff (0000-0001-8535-0920); Howard Andrews (0000-0002-7726-0551); Cheng-Shiun Leu (0000-0002-0301-8316).

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**Correspondence to:** Neera Gupta, MD, MAS, Associate Professor, Division of Gastroenterology and Nutrition, Department of Pediatrics, Weill Cornell Medicine, 505 East 70<sup>th</sup> Street, Helmsley Tower, 3<sup>rd</sup> Floor, New York, NY 10021, United States. [neg9020@med.cornell.edu](mailto:neg9020@med.cornell.edu)  
Telephone: +1-646-9623869  
Fax: +1-646-9620246

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## Abstract

### AIM

To determine the distribution of anthropometric parameter (AP)-z-scores and characterize associations between medications/serum biomarkers and AP-z-scores in pediatric Crohn's disease (CD).

### METHODS

CD patients [ $<$  chronological age (CA) 21 years] were enrolled in a cross-sectional study. Descriptive statistics were generated for participants' demographic characteristics and key variables of interest. Paired *t*-tests were used to compare AP-z-scores calculated based on CA (CA z-scores) and bone age (BA) (BA z-scores) for interpretation of AP's. Linear regression was utilized to examine associations between medications and serum biomarkers with AP-z-scores calculated based on CA ( $n = 82$ ) and BA ( $n = 49$ ). We reported regression coefficients as well as their corresponding p-values and 95% confidence intervals.

### RESULTS

Mean CA at the time of the study visit was  $15.3 \pm 3.5$  (SD; range = 4.8-20.7) years. Mean triceps skinfold ( $P = 0.039$ ), subscapular skinfold ( $P = 0.002$ ) and mid-arm circumference (MAC) ( $P = 0.001$ ) BA z-scores were higher than corresponding CA z-scores. Medications were positively associated with subscapular skinfold [adalimumab ( $P = 0.018$ ) and methotrexate ( $P = 0.027$ )] and BMI CA z-scores [adalimumab ( $P = 0.029$ )]. Azathioprine/6-mercaptopurine were negatively associated with MAC ( $P = 0.045$ ), subscapular skinfold ( $P = 0.014$ ), weight ( $P = 0.002$ ) and BMI ( $P = 0.013$ ) CA z-scores. ESR, CRP, and WBC count were negatively associated, while albumin and IGF-1 BA z-scores were positively associated, with specific AP z-scores ( $P < 0.05$ ). Mean height CA z-scores were higher in females, not males, treated with infliximab ( $P = 0.038$ ). Hemoglobin ( $P = 0.018$ ) was positively associated, while platelets ( $P = 0.005$ ), ESR ( $P = 0.003$ ) and CRP ( $P = 0.039$ ) were negatively associated with height CA z-scores in males, not females.

### CONCLUSION

Our results suggest poor efficacy of thiopurines and a possible sex difference in statural growth response to infliximab in pediatric CD. Prospective longitudinal studies are required.

**Key words:** Inflammatory bowel disease; Azathioprine/6-mercaptopurine; Biologics; Nutrition

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**Core tip:** Azathioprine/6-mercaptopurine were negatively associated with specific anthropometric parameters, suggesting a possible negative effect vs poor efficacy of thiopurines in pediatric Crohn's disease (CD). Infliximab was positively associated with standardized height in females only, suggesting a possible sex difference in response to infliximab from the standpoint of statural growth in pediatric CD. Specific serum biomarkers were associated with standardized height in males only, supporting that inflammation has a more detrimental effect on statural growth in males with pediatric CD.

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## INTRODUCTION

Several studies document alterations in anthropometric parameters in pediatric Crohn's disease (CD) such as lean mass deficits<sup>[1-5]</sup>, reductions in fat free mass<sup>[6,7]</sup>, fat mass deficits<sup>[3,5,7]</sup>, low body mass index (BMI)<sup>[1-3,5-8]</sup>, high BMI<sup>[7,8]</sup>, and low height<sup>[1-3,5,9,10]</sup>. Similar to impaired statural growth (height velocity), a dynamic marker of disease status, body composition deficits may reflect poorly controlled disease despite the absence of overt clinical intestinal symptoms.

Delayed bone age (BA) is common in pediatric CD<sup>[10-16]</sup>. BA assessed by left hand X-ray is regarded as a valid measure of skeletal maturity<sup>[13-14,17-19]</sup>. Determination of BA allows clinically meaningful interpretation of growth in the context of skeletal maturity in pediatric CD<sup>[11]</sup>. Mean height, weight and BMI z-scores calculated based on BA (BA z-scores) are higher than corresponding z-scores calculated based on chronological age (CA) (CA z-scores) in pediatric CD<sup>[11]</sup>.

