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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. No study has assessed physical fitness in youths with IBD. 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 (CNIL). 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 NCT04647578.

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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.
- 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.

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INTRODUCTION

Increase in the incidence of paediatric inflammatory bowel disease

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. IBD has become a concern for health epidemiologists because of the increase in its incidence in newly industrialised countries since the 1990s.[1] This also applies to paediatric populations.[2] For example, from 1988 to 2011, the incidence of IBD increased by 126% for CD and 156% for UC among teenagers in northern France.

Consequences of IBD

The high incidence of IBD in children and adolescents can be considered as a public health issue because of the increased health-care consumption and multiple consequences for the global health status.[3] 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.[3-6] 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.[7-8]

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Physical fitness as a marker of health

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".[9] 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 physical fitness includes muscular strength, speed/agility, cardiorespiratory fitness and body composition.[10]

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.[11-14] Low PF is a risk factor for cardiovascular disease and is more important than other known risk factors such as dyslipidaemia, hypertension or obesity.[15] 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.[16-17] By contrast, low muscular strength and cardiorespiratory fitness in adolescence are strongly associated with risk factors for major causes of death in young adulthood.[18-19]

Physical fitness in people with IBD

Only two previous studies of PF and IBD have been published.[20-21] Vogelaar et al. showed that fatigued adults with IBD have impaired PF compared with non-fatigued adults with IBD.[21] Melinder et al. assessed whether fitness in adolescence is associated with subsequent IBD risk independent of markers of risk and prodromal disease activity.[20] They concluded that an inverse association of PF with IBD risk is consistent with a protective role of exercise. To our

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knowledge, no study has assessed PF levels in children and adolescents with IBD compared with those in healthy youths.

Primary and secondary objectives

The main objective of the study is to assess the cardiorespiratory endurance (main component of PF) of children and adolescents with IBD and to compare this with that of age- and sex-matched healthy controls.

The secondary objectives are as follows: (*i*) 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- and sex-matched healthy controls; (*ii*) 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; (*iii*) using published cardiorespiratory fitness thresholds, to assess cardiovascular risk in adulthood in children and adolescents with IBD compared with healthy youths; and (*iv*) to determine whether PF is related to quality of life, fatigue state and daily PA in children and adolescents with IBD.

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 2021 and will be completed in 2023. From 2021 onwards, consecutive paediatric patients with IBD followed in two Northern France university hospitals (Lille and Amiens) have been

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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 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 samples 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; SAE: Serious Adverse Event; PCDAI: Pediatric Crohn's Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Disease Activity Index

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 exams. First, a physical

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examination will be performed, anthropometric measures and body composition will be assessed and a blood sample (8.5 mL) will be drawn. The patients will complete two questionnaires on their quality of life and fatigue. 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 7 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 physical fitness 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: (*i*) age between 10 and 18 years; (*ii*) assent form signed by the patient and informed consent signed by the parents or guardians; and (*iii*)

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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), body mass index (BMI) class status and being sex-matched with a patient with IBD.

The exclusion criteria for both groups are as follows: (*i*) acute or chronic disease (other than IDB) that would interfere with PF assessment; (*ii*) no written assent from the patient or consent by the parents or guardians; or (*iii*) positive blood pregnancy test at the baseline visit. The supplementary exclusion criteria are as follows: (*i*) any recent event (within 15 days) that could affect PF (e.g., sprain, fracture, recent arthritis, anoperineal lesions, severe skin lesions); (*ii*) an active disease (paediatric Crohn's disease activity index (PCDAI) >30 for patients with CD and or paediatric ulcerative colitis activity index (PUCAI) >35 for patients with UC).[22-23]

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.[24]

Cardiorespiratory fitness will be assessed using a 20 m shuttle run test.[25] 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.h^{-1}, and this will be increased by 0.5 km.h^{-1} 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

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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 cm. 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 handgrip 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.[26] The grip strength will be recorded in kg. 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 cm, and the average of the distances for both legs will be used for statistical analysis.

