# Physical fitness in children and adolescents with inflammatory bowel disease: protocol for a case–control study

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## ABSTRACT

**Introduction** Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract, associated with adverse health consequences that may adversely influence physical activity and body composition in youth. These effects may lead to changes in physical fitness, which is positively associated with health-related outcomes. The aim is to assess health-related physical fitness levels in paediatric patients with IBD and to compare these levels with those in healthy matched controls.

**Methods and analysis** This trial is a bicentric case–control study. Fifty paediatric patients with IBD and 50 matched healthy controls will be recruited (1:1), and physical fitness levels (cardiorespiratory fitness, muscular strength, speed/agility and flexibility) will be assessed. The primary outcome is cardiorespiratory fitness, which will be compared between children and adolescents with IBD and healthy controls matched for age, sex and body mass index class. We will assess whether the two groups differ with respect to other physical fitness components and cardiovascular risk in adulthood according to sex-specific cut-offs for a healthy cardiorespiratory fitness level in adolescents. We will identify relationships between physical fitness and characteristics of IBD, quality of life and daily physical activity.

**Ethics and dissemination** This study was approved by the Research Ethics Committee (Comité de Protection des Personnes, Centre-Ouest I, Tours, France; No 2019-A02651-56) and was declared to the Commission Nationale de l'Informatique et des Libertés. All procedures will be performed according to the ethical standards of the 1975 Declaration of Helsinki, as revised in 2008, and the European Union's Guidelines for Good Clinical Practice. Written informed consent will be obtained from the youths and their parents. Research findings will be disseminated in peer-reviewed journals and scientific meetings, as well as in social media and IBD family support groups.

**Trial registration number** NCT04647578.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to assess health-related physical fitness in children and adolescents with inflammatory bowel disease compared with healthy matched controls.
⇒ Physical fitness will be measured using two widely recognised tests (Eurofit and FitnessGram), which have good reliability in children.
⇒ The results obtained in this study will not allow for comparison between Crohn's disease and ulcerative colitis because of the small sample size.

## INTRODUCTION

Inflammatory bowel disease (IBD) is a family of chronic disorders that cause inflammation of the gastrointestinal tract. Crohn's disease (CD), ulcerative colitis (UC) and IBD-unclassified (IBD-U) are the three known types of IBD. While the ultimate aetiology of IBD remains unclear, genetics, the gut microbiome, environmental factors and the immune system have all been shown to contribute to the disease pathophysiology.[1] IBD has become a concern for health epidemiologists because of the increase in its incidence in newly industrialised countries since the 1990s.[2] This also applies to paediatric populations.[3] For example, from 1988 to 2011, the incidence of IBD increased by 126% for CD and 156% for UC among teenagers in northern France.

The high incidence of IBD in children and adolescents can be considered as a public health issue because of the increased healthcare consumption and multiple consequences for the global health status.[4] IBD has a broad set of consequences in paediatric patients including elevated risk of osteoporosis, low body weight, pubertal delay, depression, low calcium intake, intestinal malabsorption, sleep disturbances leading to fatigue and impaired quality of life.[4–7] In addition, several IBD symptoms, such as abdominal pain, diarrhoea, fatigue and poor nutritional status, may reduce participation in physical activity (PA) and increase

sedentary status, which in turn have negative effects on physical fitness (PF) status.[8 9]

PF is defined as 'the ability to carry out daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies'.[10] PF can be described using two models: one related to skills, which is used mainly to assess physical performance in sport practitioners; and the other related to health. Health-related PF includes muscular strength, speed/agility, cardiorespiratory fitness and body composition.[11]

Studies in adults have shown that cardiorespiratory fitness and muscular strength are important prognostic factors for cardiovascular diseases and other chronic diseases such as type 2 diabetes, respiratory diseases and obesity.[12–15] Low PF is a risk factor for cardiovascular disease and is more important than other known risk factors such as dyslipidaemia, hypertension or obesity.[16] In children and adolescents, a high PF level is associated with health benefits such as better bone health, quality of life, self-esteem and cognitive performance, and fewer cardiovascular disease risk factors.[17 18] By contrast, low muscular strength and cardiorespiratory fitness in adolescence are strongly associated with risk factors for major causes of death in young adulthood.[19 20]

Only two previous studies of PF and IBD have been published.[21 22] Vogelaar *et al* showed that fatigued adults with IBD have impaired PF compared with non-fatigued adults with IBD.[22] Melinder *et al* assessed whether fitness in adolescence is associated with subsequent IBD risk independent of markers of risk and prodromal disease activity.[21] They concluded that an inverse association of PF with IBD risk is consistent with a protective role of exercise. To our knowledge, no study has assessed PF levels in children and adolescents with IBD compared with those in healthy youths.