The impact of accounting for BA in the interpretation of body composition is unclear. Accurate interpretation of body composition is important since it reflects nutritional<sup>[4]</sup> and disease status. Not only is nutritional status an important determinant of pubertal development and growth velocity<sup>[20]</sup>, it is a prognostic factor for disease course<sup>[21-28]</sup>. Several factors affect nutritional status, including inflammation, medications, nutrient intake, and hormones<sup>[4,29,30]</sup>. The association between medications and serum inflammatory and hormonal biomarkers with anthropometric measurements is not well delineated in pediatric CD, particularly after adjusting for maturational status (BA).

Nutritional status is an important factor to consider when making therapeutic decisions given its association with poor outcomes<sup>[21-28]</sup>. Yet, the impact of treatments

on anthropometric measurements is poorly defined and has not received sufficient attention<sup>[31]</sup>. While there are well-documented sex differences in risk for statural growth impairment<sup>[9-10,14,21,32-35]</sup>, sex differences in nutritional status require further study. Data regarding the relationship between medications and serum biomarkers with anthropometric parameters by sex, an important biological variable, are lacking.

Here we assessed body composition by skinfold measurements in pediatric CD. Our aims were to (1) determine the distribution of anthropometric parameters based on CA (CA z-scores) and BA (BA z-scores); and (2) characterize the associations between medications and serum biomarkers with anthropometric parameter z-scores in pediatric CD.

## MATERIALS AND METHODS

Pediatric CD patients < CA 21 years enrolled in this cross-sectional study at University of California, San Francisco (UCSF) between January 2007 and July 2009 as previously described<sup>[10-11,36]</sup>. We excluded patients who received growth hormone ever or corticosteroids within 2 mo prior to study participation since more recent use would suppress the somatotrophic axis and interfere with accurate assessment of insulin-like growth factor-1 (IGF-1) levels. Eighty-two patients completed the study.

Mid-arm circumference measurements and skinfold thickness measurements were collected to the nearest 0.1 mm from the non-dominant side of the body in triplicate and averaged. A measuring tape was used for mid-arm circumference measurements and Lange skinfold calipers were used for skinfold thickness measurements. The mid-arm circumference measurement was obtained at the mid-point between the olecranon process and acromion. The triceps skinfold measurement was obtained at the mid-point of the upper arm, halfway between the acromion and the olecranon. The subscapular skinfold was measured at a 45° angle just below the inferior angle of the scapula. One of two registered dietitians obtained the measurements. Both were trained using standardized NHANES methodologies with established inter-rater reliability<sup>[37]</sup>. Weight and height were measured using a digital scale (Scale-Tronix, White Plains, NY, United States) to the nearest 0.1 kg and stadiometer (Proscale, Accurate Technology, Inc., Cincinnati, OH, United States) to the nearest 0.1 cm, respectively. Body mass index (BMI) was calculated as the weight in kg divided by the square of the height in meters. Self-Tanner staging was performed<sup>[38]</sup>. Left hand x-rays obtained for BA were blindly interpreted by RL using the standards of Greulich and Pyle<sup>[17]</sup>.

Medications of interest included adalimumab, 5-aminosalicylates, antibiotics, azathioprine/6-mercaptopurine (thiopurines), infliximab, and methotrexate.

We classified disease location as esophagus or stomach; small bowel, no colon; small bowel and colon; colon, no small bowel; perianal.

A lab draw was performed to measure serum IGF-1, insulin-like growth factor binding protein 3 (IGFBP-3), testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), albumin, alkaline phosphatase, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, platelets, and white blood cell (WBC) count. Tubes for serum hormone levels and routine clinical labs were processed by Esoterix Endocrinology (Calabasas Hills, CA, United States) and UCSF clinical lab, respectively. Clinical information was collected.

### Statistical analysis

We calculated CA z-scores for IGF-1, IGFBP-3, estradiol, testosterone, FSH, LH, mid-arm circumference, triceps skinfold, subscapular skinfold, weight, height, and BMI using reference values based in part on CA. Because pubertal growth acceleration correlates more closely with BA than CA<sup>[39]</sup>, we also calculated BA z-scores for all 17 females ≤ CA 15 and 32 males ≤ CA 17 years, as epiphyses close at BA 15 in females and 17 years in males. We excluded all females > CA 15 and males > CA 17 years from BA analyses because sufficient reference data on variability of BA beyond these CA thresholds are not available. We transformed mid-arm circumference, triceps skinfold, subscapular skinfold, weight, height, and BMI measurements to z-scores<sup>[40-45]</sup>. Means and standard deviations (SDs) provided by Esoterix Endocrinology were used to calculate IGF-1 and IGFBP-3 z-scores. The mean and the upper and lower bounds of the normal ranges (specific to sex, age, and Tanner stage), accounting for asymmetry about the mean if present, were used to compute SDs for gonadotropins and sex hormones. Low and high z-scores are defined as z-scores < -2.0 and > 2.0, respectively.