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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.[27] The ActiGraph Monitor (model GT3X; ActiGraph, Pensacola, FL, USA), which is used widely in clinical and epidemiological studies, will be used to measure daily PA.[28] In children, accelerometer wrist placement promotes better compliance than hip placement.[29] Therefore, the patients will wear the accelerometer on the non-dominant wrist for 7 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 (version 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).[30]

Body composition

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

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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.[31]

Questionnaires

Quality of life will be assessed using the Pediatric Quality of Life Inventory (PedsQL; version 4.0), which is divided into age groups 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. Fatigue will be assessed using the pediatric Functional Assessment of Chronic Illness Therapy-Fatigue (pedsFACIT-F) questionnaire.[32] This questionnaire comprises 13 questions, which are scored using a five-point Likert scale ranging from 0 (never) to 4 (every time).

Clinical and biological assessment

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.[33] 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.[22-23] Lastly, during medical examination, the physician will record any events that could influence the PF assessment.

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Outcome measures

The primary outcome is the cardiorespiratory fitness expressed as mL.kg.min^{-1}. The secondary outcomes are as follows.

Other PF components: lower-body muscular strength expressed in cm, upper-body muscular strength expressed in kg, speed/agility expressed in s, and flexibility expressed in cm.

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 cm; 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^{-1} in boys and 34.6 mL.kg.min^{-1} in girls).[34]

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^{-1} in the participants with IBD.

Safety outcomes

AEs are undesirable effects occurring during a trial. 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 (e.g., 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.

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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 h) 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 co-ordinator 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^{-1} in a healthy paediatric population.[35] Considering a mean decrease in cardiorespiratory fitness of 5 mL.kg.min^{-1} 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

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≥90% and assuming a standard deviation of 7.4 mL.kg.min^{-1}. 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 (SAS Institute Inc, 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 (±standard deviation) or median (interquartile range) 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% confidence intervals 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's signed-rank test, and standardised differences will be calculated using rank-transformed data to determine the effect size. The comparisons of secondary physical fitness 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^{-1} for boys and <34.8 mL.kg.min^{-1} for girls) will be compared between the two groups using a logistic mixed model including the matched sets as the random

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effect. The odds ratios 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, number 2019-A02651-56) and the Agence Nationale de Sécurité du Médicament et des Produits de Santé, Paris, France (ANSM). 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 (CNIL). 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).

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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 (e.g., through letters, posters and conferences).

Authors' contributions

Design of the study: JV led 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. Wrote the manuscript: JV, LB, DL and DT wrote the first draft. JV, LB, DL, SC, JL, DT and DD contributed to subsequent drafts, read and approved the final manuscript. Patients and public were not involved in this contribution.

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Competing interests statement.

The authors have no competing interests.

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Data sharing statement

Data are available upon reasonable request. Data will be made available following the conclusion of the project's period of funding.

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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 (CNIL). 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 NCT04647578.

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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 to 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.

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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 etiology 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 health-care 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

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mainly to assess physical performance in sport practitioners; and the other related to health. Health-related physical fitness 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 physical activity (PA).[23-24] A systematic review concluded that children with IBD are less active than healthy children and spend more time in sedentary behaviors.[25] These patterns may lead to reduced PF levels in youth with IBD. Therefore, we hypothesized that PF levels are lower in children and adolescents with IBD compared to their age- and sex-matched healthy controls.

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Primary and secondary objectives

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

The secondary objectives are as follows: (*i*) 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- and sex-matched healthy controls; (*ii*) 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; (*iii*) using published cardiorespiratory fitness thresholds, to assess cardiovascular risk in adulthood in children and adolescents with IBD compared with healthy youths; and (*iv*) to determine whether PF is related to quality of life, fatigue state and daily PA in children and adolescents with IBD.