Robust and consistent evidence supports that PF is strongly associated to PA.[23 24] A systematic review concluded that children with IBD are less active than healthy children and spend more time in sedentary behaviours.[25] These patterns may lead to reduced PF levels in youth with IBD. Therefore, we hypothesised that PF levels are lower in children and adolescents with IBD compared with their age-matched and sex-matched healthy controls.

### Primary and secondary objectives

The main objective of the study is to compare the cardiorespiratory fitness between children and adolescents with IBD and age-matched and sex-matched healthy controls.

The secondary objectives are as follows: (1) to assess other components of PF (muscular strength and endurance, flexibility and agility/coordination) in youths with IBD and to compare these with levels in age-matched and sex-matched healthy controls; (2) to determine whether PF is related to determinants of IBD such as age at diagnosis, duration of IBD, type of IBD (CD, UC or IBD-U), disease activity, weight status, height for age and weight for age, pubertal status and treatment; (3) using published cardiorespiratory fitness thresholds to assess cardiovascular risk in adulthood in children and adolescents with IBD compared with healthy youths; and (4) to determine whether PF is related to quality of life, fatigue state and daily PA in children and adolescents with IBD.

**Table 1** Flow chart of the study for children with IBD

| Visit | (V-1) | V1 | V2 (+7 days) |
|---|---|---|---|
| Information process | X | | |
| Written consent process | | X | |
| Inclusion and exclusion criteria review | | X | |
| Clinical assessment | | X | |
| Vital signs assessment | | X | |
| Anthropometric measurements | | X | |
| Blood sample process | | X | |
| PCDAI/PUCAI questionnaire process | | X | |
| Body composition measurements | | X | |
| Concomitant medication evaluation | | X | |
| Quality of life/fatigue score assessment | | X | |
| AE and SAE monitoring | | | X |
| Physical fitness measurements | | X | |
| Physical activity measurements | | X | |
| Phone call | | | X |

AE, adverse event; IBD, inflammatory bowel disease; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; SAE, serious adverse event.

## METHODS AND ANALYSIS

### Study design and setting

This study is a multicentre prospective case–control (1:1) study to be performed in two tertiary university hospitals in France. This case–control study aims to assess the PF of boys and girls with IBD and to compare these levels with those of matched healthy controls. The study began in December 2020 and will be completed in July 2022. From 2020 onwards, consecutive paediatric patients with IBD followed in two northern France university hospitals (Lille and Amiens) have been asked to participate in this study. The study involves three visits for children and adolescents with IBD (table 1) and two visits for healthy controls (table 2).

Table 2 Flow chart of the study for healthy controls

| Visit | (V-1) | V1 |
|---|---|---|
| Information process | X | |
| Written consent process | | X |
| Inclusion and exclusion criteria review | | X |
| Vital signs assessment | | X |
| Anthropometric measurements | | X |
| Body composition measurements | | X |
| Physical fitness measurement | | X |

Written and informed consent will be obtained from paediatric patients with IBD and their parents at the first visit (V-1), and the patients will undergo several examinations. First, a physical examination will be performed, anthropometric measures (height, weight and body mass index (BMI)) and body composition (skinfold thickness) will be assessed and a blood sample (8.5 mL) will be drawn in order to assess inflammatory status and calculate disease activity. The patients will complete two questionnaires on their quality of life (Pediatric Quality of Life Inventory, PedsQL) and fatigue (Pediatric Functional Assessment of Chronic Illness Therapy-Fatigue, pedsFACIT-F). PF will then be assessed in each child or adolescent with IBD. At the end of this visit, the patients will be asked to wear an accelerometer for seven consecutive days to provide an assessment of their PA. Patients will receive a follow-up telephone call after 7 days to record any adverse events (AEs) or serious adverse events (SAEs) that could impact adversely on PA.

Written and informed consent will also be obtained from the controls and their parents or legal guardians. The controls will undergo a short medical examination, and body mass, height and body composition will be measured (table 2). The control youths will then perform the PF tests. Blood samples, questionnaires and accelerometery will not be required of the control group.

## Patient and public involvement

Patients in this study will not be involved in the design, recruitment or conduct of the study. After the visit, patients will be informed by the study's physician of the results of the PF test in the form of pictures and text. The physician in charge of each patient will be also informed of the results to optimise disease management.