Descriptive statistics were generated for participants' demographic characteristics and key variables of interest. Paired t-tests were used to compare CA z-scores and BA z-scores for interpretation of anthropometric parameters. We employed linear regression to assess the associations between predictors (medications and serum biomarkers) and outcomes (anthropometric parameter CA z-scores and BA z-scores). For outcomes based on CA z-scores ( $n = 82$ ), we also conducted analyses including CA at study visit, sex, CRP, albumin, ESR, and hemoglobin in the model to adjust for potential confounding. We conducted additional analyses adjusting for disease activity indices, disease duration, stricturing disease and penetrating disease in these models. We analyzed height CA z-scores separately by sex because of well-established sex differences in risk for statural growth impairment<sup>[9-10,14,21,32-35]</sup>. We reported regression coefficients as well as their corresponding p-values and 95% confidence intervals (CI); P-values < 0.05 were considered as statistically significant. Data were analyzed using IBM SPSS Statistics 23.

### Ethical considerations

We obtained Institutional Review Board Approval for the study protocol. Informed consent/assent were obtained

**Table 1 Demographics, Tanner stage, disease location, and medications**

Item	n (%)
Race	
Asian	12 (14.6)
East Asian	6
South Asian	6
Black/African American	1 (1.2)
Other	4 (4.9)
White	65 (79.3)
Ethnicity	
Hispanic or Latino	7 (8.5)
Not Hispanic or Latino	75 (91.5)
Tanner stage	
1	8 (9.8)
2	15 (18.3)
3	16 (19.5)
4	24 (29.3)
5	19 (23.2)
Disease location	
Esophagus or stomach	9 (11)
Small bowel, no colon	12 (14.6)
Colon, no small bowel	17 (20.7)
Small bowel and colon	53 (64.6)
Perianal disease	49 (59.8)
Medication	
Adalimumab	4 (4.9)
5-Aminosalicylates	50 (61.0)
Antibiotics	14 (17.1)
Azathioprine/6-Mercaptopurine	44 (53.7)
Infliximab	20 (24.4)
Methotrexate	7 (8.5)
Steroids ever	55 (67.1)

from parents/patients.

## RESULTS

### Participant characteristics

82 patients completed the study; 35 (43%) were female<sup>[10]</sup>. Mean CA at the time of the study visit was  $15.3 \pm 3.5$  (SD; range = 4.8-20.7) years<sup>[10]</sup>. Mean CA at the time of inflammatory bowel disease (IBD) diagnosis was  $12.1 \pm 3.8$  (0.5-17.9) years. Mean time since IBD diagnosis was  $3.4 \pm 2.8$  (0.01-12.0) years. Race/ethnicity, Tanner stage, disease location, and medications are summarized in Table 1. History of corticosteroid use did not differ by sex<sup>[10]</sup>.

### Monotherapy vs combination therapy

Of the 44 patients on azathioprine/6-mercaptopurine, 33 (75%) were on thiopurine monotherapy, 10 (23%) were on combination therapy with infliximab and 1 (2%) was on combination therapy with adalimumab.

Of the 7 patients on methotrexate, 3 (43%) were on monotherapy, 2 (28.5%) were on combination therapy with infliximab and 2 (28.5%) were on combination therapy with adalimumab.

Of the 20 patients on infliximab, 8 (40%) were on monotherapy, 10 (50%) were on combination therapy with thiopurines and 2 (10%) were on combination therapy with methotrexate.

Of the 4 patients on adalimumab, 1 (25%) was on monotherapy, 1 (25%) was on combination therapy with thiopurines, 2 (50%) were on combination therapy with methotrexate.

### Anthropometric parameters

Anthropometric parameters are summarized in Table 2.

### Bone age vs chronological age for the interpretation of anthropometric parameters

For the 49 patients qualifying for BA analyses, mean BA ( $12.2 \pm 2.9$  years) was significantly lower than mean CA ( $13.1 \pm 2.6$  years) ( $P < 0.0001$ )<sup>[10]</sup>. Mid-arm circumference (0.35 units, 95%CI: 0.14-0.55;  $P = 0.001$ ), subscapular skinfold (0.10 units, 95%CI: 0.04-0.16;  $P = 0.002$ ), and triceps skinfold (0.05 units, 95%CI: 0.003-0.11;  $P = 0.039$ ) BA z-scores were systematically higher than corresponding CA z-scores.

