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**THE IMPACT OF EXERCISE ON BONE
MINERAL DENSITY AND MUSCULAR
FUNCTION IN ADULTS WITH
CROHN'S DISEASE**

K H JONES

PhD

2020

**THE IMPACT OF EXERCISE ON BONE
MINERAL DENSITY AND MUSCULAR
FUNCTION IN ADULTS WITH
CROHN'S DISEASE**

KATHERINE HELEN JONES

A thesis submitted in partial fulfilment of the requirements of the
University of Northumbria at Newcastle for the degree of Doctor of
Philosophy

Research undertaken in the Faculty of Health and Life Sciences,
Department of Sport, Exercise and Rehabilitation and in collaboration
with Newcastle Upon Tyne Hospital NHS Foundation Trust

2020

Abstract

Reduced bone mineral density (BMD) and muscle dysfunction are recognised secondary complications of Crohn's disease (CD), likely to be as a result of proinflammatory cytokines, glucocorticoid usage and malnutrition. The perceived benefits of exercise has been suggested to counteract these disease-specific complications with different exercise training stimuli eliciting corresponding psychological and physiological adaptations. However, the role of exercise as a therapeutic option remains poorly understood, with few prospective trials conducted in this high-risk group. Moreover, these existing studies are significantly limited by their small sample size, methodological robustness and lack of blinded outcome assessors highlighting the need for robust clinical research. Therefore, the overarching aim of this thesis is to expand the existing body of knowledge and provide novel data on the impact of exercise on bone and muscle health in CD.

Firstly, a systematic review (Chapter 3) utilising the current literature was undertaken to evaluate the evidence of the benefits and harms of exercise interventions to allow the integration of the best evidence available to inform exercise recommendations. Results identified that the benefits of exercise have not been sufficiently researched, particularly in outcomes such as immune parameters, BMD, muscular function and fatigue. However, it did demonstrate that low to moderate-intensity exercise was safe, feasible and potentially beneficial at counteracting some disease-specific complications in persons with an inactive to mildly active disease. Further supporting the perceived benefits of exercise. However, the majority of interventions involved modes of exercise such as yoga or walking that are sub-optimal for improving bone health.

As a prelude to experimental research, Chapter 5 investigated the test-retest reliability of outcome measures grip strength, isokinetic muscular strength, muscular endurance and BMD. Test-retest reliability was excellent in all outcome measures, highlighting these methods as reliable to facilitate the assessment and effectiveness of an intervention. Chapter 6 reports the prevalence and risk factors associated with bone and muscle health in inactive to mildly active CD participants. These data strengthen the evidence base that adults with CD are at an increased risk of osteopenia or osteoporosis, in addition to identifying longer disease duration, lower physical activity habits, females and smokers as correlates of BMD. Moreover, adults with CD also showed a significantly reduced upper and lower muscular endurance and lower muscular strength when matched to healthy controls.

These findings informed the design of Chapter 7. This two arm, parallel-group, assessor-blind randomised controlled trial explored the effects of a 6-month combined impact and resistance home-based exercise intervention on primary outcomes BMD and muscular function. This study provided novel findings, identifying significant improvements between groups in lower and upper muscular endurance and strength, handgrip strength and BMD at the lumbar spine and femoral neck. In view of these results, a combined impact and resistance training programme is a potent stimulator for skeletal growth, structure and maintenance and should be considered as therapeutic option for the perseveration of bone and muscle parameters. Collectively, these studies provide corroborating evidence that exercise is a safe and feasible option and can be used to elicit favourable physiological and psychological changes in adults with CD.

Publications and Conference Proceedings

Arising from Thesis

Publications

Jones, K., Baker, K., Speight, R.A., Thompson, N.P and Tew, G.A. (2020) Randomised clinical trial: Combined impact and resistance training in adults with stable Crohn's disease. *Alimentary Pharmacology & Therapeutics.* 52(6) p 964-975.

Conference Communications: Oral Presentations

Jones, K., Tew, G.A and Baker, K. (2018) Resistance Training in Inactive or Mildly Active Crohn's Disease Patients: Study Protocol for a Randomised Controlled Trial. Gastroenterology Researchers Meeting, Freeman Hospital, 23rd March 2018.

Jones, K., Baker, K., Speight, R.A., Thompson, N.P and Tew, G.A. (2019) Resistance Training in Inactive or Mildly Active Crohn's Disease Patients: Study Protocol for a Randomised Controlled Trial. IBD Researchers Event, York Medical Society, 13th June 2019.

Jones, K., Baker, K., Speight, R.A., Thompson, N.P and Tew, G.A. (2020) Combined impact and resistance training in adults with stable Crohn's disease: the PROTECT randomised controlled trial. York Trials Unit Researchers Event, University of York, 8th June 2020.

Jones, K., Baker, K., Speight, R.A., Thompson, N.P and Tew, G.A. (2020) Combined impact and resistance training in adults with stable Crohn's Disease: PROTECT randomised controlled trial. British Society of Gastroenterology, postponed to May 2021. *Gut* [ahead of print].

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Jones, K., Tew, G.A and Baker, K. (2018) Patterns and predictors of self-reported sedentary behaviour in people with inflammatory bowel disease. BASES Student Conference, Northumbria University, 12-13th April 2018.

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Table of Abbreviations

ACSM	American College of Sports Medicine	EIM	Extraintestinal Manifestation
AE	Adverse Event	FC	Faecal Calprotectin
ANCOVA	Analysis of Covariance	GDPR	General Data Protection Regulation
ANOVA	Analysis of Variance	GP	General Practitioner
ATP	Adenosine Triphosphate	HADS	Hospital Anxiety and Depression Scale
BCT	Bicep Curl Test	HBI	Harvey Bradshaw Index
BDI-II	Beck Depression Inventory II	HIIT	High-Intensity Interval Training
BMI	Body Mass Index	HGS	Handgrip Strength
CAI	Clinical Activity Index	HRA	Health Research Authority
CAM	Complementary and Alternative Medicine	HRQOL	Health-Related Quality of Life
CARD15	Caspase-Activating Recruitment Domain Family, Number 15	IBD	Inflammatory Bowel Disease
CD	Crohn's Disease	IBD-F	IBD Fatigue Scale
CDAI	Crohn's Disease Activity Index	IBDSI	IBD Stress Index
CON	Controls	IBD-U	IBD-Unclassified
CRC	Colorectal Cancer	IBDQ	IBD Quality of Life Questionnaire
CRF	Case Report Form	ICC	Intraclass Correlation Coefficient
CRP	C-Reactive Protein	ICTRP	International Clinical Trials Registry
CSA	Cross-Sectional Area	IFN-y	Interferon Gamma
CST	Chair Stand Test	IgA	Immunoglobulin A
DEXA	Dual-Energy X-ray Absorptiometry	IGF-1	Insulin-Like Growth Factor

DHEAS	Dehydroepiandrosterone Sulphate	IL	Interleukin
IQR	Interquartile Range	RCT	Randomised Controlled Trial
IRAS	Integrate Research Application System	ROM	Range of Motion
ISRCTN	International Standard Randomised Controlled Trial Number	SAE	Serious Adverse Event
LOA	Limits of Agreement	SCI	Simple Colitis Index
MICT	Moderate-Intensity Continuous Training	SD	Standard Deviation
MVIS	Maximum Voluntary Isokinetic Strength	SEM	Standard Error of Mean
NICE	National Institute for Health and Care Excellence	SPAQ	Scottish Physical Activity Questionnaire
NIH	National Centre for Complementary and Integrative Health	STAI	State Trait Anxiety Inventory
NHS	National Health Service	TBARS	Thiobarbituric Acid Reactive Substances
NOD	Nucleotide-Binding Oligomerization Domain Containing	TGF	Transforming Growth Factor
NOS	National Osteoporosis Foundation	TGF-β	TGF-Beta
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs	Th	T Helper
NUTH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	TNF-α	Tumour Necrosis Factor Alpha
OPG	Osteoprotegerin	UC	Ulcerative Colitis
PI3K/ AKT	Phosphatidylinositol 3-Kinase-Akt Signalling Pathway	VO2	Maximal and Peak Oxygen Consumption
QOL	Quality of Life	W peak	Peak Aerobic and Anaerobic Mechanical Power
R&D	Research and Development	WHO	World Health Organisation

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Declaration of Originality

Author's Declaration

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance for the research presented in this thesis has been approved.

Approval has been sought and granted by the Faculty of Health and Life Sciences Ethics committee for each study and from the Health Research Authority (ref: 226369; Appendix 4i).

I declare that the word count of this thesis is 48,909 words

Name: Katherine Jones

Signature:

Date: 7th August 2020

CHAPTER

1

Introduction

1.1 Background

Crohn's disease (CD) and ulcerative colitis (UC) are immunologically mediated idiopathic chronic inflammatory disorders of the gastrointestinal tract, collectively referred to as inflammatory bowel disease (IBD) (Sartor, 2006). The peak age of onset for IBD is 15 to 30 years, although it can occur at any age and affects approximately one person in every 250 of the UK population (Crohn's and Colitis UK, 2016). Despite extensive studies, the aetiology and pathophysiology of IBD remains largely unknown, however the general consensus is that the condition is thought to result from a combination between genetic and environmental factors that initiate a dysfunctional mucosal immune response (Fedorak and Madsen, 2004; Baumgart and Sandborn, 2007).

CD and UC are characterised by a cyclical nature alternating between active and quiescent states that can negatively impact a person's quality of life (QOL) (Abraham and Cho, 2009). Over 75% of adults with CD and 23-45% with UC require surgery, and up to half relapse every year experiencing typical clinical features such as malnutrition, diarrhoea, abdominal pain and blood loss (Carter et al., 2004; Levine and Burakoff, 2011). However, even when the disease is in remission, more than one third of adults with IBD are affected by extra-intestinal manifestations beyond the intestinal tract such as musculoskeletal, specifically reduced bone mineral density and muscle dysfunction and dermatological disorders, liver disease and ocular, renal and pulmonary system involvement, which can be just as debilitating as the primary disease (Narula and Fedorak, 2008; Ott and Scholmerich, 2013). Although these manifestations have been observed in both CD and UC, a greater prevalence has been reported in CD, likely as a result of disease specific proinflammatory cytokines, medications, malnutrition and surgical interventions (Repiso et al., 2006; Vavrikca et al., 2015).

CHAPTER 1: INTRODUCTION

With limited treatment options, the need for effective symptom management is becoming ever more pressing. Dietary manipulation and psychological strategies, while not mainstream therapies combat high-risk factors such as poor nutrition, depression, stress and anxiety that negatively affect disease activity. Physical activity and exercise has been suggested to counteract aforementioned disease-specific complications with different exercise training stimuli eliciting corresponding psychological and physiological adaptations (Buchman, 1999; Peters et al., 2001; Perez, 2009). However, the role of exercise as a therapeutic option remains poorly understood, with exercise guidelines being based on the beneficial effects found among healthy individuals and not specifically within this population (Narula and Fedorak, 2008). To date the evidence for exercise in this population remains sparse, with only a few intervention studies, which are significantly limited by their small sample size, methodological robustness, lack of long-term follow up and lack of blinded outcome assessors. Therefore, the purpose of this thesis is to expand the existing body of knowledge and provide novel data on the impact of exercise on bone and muscle health in CD. The specific focus of each subsequent chapter is as follows:

Chapter Two: A comprehensive summary of the current knowledge surrounding IBD, including the pathophysiology, epidemiology, impact and disease management. In addition to highlighting the prevalence of extraintestinal manifestations and the susceptibility to the development of these complications varying greatly depending on archetypal phenotypes: CD and UC, which will provide a focus of this thesis.

Chapter Three: A systematic review to assess, utilise and synthesise the literature on the benefits and harms of physical activity interventions in this population to allow the integration of the best evidence available to inform physical activity recommendations.

Chapter Four: A justification and rationale of the design and methods employed.

CHAPTER 1: INTRODUCTION

Chapter Five: Prior to experimental research, this study aimed to determine the test-retest reliability of outcome measures to evaluate and facilitate the assessment and effectiveness of an intervention.

Chapter Six: The prevalence and risk factors associated with bone and muscle health in CD vary significantly depending on the study population, study location and study design. Therefore, the aims of this study were to assess current bone and muscle health and identify possible risk factors associated with and contributing to low BMD in CD in the UK.

Chapter Seven: Despite the mechanical properties of weight bearing exercises and its widespread clinical use in osteoporosis, sarcopenia and postmenopausal women to increase BMD, muscular strength and endurance, little is known about the beneficial effects in adults with CD. Therefore, the primary aim of this study were to investigate the effects of a combined impact and resistance training programme on muscle function and BMD in adults with CD.

Chapter 8: An overall discussion interpreting and supporting the implications of the research findings.

Overall, with the lack of sufficient evidence and exercise guidelines for individuals with CD it remains unclear what type, duration, frequency or intensity is safe and beneficial to recommend as a therapy to counteract these disease-specific complications. It is intended that this research will allow the integration of the best evidence available to inform evidence-based recommendations.

CHAPTER

2

IBD: Epidemiology, Impact and Treatment

2.1 What is Inflammatory Bowel Disease?

Inflammatory bowel disease (IBD) is an immunologically mediated idiopathic chronic inflammatory disorder of the gastrointestinal (GI) tract, classified into two most common archetypal phenotypes; Crohn's disease (CD) and ulcerative colitis (UC) (figure 1) (Sartor, 2006). These chronic diseases are characterised by a cyclical nature alternating between active and quiescent states. Although they may share overlapping epidemiological, clinical and therapeutic characteristics, they present distinguishable endoscopic, pathological and radiological features (Zhang and Li, 2014).

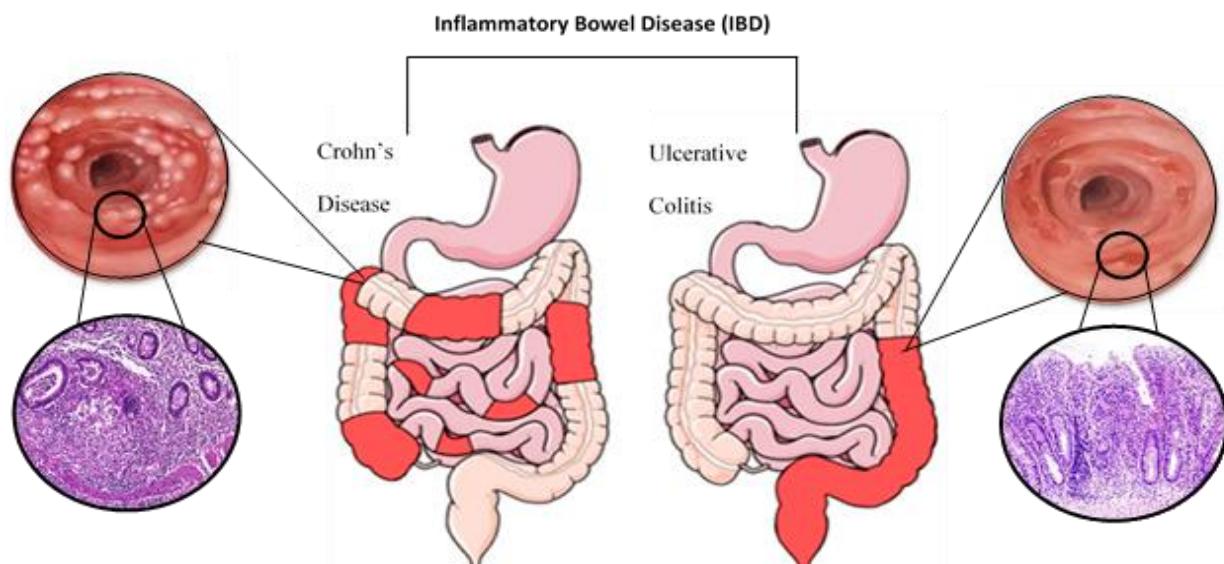


Figure 1. Anatomic distribution of CD and UC (Hoter and Naim, 2019), endoscopic (top) (Athersys, 2019) and histological (bottom) appearance (PathologyOutlines.com, 2018)

CD presents as a deep transmural pattern of cobblestone inflammation involving discontinuous mucosal segments of lesions intervened with portions of otherwise normal areas of mucosa (Zhang and Li, 2014). In approximately 27% of cases, there are non-necrotising granulomas composed of epithelioid histiocytes (Mazor et al., 2010). Whilst

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initially only small segments are involved, there is potential for the disease to progress extensively throughout the gastrointestinal tract from the oropharynx to the perianal area, with the ileocecal region most frequently involved (Hendy and Hart, 2013). In contrast, UC is confined to the colon, consisting of a continuous pattern of inflammation involving variable severity with ulceration, oedema and haemorrhage extending proximally from the rectum involving the mucosa and superficial submucosa. Histological features include goblet cell depletion, crypt abscesses and distortion (Nielson et al., 2001; Strober, 2007). However with no differentiating single gold standard measure, distinguishing between the two disorders can be difficult when making a definitive diagnosis. Indeterminate colitis, while somewhat controversial has been adopted by clinicians when no endoscopic, pathological or radiological features of CD or UC are present due to the overlapping features and unusual presentation of disease (Guindi and Riddell, 2004). Approximately, 10-15% of patients are categorised as indeterminate colitis, a figure that has not changed over the past 30 years. Although the majority of these individuals develop UC, there are also individuals who persist at in-between stages, not responding to medication as well as UC patients but faring better than patients with CD, suggesting IC may be a third disease entity (Wells et al, 1991; Tremaine, 2011).

2.2 Aetiology and pathogenesis

Despite extensive studies the aetiology and pathophysiology of IBD remains largely unknown. The general consensus suggests that IBD is initiated by a combination of environmental agents along with a dysfunctional mucosal immune response or imbalanced interaction with microbes in genetically susceptible individuals (figure 2) (Fedorak and Madsen, 2004; Baumgart and Sandborn, 2007).

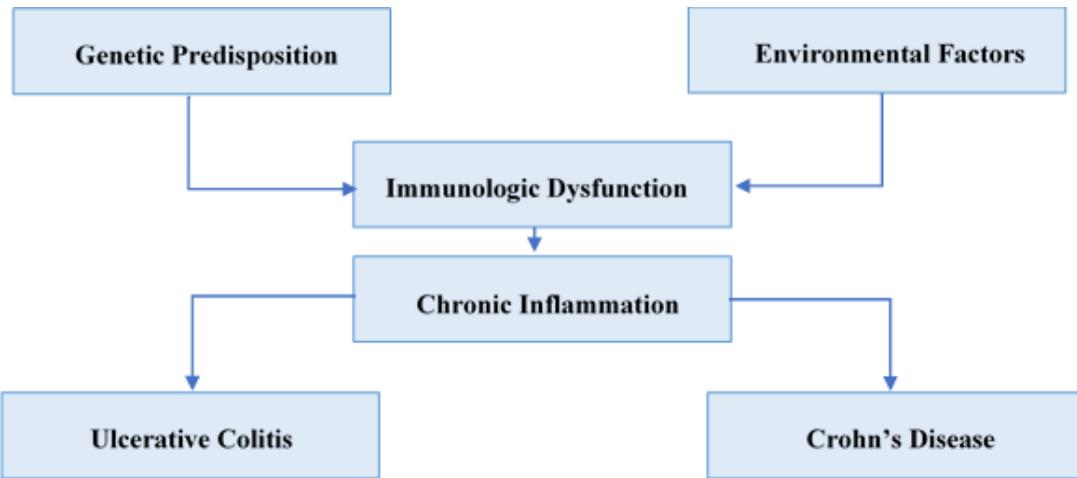


Figure 2. Overview of the pathogenesis of IBD

2.2.1 Immunological factors

Despite its complexity, investigations into the pathogenesis of IBD has been dominated by studies of mucosal immunity, in particular abnormal T cell responses. Recently, the concept that CD was an interleukin (IL)-12 driven T-helper (Th) 1 mediated disease and that UC was an IL-13 driven Th2 mediated disease became largely eclipsed following the discovery of new T-helper cells, particularly Th17 through the over production of proinflammatory cytokines: IL-17, IL-21 and IL-22 (Aggarwal et al., 2003; Yen et al., 2006). These proinflammatory cytokines are induced by a combination of IL-6, transforming growth factor (TGF)- β and IFN- γ and promoted by IL-23, a heterodimeric cytokine that shares a subunit chain with IL-12, which could potentially explain why IL-12 was initially thought to be a disease mediator (Oppman et al., 2000; Strober and Fuss, 2011).

The involvement of Th17 cells and its signature cytokine IL-17 in intestinal inflammation has been extensively studied with evidence suggesting IL-17 induces IL-21 production and prompts its interaction with TGF- β and IL-23 to promote the differentiation of Th17 cells (Veldhoen et al., 2006). However, there is evidence that differentiation of Th17 cells induced

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in the absence of IL-23 lack the potential to induce inflammation, possibly due to the under-production of IL-10 under these circumstances, an anti-inflammatory cytokine and a poor inducer of inflammation (McGeachey et al., 2007; Strober et al., 2010). Regardless, the differentiated Th17 cells interact with IL-23, expressing an IL-23 receptor (IL-23R) which triggers a series of chemical signals that promote inflammation (Teng et al., 2015). Several variations of the IL-23R have been found to influence the risk of developing IBD, as researchers believe that the receptors role in triggering inflammation in the intestinal walls may underlie its connection with this disease (Tsianos et al., 2012). The stimulation of IL-23R, under the influence of IL-23 signalling is essential for the terminal differentiation and persistence of IL-17 producing cells, which trigger and amplify inflammation reflected in the increased mucosal levels in IBD (Sakuraba et al., 2009; Rovedatti et al., 2009). However, these associations have only been found in murine studies and further exploration of the role of IL-23R variations in the pathogenesis of IBD is now required.

At present, Th17 cells are considered a main pathogenic factor in IBD, however many questions still remain. Although murine models of intestinal inflammation provide a useful insight into the pathogenesis of the complex inflammatory response in IBD, reproducing these studies in humans may not have the same effect and therefore it continues to be a work in progress with the constant discovery of additional information.

2.2.2 Genetic factors

Huge advances in the understanding of genetic contributions to IBD have been made over the past decade, due to improvements in molecular techniques, generation sequencing of human genomes and availability of multinational databases (Duerr, 2007; Durmaz et al., 2015). At present, genome-wide association studies have found a significant link between

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chromosomes 1, 3, 6, 7, 12, 14, 16 and 19 and the development of IBD (Hanauer, 2006). In addition, 163 gene loci, a position on a chromosome where a genetic marker is located, appear to influence the likelihood of developing IBD, some of which are more specific to CD and some of which are more specific to UC (figure 3) (Weronica et al., 2014). A mutation in the nucleotide-binding oligomerization domain containing 2 (NOD2) gene and protein, was the first susceptibility gene identified for CD, but not UC (Khor et al., 2011; Liu and Stappenbeck, 2016). Defects in the NOD2 account for 17-27% of cases with CD, with individuals who are homozygous (that is, who have two identical alleles of the variant NOD2) have a 20-fold increase risk of developing CD (Hugot et al., 2001). The mechanisms that cause the defect in the NOD2 gene to lead to the development of IBD remains unclear. The onset of UC, on the other hand, is thought to establish from a dysregulation of key epithelial barrier genes such as ECM1 and HNF4a have shown to predispose individuals to UC, but not CD (Thompson and Lees, 2011; Liu and Stappenbeck, 2016).