## Participant eligibility

To be eligible for participation in the study, the children and adolescents must meet the following inclusion criteria and not meet any exclusion criteria.

The inclusion criteria for both groups are as follows: (1) age between 10 and 18 years; (2) assent form signed by the patient and informed consent signed by the parents or guardians; and (3) no simultaneous inclusion in other biomedical research studies. A supplementary inclusion criterion for children with IBD is a diagnosis of IBD (CD, UC or IBD-U) for at least 6 months. For healthy children, the supplementary inclusion criteria are age (±1 year), BMI class status and being sex matched with a patient with IBD.

The exclusion criteria for both groups are as follows: (1) acute or chronic disease (other than IBD) that would interfere with PF assessment; (2) no written assent from the patient or consent by the parents or guardians; or (3) positive blood pregnancy test at the baseline visit. The supplementary exclusion criteria are as follows: (1) any recent event (within 15 days) that could affect PF (eg, sprain, fracture, recent arthritis, anoperineal lesions, severe skin lesions); (2) an active disease (Pediatric Crohn's Disease Activity Index (PCDAI) >30 for patients with CD and/or Pediatric Ulcerative Colitis Activity Index (PUCAI) >35 for patients with UC).[26 27]

## Measurements

### Physical fitness

The health-related PF components will be assessed using five PF tests. These tests are used to assess cardiorespiratory fitness, muscular strength (upper and lower limbs), speed/agility and flexibility. All tests will be performed twice, and the best score will be recorded, except for the test of cardiorespiratory fitness, which is performed only once at the end of the session. Good reliability has been reported in children and adolescents for all tests used in the study.[28]

*Cardiorespiratory fitness* will be assessed using a 20 m shuttle run test.[29] The participants will run between two lines, 20 m apart, while keeping pace with audio signals emitted from a pre-recorded CD. The initial speed is 8.5 km/hour, and this will be increased by 0.5 km/hour for each 1 min stage. Children will be instructed to run in a straight line to pivot on completing a shuttle and to pace themselves to the audio signals. The test ends when the participant fails to reach the end lines concurrent with the audio signals on two consecutive times. Otherwise, the test ends when the participant stops because of fatigue. All tests will be administered under standard conditions in an indoor rubber-floored gymnasium. The children will be encouraged to keep running as long as possible throughout the test. The last completed stage or half stage at which the participant stops will be recorded.

*Lower body muscular strength* will be tested using the standing broad jump test. From a starting position immediately behind a line and standing with the feet shoulder width apart, the participant will jump as far as possible with the feet together. The result will be recorded in centimetres. A non-slip hard surface, chalk and a tape measure will be used for the test.

*Upper body muscular strength* will be assessed using the hand grip test on a hand dynamometer with an adjustable grip (Hand Grip Digital Dynamometer TKK 5401 Grip D; Takei, Japan). In the standing position and with the elbow in full extension, the participant squeezes the dynamometer gradually and continuously for at least 2 s. The test is performed again with the opposite arm. The

grip span of the dynamometer will be adjusted according to each participant's hand size using an equation specifically developed for adolescents.[30] The grip strength will be recorded in kilograms. The maximum score for the two hands will be used to compute the mean, and the mean will be used for statistical analysis.

*Flexibility* will be assessed using the back-saver sit-and-reach test. The test is performed using a standard box with a small bar, which is pushed forward as the participant reaches forward. Starting from a seated position, the participant bends the trunk and reaches forward as far as possible, with one leg straight and the other bent at the knee. The test is then performed again with the opposite leg. The farthest position of the bar reached for each leg will be scored in centimetres, and the average of the distances for both legs will be used for statistical analysis.

*Speed/agility* will be assessed using the 4×10 m shuttle run test. Two parallel lines are drawn on the floor 10 m apart. The participant runs as fast as possible from the starting line to the other line and returns to the starting line, crossing each line with both feet each time. This is performed twice, covering a total distance of 40 m. Every time while crossing a line, the participant must pick up (the first time) or exchange (second and third times) a sponge placed behind the lines. The stopwatch will be stopped when the participant crosses the end line with one foot. The time taken to complete the test will be recorded to the nearest 0.1 s.