### Medications, serum biomarkers, and anthropometric parameters

Tables 3 and 4 show the unadjusted and adjusted associations, respectively, between medication treatment, serum biomarkers and anthropometric parameter CA z-scores (height CA z-scores presented separately) that achieved statistical significance. Infliximab was not statistically significantly associated with mid-arm circumference, triceps skinfold, subscapular skinfold, weight or BMI CA z-scores (data not shown). Results did not change when disease activity indices, disease duration, stricturing disease or penetrating disease were included in the adjusted models.

Table 5 shows the unadjusted associations between serum biomarkers and anthropometric parameter BA z-scores (height BA z-scores presented separately). Medication treatments were not statistically significantly associated with anthropometric parameter BA z-scores.

Table 6 shows the unadjusted associations between medications, serum biomarkers and height CA z-scores by sex.

Table 7 shows the unadjusted association between serum biomarkers and height BA z-scores. Medications were not statistically significantly associated with height BA z-scores.

## DISCUSSION

In our prospective, cross-sectional study, azathioprine/6-mercaptopurine were negatively associated with lean tissue mass (mid-arm circumference CA z-scores) and fat store (subscapular CA z-scores) measurements, and weight CA z-scores and BMI CA z-scores in pediatric CD. We previously reported thiopurine treatment was associated with lower standardized BA results<sup>[11]</sup>. From a mechanistic perspective, it is unlikely these associations represents a direct negative impact of thiopurines on skeletal maturation or anthropometric parameters. When examining the association between

**Table 2 Summary of anthropometric parameters**

Variable ( <i>n</i> )	Mean ± SD	Range	Percent with z-scores > 2 (%)	Percent with z-scores < -2 (%)
Mid-arm circumference-CA-z-score <i>n</i> = 82	-0.64 ± 1.39	-5.03 to 2.88	2	17
Mid-arm circumference-BA-z-score <i>n</i> = 49	-0.54 ± 1.30	-2.86 to 2.50	2	16
Subscapular skinfold-CA-z-score <i>n</i> = 81	0.59 ± 0.83	-1.56 to 2.31	3	0
Subscapular skinfold-BA-z-score <i>n</i> = 48	0.64 ± 0.87	-1.17 to 2.27	4	0
Triceps-CA-z-score <i>n</i> = 81	1.02 ± 0.74	-0.88 to 2.79	11	0
Triceps-BA-z-score <i>n</i> = 49	1.10 ± 0.72	-1.17 to 2.47	8	0
Height-CA-z-score <i>n</i> = 82	-0.30 ± 1.02	-2.74 to 2.34	1	6
Height-BA-z-score <i>n</i> = 49	0.17 ± 1.12	-3.29 to 2.53	4	2
Weight CA-z-score <i>n</i> = 82	-0.17 ± 1.10	-3.49 to 2.20	4	5
Weight BA-z-score <i>n</i> = 49	0.11 ± 0.91	-2.52 to 1.97	0	2
BMI-CA-z-score <i>n</i> = 82	-0.07 ± 1.04	-2.78 to 2.17	4	4
BMI BA-z-score <i>n</i> = 49	0.05 ± 0.86	-2.58 to 2.09	2	2

BA z-score: z score based on bone age; BMI: Body mass index; CA z-score: z score based on chronological age.

**Table 3 Significant associations between medications/serum biomarkers and anthropometric parameters [z-scores based on chronological age (*n* = 82)] - unadjusted analyses**

Variable	Mid-arm circumference CA-z-scores	Subscapular skinfold CA-z-scores	Weight CA-z-scores	BMI CA-z-scores
Adalimumab		0.90 <sup>1</sup> (0.08, 1.72) <sup>2</sup> 0.033 <sup>3</sup>		1.09 (0.05, 2.13) 0.04
Azathioprine	-0.65 (-1.25, -0.05) 0.033	-0.5 (-0.85, -0.14) 0.006	-0.7 (-1.16, -0.23) 0.004	-0.56 (-1.004, -0.12) 0.014
Methotrexate		0.75 (0.06, 1.43) 0.032		
ESR	-0.024 (-0.05, -0.002) 0.036		-0.03 (-0.05, -0.02) 0.0003	-0.02 (-0.04, -0.006) 0.009
Hemoglobin			0.19 (0.04, 0.34) 0.015	

<sup>1</sup>Regression coefficient for unadjusted analyses [*i.e.*, one medication or serum biomarker (independent variable) per model and no adjustment for potential confounding]; <sup>2</sup>(95% confidence interval); <sup>3</sup>P-value. BMI: Body mass index; CA z-score: z score based on chronological age; ESR: Erythrocyte sedimentation rate.

azathioprine/6-mercaptopurine and BA z-scores for these specific anthropometric parameters, the direction of the association remained negative between thiopurines and subscapular skinfold BA z-scores (though did not achieve statistical significance due to smaller sample size (*n* = 49 for BA analyses vs *n* = 82 for CA analyses). This continued negative association between thiopurines and subscapular skinfold BA z-scores in combination with our previously reported finding of a negative association between thiopurines and standardized BA results<sup>[11]</sup> calls into question the efficacy of thiopurines for treating pediatric CD. Our findings highlight the importance of considering BA in the interpretation of anthropometric parameters because its inclusion clarifies the relationship between medications and these outcomes.

