Received: 31 August 2024 | Accepted: 10 April 2025

DOI: 10.1002/jpn3.70091

JPGN

ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

Impaired physical fitness in pediatric inflammatory bowel disease

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Funding information

Foundation for Pediatric Research; State Funding for University-level Health Research, Tampere University Hospital, Wellbeing Services County of Pirkanmaa; Päivikki and Sakari Sohlberg Foundation; Finnish

Abstract

Objective: There are only a few studies on physical fitness in pediatric inflammatory bowel disease (PIBD). We compared physical fitness in PIBD patients versus healthy controls and analyzed the role of contributing disease- and patient-related factors.

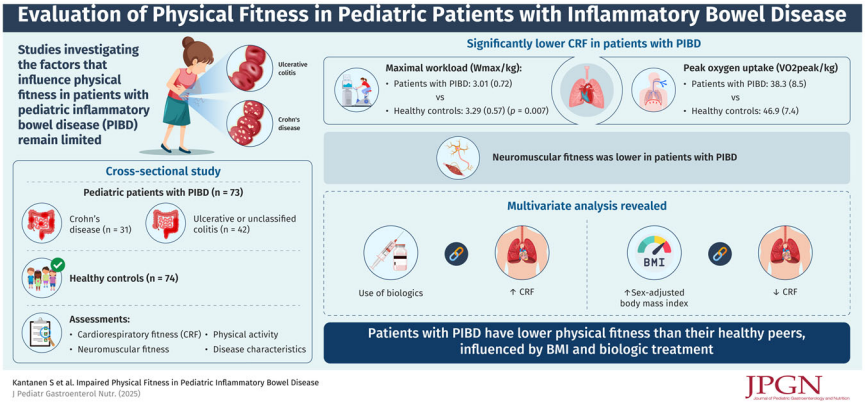
Methods: This cross-sectional study included 73 patients with PIBD aged 13.0 (2.8) (mean [standard deviation]) years from two Finnish university hospitals, 31 with Crohn's disease and 42 with ulcerative or unclassified colitis, and 74 age- and sex-matched controls. Cardiorespiratory and neuromuscular fitness were assessed, physical activity (PA) was measured, and disease characteristics concerning physical fitness were analyzed.

Results: Cardiorespiratory fitness, that is, maximal workload (W_{max}/kg) and peak oxygen uptake (VO_2peak/kg) were lower in patients with PIBD than in controls: W_{max}/kg 3.01 (0.72) versus 3.29 (0.57) W/kg, $p = 0.007$; VO_2peak/kg 38.3 (8.5) versus 46.9 (7.4) mL/kg/min, $p < 0.001$, respectively. Neuromuscular fitness, as evaluated using sit-up, standing long jump, grip strength, and shuttle run tests, was lower in patients compared with controls. Disease activity, severity, and duration, or PA, were not related to W_{max}/kg and VO_2peak/kg in univariate analysis. However, in multivariate analysis, the use of biological medications was associated positively, and higher age- and sex-adjusted body mass index for children and adolescents was associated negatively with W_{max}/kg and VO_2peak/kg.

Discussion: Patients with PIBD had lower physical fitness than age- and sex-matched controls. The causes of lower physical fitness in PIBD are likely complex, warranting the need for longitudinal studies examining the associations of factors like body composition, visceral fat, and control of disease severity with physical fitness.

Pekka Arikoski and Pauliina Hiltunen are shared senior authors.

Foundation for Cardiovascular Research; Pediatric Clinic Foundation



KEYWORDS

Crohn's disease, neuromuscular fitness, physical activity, ulcerative colitis

1 | INTRODUCTION

Inflammatory bowel disease (IBD) including Crohn's disease (CD), ulcerative colitis (UC) and unclassified IBD (IBDU) is a lifelong chronic illness with a relapsing nature.[1] Physical activity (PA) may reduce the risk for relapses,[2] have a protective effect in diseases with chronic systemic low-grade inflammation,[3] and improve the quality of life in adults with IBD.[4]

PA seems to be reduced in patients with active pediatric IBD (PIBD).[5–7] However, patients with PIBD in remission and healthy controls had similar levels of PA assessed by actimeters.[6] Data on cardiorespiratory fitness (CRF) and neuromuscular fitness in PIBD patients are scarce. A Canadian study reported lower aerobic exercise capacity measured by ergospirometry in seven children with CD compared to controls.[8] In another Canadian study involving 29 patients with PIBD, those with CD had lower CRF compared to reference values.[9] In a Dutch study, including 15 adolescents with PIBD, CRF was lower than in controls. However, CRF improved slightly after a few months of guided training.[10] Still, little is known about disease characteristics related to physical fitness in PIBD.