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 2020 and will be completed in 2023. 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 1. Flow chart of the study for children with IBD

Visit	(V-1)	V1	V2† (+ 7 days)

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Information process	X		
Written consent process		X	
Inclusion and exclusion criteria review		X	
Clinical assessment		X	
Vital signs assessment		X	
Anthropometric measurements		X	
Blood samples 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; SAE: Serious Adverse Event; PCDAI: Pediatric Crohn's Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Disease Activity Index

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 exams. First, a physical examination will be performed, anthropometric measures (height, weight and BMI) and body composition (skinfolds 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 (PedsQL) and 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 7 consecutive days to provide an assessment of their PA.

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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 physical fitness 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: (*i*) age between 10 and 18 years; (*ii*) assent form signed by the patient and informed consent signed by the parents or guardians; and (*iii*) 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), body mass index (BMI) class status and being sex-matched with a patient with IBD.

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The exclusion criteria for both groups are as follows: (*i*) acute or chronic disease (other than IBD) that would interfere with PF assessment; (*ii*) no written assent from the patient or consent by the parents or guardians; or (*iii*) positive blood pregnancy test at the baseline visit. The supplementary exclusion criteria are as follows: (*i*) any recent event (within 15 days) that could affect PF (e.g., sprain, fracture, recent arthritis, anoperineal lesions, severe skin lesions); (*ii*) an active disease (paediatric Crohn's disease activity index (PCDAI) >30 for patients with CD and or paediatric 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 $km.h^{-1}$, and this will be increased by 0.5 $km.h^{-1}$ 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

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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 cm. 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 handgrip 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 kg. 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 cm, 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

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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, FL, 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 7 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 (version 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 three 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 minutes per day of sedentary, light (LPA), moderate (MPA), and vigorous PA (VPA).[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

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(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 Pediatric Quality of Life Inventory (PedsQL; version 4.0), which is divided into age groups 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. Fatigue will be assessed using the pediatric Functional Assessment of Chronic Illness Therapy-Fatigue (pedsFACIT-F) questionnaire.[39] This questionnaire comprises 13 questions, which are scored using a five-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.

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Outcome measures

The primary outcome is the cardiorespiratory fitness expressed as mL.kg.min^{-1}. The secondary outcomes are as follows.

Other PF components: lower-body muscular strength expressed in cm, upper-body muscular strength expressed in kg, speed/agility expressed in s, and flexibility expressed in cm.

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 cm; 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^{-1} in boys and 34.6 mL.kg.min^{-1} 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^{-1} in the participants with IBD.

Safety outcomes

Adverse Events (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 (e.g., need for concomitant treatment) and outcome. According to the severity of AEs, the

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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 h) 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 co-ordinator 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^{-1} in a healthy paediatric population.[41] Considering a mean decrease in cardiorespiratory fitness of 5 mL.kg.min^{-1} in youths with IBD compared with their

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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 a standard deviation of 7.4 mL.kg.min^{-1}.[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 (SAS Institute Inc, 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 (±standard deviation) or median (interquartile range) 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% confidence intervals 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's signed-rank test, and standardised differences will be calculated using rank-transformed data to determine the effect size. The comparisons of secondary physical fitness outcomes will be adjusted for multiple comparisons using the Holm–Bonferroni method.

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The percentages of participants classified with cardiovascular risk according to the primary PF outcome (<43.8 mL.kg.min^{-1} for boys and <34.8 mL.kg.min^{-1} for girls) will be compared between the two groups using a logistic mixed model including the matched sets as the random effect. The odds ratios 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, number 2019-A02651-56) and the Agence Nationale de Sécurité du Médicament et des Produits de Santé, Paris, France (ANSM). 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 (CNIL). 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

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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 (e.g., through letters, posters and conferences).

Authors' contributions

Design of the study: JV led development of the original proposal in collaboration with LB, DL, SC, FG and DT. JV, LB, DL SC, JL, FG and DT contributed to the development of the common protocol and procedures. Coordination of the study: JV, SC, DL,, FG DD and DT. Wrote the manuscript: JV, LB, FG, DL and DT wrote the first draft. JV, LB, DL, SC, JL, FG, DT and DD contributed to subsequent drafts, read and approved the final manuscript. Patients and public were not involved in this contribution.

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Competing interests statement.