Previously published data on the impact of thiopurines on anthropometry for comparison to our findings are limited, but also raise concerns about the efficacy of these medications. Csontos *et al.*<sup>[31]</sup> reported no statistically significant difference in the change in fat free mass index, skeletal muscle index, or body fat mass index in adult IBD patients on vs not on

azathioprine during initiation of biologic therapy. In newly diagnosed CD children randomized to treatment with 6-mercaptopurine plus steroids vs placebo plus steroids, Markowitz *et al.*<sup>[46]</sup> did not detect a difference in statural growth.

Regarding a possible negative impact of utilizing thiopurines, in a pediatric IBD cohort, Hyams *et al.*<sup>[47]</sup> reported thiopurine exposure is an important preceding event for the development of malignancy or hemophagocytic lymphohistiocytosis. Our data identify another negative signal associated with thiopurines, given the constellation of findings of statistically significant negative associations between azathioprine/6-mercaptopurine and mid-arm circumference, subscapular skinfold, weight and BMI CA z-scores and persistent negative association with subscapular skinfold BA z-scores (though did not achieve statistical significance due to smaller sample size available for BA analyses), in combination with our previously reported finding of a statistically significant association with lower standardized BA results<sup>[11]</sup>. Prospective longitudinal study is required to examine the longitudinal pattern of these associations and to investigate whether

**Table 4 Significant associations between medications/serum biomarkers and anthropometric parameters [z-scores based on chronological age (*n* = 82)] - adjusted analyses**

Variable	Mid-arm circumference CA-z-scores	Subscapular skinfold CA-z-scores	Weight CA-z-scores	BMI CA-z-scores
Adalimumab		1.02 <sup>1</sup> (0.18, 1.86) <sup>2</sup>		1.17 (0.13, 2.21)
Azathioprine	-0.64 (-1.26, -0.02)	0.018 <sup>3</sup> -0.47 (-0.83, -0.10)	-0.73 (-1.17, -0.29)	0.029 -0.58 (-1.03, -0.12)
Methotrexate	0.045	0.014 0.81 (0.10, 1.53)	0.002	0.013
ESR		0.027	-0.03 (-0.05, -0.01)	-0.03 (-0.05, -0.004)
			0.01	0.024

<sup>1</sup>Regression coefficient for adjusted analyses [*i.e.*, one medication or serum biomarker (independent variable) per model and CA at study visit, sex, CRP, albumin, ESR and hemoglobin are included in the model to adjust for potential confounding]; <sup>2</sup>(95% confidence interval); <sup>3</sup>P-value. BMI: Body mass index; CA z-score: z score based on chronological age; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

**Table 5 Significant associations between serum biomarkers and anthropometric parameters [z-scores based on bone age (*n* = 49)] - unadjusted analyses**

Variable	Mid-arm circumference BA-z-scores	Subscapular skinfold BA-z-scores	Triceps skinfold BA-z-scores	Weight BA-z-scores	BMI BA-z-scores
WBC	-0.19 <sup>1</sup> (-0.36, -0.02) <sup>2</sup>	-0.12 (-0.24, -0.01)		-0.16 (-0.28, -0.04)	
ESR	0.029 <sup>3</sup>	0.04		0.008 -0.03 (-0.04, -0.01)	-0.02 (-0.03, -0.001)
CRP			-0.03 (-0.07, -0.0001)	0.003 -0.06 (-0.10, -0.02)	0.037
Albumin			0.049	0.008 0.73 (0.28, 1.18)	
IGF-1 BA-z-scores				0.002 0.2 (0.01, 0.38)	
				0.039	

<sup>1</sup>Regression Coefficient for Unadjusted Analyses [*i.e.*, one serum biomarker (independent variable) per model and no adjustment for potential confounding]; <sup>2</sup>(95% confidence interval); <sup>3</sup>P-value. BA z-score: z score based on bone age; BMI: Body mass index; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; IGF-1: Insulin-like growth factor-1; CRP: C-reactive protein.

these findings represents a lack of efficacy of thiopurines (given that anthropometric parameters and skeletal maturation reflect nutritional status/disease status) vs a direct negative impact of thiopurines in pediatric CD. Patients with lower body composition z-scores and lower standardized BA results were not selectively placed on thiopurines vs another medication such as methotrexate, infliximab, or adalimumab as these measurements were obtained at the time of the study.