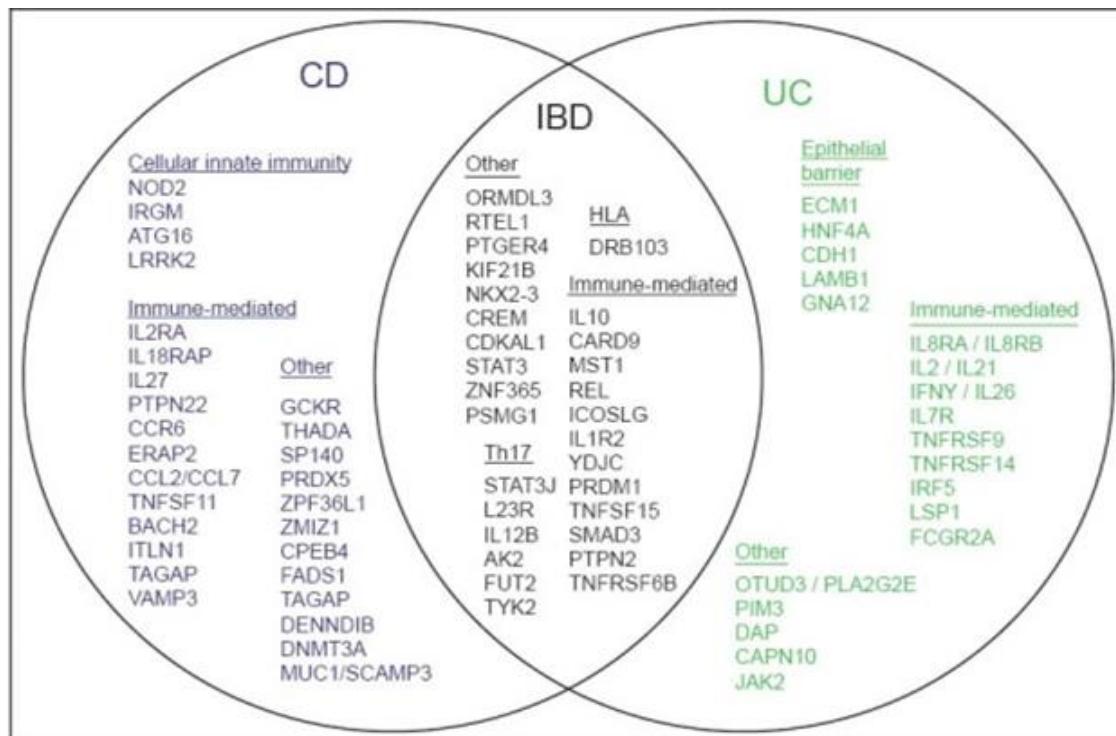


Figure 3. Loci associated with IBD, CD and UC (Ek et al., 2014)

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An aggregation of cases in family studies in IBD have been widely researched, with 5-30% of participants reporting a parent or sibling has been diagnosed with IBD (Weronica et al., 2014). However, these figures vary greatly depending on the study type, with referral-based studies reporting 20-30% of cases and population-based surveys reporting 5-23% (Binder, 1998; Weronica et al., 2014). The estimated relative risk, however to a sibling of a person with IBD is higher, ranging from 13-36 for CD whereas figures for UC are 7-17 (Ahmad et al., 2001). Although these estimates are difficult to be precise due to difficulties in correcting for age-adjusted incidence rates (Bennett et al., 1991; Ahmad et al., 2001; Laharie et al., 2001). Concordance rates are even higher in twins, with monozygotic ‘identical’ twins more likely to develop IBD rather than dizygotic ‘fraternal’ twins, reflecting the influence of genetics in the disease pathogenies (Tysk et al., 1988). Studies from Sweden, Denmark and Germany demonstrated a concordance rate for CD to be between 52.4-63.6% in monozygotic twins and 0-6.7% in dizygotic twins and for UC to be 6.6-27.9% in monozygotic twins and 0-4.5% in dizygotic twins (Tysk et al., 1988; Orholm et al., 2000; Halfvarson et al., 2006; Spehlmann et al., 2008; Halfvarson, 2011). Overall, the concordance rates are higher in monozygotic twins and more pronounced in CD than UC. However, the genetic predisposition cannot be solely responsible for disease aetiology when only one monozygotic twin is affected by the disease.

Although population-based studies have provided compelling evidence of the influence of genetic predisposition in the aetiology of IBD by demonstrating differences in prevalence rates among different members, twins and association with genetic syndromes, the major influence appears to be due to environmental factors (Zhang and Li, 2014; Guan, 2019).

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2.2.3 Environmental factors

Several environmental factors have been considered as risk factors that may interact with the immune system, resulting in an abnormal inflammatory response to intestinal microflora (Koloski et al., 2008). Factors that have been explored include smoking, diet, drugs, stress and sleep (Loftus et al., 2004; Abedunde et al., 2016). A meta-analysis of smoking in IBD concluded that current smokers were less likely to develop UC than those who had never smoked or were previous smokers, with Cosnes (2001) adding heavy smokers had a lower rate of relapse (Cosnes 2008; Lakatos et al., 2007). Contrary to its protective effect on UC, smoking has been shown to increase the risk of developing CD with a higher rate of postoperative disease (Birrenbach and Bocker, 2004). Although the exact mechanisms around how smoking influences IBD are unknown, it is thought to result from nicotine which has an inhibitory effect on Th2 cell function, but no effect on Th1 cell function (Razani-Boroujerdi et al., 2007).

There is a growing appreciation between nutrition and microbes in susceptible individuals, with a higher intake of fibre, fruit and vegetables consumption associated with a decreased risk of IBD, thought to be related to their ability to modify enzymes (Sakamoto et al., 2005; Amre et al., 2007). Fast foods containing higher levels of total, monounsaturated, saturated and polyunsaturated fats may exacerbate the development of IBD due to their role in the modification of receptors in macrophages, which are important in maintaining the delicate immune balance (Geerling et al., 2000; Lee et al., 2004; Amre et al., 2007). Limited high-quality evidence exists to support the notion that nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with the onset of IBD. Two studies have explored the relationship between NSAIDs and IBD, finding a positive association for both UC and CD (Felder et al., 2000; Ananthakrishnan et al., 2012), adding that high dose, frequent and prolonged use was

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associated with an increased risk. NSAIDs are thought to cause damage to the intestinal mucosa of the small bowel and colon and increase intestinal permeability (Berg et al., 2002).

Stress has been suggested to play a role in the onset of IBD. In animal studies, psychological stress has demonstrated an increase in intestinal permeability, and stimulated the secretion of ions, water, mucus and immunoglobulin A (IgA) as a result of alterations in the cholinergic nervous system and mucosal mast cell function (Hisamatsu et al., 2007). In turn, this increased intestinal permeability then reduces mucosal barrier function and alters bacteria-host interaction which, if broken, could cause damage to the stomach itself (Söderholm and Perdue, 2001; Hisamatsu et al., 2007). Lastly, poor sleep quality has been significantly associated with increased levels of IL-17, C-reactive protein (CRP) and markers of systemic inflammation in healthy adults, a determinant that if prolonged may lead to persistent changes in the immune system (Graff et al., 2011).

Overall, it is hard to dispute the general consensus that IBD is initiated from a complex interaction among environmental agents, genetically susceptible individuals and a dysfunctional mucosal immune response, and that one of these factors alone is unlikely to cause the disease. Although progress in the understanding of the pathogenesis of IBD has been achieved, further insight into the mechanisms and pathways of how and why these factors impact immunity and inflammation in susceptible individuals.

2.3 Classification of IBD

The Montreal classification (2005) (Table 1) took over the Vienna classification in adults and was established to address the complex issues involved in classifying the extent and behaviour in IBD. From the clinician's perspective, accurate classification of these two

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phenotypes is important for choosing the most appropriate medical and surgical therapy, monitoring changes in disease location, surveillance and to assess the disease prognosis. A recent systematic review in UC (n=15,316) established that the likelihood of colectomy is dependent on disease extent, demonstrating that the 10-year colectomy rate was highest in individuals with extensive colitis (19%), left-sided colitis (8%) and proctitis (5%), with rates increased further if the individual was male, young and had elevated inflammatory markers at diagnosis (Fumery et al., 2018). Likewise with CD, individuals who present with ileocolonic or isolated upper CD disease are more likely to experience more stricturing behaviour and require more abdominal surgeries (Lazarev et al., 2013). This is an association that is dependent greatly upon the duration of disease, with the majority of individuals presenting with non-stricturing non-penetrating disease at diagnosis. However, the behaviour of CD changes during the course of the disease and after 25 years the majority present with a stricturing or penetrating pattern in which environmental, genetic and immunological factors may influence the disease behaviours inclination and speed of evolution (Louis et al., 2001; Louis et al., 2003).

Table 1. Montreal Classification in CD and UC

Crohn's Disease			Ulcerative Colitis		
Age at diagnosis	A1	<17	Extent	E1	Ulcerative Proctitis
	A2	17-40		E2	Left-sided UC (distal UC)
	A3	>40		E3	Extensive UC (pancolitis)
Location	L1	Ileal	Disease	S0	Remission
	L2	Colonic		S1	Mild
	L3	Ileocolonic		S2	Moderate
	L4	Isolated upper disease		S3	Severe
Behaviour	B1	Non-stricturing, Non-penetrating	Severity		
	B2	Stricturing			
	B3	Penetrating			
	P	Perianal disease modifier			

2.4 Prevalence and incidence

The onset of this heterogeneous disease can occur at any age but the incidence rate typically peaks at 15 to 30 years of age, with no differences noted between males and females (Crohn's and Colitis UK, 2015). Approximately 20-25% of people are diagnosed before 16 years of age, a predictor associated with a more extensive disease, complications and more frequent disease activity (Malmborg et al., 2013). The number of individuals worldwide living with IBD is approximately 6.8 million, with North America noting the highest prevalence of 1.8 million and Oceania reporting the lowest prevalence of 2302 individuals (figure 4) (GBD 2017 IBD Collaborators, 2020). Nevertheless, the incidence rates and prevalence of IBD has increased remarkably in recent years, with an increase of 85.1% in global prevalent cases from 1990 to 2017 (GBD 2017 IBD Collaborators, 2020). The highest percentage change in prevalence were seen in the Solomon Islands (139.8%) and Kiribati (138.1%), while the lowest percentage change was identified in Cuba (-63.7%) and Barbuda (-62%).

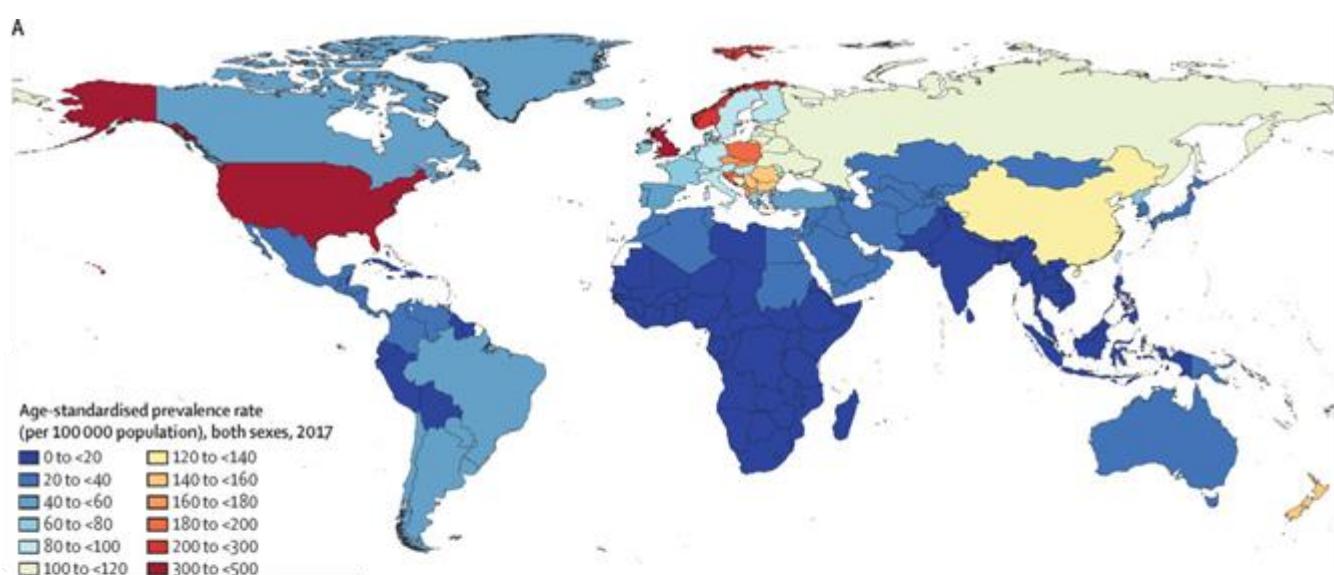


Figure 4. Global burden of inflammatory bowel disease in 195 countries (GBD 2017 IBD Collaborators, 2020)

In the UK IBD affects approximately 396 people in every 100,000, however with an 83.7% increase in cases from 1990 to 2017 projected annual costs to the NHS are expected to

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increase from £720 million to £1.5 billion by 2040 (Stone et al., 2003; Ghosh and Premchand, 2015). These trends demonstrate that the prevalence of IBD in the UK is expected to continue increasing, with detrimental health and economic effects. Cost effective health innovations implemented by health-care professionals need to be addressed to manage this complex and costly disease.

2.5 The impact of IBD

2.5.1 Mortality/ life expectancy

Population based data are sparse and conflicting when it comes to life expectancy in adults with IBD. Eight studies in CD reported a slight decrease (95% CI 1.29-3.01) in life expectancy compared to the general population, identifying disease duration, disease location and being female has been associated to increased mortality (Weterman et al., 1990; Ekbom et al., 1992; Persson et al., 1996; Palli et al., 1998; Farrokhyar et al., 2001; Jess et al., 2002; Masala et al., 2004; Jess et al., 2006). In contrast to these findings, two studies reported no differences in life expectancy in CD individuals (Probert et al., 1992; Cottone et al., 1996). The majority of UC population based studies have demonstrated a normal or increased life expectancy than the general population (Palli et al., 1998; Loftus et al., 2000; Farrokhyar et al., 2001; Viscido et al., 2001; Winther et al., 2003). Interestingly, geographical differences may influence these findings, as four studies all conducted in Scandinavia, reported a reduced life expectancy in UC, as a result of colorectal cancer (CRC), pulmonary embolisms and/or chronic lung diseases. However, these studies do not account for the recent major advances in pharmacological, non-pharmacological and surgical interventions for CD and UC. Most recently, a systematic analysis of the global burden of IBD in 195 countries from 1990-2017

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identified an increase in the number of IBD-related deaths worldwide, increasing from 23,000 to 38,000 (67%). However, this increase in mortality could be the result of a substantial increase of 85.1% in the prevalence of IBD worldwide. Nevertheless, in 2017 0.07% of deaths worldwide were caused by IBD, with the highest numbers reported in females aged 85-89 and males 80-84 (GBD 2017 IBD Collaborators, 2020), perhaps due to comorbidities, longer disease course, polypharmacy and slower recovery following surgery. Thus, attention needs to be directed toward elderly individuals with IBD to address risk factors that may help decrease IBD-related mortality.

2.5.2 Clinical features

Although CD and UC share similar symptoms including diarrhoea, abdominal pain, fatigue, blood loss and joint pain, these symptoms can vary greatly depending on the location and depth of the inflammation (Kim and Cheon, 2017). Individuals with severe UC (figure 5a), often as a result of a subtotal disease (pancolitis) experience frequent diarrhoea, urgency, blood with mucus, abdominal pain and unintentional weight loss. Moderately active UC (figure 5b) individuals often experience lower left-sided abdominal pain, rectal bleeding and sometimes urgency. Proctitis UC (figure 5c) causes rectal bleeding and mucous discharge (Rampton and Shanahan, 2016). Whereas individuals with ileocecal and terminal ileal (figure 5d) CD experience abdominal pain, tender mass in the right iliac fossa sometimes with diarrhoea and weight loss. As well as the symptoms mentioned individuals with ileocolonic CD (figure 5e) may also experience malabsorption, anaemia and altered body composition as a result of poor absorption. Lastly, colonic CD (figure 5e) symptoms are similar to those with a severe UC, however bleeding is less common. (Levine and Burakoff, 2011).

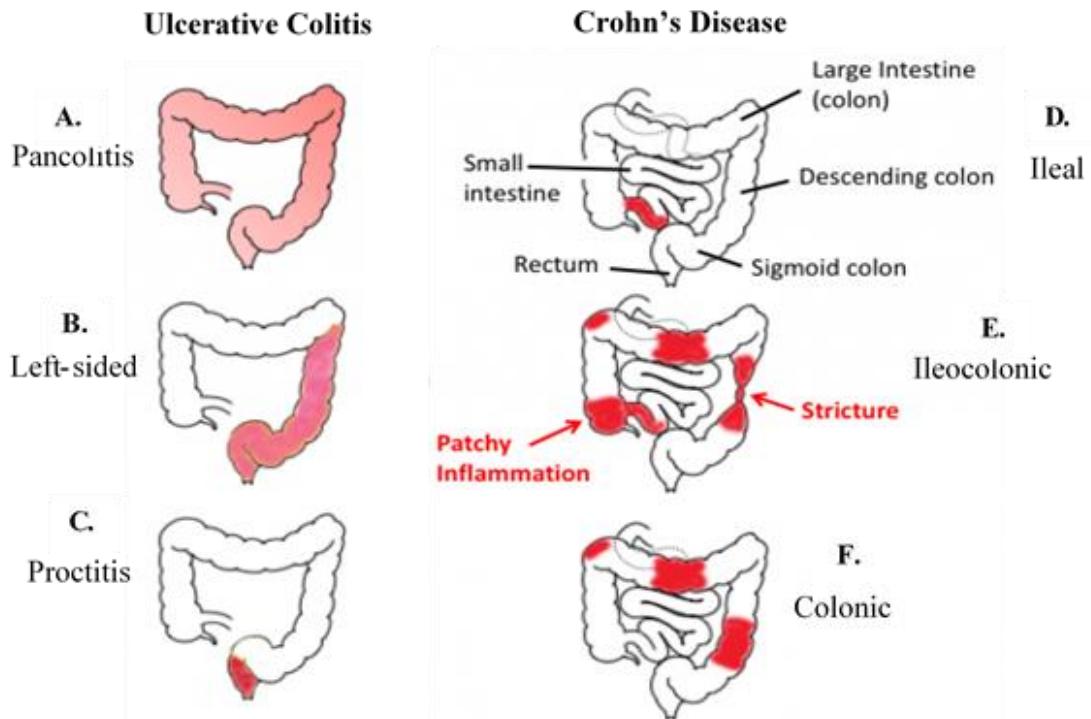


Figure 5. Types of UC (A-C) and CD (D-F) (DokuWiki Community, 2019)

2.5.3 Intestinal Complications

Even when the disease is in remission, impaired nutritional status is estimated in 65-75% of individuals with CD and 18-62% with UC, as a result of poor food intake, impaired digestion and absorption, medication side effects, surgical intervention and systemic inflammation due to active disease (Ispas et al., 2015; Spooren et al., 2015). These deficiencies can lead to premature and accelerated development of sarcopenia, a degenerate disease, identified in up to 60% of individuals with IBD, characterised by low muscle mass, strength and physical performance. Although considered to be age-related, deficits have been associated with morbidity, mortality and reduced QOL (Greenland and Nair, 2003).

Tears or splits in the anal tissue are common in IBD, also known as fissures (figure 6). This is as a result of increased toilet frequency, typically causing pain and bleeding (D'Ugo et al., 2015). Unlike UC, CD is commonly associated with fistulas, an abnormal passageway in the

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digestive tract causing gastric fluid to seep through the intestinal lining (figure 6), which then causes abdominal pain, fevers and dehydration. Strictures are also a complication of CD, with at least one-third of individuals developing a stricture within the first 10 years of diagnosis.

Strictures (figure 6) are a narrowing in the intestine that can lead to bowel obstruction.

Another complication is abscesses (figure 6), collections of pus formed due to deep inflammation in the wall of the intestine, which occur in approximately 10-30% of people with CD causing severe abdominal pain and which then often require surgical drainage. If not properly managed these complications could lead to further tissue damage, uncontrolled infection and in some cases death (Rampton and Shanahan, 2016).

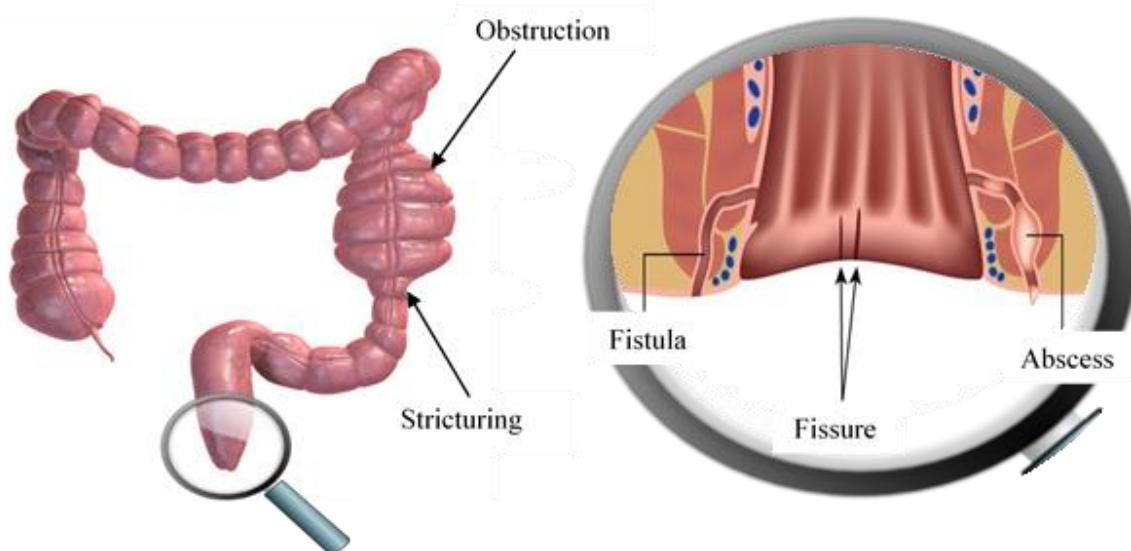


Figure 6. Intestinal Complications (IBDrelief, 2019; Harvard Health Publishing, 2018)

2.5.4 Extraintestinal Complications

Even when the disease is in remission, more than one third of individuals with IBD are affected by extra-intestinal manifestations (EIM) beyond the intestinal tract such as musculoskeletal and dermatological disorders, liver disease and ocular, renal and pulmonary system involvement. These can be just as debilitating as the primary disease (figure 7)

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(Narula and Fedorak, 2008; Ott and Scholmerich, 2013). The EIM that are most prevalent in IBD are at the bones (osteopenia:22-77%; osteoporosis:17-41%), joints (ankylosing spondylitis:5-10%, enteropathic arthropathy:30%), skin (erythema nodosum:10-20%; psoriasis:10%; pyoderma gangrenous:<1%) and eyes (uveitis:3-11%; episcleritis:<1%; scleritis:<1%) (Rudwaleit and Baeten, 2006; Arvikar and Fisher, 2011; Ferreira et al., 2018; National Psoriasis Foundation, 2019). Although these manifestations have been observed in both CD and UC, a greater prevalence, has been reported in CD compared to UC (Repiso et al., 2006; Miznerova et al., 2013; Vavrikca et al., 2015).

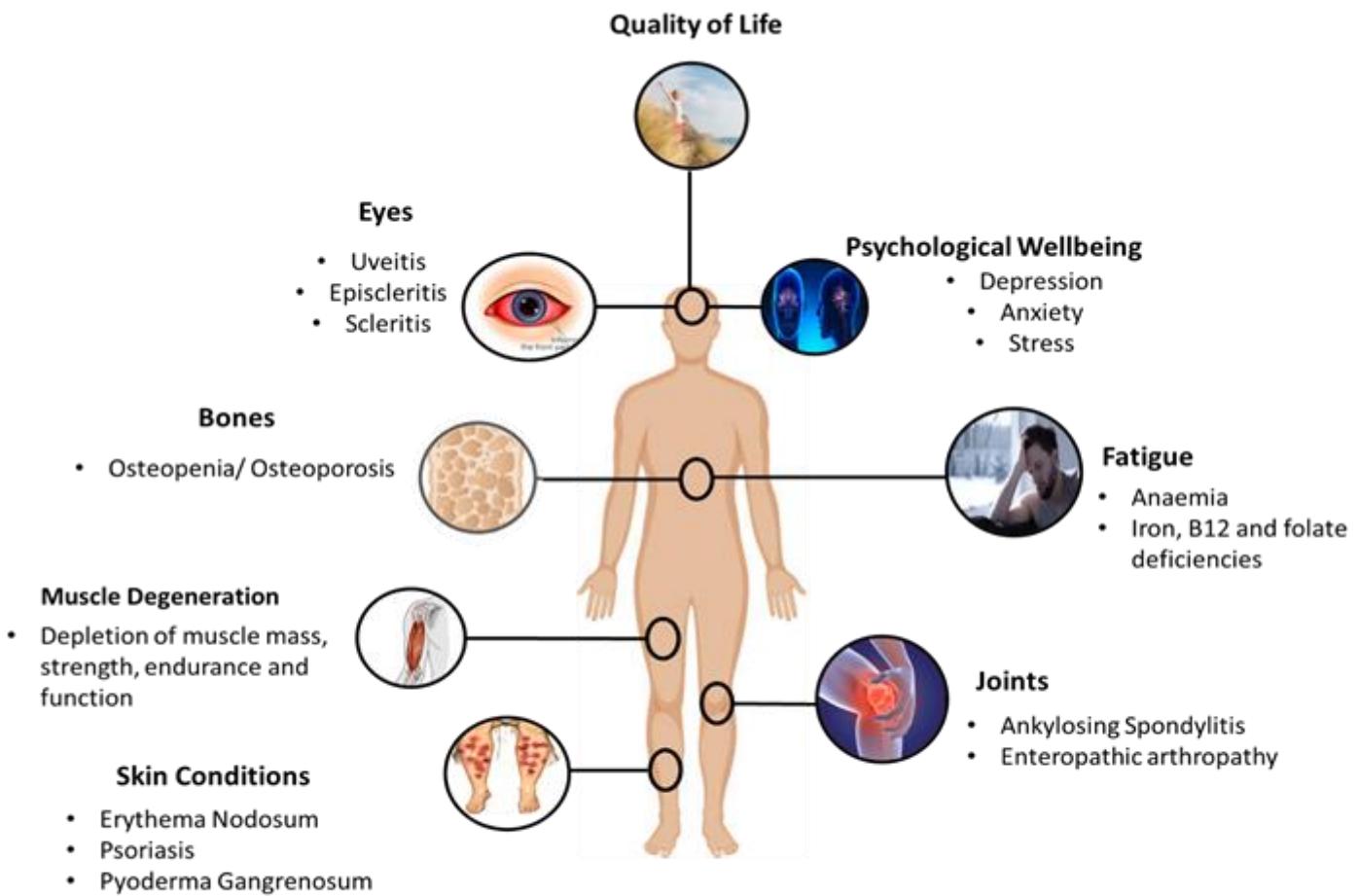


Figure 7. Secondary complications of IBD

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2.5.4.1 Osteoporosis and related fractures

Osteoporosis and osteopenia, are skeletal disorders characterised by microarchitectural deterioration of bone tissue and strength, consequently resulting in increased bone fragility and high propensity to fractures (National Institutes of Health, 2014). Skeletal disorders that contribute to poor quality of life, increased morbidity, loss of independence and huge economic burden of £4.4 billion a year attributable to hip and vertebrae in the UK (Berstein et al, 2000; National Osteoporosis Society, 2017).

