Full title: Randomised clinical trial: Combined impact and resistance training in adults with stable Crohn's disease

Short title: Exercise training and Crohn's disease

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Guarantor of the article: None.

Author contributions: GAT and KJ wrote the protocol. KB, RAS and NT refined the protocol. GAT was the Chief Investigator and oversaw the study. KJ was the trial manager and intervention facilitator. KB was the main academic supervisor for KJ. RAS and NT recruited participants to the study and provided clinical oversight. GAT wrote the first draft of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Summary

Background: Crohn's disease (CD) is a predisposing factor for bone and muscle dysfunction, which could lead to osteoporotic fractures and physical disability, respectively.

Aim: To assess the effect of 6 months of combined impact and resistance training on bone mineral density (BMD) and muscle function in adults with CD.

Methods: In this randomised controlled trial, 47 adults with stable CD were assigned to exercise (n=23) or control (n=24) groups and followed for 6 months. The exercise group received usual care plus a 6-month combined impact and resistance training programme, involving three, 60-minute sessions per week and a gradual tapering of supervision to self-management. The control group received usual care alone. The primary outcomes were BMD (via dual energy X-ray absorptiometry) and muscle function (measures of upper- and lower-limb strength and endurance) at 6 months.

Results: At 6 months, BMD values were superior in the exercise group with statistical significance at lumbar spine (adjusted mean difference 0·036 g/cm^2, 95% CI 0·024–0·048; p<0·001), but not at femoral neck (0·018 g/cm^2, 0·001–0·035; p=0·059) or greater trochanter (0·013 g/cm^2, -0·019–0·045; p=0·415) after correcting for multiple outcomes. The exercise group also had superior values for all muscle function outcomes (p<0·001; unadjusted mean differences ranging 22.6–48.2%), and lower fatigue severity (p=0·005). Three exercise-related adverse events were recorded: two instances of light-headedness and one of nausea.

Conclusions: The intervention improved BMD and muscle function in adults with CD and appears a suitable model of exercise for reducing future risk of osteoporotic fractures and disability.

Trial registration: ISRCTN11470370

Key words: randomized controlled trial; inflammatory bowel disease; exercise

1. INTRODUCTION

People with Crohn's disease (CD) have an increased risk of osteoporosis and osteoporotic fractures compared with the general population.[1] Factors contributing to bone loss in CD include chronic inflammation, reduced vitamin and mineral absorption, extensive small-bowel disease or resection, corticosteroid use, older age, physical inactivity, smoking, and nutritional deficiencies.[2] Bone mineral density (BMD) is one of the most important determinants of fracture risk, accounting for 60-70% of the variance in bone strength.[3] A 2016 Guideline/Consensus paper from the European Crohn's and Colitis Organisation (ECCO) stated that weight-bearing exercise, stopping smoking, and maintaining adequate dietary calcium (1g/day) may help to prevent bone loss in inflammatory bowel disease;[4] however, few prospective trials of preventative interventions have been conducted in this increased-risk group.

Physical activity and exercise are important determinants of bone health.[5] Gravity-derived impact loads and muscle forces during exercise produce strain within the axial skeleton, which is osteogenic, stimulating bone formation.[6] Observational studies and randomised controlled trials (RCTs) indicate that physical activity and exercise can have beneficial effects on bone mass and strength across the age spectrum, thus reducing the risk of fractures.[5] Load intensity is one of the most important training variables, with guidelines and evidence syntheses indicating that adults should undertake a combination of impact activities (e.g. jumping) and high-intensity resistance training to optimise bone health.[7-9] Resistance training can also improve muscle mass and function,[8] which may be of importance in CD where low muscle mass and strength is common and predictive of osteopenia/osteoporosis.[10,11]

Empirical evidence on the effects of exercise in CD is sparse, with only a handful of intervention studies, all of with have focused on modes of exercise that are sub-optimal for improving bone health (e.g. walking, cycling, yoga).[12] Only one RCT has investigated the effect of exercise on BMD, but the intervention was low-impact resistance training, i.e. not a specific bone-loading programme.[13] To address this evidence gap, we conducted an RCT called PROTECT (PROgressive resistance Training Exercise and Crohn's disease Trial), which aimed to evaluate the effects of a 6-month combined

impact and resistance training programme on BMD and muscle function in adults with CD. The programme was designed to be practical to deliver by including a gradual tapering of supervision to self-management. Secondary aims were to explore the safety of the exercise programme and its effects on other health markers (e.g. fatigue, health-related quality of life), and to evaluate differences in BMD and muscle function between patients and matched healthy controls.

2. METHODS

2.1 Study design

PROTECT was a two-arm, randomised, parallel-group, and assessor-blind trial. Participants were randomised 1:1 to receive usual care plus a 6-month impact and resistance training programme (intervention) or usual care only (control). Study assessments were conducted at baseline and at 3 and 6 months after randomisation. Recruitment was from a large Hospital Trust in Northern England: Newcastle upon Tyne Hospitals NHS Foundation Trust. The exercise and assessment sessions were delivered in the exercise science facilities of Northumbria University. The trial was prospectively registered with the International Standard Randomised Controlled Trial Number registry, number ISRCTN11470370. Ethics approval was granted by the North East - Tyne & Wear South Research Ethics Committee (reference 17/NE/0308).

2.2 Participants

We included male and female patients aged 16 years or older with a clinical diagnosis of CD. Patients had to have a stool calprotectin of <250 μg/g, stable medication (>4 weeks), and quiescent or mildly-active disease, as indicated by a Crohn's Disease Activity Index (CDAI) of <150 or 150–219, respectively. Exclusion criteria were contraindication to exercise testing or training,[14] pregnant, planned pregnancy or major surgery within the first 6 months after randomisation, and current

participation in 2 or more sessions per week of resistance exercise (self-reported) or another clinical trial where concurrent participation was deemed inappropriate.