Adalimumab and methotrexate were positively associated (statistically significant) with measurements of fat mass [subscapular CA z-scores (adalimumab/methotrexate)] and BMI CA z-scores (adalimumab). While these medications were not statistically significantly associated with these outcome BA z-scores due to a smaller sample size available for BA analyses, the direction of these associations (positive) remained

unchanged and the effect sizes were similar to only mildly decreased compared with the statistically significant positive associations between these medications and these outcome CA z-scores, supporting a positive association between adalimumab and methotrexate with these anthropometric parameter BA z-scores.

Similar to our finding of a positive association between the anti-tumor necrosis factor alpha (TNF- $\alpha$ ) agent, adalimumab, and BMI, Diamanti *et al.*<sup>[48]</sup> reported that weight and BMI improved in children treated with infliximab, but not with mesalazine and azathioprine. Wiese *et al.*<sup>[49]</sup> reported a significant increase in BMI with infliximab treatment in adult CD.

In a pediatric CD study, investigators reported specific medications were associated with greater increases in race- and sex-specific z-scores for both lean mass (infliximab) and fat mass (infliximab, glucocorticoid,

**Table 6 Significant associations between medications/serum biomarkers and height z-scores by sex (based on chronological age (female *n* = 35; male *n* = 47)) - unadjusted analyses**

Variable	Height CA z-scores	Point estimate <sup>1</sup>	95%CI	P value
Infliximab	Females	0.65	0.04, 1.25	0.038
CRP	Males	-0.04	-0.079, -0.002	0.039
ESR	Males	-0.03	-0.051, -0.011	0.003
Hemoglobin	Males	0.23	0.04, 0.42	0.018
Platelets	Males	-0.004	-0.006, -0.001	0.005

<sup>1</sup>Regression coefficient for unadjusted analyses [*i.e.*, one medication or serum biomarker (independent variable) per model and no adjustment for potential confounding]. CA z-score: z score based on chronological age; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

**Table 7 Significant associations between serum biomarkers and height z-scores [based on bone age (*n* = 49)] - unadjusted analyses**

Variable	Height BA-z-scores	Point estimate <sup>1</sup>	95%CI	P value
Albumin	Males and females	0.8	0.22, 1.36	0.008
CRP	Males and females	-0.06	-0.11, -0.006	0.03
ESR	Males and females	-0.02	-0.05, -0.003	0.029
IGF-1 BA-z-scores	Males and females	0.26	0.03, 0.48	0.025

<sup>1</sup>Regression coefficient for unadjusted analyses [*i.e.*, one serum biomarker (independent variable) per model and no adjustment for potential confounding]. BA z-score: z score based on bone age; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; IGF-1: Insulin-like growth factor-1; CRP: C-reactive protein.

and methotrexate) relative to height<sup>[50]</sup>. Similarly, we identified a positive association between methotrexate and subscapular skinfold CA z-scores. In a CD patient cohort, age 5-25 years, Sentongo *et al.*<sup>[14]</sup> reported triceps skinfold z-scores, also a measure of adiposity, were significantly correlated with corticosteroid exposure. Our findings do not reveal a statistically significant association between history of corticosteroid therapy and current anthropometric parameters.

Csontos *et al.*<sup>[31]</sup> reported baseline BMI increased significantly during initiation of adalimumab/infliximab therapy in adult IBD, in agreement with our identified positive association between adalimumab and BMI. They found fat free mass index also increased. They found no significant differences between the effects of adalimumab and infliximab on body composition, whereas we identified significant associations between body composition and adalimumab only, not infliximab. Notably, fat free mass index and skeletal muscle mass index significantly improved only in males. Subramaniam *et al.*<sup>[51]</sup> reported infliximab was associated with significant gains in muscle volume that correlated with male sex in adult CD<sup>[51]</sup>. Supporting these sex differences in response to infliximab, in a mouse model of pulmonary inflammation in which TNF- $\alpha$  was over expressed in mouse lungs, lower body and muscle mass were evident only in males<sup>[52]</sup>.

Our study does not reveal a sex difference in the association between medications and body composition, but does identify a statistically significant positive association between infliximab and height CA z-scores in females only. A positive relationship between infliximab and height BA z-scores was also identified in females only, but did not reach statistical significance, likely due to the smaller sample size available for BA analyses (*n*

= 17 females for BA analyses vs *n* = 35 females for CA analyses). The combination of findings described here between infliximab and height z-scores (based on CA and BA) supports a possible sex difference in response to infliximab from the standpoint of statural growth. Taken together, these findings of sex differences in response to infliximab add to the growing body of literature indicating that there may be sex differences in the molecular pathways affecting statural growth and body composition in CD. Our findings in combination with the existing literature raise an intriguing question: does TNF- $\alpha$  play an important role in compromising body composition in CD males but statural growth in females, and if so, why? Tang *et al.*<sup>[52]</sup> speculated that estrogen has protective effects against the actions of TNF- $\alpha$ . Ordas *et al.*<sup>[53]</sup> reported that clearance of monoclonal antibodies is higher in men. Ternant *et al.*<sup>[54]</sup> theorized that the central volume of distribution may be higher in men because for a given body weight, plasma volume is lower in women.