### Physical activity

Daily PA will be assessed using accelerometery, which provides an objective measure of PA in youths.[31] The ActiGraph Monitor (model GT3X; ActiGraph, Pensacola, Florida, USA), which is used widely in clinical and epidemiological studies, will be used to measure daily PA.[32] In children, accelerometer wrist placement promotes better compliance than hip placement.[33] Therefore, the patients will wear the accelerometer on the non-dominant wrist for seven consecutive days in free living conditions during which they will follow their normal daily routine. After the 7 days, the accelerometer will be removed and the data will be downloaded to a personal computer using ActiLife software (V.6.13.4, ActiGraph). Data will be analysed using the R-package GGIR facilitating data cleaning (non-wear detection) and data analysis (time spent in sedentary behaviours and moderate to vigorous PA).[34] Consistent with consensus recommendations for assessing PA in youth, patients who will not report at least 3 days with a minimum of 10 hours of PA per day will be excluded from analyses.[35] Cut-off points developed by Chandler *et al* will be used to translate acceleration counts into min/day of sedentary light PA, moderate PA and vigorous PA.[36]

### Anthropometric data and body composition

The physical examinations will be performed with participants barefoot and wearing underwear. Body weight and height will be measured using an electronic scale and a stadiometer, respectively. BMI will be calculated as body weight (kg) divided by height squared ($m^2$). The BMI class (underweight, normal weight, overweight and obese) will be assessed using the International Obesity Task Force scale.[37]

Body composition (fat mass and fat-free mass) will be assessed using the skinfold thickness method. Skinfolds on the left side of the body will be measured using a Holtain skinfold calliper at the biceps, triceps, subscapular, suprailiac, thigh and medial calf sites. Measurements will be made three times at each site, and the average of the three measurements will be used in the statistical analysis. Fat mass is calculated using the Slaughter equation.[38]

### Questionnaires

Quality of life will be assessed using the PedsQL (version 4.0), which is divided into age groups 8–12 and 13–18 years. Each age group version has 23 questions comprising four dimensions: (1) physical functioning, (2) emotional functioning, (3) social functioning, and (4) school functioning. Fatigue will be assessed using the pedsFACIT-F questionnaire.[39] This questionnaire comprises 13 questions, which are scored using a 5-point Likert scale ranging from 0 (never) to 4 (every time).

### Clinical and biological assessment

A blood sample will be collected by a study nurse for measuring haematocrit, C-reactive protein and albumin concentrations, and erythrocyte sedimentation rate to identify inflammation and calculate disease activity. The PCDAI will be used for patients with CD and the PUCAI for patients with UC, but no measure of disease activity will be used for patients with IBD-U.[26 27] Lastly, during medical examination, the physician will record any events that could influence the PF assessment.

## Outcome measures

The primary outcome is the cardiorespiratory fitness expressed as mL/kg/min. The secondary outcomes are as follows.

*Other PF components*: lower body muscular strength expressed in centimetres, upper body muscular strength expressed in kilograms, speed/agility expressed in seconds and flexibility expressed in centimetres.

*Determinants of IBD*: age at the time of diagnosis, duration of IBD expressed in months; type of IBD (CD, UC or IBD-U); weight status expressed as underweight, normal weight, overweight or obese; height and weight growth expressed in centimetres; and pubertal status expressed as stage and treatment.

*Cardiovascular risk in adulthood* according to sex-specific cut-offs for a healthy cardiorespiratory fitness level in adolescents (43.8 mL·kg/min in boys and 34.6 mL·kg/min in girls).[40]

*Quality of life* expressed as the total score for the PedsQL.

*Fatigue* expressed as the total score of the pedsFACIT-F questionnaire.

*Time spent in moderate to vigorous PA* as expressed as min/day in the participants with IBD.

### Safety outcomes

AEs are undesirable effects occurring during a trial. AEs considered in this trial are those which modify daily PA. All AEs will be recorded in the medical files and reported in the electronic case report form (eCRF), including the nature of each event, date of onset, duration, intensity, assessment of cause, causal relationship with the trial, action taken (eg, need for concomitant treatment) and outcome. According to the severity of AEs, the investigator will determine whether the participant should be withdrawn from the study and which follow-up procedures should be performed.

An SAE is defined as any untoward occurrence or effect that is life threatening, requires prolonged hospitalisation, results in persistent significant disability, leads to a congenital anomaly or birth defect or causes death. For any SAEs noted, the investigator will report (within 24 hours) to the trial sponsor (Vigilance Unit of the Lille University Hospital Research Directorate) using the specific written form and will record the SAE on the eCRF with signature and date.

### Data collection

All data will be recorded by trained clinical investigators and/or the study coordinator using the eCRF developed using Clinsight (ENNOV) software (https://ecrf.chru-lille.fr/CSOnline/). Data safety and security measures at the different study sites will include restricted staff access, password protection and firewall and virus spyware protection. To ensure the data quality, a study monitor from the trial sponsor will verify and cross-check all data against the investigator's source document records. In addition, the data will be monitored by the data management team of the Data Management Department of the Lille University Hospital using the predefined rules. In case of discrepancies, queries will be sent to the investigator and study coordinator for resolution. Data analysis will not be performed until the full database is closed.