2.5.4.1.1 Assessment of BMD

Although there are different imaging modalities to diagnose these skeletal disorders through the assessment of BMD, the dual energy X-ray absorptiometry is the preferred method due to its versatility, high precision, accuracy and reproducibility (Zack et al., 2002; Small et al., 2005). Current evidence recommends scans are undertaken at the hip (femoral neck, trochanteric region and wards triangle) as this is the most reliable site for predicting fracture risk and the spine to monitor treatment (Arabi et al., 2007; Blake et al., 2007; National Osteoporosis Foundation, 2008). The quantitative computed tomography (QCT) is another method to determine BMD. This non-invasive method, is quick, not limited by a person's size and can be used as an alternative for individuals suspected of having osteoarthritis, due to the DEXA demonstrating falsely elevated BMD (Adams, 2009). However, the QCT is not without limitations including higher doses of radiation, fewer standardised scoring ranges and occasionally producing low results in an individual with normal T-scores on other imaging modalities, thought to be as a result of increased marrow fat with advancing age (Sheu and Diamond, 2016). Ultrasonography is also another method to calculate BMD, with no ionising radiation and portability, this method may seem as an attractive alternative (Gluer et al., 2004). However, the manufacturer and operator guidelines vary significantly, making it

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difficult for comparison and at the time of writing the ultrasound is not currently recommended for screening of these skeletal disorders (Sheu and Diamond, 2016).

2.5.4.1.2 Prevalence and aetiology

The prevalence of these skeletal disorders in IBD varies significantly depending on the study population, design and location, but ranges between 22-77% for osteopenia (T score between -1 and -2.5) with 17-41% subsequently progressing to develop osteoporosis (T score <-2.5) (Lee et al., 2005; Ali et al., 2009). A risk that has been reported greater in CD when compared to UC, as discussed below (Ghosh et al., 1994; JahnSEN et al., 1997; Gokhale et al., 1998; Targownik et al., 2013; Miznerova et al.).

The aetiology and the exact mechanisms that may underpin the relationship between osteoporosis and osteopenia and IBD are yet to be fully elucidated. However are likely to be multifactorial with several contributing factors. One hypothesised contributing factor is the elevated proinflammatory osteoclast activators including IL-1 (α and β), IL-6, IL-11, IL-15, and IL-17, TNF- α and prostaglandin E2 that interfere with the pathway involved in bone metabolism, known as RANK-RANKL-OPG, and thus change the rate of bone formation, bone resorption and overall bone homeostasis (Bernstein and Leslie, 2003; Bernstein et al., 2005; Mundy, 2007). RANKL (receptor activator of NF- κ B ligand) stimulates mature osteoclasts to resorb bone by binding to osteoprotegerin (OPG), which is produced by osteoblasts and responsible for blocking the interaction between RANK and RANKL, an interaction that causes osteoclasts to differentiate and mature resulting in bone loss (Wei et al., 2001; Ali et al., 2009).

Corticosteroids (CS) have been thought to impair osteoblast function, induce osteoblast apoptosis, reduce intestinal calcium absorption and increase renal excretion of calcium (Mitra, 2011; Targownik et al., 2013). In high concentrations CS have been shown to impair

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osteoblast function and synthesis of OPG. While the production of RANKL is stimulated, the interaction with receptor involved in signally RANKL is inhibited causing an increase in the activity, proliferation and maturation of osteoclasts (American College of Rhumatology, 1996; Bernstein et al., 2003). Reid and Heap (1990) supported this finding demonstrating participants (n=35) receiving greater than 12.5mg of prednisone per day had significantly greater bone loss ($r = -0.380$) than those who were on a lower dose. A cross-sectional study of 117 adults with CD found both current steroid use and long-term use as major determinants of BMD at the lumbar spine ($p < 0.02$) and femoral neck ($p = 0.02$) (Robinson et al., 1998). Similarly, Jahnsen et al's (1997) cross-sectional study showed that cumulative steroid dose correlated significantly with BMD at the lumbar spine ($r = -0.313$, $p = 0.018$) and total body ($r = -0.421$, $p = 0.0008$) in CD, but interestingly not in UC. However, the calculated dose of CS use was significantly higher in the CD group in comparison to the UC group (7.2g vs 1.8g), partially supporting the previous theory where the GS threshold has been exceeded. Moreover, CS decrease the synthesis of calcium binding, leading to increased calcium excretion, particularly in CD individuals who have demonstrated significantly higher calcium excretion rates than UC (Abreu et al., 2004; Barnes, 2007). This could contribute to the higher prevalence of reduced BMD in CD.

Other pathogenic mechanisms considered as risk factors for bone loss in IBD include diet and malabsorption. In disease states where the function of the digestive system may be compromised it is essential that nutritional intake is sufficient, particularly calcium and vitamin D, for skeletal health. However, this can pose as a problem, as people living with IBD often avoid or limit certain foods believing they may aggravate gastrointestinal symptoms and it is thus not surprising that up to 75% and 62% of CD and UC individuals, respectively suffer from nutritional deficiencies (Prince et al., 2011; Li et al., 2019). Furthermore, prolonged low concentrations of calcium and vitamin D have inversely been

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associated with elevated levels of markers of bone turnover and increased concentrations of uncarboxylated osteocalcin, a predictor of risk fracture (Szulc et al., 1996; Duggan et al., 2004). In particular, in CD the involvement of the terminal ileum may affect the bile salt enterohepatic circulation, consequently resulting in reduced vitamin D concentrations (Sgambato et al., 2019). Supporting the higher prevalence of reduced BMD in CD individuals. Vitamin K may also be reduced in IBD, especially CD with distal ileum involvement, which plays a major role in regulating osteoblastic markers, suppressing bone resorption and regulating osteoclasts formation (Ghishan and Kiela, 2017). Potential causes for these deficiencies could be as a result of intestinal resection, more commonly performed in CD, the efficiency of intestinal absorption or the increased cytokines released by the disease itself (Hylander et al., 1990; Gilman et al., 2006).

Measures to treat osteoporosis and osteopenia in this high-risk group have not yet been well established. Despite the benefits of resistance training interventions being well documented in the healthy population and chronic conditions, the role of gravitational and muscle loading exercises in the prevention or treatment of CD-related bone loss has received little attention. To prevent further disability and future personal and socio-economical costs, clinical trials are warranted to identify the optimal exercise prescription (mode, intensity, duration and frequency) for bone health in IBD, particularly focusing on CD individuals who are at an increased risk.

2.5.4.2 Muscular Dysfunction

The maintenance of skeletal muscle involves underlying molecular mechanisms between multiple signalling pathways that interplay to control and coordinate hypertrophic and atrophic messages between muscle protein synthesis and proteolysis (Egerman and Glass,

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2014). IGF-1 (insulin-like growth factor) and insulin are responsible for stimulating protein synthesis in skeletal muscle through the phosphatidylinositol 3-kinase-Akt signalling pathway (PI3K/AKT) which inhibits protein degradation and results in skeletal muscle hypertrophy, an increase in muscle mass and cross-sectional area (CSA) and improving work capacity (Minetti, 2002; Zamparo et al., 2002). Evidence suggests that increasing skeletal muscle hypertrophy can produce muscle strength gains and the ability to produce force against an external resistance, as a result of increased muscle fibre CSA that alter the force-velocity of the muscle (Stone et al., 2016; Suchomel et al., 2018). Whereas improving the working capacity of skeletal muscle, allows the oxidisation of substrates to produce adenosine triphosphate, a protein that regulates muscle endurance, defined as the ability to hold or repeat a muscular contraction for a long time (Wan et al., 2017; Hody et al., 2019).

2.5.4.2.1 Assessment of Muscular Function

Muscle dysfunction is defined by the loss of strength, the ability to perform or develop maximal effort, and/or endurance and the ability to maintain submaximal effort for a certain timeframe (Gea et al., 2015). Muscular strength and endurance of upper and lower limbs are key components of daily living tasks, evaluating the physical performance of these limbs is important to identify areas of weakness and imbalance (Zaltman et al., 2014; Bohannon, 2019). Although there are different modalities to assess muscular strength, dynamometric testing is seen as the ‘gold standard’ to evaluate how much tension a muscle exerts during a contraction. In particular, the isokinetic dynamometer allows for the isolation of particular muscle groups, ROM and muscle contraction type to be determined (Meyer et al., 2013). This provides an objective way to obtain muscular strength measures that have demonstrated the highest correlation coefficients for reliability, accuracy, validity and reproducibility that remain unmatched. Although this method provides accurate assessments of dynamic and static muscle strength, it is costly, not portable and requires operator training. Therefore, the

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use of hand-held devices such as a handgrip strength dynamometer are becoming more widely used, due to accessibility, low costs and standardised scoring (Martin et al., 2006; Bliven and Anderson, 2013).

Another commonly used method, often used by physiotherapists, is the Medical Research Council Manual Muscle Testing scale. This method involves the participant resisting pressure from the examiner who then grades the assessment on a scale from 0-5, 0 reflecting no muscle activation and 5 reflecting muscle activation against the examiners full resistance, with full range of motion. Although commonly used, due to its inexpensive nature, readily available and no need for any specialised equipment this method relies heavily on subjective observation. Therefore, results may vary greatly depending on the examiner taking the measurement. The one repetition maximum test (1-RM), is another method to assess muscular strength. This method involves readily available equipment (free weights or other gym equipment) and is cost effective, given its practicality and ease although this is seen as the preferred method for personal trainers performing a maximum weight lift is not recommended for novices, due to the increased risk of more serious injury as these individuals are not accustomed to weight training (Braith et al., 1993; Dohoney et al., 2002).

Numerous methods have been developed to measure muscular endurance including the: squat test, single leg squat, wall squat test, 30-s bicep curl test, 30-s chair stand test, push up test, 60-s sit up test, box jumps and pull ups. Although there is no ‘gold standard’ for determining muscular endurance, it is recommended that tests are selected based on the participants age, physical limitations, current training status and muscle group of interest (Mayo and Kravitz, 1997).

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2.5.4.2.2 Prevalence and aetiology

Despite the importance of skeletal muscle strength and endurance in daily living and future disability, loss of muscular strength and endurance are two of the least researched EIM associated with IBD (van Langenberg and Gibson, 2010; Hommes et al., 2012). Even during states of remission, up to 60% of people living with IBD have a reduced muscular CSA, mass, strength and endurance when compared to healthy controls (Geerling et al., 2000; Wiroth et al., 2005; Werksetter et al., 2011; van Langenberg, 2013). Werksetter et al (2012) reported a significantly lower grip strength (-1.02 [-1.58; -0.47]) in paediatric IBD individuals with a median disease duration of 3.5 years when compared to healthy controls. They also identified a significantly lower grip strength in those who were newly diagnosed when compared to those with a longstanding disease, thus highlighting the importance of introducing interventions at diagnosis to increase muscular strength. Strength parameters were also assessed in 41 adults with CD in clinical remission, with findings demonstrating a significant reduction in maximal isometric strength (-24.6%, p<0.001) and endurance (-25.8%; p<0.001) of the leg extensors and functional capacity (-25.1%, p<0.001), assessed by the 12-repetition sit-up test (Wiroth et al., 2005). Interestingly, a more recent study assessing upper and lower limb muscle strength in UC individuals reported significantly decreased maximal quadriceps strength (-6%; p=0.012), sit-up test (-32%; p=0.00001) and gait speed (-17%; p=0.0004), but not in handgrip strength (HGS) (p=0.362) (Zaltman et al., 2014).

The aetiology of muscle dysfunction in IBD is not fully understood and is likely to be multifactorial involving several contributing factors. One hypothesised contributing factor is the decreased circulating IGF-1 levels, a hormone that stimulates the proliferation of muscle progenitor cells and their integration with existing muscle fibres during the muscle repair process, and the elevation of thiobarbituric acid reactive substances (TBARS), a marker of oxidative stress (Machida and Booth, 2004). The combination of these changes decreases the

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PI3K/AKT signalling pathway, which is involved in inducing skeletal muscle hypertrophy and therefore is thought to play a role in the reduction in muscle mass and muscle CSA in IBD (Cominelli, 2004). This is supported by the findings from a cross-sectional study that obtained muscle biopsies from 27 adults with CD and compared them to healthy controls. Results demonstrated a 37% reduction in IGF-1 ($p<0.01$), a 54% lower phosphorylated:total Akt ratio ($p<0.05$) and increased serum TBARS ($p<0.05$). Suggesting impaired activation of muscle protein IGF-1-Akt pathway to play a role in the regulation and reduction of skeletal muscle growth (van Langenberg et al., 2014). Additionally, proinflammatory cytokines such as TNF- α and IL-6 are also, elevated and have shown to be associated with lower muscle mass and strength in an elderly population (Visser et al., 2002). Interestingly, several groups have reported that circulating IL-6 concentrations are higher in CD compared to UC and healthy controls (Mahida et al., 1991; Duclos et al., 1991; Gross et al., 1992). This may explain why the rate of sarcopenia, defined as “progressive and generalised loss of skeletal muscle mass and strength” (Santilli et al., 2014), has been reported in a recent meta-analysis as significantly higher in patients with CD than those with UC (60.7% vs 36.7%, $p=0.044$) (Eros et al., 2019).

The use of glucocorticoids has been suggested to induce loss of skeletal muscle mass and muscle weakness, contributing to a reduction in muscular strength and endurance (Sato et al., 2017). The debilitating effects of glucocorticoids in muscle deterioration are rapid and detected as early as 7 days after administration (Minetto et al., 2015). As muscles are a large site of protein, it is thought this deterioration occurs due to glucocorticoids suppressing protein synthesis, the naturally occurring process in which protein is produced to repair muscle damage, by glucocorticoids (Al-Jaouni et al., 2002). This causes a protein imbalance resulting in muscle wasting. A similar finding was noted in the elderly population, whereby there is a gradual decrease (3-5% every 10 years) in lower limb muscles and fewer changes in

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the upper body while taking steroids. However, it also showed that muscle performance was not independently associated with cumulative dose of corticosteroids or disease duration or severity (Izquierdo et al., 1999).

Malnutrition, particularly deficiencies in vitamin D as discussed previously is more prevalent in CD, has also been considered to contribute to muscle wasting and dysfunction. As skeletal muscle is a major reservoir for vitamin D, which is expressed in muscle cells and considered critical in the mediation of myogenesis, formation of muscle tissue, and contractility, changes in the length of muscle (Boland, 2011). These findings were supported by a cross-sectional study assessing strength performance in malnourished and well-nourished IBD individuals (n=94 CD, n=50 UC) and BMI, age and gender matched healthy controls (Valentini et al., 2008). This study identified significant reductions in HGS in malnourished people with CD (32.8kg; 95% CI 26.0-41.1; p=0.005) and with UC (31.0kg; 27.3–37.8; p=0.001) compared to well-nourished IBD participants. Interestingly, they also identified HGS was significantly decreased (p=0.005) in well-nourished IBD individuals in comparison to the healthy control group. These findings highlight the importance of detecting muscle weakness in people with IBD, particularly CD, and introducing interventions to stop any further impairment and improve physical performance.

2.5.4.3 Health-related quality of life

Quality of life (QOL) and health-related quality of life (HRQOL) are often used interchangeably in the literature and are complex, multidimensional concepts that usually involve subjective evaluations of both positive and negative aspects of life. QOL is a broader term covering all aspects of life. The World Health Organisation (WHO) (2019) define QOL as “an individual’s perception of their position in life in the context of the culture and value

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systems in which they live and in relation to their goals, expectations, standards and concerns” (WHO, 2019). Whereas, HRQOL is defined as “the state of well-being that is a composite of two components: (1) the ability to perform everyday activities that reflect physical, psychological and social well-being and (2) patient satisfaction with levels of functioning and control of the disease” (The Centre of Disease Control, 2018). It focuses on the socio-demographic, clinical and psychological effects of illness and the treatment-related determinants, encompassing several dimensions of life including physical functioning, psychosocial functioning, role functioning, mental health and general health perceptions (Cohen, 2002; Sainsbury and Heatley, 2005).

Although the presenting symptoms of IBD are mostly physical, the variability between active and quiescent disease states, uncertain disease course and prognosis, medical and surgical side effects and social and financial repercussions all contribute to an increased risk of depression and anxiety and further profoundly affect a person’s QOL (Sainsbury and Heatley, 2005; Graff et al., 2010). Bannaga and Selinger (2015) identified that up to 40% of people with IBD experience abnormal anxiety levels, and further went on to report higher rates of anxiety in IBD in comparison to the general population and other types of chronic diseases (Bannaga and Selinger, 2015). Similarly, rates of depression were three times higher compared to the healthy population in a large Canadian population-based study (Fuller-Thomson and Sulman, 2006). This is worrying, as 40-50% of people with IBD reporting high anxiety and depression scores were identified as more likely to flare-up within 6 months than those reporting lower scores (Bannaga and Selinger, 2015). The presence of these psychological co-morbidities has also been significantly associated with increased rates of hospitalisation (van Langenberg et al., 2010), poor sleep (Kinnucan et al., 2013) and fatigue (Jelsness-Jordensen et al., 2010). These are determinants that have all significantly been associated with reduced QOL scores at univariate analyses (all $p<0.003$) (Habibi et al., 2017).

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Disease activity remains the most significant predictor of physical and mental HRQOL and psychological impairments in IBD (Zhang et al., 2015). With moderate correlations identified between the Clinical Activity Index (CAI) ($r = -0.623$, $p=0.0003$), Endoscopic Activity Index ($r = -0.511$, $p=0.005$), Crohn's Disease Activity Index (CDAI) ($r = -0.506$, $p<0.001$) and Harvey Bradshaw Index (HBI) ($r = -0.600$, $p<0.001$) to disease specific, self-assessed QOL questionnaire (Kim et al., 1999; Zahn et al., 2006). However, disease activity does not explain the decrements completely, with more than 30% of asymptomatic individuals reporting an impaired QOL, suggesting a role for other determinants (Sajadinejad et al., 2012; Theede et al., 2015). While the American College of Sports Medicine (ACSM) (2014) suggests that individuals with chronic illnesses should counteract these detrimental psychological effects with exercise, the beneficial effects of exercise on the gastrointestinal tract in IBD have so far been little studied, with recommendations being based on studies involving healthy individuals (Moeller, 2005).

2.5.4.4 Fatigue

Fatigue is one of the most burgeoning and prevalent symptoms reported in people with IBD, experienced in nearly 80% of those with an active disease and in more than 50% of those with a quiescent disease it remains one of the leading and greater concerns identified by people with IBD, after diarrhoea (Levenstein et al., 2001; Romkens et al., 2011; Czuber-Dochan et al., 2015). It is understandable that fatigue increases during periods of active gut inflammation, however for it to persist in half of individuals with clinical and endoscopic remission affects both direct and indirect health costs (Bassi et al., 2004; Odes et al., 2006; Gibson et al., 2008). Although research in this area remains sparse, it has suggested that

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fatigue may be more common in women, and may be worse in people with Crohn's (Crohn's and Colitis UK, 2017).

A frequently used definition of fatigue is 'difficulty or inability to initiate or maintain activity', although given its multifactorial nature a simple definition may not capture the complexity of fatigue (Narayanan and Koshy, 2009). Fatigue can universally affect everyone, as much as 8% of the general population at any given time (Cullen et al., 2002) however in individuals with IBD it can appear differently and qualitatively of greater severity than in the general population (van Langenberg and Gibson, 2010). People with IBD have described fatigue as subjective, distressing and debilitating causing poor physical function and continued tiredness with sudden phases of overwhelming lack of energy, weariness and exhaustion that is not relieved following rest or sleep (Minderhoud et al., 2007; Czuber-Dochan et al., 2014). Similar fatigue components have been identified in other chronic conditions and end of life care, consisting of weakness, inability or difficulty initiating or maintaining everyday activities and poor concentration, memory and emotional stability (Carlson et al., 2004; Markowitz and Rabow, 2007).

Although it remains a major concern for people with IBD, optimal management of fatigue is poorly understood and literature on treatment strategies remain scarce. The Global Burden of Disease Study (2010) described 'health as more than avoiding death', with growing recognition of the importance of subjective symptoms. When applied to IBD this could mean more than 'achieving endoscopic and clinical remission'. Fatigue remains an under-recognised symptom and given its subjective and multifaceted nature it remains difficult to understand, measure and diagnose, a key obstacle in fatigue-related research (Graff et al., 2011). Several self-reported questionnaires have been developed to define and quantify fatigue, assessing fatigue for single to multiple dimensions covering domains such as mental, physical and social contexts (Guyatt et al., 1989; Czuber-Dochan et al., 2014). However, such

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questionnaires are not frequently used by clinicians due to time constraints and lack of knowledge of supportive tools when assessing individual needs, despite recommendations of national guidelines (National Institute for Clinical Excellence, 2004).

Research into the pathophysiological basis of fatigue is severely lacking and in need of a multidisciplinary approach to identify contributing factors, non-uniform mechanisms and subtypes of fatigue within the IBD population. There is an important need for prospective clinical trials involving pharmacological and non-pharmacological interventions to better understand this problematic burgeoning symptom, to compare effectiveness and allow the discovery of better treatment algorithms, therapeutic interventions and structured support for people with IBD.

2.6 Costs

The most recent care model in the UK estimated annual costs for treating UC to be £3084 and CD to be estimated at £6156 per individual (Ghosh and Premchand, 2015). However, these costs varied greatly depending on disease activity, with estimated annual costs for UC and CD in clinical remission ranging between £1693-£1800, respectively, and with a severely active disease between £10,513-£10,760 for CD and UC, respectively (Table 2).

A breakdown of these costs was based on the major medical and surgical treatment options, the adverse events of treatment therapies and IBD-specific complications (Appendix 2a). In contrast, another retrospective study identified mean costs for UC and CD to be £1256 and £1652 per person, respectively (Bassi et al., 2004). However, this study was conducted in 2004 when prevalence rates were significantly lower. Moreover, the use of biologics such as infliximab and adalimumab were not routinely used and as identified in Appendix 2a, these

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two different drug therapies are considerably more expensive than mesalazines and prednisolone which were the first line of treatment. While a UK audit estimated costs to be approximately £3,000 per person per year (UK IBD Audit Steering Group, 2012). This study did not take into consideration the adverse events of treatment or the complications associated with IBD and therefore is not thought to fully reflect the costs of IBD. With up to half of people relapsing every year and over 10,000 newly diagnosed cases every year, non-pharmacological interventions targeting secondary complications and thereby avoiding adverse events caused by treatment are warranted to reduce the financial burden and projected financial burden on the NHS.