Recruitment methods included liaisons with members of the direct care team during routine hospital appointments, postal invitations to patients who had previously consented to be contacted about future studies, and advertisements in hospital clinics and on social media. All participants provided written informed consent before enrolment.

2.3 Randomisation and masking

Participants were randomly assigned 1:1 to one of the two trial arms using a computer-generated randomisation schedule stratified by gender and baseline disease status (quiescent [CDAI < 150] or mildly-active [CDAI 150–219]). The randomisation process was managed by an investigator at Northumbria University (GT) who was not involved in recruitment, intervention delivery or data collection. A researcher (KJ) emailed this investigator for notification of group allocation once the participant had consented and completed baseline assessments. Following notification, the researcher contacted the participant to inform them of their allocation. Due to the nature of the intervention, participants and intervention facilitators were not masked to group allocation. Outcome assessors were masked to group allocation, and participants were asked to not disclose their allocation. This instruction was adhered to by all participants.

2.4 Procedures

Both groups received usual care, which comprised evidence-based medical treatment optimisation. Participants allocated to the control group did not receive any supervised exercise or exercise advice during the trial; however, following their final assessment they were offered a telephone-based consultation with a researcher who discussed their individual facilitators/barriers to exercise, and provided general advice on incorporating exercise into their lifestyle.

Participants allocated to the exercise group were encouraged to complete three, 60-minute exercise sessions on non-consecutive days each week for 26 consecutive weeks, commencing the week following their group allocation. Twelve sessions were supervised and 66 were unsupervised, with a gradual tapering of supervision to self-management as follows: two supervised sessions per week in weeks 1 and 2; one supervised session per week in weeks 3 and 4; one supervised session every fortnight in weeks 5/6 and 7/8; one supervised session every month from week 9 onwards. The supervised sessions aimed to motivate participants to exercise regularly and teach them how to exercise correctly.

Each session involved a warm-up, a main conditioning phase, and a cool-down. The warm-up lasted approximately 5 minutes and included several pulse-raising exercises (e.g. marching on the spot, squat and punch) and dynamic stretches (e.g. big arm circles, forward and backward leg swings). The main conditioning phase lasted approximately 50 minutes and involved a combination of impact and high-effort resistance exercises to maximise improvements in BMD and muscle function.[7-9] The impact exercises included rope skipping (up to 5 minutes) and several multi-directional jumps (e.g. squat jump, broad jump, scissor jump; 2-3 sets of 10-15 repetitions for 5 different jumps). The resistance exercises targeted the major muscle groups of the upper-body, lower-body and mid-section (e.g. squat, lunge, press-up, reverse fly, lateral raise, bicep curl, triceps extension, bridge; 2-3 sets of 10-15 repetitions for 8-10 exercises) with resistance provided using the participant's own body weight and TheraBand® elastic bands. The intended intensity for each set was moderate-to-hard, which was self-rated using the Resistance Intensity Scale for Exercise.[15] The cool-down lasted approximately 5 minutes and included static stretches for the major muscle groups.

Each exercise participant was given four TheraBand elastic bands and a skipping rope to keep. They also received an exercise booklet (see Supporting Information) that included information about how to perform and progress the exercises, tables for self-monitoring of adherence, information about TheraBand care and travelling to the University, and contact details of the research team. Participants were free to contact the intervention facilitator (KJ) by telephone or email at any time with questions.

We had planned to use a telehealth app (Florence; www.getflorence.co.uk/) to send the exercise participants regular motivational messages to support exercise adherence, but this was unavailable during the period of intervention delivery. The intervention facilitator did however contact these participants every 4 weeks to provide motivation and support.

Face-to-face assessment visits were conducted before (baseline), and 3 and 6 months after group allocation. Demographic and clinical characteristics were assessed at baseline only. The following outcomes were assessed at baseline and both follow-up time-points: muscle function, body mass, stature, resting blood pressure and heart rate, health-related quality of life, fatigue, physical activity, and medications. BMD was assessed at baseline and 6 months only. Adverse events and exercise enjoyment were assessed at the two follow-up time-points. The acceptability of the intervention was also assessed using participant feedback via telephone interviews conducted after the 6-month assessments.

With local institutional approval, 33 healthy adults were also recruited from the local community to allow a case-control comparison of BMD, muscle function and quality of life outcomes using the trial participants' baseline data. Participants were matched for age (+/-5 years), gender, physical activity status, body mass index category, and ethnicity. Healthy control participants completed the assessments twice, one week apart, to allow test-retest reliability statistics (two-way random effects intra-class correlation coefficient, ICC) to be calculated. ICC values of between 0·75 and 0·90 and greater than 0·90 were considered indicative of good and excellent reliability, respectively.

2.5 Outcomes

The primary outcomes were BMD and muscle function at 6 months. BMD (in g/cm^2) was assessed at the hip (left femoral neck and greater trochanter; both ICC=0·999) and lumbar spine (L2-L4; ICC=0·998) using dual energy X-ray absorptiometry (Horizon DXA System, Hologic, UK). Muscle function was assessed using several measures of upper-body and lower-body strength and endurance. Grip strength (in kg) of the non-dominant hand was assessed as the best of three attempts using a

calibrated Jamar® hydraulic hand dynamometer (ICC=0·992). Lower-body muscular endurance was assessed using a chair stand test,[16] in which participants complete as many sit-to-stand repetitions as they can in 30 seconds (ICC=0·881). Upper-body muscular endurance was assessed using an arm curl test,[16] in which participants complete as many full-range curls of their non-dominant arm as they can in 30 seconds while holding a dumbbell (5 lb for women, 8 lb for men; ICC=0·875). Isokinetic strength of knee extensors and elbow flexors was assessed as peak torque (in Nm) measured during maximal voluntary actions at two angular velocities (3-5 repetitions at 60 and 180 °/s for knee extension, 3-5 repetitions at 60 and 120 °/s for elbow flexion) on an isokinetic dynamometer (System 4 Pro, Biodex, UK). Peak torque values from both limbs were averaged for use in the analysis (ICC=0·931 to 0·991).