We assessed the CRF and neuromuscular fitness of PIBD patients in a cross-sectional case–control study design to gain information on factors related to physical fitness.

What is Known

- Inflammatory bowel diseases (IBDs) with the relapsing nature of gastrointestinal symptoms and fatigue reduce daily activity and physical performance in adults.
- Previous studies suggest that physical fitness in pediatric IBD (PIBD) patients is also compromised.

What is New

- Ergospirometry with breathing gas analysis combined with measurements of muscular strength, agility, and physical activity (PA) showed impaired cardiorespiratory and neuromuscular fitness in patients with PIBD compared with healthy controls.
- PA or disease activity did not correlate with cardiorespiratory fitness (CRF).
- The use of biological medications was positively associated, and higher adiposity was negatively associated with CRF in PIBD.

2 | METHODS

2.1 | Participants

We recruited 6- to 17-year-old patients with PIBD who had sufficient co-operative skills and physical abilities to attend study visits at the Departments of Pediatrics at Tampere University Hospital and Kuopio University Hospital, both tertiary centers in Finland. A total of 145 eligible patients were invited to participate between the years 2017 and 2019, and 73 (50%) agreed.

For every patient, an age- and sex-matched control was gathered. Altogether, 56 of the controls were selected from the participants of the ongoing Physical Activity and Nutrition in Children study (ClinicalTrials.gov: NCT01803776).[11–15] Seventeen of the controls aged 11–14 years were recruited through the Population Registry and among healthy children locally.

2.2 | Assessment of disease and participant characteristics

Clinical disease activity of UC was determined by the Pediatric Ulcerative Colitis Activity Index (PUCAI), with remission defined as <10, mild activity 10–34, moderate activity 35–64, and severe disease ≥65.[16] Clinical disease activity of CD was determined by the Pediatric Crohn's Disease Activity Index (PCDAI), with remission defined as <10, mild activity 10–30, and moderate to severe disease >30.[17] Physician's global assessment (PGA)[18] was also applied as follows: 1 for remission or mild disease activity, 2 for moderate activity, and 3 for severe disease.

Growth and waist circumference were measured, and puberty assessed. PA over the past 12 months was assessed through a questionnaire including supervised and unsupervised PA, walking or cycling to and from school, and PA during holidays. The questionnaire was filled out by the guardian for children in the first six grades of school, or by children over 12 years old themselves. Ongoing medication, as well as medication 6 and 12 months before the study, were recorded.

Inflammation was assessed by leukocyte count, erythrocyte sedimentation rate, blood hemoglobin,[19] C-reactive protein (CRP), high-sensitive-CRP (hs-CRP), albumin, and fecal calprotectin (FC). Based on FC, the patients were grouped into three classes of disease activity: 0–99 μg/g (remission or mild), 100–999 μg/g (moderate), and ≥1000 μg/g (severe).[20]

2.3 | Assessment of CRF

CRF was assessed with a maximal exercise test using an electromagnetic cycle ergometer (Ergoline) and a pediatric saddle module with respiratory gas analysis.[11] Heart rate was measured by a 12-lead electrocardiogram (ECG) for 5 min before the exercise test using the Cardiosoft ECG software, Version 6.5 (GE Healthcare). The participants were instructed to avoid strenuous PA for at least 24 h and caffeinated drinks for at least 12 h before the visit.

The test protocol included a 3-min warm-up on the bike with a minimal load of 5 W. In Kuopio, the workload was steadily increased at a rate of 1 W per 6 s including the steady state recording.[11] In Tampere, the initial baseline load was 20 W, and the increase in workload was comparable to Kuopio. The children were instructed to keep the cadence stable within 70–80 rounds per minute until voluntary exhaustion. Perceived level of exertion (Borg scale 6–20)[21] was asked every 2 min and at the end of the exercise (children ≥10 years of age). ECG was registered throughout the exercise. Blood pressure was measured at multiple points, and the highest blood pressure value was recorded.

The exercise test was considered maximal when the heart rate exceeded 85% of the calculated maximal heart rate, and the participant could no longer continue due to exhaustion, or could not keep up a revolution rate over 65 per minute. Motivation was evaluated as good if the participant continued despite fatigue and inconvenience, and maximal effort was observed.