Table 2. Cost per person per year with UC and CD

	Treatment	Adverse Events	Complications	Total Cost
UC				
Clinical Remission	£891.18	£40.60	£761.47	£1693.25
Mild to Moderate Disease	£1263.57	£878.19	£761.47	£2903.24
Severe Disease	£8016.82	£1981.94	£761.47	£10,760.23
Any individual with UC	£1752.70	£569.77	£761.47	£3083.94
CD				
Clinical Remission	£975.59	£145.83	£678.43	£1799.85
Clinical Relapse	£8627.50	£1207.10	£678.43	£10,513.03
Any individual with CD	£4801.54	£676.43	£678.43	£6156.44

2.7 Detection and diagnosis

Generally, the diagnosis of IBD is established on clinical presentation, physical examination, imaging studies and endoscopic/histological findings, however in some cases extra-intestinal manifestations, particularly in CD, such as ankylosing spondylitis, arthritis, erythema nodosum and uveitis are the initial presentation of IBD. The first line of investigations in

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people presenting symptoms such as abdominal pain and change in bowel habits are haematology and biochemistry blood tests, normally requested by a general practitioner (GP). Test results revealing anaemia, raised platelet count, low serum B12, low folate, iron deficiency, raised CRP and/or low serum albumin levels may suggest or detect an active IBD, but are not diagnostic (Crohn's and Colitis Foundation of America, 2010). However, tests could warrant further investigation and/ or referral to a gastroenterologist. A gastroenterologist suspecting a person with IBD would then request a faecal calprotectin (FC), if not already done by the GP, this provides an overview of the intestinal inflammatory status, if inflammation of the intestinal mucosa is present, polymorphonuclear neutrophils circulate around the inflammation and release calprotectin. FC concentration is positively associated with the intensity of the neutrophilic infiltration in the gut mucosa, i.e. the more inflammation present the higher the concentration of calprotectin (Roseth et al., 1999).

Although not yet widely used, FC is a useful adjunct to routine outpatient clinical assessment.

Endoscopies remain part of the first line investigations for IBD, providing immediate confirmation of the disease and its activity (figure 8a). Although an ileo-colonoscopy including segmental colonic and ileal biopsies is established as the first line of investigation for suspected CD, other methods such as computed tomography (CT), barium x-rays (figure 8b) and other radiological imagery are used to complement this diagnosis and determine ileal CD which is unreachable during an endoscopy. In UC, a colonoscopy of the large intestine is performed and biopsies obtained to determine the location and severity. However, as the disease extent can change after diagnosis, with up to half of individuals with ulcerative proctitis expected to develop a more extensive disease, usually within a year an ileo-colonoscopy is performed to definitively confirm the diagnosis of UC not CD and biopsies are taken to map the extent of the disease (Lanholz et al., 1996; Fumery et al., 2018).

Abdominal X-rays can also be performed in people with UC presenting with an active

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disease, to exclude colonic dilation (figure 8c). If histologic and clinical features are not typical of UC, an evaluation through CT or magnetic resonance imaging (MRI) of the small bowel is required to rule out CD (Gomollon et al., 2016).

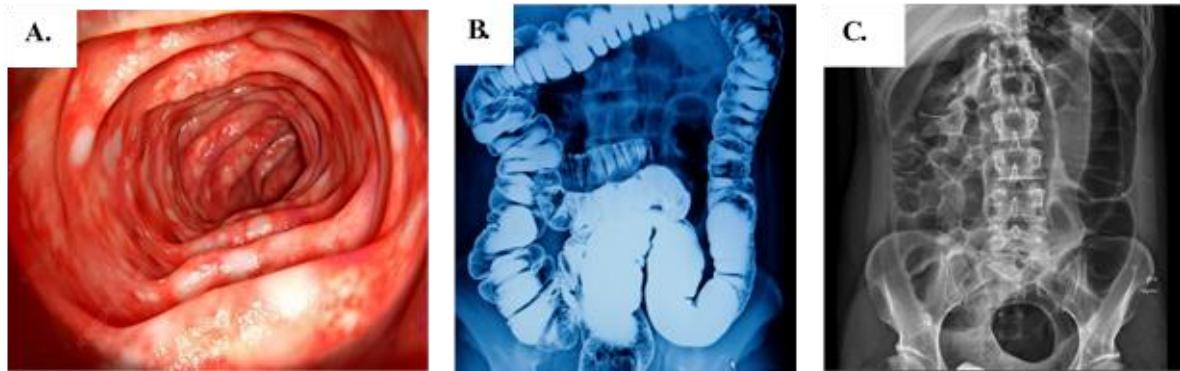


Figure 8. Detection and diagnosis. (A) Colonoscopic view of acute UC (Science Photo Library, 2019) (B) Barium follow through in active CD (IBDrelief, 2019) (C) Acute colonic dilation affecting the transverse colon in UC (Allan, 2018)

2.8 Pathway of care

Figure 9 illustrates the National Institute for Health and Care Excellence [NICE] (2019) overview pathway of care for CD and UC, respectively. Following the diagnosis of IBD, information and support is provided. Discussions about the disease, associated symptoms, treatment options, side effects and disease monitoring with the individual, family members and the multidisciplinary team are conducted and applied within the NICE's recommendations on a person's experience in adult NHS services. Individuals are advised in line with published NICE guidance on smoking cessation, medicine adherence, fertility, prognosis, cancer risk, surgery, diet and nutrition and contact details for support groups are provided.

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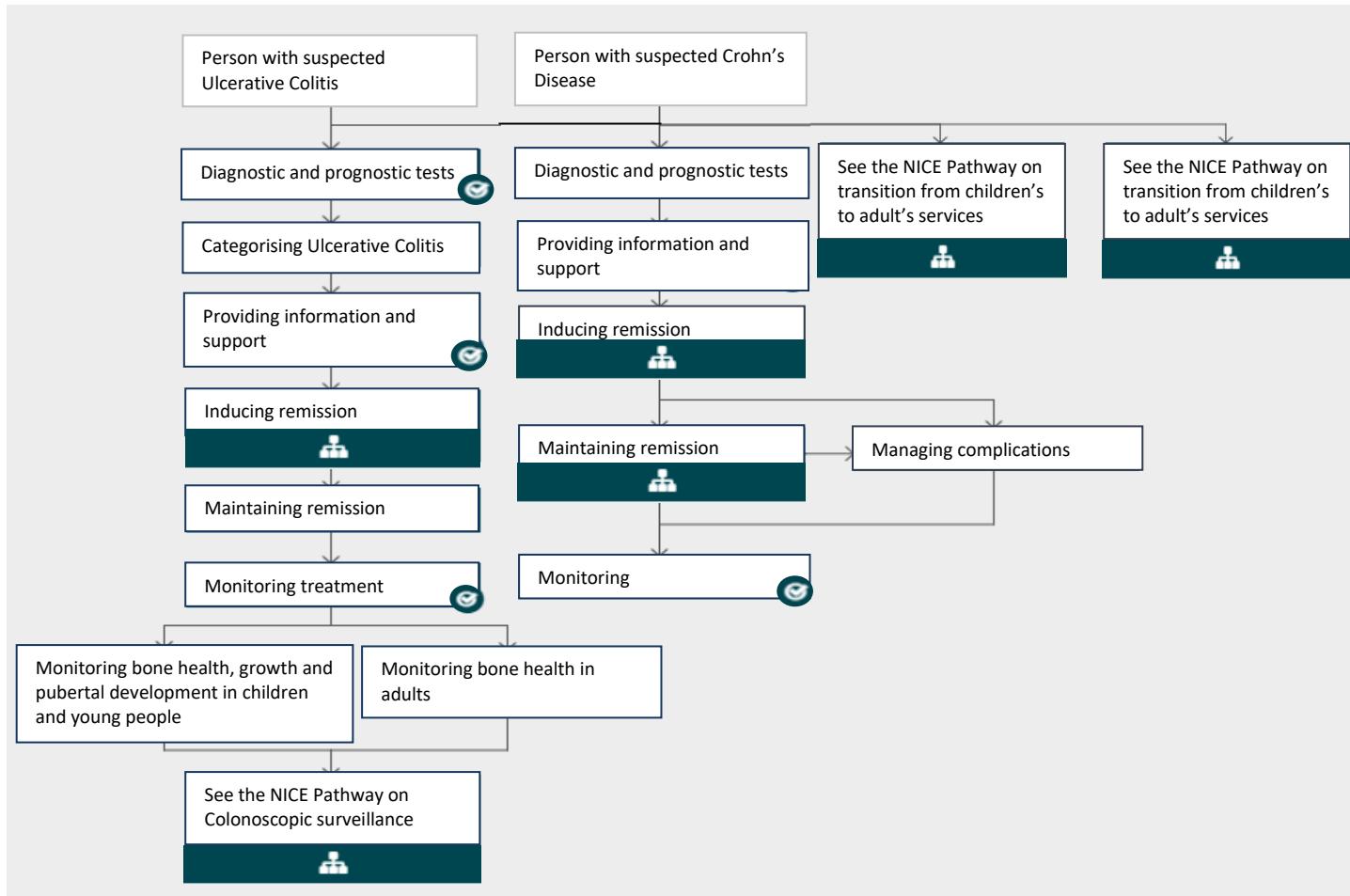


Figure 9. NICE Pathway of care for UC and CD overview (NICE, 2019)

Maintaining remission in IBD (figure 10 and 11) involves discussing how a person can manage their disease during periods of remission, including both no treatment and treatment options. Discussions that include the risk of exacerbations with and without drug therapies and potential side effects of drug treatments. Depending on the severity and location of the disease, medications such as aminosalicylates and immunosuppressant in UC and immunosuppressants and biologics in CD are suggested to maintain remission (NICE, 2019). However, maintaining and achieving clinical remission remains a clinical challenge with nearly half of people with IBD relapsing every year (Levine and Burakoff, 2011).

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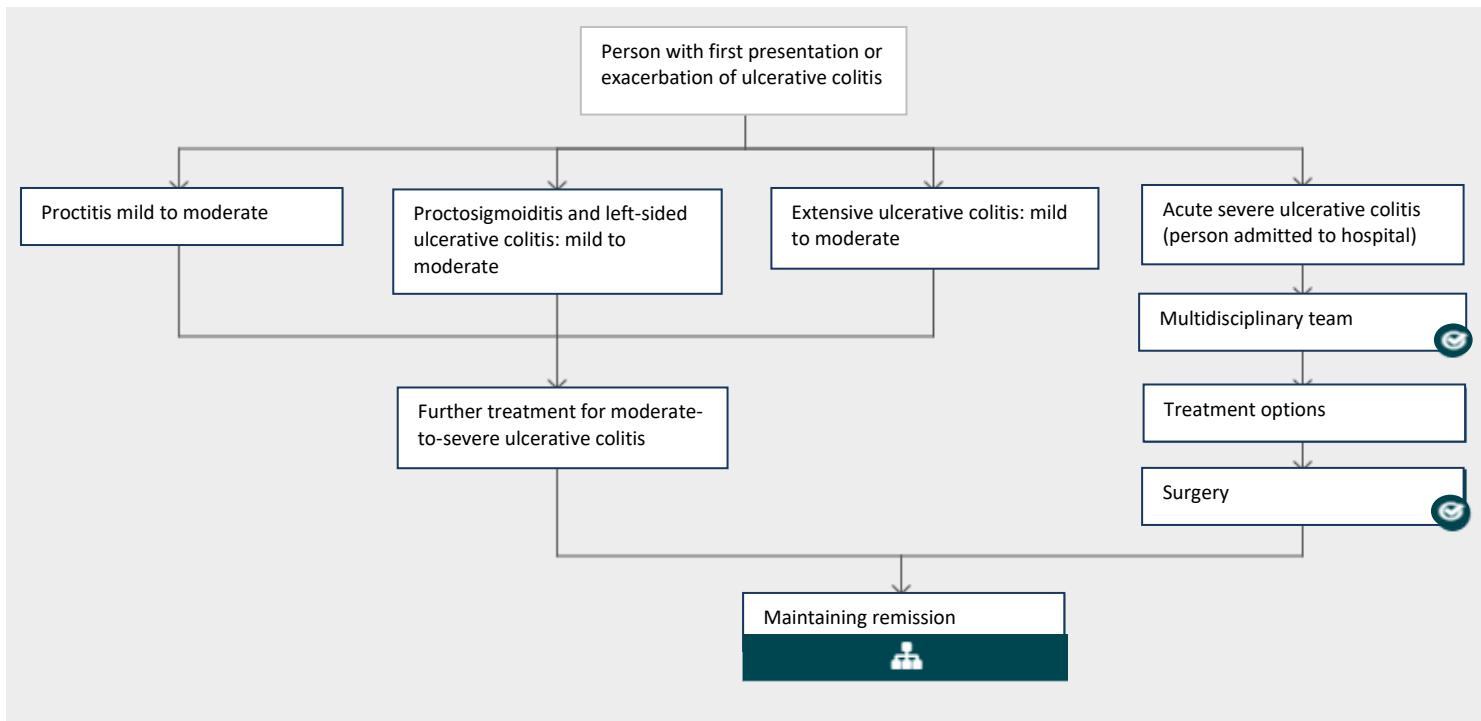


Figure 10. NICE Pathway for inducing remission in people with UC (NICE, 2019)

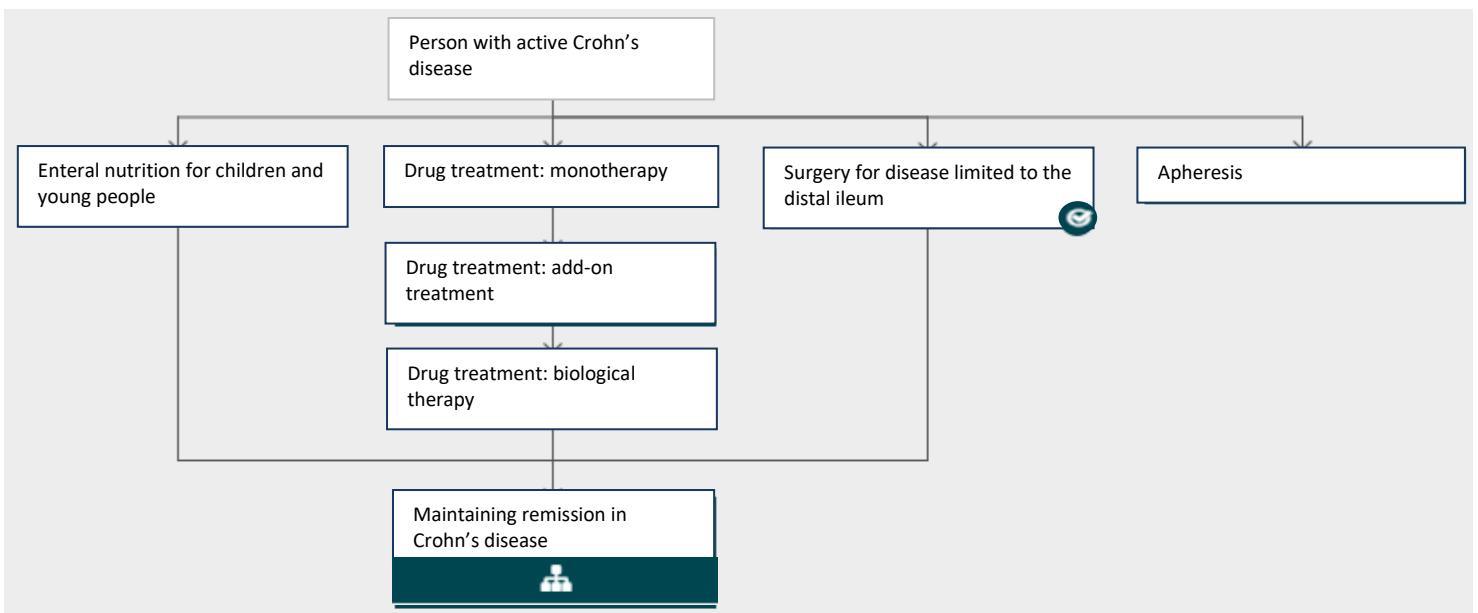


Figure 11. NICE Pathway for inducing remission in people with CD (NICE, 2019)

Monitoring the effects of drug treatment for toxicity, infection and liver cirrhosis in IBD is advised in the British National Formulary and often involves monitoring full blood count on a weekly basis for a set time and thereafter at reduced frequency to at least every 3 months. For

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monitoring infusions, individuals are observed for 1-2 hours with resuscitation equipment available, until at least 6 months into the treatment (BNF, 2019). NICE guidelines also recommend DEXA (dual-energy X-ray absorptiometry) screening in people with IBD with a history of vertebral fractures, are postmenopausal or male >50 years of age and vitamin D (400-800 IU/day) and calcium (0.5-1g/day) supplements for people with IBD with low BMD (American Gastroenterological Association, 2003; NICE, 2019).

2.9 Measuring disease activity

A summary of the tools available to measure disease activity are detailed in table 3. Measuring inflammatory activity remains important to assess the efficacy of medication, prevent disease progression and rule out the presence of intestinal complications, as discussed previously (Section 2.5.3). Disease activity has also been identified as a predictive factor of clinical relapse, surgery and refractoriness to medical treatments (Hanauer et al., 2002; Schnitzler et al., 2009), thus emphasising the importance of measuring and monitoring inflammation.

Considered the ‘gold standard’ for examining mucosal activity, an endoscopy provides direct evaluation and visualisation of mucosal healing, against validated scoring (D’Inca and Caccaro, 2014). Despite its benefits and important step in assessing disease activity, this method is invasive and is limited to examination of the mucosa and not deeper layers of the intestinal wall. In addition, the small bowel remains inaccessible by a conventional endoscopy method and an endoluminal examination of the small bowel involving a capsule endoscopy, push enteroscopy or balloon-assisted technology is required (Benitez et al., 2013). Therefore, cross sectional imaging techniques such as magnetic resonance imaging

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(MRI), computed technology (CT) and ultrasound (US) are emerging as appealing alternative tools to determine disease activity. These imaging techniques, particularly MRI, can provide information and evaluation of small bowel and colon, transmucosal activity and rule out complications such as wall thickening or stiffness, strictures, fistulae, narrowing or abscesses (Mizio et al., 2004; Maconi et al., 2006; Panes et al., 2011; D’Inca and Caccaro, 2014).

Although cross-sectional imaging techniques provide objective methods for assessing disease activity, they are not without their individual limitations and risks as reported in table 3. In addition, neither endoscopic or cross-sectional imaging are suitable for frequent assessment. Therefore, biomarkers such as C-reactive protein (CRP) and faecal calprotectin (FC) have been proposed as surrogate markers of intestinal inflammation. Despite the paucity of research to support the use of these non-invasive markers in the management and monitoring of IBD, they can confirm the presence of intestinal inflammation and should be used as a preliminary step to identify individuals requiring further investigation (D’Inca and Caccaro, 2014). Nevertheless, clinicians have a wide range of tools and should adopt a patient-tailored strategy combining these procedures to assess to determine disease activity, complications and efficacy of medication for the purpose of adjusting or changing treatment or for surgical referrals, as appropriate.

Table 3. Advantages and disadvantages of endoscopic, cross-sectional imaging and biomarker techniques for monitoring disease activity in IBD

Method	Advantages	Disadvantages
Endoscopy	<ul style="list-style-type: none">• Direct evaluation and visualisation of mucosal healing• Validated scores• High quality images comparable to other imaging modality• Biopsies can be taken	<ul style="list-style-type: none">• Invasive• Bowel preparation• Costs• Increased operative time and extensive knowledge• Limited to the examination of the mucosa

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-
- | | |
|---|---|
| <ul style="list-style-type: none"> • No radiation exposure | <ul style="list-style-type: none"> • Incomplete small-bowel examination |
| | <ul style="list-style-type: none"> • Poorly received by patients |
| | <ul style="list-style-type: none"> • Generally safe, but complications may occur |
| | <ul style="list-style-type: none"> • Sedation required |
-

Cross-Sectional Imaging

MRI	<ul style="list-style-type: none"> • Evaluation of small bowel • Detect complications • Non-invasive • No sedation required • No radiation exposure • Assessment of transmural and extramural activity 	<ul style="list-style-type: none"> • Costs • Requires bowel preparation/ contrast • Not suitable for some patients due to enclosed space (claustrophobic, obesity) or pacemakers • Time consuming • Movement impacts results • Technological expertise
CT	<ul style="list-style-type: none"> • Evaluation of small bowel • Detect complications • Quick nature • High quality images • Widely available and standardised use • Highly sensitive • Assessment of transmural and extramural activity 	<ul style="list-style-type: none"> • Radiation exposure • No validated scores • Requires IV contrast
US	<ul style="list-style-type: none"> • No radiation exposure • Non-invasive • Widely available • Useful for examining the terminal ileum and colon • Detect complications • Quick nature 	<ul style="list-style-type: none"> • Results depending on the knowledge and experience of the sonologist • Difficult to assess the proximal ileum, jejunum, transverse colon and rectum

Biomarkers

CRP	<ul style="list-style-type: none"> • Non-invasive • Cost-effective • Identify presence of inflammation • Quick to analyse 	<ul style="list-style-type: none"> • Can't determine the specific location of inflammation
FC	<ul style="list-style-type: none"> • Non-invasive • Cost-effective 	<ul style="list-style-type: none"> • May behave differently between patients • Uniform cut-off values

- Identify presence of inflammation
- Quick to analyse
- High sensitivity

IBD, Inflammatory Bowel Disease; MRI, Magnetic Resonance Imaging; CT, Computed Technology; US, Ultrasound; CRP, C-Reactive Protein; FC, Faecal Calprotectin

2.10 Management strategies

The primary target of medical therapy in IBD is a controversial issue, with many parameters suggesting remission is both clinical and endoscopic. However, there is no agreed definition.

An Australian retrospective study of 246 participants of whom 61% were in clinical remission, showed that only 35% demonstrated clinical and endoscopic remission features according to the Mayo endoscopic score (subscore of <1). Moreover only 16% were in histological remission (Bryant et al., 2017). There is a lack of evidence around histological remission, despite it being used as an outcome in many drug trials (Ardizzone et al., 2011; Colombel et al., 2011; Walsh et al., 2014; Bryant et al., 2014). Therefore, the growing consensus is that the treatment aim for IBD should be symptomatic remission combined with mucosal healing, from clinical, individual-reported and endoscopic features in addition to reducing rates of disease-related complications, surgery and hospitalisation (Levesque et al., 2015; Lamb et al., 2019). However, a widely used definition for clinical, endoscopic and histological remission is needed in clinical practice.

At present, there is no known cure for IBD, with overall disease management and treatment aims focused on reducing symptoms and maintaining or improving QOL (NICE, 2019).

Treating IBD often involves medications that can diminish symptoms and reduce the inflammation in the colon lining. Therapeutic decisions depend greatly on the disease activity and severity, however the most commonly used drug therapies in IBD are:

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- Aminosalicylates such as mesalazine or 5-amino salicylic acid (5-ASA) which act on the epithelial cells to moderate the release of cytokines and other mediators (Carter et al., 2004).
- Immunomodulators such as mercaptopurine or azathioprine suppress the immune system from attacking itself and thereby reduce the levels of inflammation (Lee et al., 2014).
- Corticosteroids (CS) such as prednisolone and budesonide are superior to aminosalicylates and immunosuppressants for inducing remission in IBD by reducing the activity of the immune system. However, the systemic side effects such as hypertension, cataracts, osteoporosis and hyperglycaemia have prompted a search for a safer alternative (Rampton and Shanahan, 2016). Guidance from the latest British Society of Gastroenterology consensus guidelines (Lamb et al., 2019) recommend that CS should be reserved for individuals with a mild to severe disease, with failure of response or those who are intolerant to other medical therapies.
- Anti-TNF- α drugs such as infliximab, adalimumab, vedolizumab, ustekinumab and methotrexate have changed the way of treating IBD and have been shown to be more effective for inducing and maintaining remission in CD than other drug therapies. However, using anti-TNF- α therapies in UC remains controversial with cohort studies demonstrating 67-78% of people with UC failing to respond to infliximab and 70-73% to methotrexate (Ferrante et al., 2008; Oussalah et al., 2010; Herfarth et al., 2018). Data around the use of vedolizumab and adalimumab in UC remain sparse and limited, however initial studies have demonstrated maintained remission in up to 25% of individuals (Colombel et al., 2014; Feagan et al., 2017). At the time of writing, ustekinumab does not have a licence or NICE approval for use in UC.

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While efficient in reducing the extent of the inflammation, most pharmaceutical compounds present a wide range of side effects such as insomnia, drowsiness, vomiting, weight gain and immune susceptibility that can reduce compliance, QOL and result in worsening of the condition (Rampton and Shanahan, 2016). In addition, when medical therapy fails or complications occur, surgical interventions may be required. With up to 8 in 10 people with CD and 23-45% with UC requiring surgery at some point throughout their diagnosis, the most common surgical procedures for IBD include (Crohn's and Colitis UK, 2019):

- Colectomy with ileostomy (figure 12a) involves the removal of all (subtotal) or most of the large intestine. The small intestine is then brought out through an opening in the abdomen wall and a bag is fitted.
- Stricturoplasty (figure 12b) to repair strictures and blockages by opening the narrowing that has occurred
- Resection (figure 12c) to remove the inflamed part of the intestinal tract and joining (anastomosis) the two ends together. Ileocaecal resection is similar, however involves the removal of the last part of the small intestine and first part of the large intestine.