Resting blood pressure and heart rate were assessed using an automated monitor (V100 Dinamap Vital Signs Monitor, GE Carescape, UK). Disease-specific health-related quality of life was assessed using the total score on the long version of the Inflammatory Bowel Disease Quality of Life Questionnaire (IBDQ).[17] Generic health-related quality of life was assessed using the EQ-5D-5L utility index.[18] Fatigue was assessed using the Fatigue Assessment Scale from the IBD Fatigue (IBD-F) Scale.[19] Physical activity was assessed as minutes per week of physical activity using the Scottish Physical Activity Questionnaire.[20] Exercise enjoyment was assessed using the total and sub-scale scores on the Physical Activity Enjoyment Scale.[21] We documented all serious adverse events, and all non-serious adverse events that were either deemed to be related to participation in the research or resulted in withdrawal from the exercise programme or study. An event was classed as serious if it met any of the following criteria: fatal; life threatening (i.e. event in which patient is at risk of death at the time of the event occurring); requiring unplanned or prolonged hospitalisation; resulting in persistent or significant disability or incapacity; or resulting in a congenital abnormality or birth defect. Non-serious adverse events were defined as any untoward medical occurrence that did not fulfil any of the serious adverse event criteria.

2.6 Statistical considerations

We used the distribution-based approach for the sample size calculation because a minimum clinically important difference has not been established for BMD in adults with CD. A target difference of 0·4 SD (i.e. a small-to-moderate effect) was selected because this effect size was reported for femoral neck BMD in a meta-analysis of combined impact and resistance training programmes in post-menopausal women.[9] Using the sample size calculation methods of Borm et al.,[22] and assuming 80% power, a two-sided α level of 0·05, and a pre-post correlation between of r=0·9, we required 38 participants in total. Allowing for 20% loss to follow-up at 6 months, we calculated that 50 participants needed to be recruited and randomised.

We used descriptive statistics to show the baseline characteristics of the participants who were enrolled, by treatment group. The effect of the intervention was evaluated using separate analysis of covariance models for the 3- and 6-month outcomes. The outcome at 3 or 6 months was the dependent variable and group (intervention, control) was the independent variable. The baseline value of the outcome, gender and disease activity status were included as covariates.

The primary analysis used a modified intention-to-treat population that included all randomised participants for whom treatment was allocated as per the randomised list regardless of circumstances after randomisation and who had both baseline and follow-up outcome data (i.e., complete-case analysis). Best-case and worst-case sensitivity analyses were also done to explore the impact of missing data, using the group mean plus 1 SD of the group mean as a 'beneficial outcome' and the group mean minus 1 SD of the group mean as a 'harmful outcome'.[23] We report adjusted and unadjusted means for each group and the adjusted mean difference (with 95% CI and p value) between treatment groups at 3 and 6 months. All statistical tests were two-sided at the 5% significance level. In the primary analysis, p-values were corrected for multiple testing using the Benjamini-Hochberg procedure.[24]All analyses were performed using IBM SPSS Statistics (version 24, IBM Corporation, UK).

3. RESULTS

Between February 20, 2018, and March 14, 2019, we screened 76 individuals, of whom 47 were recruited and randomly assigned to the exercise or control groups (Figure 1). Forty-three (91%) participants completed the trial, achieving our target sample size. Table 1 shows the participant characteristics at baseline. Thirty-two (68%) participants were female and the mean age was 49·3 years (SD 13·0). All participants were of white ethnicity, none were current smokers, and most had quiescent disease (66%) and were in paid employment (55%). The median time since diagnosis was 216 months (IQR 60-388). Based on the baseline BMD measurements, 12 (25%) participants had evidence of osteopenia or osteoporosis at the lumbar spine and 20 (43%) at the left hip. The most common medications used for CD were immunosuppressants (43%) and biologics (40%), and no participants were taking corticosteroids. Twenty-seven (58%) participants had received one or two prior resections for CD, whereas seven (15%) had received three or more. Seven (15%) participants had a stoma.

Of the 1,716 exercise sessions that were prescribed in total, 1,057 (62%) were completed (214/264 [81%] supervised, 843/1,452 [58%] unsupervised). The median (IQR) number of exercise sessions completed by each participant was 50 (36-59) out of a possible 78 (10/12 [8-12] supervised, 39/66 [24-48] unsupervised). This corresponds to an average of 2 sessions each week, which is consistent with physical activity guidelines for the general adult population.[25] The mean (SD) total PACES enjoyment scores at 3 and 6 months out of a possible 126 were 104 (13) and 104 (15), respectively, demonstrating a high level of enjoyment (see Supporting Information figures 1 and 2 for PACES sub-item data). The most commonly cited reasons for sessions being missed were work-related tiredness (46 sessions), holiday (30 sessions) and work commitments (26 sessions).

Twenty-one exercise participants completed a telephone interview after the 6-month follow-up. All interviewees provided positive feedback and said that they would recommend the programme to other people with CD. Most/all of the participants expressed that the exercise intervention had an appropriate frequency of sessions (n=19), duration of sessions (n=20), intensity of training (n=20),

mode of training (n=21), and overall programme duration (n=19). Two participants thought that thrice weekly was too often to fit in with their lifestyle, one thought that 60-minute sessions were too long, one thought that the sessions were too hard for their level of fitness, and two thought that the programme duration should be greater than 6 months. Table 2 shows summary statistics for primary and secondary outcome measures at each assessment time-point. Figure 2 shows 6-month percentage change scores in primary outcome measures. Tables 3 and 4 show adjusted means and group differences for primary and secondary outcome measures, respectively. Forty-three (91·5%) participants (n=22 exercise group, n=21 control group) provided complete outcome datasets at 3 and 6 months.