Respiratory gases were measured directly by the breath-by-breath method (CPX Vyntus® or Oxycon Pro®, Jaeger) using a mask (Hans-Rudolph) starting from 2.5 min rest before the exercise warm-up until the end of the 4-min postexercise cool-down period. Peak oxygen uptake (VO_2peak) was defined as the highest 15-s average value during the last minute of maximal exercise. Maximal workload (W_{max}) and VO_2peak divided by body weight were used as measures of CRF.

Tests assessing neuromuscular fitness are described in Supporting Information S1: Table 1.

2.4 | Statistical analyses

IBM SPSS Statistics, Version 26, and Stata, Version 17.0 (StataCorp) were used for statistical analyses. For normally distributed variables, means and standard deviations (SDs) are presented. Medians and interquartile ranges (IQRs) are used for skewed distributions. Data are presented as numbers and percentages for categorical variables.

The unpaired *t* test or the Mann–Whitney *U* test was used for comparisons of continuous variables in patients with PIBD. To compare groups for a binomial outcome, the Chi-square test or Fisher's exact test was used. The paired samples *t* test and the McNemar's test were used to compare PIBD patients and controls. The balance test results were analyzed using the Wilcoxon signed-rank test.

Univariate linear regression analysis was used to assess possible correlates of the measures of CRF and neuromuscular fitness. Variables that were statistically significantly associated with measures of physical fitness were included in the multivariate linear regression analysis. Normality of the residuals was assessed by plotting the histograms. The results of the regression analyses were presented as unstandardized (*B*) and standardized (β) regression coefficients and 95% confidence intervals (CIs). Conditional logistic regression analysis was used for pairwise comparisons between PIBD patients and controls. In the statistical analyses, the patients with IBDU and UC were combined. The p-value < 0.05 was used as the criterion for statistical significance.

2.4.1 | Ethics statement

The study was approved by the Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland. The parents and age-appropriate patients and controls provided written informed consent.

3 | RESULTS

3.1 | Characteristics of participants

The study group comprised 31 children with CD and 42 with UC/IBDU (58 examined in Tampere and 15 in Kuopio) (Table 1 and Supporting Information S1: Table 2). The study visit was rescheduled for four participants due to acute infections and for one UC patient due to severe disease activity.

The mean age of the patients was 13.0 years, with a balanced distribution of sex and pubertal stage across the study groups. Median disease duration was 1.2 years for CD, and 1.7 years for UC (Table 1). Most patients with UC belonged to the ever severe class of the Paris classification.[22] Within the preceding year, 16% of the patients with CD and 12% with UC had experienced severe disease (defined as PGA Class 3; $p = 0.73$ between the groups) (Supporting Information S1: Table 3A and 3B). Systemic corticosteroid was used by 43% of the UC patients and 39% of the CD patients 6 months before the study visit. At the time of the study, 13% were on corticosteroids (<10 mg/day). In the UC group, corticosteroids (a median dose of 10 mg/day; IQR: 5.0–22.5 mg) were used by 24% (Table 1).

Most patients with CD had an ileocolonic luminal disease. The most common phenotype in UC was pancolitis. All patients with CD were in remission or had mild disease activity during the study according to the PCDAI, whereas 29% had moderate disease activity by PGA. Of the UC patients, 69% were in remission (PUCAI < 10), while only one had a severe disease as assessed by PGA (Table 1).

Most patients had normal hemoglobin, erythrocyte sedimentation rate, and albumin levels; half had elevated hs-CRP. FC was normal in 36% of the CD and 45% of the UC patients (Table 1).

3.2 | Physical fitness

3.2.1 | CRF

W_{max}/kg and VO_2peak/kg were lower in patients compared with controls (Table 2). UC patients had lower W_{max}/kg than controls, but no difference was observed between CD patients and controls. Patients had higher peak systolic blood pressure during the exercise compared with controls (Table 2).

At the end of the exercise test, perceived exertion was high, the median Borg scale being 19.5 for patients and 20 for controls. However, the percentage of highly motivated patients was lower compared with that of controls (83% vs. 97%, $p < 0.001$). The exercise test was maximal for 94% of patients and 100% of controls. Four participants with a submaximal exercise test and three with technical problems were excluded from the analyses.

3.2.2 | Neuromuscular fitness

The hand grip strength was lower in patients compared with controls (Table 3). Girls had lower grip strength compared with controls (UC: 142 kPa vs. 164 kPa, $p = 0.036$; CD: 139 kPa vs. 155 kPa, $p = 0.029$, respectively). There were no differences in grip strength between boys with UC ($p = 0.361$) or CD ($p = 0.066$) and controls. Also, sit-up tests and standing long jump performances were lower in patients, especially in patients with UC, compared with controls (Table 3). In the shuttle run test, patients were also slower than controls. There were no differences in the balance or box and block test performances between the PIBD group and controls (Table 3).