We found hemoglobin was positively associated, while platelets, ESR, and CRP were negatively associated, with height CA z-scores in males only, supporting our previously reported findings of a greater detrimental effect of inflammation on statural growth in males<sup>[10]</sup>. Several investigators have documented that growth impairment is more frequent in males<sup>[9,10,14,21,32-35]</sup>. Perhaps the molecular pathways that lead to growth impairment in males are different than in females, and less responsive to currently used medications, such as infliximab. As expected, albumin and IGF-1 BA z-scores were positively associated, while ESR and CRP were negatively associated with height BA z-scores. In contrast, no treatment (5-aminosalicylate, corticosteroids, immunomodulators, infliximab, nutritional therapy,



surgical resection) was associated with height, weight or BMI at maximal follow up in a pediatric CD cohort in Northern France<sup>[21]</sup>.

The relationships between medications and anthropometric parameters may reflect efficacy of medications, side effects of medications, or confounding by indication. Since body composition measurements were obtained as part of a study protocol and not standard of care, it is unlikely these relationships reflect confounding by indication since these body composition measurements were not available to the care provider. Our results suggest methotrexate, infliximab and adalimumab are more effective than thiopurines for treating pediatric CD.

As expected, body composition BA z-scores were systematically higher than corresponding body composition CA z-scores. Patients did not exhibit severe deficiencies in fat stores, as reflected by standardized subscapular and triceps skinfold measurements. Depending on the measurement obtained, 3% to 11% had subscapular or triceps skinfold measurement CA z-scores or BA z-scores > 2.0, reflecting excess fat stores. In contrast, 16%-17% had deficiencies in lean mass tissue as reflected by mid-arm circumference z-score measurements < -2.0 and only 2% with mid-arm circumference z-score measurements > 2.0. We identified a negative association between thiopurines and mid-arm circumference CA z-scores. The published literature surrounding the relationship between medications and lean mass tissue is conflicting<sup>[31,50-51]</sup>. More studies are needed to identify the most effective treatments for improving lean mass tissue in pediatric CD.

Correlations between inflammatory markers/disease activity indices and anthropometric parameters have been reported by other investigators<sup>[5,14,50,55,56]</sup>, similar to our findings. Enhancing our understanding of the specific inflammatory cytokines involved in molecular pathways affecting body composition and growth is critical for optimizing treatment.

### Limitations

The etiology of compromised nutritional status/disease status is multifactorial. The cross-sectional study design does not permit longitudinal assessment of changes in anthropometric parameters with respect to medication treatment and serum biomarkers to be determined. Within-subjects characterization of the influence of disease activity and hormone levels on changes in anthropometric parameters may clarify the effects of long-term inflammation on nutritional status/disease status. Nevertheless, our results suggest a mechanistic relationship between medications, inflammation and anthropometric status/disease status, as well as a difference by sex. Prospective longitudinal study, collecting additional markers of disease activity/disease status such as fecal calprotectin, cross-sectional imaging and endoscopic assessment, is required as a next step

to further investigate these intriguing findings and would allow further risk stratification which will improve patient counseling, guide expectations, and facilitate an individualized treatment approach. Future studies should examine the impact of monotherapy vs combination therapy (including duration of treatment and drug levels) on anthropometric status/disease status.

### Summary and Conclusions

Complex processes regulate body composition and growth in pediatric CD. We examined the relationship between medication treatments and serum inflammatory and hormonal biomarkers with anthropometric parameters in a well-characterized pediatric CD cohort. Our findings reinforce the importance of accounting for BA when interpreting anthropometric parameters in pediatric CD. The main findings of our study raise intriguing questions.

Thiopurines were negatively associated with specific anthropometric parameters. Do thiopurines have a negative effect on nutritional status/disease status? Alternatively, is the efficacy of thiopurines suboptimal? This interesting finding may have significant implications for pediatric CD treatment and requires further investigation in a prospective longitudinal study to determine if thiopurines should continue to be utilized as a treatment for pediatric CD.

