Physical activity is associated with improved bone health in children with inflammatory bowel disease.

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Article title: Physical activity is associated with improved bone health in children with inflammatory bowel disease

Short running head: Bone health and physical activity

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Abbreviations: Body Mass Index (BMI), Bone Mineral Density (BMD), Crohn's Disease (CD), Inflammatory Bowel Disease (IBD), Physical Activity (PA), Moderate-to-Vigorous Physical Activity (MVPA), Ulcerative Colitis (UC).

† This work is dedicated to the memory of Dr Laurent Michaud.

Abstract

Background & Aims: Bone health is an important concern in patients with inflammatory bowel disease (IBD). Low bone mineral density (BMD) is a powerful predictor of fracture risk in IBD patients. Physical activity (PA) plays an important role in bone health. However, PA data for children and adolescents with IBD are scarce. The primary aim is to evaluate the relationship between PA and BMD in children with IBD. The secondary aim was to assess the relationship between PA and quality of life.

Methods: Eighty-four IBD pediatric patients (45 boys) aged 14.3 ± 2.7 years were included (disease activity: (*i*) remission, n=62; (*ii)* mild, n=18; (*iii*) severe disease, n=1). BMD was measured using dual-energy X-ray absorptiometry and expressed as age- and sex-based Z-scores. Each patient wore a triaxial accelerometer for seven consecutive days for objective PA quantification. Quality of life was assessed using the PedsQL™ and energy intake was assessed prospectively for three days using a dietary diary.

Results: BMD Z-score was –0.96 ± 1.11. Only five patients (6%) fulfilled the recommendation of 60 min of daily moderate-to-vigorous PA (MVPA). The proportion of children with osteopenia and osteoporosis was 51% and 4%, respectively. After adjustment for confounders (pubertal status and body mass index), total PA and time in MVPA were positively associated with BMD (regression coefficient per one standard deviation increase in PA parameters=0.26; $P<0.05$). There was no association between time spent in MVPA and total PA, and total quality of life score.

Conclusions: PA likely is associated with improved bone health in IBD children. Intervention studies investigating a causal relationship between PA and BMD in pediatric patients with IBD are warranted.

Keywords: Lifestyle habits, bone mineral density, pediatrics, inflammation.

40

INTRODUCTION

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD), ulcerative colitis (UC) and IBD-unclassified (IBD-U), are characterised by chronic inflammation of the gastrointestinal tract. Over the past 50 years, the incidence of IBD has increased globally, with the highest increase in industrialised countries [1]. During the last 25 years, the incidence of IBD has increased dramatically among teenagers in northern France, with an increase of 126% and 156% for CD and UC, respectively [2].

Bone mass acquisition during childhood and adolescence is a major determinant of skeletal health later in life [3]. Bone health is an important concern in patients with IBD. The prevalence of low bone mineral density (BMD) in children and adolescents with IBD ranges from 8% to 65% [4-6]. Bone mineralisation abnormalities in paediatric IBD are associated with the use of corticosteroids, disease activity, low body weight, young age at onset, pubertal delay, vitamin D deficiency, low calcium intake and intestinal malabsorption [7-9]. Low BMD is a powerful predictor of fracture risk in IBD patients [10].

Physical activity (PA), widely recognised as an important health determinant, plays an important role in growth and development. Increased participation in moderate-to-vigorous PA (MVPA) has major health benefits, including a lower risk of cardiovascular and pulmonary disease, musculoskeletal disorder, psychiatric, neurological and metabolic disease as well as cancer [11]. According to international PA recommendations, 60 min of MVPA daily are needed to positively impact child and adolescent health [12]. In contrast, a sedentary lifestyle is associated with adverse health consequences and increased morbidity and mortality in adulthood [13]. However, PA data for children and adolescents with IBD are scarce.

Thus, the primary aim of the study was to evaluate the relationship between PA and bone health in IBD paediatric patients. The secondary aim was to assess the relationship between PA and quality of life.