3.2.3 | PA

Patients were physically less active than their controls (1.7 h/day vs. 2.2 h/day, $p = 0.013$, respectively). PA was similar in girls with UC or CD and controls, but boys with UC (1.7 h/day vs. 2.3 h/day, $p = 0.037$) and CD (1.7 h/day vs. 2.8 h/day, $p = 0.017$) had lower PA compared with controls. Controls were more often involved in sports activities than patients ($n = 38$ vs. $n = 4$). However, there was no significant difference in active time between those with or without sports activities in the whole study group or between controls with or without sports activities.

3.2.4 | Factors related to physical fitness in PIBD

Having PIBD was associated with decreased W_{max}/kg (B: −0.3 W/kg, 95% CI: −0.510 to −0.084 W/kg, $p = 0.007$) and decreased VO_2peak/kg (B: −8.03 mL/kg/min, 95% CI: −10.90 to −5.17 mL/kg/min, $p < 0.001$). VO_2peak/kg remained lower in patients after further adjustment for PA in conditional regression analysis, and the difference was statistically significant for both the CD (odds ratio [OR]: 0.88; 95% CI: 0.77–1.0) and UC

TABLE 1 Background characteristic comparisons between patients and matched controls, and between patients with Crohn's disease and patients with UC.

	Controls ($N = 73$)	Patients ($N = 73$)	p value	Crohn's disease ($n = 31$)	UC ($n = 42$)	p value
Age, years (mean, SD)	12.9 (3.0)	13.0 (2.8)	0.32	13.2 (2.5)	12.8 (3.1)	0.51
Female (*N*/%)	41 (56.2)	41 (56.2)		16 (51.6)	25 (59.5)	0.63
Pubertal stage (*N*/%)			0.55			0.38
Pre	18 (24.7)	20 (27.4)		6 (19.4)	14 (33.3)	
Mid	27 (37.0)	28 (38.4)		14 (45.2)	14 (33.3)	
Post	28 (38.4)	25 (34.2)		11 (35.5)	14 (33.3)	
Pubertal delay (*N*/%)	1 (1.4)	1 (1.4)		0	1 (2.4)	1.0
Height, *z*-score (mean, SD)	0.1 (1.0)	0.0 (1.1)	0.62	−0.3 (1.1)	0.2 (1.1)	0.068
Growth failure (*N*/%)	3 (4.1)	2 (2.7)	1.0	1 (3.2)	1 (2.4)	1.0
Weight, *z*-score (mean, SD)	0.0 (1.2)	0.6 (1.8)	**0.024**	0.6 (1.8)	0.6 (1.8)	0.91
ISO-BMI, kg/m^2 (mean, SD)	21.3 (2.6)	22.3 (3.6)	0.067	22.2 (3.4)	22.4 (3.8)	0.78
Weight category[a] (*N*/%)			0.102			0.71
Underweight	2 (2.7)	4 (5.5)		2 (6.5)	2 (4.8)	
Normal	65 (89.0)	54 (74.0)		24 (77.4)	30 (71.4)	
Overweight	6 (8.2)	15 (20.5)		5 (16.1)	10 (23.8)	
Waist circumference, cm (mean, SD)	59.5 (6.8)	74.1 (11.4)	**<0.001**	74.4 (10.8)	73.9 (11.9)	**<0.001**
Age at diagnosis, years [median, IQR]		10.2 [6.8–12.7]		10.2 [6.8–12.9]	10.0 [6.7–12.5]	0.76
Duration of disease, years [median, IQR]		1.6 [0.7–4.9]		1.2 [0.7–6.9]	1.7 [0.7–4.9]	0.85
Disease characteristics						
Paris classification (*N*/%)						
L1 ileal				4 (13)		
L2 ileocolonic				18 (58)		
L3 colonic				5 (16)		
L4 upper disease				3 (10)		
P perianal				6 (19)		
Behavior						
B1 nonstricturing/nonpenetrating				24 (77)		
B2 stricturing				4 (13)		
B3 penetrating				3 (10)		
Montreal classification (*N*/%)						
E1 ulcerative proctitis					3 (7.1)	
E2 left-sided UC (distal to splenic flexure)					8 (19.0)	
E3 pancolitis					31 (73.8)	
S1 ever severe					32 (78)	
Disease activity (*N*/%)						
PGA						0.62[b]
Remission or mild				22 (71)	31 (73.8)	