In the trial, at 6 months, the BMD values for the exercise group were superior to those for the control group with statistical significance at lumbar spine (adjusted mean difference 0·036 g/cm^2, 95% CI 0·024 to 0·048; p<0.001), but not at femoral neck (adjusted mean difference 0·018 g/cm^2, 95% CI 0·001 to 0·035; p=0·059) or greater trochanter (adjusted mean difference 0·013 g/cm^2, 95% CI -0·019 to 0·045; p=0·415) after correcting for multiple outcomes. When expressed as a percentage change from baseline, unadjusted mean differences were as follows: lumbar spine 3·8% (95% CI 2·6 to 5·1, p<0·001), femoral neck 2·3% (95% CI 0·4 to 4·1, p=0·018), and greater trochanter 1·4% (95% CI -2·2 to 5·1, p=0·426). Post-hoc exploratory analyses revealed a moderately-strong association between the number of exercise sessions completed and the 6-month change score for lumber spine BMD (r=0.563, p=0.006) and femoral neck BMD (r=0.453, p=0.034), but not for greater trochanter BMD (r=0.090, p=0.691). All muscle function outcomes were also superior in the exercise group at 6 months (Table 3; unadjusted mean differences ranging from 22.6% to 48.2%). For example, adjusted mean differences were 8·3 kg grip strength (95% CI 6·2 to 10·5; p<0·001), 4 repetitions for the chair stand test (95% CI 3 to 6; p<0·001), and 7 repetitions for the bicep curl test (95% CI 5 to 8; p<0·001).

At 3 months, all muscle function outcomes were superior in the exercise group (Table 4). For example, adjusted mean differences were 12·9 Nm for isokinetic knee extension at 60°/s (95% CI 2·5 to 23·3; p=0·016) and 5·2 Nm for isokinetic elbow flexion at 60°/s (95% CI 2·8 to 7·6; p<0·001). There were no between-group differences at either time-point for systolic blood pressure, diastolic

blood pressure or physical activity (Table 4). Resting heart rate values were lower in the exercise group at both 3 and 6 months (adjusted mean differences -5 [95% CI -10 to 0] and -6 beats/min [95% CI -12 to -1], respectively; both p=0·032). Measuring disease-specific health-related quality of life with the IBDQ total score, we saw evidence of improvement in the exercise group at 3 months (adjusted mean difference 17, 95% CI 7 to 26; p=0·001), but this difference was not evident at 6 months (adjusted mean difference 6, 95% CI -3 to 15; p=0·175). Generic health-related quality of life, assessed using the EQ-5D utility index was superior in the exercise group at both 3 and 6 months (adjusted mean differences 0·117 [95% CI 0·023 to 0·211, p=0·016] and 0·109 [95% CI 0·038 to 0·181, p=0·004], respectively). Fatigue (IBD-F score) was lower in the exercise group at 6 months (adjusted mean difference -2, 95% CI -4 to -1; p=0·005), but not 3 months (adjusted mean difference -1, 95% CI -3 to 1; p=0·249).

Three exercise-related adverse events were recorded: two instances of light-headedness and one of nausea. Other adverse events, which were recorded but deemed unrelated to the research, included a transient ischaemic attack (exercise group), a disease flare-up (control group), and an allergic reaction to Infliximab (control group). The latter two resulted in withdrawal from the study. At 6 months, the median (IQR) scores for CDAI and faecal calprotectin were 76 (31-104) and 34 (26-97), respectively, for the exercise group and 116 (62-165) and 141 (59-245), respectively, for the control group. One control participant experienced disease relapse between baseline and 6 months, as defined by an increase in CDAI of ≥100 points to a score ≥150.

Data for the best-case and worst-case sensitivity analyses are shown in tables 1 and 2 of the Supporting Information file, respectively. The effect sizes and significance values were not substantially altered for any of the muscle function outcomes. The BMD outcomes appeared more sensitive to missing data; for example, effect sizes for lumbar spine and femoral neck BMD at 6 months were increased in the best-case sensitivity analysis (adjusted mean differences 0·085 g/cm^2 [95% CI 0·027 to 0·124, p=0·005] and 0·052 g/cm^2 [95% CI 0·010 to 0·095, p=0·017], respectively), and reduced in the worst-case sensitivity analysis (adjusted mean differences 0·014 g/cm^2 [95% CI -0·030 to 0·059, p=0·521] and 0·006 g/cm^2 [95% CI -0·026 to 0·037, p=0·704], respectively).

Data for the case-control comparisons are presented in tables 3 and 4 of the Supporting Information file. The trial participants (n=33) and healthy controls (n=33) were well matched for age, gender, ethnicity, body mass index, smoking status, and blood pressure; however, resting heart rate was higher in trial participants (79 [9] versus 70 [13] beats/min; p=0·002). Compared with the healthy controls, trial participants had lower BMD values at the lumbar spine (0·957 [0·116] versus 1·020 [0·143] g/cm^2) and femoral neck (0·734 [0·122] versus 0·796 [0·160] g/cm^2). The mean difference adjusting for age, gender, smoking status and physical activity was 0·066 g/cm^2 (95% CI 0·003 to 0·129; p=0·040) and 0·063 g/cm^2 (95% CI 0·001 to 0·125; p=0·045), respectively. The between-group difference in greater trochanter BMD was small and non-significant (Supporting Information, table 4). Trial participants had inferior scores for all of the muscle functions outcomes except isokinetic elbow flexion (Supporting Information, table 4). For example, grip strength was 32·7 kg (11·3) in trial participants and 35·7 kg (11·7) in healthy control (adjusted mean difference 3·3 kg, 95% CI 0·2 to 6·3; p=0·037). The EQ5D utility index scores also indicated that, at baseline, trial participants had lower health-related quality of life (adjusted mean difference 0·098, 95% CI 0·032 to 0·165; p=0·004).

