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ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

The impact of age, disease severity, and BMI on bone health and growth in children and young people with Crohn's disease

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Abstract

Objectives: The objective of this study was to explore the correlation between paediatric Crohn's disease (CD) characteristics, bone health and growth parameters at diagnosis and follow-up.

Methods: Retrospective data was collected for 47 children aged 4–16 who were newly diagnosed with CD between January 2018 and December 2019. Mean follow-up time was 2.5 years.

Results: Eleven (24%) children had growth delay at diagnosis, which persisted in 4 (44%) of 9 recorded children at follow-up. Of the 35 children tested, 20 (57%) had inadequate Vitamin D levels (<50 mmol/L) at diagnosis. Thirty-seven (79%) children had a dual-energy X-ray absorptiometry scan at diagnosis, with 20 of them having at least 1 low *Z*-score. Children with poorer bone mineral density and bone mineral concentration *Z*-scores for age had a younger age at diagnosis ($p = .042$ and $p = .021$), more severe disease ($p = .04$ and $p = .029$) and a lower BMI ($p < .001$) at diagnosis. Children diagnosed with CD ≥11 years had a lower-than-expected height velocity ($p < .0001$ and $p < .001$). Multivariate regression analysis demonstrated an older age of diagnosis was a significant predictor of a lower height velocity at follow-up.

Conclusion: Disease severity and age of diagnosis are important CD-related factors that influence bone health and growth. Vitamin D is an accessible component that if optimised can improve all three factors. Monitoring and optimising each aspect systematically has the potential to enable children to achieve their bone health and growth potentials.

KEYWORDS

bone density scan (DEXA), bone mineral density (BMD), inflammatory bowel disease (IBD), paediatrics

[Correction added on 15 January 2024, after first online publication: The co-author Nick Crof was updated to Nicholas M Croft.]

1 | INTRODUCTION

Growth failure is a common manifestation of paediatric Crohn's disease (CD), presenting in up to 85% of children and persisting in 15%–40%.[1–3] Childhood and adolescence is a period of rapid growth and bone development.[4] The degree of inflammation and the presence of pro-inflammatory can impact this, in addition to a child's nutritional status and physical activity levels.[4–6]

During pubertal and prepubertal years, there are rapid rates of bone mass and bone mineral density (BMD) accumulation and relatively slower rates of bone resorption.[4] However in young people with chronic inflammatory processes, there is a relatively increased rate of bone resorption compared with the average healthy child, contributing to the depletion of BMD and bone mineral concentration (BMC). Additionally, chronic inflammation perpetuates the malabsorptive state resulting in nutritional deficiencies.[6–9] Undernutrition plays a role in growth failure and pubertal delays which further limits accumulation of BMD.[9] These factors create a vicious circle that interplay with one another to culminate in poor bone health and growth outcomes. Growth impairment often precedes the diagnosis of CD, and decreased height velocity is a sensitive indicator of it.[1,3,6,10–13] A 2021 systematic review and consensus statement found a younger age of disease onset, male sex, small bowel centred disease and a higher level of disease activity all correlated with growth impairment.[6]

Higher levels of disease activity resulting in more pronounced intestinal inflammation can result in nutritional deficiencies, in particular Vitamin D (25OHD), which is found in 62% of children.[6,14–16] 25OHD has been shown to impact intestinal inflammation, growth and bone health.[17–20] The role of 25OHD in calcium absorption and bone mineralisation are well established.[19,21] Some in vivo evidence suggests 25OHD also plays an immunomodulatory role by downregulating tumour necrosis factor-alpha.[22,23] In particular, mice that had 25OHD deficiencies had comparatively more inflammatory bowel disease symptoms.[24] Gaining good disease control and correction of nutritional status is a vital step towards normalising growth, despite this, some children may be left with deficits in their final adult height.[25]

To date, there are few studies that observe the extent of the impact bone health, growth and disease factors have on each other, without interventions, particularly in the UK.[6,11,16,26] Furthermore, bone health and growth are not adequately addressed in national and international guidelines. The primary aim of this study is to explore the correlation between CD characteristics, bone health and growth factors at diagnosis and follow-up (Figure 1). The secondary aim is to identify potential strategies for bone health and growth optimisation.

What is Known

- Growth failure occurs in up to 85% of children diagnosed with Crohn's disease and persists in up to 40%.
- Vitamin D plays a role in bone health (BH), growth, and intestinal inflammation.
- Chronic inflammation and undernutrition are key factors behind poor BH and growth failure.

What is New

- Children with poorer BH are younger, have more severe disease and a lower body mass index at diagnosis.
- An older age of diagnosis is an independent predictor of lower-than-expected height velocity in the future.

2 | METHODS

2.1 | Patients

Retrospective data was collected for 47 patients that met the inclusion and exclusion criteria. Inclusion criteria: age under 18 years at the time of CD diagnosis between January 2018 and December 2019 at The Royal London Hospital (RLH), a tertiary paediatric gastroenterology unit. All patients in this study had a CD diagnosis based on the revised Porto criteria.[27] Exclusion criteria: more than 50% data missing.

2.2 | Data collection

Clinical variables relating to growth, bone health and disease factors were collected from the hospital electronic patient records. Paediatric Crohn's Disease Activity Index (PCDAI) scores were retrospectively calculated to assess disease severity at diagnosis.[28] A C-Reactive Protein of >10 mg/L and a Faecal Calprotectin ≥250 mcg/g were classed as high, respectively, as per ECCO-ESPGHAN guidelines.[29]

Growth delay (Paris classification G1) was defined as involuntary stable weight or weight loss of 10% or more over the previous 6 months, and/or a decrease in height by ≥1 centile or height velocity by ≥1 standard deviations. This definition was used to define growth delay at diagnosis and follow-up. Height velocity was calculated (height at follow-up in cm—height at diagnosis in cm)/(age at follow-up in years—age at diagnosis in years). Patients were stratified based on whether their anagraphic age was prepubertal (≤10 years) or pubertal (≥11 years) at the time of diagnosis and they were compared with average height