(Continues)

TABLE 1 (Continued)

	Controls (*N* = 73)	Patients (*N* = 73)	*p* value	Crohn's disease (*n* = 31)	UC (*n* = 42)	*p* value
Moderate				9 (29)	10 (23.8)	
Severe				0	1 (2.4)	
PCDAI (*N*/%)						
Remission				21 (68)		
Mild				10 (32)		
Moderate to severe				0		
PUCAI (*N*/%)						
Remission					29 (69)	
Mild activity					10 (24)	
Moderate activity					3 (7)	
Severe disease					0	
Laboratory parameters						
Erythrocyte sedimentation rate level abnormal (*N*/%)				4 (12.9)	3 (7.1)	0.448
Serum CRP level above the cutoff for a raised value (*N*/%)				3 (9.7)	4 (9.5)	1
High sensitive CRP, mg/L [median, IQR]		0.12 [0.0–0.53]		0.16 [0.0–0.91]	0.06 [0.0–0.46]	0.66
High sensitive CRP abnormal (*N*/%)				14 (51.9)	15 (50)	1
Hemoglobin, g/L [median, IQR]				130 [121–138]	132 [125–136]	0.667
Anemic (*N*/%)		13 (17.8)		7 (22.6)	6 (14.3)	0.36
Albumin, g/L [median, IQR]				39 (37-41)	40 (37-42)	0.969
Fecal calprotectin,[c] µg/g [median, IQR]				482 [39–1321]	163 [16–418]	0.097
Fecal calprotectin categories						0.43
Remission (*N*/%)				11 (35.5)	19 (45.2)	
Moderate (*N*/%)				11 (35.5)	16 (38.1)	
Severe (*N*/%)				9 (29)	7 (16.7)	
Medication[d] (*N*/%)						
5-aminosalicylic acid				3 (9.7)	26 (61.9)	
Azathioprine				8 (25.8)	10 (23.8)	
Methotrexate				6 (19.4)	1 (2.4)	
Antitumor necrosis factor-α				10 (32.3)	6 (14.3)	
Other biologics				3 (9.7)	0	
Corticosteroid				4 (12.9)	10 (23.8)	

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; ISO-BMI, age- and sex-adjusted body mass index; PCDAI, Pediatric Crohn's Disease Activity Index; PGA, Physician Global Assessment; PUCAI, Pediatric Ulcerative Colitis Activity Index; SD, standard deviation; UC, ulcerative colitis.

[a]Based on ISO-BMI.

[b]Comparison of all PGA categories.

[c]There was one calprotectin value missing from the UC group.

[d]Corticosteroid was prednisolone, except for one patient with UC, who used budesonide. One patient used salazopyrin medication. Other, not listed medications (*n* = 3), two patients did not use medications: one with Crohn's and the other with orofacial granulomatosis. One patient with concomitant juvenile arthritis used golimumab with methotrexate.

TABLE 2 Cardiorespiratory fitness in patients with PIBD and controls presented as mean (standard deviation).

	PIBD			Crohn's disease				Ulcerative colitis			
	Controls	Patients	*p* value	Controls	Patients	n	*p* value	Controls	Patients	*n*	*p* value
W_{max}, W	157 (47)	147 (43)	**0.03**	159 (48)	155 (49)	29	0.62	156 (47)	140 (37)	37	**0.014**
W_{max}/kg, W/kg	3.29 (0.57)	3.01 (0.72)	**0.007**	3.30 (0.57)	3.17 (0.70)	29	0.43	3.29 (0.58)	2.87 (0.72)	37	**0.004**
VO_2peak, mL/min	2405 (556)	2039 (456)	**<0.001**	2392 (657)	2118 (528)	22	**0.024**	2414 (481)	1981 (394)	30	**<0.001**
VO_2peak/kg, mL/min/kg	46.9 (7.4)	38.3 (8.5)	**<0.001**	47.3 (7.2)	40.6 (8.4)	22	**0.004**	46.7 (7.6)	36.5 (8.3)	30	**<0.001**
Peak heart rate, % of maximal	97 (3.8)	95 (5.4)	**0.025**	97 (3.6)	95 (5.3)	29	0.062	96 (3.9)	95 (5.5)	37	0.19
Peak systolic blood pressure mmHg	139 (28)	159 (22)	**<0.001**	142 (27)	161 (21)	29	**0.001**	137 (28)	157 (23)	32	**0.002**

Note: Statistically significant *p* values highlighted using bold font.