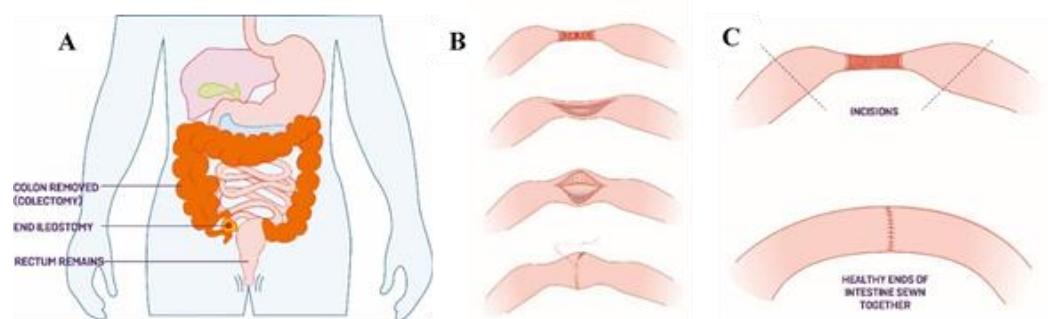


Figure 12. Common surgical interventions in IBD: colectomy with ileostomy (a), stricturoplasty (b) and resection (c) (Crohn's and Colitis, 2019)

A nutritional approach is also important in the management of IBD, however, nutritional education provided to people with IBD is given less attention in routine clinical practice due to lack of time and low quality and inconclusive evidence-based nutritional

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recommendations. Up to 68% of people with IBD manipulate their diet in an attempt to avoid the exacerbation of their disease and control symptoms (Cohen et al., 2013; Limdi et al., 2016). However, individuals often seek dietary advice from the internet, social media, friends and family or even other people with the condition, which may not be applicable to them, rather than from a healthcare professional (Hou et al., 2014). In an attempt to manage their disease by avoiding or limiting certain foods, up to 75% of CD and 62% of people with UC in remission experience an impaired nutritional status, often leading to nutritional deficiencies in B12, folic acid, calcium, iron and vitamin D that require supplementation (Ispas et al., 2015; Spooren et al., 2015). It is important that consistent advice, based on an individual basis, is provided to set realistic, evidence-based therapeutic expectations for the treatment and management of IBD.

2.11 The potential role of exercise as a management strategy

Defined as ‘any bodily movement produced by skeletal muscles that results in energy expenditure’, physical activity can be categorised into household, occupational or other activities (Caspersen et al., 1985). The ACSM (2017) defines exercise as the “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness”, including gait, balance, functional, strength, endurance and flexibility training.

As discussed previously, although EIMs such as reduced BMD and muscle dysfunction have been observed in both CD and UC, a greater prevalence has been reported in CD, likely to be as a result of proinflammatory cytokines, malnutrition and glucocorticoid usage (Repiso et al., 2006; Miznerova et al., 2013; Vavrikca et al., 2015). Therefore, exercise interventions focusing purely on CD individuals and targeting these EIMs are warranted. Although

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exercise represents as a line of treatment and has been recognised to counteract secondary complications in two diabetes mellitus, osteoporosis and arthritis, the potential benefits of exercise in CD has received little attention despite these conditions presenting similar characteristics and symptoms to CD (Schwingshacki et al., 2014; Hallsworth et al., 2015). During exercise, an osteogenic stimulus occurs, in which bone is subjected to forces induced by gravitational and muscle loading. Gravitational loads are typically reaction forces between the body weight and a substrate, whereas muscle loads involve contractile forces transmitted through the tendon that induce mechanical signals to the bone (Carter and Hinton, 2014). The size of the osteogenic effect relies greatly on the loading frequency, intensity and mode of exercise. During high strains of mechanical loading, substrate reaction forces can be up to 20 times the body weight, thus resulting in higher peak strains and a greater osteogenic effect than endurance exercises that have an approximate-substrate reaction force equivalent to body weight (Judex and Carlson, 2009). To resist the increase in mechanical strains, the bone initiates an adaptive response involving osteocytes that transduce the energy from the mechanical forces into biological signals that impact bone formation and resorption. These elicit bone deformation, stimulating the stretch-activated ion channel on osteocytes and trigger the expression of genes that mediate bone growth and increase the threshold of stress tolerance, thus eliciting an architectural modification (Zagdsuren, 2014). This explains why weight bearing and resistance exercise is often prescribed as a management or treatment option in other chronic diseases and for this reason, it is generally assumed that exercise is the best potent stimulator for skeletal growth, structure and maintenance to enhance BMD in people with IBD (Turner and Robling, 2004; Brotto and Johnson, 2014).

In 2016, the European Crohn's and Colitis Organisation (ECCO) consensus/guidelines stated that weight-bearing or resistive exercise, the cessation of smoking and excess alcohol consumption and maintaining adequate calcium intake (1g/day) should be implemented to

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prevent bone loss (Harbord et al, 2016). Despite this, few preventative interventions have been conducted in this high risk group and evidence remains inconsistent and weak with studies significantly limited by their small sample size, methodological robustness and lack of blinded outcome assessors, resulting in exercise guidelines being based on the beneficial effects found among healthy individuals and not specifically CD individuals (Narula and Fedorak, 2008).

2.12 Summary

In recent years, medical and surgical advances have been made, and a better understanding on the immune mediators of intestinal inflammation have become apparent. Although pharmaceutical and surgical interventions are effective in treating symptoms and preventing relapse, adherence to therapy can be as low as 40%, a contribution of the undesirable side effects (Kane et al., 2001). Complementary and alternative treatments or nonallopathic therapies as a primary or adjunctive therapy is widely prevalent among adults with CD with reports of 44-56% of individuals seeking alternate options (Weizman et al., 2012; Cheifetz et al., 2017). Given the benefits of exercise widely illustrated in the general population and chronic conditions including coronary heart disease, heart failure, cancer and metabolic syndrome it has become an important alternative therapy (Piña et al., 2003; Zou et al., 2014; Courneya et al., 2014). The role of exercise in the prevention, treatment and management of CD is poorly understood. Therefore, a review of the current literature on the benefits and harms of physical activity in CD will be discussed in more detail in Chapter 3 to support the development of providing safe and beneficial physical activity solutions instead of, or alongside, pharmacological therapies.

CHAPTER

3

Exercise training in adults with inflammatory
bowel disease: a systematic review

3.1 Introduction

Although the focus of this thesis is around CD, due to insufficient experimental studies looking specifically at CD and disease-specific extraintestinal manifestations this review will focus on the potential benefits of any mode of exercise, on any psychological or physiological outcome in individuals with IBD.

The burden of IBD is rising, affecting approximately 396 people in every 100,000, however with an 83.7% increase in cases from 1990 to 2017 in the UK projected annual costs to the NHS are expected to increase from £720 million to £1.5 billion by 2040 (Stone et al., 2003; Ghosh and Premchand, 2015; British Society of Gastroenterology, 2016). However, these estimates do not consider the ‘real price’ of IBD, which can impair QOL, impede career aspirations and profoundly affect psychological well-being (Bannaga and Selinger, 2015). Moreover, even during remission more than one third of adults with IBD are affected by disease-specific EIM’s beyond the intestinal tract such as low BMD, reduced muscular strength and endurance, impaired aerobic capacity and psychological well-being, which can be just as debilitating as the primary disease (Ott and Scholmerich, 2013). With detrimental health and economic effects, cost effective health innovations need to be identified and implemented to help manage this complex and costly disease.

Exercise has been suggested to counteract several IBD-specific complications, with different types of exercise eliciting corresponding physiological adaptations. Increases in stroke volume, cardiac output and oxygen uptake occurring as a result of aerobic training and adaptions of the skeletal system and muscle hypertrophy occurring as a result of resistance training (Peters et al., 2001; Perez, 2009; Rivera-Brown and Frontera, 2012). The role of exercise as a therapeutic option in IBD remains poorly understood, with exercise guidelines being based on the beneficial effects found among healthy individuals and not specifically

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IBD individuals (Narula and Fedorak, 2008). Given the insufficient evidence it remains unclear what type, duration, frequency or intensity is safe and beneficial for people with IBD. With the substantial costs to the individual and health care system and 44-56% of individuals seeking complementary therapy it is important to evaluate the potential benefits of different modes, intensities, frequencies and durations of exercise regimens and to explore the safety, attrition, adherence and acceptability of these interventions. In doing so, it will allow the integration of the best evidence available to inform evidence-based recommendations. The purpose of this review, therefore, was to systematically review experimental studies that investigated the effects of any mode of exercise intervention on physiological and psychological outcomes in adults with IBD.

3.2 Methods

This systematic review was prospectively registered in an international database of systematic reviews in health-related research (CRD42017077992; <https://www.crd.york.ac.uk/prospero/>). Deviations from the study protocol are detailed in Appendix 3a. The Cochrane Handbook and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were adhered to (Higgins and Green, 2008; Moher et al., 2009).

3.2.1 Study Selection

Types of studies

Experimental studies such as randomised controlled trials (RCT) and non-RCT's assessing the effects of exercise training, of at least 4 weeks duration, in adults with IBD were included. Unpublished trials and conference abstracts were only included if the

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methodological descriptions were provided, either in written form or by direct contact with the authors. Short papers with incomplete data presented, such as case reports, case series or qualitative research were excluded. All other study designs were excluded.

Types of participants

Participants had to be aged ≥ 18 years with a clinical diagnosis of IBD (CD, UC or IBD-unclassified) of at least 6 weeks duration (using conventional clinical, radiographic, histologic and endoscopic criteria). Any other type of colitis or irritable bowel disease were excluded. There were no restrictions on gender, previous medication, disease severity and disease activity status.

Types of interventions

All modes of exercise interventions such as aerobic, resistance, aquatic, balance and co-ordination training were included. Trials comparing one form of exercise versus another, different intensities, another non-exercise intervention, no intervention or receiving usual care were included. There were no restrictions on the exercise intervention setting or mode of supervision (e.g. inpatient, outpatient, home-based, unsupervised, supervised). Studies reporting an exercise programme with duration of less than 4 weeks were excluded.

Types of outcome measures

Studies must have reported at least one of the following outcomes for inclusion: bone health, muscular function, QOL, psychological well-being, disease activity, physical activity, body composition, cardiorespiratory fitness, immune function, fatigue, safety, feasibility and acceptability. A detailed list of outcome measures can be found in Appendix 3b. Where outcomes have been measured but not reported, authors were contacted and data requested.

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3.2.2 Search Strategy

Electronic databases from inception to May 2019 were searched: MEDLINE, EMBASE, CINHAL, Cochrane Central Register of Controlled Trials (CENTRAL) and SPORTDiscus. The search strategy and MESH terms used included: physical activity, exercise, exercise therapy, sports, resistance training, endurance training, aerobic training and physical fitness. These terms were paired with inflammatory bowel disease, IBD, Crohn's disease, ulcerative colitis and indeterminate colitis. The full strategy can be found in Appendix 3c. Reference lists and citation tracking of all included studies were searched to locate relevant further studies of interest. Search strategy terms were limited to those in English and pertaining to human participants.

Ongoing clinical trials and unpublished studies were searched on the following research registers: clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) and International Standard Randomised Controlled Trial Number Registry (ISRCTN). All searches were carried out by the same author (KJ) and search results generated by the electronic databases were exported to EndNote (V8.2), where duplicates were removed. The first 10% of abstracts and titles were examined independently by two review authors (KJ and RK), due to good agreement (k 0.855, indicating an almost perfect agreement) (McHugh, 2012), the remaining texts were screened by one reviewer (KJ). If a study appeared to meet some criteria, but was unclear, the full text article was retrieved for clarification. Discrepancies were referred to by a third author (GT or KB) and disagreements were resolved by consensus. Review authors were not blinded to the author, institution or the publication source of the study. Full text articles were retrieved for further screening and independently assessed by two reviewers (KJ and RK) who recorded reasons for exclusion (Moher, 2009).

3.2.3 Data Extraction

To facilitate data extraction, the ‘Cochrane Data Collection Form for Interventions: RCTs and non-RCT’s’ was used to extract and record information. This form was used to adhere to the Methodological Expectations of Cochrane Intervention Review standards for collecting and reporting information, recommended by Cochrane to improve and maintain quality of the systematic review (Higgins et al., 2017). One review author (KJ) independently extracted data from the included studies with a second review author (RK) independently checking the data extraction forms for accuracy and completeness, with disagreements resolved through consensus of a third review author (GT or KB). Extracted information included general information, trial characteristics, intervention details, participant characteristics, outcomes and results

Data were entered in Review Manager (RevMan 5.3) by one reviewer (KJ) and random checks on accuracy were performed by the second reviewer (RK), who kept a record of any discrepancies.

3.2.3.1 Dealing with Missing Data

Where data were missing or unclear, the primary author of the trial was contacted via email and relevant information was requested. At least two emails were sent out to the corresponding author(s).

3.2.4 Risk of Bias (RoB)

The internal validity and methodological rigor of each study was assessed independently by two review authors (KJ and RK) using the revised Cochrane ‘Risk of Bias’ tool (RoB 2.0) for

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randomised trials and the ‘Risk of Bias In Non-randomised studies-of Interventions’ (ROBINS-I) for non-randomised studies (Higgins et al., 2016). Discussion between the two review authors was utilised to resolve any discrepancies in judgment of RoB or justifications for judgement, with a third author (GT or KB) referred to in the case of any unresolved discrepancies. The RoB 2.0 addressed five domains and each domain was judged as ‘low’, ‘some concerns’ or ‘high’ risk. The ROBINS-I response for each domain was defined as ‘low’, ‘moderate’, ‘no information’, ‘serious’ or ‘critical’ risk.

3.2.5 Data Synthesis

Where appropriate, data were inputted into Review Manager and clinical and methodological diversity was independently assessed by two review authors (KJ and RK) in terms of participants, interventions, outcomes and study characteristics to determine the appropriateness of a meta-analysis. However, due to the unavailability of data, lack of intention-to-treat analysis and heterogeneity in interventions, outcome measures, metric used and study designs it was deemed that a subgroup analysis, sensitivity analysis and meta-analysis would be inappropriate.

3.3 Results

The search strategy generated 3,322 potentially eligible articles. After excluding 609 duplicates and screening 2,713 titles and abstracts, 31 articles were retrieved and examined for full-text screening. On completion of full-text screening a further 21 were excluded. Therefore, 10 articles were eligible for inclusion in this review. The PRISMA flow chart depicting the flow of study information through the different phases of this systematic review is shown in figure 13.

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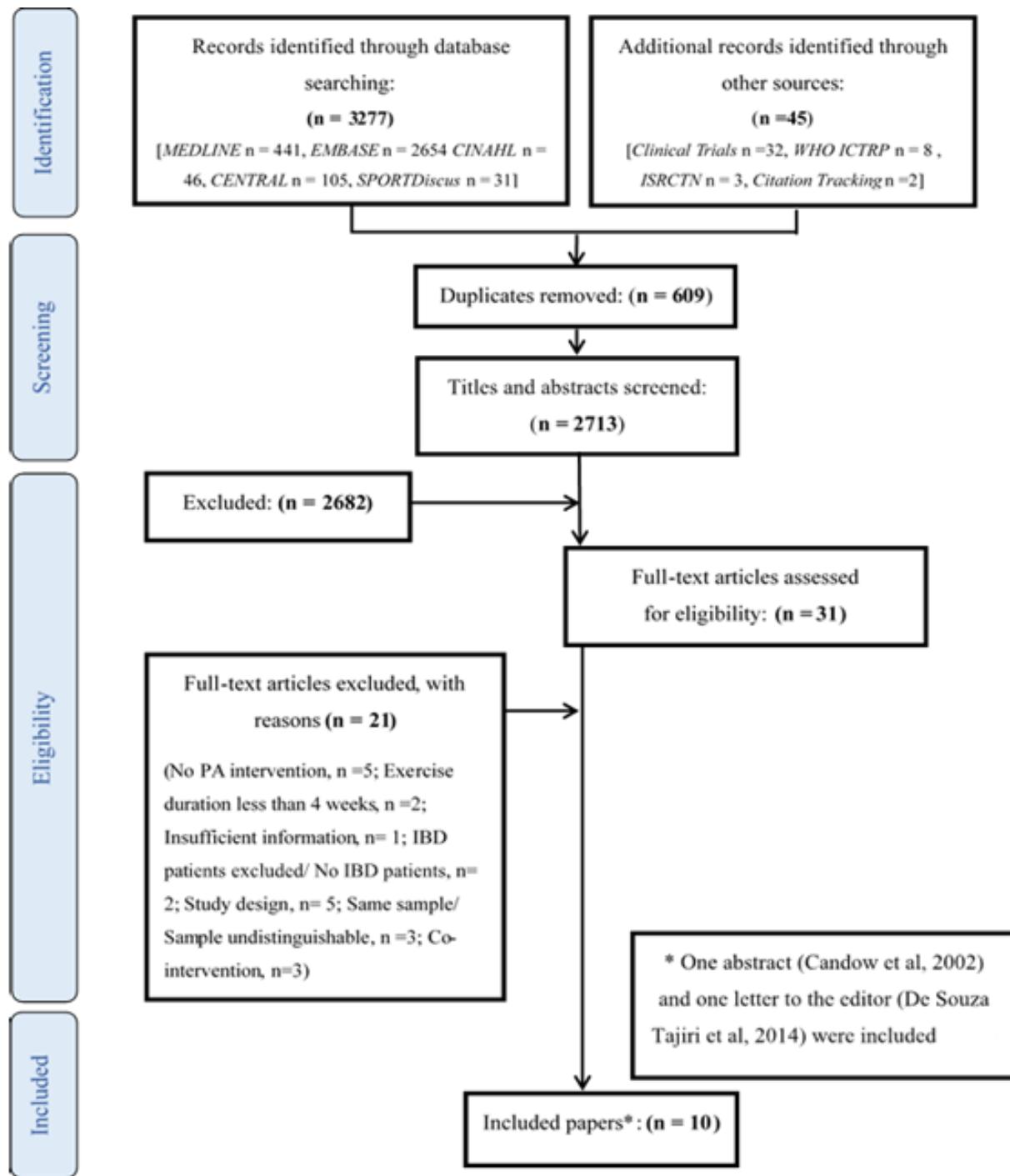


Figure 13. PRISMA flow diagram of literature search and study selection phases

n, number; CENTRAL, Cochrane Central Register of Controlled Trials; WHO ICTRP, World Health Organisation International Clinical Trials Registry Platform; ISRCTN, International Standard Randomised Controlled Trial Number Registry; PA, Physical Activity

3.3.1 Characteristics of included studies

Study characteristics are detailed in table 4. Of the ten included studies published between 1998 to 2019, five were RCT's (Robinson et al., 1998; Ng et al., 2007; Sharma et al., 2015; Klare et al., 2015; Cramer et al., 2017), one employed a feasibility RCT design (Tew et al., 2019), one delivered a randomised cross-over design (Cronin et al., 2019) and three used a quasi-experimental design: an uncontrolled pilot study (Loudon et al., 1999), an uncontrolled cohort study, published as a conference abstract (Candow et al., 2002) and one uncontrolled pilot study, published as a letter to the editor (De Souza-Tajiri et al., 2014). The conference abstract and letter to the editor were included in this review due to their relevance. Excluding the three studies with no control group (Loudon et al., 1999; Candow et al., 2002; De Souza-Tajiri et al., 2014), six studies employed a stratified block randomisation and one study (Cronin et al., 2019) employed a simple randomisation process.

The ten included articles comprised of 429 participants (39% males). Information on participant's age were unavailable for one study (De Souza-Tajiri et al., 2014), excluding this conference abstract, the mean age was 36. Four of the studies included both CD and UC participants, five included CD participants only and one included UC participants only. In seven studies, participants had inactive or mildly active disease ($n=7$), in one study participants had a mild to moderately active disease ($n=1$) and in two studies disease activity status was not specified.

Of the ten studies, two delivered a walking programme, two delivered a yoga intervention, one delivered a running programme, one delivered high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) programmes, three delivered a resistance training intervention and one delivered a combined resistance and aerobic training programme. The mode of delivery, was supervised in five studies (Loudon et al., 1999;

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Klare et al., 2015; Cramer et al., 2017; Cronin et al., 2019; Tew et al., 2019), home-based in Ng et al's (2007) study, supervised and home-based in Robinson et al's (1998) study and home-based following an introductory session in Sharma et al's (2015) study. Two studies did not provide information on the mode of delivery (Candow et al., 2002; De Souza-Tajiri et al., 2014).

Included studies had a median sample size of 31 (range 12–107) per study, 12 to 60 per exercise intervention and 0 to 57 per control group. Study duration was between 8 weeks and 12 months, with a median duration of 12 weeks ranging from 1 to 3 sessions a week and 20 minutes to 90 minutes per session, excluding 5 studies (Robinson et al., 1998; Loudon et al., 1999; Candow et al., 2002; Klare et al., 2015; Cronin et al., 2019) who did not report exercise duration or had a progressive programme that increased duration throughout the study. A low intensity exercise intervention was delivered in four studies, two studies implemented a moderate intensity programme and one study delivered HIIT and MICT. Three studies did not quantify exercise intensity (Loudon et al., 1999; Candow et al., 2002; De Souza-Tajiri et al., 2014). A usual care group was included in six out of the ten studies, there was no control group in three studies and one study included a self-care group involving books on the pathology and pathophysiology of UC (Cramer et al., 2017).

Of the outcome variables measured in the ten included studies, two studies measured stress using the IBD Stress Index (IBDSI) (n=2). Six studies assessed disease activity using the HBI (n=4), CDAI (n=1), Rachmilewitz Index (RI) (n=2), CRP (n=2), FC (n=1) and Simple Colitis Index (SCI) (n=1). Immune parameters such as leucocytes (n=1), T lymphocyte subsets [Th1/Th2/Th17] (n=1), serum eosinophilic cationic protein (n=1), soluble interleukin-2 receptor (n=1), IL-8 (n=1), IL-10 (n=1), IL-6 (n=1), and TNF-a (n=1) were examined in two studies. BMD at the femoral neck, greater trochanter and lumbar spine was measured using a DEXA in one study. HRQOL was measured in six studies using the IBD QOL Questionnaire

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(IBDQ) (n=5), EuroQol EQ-5D-5L (n=1) and the short form 36 (SF-36) (n=1).

Maximal isometric knee extension strength (n=1), knee extension 1 repetition maximum (1-RM) (n=1), 1-RM leg press and chest press (n=1) were examined in two studies.

Cardiorespiratory fitness was assessed using the Canadian fitness step test to measure $\dot{V}O_2$ max in one study and a cycle ergometer to measure ventilatory threshold and peak oxygen uptake in another study. Two studies measured anxiety using the State and Trait Anxiety Scale (STAI) and depression using the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory II (BDI-II) was used in one study. Three studies determined body composition and only one measured fatigue, using the IBD Fatigue Scale (IBD-F) (Tew et al., 2019).