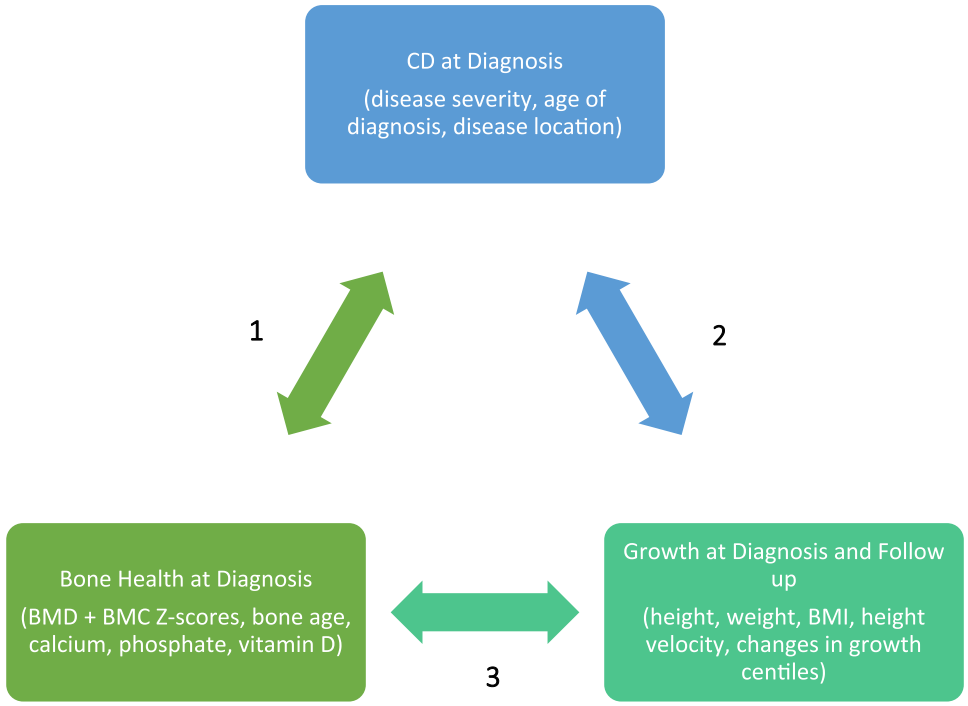

FIGURE 1 A visual representation of the primary aims of this study and how each of the factors interlink with one another. Each numbered arrow corresponds to the aims. BMC, bone mineral concentration; BMD, bone mineral density; BMI, body mass index; CD, Crohn's disease.

velocity values for their age and sex.[30] Body mass index (BMI) categories used were in accordance to the World Health Organisation cut-offs.[31] The same parameters were also assessed at the most recent follow-up. Information not available in the preceding 6 months, was classified as "Not Available" (N.A).

Dual-energy X-ray absorptiometry (DXA) scan *Z*-scores were recorded for total body less head (TBLH) and subtotal body and neck of femur. At our Institution, these were adjusted for bone age, height, age, sex and ethnicity, but not pubertal stage. A low BMD or BMC *Z*-score was considered if ≤−2.0 SD.[32] A suboptimal BMD or BMC score was considered if ≤−1.0 SD.[11] Bone age was established through a wrist X-ray of the left hand based on the Greulich and Pyle Atlas.[33]

Inorganic phosphate and calcium levels (corrected for hypoalbuminemia using Payne's formula) were recorded at the time of diagnosis. The normal ranges were 2.2–2.6 and 0.9–1.8 mmol/L, respectively.

25OHD levels (nmol/L) were assessed at the time of diagnosis and at follow-up. 25OHD levels were considered adequate if >50 nmol/L and inadequate if <50 nmol/L; specifically, deficiency was classed as <30 nmol/L, insufficiency as 30–50 nmol/L.

Clinical variables reflecting disease treatment and management throughout the follow-up were noted. Maintenance therapies and dosages were recorded, however, for the purposes of analysis they were grouped into "Step 1" which includes 5-amino-salycilates, Azathioprine or Methotrexate, and "Step 2" consisting of biologic treatments (e.g., anti-TNFa (Infliximab or Adalimumab), or anti-IL-12/23 (Ustekinumab)). Similarly, the number of steroid therapies and the cumulative duration the child was exposed to steroids were noted and categorised into <3 months, ≥3 months and >1 year.

2.3 | Statistical analysis

Power calculation was conducted to ensure the cohort was a sufficient size to provide with statistically relevant results. For a two-sided test, using an α of 0.05, a sample of 42 was needed to have 80% power. This was based on a documented incidence of growth failure at follow-up of 40%, and an expected incidence of at least 20% in our study.[3] Similarly for bone health, the incidence in the population for low BMD is up to 44% and we expect an incidence of around 24% in our smaller cohort.[34] Our study with 47 patients was therefore deemed sufficiently powered.

Inferential statistical analysis was performed using IBM SPSS Statistics v28.0. Pearson's χ^2 tests for 2×2 and 2×3 tables was used for categorical data. In instances for 2×2 tables, where the expected count was <5 for more than 20% of cells, Fisher's Exact Test was used to recheck accuracy, and reported if it resulted in a change of statistical significance. The Bonferroni correction was applied to correct for multiple testing,

additionally, Phi and Cramers V were measured to establish the effect size. Correlations for continuous and ordinal variables were assessed through Spearman's Rank Correlation Coefficient. Linear regression was used for height velocity and the age of diagnosis to establish the relationship and the equation that could be used to extrapolate the results. Multiple regression analysis was conducted using a stepwise model. p Values of <0.05 were considered as significant.

2.4 | Ethical approval

This project was registered as a Quality Improvement Audit at Barts Health NHS Trust (Audit ID 12858) and the patients' data were anonymised. Ethical approval was therefore not required.

3 | RESULTS

Forty-seven newly diagnosed CD patients (33 males, mean age 12 years, range 4–16 years) were followed up on average for 2.5 years (SD ± 0.87, range: 1–4 years). Baseline information at the time of diagnosis is displayed in Table 1. Information gathered during follow-up is displayed in Table 2.