Abbreviations: PIBD, pediatric inflammatory bowel disease; VO_2peak, peak oxygen uptake; VO_2peak/kg, peak oxygen uptake per kilogram; W_{max}, maximal workload; W_{max}/kg, maximal workload per kilogram.

TABLE 3 Neuromuscular fitness in pediatric inflammatory bowel disease patients and controls.

	Pediatric inflammatory bowel disease			Crohn's disease				Ulcerative colitis			
	Controls	Patients	*p* value	Controls	Patients	*n*	*p* value	Controls	Patients	*n*	*p* value
Grip strength, sum of both hands, kPa	162 (51)	145 (53)	**0.001**	165 (53)	150 (53)	30	**0.003**	160 (51)	141 (53)	42	**0.029**
Balance test, support/30 s	1.0 [0–3.0]	2.0 [1.0–4.0]	**0.05**	1 [0–2.3]	1.5 [0.8–3.0]	18	0.168	1.0 [0–3.0]	3.0 [1.0–5.0]	24	0.11
Sit-ups,/30 s	19 (5)	15 (5)	**0.001**	19 (5)	17 (6)	30	0.058	18 (5)	15 (5)	40	**0.005**
Long jump, cm	169 (33)	155 (28)	**0.001**	172 (33)	164 (22)	29	0.118	168 (34)	148 (31)	38	**0.004**
Shuttle run, s	21.4 (2.2)	22.9 (2.5)	**<0.001**	21.1 (1.7)	22.4 (2.3)	30	**0.003**	21.7 (2.6)	23.3 (2.6)	37	**0.009**
Box and block, test sum	132 (22)	135 (18)	0.46	134 (21)	137 (17)	31	0.51	131 (23)	133 (19)	42	0.68

Note: Statistically significant *p* values highlighted using bold font. Results are presented as mean (standard deviation) or median [interquartile range].

groups (OR: 0.71; 95% CI: 0.53–0.95) compared with controls.

In univariate analysis (Supporting Information S1: Table 4), FC, hs-CRP, hemoglobin, CRP, albumin, erythrocyte sedimentation rate, corticosteroid use, age at diagnosis, or PGA were not significantly associated with W_{max}/kg or with VO_2peak/kg, nor was the diagnostic subgroup of PIBD. CRF was negatively associated with age- and sex-adjusted body mass index for children and adolescents (ISO-BMI) and waist circumference, and positively with the use of biological medication. In multivariate analysis, higher ISO-BMI was associated with lower W_{max}/kg and VO_2peak/kg, and the use of any biological medication with higher W_{max}/kg and VO_2peak/kg (Table 4).

In the univariate analyses of neuromuscular fitness within the PIBD group, a higher age at diagnosis was associated with better performance in long jump, grip strength, and balance test, and the use of biological medication was associated with better sit-up performance. Having UC was associated with lower balance and long jump performance. Higher PA was associated with faster running performance. In multivariate analysis (Table 4), the association of UC with long jump performance, and PA with running performance, remained significant.

4 | DISCUSSION

We studied cardiorespiratory and neuromuscular fitness in a group of patients with pediatric-onset IBD and compared the findings to age- and sex-matched healthy controls. In addition, we related the findings to reported PA and the level of inflammation. Our main finding was that CRF, as measured by W_{max}/kg and VO_2peak/kg, was significantly lower in patients compared to the controls. Patients were also physically less active than controls, but the level of PA was not associated with CRF. We found a positive association

TABLE 4 Associated factors for cardiorespiratory fitness and neuromuscular performance in pediatric inflammatory bowel disease in linear regression analysis.