4. DISCUSSION

In this RCT involving adults with quiescent or mildly-active CD, the offer of a combined impact and resistance exercise programme with gradual tapering of supervision to independent practice improved BMD and muscle function at 6-month follow-up compared with usual care control. The intervention was also associated with improvements in generic health-related quality of life and fatigue at 6 months. The exercise programme required minimal direct supervision and appeared acceptable and safe for participants.

Consensus guidelines on the management of inflammatory bowel disease state that weight-bearing and resistive exercises should be promoted to help prevent bone loss.[4,26] However, specific exercise prescriptions are not provided, and the recommendation is based largely on research in the general population.[27] Findings from the general population are unlikely to be generalisable to people with CD because this condition can pose specific barriers to participation in exercise (e.g. fatigue, abdominal pain, faecal urgency, perianal symptoms[28]) and can have disease-specific effects that limit improvements in BMD and muscle function (e.g. chronic inflammation, reduced vitamin and mineral absorption).[2] PROTECT therefore provides novel data on the feasibility and efficacy of a specific bone-loading exercise programme in this population, which may help guide clinical practice.

Our findings suggest that the exercise programme was acceptable and safe, and that it can improve BMD to a similar extent as to that seen previously in post-menopausal women. For example, the mean treatment effects of 3.8% and 2.3% at the lumbar spine and femoral neck, respectively, are similar to those reported in the recent LIFTMOR trial (4.1% and 2.3%, respectively), which tested an 8-month combined impact and resistance training programme (two supervised 30-minute sessions per of week),[29] and the findings of an earlier meta-analysis from 2015 (1.8% [10 RCTs, n=1147] and 2.4% [7 RCTs, n=940], respectively).[9] Such improvements may be considered as clinically important because a recent meta-regression analysis indicated that a 2% improvement in lumbar spine or femoral neck BMD was associated with a 28% reduction in vertebral fracture risk, and a 15-22% reduction in hip fracture risk.[30] However, it is important to acknowledge that training effects may

disappear if training is discontinued,[31] so exercise training would need to be maintained in the long-term to prevent osteoporosis and osteoporotic fractures in later life.

Skeletal muscle weakness is a peripheral manifestation of CD,[10,11] and a risk factor for falls and fall-related fractures,[32] mobility disability,[33] and major post-operative complications.[34] Consequently, a reduction in the risk of these adverse outcomes may be achieved through exercise programmes that improve muscle function. We have shown that combined impact and resistance training enhances a broad range of muscle function outcomes, including measures of upper- and lower-body muscular strength and endurance, in adults with CD. Therefore, the exercise programme seems to be suitable for improving BMD and muscle function simultaneously. It is also notable that the deficits in muscle function that were observed relative to healthy controls at baseline were no longer apparent at the 6-month follow-up.

Fatigue is a common and burdensome symptom in people with CD, even for those in clinical remission.[35] It can have a negative impact on personal and social life, on work and employment, and the ability to think clearly.[36] At present, there is no consensus on how to manage CD-related fatigue, which may be explained by its varied and incompletely-understood aetiology, and a lack of intervention-based research on this topic.[35] Observational studies have revealed fatigue to be negatively associated with physical activity, cardiorespiratory fitness and muscle strength;[28,37] therefore, highlighting exercise as a candidate intervention. The current study provides support for a beneficial role of exercise by demonstrating that fatigue severity (IBD-F score) was an average of 2 points lower in the exercise group at 6 months (95% CI -4 to -1; p=0·005). Only two other trials have examined the effect of exercise on IBD-related fatigue, with inclusive findings. McNelly et al. conducted a 2×2 factorial trial of self-managed exercise and omega-3 supplementation in 60 adults with inactive IBD.[38] The exercise intervention involved individualised advice to increase physical activity levels by at least 30%, supported goal setting and diary-based monitoring of exercise behaviour. At the 12-week follow-up, fatigue severity, as measured by the IBD-F scale, was lower in participants receiving the exercise intervention versus placebo control (mean difference -2, 95% CI -3·8 to -0·2; p=0·03). However, there was no significant difference in fatigue when measured by the

FACIT-F score (p=0·38). A recent three-arm RCT that explored the feasibility of high-intensity interval training and moderate-intensity continuous training (both on a cycle ergometer) in adults with CD (n=36) also had unclear effects on fatigue (IBD-F score), although the study was underpowered to assess efficacy.[39] Larger studies investigating the effect of exercise training on IBD-related fatigue are warranted.

Although not a primary focus of this study, we also observed that the exercise programme had a beneficial effect on generic health-related quality of life assessed using the EQ-5D utility index (Table 4). Inspection of the summary data in Table 2 indicated that the between-group differences at follow-up were as much explained by a deterioration in quality of life in the control group as an improvement in the intervention group. This was an unexpected finding because the control group had unrestricted access to usual care and did not receive any specific advice against exercising. It also stands in contrast to both our IBDQ data (Table 2) and EQ-5D data from previous studies that have used a similar study design.[39-41] Nevertheless, we cannot totally rule out the potential harm of randomising patients who may be interested in an exercise-based intervention to a comparator group that does not receive exercise. This point is worthy of consideration by researchers designing future trials in this area.

Strengths of this study include the combination of RCT and case-control components, a trial population that appears representative of the wider clinical population,[42] the use of objective and reliable measures to assess BMD and muscle function, and the intervention design, which included an evidence-based exercise prescription for improving bone health and a practical mode of delivery to facilitate translation of the findings into routine practice. However, a limitation was the sole use of BMD to measure changes in bone strength. Although BMD has been shown to account for approximately 60% to 70% of the variation in bone strength, it does not account for other aspects of bone quality such as microarchitecture, the amount of fatigue damage it has sustained, and changes in its bulk material properties. Thus, the potential benefits of exercise on bone strength, when limited to BMD, may be underestimated. Another limitation was that the intervention did not involve any

impact exercises for the upper-limbs (e.g. punching), thus future research should include a focus on upper-body bone health.

In summary, a 6-month combined impact and resistance training programme improved BMD and muscle function in adults with CD. The intervention appears a suitable model of exercise for reducing the future risk of osteoporotic fractures and physical disability in this increased-risk population.