SUBJECTS AND METHODS

Study design

From October 2014 to March 2017, consecutive paediatric patients with IBD who were followed in hospitals in northern France were invited to participate in this prospective study. Inclusion criteria were: (i) age 6–18 years; (ii) informed consent signed by the patient and his/her parents; (iii) IBD diagnosis (CD, UC, IBD-U) at least six months prior; and (iv) not currently participating in another biomedical study. Exclusion criteria were: (i) acute or chronic disease (other than IBD) associated with a decrease in PA; and (ii) any recent event (≤15 days) that could affect PA. Eighty-four patients were included.

Before participating, the study aims and objectives were carefully explained to, and written informed consent obtained from, each patient and his/her parents. The study was approved by the Research Ethics Committee of the University of Lille (Comité de Protection des Personnes, Nord Ouest IV, Lille, France). All procedures were performed according to the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and European Good Clinical Practice.

Measurements

Physical activity

PA was assessed using accelerometry, an objective method for use with youth [14]. The triaxial accelerometer was the ActiGraph® Monitor (Model GT3X; ActiGraph, Pensacola, CA, USA), with dimensions 46 × 33 × 15 mm and weight 19 g. The accelerometer measures acceleration in three spatial dimensions according to vertical (x), antero-posterior (y) and medio-lateral (z) vectors. The vector magnitude (VM) was calculated as: $VM = \sqrt{(x^2+y^2+z^2)}$. The epoch length was set at 1 sec. A computer was used to initialise and synchronise the accelerometer, which was calibrated based on patient age, height and weight. The GT3x accelerometer has been validated for measuring PA against oxygen consumption and heart rate [15]. The inter-instrument reliability for this device is better for moderate and vigorous activity than for sedentary activity [16]. Consistent with consensus recommendations for assessing PA in youth, patients who did not report at least three days with a minimum of 10 hours of PA per day were excluded from analyses [17]. PA activity levels were classified as: sedentary (0–180 counts.15sec^{-1}); light (181–757 counts.15sec^{-1}); moderate (758–1112 counts.15sec^{-1}); and vigorous (>1112 counts.15sec^{-1}) [15].

Patients wore the accelerometer on their lower back, beneath their clothing, using an elastic belt with adjustable buckle. They were asked to follow their normal daily routine and instructed to remove the device during contact sports, water-based activities (e.g., swimming, showering, bathing) and overnight. The accelerometer was used to record activity over seven consecutive days during free-living conditions. In addition, patients and parents were instructed to keep a PA diary while the patient wore the accelerometer.

Bone mineral density and body composition

BMD and body composition (fat mass and fat free mass) were measured with dual-energy X-ray absorptiometry (DEXA; Hologic Corp., Discovery Type, Software 12.6, Bedford, MA,

USA). Patients were scanned in the supine position at high resolution. BMD, fat mass and fat free mass were determined based on whole body scan analyses.

Because BMD measurements are age- and sex-specific, standardised Z-scores were calculated by subtracting the age- and sex-specific mean and dividing by the standard deviation. According to World Health Organisation recommendations, normal BMD T-scores are ≥−1 standard deviation (SD), osteopenia T-scores <−1 to >−2.5 SD and osteoporosis T-scores ≤−2.5 [18].

Quality of life

The IMPACT III was not used herein because it has not been validated among French youth. Instead, quality of life was assessed with the Pediatric Quality of Life Inventory (PedsQL^{TM}) (Version 4.0), which is divided into age groups 5–7 years, 8–12 years and 13–18 years. Each age group version has 23 questions comprising four dimensions: (i) physical functioning; (ii) emotional functioning; (iii) social functioning; and (iv) school functioning. The PedsQL^{TM} provides a total score and two subscale dimensions: (i) physical health (physical functioning scale score); and (ii) psychosocial health (emotional, social and school functioning scale scores). For children 8 to 18 years, each question is scored using a 5-point Likert scale ranging from 0 (never) to 4 (almost/always). Appropriate items were reverse scored and total scores were linearly transformed to a 0–100 scale where: 0 = 100; 1 = 75; 2 = 50; 3 = 25; and 4 = 0. For children 5 to 7 years, each question is scored using a 3-point Likert scale ranging from 0 (not at all), 2 (sometimes) and 4 (a lot). Higher scores indicate a better quality of life. Based on scoring recommendations, patients replied to at least 50% of the questions.