	Multivariable			
Outcome	**Unstandardized *B***	**95% CI**	**Standardized *β***	***p* value**
W_{max}/kg ($R^2 = 0.46$)				
Age	−0.04	−0.09 to 0.01	−0.15	0.11
Female	−0.39	−0.67 to −0.11	−0.28	**0.007**
ISO-BMI	−0.09	−0.13 to −0.06	−0.48	**<0.001**
Waist circumference, cm	n.e			
Biological medication in use	0.35	0.05–0.66	0.22	**0.025**
VO_2peak/kg ($R^2 = 0.60$)				
Age	−0.76	−1.29 to −0.24	−0.24	**0.005**
Female	−5.25	−8.21 to −2.28	−0.31	**0.001**
ISO-BMI	−1.16	−1.54 to −0.78	−0.49	**<0.001**
Waist circumference	n.e			
Biological medication in use	4.70	1.41–7.99	0.24	**0.006**
Grip strength[a] ($R^2 = 0.40$)				
Age	11	6–16	0.60	**<0.001**
Waist circumference	0.53	−0.56 to 1.62	0.12	0.33
Age at diagnosis	−0.73	−3.56 to 2.10	−0.06	0.61
Balance, support/30 s ($R^2 = 0.14$)				
Age	−0.17	−0.38 to 0.044	−0.20	0.12
UC/IBDU-group	1.0	−0.04 to 2.06	0.21	0.059
Age at diagnosis	−0.13	−0.28 to 0.026	−0.21	0.10
Sit up/30 s ($R^2 = 0.09$)				
Biological medication in use	*			
Long jump, cm ($R^2 = 0.29$)				
Age	3	1–6	0.33	**0.007**
UC/IBDU-group	−18	−29 to −6	−0.30	**0.004**
Hemoglobin, g/L	0.6	0.1–1.2	0.23	**0.024**
Age at diagnosis	0.81	−0.92 to 2.54	0.11	0.35
Shuttle run, s ($R^2 = 0.29$)				
Age	−0.37	−0.55 to −0.18	−0.42	**<0.001**
Physical activity, hours/week	−0.15	−0.23 to −0.07	−0.42	**<0.001**
Box and block, test sum ($R^2 = 0.26$)				
Age	3.3	1.6–4.9	0.51	**<0.001**
Female	5.3	−2.2 to 12.7	0.15	0.16
Waist circumference	−0.03	−0.4 to 0.4	−0.02	0.89

Note: Statistically significant *p* values highlighted using bold font.

Abbreviations: CI, confidence interval; IBDU, inflammatory bowel disease unclassified; ISO-BMI, age- and sex-adjusted body mass index for children and adolescents, kg/m^2; n.e., not entered because of high correlation with ISO-BMI; UC, ulcerative colitis; VO_2peak/kg, peak oxygen uptake per kilogram, mL/min/kg; W_{max}/kg, maximal workload per kilogram, W/kg.

*The only statistically significant variable in univariate analysis, and therefore, multivariable analysis was not done.

[a]Sum of both hands, kPa.

between biological medication and both W_{max}/kg and VO_2peak/kg, highlighting the importance of effective disease control for CRF. Most patients had mild disease activity, and none of the inflammatory markers were independently associated with CRF. Neuromuscular fitness, muscle strength, and agility were inferior in patients compared with controls.

A sedentary lifestyle has become more common in healthy children and adolescents, and physical fitness has declined.[23] Studies on physical fitness in PIBD are few. There are only a few studies in which CRF has been measured by an exercise test in PIBD.[8–10,24] Therefore, we assessed physical fitness consisting of CRF and neuromuscular fitness in a larger cohort of PIBD patients. Physical fitness is positively associated with multiple health-related factors, and better physical fitness may also reduce low-grade inflammation, which is common in IBD.[10,25] Our findings are consistent with those of a study by Ploeger et al.,[9] showing that peak aerobic workload and peak oxygen uptake were below reference values in PIBD patients. Moreover, disease activity or duration was not correlated with CRF,[9] in line with our results. They speculated that lower exercise capacity may result from lower hemoglobin levels or increased inflammatory mediators, such as antitumor necrosis factor-α. Pro-inflammatory mediators have been associated with cachexia, which can impair aerobic capacity regardless of the type of inflammatory disease.[9] In the present study, 18% of patients with PIBD were anemic, but hemoglobin values were not associated with CRF. Likewise, none of the markers of disease activity, including FC, hs-CRP, albumin, erythrocyte sedimentation rate, or PGA, were independently associated with CRF, indicating that there are multiple factors affecting CRF in PIBD. Furthermore, there were no signs of cachexia in our PIBD cohort. We observed that higher ISO-BMI and waist circumference were negatively associated with CRF. This association could be due to decreased PA contributing to increased weight gain and waist circumference compared to controls. Most patients were in remission (68% CD, 69% UC) or had a mild disease activity (32% CD, 24% UC). Hence, regardless of a relatively low inflammatory status, CRF was impaired in our cohort.

Medicines that are used to treat PIBD can also affect CRF. Ploeger et al. observed that PIBD patients using corticosteroids had a lower maximal workload and a tendency to reduced aerobic capacity.[9] We observed no independent association of corticosteroids with CRF. This difference could be due to a higher percentage of patients receiving corticosteroids in the study of Ploeger et al. compared to our PIBD cohort (65% vs. 19%, respectively).