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Table 1. Baseline characteristics

	Exercise (n=23)	Control (n=24)	Total (n=47)
Age (years)	46·1 (11·9)	52·3 (13·6)	49·3 (13·0)
Male gender	7 (30)	8 (33)	15 (32)
Body mass index (kg/m^2)	26·0 (3.1)	27·1 (5·1)	26·6 (4·3)
Employment status			
Working full- or part-time	11 (48)	15 (62·5)	26 (55)
Student	3 (13)	3 (12·5)	6 (13)
Other	9 (39)	6 (25)	15 (32)
CD duration (months)	216 (60-388)	198 (61-374)	216 (60-388)
CD location			
Ileum	5 (22)	10 (42)	15 (32)
Colon	8 (35)	4 (17)	12 (26)
Ileum-colon	9 (39)	9 (37)	18 (38)
Ileum-colon and upper GI	1 (4)	1 (4)	2 (4)
CD behaviour			
Non-stricturing, non-penetrating	14 (61)	17 (71)	31 (66)
Stricturing	5 (22)	6 (25)	11 (23)
Penetrating	4 (17)	1 (4)	5 (11)
CD activity status			
Quiescent	15 (65)	16 (67)	31 (66)
Mildly active	8 (35)	8 (33)	16 (34)
CDAI	98 (50-151)	112 (78-188)	101 (65-159)
Medication for CD			
Immunosuppressants	13 (57)	7 (29)	20 (43)
Biologics	7 (30)	12 (50)	19 (40)
Number of resections			
0	6 (26)	7 (29)	13 (28)
1	10 (43)	11 (46)	21 (45)

2	3 (13)	3 (12·5)	6 (13)
3 or more	4 (17)	3 (12·5)	7 (15)
Stoma	5 (22)	2 (8)	7 (15)
Serum C-reactive protein			
<5 mg/L	22 (96)	21 (87·5)	43 (91)
≥5 mg/L	1 (4)	3 (12·5)	4 (9)
Faecal calprotectin (µg/g)	36 (26-52)	47 (26-139)	41 (26-93)

Data are n (%), mean (SD), and median (IQR). CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; GI = gastrointestinal.

Table 2. Summary of outcomes

	Exercise group			**Control group**		
	Baseline (n=23)	3 months (n=22)	6 months (n=22)	Baseline (n=24)	3 months (n=21)	6 months (n=21)
Bone mineral density (g/cm^2)						
Lumbar spine	1·068 (0·156)	-	1·111 (0·151)	1·037 (0·219)	-	1·032 (0·236)
Greater trochanter	0·728 (0·113)	-	0·737 (0·112)	0·678 (0·102)	-	0·676 (0·108)
Femoral neck	0·812 (0·142)	-	0·845 (0·154)	0·753 (0·129)	-	0·759 (0·129)
Grip strength (kg)	36·4 (13·1)	39·4 (12·1)	42·4 (12·6)	32·2 (12·2)	31·8 (10·8)	31·0 (11·6)
Chair stand test (repetitions)	14 (3)	17 (3)	19 (3)	13 (3)	14 (3)	14 (3)
Arm curl test (repetitions)	16 (3)	20 (3)	24 (3)	16 (4)	17 (4)	17 (3)
Isokinetic strength (Nm)						
Knee extension 60°/s	82·5 (44·0)	98·2 (47·5)	104·3 (52·6)	74·9 (36·2)	77·9 (38·4)	74·4 (34·7)
Knee extension 180°/s	51·9 (32·7)	62·7 (34·6)	67·8 (34·2)	47·6 (23·1)	47·8 (26·4)	47·0 (34·2)
Elbow flexion 60°/s	30·2 (16·0)	34·1 (16·4)	36·5 (16·5)	26·4 (10·9)	25·3 (11·3)	26·2 (11·6)
Elbow flexion 120°/s	25·5 (12·1)	29·6 (14·9)	30·6 (14·0)	23·6 (10·0)	22·0 (10·1)	22·7 (11·2)
Systolic blood pressure (mmHg)	136 (21)	126 (15)	129 (14)	132 (20)	131 (16)	127 (18)
Diastolic blood pressure (mmHg)	81 (13)	75 (11)	76 (9)	75 (9)	76 (7)	77 (10)
Resting heart rate (beats/min)	79 (10)	73 (8)	75 (11)	80 (11)	79 (12)	82 (11)

IBDQ total score (32 to 224)	183 (23)	191 (20)	187 (23)	166 (25)	162 (26)	166 (29)
EQ-5D utility index (-0·285 to 1)	0·856 (0·123)	0·872 (0·115)	0·885 (0·128)	0·810 (0·113)	0·729 (0·189)	0·749 (0·137)
Fatigue score (0 to 20)	6 (4)	6 (4)	5 (3)	9 (4)	9 (4)	10 (5)
Physical activity (min/week)	1498 (1049)	1544 (1057)	1456 (924)	794 (782)	728 (621)	1032 (917)

Data are mean (SD). IBDQ = Inflammatory Bowel Disease Questionnaire.