11/46 (24%) children had evidence of growth delay at diagnosis, as defined by the Paris Classification. Specifically looking at prepubertal children, 44% (6/14) had growth delay. In terms of bone health, 5 (12%) patients had a delayed bone age according to their left wrist X-ray, 30 (71%) were normal and the rest were advanced. Thirty-eight (81%) patients received a DXA scan at diagnosis. Of them, 29 (76%) had ≥1 suboptimal DXA score and 20 (53%) had ≥1 low DXA score. There was some overlap with patients who had low or suboptimal DXA scores and their PCDAI score at diagnosis, as well as growth delay at diagnosis (Table, Supporting Information: Digital Content 1, Stratification of DXA result with patient factors). Of the children that were underweight at diagnosis, 19 (50%) had at least 1 low BMD or BMC Z-score.

25OHD levels at diagnosis were assessed in 35 patients of which 20 had inadequate levels (≤50 mmol). Four did not receive any form of supplementation, nine (45%) patients received 400 IU of 25OHD supplementation per day, six had inadequate doses according to local guidelines, only one was prescribed the recommended dose (Table, Supporting Information: Digital Content 2, Stratification of Vitamin D levels and supplementation).

Growth delay at follow-up was considered if they had any decrease in height centile (Figure 2). Irrespective of whether children had growth delay at diagnosis, 40% (14/35) had growth delay at follow-up. 4/9 (44%) patients who had growth delay at diagnosis also had growth delay at follow-up.

24/34 (70.5%) patients had a lower-than-expected height velocity. According to the most recent follow-up, BMI classification was either maintained or increased; with 10 children being overweight or obese.

At follow-up, 26 (55%) patients did not have a follow-up 25OHD level. Out of those that did, 13 (62%) had inadequate levels. 45 out of 47 (96%) of patients did not have a repeat DXA scan throughout the course of follow-up.

3.1 | CD characteristics and bone health at diagnosis

DXA scans performed around the time of diagnosis revealed that children diagnosed at a younger age had worse bone health, mainly affecting TBLH BMD for age ($r = 0.336$, $p = .042$), TBLH BMC for age ($X^2 = 7.77$, $p = .021$) and TBLH BMD for height ($X^2 = 6.17$, $p = .046$ and $r = 0.371$, $p = .026$). Poor bone health, specifically TBLH BMD and BMC for age, was also linked to a more severe disease at diagnosis ($r = -0.344$; $p = .04$ and $r = -0.365$; $p = .029$ respectively). However, there were no statistically significant associations between disease severity and the age of diagnosis.

3.2 | CD characteristics and vitamin D

Disease location had a significant association with improved 25OHD levels at follow-up. Children with exclusive ileal disease were more likely to have improved their 25OHD levels, compared with those with more extensive ileo-colonic disease ($X^2 = 8.27$, $p = .016$). There was a large effect size reflecting a large difference between the groups ($\varphi_c = 0.678$). Moreover, children who had a higher 25OHD level at diagnosis also maintained a higher 25OHD level at follow-up ($r = 0.746$, $p = .014$). However, there was no significant difference between 25OHD levels at follow-up irrespective of whether 25OHD supplementation was taken, and of the duration it was taken for.

3.3 | CD at diagnosis and growth parameters at diagnosis and during follow-up

Children diagnosed with CD ≥11 were more likely to have a lower-than-expected height velocity, after adjusting for age and sex ($X^2 = 29.62$, $p < .0001$ and $r = -0.766$, $p < .001$) (Figure 3A). Using the equation from the line of best fit (Height velocity = 12.91–0.73*Age at Diagnosis), the predictive value was calculated as shown in Figure 3B.

There was a nearly significant correlation between the age of diagnosis and whether the child had growth delay at diagnosis ($p = .065$, $\varphi_c = 0.294$). The proportion

TABLE 1 Baseline characteristics and clinical information collected at the time of diagnosis.

Category	Subcategory	*n* (%)[a]	Mean ± SD (Range)
Disease characteristics			
Age	Pubertal >10	33/47 (68.8)	12 ± 3 (4–16)
Sex	Male	33/47 (68.8)	
Disease location (Paris classification)	L1- Ileal	20/47 (42.6)	
	L2- Colonic	5/47 (10.6)	
	L3- Ileocolonic	22/47 (46.8)	
	L4- Upper GI tract	20/47 (42.6)	
	p- Perianal disease	14/47 (29.8)	
Growth delay	G1	11/46 (23.9)	
PCDAI	Mild (11-30)	29/45 (64.4)	26 (10–47.5)
	Moderate/Severe (>30)	15/45 (33.3)	
CRP (mg/L)	High (>10)	36/47 (76.6)	(1–186)
FCP (mcg/L)	High (≥250)	30/35 (85.7)	
Induction treatment	EEN	41/47 (88.6)	
	Steroids	6/47 (11.4)	
Growth parameters			
Weight centile	–	–	9–25th
Height centile	–	–	25–50th
BMI (kg/m^2)	Underweight (<18.5)	30/44 (68.1)	16.9 ± 3.3 (11.3–24.5)
Bone health			
Vitamin D (nmol/L)	Insufficient (30–50)	11/35 (31.4)	51 (12–150)
	Deficient (<30)	9/35 (25.7)	
Adjusted calcium (mmol/L)	Low (<2.2)	2/45 (4.4)	(2.11–2.51)
Phosphate (mmol/L)	Low (<0.9)	1/45 (2.2)	(0.86–1.73)
Bone age	Delayed (≤−2SD)	5/42 (11.9)	
	Advanced (≥2 SD)	7/42 (16.7)	
At least 1 suboptimal DXA *Z*-score (≤−1.0 SD)	–	29/38 (76.3)	
At least 1 low DXA *Z*-score (≤−2.0 SD)	–	20/38 (52.6)	
DXA lumbar spine: BMD *Z*-score for age	Suboptimal (≤−1.0 SD)	11/38 (28.9)	(−3.7–1.8)
	Low (≤−2.0 SD)	3/38 (7.9)	
DXA TBLH: BMD *Z*-score for age	Suboptimal (≤−1.0 SD)	11/37 (29.7)	(−4.2–1.4)
	Low (≤−2.0 SD)	14/37 (37.8)	
DXA TBLH: BMC *Z*-score for age	Suboptimal (≤−1.0 SD)	16/37 (43.2)	(−4.3–1.5)
	Low (≤−2.0 SD)	11/37 (29.7)	
DXA TBLH: BMD *Z*-score for height	Suboptimal (≤−1.0 SD)	10/36 (27.8)	(−3.1–0.8)
	Low (≤−2.0 SD)	9/36 (25.0)	
DXA TBLH: BMC *Z*-score for height	Suboptimal (≤−1.0 SD)	6/36 (16.7)	(−4–0.5)
	Low (≤−2.0 SD)	14/36 (38.9)	