Both CD and UC patients had lower grip force and speed in the shuttle run compared with controls. UC patients also had lower results in the standing long jump tests and a tendency towards lower balance performance in multivariate analysis. The causes for these results are not clear. Higher hemoglobin levels were associated with better results in the standing long jump, but no other markers were associated with the performance. Girls with PIBD had decreased grip strength compared with controls, but no such difference was found in boys. This contrasts the results of a German study, where grip strength was decreased, particularly in boys and especially in those with CD.[5] All their PIBD patients were in remission or had a mild disease activity, comparable to our cohort. Therefore, it is likely that current disease activity is not the only factor impairing the neuromuscular parameters.

Previous studies have reported that both adult and pediatric patients with IBD have an elevated risk for cardiovascular diseases.[9,26,27] Impaired physical fitness, combined with systemic inflammation, could be factors that increase the risk of cardiovascular diseases.[9,27] In addition to lower physical fitness, we found a higher peak systolic blood pressure during the exercise test in patients with PIBD compared with controls. This could imply an increased risk of developing cardiovascular disease later in life, but further longitudinal studies are needed. Bjelica et al. found that 16 weeks of supervised exercise training in patients with PIBD increased aerobic fitness, lean mass, and vigorous PA levels speculating that this could reduce the future risk of cardiovascular disease in these patients.[24] Trivic et al. observed that a 6-month home-based exercise program significantly improved lean body mass, muscle strength, and endurance in children and adolescents with IBD.[28]

To our knowledge, this is the largest study published thus far assessing physical fitness in patients with PIBD using an objective method of ergospirometry with breathing gas analysis combined with measurements of muscular strength, agility, and PA. Previous studies have often been retrospective, questionnaire-based, or limited to small numbers of patients.[5,6,9,10,25,27,29] Ergospirometry with the measurement of peak oxygen uptake is considered the gold standard for assessing CRF.[10,30] Another strength of our study was the use of age- and sex-matched, population-based control groups, which represented children and adolescents from two different areas in Finland, a high-incidence region for PIBD.[31] Most of the patients were in remission or had mild disease activity, which underscores the finding of impaired physical fitness in PIBD compared with healthy peers. In our study, disease activity was measured using an objective surrogate marker of inflammation (FC), in addition to clinical activity indices.

As a limitation, some data from the control group were previously collected, and PA levels in the pediatric population are known to have changed over time. Furthermore, the disease duration of PIBD was short,

and the study design was cross-sectional. Therefore, prospective studies are needed to assess the long-term development of CRF and neuromuscular fitness in PIBD.

5 | CONCLUSION

Patients with PIBD had lower CRF and neuromuscular fitness, and they were physically less active compared with healthy age- and sex-matched controls. Higher ISO-BMI and waist circumference were associated negatively, and the use of biological drugs was positively associated with physical fitness. However, factors related to physical fitness in PIBD are likely to be complex, warranting the need for longitudinal studies on the associations of variables such as body composition, visceral fat, and systemic inflammation with physical fitness. Lower physical fitness has been associated with poorer disease control, impaired quality of life, and increased risk of cardiovascular diseases in PIBD. This emphasizes the importance of assessing and improving physical fitness in these patients as a part of their multidisciplinary treatment.

ACKNOWLEDGMENTS

The authors thank all the participating children and adolescents and their families, the nurses of the Pediatric Outpatient Clinics in Tampere and Kuopio University Hospitals, and the staff of the Laboratory of Clinical Physiology in Tampere University Hospital and at the Kuopio Research Institute of Exercise Medicine. The authors also thank the Foundation of Pediatric Research and the Competitive State Research Financing of the Expert Area of Tampere University Hospital for the financial support. The study was supported by the Foundation for Pediatric Research; the State Funding for University-level Health Research, Tampere University Hospital, Wellbeing Services County of Pirkanmaa; the Päivikki and Sakari Sohlberg Foundation; the Finnish Foundation for Cardiovascular Research; and the Pediatric Clinic Foundation. The funders had no role in study design, data collection and analysis, the decision to publish, or in the preparation of the present manuscript. Open access publishing facilitated by Tampere University and Tampere University of Applied Sciences, as part of the Wiley - FinELib agreement.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: Kantanen S, Räsänen K, Kolho K-L, et al. Impaired physical fitness in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2025;1-11. doi:10.1002/jpn3.70091