Patients were asked to complete the age-appropriate PedsQL^{TM} forms and rate the degree to which each item had been a problem for them during the past month, on a 5-point Likert scale

for children 8 to 18 years and a 3-point Likert scale for children 5 to 7 years. Total score and subscale dimensions are expressed as percentages of the maximum points possible.

Energy intake

Energy intake was assessed using a prospective dietary diary for three consecutive days, including one weekend day. Patients were interviewed about the types of foods consumed during the three 24-hour periods. For the greatest precision possible, patients could complete the dietary diary with their parents. The same dietitian reviewed all dietary diaries. Patients were assisted by an instruction manual for food codification, including validated photographs of more than 250 foods represented in three different portion sizes. Foods were presented in three sizes permitting, with intermediate and extreme positions, seven choices of the amount [19]. All quantities were then calculated using KIDMENU® software (SHS, Paris, France) to compute energy intake using food composition tables from the French Food Safety Agency [20].

Clinical assessment

Each patient underwent a detailed medical examination. Pubertal status was assessed by direct observation according to Tanner and Whitehouse [21]. Body mass was measured to the nearest 0.1 kg using an electronic scale (Seca, Hamburg, Germany) after removal of shoes and heavy outer garments. Height was measured to the nearest 0.1 cm using a stadiometer (Seca, Hamburg, Germany). Body mass index (BMI) was calculated as weight (kg) divided by height² (m^2). Patients had a plain radiograph of the left hand; wrist and bone age were expressed in years using the Greulich and Pyle atlas [22]. In addition, 25(OH)vitamin D, haematocrit, C-reactive protein, albumin and erythrocyte sedimentation rate were measured to

assess inflammation and calculate disease activity. The Pediatric CD Activity Index (PCDAI) was used for patients with CD and the Pediatric Ulcerative Colitis Activity Index (PUCAI) for patients with UC [23-24]. The PCDAI comprises three domains: (i) history (one-week recall of abdominal pain, stools, patient functioning, general well-being); (ii) laboratory results (haematocrit, erythrocyte sedimentation rate, albumin); and (iii) physical examination (weight, height, abdomen, perirectal disease, extra-intestinal manifestations). The PUCAI comprises six domains: (i) abdominal pain; (ii) rectal bleeding; (iii) stool consistency; (iv) number of stools per 24 hours; (v) nocturnal stools; and (vi) activity level. Remission was defined as scores <10 and mild activity as scores 10–27.5 on the PCDAI and 10–34 on the PUCAI. Values >37.5 on the PCDAI or >34 on the PUCAI indicated moderate to severe activity. Drug therapy, including 5-ASA, corticosteroids, immunomodulators (azathioprine, methotrexate) and anti-TNF therapy (infliximab, adalimumab) was recorded.

Sample size calculation and statistical analysis

The study objective was to evaluate the association between PA and BMD in children with IBD. Classification of correlation coefficients was based on Cohen's rule, where <0.3 is weak, 0.3–0.6 moderate and >0.6 high [25]. Sample size calculation was based on: H_0: r = 0 (no correlation between parameters) vs. H_1: r = 0.3 (average correlation between parameters). For alpha = 5% and power = 80%, N = 84 participants were needed.

Data are presented as counts (percentages) for categorical variables and mean±SD or median [range] for quantitative variables. Normality of distribution was assessed visually using histograms and by using the Shapiro–Wilk test. Associations of PA parameters with outcomes (BMD Z-score and quality of life) were analysed using linear regression models with and without adjustment for confounding factors. For each outcome, confounding factors were

selected according to bivariate analyses ($p<0.10$). Associations of each outcome with potential confounding factors were assessed using Student's *t*-test for categorical confounding factors and Pearson (or Spearman's rank) correlation coefficients for quantitative (or ordinal) confounding factors. All statistical tests were done at the two-tailed α level of 0.05. Data were analysed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Sample characteristics are presented in Table 1. Mean BMD Z-score (±SD) was –0.96±1.11. The computer analysis of the accelerometer data showed that 82 participants wore the accelerometer during at least three days with a minimum of 10 hours of PA per day. Two participants were excluded from the analysis because of monitoring failure. Only five patients (6%) fulfilled the recommendation of 60 min of MVPA daily. The prevalence of osteopenia and osteoporosis was 51% and 4%, respectively. Drug therapy is also depicted in Table 1.