The authors have no competing interests.

Data sharing statement

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Data are available upon reasonable request. Data will be made available following the conclusion of the project's period of funding.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Page 1 Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Page 2, 16 Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
N/A	2b	All items from the World Health Organization Trial Registration Data Set
N/A Protocol version	3	Date and version identifier
Page 17 Funding	4	Sources and types of financial, material, and other support
Page 1, 17 Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
Page 17	5b	Name and contact information for the trial sponsor
Page 17	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
N/A	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Page 4-6 Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
N/A	6b	Explanation for choice of comparators
Page 5-6 Objectives	7	Specific objectives or hypotheses
Page 6-7 Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

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	Methods: Participants, interventions, and outcomes		
Page 6	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Page 8-9	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
NA	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
Page 13		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
NA		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
Page 13-14		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Page 12-13	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Page 6,7	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Page 14-15	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Page 6-8	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
NA	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

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NA	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
NA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
N/A	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
N/A		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
Page 9-12	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
Page 6-7		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Page 14	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Page 15-16	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
N/A		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
NA		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
N/	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

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N/A		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Page 8, 12	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
N/A	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
Page 15-16	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
N/A	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Page 15	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
N/A		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Page 13	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Page 21	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Page 13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
N/A	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Page 16	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
N/A		31b	Authorship eligibility guidelines and any intended use of professional writers
N/A		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

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Appendices

~~N/A~~ Page 8	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
N/A	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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

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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 (CNIL). 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 NCT04647578.

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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 to 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.

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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 etiology 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 health-care 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

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mainly to assess physical performance in sport practitioners; and the other related to health. Health-related physical fitness 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 physical activity (PA).[23-24] A systematic review concluded that children with IBD are less active than healthy children and spend more time in sedentary behaviors.[25] These patterns may lead to reduced PF levels in youth with IBD. Therefore, we hypothesized that PF levels are lower in children and adolescents with IBD compared to their age- and sex-matched healthy controls.

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Primary and secondary objectives

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

The secondary objectives are as follows: (*i*) 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- and sex-matched healthy controls; (*ii*) 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; (*iii*) using published cardiorespiratory fitness thresholds, to assess cardiovascular risk in adulthood in children and adolescents with IBD compared with healthy youths; and (*iv*) to determine whether PF is related to quality of life, fatigue state and daily PA in children and adolescents with IBD.

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 1. Flow chart of the study for children with IBD

Visit	(V-1)	V1	V2† (+ 7 days)

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Information process	X		
Written consent process		X	
Inclusion and exclusion criteria review		X	
Clinical assessment		X	
Vital signs assessment		X	
Anthropometric measurements		X	
Blood samples 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; SAE: Serious Adverse Event; PCDAI: Pediatric Crohn's Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Disease Activity Index

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 exams. First, a physical examination will be performed, anthropometric measures (height, weight and BMI) and body composition (skinfolds 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 (PedsQL) and 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 7 consecutive days to provide an assessment of their PA.

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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 physical fitness 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: (*i*) age between 10 and 18 years; (*ii*) assent form signed by the patient and informed consent signed by the parents or guardians; and (*iii*) 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), body mass index (BMI) class status and being sex-matched with a patient with IBD.

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The exclusion criteria for both groups are as follows: (*i*) acute or chronic disease (other than IBD) that would interfere with PF assessment; (*ii*) no written assent from the patient or consent by the parents or guardians; or (*iii*) positive blood pregnancy test at the baseline visit. The supplementary exclusion criteria are as follows: (*i*) any recent event (within 15 days) that could affect PF (e.g., sprain, fracture, recent arthritis, anoperineal lesions, severe skin lesions); (*ii*) an active disease (paediatric Crohn's disease activity index (PCDAI) >30 for patients with CD and or paediatric 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 $km.h^{-1}$, and this will be increased by 0.5 $km.h^{-1}$ 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

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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 cm. 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 handgrip 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 kg. 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 cm, 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

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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, FL, 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 7 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 (version 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 three 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 minutes per day of sedentary, light (LPA), moderate (MPA), and vigorous PA (VPA).[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

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(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 Pediatric Quality of Life Inventory (PedsQL; version 4.0), which is divided into age groups 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. Fatigue will be assessed using the pediatric Functional Assessment of Chronic Illness Therapy-Fatigue (pedsFACIT-F) questionnaire.[39] This questionnaire comprises 13 questions, which are scored using a five-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.