Table 3. Adjusted means and group differences for primary outcomes at 6 months

	Exercise group	Control group	Difference	p value
Bone mineral density (g/cm^2)				
Lumbar spine	1·091 (1·082 to 1·099)	1·055 (1·046 to 1·063)	0·036 (0·024 to 0·048)	<0·001
Greater trochanter	0·713 (0·691 to 0·735)	0·700 (0·678 to 0·723)	0·013 (-0·019 to 0·045)	0·415
Femoral neck	0·812 (0·800 to 0·823)	0·794 (0·782 to 0·806)	0·018 (0·001 to 0·035)	0·059
Grip strength (kg)	40·9 (39·4 to 42·4)	32·5 (31·0 to 34·1)	8·3 (6·2 to 10·5)	<0·001
Chair stand test (repetitions)	18 (17 to 20)	14 (13 to 16)	4 (3 to 6)	<0·001
Arm curl test (repetitions)	23 (22 to 25)	17 (15 to 18)	7 (5 to 8)	<0·001
Isokinetic strength (Nm)				
Knee extension 60°/s	100·7 (93·4 to 107·9)	78·2 (70·8 to 85·6)	22·4 (12·1 to 32·8)	<0·001
Knee extension 180°/s	65·8 (60·4 to 71·2)	49·1 (43·5 to 54·6)	16·8 (9·0 to 24·5)	<0·001
Elbow flexion 60°/s	34·8 (32·8 to 36·7)	28·0 (26·0 to 30·0)	6·8 (3·9 to 9·6)	<0·001
Elbow flexion 120°/s	29·8 (27·8 to 31·9)	23·6 (21·4 to 25·7)	6·3 (3·3 to 9·3)	<0·001

Data are mean and adjusted mean difference with 95% CIs in parentheses.

Table 4. Adjusted means and group differences for secondary outcomes

	Exercise group	Control group	Difference	p value
Muscle function at 3 months				
Grip strength (kg)	37·7 (36·4 to 39·0)	33·6 (32·3 to 35·0)	4·0 (2·1 to 5·9)	<0·001
Chair stand test (repetitions)	16 (15 to 17)	14 (13 to 15)	3 (1 to 4)	<0·001
Arm curl test (repetitions)	20 (19 to 21)	17 (16 to 18)	3 (1 to 5)	<0·001
Knee extension 60°/s (Nm)	94·6 (87·4 to 101·8)	81·7 (74·3 to 89·1)	12·9 (2·5 to 23·3)	0·016
Knee extension 180°/s (Nm)	60·4 (55·8 to 65·0)	50·3 (45·6 to 54·9)	10·1 (3·6 to 16·7)	0·003
Elbow flexion 60°/s (Nm)	32·3 (30·7 to 34·0)	27·1 (25·4 to 28·8)	5·2 (2·8 to 7·6)	<0·001
Elbow flexion 120°/s (Nm)	28·7 (27·1 to 30·4)	23·0 (27·1 to 24·6)	5·8 (3·5 to 8·1)	<0·001
Systolic blood pressure (mmHg)				
3 months	125 (120 to 130)	132 (127 to 137)	-7 (-14 to 0)	0·060
6 months	128 (122 to 133)	128 (122 to 134)	-1 (-9 to 8)	0·884
Diastolic blood pressure (mmHg)				
3 months	73 (70 to 77)	77 (73 to 81)	-4 (-9 to 2)	0·178
6 months	75 (71 to 78)	78 (75 to 82)	-3 (-8 to 2)	0·180
Resting heart rate (beats/min)				
3 months	74 (70 to 77)	79 (75 to 82)	-5 (-10 to 0)	0·032

6 months	75 (71 to 79)	82 (78 to 86)	-6 (-12 to -1)	0·032
IBDQ total score (32 to 224)				
3 months	185 (179 to 191)	169 (162 to 175)	17 (7 to 26)	0·001
6 months	180 (174 to 186)	174 (167 to 180)	6 (-3 to 15)	0·175
EQ-5D utility index (-0.285 to 1)				
3 months	0·859 (0·793 to 0·925)	0·742 (0·677 to 0·808)	0.117 (0·023 to 0·211)	0·016
6 months	0·875 (0·825 to 0·924)	0·765 (0·715 to 0·816)	0·109 (0·038 to 0·181)	0·004
Fatigue score (0 to 20)				
3 months	7 (5 to 8)	8 (7 to 9)	-1 (-3 to 1)	0·249
6 months	6 (5 to 7)	8 (7 to 10)	-2 (-4 to -1)	0·005
Physical activity (min/week)				
3 months	1348 (1037 to 1658)	934 (616 to 1253)	414 (-47 to 875)	0·077
6 months	1239 (917 to 1561)	1260 (929 to 1590)	-21 (-499 to 457)	0·930

Data are mean and adjusted mean difference with 95% CIs in parentheses. IBDQ = Inflammatory Bowel Disease Questionnaire.