Bivariate analyses assessing the relationships between BMD-Z score and potential confounding factors are shown in Table 2. BMI and pubertal status (Tanner grade) were positively associated with BMD Z-score ($p<0.05$ for both associations).

As shown in Table 3, BMD was not significantly related to any of the PA parameters in bivariate analyses. However, after adjustment for confounding factors, total PA and time spent in MVPA were positively associated during the weekdays with BMD ($p=0.041$ and $p=0.046$, respectively).

The PedsQL^{TM} total score (±SD) was 81.6±13.4. Associations of quality of life score and potential confounding factors are presented in Table 4. A positive significant association was found between pubertal status and quality of life ($r=0.23$).

As shown in Table 5, no significant association was found between time spent in MVPA/total PA and quality of life in multivariable linear regression models adjusted for pubertal status.

DISCUSSION

Osteoporosis is a common skeletal disease and is associated with high morbidity and mortality in adulthood [26]. Even if our study shows that mean BMD Z-score of IBD paediatric patients was within normal range, it is of note that osteopenia was found in half of the patients while osteoporosis was rare. BMD-Z score and quality of life score did not differ significantly according to disease severity. Only a non-significant higher quality of life score in children in remission was found compared to children with mild or severe disease (mean: 83 ± 13 vs. 76 ± 15; p=0.058). In relation to our primary objective, the present study shows a positive association between BMD and both amount of PA and time spent in MVPA. This result is consistent with those reported for healthy children [27-28]. Vicente-Rodriguez et al. observed a negative association between sedentary lifestyle and bone health in healthy adolescents. More than three hours daily of sedentary behaviour (e.g., watching TV) was associated with increased risk for low bone mineral content in males [27]. In healthy young adults, PA is associated with improved BMD independent of gender and vitamin D status [28]. To our knowledge, the only study assessing bone health and PA in IBD has been performed in adult patients [29]. Patients were randomised to a control group or a low-impact exercise program with increasing intensity across a 12-month period [29]. In patients who were able to fully comply with the exercise program, the only significant BMD gain was observed at the greater trochanter (+4.7%); these findings were independent of changes in potential confounding variables (e.g., steroid dose, weight, diet).

IBD have a well-known negative impact on health-related quality of life (HRQoL) [30]. Ng et al studied PA as non-pharmacological approach in the management of IBD for improving or maintaining HRQoL [31]. Another study showed that adult patients engaged higher volumes of MVPA above 150 min/week and walking, particularly above 60 min/week, improved their quality of life [32]. Similar results have been found in people with other chronic diseases or in healthy people [33-35]. Results from our study do not concur with previous research.

According to youth PA guidelines, children and adolescents should accumulate a minimum of 60 min of MVPA daily through transportation, physical education, sports, free play and planned exercise for positive health outcomes [12]. A very low proportion of our study sample followed this recommendation. These data are alarming in relation to studies of healthy children [36-37]. In 2004, among 2185 children and adolescents assessed with accelerometry, 90% of boys and 80% of girls achieved health-related PA recommendations [36]. In a population of 2200 European adolescents, 57% of boys and 28% of girls followed the PA recommendations, based on accelerometer [37]. Wekstetter et al. compared PA levels between IBD paediatric patients and healthy controls [38]. The differences in PA duration and number of steps between groups did not reach statistical significance; however, female patients had a significantly shorter duration of PA (in total and moderate level). In our study, between patients in remission and patients with mild or severe disease activity, no difference was found in total PA (158.1 *vs* 176.4 counts.min^{-1}, p = 0.40) and time spent in MVPA (44.8 *vs* 42.9 min.day^{-1}, p = 0.47).