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Outcome measures

The primary outcome is the cardiorespiratory fitness expressed as mL.kg.min^{-1}. The secondary outcomes are as follows.

Other PF components: lower-body muscular strength expressed in cm, upper-body muscular strength expressed in kg, speed/agility expressed in s, and flexibility expressed in cm.

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 cm; 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^{-1} in boys and 34.6 mL.kg.min^{-1} 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^{-1} in the participants with IBD.

Safety outcomes

Adverse Events (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 (e.g., need for concomitant treatment) and outcome. According to the severity of AEs, the

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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 h) 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 co-ordinator 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^{-1} in a healthy paediatric population.[41] Considering a mean decrease in cardiorespiratory fitness of 5 mL.kg.min^{-1} in youths with IBD compared with their

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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 a standard deviation of 7.4 mL.kg.min^{-1}.[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 (SAS Institute Inc, 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 (±standard deviation) or median (interquartile range) 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% confidence intervals 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's signed-rank test, and standardised differences will be calculated using rank-transformed data to determine the effect size. The comparisons of secondary physical fitness outcomes will be adjusted for multiple comparisons using the Holm–Bonferroni method.

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The percentages of participants classified with cardiovascular risk according to the primary PF outcome (<43.8 mL.kg.min^{-1} for boys and <34.8 mL.kg.min^{-1} for girls) will be compared between the two groups using a logistic mixed model including the matched sets as the random effect. The odds ratios 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, number 2019-A02651-56) and the Agence Nationale de Sécurité du Médicament et des Produits de Santé, Paris, France (ANSM). 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 (CNIL). 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

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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 (e.g., through letters, posters and conferences).

Authors' contributions

Design of the study: JV led development of the original proposal in collaboration with LB, DL, SC, FG and DT. JV, LB, DL SC, JL, FG and DT contributed to the development of the common protocol and procedures. Coordination of the study: JV, SC, DL,, FG DD and DT. Wrote the manuscript: JV, LB, FG, DL and DT wrote the first draft. JV, LB, DL, SC, JL, FG, DT and DD contributed to subsequent drafts, read and approved the final manuscript. Patients and public were not involved in this contribution.

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Competing interests statement.

The authors have no competing interests.

Data sharing statement

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Data are available upon reasonable request. Data will be made available following the conclusion of the project's period of funding.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Page 1 Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Page 2, 16 Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
N/A	2b	All items from the World Health Organization Trial Registration Data Set
N/A Protocol version	3	Date and version identifier
Page 17 Funding	4	Sources and types of financial, material, and other support
Page 1, 17 Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
Page 17	5b	Name and contact information for the trial sponsor
Page 17	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
N/A	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Page 4-6 Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
N/A	6b	Explanation for choice of comparators
Page 5-6 Objectives	7	Specific objectives or hypotheses
Page 6-7 Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

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	Methods: Participants, interventions, and outcomes		
Page 6	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Page 8-9	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
NA	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
Page 13		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
NA		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
Page 13-14		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Page 12-13	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Page 6,7	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Page 14-15	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Page 6-8	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
NA	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

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NA	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
NA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
N/A	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
N/A		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
Page 9-12	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
Page 6-7		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Page 14	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Page 15-16	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
N/A		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
NA		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
N/	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

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N/A		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Page 8, 12	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
N/A	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
Page 15-16	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
N/A	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Page 15	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
N/A		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Page 13	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Page 21	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Page 13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
N/A	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Page 16	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
N/A		31b	Authorship eligibility guidelines and any intended use of professional writers
N/A		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

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Appendices

~~N/A~~ Page 8	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
N/A	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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