Infliximab was positively associated with standardized height in females only. Is there a sex difference in response to infliximab from the standpoint of statural growth? Specific serum biomarkers were associated with standardized height in males only, supporting the hypothesis that inflammation has a more detrimental effect on statural growth in males. The combination of these findings lends further support to the theory that sex differences in the molecular pathways driving statural growth impairment in pediatric CD exist and should be delineated in a prospective longitudinal study utilizing height velocity BA z-scores as the primary outcome. An improved understanding of this sex difference in response to treatment would be a huge step towards enhancing risk prediction and individualized treatment.

The studies presented herein contribute to a better understanding of the relationship between medications and serum inflammatory and hormonal biomarkers with anthropometric parameters in pediatric CD. These findings serve as a foundation on which to build future studies with the goal of identifying patients at highest risk for poor outcomes, enhancing treatment algorithms, and ultimately developing individual treatment approaches based on risk stratification. The present study may provide a basis for mechanistic studies in many pediatric chronic inflammatory conditions.

## ARTICLE HIGHLIGHTS

### Research background

Similar to impaired statural growth (height velocity), a dynamic marker of

disease status, body composition deficits may reflect poorly controlled disease despite the absence of overt clinical intestinal symptoms. Delayed bone age (BA) is common in pediatric Crohn's disease (CD). Determination of BA allows clinically meaningful interpretation of growth in the context of skeletal maturity in pediatric CD. The impact of accounting for BA in the interpretation of body composition is unclear. Accurate interpretation of body composition is important since it reflects nutritional and disease status. Not only is nutritional status an important determinant of pubertal development and growth velocity, it is a prognostic factor for disease course. The association between medications and serum inflammatory and hormonal biomarkers with anthropometric measurements is not well delineated in pediatric CD, particularly after adjusting for maturational status (BA).

### Research motivation

Nutritional status is an important factor to consider when making therapeutic decisions given its association with poor outcomes. Yet, the impact of treatments on anthropometric measurements is poorly defined and has not received sufficient attention.

### Research objectives

Our aims were to determine the distribution of anthropometric parameters based on CA (CA z-scores) and BA (BA z-scores) and characterize the associations between medications and serum biomarkers with anthropometric parameter z-scores in pediatric CD.

### Research methods

CD patients [ $<$  chronological age (CA) 21 years] were prospectively enrolled in a cross-sectional study. Descriptive statistics were generated for participants' demographic characteristics and key variables of interest. Paired *t*-tests were used to compare anthropometric parameter z-scores calculated based on CA (CA z-scores) and BA (BA z-scores) for interpretation of anthropometric parameters. Linear regression was utilized to examine associations between medications and serum biomarkers with anthropometric parameter z-scores calculated based on CA ( $n = 82$ ) and BA ( $n = 49$ ). We reported regression coefficients as well as their corresponding p-values and 95% confidence intervals.

### Research results

Mean CA at the time of the study visit was  $15.3 \pm 3.5$  (standard deviation; range = 4.8-20.7) years. Mean triceps skinfold, subscapular skinfold and mid-arm circumference (MAC) BA z-scores were higher than corresponding CA z-scores. Medications were positively associated with subscapular skinfold (adalimumab and methotrexate) and BMI (adalimumab) CA z-scores. Azathioprine/6-mercaptopurine were negatively associated with MAC, subscapular skinfold, weight and BMI CA z-scores. ESR, CRP, and WBC count were negatively associated, while albumin and IGF-1 BA z-scores were positively associated with specific AP z-scores. Mean height CA z-scores were higher in females, not males, treated with infliximab. Hemoglobin was positively associated, while platelets, ESR and CRP were negatively associated with height CA z-scores in males, not females.

### Research conclusions

Our findings reinforce the importance of accounting for BA when interpreting anthropometric parameters in pediatric CD. The main findings of our study raise intriguing questions. Thiopurines were negatively associated with specific anthropometric parameters. Do thiopurines have a negative effect on nutritional status/disease status? Alternatively, is the efficacy of thiopurines suboptimal? Infliximab was positively associated with standardized height in females only. Is there a sex difference in response to infliximab from the standpoint of statural growth? Specific serum biomarkers were associated with standardized height in males only, supporting the hypothesis that inflammation has a more detrimental effect on statural growth in males. Our results suggest a mechanistic relationship between medications, inflammation and anthropometric status/disease status, as well as a difference by sex. The studies presented herein contribute to a better understanding of the relationship between medications and serum inflammatory and hormonal biomarkers with anthropometric parameters in pediatric CD. Prospective longitudinal study is required as a next step to further investigate these intriguing findings and would allow further risk

stratification which will improve patient counseling, guide expectations, and facilitate an individualized treatment approach.

### Research perspectives

These findings serve as a foundation on which to build future studies with the goal of identifying patients at highest risk for poor outcomes, enhancing treatment algorithms, and ultimately developing individual treatment approaches based on risk stratification. The present study may provide a basis for mechanistic studies in many pediatric chronic inflammatory conditions.

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