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Table 4. Characteristics of included studies

Author/Year	Study Design	Participants	Interventions	Outcome measures
Robinson et al (1998)	RCT	107 CD participants with mild to moderate disease activity [IG=60, CG=57]. 48 males. Mean age 40.7	IG: 12-month twice-weekly home-based low-impact progressive resistance training programme	BMD (DEXA) at the femoral neck, greater trochanter and lumbar spine taken at baseline and 12 months
			CG: Usual care	
Loudon et al (1999)	Uncontrolled pilot study	12 CD inactive or mildly active participants, no controls. 2 males. Mean age 38.5	12-week supervised (indoor track) and unsupervised (outdoors) walking programme 3 sessions (20 min per session, leading to 35 min) a week	Stress (IBBSI), HRQOL (IBDQ), disease activity (HBI), aerobic fitness (VO ₂ Max), BMI at 1 and 3 months
Candow et al (2002)	Conference abstract; Uncontrolled cohort study	12 CD participants, no controls. 5 males. Age range 34-51	Resistance training programme consisting of 3 sets, 8-10 repetitions, 12 exercises working at 60-70% of 1RM 3 times a week over 12 weeks	Disease activity (HBI), muscle strength (1-repetition maximum leg press and chest press) at 1 and 3 months
Ng et al (2007)	RCT; Stratified randomisation	Inactive or mildly active 32 CD participants [IG=16, CG=16]. 14 males. Mean age 38.8	IG: 3-month independent low intensity walking programme, working at 40% of aerobic capacity for 30 minutes, 3 times a week	HRQOL (IBDQ), stress (IBDSI) disease activity (HBI) at baseline, 1, 2 and 3 months. PA habits (IPAQ-Long) at baseline and 3 months
			CG: Usual care and asked to maintain their habitual PA levels	

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De Souza-Tajiri et al (2014)	Letter to the editor; Uncontrolled pilot study	19 women with IBD [CD=10, UC=9] and quadriceps weakness. No controls	8-week progressive supervised resistance training programme twice a week lasting 20 minutes	HRQOL (IBDQ) and quadriceps strength (maximal isometric quadriceps strength and quadriceps 1-RM)
Sharma et al (2015)	RCT	87 IBD [CD=36, UC=51] participants in clinical remission [IG=50, CG=50]. 54 males. Mean age 34.7	IG: One supervised yoga session, followed by 7 weeks 1 hour daily home-based sessions CG: Usual care	Cardiovascular autonomic functions (heart rate variability through ECG), immune markers (ECP, sIL-2R) and anxiety (STAI) at baseline and 2 months. Clinical symptoms (diary) were recorded
Klare et al (2015)	RCT	30 IBD participants [CD=19, UC=11] with an inactive to moderate disease [IG=15, CG=15]. 8 males. Mean age 41.1	IG: Supervised moderate intensity outdoor running, 3 times a week for 10 weeks CG: Asked to maintain their current lifestyle behaviours and avoid PA exceeding two hours per week	HRQOL (IBDQ), disease activity (CDAI and RI), BMI, inflammatory markers (CRP and FC) and immune parameters (LC) at baseline and 10-week follow-up
Cramer et al (2017)	RCT	77 UC participants [IG=39, CG=38] in clinical remission. 19 males. Mean age 45.8	IG: 12-week traditional hatha yoga programme, 90 minutes per week CG: Received two evidence-based self-care books and were offered the same yoga classes at week 24	HRQOL (IBDQ) and disease activity (CAI) at week 1, 12 and 24
Cronin et al (2019)	RCT partial cross-over trial	17 IBD participants [CD=7, UC=13] in clinical remission.	IG: Combined progressive aerobic and resistance, 3 times a week for 8 weeks.	QOL (SF-36), disease activity (HBI and SCI), psychological well-being (HADS,

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		15 males. Median age of IG=33 and CG=31		STAI and BDI-II), body composition (DEXA), pro-inflammatory cytokines (IL6, IL8, IL10 and TNF-a), gut microbiome (α and β -diversity) at baseline and 8 weeks
			CG: Usual care, followed by exercise phase after 8 weeks	
Tew et al (2019)	Pilot RCT	Inactive or mildly active 36 CD participants [IG1=13, IG2=12, CG=11]. 17 males. Mean age of IG1=37, IG2=38.5 and CG=25	IG1: HIIT of ten 1-minute bouts of cycling at 90% of Wpeak interspersed with 1-minute bouts of 15% of Wpeak 3 times a week for 12 weeks	Feasibility, acceptability, safety, HRQOL (IBDQ), QOL (EQ-5D), Fatigue (IBD-F), psychological well-being (HADS) and physical activity habits (IPAQ) at week 1, 13 and 26. Body mass, waist circumference, blood pressure, resting heart rate, cardiorespiratory fitness (Ventilatory threshold and peak oxygen uptake), disease status (CDAI) and inflammatory status (FC) at week 1 and week 13.
			IG2: MICT of 30 minutes of cycling at 35% Wpeak. 3 times a week for 12 weeks	
			CG: Usual care group, offered an exercise consultation following study completion	

IG, Intervention Group; CG, Control Group; CD, Crohn's Disease; UC, Ulcerative Colitis; HRQOL, Health-Related Quality of Life; BMI, Body Mass Index; IBD, Inflammatory Bowel Disease; IBDQ Inflammatory Bowel Disease Questionnaire; HBI, Harvey Bradshaw Index; RCT, Randomised Controlled Trial; FC, Faecal Calprotectin; CRP, C-reactive Protein; RI, Rachmilewitz Index; DEXA, Dual-Energy X-Ray Absorptiometry; PA, Physical Activity; IPAQ, International Physical Activity Questionnaire; ECG, Electrocardiogram; CAI, Clinical Activity Index; SCI, Simple Colitis Index; STAI, State and Trait Anxiety Index; BDI-II, Beck Depression Inventory-II; SF-36, Short-Form 36; LC, Leucocytes; sIL-2R, Soluble Interleukin-2 Receptor; ECP, Eosinophilic Cationic Protein; HIIT, High-Intensity Interval Training; MICT, Moderate-Intensity Continuous Training; WPeak, Peak Power Output

3.3.2 Risk of Bias

Figure 14 and 15 illustrates a graph (A) and summary (B) of the risk of bias decisions made per category using the RoB 2.0 tool and ROBINS-I, respectively. Regarding the no information domain, study authors were contacted for further clarification. Due to the nature of the interventions, all participants in all studies were aware of their group allocation which is of particular importance when considering outcome measures such as physical activity habits that could be influenced by the lack of blinding. Following the elaboration and algorithm guidance from the RoB 2.0 tool (2019), only 3 of these studies (Ng et al., 2007; Sharma et al., 2015; Cramer et al., 2017) were considered to have some concerns due to lack of a blinded outcome assessor, no information reported on whether deviations arose and no information on adherence to the intervention that could have affected outcome measures.

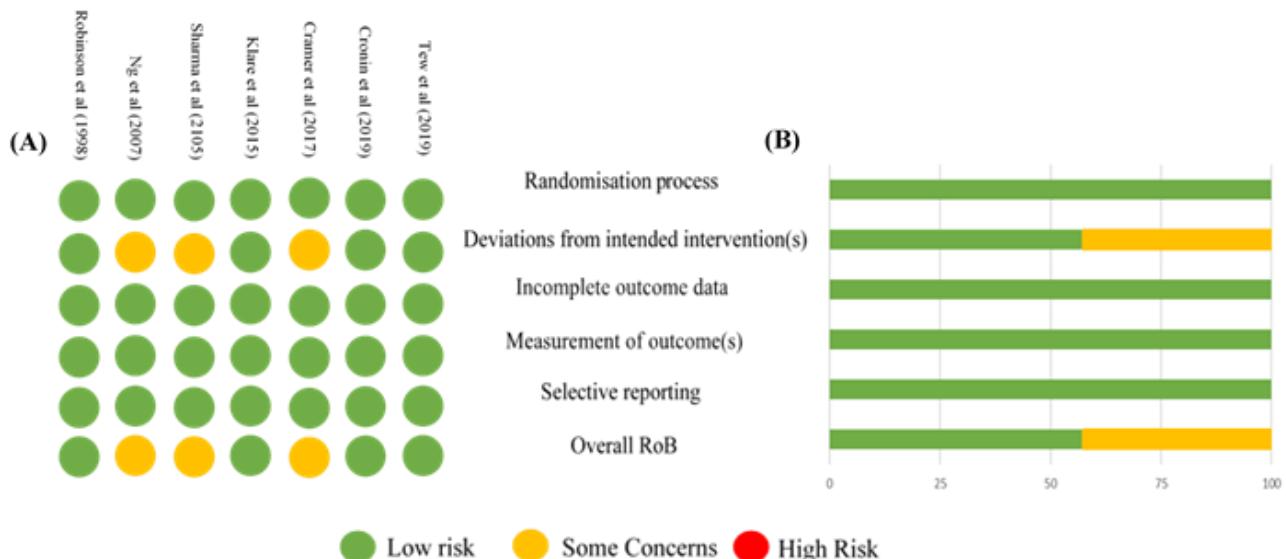


Figure 14. Risk of bias graph (A) and summary (B) using the RoB 2.0 tool

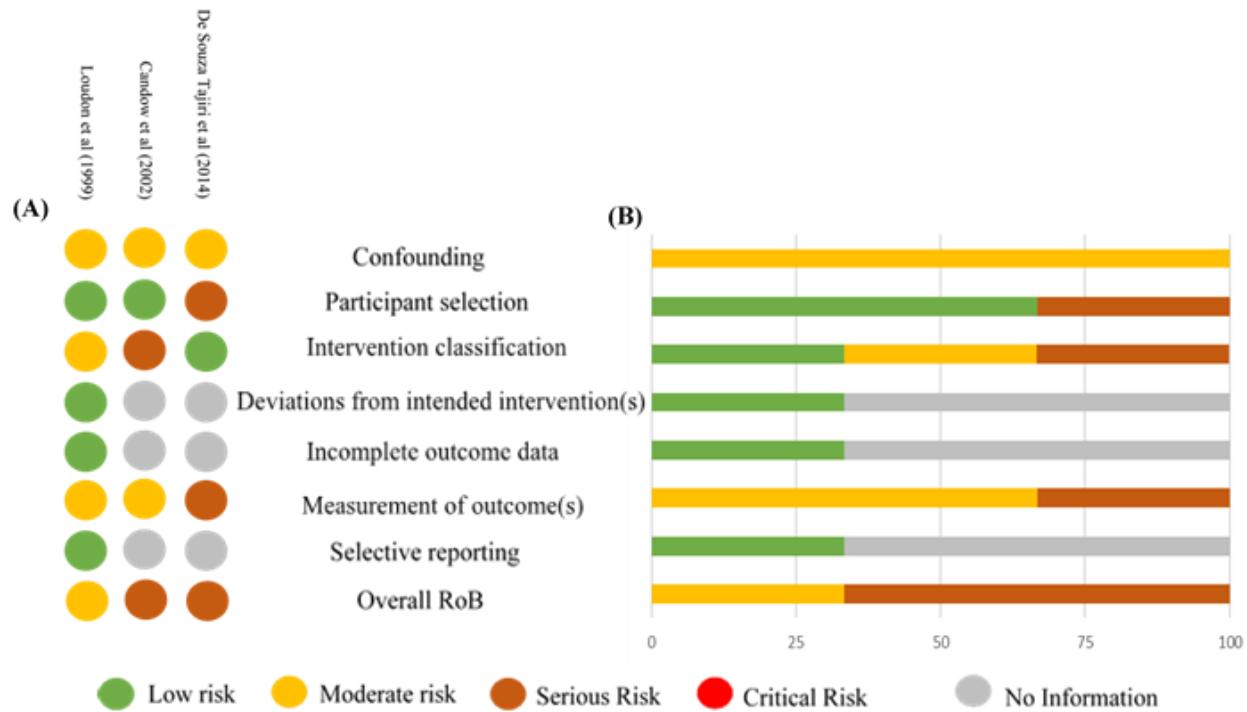


Figure 15. Risk of bias graph (A) and summary (B) using the ROBINS-I

Following the elaboration and algorithm guidance from the ROBINS-I tool (2016), all studies were suggested to have a moderate risk for bias of confounding due to them being non-randomised studies and they therefore cannot be considered comparable to a well-performed RCT. No information for bias of deviations from intended intervention, incomplete data and selective reporting were available for two studies, as one was an abstract and the other a letter to the editor. Measurement of outcome(s) bias was moderate to serious for all studies due to the lack of blinded outcome assessor.

3.3.3 Bone Health Outcomes

Only one included study explored the effects of an exercise intervention on bone health. This study evaluated a 12-month home-based low-impact resistance training programme on BMD, measured by dual energy x-ray absorptiometry (Lunar DPX) in 107 CD participants with mild to moderate disease activity (Robinson et al., 1998). This twice-weekly resistance

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training programme involved 12 floor exercises using resistance tubing or free weights. Following the conclusion of this RCT, although differences in means were seen at the greater trochanter ($\Delta=0.86\%$; 95% CI -1.95-3.65; $p=0.55$), femoral neck ($\Delta=0.50\%$; 95% CI -1.39-2.39; $p=0.60$) and lumbar spine ($\Delta=0.77\%$; 95% CI -0.97-2.51; $p=0.32$) in the exercise group ($n=53$) compared to the control group ($n=54$), the 95% confidence intervals and p values at all sites do not demonstrate strong evidence of BMD improving. However, due to the cyclical nature of CD only 13% of the exercise cohort were fully compliant, interestingly those who were fully compliant ($n=14$) showed a statistically significant difference at the greater trochanter ($\Delta=4.67\%$; 95% CI 0.86-8.48; $p=0.02$) and greater mean difference improvements at the femoral neck ($\Delta=2.99\%$; 95% CI -7.67-1.68; $p=0.19$) and lumbar spine ($\Delta=2.21\%$; 95% CI -6.74-2.30; $p=0.30$).

3.3.4 Muscular Function

Two studies examined the effect of resistance training on muscular function. The first study (Candow et al., 2002) examined the effects of a thrice-weekly supervised intervention in 12 CD participants. This programme consisted of 3 sets of 8-10 repetitions using 12 different machines working at 60-70% of 1-RM. Similarly, De Souza-Tajiri et al's (2014) supervised study of 19 IBD participants (CD=10, UC=9), focusing on the quadriceps only, twice weekly for 8 weeks consisted of 20 minute sessions working at 50% maximum load with a gradual increase of 10% every week until 80% maximum load was reached, performing 3 sets of 12 repetitions. Both of these uncontrolled studies identified a significant increase in muscle strength ($p<0.05$ and $p<0.01$, respectively), with Candow et al (2002) reporting no changes in disease activity assessed using the HBI. This indicates that, although more research is needed, these preliminary studies provide support to resistance training being safe for individuals with IBD.

3.3.5 Fatigue

Only one study assessed fatigue; the study of Tew et al. (2019), which explored the effects of 12 weeks of HIIT or MICT in adults with inactive or mildly active CD. This recent pilot trial randomised 36 participants to either HIIT, MICT or usual care. Participants allocated to the HIIT took part in ten 1-minute bouts of cycling at 90% of peak power output (Wpeak) interspersed with 1-minute bouts of 15% Wpeak. The MICT involved 30 minutes of cycling at 35% Wpeak. Intensity for both groups was progressed after weeks 4 and 8 based on Wpeak recordings during testing visits. After the initial 12-week supervised intervention, exercise participants were encouraged to continue exercising at a similar intensity, duration, frequency and type at their home or in a community setting.

Following the intervention the mean change in total fatigue severity, frequency and duration, assessed using the IBD-F from baseline to 3 months and 6 months was (0.1;-0.7) in the HIIT group and (0.5;-0.5) in the MICT group. However, given the intentionally small sample size the study was underpowered to detect effect and therefore results should be interpreted with caution. Nevertheless, post exit interviews confirmed 8 participants reported feeling more energised.

3.3.6 QOL and Psychological Well-Being

The effects of an exercise intervention on QOL and psychological well-being has been explored in seven and three studies, respectively. The first study (Loudon et al., 1999) examined the effects of a supervised (indoor track) and unsupervised (outdoors) thrice-weekly progressive low-intensity walking programme in CD participants (n=12) in clinical remission or with a mildly active disease. Sessions started at 20 minutes and were progressed

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to 35 minutes for 12 weeks. HRQOL, assessed using the total IBDQ score, was significantly improved from baseline to follow-up ($\Delta= 17$; $p=0.01$). Improvements in stress (IBDSI) were also reported ($p<0.001$). Ng et al (2007) built on this preliminary work by examining the effects of a thrice-weekly independent low intensity intervention on HRQOL and stress in CD participants ($n=16$) and a control group ($n=16$), which Loudon et al's (1999) study lacked. Participants with an inactive or mildly active disease walked at 40% of aerobic capacity for 30 minutes over 3 months. This prospective RCT reported mean change improvements in HRQOL (baseline= 5.19, follow-up= 5.98; $p<0.05$) and reductions in stress (baseline= 31.4, follow-up= 18.75; $p<0.05$) at 3 months, determined using the IBDQ and IBDSI, respectively.

De Souza-Tajiri et al's (2014) pilot study, as mentioned previously, also identified significant improvements in all HRQOL components: bowel symptoms, emotional health, systemic systems and social function ($p=0.0001$) measured using the IBDQ following an 8-week progressive resistance training programme. In another study (Klare et al., 2015), exploring the effects of a thrice-weekly supervised moderate intensity outdoor running programme, defined as ‘still able to talk while running’, in participants with mild to moderate IBD (CD=19, UC=11) observed significant within-group differences in all IBDQ domains (all $p<0.01$) in the exercise cohort. However, significant between-group differences were only observed in the social function IBDQ dimension ($p=0.026$) following the conclusion of this 10-week intervention.

More recently, improvements in HRQOL were demonstrated in a 12-week traditional hatha yoga programme vs self-care of 77 UC participants in clinical remission (Cramer et al., 2017). This 90-minute supervised weekly intervention demonstrated significant group differences in HRQOL using the total IBDQ from week 1 to week 12 ($\Delta=14.7$; 95% CI 2.4-26.9; $p=0.018$) and were sustained at week 24 ($\Delta=16.4$; 95% CI 2.5-30.3; $p=0.022$) (Cramer

et al., 2017). Group differences were also identified to favour the intervention over self-care at week 12 and week 24 in subscales of the IBDQ bowel symptoms ($\Delta=4.9$; $p=0.014$, $\Delta=5.7$; $p=0.015$), systemic symptoms ($\Delta=2.5$; $p=0.016$, $\Delta=2.8$; $p=0.006$) and emotional function ($\Delta=5.4$; $p=0.023$, $\Delta=5.8$; $p=0.030$), respectively. No changes were reported in social function. Tew et al's (2019) supervised HIIT and MICT study also reported QOL and psychological well-being, using the total IBDQ, EQ-5D and HADS. From baseline to 3 months, improvements were seen in all indices [(IBDQ= HIIT 184 vs 186; MICT 181 vs 192), EQ-5D= HIIT 0.85 vs 0.85; MICT 0.83 vs 0.87), (anxiety= HIIT 5.5 vs 5.2; MICT 6.8 vs 5.5), (depression HIIT=3.6 to 2.7; MICT=3.8 to 2.7)]. Following the intervention end point (3 months) and at the 6-month follow-up results were not sustained in QOL or depression scales, but improvements were seen in anxiety measures (HIIT -1.4; MICT -0.2). However between-group comparisons were not conducted due to the study's feasibility and underpowered nature to assess efficacy.

Interestingly, a randomised controlled cross-over trial exploring the influence of an 8-week combined moderate aerobic and resistance training programme in 17 IBD participants in clinical remission reported no changes in QOL using the Short form-36 (SF-36), or depression and anxiety scores measured using the HADS, STAI and BDI-II (Cronin et al., 2019). However, an 8-week home-based yoga RCT of 87 IBD participants (CD=36, UC=51) in clinical remission identified significant within pre and post differences in the STAI ($p=0.01$), although only in the UC group (Sharma et al., 2015).

3.3.7 Body Composition

Body composition changes were assessed in three out of the ten included studies. Cronin et al's (2019) randomised controlled cross-over trial explored the influence of a combined

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moderate aerobic and resistance training programme in 17 IBD participants in clinical remission (Cronin et al., 2019). Participants were initially randomised 1:1 to the exercise cohort (n=8) or control group (n=7). Following the 8-week intervention period/control phase the control group then received the same training programme as the exercise cohort (n=13). This thrice-weekly moderate intensity progressive aerobic exercise programme consisted of walking and jogging between 5 and 7 of 10 on the modified Borg rating of perceived exertion scale. The progressive resistance programme involved 3 sets of 8 repetitions using 7 machine-based resistance exercises, starting at an intensity of 70% of the participants 1-RM and increasing 15-20% over the 8 weeks. Following the conclusion, significant improvements in body composition assessed by DEXA were achieved by the exercise group demonstrating a median decrease of 2.1% (-2.15, -0.45) ($p=0.022$) body fat and a median increase of 1.59kg (0.68, 2.69) ($p=0.0003$) lean tissue mass when compared to the non-exercising cohort. Lower intensity programmes also identified improvements in BMI in two studies (Loudon et al., 1999; Klare et al., 2015), however neither of these were statistically significant (both $p=0.07$).

3.3.8 Disease Activity and Immune Parameters

Six studies included in this review examined the effects of exercise on disease activity and three on immune parameters. In three studies, disease activity improvements were identified. Firstly, in Loudon et al's (1999) thrice-weekly progressive walking programme in adults with CD, following this 12-week pilot study significant improvements were seen in the HBI (pre- and post-exercise scores 5.9 ± 5.0 vs 3.6 ± 3.1 ; $p=0.02$). Ng et al's (2007) follow-up study, also involving a thrice-weekly walking programme in adults with CD for 12 weeks, identified similar improvements in the HBI (6.69 vs 3.63, $p<0.01$). This suggests that a low-intensity

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progressive walking programme is feasible to reduce disease activity in people with IBD.

Lastly, Cramer et al's (2017) 12-week yoga intervention in adults with UC reported significant group differences at week 24 between the yoga group and self-care group ($\Delta = -1.2$; $p=0.029$) assessed using the CAI. Interestingly, although at week 12 CAI scores increased in the self-care group (2.0 ± 1.5 to 2.6 ± 2.6) and decreased in the yoga group (2.5 ± 1.4 to 2.4 ± 2.2) these did not reach statistical significance within or between-group differences suggesting that, to achieve significant disease activity differences in yoga, a longer intervention is required.

In contrast, Candow et al's (2002) 12-week resistance training programme found no improvements in disease activity scores using the HBI. Although Klare et al's (2015) 10-week running programme in inactive to moderately active IBD detected a change in FC within the exercise cohort (mean increase 185.0 ± 324.8 mg/kg; $p=0.062$), this was not statistically significant. Similarly, significant within-group differences were observed in leucocyte counts (7.0 ± 2.2 vs 5.6 ± 1.5 ; $p=0.016$), however significant between-group differences were not reported ($p=0.390$). No other differences in disease activity markers (CRP, haemoglobin, CDAI and Rachmilewitz Index) were observed in Klare et al's (2015) RCT. No disease activity, immune parameter or inflammatory biomarker changes were identified in Cronin et al's (2019) 8-week combined aerobic and resistance programme determined with CRP, HBI, SCI or proinflammatory cytokines (IL-8, IL-10, IL-6 and TNF-*a*) and although not statistically significant there was a modest increase in gut microbiota a-diversity after the study period. However, no differences were detected between the exercise and control groups in a-diversity or in taxonomic b-diversity. Similarly, Sharma et al's (2015) yoga intervention in 87 IBD participants in clinical remission identified no changes in immune markers (serum eosinophilic cationic protein and soluble interleukin-2 receptor) following the conclusion of this 8-week RCT. A HIIT and MICT programme, thrice-weekly

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for 12 weeks observed no changes on disease activity parameters (CDAI and FC) (Tew et al., 2019). Thus supporting previous data that exercise is feasible in IBD and furthermore suggesting that individuals in remission or suffering from a mild to moderately active disease are capable of performing symptom-free without experiencing an exacerbation of symptoms.

3.3.9 Cardiopulmonary Outcomes

Three studies examined the effect of cardiovascular training on cardiorespiratory fitness. Using the Canadian Aerobic Fitness Step Test, Loudon et al's (1999) walking programme demonstrated significant improvements in $\text{VO}_2 \text{ max}$ between pre and post measures (30.6 ± 4.7 , 32.4 ± 4.8 , $p=0.0013$). Combining progressive resistance training and cardiovascular training also demonstrated significant improvements in physical fitness determined with a submaximal assessment of peak aerobic capacity of the Rockport one-mile walk test (Cronin et al., 2019). Following the conclusion of this 8-week randomised cross-over trial, median physical fitness ($\text{VO}_2 \text{ max}$) scores improved from 43.4 mL/kg/min to 46.0 mL/kg/min ($p=0.03$). Similarly, Tew et al's (2019) feasibility RCT, saw a mean change in peak oxygen uptake and ventilatory threshold from baseline to 3 months in the HIIT (27.3 vs 29.7 mL/kg/min ; 16.5 vs 16.8 mL/kg/min , respectively) and MICT (28.7 vs 29.3 mL/kg/min ; 16.0 vs 18.2 mL/kg/min) groups.

Sharma et al (2015) evaluated cardiovascular autonomic functions in an RCT of 87 IBD participants (CD=36, UC=51) in clinical remission. Participants were block randomised to either a one hour daily home-based 8-week yoga programme working at the same intensity or usual care. No group differences or within group differences were reported in cardiovascular autonomic activity, however there was a strong trend towards a reduction in low sympathetic activity frequency in the yoga group [median= 404.95 ms^2 (IQR= 145.04 ms^2 , 659.57 ms^2) vs

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171.54 ms² (72.08 ms², 498.01 ms²), p=0.052]. No group or within differences were reported on cardiovascular parasympathetic, sympathetic reactivity, heart rate responses or blood pressure.