Abbreviations: BMC, bone mineral concentration; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; DXA, dual-energy X-ray absorptiometry; FCP, faecal calprotectin; PCDAI, paediatric Crohn's disease activity index; TBLH, total body less head.

[a]Percentages are calculated based on the amount of data available for each parameter.

TABLE 2 Characteristics and parameters measured during disease course and follow-up.

Category	Subcategory	*n* (%)	Mean (Range)
Disease characteristics			
Maintenance treatment step 1	Azathioprine	35	
	Methotrexate	5	
	5-ASA	4	
	Not needed	8	
Maintenance treatment step 2	Infliximab	19	
	Adalimumab	11	
	Ustekinumab	1	
	Not needed	18	
Number of steroid courses	0	26/47 (55.3)	
	1	14/47 (29.8)	
	2	5/47 (10.6)	
	3	0/47 (0.0)	
	4	2/47 (4.3)	
Duration of steroid course	≤3 months	14 (66.7%)	
	>3 months	7 (33.3%)	
Growth characteristics			
Weight centile	Baseline	–	9–25th
	Follow up	–	25–50th
Height centile	Baseline	–	25–50th
	Follow up	–	9–25th
Height velocity (cm/y) adjusted for age and sex	Higher than expected	3/34 (8.8)	4.1 ± 3 (0–10.0)
	Lower than expected	24/34 (70.6)	
BMI (kg/m^2)	Baseline	–	16.9 ± 3.3 (11.3–24.5)
	Follow up	–	21.6 ± 5 (14.0–32.0)
Bone health			
Vitamin D (±Calcium) supplementation	Yes	35/47 (74.4)	
Prescribed vitamin D (± Calcium) supplement dosage	400 IU daily	22 (62.9)	
	1000 IU daily	3 (8.6)	
	1600 IU daily	1 (2.9)	
	5000 IU daily	4 (11.4)	
	10,000 IU daily	1 (2.9)	
	30,000 IU weekly	1 (2.9)	
	40,000 IU weekly	1 (2.9)	
	Unknown dose	2 (5.7)	
Cumulative duration for vitamin D (±Calcium) supplements	<6 months	17 (48.6)	
	≥6 months	15 (42.9)	
	Unknown	3 (8.6)	
Reason for vitamin D (±Calcium) supplement	Low vitamin D	16 (45.7)	
	Steroids	18 (51.4)	

TABLE 2 (Continued)

Category	Subcategory	*n* (%)	Mean (Range)
	Low BMD	3 (8.6)	
	Delayed bone age	2 (5.7)	
Vitamin D (nmol/L) at follow-up	Insufficient (30–50)	6/21 (28.6)	48.3 (19–130)
	Deficient (<30)	7/21 (33.3)	
Change in vitamin D levels over time	Increase	10	
	Supplemented	7	
	No supplement	3	
	Decrease	8	
	Supplemented	5	
	No supplement	3	
Fracture locations during follow-up	Clavicle	1	
	Elbow	1	
	ASIS	1	
DXA lumbar spine: BMD *Z*-score for age	Suboptimal (≤−1.0 SD)	0/2 (0)	
	Low (≤−2.0 SD)	1/2 (50)	
DXA TBLH: BMD *Z*-score for age	Suboptimal (≤−1.0 SD)	0/2 (0)	
	Low (≤−2.0 SD)	1/2 (50)	
DXA TBLH: BMC *Z*-score for age	Suboptimal (≤−1.0 SD)	1/2 (50)	
	Low (≤−2.0 SD)	1/2 (50)	
DXA TBLH: BMD *Z*-score for height	Suboptimal (≤−1.0 SD)	1/2 (50)	
	Low (≤−2.0 SD)	1/2 (50)	
DXA TBLH: BMC *Z*-score for height	Suboptimal (≤−1.0 SD)	0/2 (0)	
	Low (≤−2.0 SD)	2/2 (100)	

Note: Percentages are calculated based on the amount of data available for each parameter.

Abbreviations: BMC, bone mineral concentration; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; DXA, dual-energy X-ray absorptiometry; FCP, faecal calprotectin; PCDAI, paediatric Crohn's disease activity index; TBLH, total body less head.

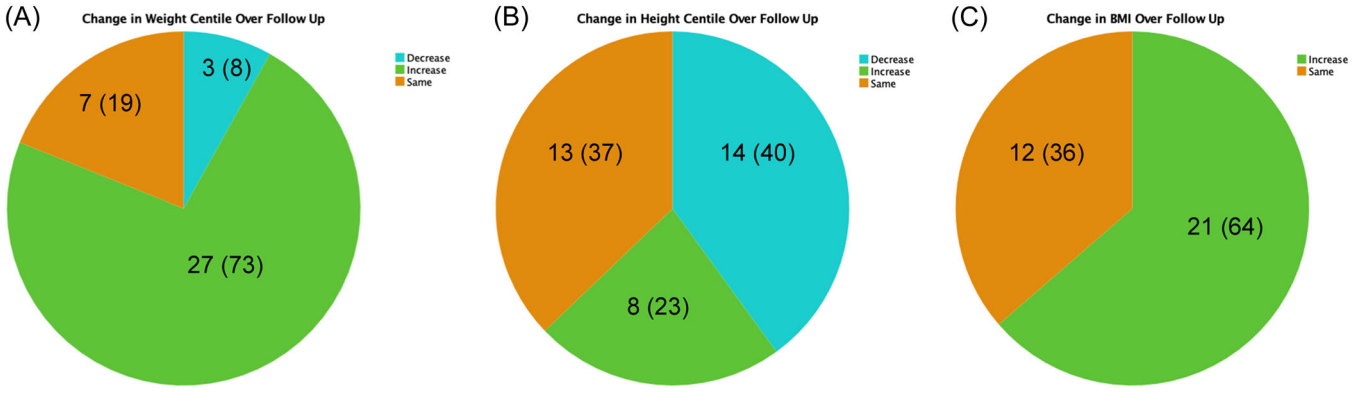

FIGURE 2 Pie charts showing the proportion of children that maintained, increased, or decreased their growth centile over the course of follow-up. $N = 47$ (%). (A) Change in weight centile over follow up. (B) Change in height centile over follow up. (C) Change in BMI over follow up.