It has been hypothetized that PA could be associated with an increased risk for exacerbation of inflammation [39]. Ploeger et al examined inflammatory cells and cytokines in response to acute bouts of moderate intensity continuous exercise and high intensity intermittent exercise in youth with CD and in healthy matched controls [39]. In CD patients, both types of exercise increased immune cells. Moderate intensity exercise induced a significantly greater increase

253 in leukocytes, neutrophils, lymphocytes, monocytes, IL-6 and IL-17, compared with high
254 intensity exercise. TNF-α did not change significantly with either exercise. These preliminary
255 results suggest that moderate PA of short duration is not associated with a deleterious effect
256 on inflammatory parameters. However, further studies are needed to assess the effects of
257 regular exercise on inflammation in IBD pediatric patients.

258 The current study has both strengths and limitations. Importantly, strong objective methods
259 were used to assess both PA (using accelerometry) and bone health (using DEXA).
260 Additionally, confounding factors were accounted for in the statistical analyses. The study
261 limitations include its observational design, which means that associations cannot be
262 interpreted as causal. Moreover, the sample size did not allow to study the impact of gender
263 on PA, quality of life and BMD-Z score, and to test the heterogeneity in PA and BMD score
264 according to disease severity. Regarding the multiple testing issue, we could not exclude false
265 positive findings. Moreover, we could not exclude bias in estimates due to missing data. In
266 addition, the thresholds used to classify PA may have affected the results, as previously
267 described [40]. Variations in weather conditions (e.g., wind, rain, sunshine) during PA
268 assessments were not recorded but may also have affected our results. Another limitation of
269 our study is the lack of information on the type of PA. Animal data showed that mechanical
270 stress (*i.e.*, mechanical loading) on bone can enhance bone mass [41-44]. Results in healthy
271 adolescents concur with animal studies. PA involving weight bearing (e.g walking, running) is
272 more beneficial to bone mass as compared to PA with minimal weight bearing (e.g cycling,
273 swimming) [45-46]. Another limitation of the current study is that the small sample size did
274 not allow to compare CD patients and UC patients.

275 In summary, PA was found to be positively associated with BMD in paediatric patients with
276 IBD. Intervention studies investigating a causal relationship between PA and BMD are thus
277 warranted in order to determine whether IBD paediatric patients could benefit from PA

278 promotion programs. In addition, these studies should aim at determining the most adequate
279 PA, including type, intensity, duration and frequency.

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Conflict of interest

The authors do not have any competing interests.

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430 **Legends**

431 **Table 1.** Characteristics of the study patients

432 **Table 2.** Associations between BMD_{wb} Z-score and potential confounding factors

433 **Table 3.** Associations between BMD_{wb} Z-score and physical activity

434 **Table 4.** Associations between quality of life and potential confounding factors

435 **Table 5.** Associations between quality of life and physical activity

436

Table 1. Characteristics of the study patients

	N	Values
Boys	84	45 (53.6)
Age (*years*)	84	14.3 ± 2.7
Height (*cm*)	84	160 ± 15
Height-Z score (*mean* ± *SD*)	84	0.38 ± 1.6
Weight (*kg*)	84	50 ± 15
Weight-Z score (*mean* ± *SD*)	84	0.4 ± 1.2
Body mass index ($kg.m^{-2}$)	84	19.5 ± 3.4
Body mass index-Z score (*mean* ± *SD*)	84	0.21 ± 1.3
Pubertal status (Tanner grade)	82	
I		17 (21%)
II		11 (13%)
III		12 (15%)
IV		26 (32%)
V		16 (20%)
Age at diagnosis (*years*)	83	10.9 ± 2.8
Disease duration (*months*)	83	34 [range: 17-65]
IBD diagnosis	84	
Crohn's disease		58 (69%)
Ulcerative colitis		16 (19%)
Inflammatory bowel disease-unclassified		10 (12%)
Vitamin D ($ng.mL^{-1}$)	83	25 [range: 18-32]
C-reactive protein ($mg.L^{-1}$)	83	2 [range: 2-8]
BMD_{wb} Z-score	78	-0.96 ± 1.11
BMD_{wb} ($g.cm^{-2}$)	79	0.93 ± 0.14
Fat mass (*%*)	79	22.4 ± 7.9
Fat free mass (*%*)	79	77.6 ± 7.9
Bone age (*years*)	82	13.7 ± 2.8
Intensity of disease	81	
I (remission)		62 (77%)
II (mild activity)		18 (22%)
II (moderate to severe activity)		1 (1%)
Corticosteroids ever	84	35 (42%)
Corticosteroids lifetime	83	
I (ever use or usage ≤ 3 months)		55 (66%)
II (usage > 3 months)		28 (34%)
Drug therapy during the study period	84	
Corticosteroids		4 (5%)
5-ASA		28 (33%)
Azathioprine		14 (17%)
Methotrexate		6 (7%)
Anti-TNF therapy		36 (43%)
Energy intake ($Kcal.day^{-1}$)	82	1748 [range: 1399-2212]
Calcium intake ($mg.day^{-1}$)	82	580 [range: 429-844]
Phosphorus intake ($mg.day^{-1}$)	82	652 [range: 481-941]
Fruits and vegetables ($Portion.day^{-1}$)	82	1.7 [range: 1.0-2.7]
Total PA (*counts*)	82	163 [range: 124-217]
Sedentary time ($min.day^{-1}$)	82	554 [range: 488-599]
MVPA ($min.day^{-1}$)	82	45 [range: 33-66]
Fulfilling PA recommendations	82	5 (6%)
PedsQL™ total score	84	84.8 [range: 75.0-91.3]