#### Sample size calculation

The sample size calculation was based on a previous study reporting a mean cardiorespiratory fitness of 40.8±7.4 mL·kg/min in a healthy paediatric population.[41] Considering a mean decrease in cardiorespiratory fitness of 5 mL·kg/min in youths with IBD compared with their healthy peers as a clinically relevant difference, 50 participants per group are needed to demonstrate this difference using a two-sided t-test at the 0.05 significance level with a power ≥90% and assuming an SD of 7.4 mL·kg/min.[42] As a conservative approach, this sample size calculation did not take into account the matched design.

#### Data analysis strategy

Statistical analysis will be performed by the Biostatistics Department of Lille University Hospital. Data will be analysed using SAS software (release 9.4; SAS Institute, Cary, NC, USA), and all statistical tests will be performed with a two-tailed alpha level of 0.05. Descriptive analysis will be performed using the mean (±SD) or median (IQR) for quantitative variables according to the normality of distributions or using the frequency and percentage for categorical variables. The normality of distributions will be assessed graphically and using the Shapiro-Wilk test.

The primary PF outcome (cardiorespiratory fitness) and all secondary PF outcomes (lower and upper body muscular strength, flexibility, speed and agility) will be compared between patients with IBD and their matched healthy controls using linear mixed models that will include the matched sets as a random effect to account for the matched design and the possibility of missing data. The mean differences with 95% CIs between the patient and control groups will be derived using a linear mixed model to calculate the effect size. In cases of deviation from normality of the linear mixed model residuals, the two groups will be compared using Wilcoxon signed-rank test, and standardised differences will be calculated using rank-transformed data to determine the effect size. The comparisons of secondary PF outcomes will be adjusted for multiple comparisons using the Holm-Bonferroni method.

The percentages of participants classified with cardiovascular risk according to the primary PF outcome (<43.8 mL·kg/min for boys and <34.8 mL·kg/min for girls) will be compared between the two groups using a logistic mixed model including the matched sets as the random effect. The ORs for IBD relative to healthy controls will be derived from the logistic model to calculate the effect size. In cases of failed convergence or low number of events (<10), between-group comparisons will be made using the exact McNemar test. In the IBD group, the association between the primary PF outcome and IBD characteristics, quality of life and daily PA will be assessed using bivariate analyses and Pearson or Spearman rank correlational analysis for quantitative variables, Student's t-test or Mann-Whitney U test for binary categorical variables and one-way analysis of variance or Kruskal-Wallis test for non-binary categorical variables.

## ETHICS AND DISSEMINATION

Before acceptance into the study, the aims and objectives of this study will be carefully explained by the physician, and written informed consent will be obtained from each patient or healthy control and their parents or legal guardians. The study was approved by the Research Ethics Committee (Comité de Protection des Personnes, Centre-Ouest I, Tours, France, No 2019-A02651-56) and the Agence Nationale de Sécurité du Médicament et des Produits de Santé, Paris, France. All procedures will be performed according to the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and the European Union's Guidelines for Good Clinical Practice. According to the General Data Protection Regulation, data collection was approved by the National Commission on Informatics and Liberty (Commission Nationale de l'Informatique et des Libertés). At the end of this study,

all documents (case report forms, patient source documents and written informed consent forms) will be sealed and archived for 15 years at an archiving company (Iron Mountain, Wattrelos, France). In addition, all data from the eCRF will be saved, burned onto a DVD and archived for 15 years. The study protocol has been registered at www.clinicaltrials.gov (NCT04647578).

The outputs of this project will be disseminated in peer-reviewed journals and presented at scientific meetings on nutrition, sport sciences, gastroenterology, paediatric gastroenterology and IBD. One of the key objectives is to make the results available for patients and patient organisations such as the Association François Aupetit (https://www.afa.asso.fr/). The findings of this study will be disseminated in writing and orally (eg, through letters, posters and conferences).

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**Contributors** Design of the study: JV led the development of the original proposal in collaboration with LB, DL, SC and DT. JV, LB, DL, SC, JL and DT contributed to the development of the common protocol and procedures. Coordination of the study: JV, SC, DL, DD and DT. JV, LB, DL and DT wrote the first draft. JV, LB, DL, SC, JL, DT and DD contributed to subsequent drafts, and read and approved the final manuscript.

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**Competing interests** None declared.

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