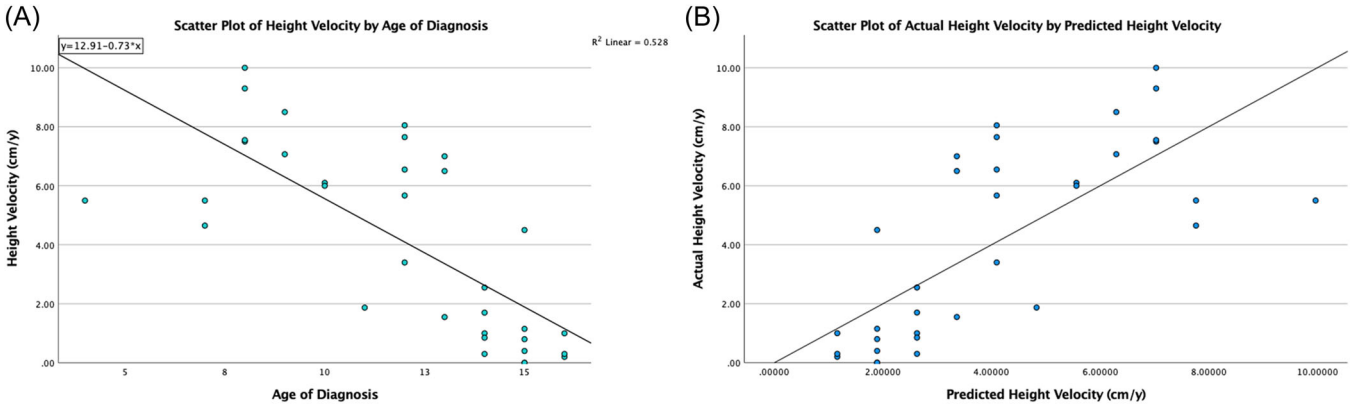

FIGURE 3 (A) A scatter graph to show how height velocity changed as age of diagnosis changed. (B) A scatter graph to show the predictive value of the equation of the line of best fit for height velocity, as compared with the actual height velocity.

of children that had a growth delay at diagnosis tended to be younger. The height velocity of the children who were diagnosed younger was better overall.

Sex did not have any significant association with the presence of growth delay at diagnosis ($X^2 = 0.068$, $p = .794$) or with height velocity at follow-up ($X^2 = 0.036$, $p = .850$).

There was a significantly positive correlation between age of diagnosis and BMI at diagnosis ($r = 0.533$, $p < .001$) and BMI at follow-up ($r = 0.394$, $p = .021$), respectively. Younger children were more likely to be underweight.

Children with a more severe disease at diagnosis, also had a lower weight centile ($r = -0.315$, $p = .035$) and lower BMI at diagnosis ($r = -0.403$, $p = .007$). Disease severity had no significant effect on height centile or height velocities. Additionally, children with more severe disease did not seem to have a higher incidence of growth delay at diagnosis.

3.4 | Bone health at diagnosis and growth parameters from diagnosis to follow-up

The higher the BMI of the child, the higher was their BMD and BMC. BMI was strongly positively correlated to all the DXA *Z*-scores that were assessed; lumbar BMD ($r = 0.486$, $p = .002$), TBLH BMD and BMC for age ($r = 0.729$, $r = 0.679$, respectively, $p < .001$) and TBLH BMD and BMC for height ($r = 0.788$, $r = 0.630$, respectively, $p < .001$).

There was a significant difference between the children that maintained or improved their height centile over time and their BMD and BMC for age at diagnosis ($X^2 = 5.93$, $p = .051$; $X^2 = 12.36$, $p = .002$, respectively). However, there was no significant relationship between children's bone health parameters at diagnosis and changes in their height centile over time. Additionally, only 19% of changes in height centile can be explained by DXA *Z*-scores ($R^2 = 0.189$).

3.5 | Multivariate analysis

Multiple regression analysis revealed that height velocity had significant associations with the age of diagnosis and lumbar BMD. Together, these two parameters explained 72.3% of the changes in height velocity ($r^2 = 0.723$). As the age of diagnosis increased by 1 year, the height velocity decreased by 0.92 cm/year (95% CI: −1.188 to −0.633; $p < .001$). This reaffirms the correlations found with univariate analysis.

4 | DISCUSSION

This was a single-centre study that collected and analysed data from 47 newly diagnosed patients with CD at a tertiary paediatric gastroenterology unit from January 2018 to December 2019. (Figure, Supporting Information: Digital Content 3, Summary of Key Findings)

The main findings of this study highlight the close relationship disease factors, bone health and growth have, with changes in one area impacting the other two. The age of diagnosis and disease severity at that time are key CD related factors that impacted bone health and growth. Additionally, bone health and growth factors like BMC, BMD and BMI also significantly influenced each other. This highlights the importance of closely monitoring and optimising CD, bone health and growth parameters in tandem with each other.