437 Values are expressed as count (percentage), mean ± SD or median [IQR].

438 Abbreviations: IBD= Inflammatory bowel diseases ; IQR=interquartile range; BMDwb= Bone
439 Mineral Density of whole body, MVPA= Moderate to Vigorous Physical Activity; PA=physical
440 activity; SD=standard deviation.
441

442

Table 2. Associations between BMD_{wb} Z-score and potential confounding factors

	Values	**P**
Age (*years*)	-0.04	0.76
Sex		
Boys	-0.91 ± 1.04	0.70
Girls	-1.01 ± 1.20	
Body mass index	**0.54**	**<0.001**
Intensity of disease		
Remission	-0.88 ± 1.12	0.22
Mild to severe activity	-1.25 ± 1.11	
Pubertal status (Tanner grade)	**0.27**	**0.019**
Corticosteroids lifetime		
Ever use or usage ≤ 3 months	-0.93 ± 1.10	0.49
Usage > 3 months	-1.11 ± 1.03	
Anti-inflammatory therapy		
No	-0.84 ± 1.34	0.74
Yes	-0.93 ± 0.14	
Age at diagnosis (*years*)	0.02	0.85
Energy intake ($Kcal.day^{-1}$)	0.11	0.33
Calcium intake ($mg.day^{-1}$)	0.09	0.45
Phosphorus intake ($mg.day^{-1}$)	0.11	0.34
Fruits and vegetables ($Portion.day^{-1}$)	0.05	0.66
Fat mass (*%*)	<0.01	0.99
Fat free mass (*%*)	<0.01	>0.99
Bone age (*years*)	0.14	0.23
Disease duration (*months*)	<0.01	0.95
Vitamin D ($ng.mL^{-1}$)	-0.02	0.85
C-reactive protein ($mg.L^{-1}$)	-0.02	0.84

Values are mean ± standard deviation for categorical variables and correlation coefficient for continuous variables.