3.3.10 Feasibility and Acceptability Outcomes

Eight studies provided data on compliance and withdrawals. Compliance to the interventions was well received ranging from 52% to 87.5%. Withdrawals were reported in 6 studies. Out of 250 exercising participants 34 withdrew due reasons such as lack of motivation/ loss of interest (n=9), scheduling issues (n=8), active disease (n=4), pregnancy (n=4), moved away (n=2) or other (n=7). Excluding the studies with no controls, 23 withdrawals were reported in control groups and 28 in the exercise groups.

3.3.11 Safety

Eight studies provided data on adverse events. Exercise-related non-serious adverse events were reported in two studies (Cramer et al., 2017; Tew et al., 2019). Events included acute flares (n=3), colorectal cancer diagnosis (n=1) (Cramer et al., 2017) and mild headaches (n=1), vomiting following exercise (n=1) and chest infection following randomisation (n=1) (Tew et al., 2019). No serious adverse events were reported.

3.3.12 Ongoing Trials

Ongoing clinical trials and unpublished studies were searched on ClinicalTrials.gov, WHO ICTRP and ISRCTN registry. One study was identified on ClinicalTrials.gov (NCT02463916) with a status of ongoing. The author was contacted to obtain an update on its

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progress. The study title and clinical population detailed on this record had since changed and the recent study was included in this review (Cronin et al., 2019). Two studies remain classified as ongoing (ISRCTN registry: ISRCTN11470370, ClinicalTrials.gov: NCT02861053). The first study is being conducted as part of this thesis and remains in an ongoing status with recruitment completed. Attempts were made to obtain an update on the progress of the latter study, with no success.

3.4 Discussion

This systematic review investigated the effects of any mode of exercise intervention on physiological and psychological outcomes in adults with IBD. Results provide corroborating evidence that exercise is safe, feasible and acceptable and may be potentially beneficial in improving BMD, QOL, muscle function, psychological well-being, fatigue, immune markers, body composition, disease activity and cardiopulmonary measures for inactive to mildly active CD. The safety or potential benefits in people with a severely active disease has yet to be established.

3.4.1 BMD

The prevalence of bone loss in people with IBD ranges from 70-80%, with 22-77% of these individuals later going on to be diagnosed with osteopenia and a further 17-41% subsequently developing osteoporosis (Lee et al., 2005; Ali et al., 2009). Despite this only one published study (Robinson et al., 1998) has explored the potential of a progressive resistance training programme (PRT) as an adjunct therapy for BMD in CD. Although the results of this study suggests that improvements in BMD are positively related to the amount of exercise

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performed, 95% confidence intervals do not support strong improvements at the femoral neck or lumbar spine. As discussed in Chapter 2, the higher the strains of mechanical loading the greater the osteogenic effect. Robinson et al's (1998) study was limited to resistance training only, therefore to maximise the potential bone loading effects integrating high-impact exercise may be more effective for preserving BMD. In addition, this study did not take into consideration a person's past or present medication, smoking history, disease location or surgical history, variables that may contribute to BMD loss (Grey, 2007).

An unpublished study also assessed the impact of a 12-month thrice-weekly PRT programme, with supplementation in 60 participants with UC in clinical remission (Sanges et al., 2013). Both the exercise and control cohorts were prescribed 1g of calcium carbonate and 800 IU vitamin D. Findings demonstrated that although improvements in BMD were seen in both groups, greater improvements were seen in the exercise group at the lumbar spine and femoral neck ($p<0.05$). This demonstrates that supplementation alone is not as effective as a combination approach including exercise. However, this study was excluded from this review as results were limited to exercise interventions only and, due to the use of a combined intervention, it was unfeasible to distinguish against the specific effects of exercise. In addition, this study reported little information on protocol deviations, adherence or allocation variables that influence the validity and methodological quality of the study.

Measures to treat osteoporosis and osteopenia in this high-risk group have not yet been well established. Despite the benefits of PRT interventions being well documented in other populations, the role of gravitational and muscle loading exercises in the prevention or treatment of IBD-related bone loss has received little attention. To prevent further disability and future personal and socio-economical costs, clinical trials are warranted to identify the optimal exercise prescription (mode, intensity, duration and frequency) for bone health in the IBD population.

3.4.2 Muscular Function

Despite the importance of skeletal muscle strength and endurance in daily living, loss of muscular strength and endurance are two of the least researched EIM's associated with IBD, yet are important predictors of future disability (van Langenberg and Gibson, 2010; Hommes et al., 2012). Even during states of remission, up to 60% of people with IBD have a reduced muscular CSA, mass, strength and endurance when compared to healthy controls (Geerling et al., 2000; Wiroth et al., 2005; Werksetter et al., 2011; van Langenberg, 2013). To date, only two studies (Candow et al., 2002; De Souza-Tajiri et al., 2014) have assessed the impact of an exercise intervention on muscle function parameters. Although both studies, one unpublished conference abstract and one letter to the editor, found significant improvements in muscle strength indices following a PRT 8 and 12-week programme, respectively, both studies were subject to validity and methodological limitations. Both studies lacked a control group and provided no information on the method of analysis, adherence rates to the intervention or the amount of exercise completed outside of the programme. There was no information on whether there was blinding to the intervention received or if an outcome assessor was present, factors that could influence results. In De Souza-Tajiri et al's (2014) pilot study, participants were also selected based on pre-established quadriceps weakness prior to recruitment and thus do not represent the sample of the target population or benefiting implications to be made to practice.

In addition, no trials have explored the benefits of exercise on upper muscular function or lower and upper muscular endurance. Reduced muscular strength and endurance indices have been associated with reduced QOL, morbidity and mortality in the elderly populations and in other chronic conditions such as sarcopenia, chronic obstructive pulmonary disease and Parkinson's disease. The deficiencies are responsible for a considerable health care expenditure costing an estimated annual excess cost of £2.5 billion in the UK (Pinedo-

Villanueva et al., 2018). Therefore, exercise programmes, particularly targeting muscular endurance impairments and upper muscular function in IBD, are warranted to prevent future disability and reduce the cost of health care in the UK.

3.4.3 Fatigue

Population-based and clinical studies reported 86% of people with active IBD and 41% of people with quiescent disease reported significant fatigue (Romkens et al., 2011; Czuber-Dochan et al., 2015). Given its high prevalence during states of remission, it is evident that fatigue is not solely linked to disease activity. Despite it being considered one of the most burdensome symptom of IBD, only one study has assessed the impact of an exercise intervention in relation to fatigue (Tew et al., 2019). This randomised controlled feasibility trial assessed fatigue severity, frequency and duration, using the IBD-F, found no reductions in either the HIIT or MICT group at 3 months, however small reductions in fatigue were reported in both groups from baseline to 6 months in the HIIT ($\Delta = -0.7$) and MICT ($\Delta = -0.5$) groups. In addition, the second part of the IBD-F scale determining the impact fatigue has on day to day activities did not decrease in either the HIIT or MICT at 3 or 6 months. However, the reason for this non improvement could be due to an intentionally small sample size, the study is underpowered to detect a true effect and results should be interpreted cautiously. Nevertheless, it did demonstrate that a HIIT and MICT exercise programme is feasible in this population warranting future large-scale trials.

3.4.4 Disease activity and Inflammatory biomarkers

Only a few of the included studies reported laboratory markers (Sharma et al., 2015; Klare et al., 2015; Cronin et al., 2019; Tew et al., 2019), including Lc, IL-6, IL-8, IL-10 and TNF- α

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with no studies finding any significant differences. Despite the importance of TNF- α and IL-6 demonstrating protective anti-inflammatory effects when exercising, only one study (Cronin et al., 2019) has assessed these immune parameters. Although this study observed no significant differences, there was no deterioration during or after the intervention, suggesting that, following a moderate intensity combined exercise programme, disease state remained stable throughout. However, to induce more favourable changes in the bacterial microbiome future research is needed to look at the effects of high intensity training. Interestingly, a paediatric study involving 15 CD participants examined inflammatory cells, cytokines and growth factors after an acute (30 minutes) bout of MICT and HIIT when compared to healthy-matched controls (n=15) (Ploeger et al., 2012). A significant increase in IL-6 and decrease in IGF-1 (both p<0.05) were observed in both exercise groups. However, this article was excluded from this review as results were limited to adults with IBD only and limited by the individuals gender and pubertal status and drug intake, factors that have been shown to impact the exercise response of immune cells and inflammatory cytokines (Tirakitsontorn et al., 2001).

The anti-inflammatory effect of exercise has been well investigated in mice studies. A controlled study involving 3 bouts of sustained vigorous treadmill running, observed increased levels of the anti-inflammatory cytokine IL-10 and decreased levels of TNF- α (Hoffman-Goetz et al., 2008). Similar effects were reported in other health conditions such as cardiovascular disease, cancer and type 2 diabetes, where an increase was observed in IL-6 production by muscle fibres (Lee et al., 1997; Thune et al., 2001; Lamonte et al., 2005). The increase in IL-6 stimulates the circulation of other anti-inflammatory cytokines such as IL-10 and IL-1ra that inhibit the production of the pro-inflammatory cytokine TNF- α , which explains the decrease in TNF- α values. This is a promising framework for people with IBD as TNF- α is a major pathological marker that correlates with intestinal inflammation (Muzes et

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al., 2012; Levin et al., 2016). However, the release of these cytokines is dependent upon the frequency, intensity, duration and type of exercise, with higher intensity exercise observing a 5 times higher IL-6 concentration than lower intensity exercise that requires fewer contracting muscles (Pedersen et al., 2004).

Disease activity was assessed in seven of the 10 included studies using validated metrics such as CDAI (n=1), RI (n=1), HBI (n=3) CAI (n=1), FC (n=2) and CRP (n=3). Three of the studies, two walking programmes (Loudon et al., 1999; Ng et al., 2007) and one yoga intervention (Cramer et al., 2017) demonstrated a significant positive change on disease activity using objective measures. These three programmes were all of a low intensity, suggesting that a low intensity exercise programme is feasible to inflict positive changes in disease activity in people with IBD. However, two of these studies (Loudon et al., 1999; Ng et al., 2007) used the HBI, which does not take into account whether the individual currently takes anti-diarrhoeal medication, haematocrit or person's weight, important determinants of disease activity. Therefore future research exploring higher intensity programmes using different markers of inflammation are warranted. To date, no studies using subjective markers of inflammation (FC and CRP) have observed any positive changes on disease activity, however, no negative changes were reported either. This suggests people with IBD in remission or suffering from a mild to moderately active disease are capable of performing symptom-free without experiencing an exacerbation of symptoms.

3.4.5 Quality of Life

Life expectancy is not affected by IBD, however with the relapsing nature of IBD, medical and surgical side effects and disease-specific complications it is not surprising that people with IBD have an impaired QOL. Seven of the studies reported similar effects on total

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HRQOL and subscales of HRQOL using validated metrics such as IBDQ (n=6), SF-36 (n=1) and EQ-5D (n=1). Only one study found no significant changes in QOL using the SF-36 (Cronin et al., 2019). However, this was a cross-over trial and assumptions were made that no carryover effects occurred. Contradictory results were also identified in the IBDQ sub-scale social function with Klare et al (2015) observing a significant difference ($p=0.026$) between-groups and Cramer et al (2017) finding no group differences. Potential reasons for this could be attributed to the mode, duration or intensity of exercise or the integrity of the programme was delivered, supervised (Klare et al., 2015) or unsupervised (Cramer et al., 2017). Another potential reason could be attributed to disease activity. Significant changes were seen in participants with an inactive to moderate disease who were recruited in Klare et al's (2015) prospective RCT, whereas no significant changes were identified in participants all in clinical remission (Cramer et al., 2017). It is widely known that people with IBD often get anxious or nervous when leaving the house, especially during states of an active disease (Bannaga and Selinger, 2015). Aspects that impair mental and social well-being, by introducing the social aspect of supervised sessions, like Klare et al (2015), could counteract these feelings of anxiety and prompt individuals to leave the house.

3.4.6 Stress, Anxiety and Depression

While the presenting symptoms of IBD are mostly physical, the worries and concerns identified above together with the uncertain disease course and prognosis, are all likely to contribute to an increased risk of stress, depression and anxiety and further profoundly affect a person's QOL (Sainsbury and Heatley, 2005; Graff et al., 2010). Increased rates of stress, anxiety and depression have all been associated with increased rates in hospitalisation (van Langenberg et al., 2010), lower compliance to treatment (Nigro et al., 2001) and clinical recurrence (Mikocka-Walus et al., 2016). In two out of three studies, both walking

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programmes (Loudon et al., 1999; Ng et al., 2007), showed a significant reduction in stress, using the IBDSI. With 90% of people with IBD believing that stress influences their disease activity and played a major part in the development of their disease (Drossman and Ringel, 2004; Hisamatsu et al., 2007), it is important to recognise the potential for exercise to be implemented into clinical practice and policies to benefit the individual.

Depression was assessed in two out of the 10 included studies using the HADS (Cronin et al., 2019; Tew et al., 2019). No significant differences were found in one study (Cronin et al., 2019), however depression scores were reduced from baseline to 3 months in the HIIT and MICT groups in Tew et al's (2019) feasibility study. However, Cronin et al's (2019) cross-over study had a small sample size of 17 participants, 4 of whom dropped out, leading to higher variability which may in turn lead to bias. Anxiety was assessed in three out of 10 included studies using the STAI (n=1) and HADS (n=2) (Sharma et al., 2015; Cronin et al., 2019; Tew et al., 2019). Cronin et al's (2019) cross-over design study found no significant differences in anxiety scores. Significant reductions in state and trait anxiety were seen only in the UC intervention group (Sharma et al., 2015) and anxiety reductions were observed in both the HIIT and MICT groups in Tew et al's (2019) feasibility study. However, there is a paucity of evidence that, depending on the type, duration or intensity of exercise, positive changes can be seen in stress, anxiety and depression following an exercise intervention. Possible reasons for these reductions have been suggested as a result of improved health-related self-efficacy, perceived control, fitness gains and improved self-confidence (Anderson and Shivakumar, 2013; Infurna and Gerstorf, 2014). Nevertheless, results are met with variation between studies and, with people with IBD reporting high anxiety and depression scores 40-50% are more likely to flare-up within 6 months than those with low scores (Crohn's and Colitis UK, 2014; Bannaga and Selinger, 2015), further exercise trials are

warranted to explore the impact of different modes, intensities, durations and frequencies on depression and anxiety levels.

3.5 Limitations

Several limitations should be noted. Firstly, a meta-analysis of the data was not possible due to the heterogeneity of included studies. The included studies were thought to be limited and too different, either statistically or methodologically. Demonstrating differences in the type of intervention, outcomes evaluated, metric of the same outcome, non-randomised design and other design issues, and variation in follow-up time points. Therefore, were unable to explore the potential impact of study bias, statistical heterogeneity and methodological weaknesses. It is also important to acknowledge the methodological limitations of some of the studies included such as lack of control group, lack of blinded outcome assessor, no information reported on whether deviations arose and no information provided on adherence to the intervention that could have impacted the results. In addition, some of the included studies analysed results only on participants who adequately completed the training intervention rather than using an intention-to-treat method. Lastly, despite the extensive search of the literature using clinical trial registries and major databases considered, by The Cochrane Collaboration (Higgins and Green, 2011), as the most important sources for reports of trials there is still a possibility that studies eligible for inclusion may have been missed. Lastly, the search strategy was restricted to English which may have resulted in selection and publication bias.

3.6 Conclusion

In summary, the benefits of exercise in IBD have not been sufficiently researched.

Nevertheless, low to moderate-intensity exercise has demonstrated to be safe and potentially beneficial at counteracting some IBD-specific complications in persons with an inactive to mildly active disease. With individuals looking for alternative modalities, further research is needed to explore optimal exercise prescription in regards to type, intensity, duration and frequency, tailored to meet the physical and psychological needs of the individual. Involving interventions that deliver high intensity programmes, including the least researched outcomes such as immune parameters, BMD, muscular function and fatigue in different disease states, particularly those with a more moderate to severe disease. In addition, disease type comparisons (CD vs UC) were unable to be distinguished in this review. Future studies should consider reporting the disease types separately and not collectively as IBD so any potential differences between disease type undertaking the same intervention can be identified. Lastly, methodological considerations such as the use of combination disease-specific parameters for the quantitative synthesis of future research, larger cohorts and longer follow-ups should be considered for upcoming studies.

CHAPTER

4

General Methods

4.1 Introduction

As discussed in Chapter 1, this chapter provides justification and rationale for the design and methods employed in:

- *Chapter 5*: A test-retest reliability study of outcome measures used to evaluate and facilitate the assessment of an intervention.
- *Chapter 6*: A case-control and cross-sectional study assessing current bone and muscle health and identifying correlates contributing to low BMD in people with CD compared to healthy controls.
- *Chapter 7*: An RCT evaluating the effects of an exercise intervention as a prevention, treatment or management on muscular function and BMD.

4.2 Study Design

To begin evaluating a clinically relevant question, sufficient literature needs to be searched and evaluated in order to design clinical treatment with the best possible scientific evidence. Firstly, a test-retest study design approach was deemed appropriate to determine the reliability of candidate outcome measures (Chapter 5) for an experimental research. To assess whether there was a significant difference in bone and muscle parameters in people with CD compared to healthy controls, a case-control study design was employed (Chapter 6). Case control studies are acknowledged to generate a high level of evidence and have the potential for a high external validity, enabling the data to be extrapolated to the CD population (Bondemark and Ruf, 2015). Therefore, an observational approach was deemed appropriate to provide an evidential basis for the intervention treatment. To further evaluate the evidence before implementing an intervention, a cross-sectional approach examining the relationship

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between the disease and risk factors associated with bone loss was explored (Chapter 6). This approach allowed multiple variables to be studied, to support the hypothesis that risk factors of bone loss are present in CD and to determine the risk factors to people with CD that are important for health care professionals when considering the appropriateness of DEXA scanning.

To investigate the effects of a 6-month combined impact and resistance training intervention on muscle function and BMD in adults with CD, a single-centre, two-arm, parallel-group, RCT was conducted (Chapter 7). To implement evidence-based care supported by the best level of evidence, it was important that the highest level evidence-based, ‘gold standard’ approach was used (Bondemark and Ruf, 2015; Hariton and Locascio, 2018). Although no study on its own is likely to prove causality, randomisation of participants will ensure that both known and unknown determinants were evenly distributed, thus minimising bias and providing a rigorous tool to examine cause-effect relationships between the intervention and the outcome. No other study designs, apart from RCT’s, allow this.

4.3 Eligibility Criteria and Recruitment

Details and justification on the eligibility criteria and recruitment can be found in respective chapters.

4.4 Outcome Measures

Outcome measures of each study are identified in table 5 and described in this chapter.

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Table 5.

Outcome measures for each study design

OUTCOME MEASURE	Test-Retest Reliability Study (Chapter 5)	Case Control Study (Chapter 6)	Cross-Sectional Study (Chapter 6)	RCT (Chapter 7)
BMD	✓	✓	✓	✓
Muscular Strength	✓	✓		✓
Muscular Endurance	✓	✓		✓
QOL: EQ-5D-5L		✓		✓
QOL: IBDQ				✓
Fatigue: IBD-F				✓
Physical Activity Habits		✓		✓
Disease Activity and Inflammatory Markers				✓

EQ-5D-5L, EuroQol five dimensions self-assessment questionnaire; IBDQ, Inflammatory Bowel Disease Questionnaire

4.4.1 Assessment of Anthropometric Measures

Stature was measured to the nearest 0.1 cm via a stadiometer (SECA 217). Participants were asked to remove their shoes, stand with their back and heels against the stadiometer and asked if the research assistant could place their hands under their jaw to ensure an upward pressure is transferred through the mastoid process. Participants were instructed to take a deep breath in and a gentle upward lift applied.

Body mass was measured to the nearest 0.1 kg using Avery scales (SECA 711). Participants were asked to empty their pockets, remove their shoes and asked to stand still centre on the scales with their feet wide ensuring accurate assessment.

4.4.2 Assessment of BMD

A DEXA scanner (Hologic Horizon W DEXA) was used to quantify BMD at the femoral neck, greater trochanter and lumbar spine (L2-L4), the sites most reliable for predicting fracture risk, monitoring treatment, and associated with the highest mortality and complications rates (Teng et al., 2008). Prior to every scan the DEXA machine underwent a quality control check and calibrated using a spine phantom, allowing for slight variations in tube output. To establish appropriateness for exposure, an eligibility bone health assessment form (Appendix 4a) was completed before every scan. The participant lay supine on the x-ray table for approximately 10 minutes. For the lumbar spine assessment, the participant was centred in the middle of the table with their arms resting flat on the table and their knees flexed over a 90° soft cube-shaped support to reduce the lumbar lordosis and open the intervertebral spaces (figure 16).

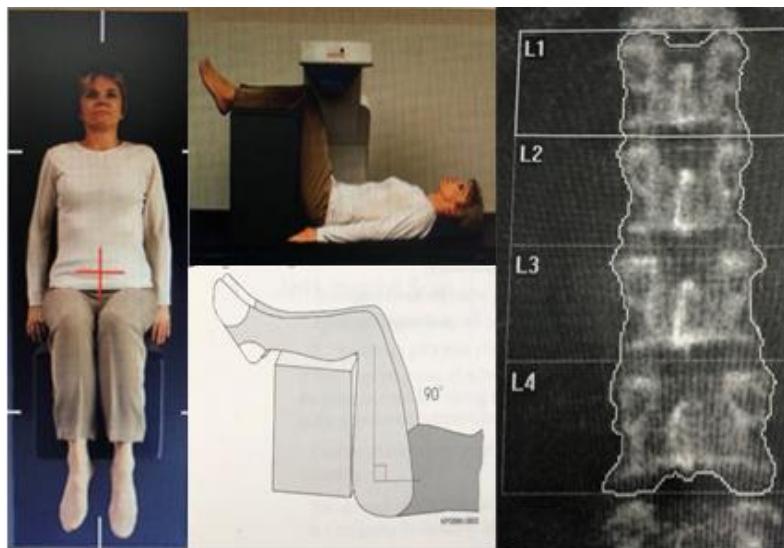


Figure 16. Lumbar spine positioning (Hologic DEXA Operating Manual, 2018)

For the left hip scan, the left leg was rotated at the knee and abducted, then fixed to the positioning fixture around the foot (figure 17). While remaining still, a large scanning arm was slowly passed over the participant, emitting a narrow beam of low-dose radiation.

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Following the DEXA, scans were analysed in accordance with the Royal Osteoporosis Society Protocol (2018). The participants gastroenterologist and GP were notified of any scan indicative of requiring treatment (Appendix 4b). A copy of the participants scans were filed in hospital records.

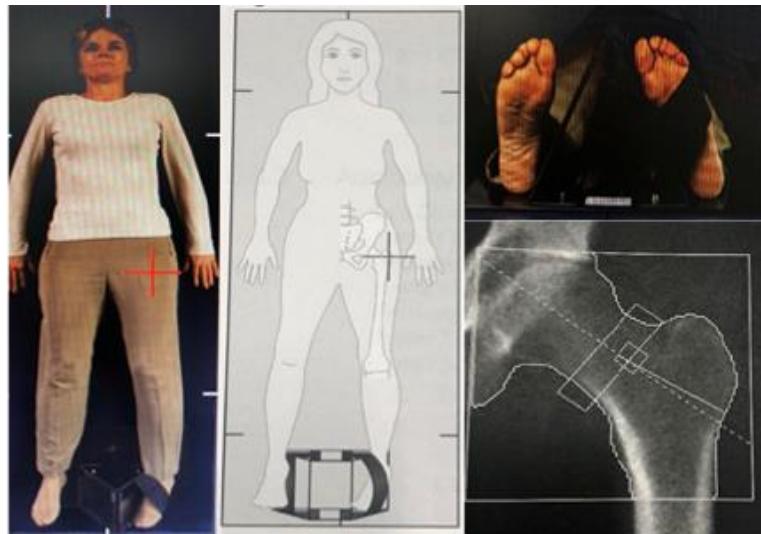


Figure 17. Left hip positioning (Hologic DEXA Operating Manual, 2018)

Seen as the ‘gold standard’ measurement tool for assessing BMD, this tool was selected due to its simple, quick and non-invasive nature that requires no special preparation, causes no physical harm and allows the participant to go home straight after (Zack et al., 2002; NHS, 2016). The reproducibility of a DEXA scan is a key issue throughout clinical research as changes in BMD are small and gradual. Several studies have explored the reliability of DEXA scans, demonstrating a high degree of reliability with low coefficients of variation (CV%) at the lumbar spine 0.92%, total proximal femur 0.92%, total forearm 0.69% and whole body 0.73% and high consistency, with correlation coefficients ranging from 0.993-0.996 ($p<0.01$) (Zack et al., 2002; Small et al., 2005; Humadi et al., 2010). The validity of DEXA when comparing two different sites, whole body and distal tibia, when excluding outliers, demonstrated correlations of 0.689 and 0.715 ($p<0.01$) (Zack et al., 2002). Although valid and reliable, results rely heavily on the expertise of the technical staff and positioning of the participant. In addition, due to constraints within this study the use of serum bone

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turnover biomarkers such as bone-specific alkaline phosphatase or osteocalcin that estimate the rate of bone formation could not be measured. However, would be a useful addition to future studies to reflect and support findings.