53% of patients that had a DXA scan had at least 1 low (≤2.0 SD) BMD or BMC *Z*-score. Generally, children who had a low BMC also had a low BMD *Z*-score. This is similar to the incidence that has been found by others, ranging from 6% to 44%.[34–36] Herzog et al.[34] found an incidence of 44% which is the closest match to ours, however, this was when adjusting for chronological age, which overestimates BMD scoring. Similarly, DXA scans at the RLH are adjusted for using bone age. The NASPGHAN guidelines and previous

work by Heuschkel et al. suggested repeating DXA scans every 1–2 years to monitor bone health.[11,13]

Patients who had higher disease severity had poorer BMC and BMD results for their age at diagnosis, highlighting the effect of inflammatory processes on skeletal health. Sylvester et al.[35] attributed the low BMD results in their study to poor bone turnover. Numerous studies have found a correlation between BMD and PCDAI scores, and suggest inflammation plays a role in determining bone loss.[37–40] Some have correlated higher levels of IL-6 with poorer bone health.[35,38,41,42] Although we did not assess inflammatory cytokine levels, this seems to be the likely explanation. Higher levels of disease activity would result in worse disease symptoms and potentially increased hospitalisations, hence limiting levels of physical activity. Frost's Mechanostat Theory describes the adaptability and modulation of bones based on their environment and the loads applied on them.[43] Mechanical loading, in the form of weight bearing exercises, is a key component to bone mass optimisation and accumulation.[44–46] Studies have shown this can be particularly beneficial in paediatric CD patients.[47,48]

25OHD is a necessary component for bone health. Studies have shown that approximately 57%–62% of IBD children have 25OHD deficiency.[14,49] At diagnosis, 75% of patients had 25OHD levels measured, and it was inadequate in 57% of those (<50 mmol/L). At follow-up, only 45% had a 25OHD level available in the preceding 6 months, and 62% of those had inadequate levels. The Inflammatory Bowel Disease (IBD) working group of the British Society of Paediatric Gastroenterology and Hepatology and Nutrition (BSPGHAN), The Royal Osteoporosis Society Guidelines, and the local National Health Service (NHS) Trust Guidelines recommend that all children with IBD have 25OHD levels monitored every 6 months and maintained at >50 nmol/L.[51,53–55]

There was a statistically significant correlation between 25OHD at diagnosis and follow-up. However, 25OHD prescription and adequate 25OHD levels at follow-up were not correlated. Closer examination of the prescriptions and baseline levels (Table 2) may shed light on potential reasons as to why supplementation did not have a significant effect on follow-up 25OHD levels. 400 IU is recommended as a maintenance dose for children with adequate levels, with some institutes recommending up to 1000 IU.[11,50–52] For those with inadequate levels and especially patients with a malabsorptive condition like CD require higher doses to compensate. In this cohort, children with terminal ileal (L1) or ileo-colonic (L3) disease locations had a lower 25OHD level at diagnosis; the latter is more extensive and would further limit absorption. Forty-five per cent of patients with inadequate 25OHD levels received 400 IU, and 20% did not receive any supplementation. There are varying recommendations for 25OHD dosages for children with CD and inadequate levels.[51,53] The consensus is between 6000 and 10000 IU per day for up to 12 weeks, with our local trust guidelines recommending 10,000 IU per day for children who are deficient and have intestinal malabsorption. No child with inadequate 25OHD levels at diagnosis was prescribed the correct dosage to normalise levels.

In our cohort, 24% of children had growth delay at diagnosis and it persisted in 44%. This is in line with previous research which suggests up to 40% of children with CD have persistent growth failure.[2,56] This emphasises how valuable it is to continually monitor and optimise growth for these children.

To our knowledge, this is the first study to show children diagnosed with CD at an older age had a lower-than-expected height velocity. There are a few explanations as to why these findings may have occurred. First, diagnosis at an older age may imply a delay in receiving a diagnosis, leading to more extensive damage which impacts growth.[25] Alternatively, it could be due to a later onset of disease, which leads to a smaller window to achieve adequate disease control. An earlier age of diagnosis enables better disease control at a younger age, so growth is less impacted during pubertal years. The average age of the cohort at diagnosis was 12 (SD ± 3), which falls in the time of peak pubertal growth for boys and girls,[57] and CD is likely to have already impacted the child's linear growth by that point.

Studies have shown the impact that bone health and growth play on each other, and optimisation of one parameter usually improves the other. One of the main findings in this study highlights the interlink between BMI, BMC and BMD at diagnosis. 60% of underweight children had a suboptimal DXA scan result, and 50% had a low result. This was augmented by the significant correlation found between higher BMI and higher BMC and BMD levels, translating to better bone health. Numerous studies have found and established this link which validates our findings.[35,38,58,59]

In particular, Sylvester et al.[35] also found an association between ≤1.0 BMD Z-score and a lower BMI. Not only suggesting that children with low BMI should be screened for low BMD, but also suggesting a forgotten group of children. Currently *Z*-scores ≤2.0 SD are classified as Low, and attention is focused there, however, children with a *Z*-score ≤1.0 may still have adverse health implications. DXA scans and bone health monitoring should be provided to children with suboptimal and low *Z*-scores, especially if they are underweight. Maintaining a good nutritional status and incorporating weight-bearing exercises to increase lean muscle mass can help optimise bone health too.[35]

Multiple regression analysis found age of diagnosis and lumbar BMD scores to be independent predictors of height velocity ($r^2 = 0.723$). This could be because almost 90% of patients had EEN as induction treatment, which has been shown to result in improved

FIGURE 4 The IBD clinic poster summarising monitoring and optimisation strategies for Crohns Disease patients. BMC, bone mineral concentration; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; PCDAI, paediatric Crohn's disease activity index.

growth.[13,60–62] Studies have shown biologics can have positive effects on growth and can result in the normalisation of height velocities, especially if provided before puberty.[63–66] Children with poorer bone health at diagnosis may have had more severe disease, hence were offered biologics like infliximab to help with disease control, and a by-product was the benefit to growth, resulting in improved height velocity.