BMD_{wb}: Bone Mineral Density of whole body

Table 3. Associations between BMD_{wb} Z-score and physical activity

	Unadjusted			Adjusted*		
	β (95%CI)	**P**	**R^2 (%)**	**β (95%CI)**	**P**	**R^2 (%)**
All days						
MVPA	0.11 (-0.16 to 0.38)	0.41	0.9	0.19 (-0.05 to 0.44)	0.13	2.5
Sedentary	0.18 (-0.08 to 0.44)	0.16	2.6	0.15 (-0.10 to 0.40)	0.25	1.5
Counts	0.05 (-0.22 to 0.32)	0.72	0.2	0.15 (-0.10 to 0.41)	0.24	1.5
Week days						
MVPA	0.20 (-0.07 to 0.47)	0.14	3.0	**0.26 (0.01 to 0.51)**	**0.041**	**4.6**
Sedentary	0.20 (-0.06 to 0.46)	0.14	3.0	0.18 (-0.08 to 0.44)	0.19	1.9
Counts	0.16 (-0.11 to 0.43)	0.23	1.9	**0.26 (0.005 to 0.52)**	**0.046**	**4.3**
Week end days						
MVPA	0.05 (-0.21 to 0.30)	0.71	0.2	0.15 (-0.08 to 0.39)	0.21	1.7
Sedentary	0.16 (-0.09 to 0.42)	0.21	2.1	0.09 (-0.14 to 0.33)	0.42	0.7
Counts	-0.04 (-0.30 to 0.21)	0.74	0.2	0.07 (-0.17 to 0.31)	0.57	3.6

Data analysis was performed on 76 patients without missing data on BMD_{wb} Z-score and physical activity parameters.

Abbrevations: BMD_{wb}= Bone Mineral Density of whole body; CI= confidence interval; MVPA= moderate to vigorous physical activity

β indicate regression coefficient per one standard deviation increase in PA parameters. R^2 indicates the squared semi-partial correlation coefficient.

* Adjusted for between-group difference in potential confounding factors at $p<0.10$ in bivariates analyses (body mass index and Tanner grade).

Table 4. Associations between quality of life and potential confounding factors

	Values	**P**
Age (*years*)	0.16	0.14
Sex		0.16
Boys	83.6 ± 10.3	
Girls	79.3 ± 16.1	
Body mass index	0.11	0.32
Intensity of disease		0.058
Remission	83.0 ± 12.7	
Mild to severe activity	76.3 ± 15.5	
Pubertal status (Tanner grade)	**0.23**	**0.039**
Corticosteroids lifetime		0.96
Ever use or usage ≤ 3 months	81.4 ± 13.4	
Usage > 3 months	81.5 ± 16.7	
Anti-inflammatory therapy		0.19
No	87.2 ± 10.3	
Yes	81.0 ± 13.6	
Age at diagnosis (*years*)	0.14	0.19
Energy intake ($Kcal.day^{-1}$)	0.01	0.91
Fruits and vegetables ($Portion.day^{-1}$)	0.08	0.46
Fat mass (*%*)	-0.18	0.11
Fat free mass (*%*)	0.18	0.11
Disease duration (*months*)	0.11	0.34

458 Values are mean ± standard deviation for categorical variables and correlation
459 coefficient for continuous variables.
460

461

Table 5. Associations between quality of life and physical activity

	Unadjusted			Adjusted*		
	β (95%CI)	**P**	**R^2**	**β (95%CI)**	**P**	**R^2**
Total score						
MVPA	-2.09 (-5.04 to 0.85)	0.16	0.025	-1.47 (-4.61 to 1.67)	0.35	0.011
Counts	-2.71 (-5.63 to 0.21)	0.069	0.041	-2.01 (-5.24 to 1.24)	0.22	0.019
Dimension I						
MVPA	-2.75 (-5.72 to 0.22)	0.069	0.041	-1.73 (-4.83 to 1.38)	0.27	0.015
Counts	**-2.98 (-5.94 to -0.03)**	**0.048**	**0.048**	-1.64 (-4.86 to 1.59)	0.31	0.013
Dimension II						
MVPA	-1.75 (-5.05 to 1.55)	0.30	0.014	-1.34 (-4.87 to 2.20)	0.45	0.007
Counts	-2.56 (-5.83 to 0.71)	0.12	0.029	-2.20 (-5.85 to 1.45)	0.23	0.019

Data analysis was performed on 82 patients without missing data on PedsQL^{TM} total and physical activity parameters (calculated for all days).

Abbrevations: CI= confidence interval; MVPA= moderate to vigorous physical activity.

Dimension I: physical health comprising of the physical functioning scale score

Dimension II: psychosocial health comprising of the emotional, social and school functioning scales score

β indicates regression coefficient per one standard deviation increase in PA parameters.

* Adjusted for between-group difference in potential confounding factors at $p<0.10$ in bivariates analyses (Tanner Grade and Intensity of disease)