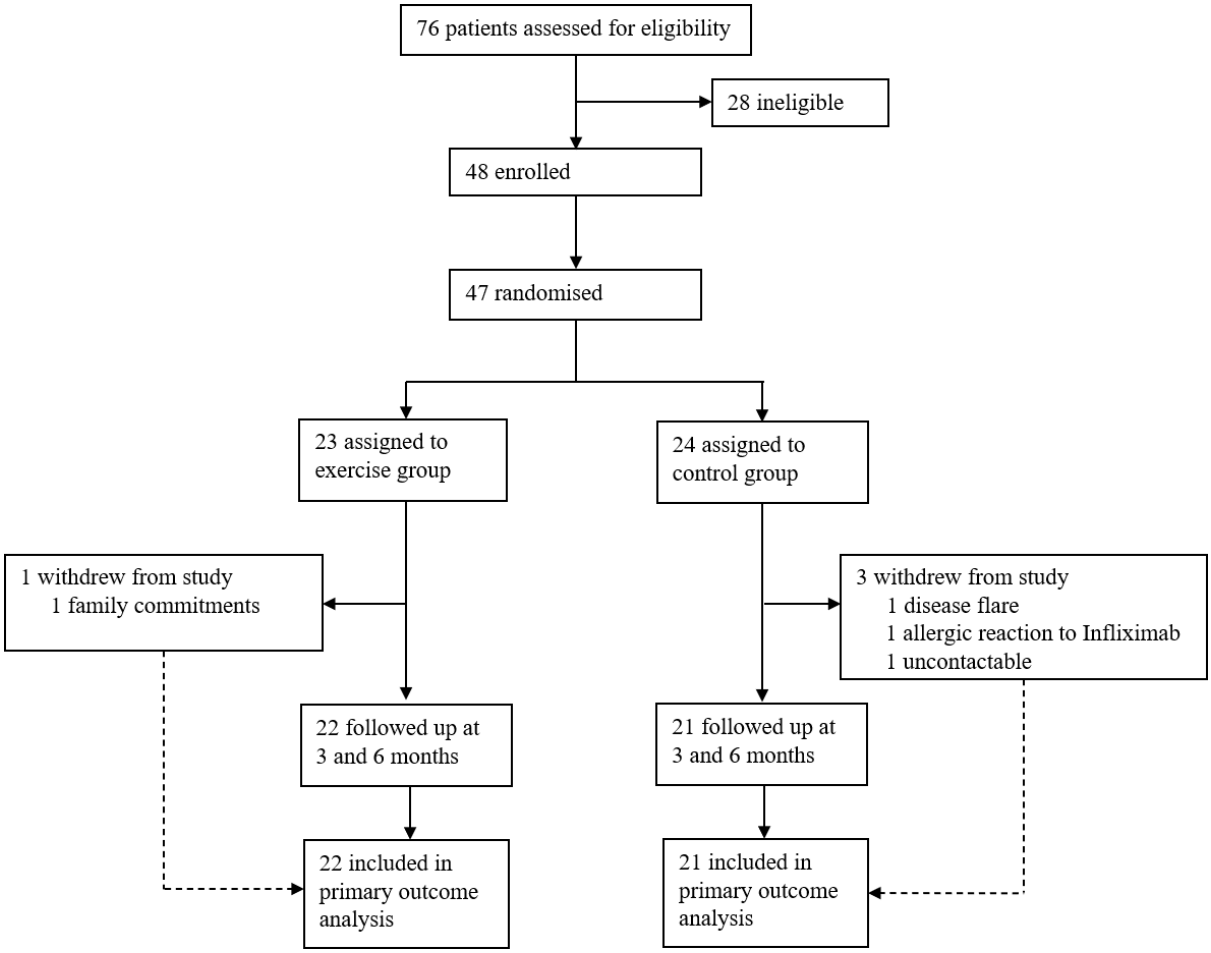

Figure 1. Trial profile

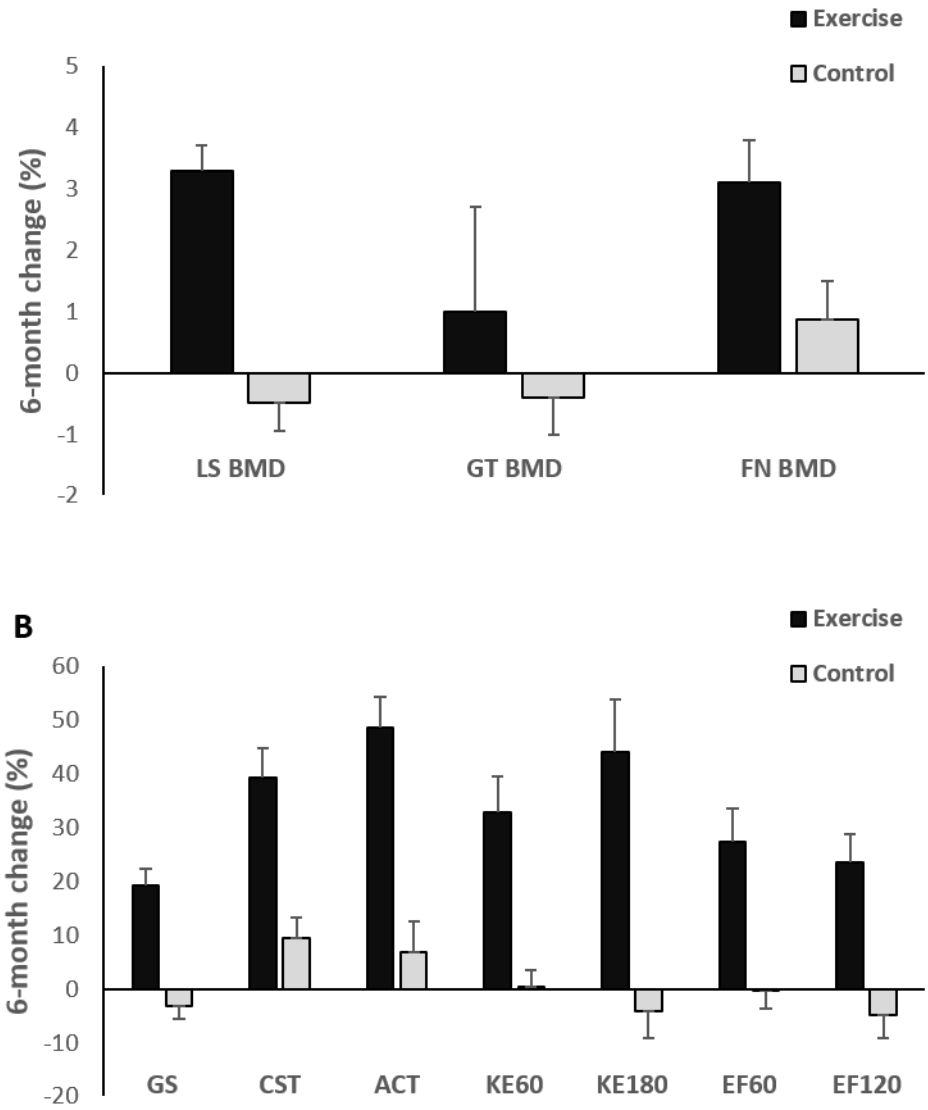

Figure 2. Six-month mean change (±SE) in (A) bone and (B) muscle function outcomes for the exercise and control groups. ACT, arm curl test; BMD, bone mineral density; CST, chair stand test; EF60, elbow flexion 60°/s; EF120, elbow flexion 120°/s; FN, femoral neck; GS, grip strength; GT, greater trochanter; KE60, knee extension 60°/s; KE180, knee extension 180°/s; LS, lumbar spine.