Our study comes with the intrinsic limitations of any retrospective work. Despite having statistical power, 47 patients is a relatively limited cohort. To make stronger, more robust conclusions, a larger cohort would be ideal. Many patients had incomplete data sets at follow-up. This could be due to requests for repeat tests being missed, as well as the impact of the COVID-19 pandemic which drove the switch to teleconsultations from March 2020 onwards. The impacts were felt during the follow-up of the study where many consultations remained virtual and basic anthropometric measurements like height and weight are not recorded consistently. Additionally, Tanner staging to assess pubertal stage was not performed at our centre. It is important to note, vitamin D levels can vary among ethnicities and across seasons which can be a limitation when using it as a proxy for understanding bone health.[67] Performing a multicentre prospective study would allow consistent data collection and ensure the reproducibility of our findings.

Our findings demonstrate that age of diagnosis and severity of CD are factors that significantly impact bone health and growth. In particular, our data demonstrate a significant impact of the age of diagnosis on height velocity. Previous research shows that optimising each on these factors individually is likely to have positive knock-on effects for the other aspects. Optimisation cannot be achieved without regular monitoring which is vital to visualise the trends in these parameters. To improve this, a poster was created and is displayed in clinic rooms (Figure 4). Monitoring and optimising 25OHD is a simple and accessible way to improve bone health and growth. Considering the interplay between the factors and optimising them will enable children to put their best foot forward as they enter their formative years.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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REFERENCES
1. Kleinman RE, Baldassano RN, Caplan A, et al. Nutrition support for pediatric patients with inflammatory bowel disease: a clinical report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2004;39(1):15-27.
2. Shamir R. Nutritional aspects in inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2009;48:S86-S88.
3. Gasparetto M, Guariso G. Crohn's disease and growth deficiency in children and adolescents. *World J Gastroenterol*. 2014;20(37):13219-13233.
4. Levine M. Assessing bone health in children and adolescents. *Indian J Endocrinol Metab*. 2012;16(suppl 2):205.
5. Steell L, Gray SR, Russell RK, et al. Pathogenesis of musculoskeletal deficits in children and adults with inflammatory bowel disease. *Nutrients*. 2021;13(8):2899.
6. Ricciuto A, Aardoom M, Orlanski-Meyer E, et al. Predicting outcomes in pediatric crohn's disease for management optimization: systematic review and consensus statements from the pediatric inflammatory bowel disease–ahead program. *Gastroenterology*. 2021;160(1):403-436.e26.e26.
7. Bass S, Delmas PD, Pearce G, Hendrich E, Tabensky A, Seeman E. The differing tempo of growth in bone size, mass, and density in girls is region-specific. *J Clin Invest*. 1999;104(6):795-804.
8. Bradney M, Karlsson MK, Duan Y, Stuckey S, Bass S, Seeman E. Heterogeneity in the growth of the axial and appendicular skeleton in boys: implications for the pathogenesis

of bone fragility in men. *J Bone Miner Res*. 2000;15(10): 1871-1878.
9. Ballinger AB, Savage MO, Sanderson IR. Delayed puberty associated with inflammatory bowel disease. *Pediatr Res*. 2003;53(2):205-210.
10. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. *Gastroenterology*. 1988;95(6):1523-1527.
11. Pappa H, Thayu M, Sylvester F, Leonard M, Zemel B, Gordon C. Skeletal health of children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2011;53(1):11-25.
12. Shamir R, Phillip M, Levine A. Growth retardation in pediatric Crohn's disease: pathogenesis and interventions. *Inflamm Bowel Dis*. 2007;13(5):620-628.
13. Heuschkel R, Salvestrini C, Beattie MR, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14(6):839-849.
14. Alkhouri RH, Hashmi H, Baker RD, Gelfond D, Baker SS. Vitamin and mineral status in patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2013;56(1):89-92.
15. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. *JAMA Pediatr*. 2015;169(11): 1053-1060.
16. Gordon RJ, Gordon CM. Bone health in pediatric patients with IBD: what is new? *Curr Osteoporos Rep*. 2021;19(4):429-435.
17. Bikle DD. Vitamin D and bone. *Curr Osteoporos Rep*. 2012;10(2):151-159.
18. Fletcher J, Cooper SC, Ghosh S, Hewison M. The role of vitamin D in inflammatory bowel disease: mechanism to management. *Nutrients*. 2019;11(5):1019.
19. Koo W, Walyat N. Vitamin D and skeletal growth and development. *Curr Osteoporos Rep*. 2013;11(3):188-193.
20. Aranow C. Vitamin D and the immune system. *J Investig Med*. 2011;59(6):881-886.
21. Saggese G, Vierucci F, Prodam F, et al. Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians. *Ital J Pediatr*. 2018;44(1):51.
22. Zhu Y, Mahon BD, Froicu M, Cantorna MT. Calcium and 1α,25-dihydroxyvitamin D3 target the TNF-α pathway to suppress experimental inflammatory bowel disease. *Eur J Immunol*. 2005;35(1):217-224.
23. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog Biophys Mol Biol*. 2006;92(1):60-64.
24. Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25-Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. *J Nutr*. 2000;130(11):2648-2652.
25. Sawczenko A, Ballinger AB, Savage MO, Sanderson IR. Clinical features affecting final adult height in patients with pediatric-onset Crohn's disease. *Pediatrics*. 2006;118(1): 124-129.
26. Jin H-Y, Lim J-S, Lee Y, et al. Growth, puberty, and bone health in children and adolescents with inflammatory bowel disease. *BMC Pediatr*. 2021;21(1):35.
27. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. 2014;58(6):795-806.
28. Hyams J, Markowitz J, Otley A, et al. Evaluation of the pediatric Crohn disease activity index: a prospective multicenter experience. *J Pediatr Gastroenterol Nutr*. 2005;41(4):416-421.
29. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of paediatric ulcerative colitis, part 1: ambulatory care—an evidence-based guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;67(2):257-291.
30. Barstow C, Rerucha C. Evaluation of short and tall stature in children. *Am Fam Physician*. 2015;92(1):43-50.
31. World Health Organization. *Physical Status: The Use and Interpretation of Anthropometry: Report of a WHO Expert Committee*WHO Technical Report Series, No. 854. World Health Organization; 1995:1-452.
32. Shuhart CR, Yeap SS, Anderson PA, et al. Executive summary of the 2019 ISCD position development conference on monitoring treatment, DXA cross-calibration and least significant change, spinal cord injury, peri-prosthetic and orthopedic bone health, transgender medicine, and pediatrics. *J Clin Densitom*. 2019;22(4):453-471.
33. Greulich WW, Idell S. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford University Press; 1959.
34. Herzog D, Bishop N, Glorieux F, Seidman EG. Interpretation of bone mineral density values in pediatric Crohn's disease. *Inflamm Bowel Dis*. 1998;4(4):261-267.
35. Sylvester FA, Wyzga N, Hyams JS, et al. Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. *Inflamm Bowel Dis*. 2007; 13(1):42-50.
36. Rozes S, Guilmin-Crepon S, Alison M, et al. Bone health in pediatric patients with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2021;73(2):231-235.
37. Posovszky C, Pfalzer V, Lahr G, et al. Age-of-onset-dependent influence of NOD2 gene variants on disease behaviour and treatment in Crohn's disease. *BMC Gastroenterol*. 2013;13:77.
38. Paganelli M, Albanese C, Borrelli O, et al. Inflammation is the main determinant of low bone mineral density in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2007;13(4): 416-423.
39. Semeao EJ, Jawad AF, Stouffer NO, Zemel BS, Piccoli DA, Stallings VA. Risk factors for low bone mineral density in children and young adults with Crohn's disease. *J Pediatr*. 1999;135(5):593-600.
40. Tsampalieros A, Lam CKL, Spencer JC, et al. Long-term inflammation and glucocorticoid therapy impair skeletal modeling during growth in childhood Crohn disease. *J Clin Endocrinol Metab*. 2013;98(8):3438-3445.
41. Yang HR. Updates on bone health in children with gastrointestinal diseases. *Ann Pediatr Endocrinol Metab*. 2020;25(1): 10-14.
42. Tilg H, Moschen AR, Kaser A, Pines A, Dotan I. Gut, inflammation and osteoporosis: basic and clinical concepts. *Gut*. 2008;57(5):684-694.
43. Frost HM. Bone “mass” and the “mechanostat”: a proposal. *Anat Rec*. 1987;219(1):1-9.
44. Public Health England. Muscle and bone strengthening activities for children and young people (5 to 18 years): a rapid evidence review. 2021.
45. Ward K, Roberts S, Adams J, Mughal M. Bone geometry and density in the skeleton of pre-pubertal gymnasts and school children. *Bone*. 2005;36(6):1012-1018.
46. Bailey DA, McKay HA, Mirwald RL, Crocker PRE, Faulkner RA. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study. *J Bone Miner Res*. 1999;14(10):1672-1679.
47. Vanhelst J, Vidal F, Turck D, et al. Physical activity is associated with improved bone health in children with inflammatory bowel disease. *Clin Nutr*. 2020;39(6):1793-1798.
48. Brooke-Wavell K, Skelton DA, Barker KL, et al. Strong, steady and straight: UK consensus statement on physical activity and exercise for osteoporosis. *Br J Sports Med*. 2022;56(15): 837-846.

49. Levin AD, Wadhera V, Leach ST, et al. Vitamin D deficiency in children with inflammatory bowel disease. *Dig Dis Sci*. 2011;56(3):830-836.
50. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. 2010.
51. Royal Osteoporosis Society. *Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management in Children and Young People*. Royal Osteoporosis Society; 2018.
52. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2009;169(6):551-561.
53. The IBD Working Group of BSPGHAN. Vitamin D in paediatric inflammatory bowel disease. In: BSPGHAN, editor. 2019.
54. Christiansen N, Allgrove J, Mustafa M. *Guidelines for the Treatment and Prophylaxis of Nutritional Vitamin D Deficiency and Rickets in Children and Adolescents in Secondary and Primary Care*. Barts and the London NHS Trust; 2017.
55. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008;122(2):398-417.
56. Motil KJ, Grand RJ, Davis-Kraft L, Ferlic LL, Smith EO. Growth failure in children with inflammatory bowel disease: a prospective study. *Gastroenterology*. 1993;105(3):681-691.
57. Taranger J, Hägg U. The timing and duration of adolescent growth. *Acta Odontol Scand*. 1980;38(1):57-67.
58. Lopes LHC, Sdepanian VL, Szejnfeld VL, de Morais MB, Fagundes-Neto U. Risk factors for low bone mineral density in children and adolescents with inflammatory bowel disease. *Dig Dis Sci*. 2008;53(10):2746-2753.
59. Schmidt S, Mellström D, Norjavaara E, Sundh VS, Saalman R. Low bone mineral density in children and adolescents with inflammatory bowel disease: a population-based study from Western Sweden. *Inflamm Bowel Dis*. 2009;15(12):1844-1850.
60. Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr*. 2000;31(1):8-15.
61. Alhagamhmad MH, Day AS, Lemberg DA, Leach ST. An update of the role of nutritional therapy in the management of Crohn's disease. *J Gastroenterol*. 2012;47(8):872-882.
62. Swaminath A, Feathers A, Ananthakrishnan AN, Falzon L, Li Ferry S. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. *Aliment Pharmacol Ther*. 2017;46(7):645-656.
63. Malik S, Wong S, Bishop J, et al. Improvement in growth of children with Crohn disease following anti-TNF-α therapy can be independent of pubertal progress and glucocorticoid reduction. *J Pediatr Gastroenterol Nutr*. 2011;52(1):31-37.
64. Walters TD, Hyams J, Baldassano R, et al. Linear growth during infliximab therapy: results of the REACH multicenter study. *J Pediatr Gastroenterol Nutr*. 2006;43:S54.
65. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. *Inflamm Bowel Dis*. 2007;13(4):424-430.
66. Walters TD, Faubion WA, Griffiths AM, et al. Growth improvement with adalimumab treatment in children with moderately to severely active Crohn's disease. *Inflamm Bowel Dis*. 2017;23(6):967-975.
67. Lin LY, Smeeth L, Langan S, Warren-Gash C. Distribution of vitamin D status in the UK: a cross-sectional analysis of UK Biobank. *BMJ Open*. 2021;11(1):e038503.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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