4.4.3 Assessment of Muscle Strength

A calibrated isokinetic dynamometer (Biodex system 4 Pro) was used to evaluate three to five maximum voluntary isokinetic strength (Nm) repetitions of concentric contractions of the knee extensors on both legs and elbow flexors on both arms performed at angular velocities between 60°/s and 180°/s, depending on the limb as detailed below. The participant was seated and strapped securely to the chair to minimise and prevent accessory movements of segments that could result in higher torque values. The muscle groups were assessed in the same order for every participant: right elbow, left elbow, right leg then left leg.

4.4.3.1 Upper extremities

The chair and dynamometer controls were rotated and set at 15° and the elbow attachment adjusted to align the centre of trochlea and capitulum of humerus (figure 18a), based on manufacturer guidelines. Starting in the fully flexed position, participants performed three maximal repetitions of reciprocal concentric elbow extension and flexion contractions at 60°/s, a 60-s rest interval followed by five repetitions at 120°/s. The total range of motion (ROM) for the elbow was 110°. Very high intraclass correlations (ICC) were demonstrated, between 0.92-0.98, for these angular velocities in other clinical populations (Pentland et al., 1993; Ekstrand et al., 2015).

4.4.3.2 Lower extremities

The chair and dynamometer were set at 90° and the knee attachment adjusted to align proximal to the medial malleoli (figure 18b), based on manufacturer guidelines. Starting in the fully flexed position, participants performed three maximal concentric knee extension and flexion contractions at 60°/s, 60-s rest interval followed by five maximal repetitions at 180°/s. The total ROM for the knee was 90°. Excellent ICC (>0.75-0.95) (Feiring et al., 1990; Fagher et al., 2016) and high reproducibility were identified at these speeds in other clinical populations (Alvares et al., 2015).

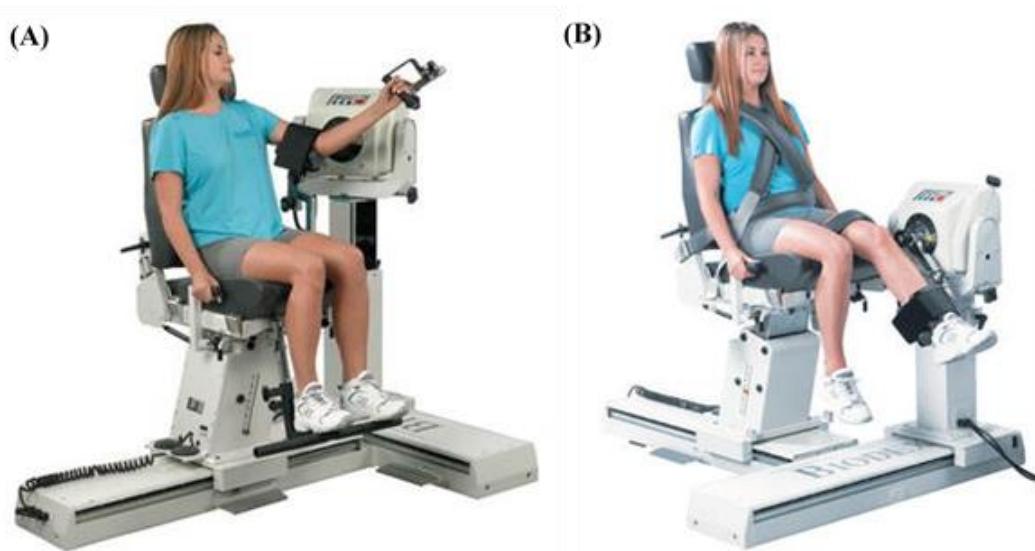


Figure 18. Elbow extension/flexion (a) and knee extension/flexion (b) positioning
(BiodeX Multi-Joint System PRO Manual, 2016)

Chair and dynamometer settings were recorded for every participant. Once the limb attachments were attached and aligned, the participant moved into position, the ROM set and the participant was educated about the procedure. Prior to any data collection, a warm-up consisting of three submaximal (60% effort) contractions on the limb being assessed were completed to allow muscles to function more efficiently and safely and to familiarise the participant with the machine. To maximise performance during testing, all participants were provided with standardised verbal encouragement ‘as hard and as fast as you can’ and ‘keep

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it going'. The highest muscle force output, known as peak torque values were taken for the left and right limbs and averaged for analysis.

Seen as the 'gold standard' for assessment of muscle strength, the isokinetic dynamometer allows for the isolation of particular muscle groups, ROM and muscle contraction type to be determined (Meyer et al., 2013). This provides an objective way to obtain muscular strength measures that have demonstrated the highest correlation coefficients for reliability, accuracy, validity and reproducibility that remain unmatched. Peak torque, average peak torque and average power of knee flexors and extensors have all demonstrated good reliability (ICC=0.80), with peak torque of knee extensors observing the highest reliability (ICC=0.99) (Maffiulett et al., 2007; Santos et al., 2013; Biomedex, 2017). Similar results were observed for upper extremities, with peak torque of elbow extensors and flexors demonstrating the highest reliability (ICC=0.87) and good reliability for the average peak torque and average power of the elbow extensors and flexors (ICC=0.82) (Starsky et al., 2005; Bassan et al., 2015).

The angular velocities and ROM protocols for muscle groups of the upper and lower extremities were selected to achieve optimal peak capacity for maximal concentric isokinetic strength while demonstrating very high to excellent reliability and reproducibility (Harbo et al., 2012). Performing maximal knee extension and flexion contractions at 60°/s and 180°/s has demonstrated excellent ICC (>0.75) (Fagher et al., 2016) (0.95, 0.96, respectively) (Feiring et al., 1990) and very high reproducibility (Alvares et al., 2015). Maximal elbow extension and flexion contractions at 60°/s and 120°/s have demonstrated ICC ranges between 0.92-0.98 and 0.91-0.98, respectively (Pentland et al., 1993; Ekstrand et al., 2015). Testing through a 90° and 110° ROM was determined based on maximal isokinetic strength of the lower and upper extremities occurring at angle-specific torques, between 25°-67° for knee flexion and extension (Ha and Han, 2017), respectively and 56°-84° for elbow flexion and extension (Yang et al., 2014), respectively.

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4.4.3.3 Grip Strength

Grip Strength, the result of forceful flexion of the finger joints with maximum voluntary force, was determined using a calibrated handgrip dynamometer (JAMAR Hydraulic). Participants were required to stand shoulder width apart, with their elbow by their side, flexed at 90° and in a neutral wrist position. The handgrip dynamometer was placed in the participants nondominant hand, to avoid training bias and the wrist strap placed around the participants wrist to prevent the dynamometer from falling (figure 19). Prior to testing, a demonstration was performed by the outcome assessor and a practice attempt conducted by the participant to ensure the instrument felt comfortable. The position of the handle was adjusted if necessary and the new handle position was recorded for future visits. Participants were informed they would feel as if there was no resistance. On ‘Go’ the participant was instructed to grip the handle with maximum isometric effort and maintain for 5 seconds. Three attempts were recorded with 30 seconds rest between attempts and the highest score analysed. Throughout the testing all participants were encouraged, using the standard phrase “Squeeze, harder, harder, and stop squeezing”. If the participant’s arm was raised while squeezing, the test was disregarded and repeated.



Figure 19. Handgrip positioning

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The Jamar dynamometer was selected due to its wide use in the clinical assessment of upper body strength, lack of invasive nature or laboratory testing and not requiring physician assessment (Bohannon et al., 2006; King, 2013). Results have demonstrated good reliability (ICC 0.84-0.93) and, when compared to certified standard weights, excellent concurrent validity ($r=0.99$) and strong concurrent validity with no significant difference (Niebuhr et al., 1994; Svens and Lee, 2005).

4.4.4 Assessment of Muscle Endurance

The 30-s chair stand test (CST) was used to measure lower-limb muscular endurance. A chair was placed against the wall to ensure stability, the participant was instructed to start seated in the middle of the chair, back straight, hands placed on their opposite shoulders crossed at the wrist and feet flat on the floor (figure 20) (Rikli and Jones, 1999). Prior to testing, a demonstration was given, and a practice attempt conducted by the participant to ensure correct technique and adequate balance. On ‘Go’ the participant was instructed to rise to a full standing position and then sit back down again and repeat this for 30 seconds. The number of full stands were recorded. If the participant was over halfway to a standing position when the 30 seconds had elapsed, this repetition was included. Incorrectly executed stands were not counted.

The 30-s CST was selected due to its extensive use throughout literature and efficient nature in assessing lower limb muscle endurance in a short period of time. Its excellent test-retest reliability ($r=0.89$: 95% CI 0.79-0.93), excellent criterion validity when compared to other assessments; leg press ($r=0.77$, 95% CI 0.64-0.85) and squat test ($r=0.71$, 95% CI 0.53-0.84);

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and excellent correlation to the 50ft walk test ICC= -0.64 (95% CI -0.75 to -0.49) were also contributing factors (Jones and Rikli, 1999; Gill and McBurney, 2008).



Figure 20. Chair stand positioning

Upper limb muscular endurance was determined using the 30-s bicep curl test (BCT). The participant was directed to sit in the middle of the chair, back straight and feet flat on the floor (figure 21). A 5lb and 8lb weight was given to women and men, respectively to be held in the nondominant hand and held palm facing towards the body with the arm in a vertically down position beside the chair. Prior to testing, a demonstration was given and a practice attempt conducted by the participant to ensure correct technique. On ‘Go’ the participant was instructed to curl their arm up through a full ROM, turning the palm up (flexion with supination) to a fully flexed position and gradually return to the starting position to a fully extended position and repeat this for 30 seconds (Rikli and Jones, 1999). The number of full arms curls were record. If the participant was over halfway to a full arm extension when the 30 seconds had elapsed, this repetition was included. Incorrectly executed arm curls were not counted.



Figure 21. Bicep curl positioning

This clinical measure was selected due to its ease and efficient nature in assessing upper limb muscle endurance in a short length of time (Jones and Rikli, 2002; Bhattacharya et al., 2016). Furthermore, it demonstrates excellent relative test-retest reliability $ICC=0.943$ (95% CI 0.883-0.973) and high absolute reliability ($r=0.79$).

4.4.5 Assessment of QOL

4.4.5.1 EQ-5D-5L

To assess generic HRQOL the EuroQol five dimensions self-assessment questionnaire (EQ-5D-5L) (Appendix 4c) was utilised by referring to health status that day (Herdman et al., 2011). Consisting of 2 pages, the first page of the EQ-5D-5L descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression scored on 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The participant was asked to indicate their health status by marking one of

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the boxes for each dimension that was most applicable. The EQ-5D-5L descriptive system was scored and coded according to the level of perceived problems, no problems=1, slight problems=2, moderate problems=3, severe problems=4 and extreme problems=5. Overall, producing a 5-digit health state profile e.g. 11211 that represents the level of reported problem for each of the five dimensions of health. A summary score of the participant's health state was derived by applying a formula (Crosswalk Index Value Calculator) to convert each domain to a single index value, reflecting the health state according to the general population specific to the United Kingdom. Scores ranged from 1.000 to -0.285, with 1 representing perfect health, 0 representing the value of a health state equivalent to death and negative values representing values worse than death. This approach ensures that the values are representative of the societal perspective (EuroQol, 2019).

The second page the EQ Visual Analogue scale (EQ VAS) records the participants' self-rated health on a 20-cm vertical, visual analogue scale numbered 0 to 100 with end points labelled 'the worst health you can imagine' and 'the best health you can imagine', respectively. Participants were asked to mark an X on the scale to indicate how their health was that day and to write the number marked on the scale in the box. If there were any discrepancies between the marked X and the number written in the box, as per instructions on scoring the EQ VAS, the number in the box was used. The EQ VAS provides important and complementary information on a participants' perspective about their own health, with higher scores representing better health status.

This standardised tool for measuring generic health status was selected due to its undemanding simplistic nature, taking only a few minutes to complete. It has been widely used throughout health surveys and in clinical research, providing a descriptive profile and value of health status for clinical appraisal (Bowling, 2005). The EQ-5D-5L has demonstrated good test-retest reliability ($r=0.90$) with Kappa coefficients up to 0.61.

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Correlation coefficients with other measures of self-related health such as the SF-36 and the Health Utilities Index (HUI-3) indicated convergent validity ($r=0.64$ and $r=0.69$).

4.4.5.2 IBDQ

Questions regarding the effects of IBD on daily function and QOL were also determined using the IBDQ and IBDQ-Stoma (Appendix 4d) for participants with a colostomy or ileostomy (Guyatt et al., 1989). Six questions (Q's 1, 5, 17, 22, 24 and 26) differ depending on the version, however both are comprised of 32 items that are graded between 1 through to 7. Participants were asked to read the questions carefully and select the number they felt best described how they were feeling over the past two weeks. The total IBDQ score ranges between 32 to 224, calculated by adding scores for all 32 items, with higher scores indicating a better QOL. Scores can also be subdivided into four functional domains: bowel symptoms, emotional health, systemic systems and social function. Each of the 4 areas were evaluated by adding up the scores for selected questions and dividing by how many questions there are in each domain, with higher scores representative of better function in that domain.

While numerous QOL assessment tools exist, the IBDQ was selected due to its multifaceted construct that has contributed to understanding the disease specific impact on HRQOL. Not only does this questionnaire provide a detailed view on a wide range of health domains (social, physical, emotional and systemic symptoms) it is easy to administer and clear to understand. Furthermore, the IBDQ has demonstrated good internal consistency, reliability and criterion validity and excellent content validity (Chen et al., 2017).

4.4.6 Assessment of Fatigue

Fatigue was measured using the standardised IBD-F self-assessment scale (Appendix 4e) by referring to a person's symptoms experienced during the previous two weeks (Czuber-Dochan et al., 2014). For the purpose of the questionnaire, Czuber-Dochan et al (2014) defined fatigue 'as a sense of continuing tiredness, with periods of sudden and overwhelming lack of energy or a feeling of exhaustion that is not relieved following rest or sleep'. The questions posed were predominantly quantitative, with an option to write comments for further clarification to allow for a comprehensive assessment of fatigue.

The first section consists of 5 questions assessing the severity and frequency of fatigue. Questions 1-4 scores ranged on an ordinal scale from 0-4, with 0 representing no fatigue and 4 severe fatigue and question 5 scored on a Likert scale of 0 representing none of the time and 4 representing all the time, with a possible total of 20. Section II consists of 30 questions rating the perceived impact and experience of fatigue on daily activities, with scores ranging on an ordinal scale from 0-4 with 0 representing none of the time and 4 representing all the time, with a possible total of 120. Six questions in section II have an option of not applicable. The last section of the IBD-F involves 5 free-text questions exploring additional issues and factors contributing to fatigue.

After calculating the sum of results for section I, scores of 0 were suggestive of no fatigue, scores of 1-10 of slight to moderate fatigue and 11-20 of severe fatigue. To adjust for N/A answers in section II the total score was calculated by using the formula: adjusted score= actual total score/(120-number N/A's x 4) x120. Scores of 0 suggested fatigue had no impact on daily activities, 1-60 considered to have a moderate effect and 61-120 considered of having a severe effect. Section III of the scale is not scored, however it provides a qualitative perspective of the impact fatigue has on an individual.

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Due to its subjective and multifaceted nature, fatigue is difficult to understand and measure and thus poses a key obstacle in fatigue-related research as no single ‘gold standard’ assessment measure can be developed that adequately captures the complexity of this debilitating and invisible symptom (Graff et al., 2011). While numerous fatigue assessment tools exist, the IBD-F self-assessment scale was selected due to its primary focus on the specific needs and experiences of people with IBD through asking questions based on the self-reports gathered from in-depth, cognitive interviews and questionnaires (Czuber-Dochan et al., 2014). This scale provides a detailed view of the severity and frequency of IBD-related fatigue, it is easy and clear to use and short enough to encourage completion (Mota and Pimenta, 2006; Eichhorn et al., 2010). In addition, it has been identified as psychometrically robust with reliability estimates falling within statistically acceptable ranges (0.80-0.90), with good content validity, acceptable test-retest stability (Section I ICC=0.74; Section II ICC=0.83) and a high degree of internal consistency (Cronbach’s alpha >0.9) comparing favourably with the multidimensional assessment of fatigue (MAF) and multidimensional fatigue inventory (MFI). The IBD-F also demonstrated a moderate convergent validity with the MAF (Section I= 0.73; Section II=0.78; p<0.001) and MFI (Section I=0.47; Section II=0.65; p<0.001) (Czuber-Dochan et al., 2014).

4.4.7 Assessment of Physical Activity Habits

Physical activity habits were determined using the Scottish Physical Activity Questionnaire (SPAQ) (Appendix 4f) by recalling leisure and occupational physical activity habits over the previous seven days (Lowther et al., 1999). The questionnaire consists of three parts. The first part comprises of a seven-day diary of leisure time physical activity with participants asked to record in minutes the amount of time spent undertaking a particular activity. Participants

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were asked to only include activities of either moderate or vigorous intensity, with examples given for each domain. Activities were sub-grouped into six domains: walking out of work, manual labour out of work, active housework, dancing, participating in a sport, leisure activity or training and other physical activity not already covered, with examples given on what activities to include. The second section comprising of a seven-day diary recorded physical activity at work, completed only if employed, with activities sub-grouped into two domains: walking at work and manual labour at work. The final section explores whether answers reflect the typical amount of physical activity usually performed, with options to identify by how much more or less.

Although the SPAQ does not distinguish between moderate and vigorous intensity activity or calculate energy expenditure, it does record all leisure and work activities. It is also easy to use, giving examples of activities to include and short enough not to discourage completion. The SPAQ has been shown to be reliable and hold a strong concurrent validity ($F[4,89] = 7.19$, $p<0.05$) and criterion validity between two measurement devices was 0.52 ($p<0.05$) (Lowther et al., 1999). Although, accelerometers are a preferred method to objectively capture intensity and quantity of physical activity. Due to the constraints within this study, the use of these devices were not feasible. However, would be a good addition to future studies to obtain objective physical activity habits.

4.4.8 Assessment of Disease Activity

Although endoscopy is considered the ‘gold standard’ for examining mucosal activity in CD, due to its invasive nature and potential complications, alternate methods were utilised.

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4.4.8.1 CDAI

Disease activity was quantified using the CDAI (Appendix 4g) by referring to disease history, disease complications and disease symptoms during the previous 7 days (Best et al., 1979).

The index is comprised of eight clinical and laboratory variables. Each parameter is summed, weighting factor applied and subtotal calculated. Parameters with a cumulative total over the last 7 days include number of liquid stools, abdominal pain graded (0-3) on severity and general well-being, subjectively assessed between well (0) and terrible (4). A weighting factor of $\times 20$ was applied to any extraintestinal complications: arthritis/arthralgia, iritis/uveitis, mouth lesions, erythema nodosum, pyoderma gangrenosum or aphthous stomatitis, anal fissure, fistula, abscess or temperature over 37.8°C in the last week. Other parameters included antidiarrheal drug use in the previous 7 days, presence of an abdominal mass assessed by a medical physician (0=none, 2=questionable and 5=definite), haematocrit volume, based on typical haematocrit of 47% in men and 42% in women, computed using the formula: $[(\text{Typical} - \text{Current}) \times 6]$ and percentage deviation from standard weight (Appendix 4h)/ observed ratio computed using the formula: $100 \times (1 - \text{current}/\text{standard})$.

After calculating the sum of results, participants are categorised into four types, those in asymptomatic remission ($\text{CDAI} < 149$), those with a mildly active disease ($\text{CDAI} = 150-219$), moderately active ($\text{CDAI} = 220-450$) and severely active ($\text{CDAI} > 450$). The CDAI is considered the gold standard for assessing disease-specific activity in CD, by basing scores on self-reported disease activity and laboratory data. It is widely used in clinical trials enabling the comparison with previous results. Results are easy to calculate and provide a disease activity threshold, allowing for monitoring of the disease throughout.

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4.4.8.2 CRP

CRP, an annular pentameric protein, was used to determine inflammatory markers in the blood. Almost exclusively produced in the liver, CRP is stimulated by IL-6 produced at sites of inflammation. As CRP has a short half-life (approx. 19 hours) when compared to other acute phase proteins, it will rise early after the onset of inflammation and rapidly decrease after resolution. Elevated CRP levels, generally between 10-40mg/l, are considered suggestive of mild inflammation or viral infections, with severe active inflammation generating CRP levels of 50-200mg/l (Vermeire et al., 2006). CRP markers were selected due to its ease, ability to indicate the level of inflammation in the body and quick turnaround for determining results. However, as CRP is not specific for determining intestinal inflammation, other biomarkers were required to provide an overview of disease activity.

4.4.8.3 Faecal Calprotectin (FC)

FC, a nonglycosylated calcium and zinc binding protein biomarker, was used to detect intestinal inflammation. When inflamed intestinal mucosa is present, polymorphonuclear neutrophils circulate around the inflammation and release calprotectin. Levels of calprotectin are directly proportional to the intensity of the neutrophilic infiltration in the gut mucosa; thus the more inflammation present the higher the concentration of calprotectin (Roseth et al., 1999). This is amply confirmed in intestinal IBD with significant correlations between FC and acute inflammation (Bjarnason, 2017). FC scores below 50 μ g/g in CD are suggestive of an inactive disease, ranging to >250 μ g/g when results are indicative of an active disease (D'Haens et al., 2012; Lehmann et al., 2015).

This non-invasive, simple and low-cost indicator was selected as it prevents the need for unnecessary endoscopy procedures and histological assessment (Sipponen et al., 2008; Langhorst et al., 2008). FC has also demonstrated a strong correlation with 111-indium-

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labelled leucocytes, a measure considered the ‘gold standard’ in determining intestinal inflammation and superior to CRP and CDAI (Costa et al., 2003).

4.5 Ethics

The principle within research ethics is that the participant should not be harmed in any way by the research. To ensure the safety of the participant all clinical measures were conducted by trained researchers and a risk assessment strategy, that complies with the current Health and Safety legislation including The Health and Safety at Work Act 1974 and the Management of Health and Safety at Work Regulations 1999, was undertaken.

4.5.1 Case Control and Reliability Study

Prior to commencement of the research, the study proposal was submitted to Northumbria University Faculty of Health and Life Sciences Research Ethics Committee (Ref: 10723) and approved. Given the nature of the research, risk assessments were carried out and adhered to with trained first aid members always present.

4.5.2 Cross-sectional Study and RCT

Prior to commencement of the research, the study proposal was then submitted and approved by Northumbria University Ethics Committee (Ref: 656). Following this approval, to allow for health research in the UK an application was submitted and obtained from the Health Research Authority (Appendix 4i) (Ref: 226369), NHS REC Newcastle and North Tyneside (Appendix 4j) (Ref: 17/NE/0308) and further approved by the research and development

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(R&D) department within the Newcastle Upon Tyne NHS Trust (NUTH) (Ref: 8488) (Appendix 4k). Following approval, an application was submitted to the National Institute for Health Research Clinical Research Network, a portfolio of high quality research studies that are eligible for support, and was deemed eligible (Ref: 35164). Given the nature of the research a research passport, an honorary research contract/letter of access, were obtained. In addition, non-NHS site approval was obtained to allow the research to be conducted at Northumbria University.

To ensure the correct conduct within clinical research, guidance and legislations governed by good clinical practice were adhered to and research conducted in accordance with the principles of the Declaration of Helsinki.

4.6 Data Management

All data collected conformed to Northumbria University guidelines, the EU General Data Protection Regulations (GDPR) and Data Protection Act (2018). Paper records such as consent forms, completed questionnaires and clinical measurements were stored in numerical order and kept secure in a locked cabinet in Northumbria University.

To ensure quality of data, all outcome data such as completed questionnaires were checked manually by the study coordinator for completeness, clarity of answers and consistency before being entered electronically into Microsoft Excel. Data entry involved labelling numeric codes (male=1, female=2), so data could be filtered. Checks after data entry were performed by the blinded outcome assessor, any discrepancies were checked against the original questionnaires and clinical measurement sheets.

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Electronic data was stored on a password-protected computer and treated in accordance with the university and GDPR guidelines and all data gathered will be destroyed after 2 years following study conclusion. Personal data necessary for scientific research were treated in accordance with safeguards, transparency and fairness. Any identifiable information such as contact information was destroyed/deleted as soon as possible. Except for healthcare professionals, only the study-coordinator had access to identifiable information, which was kept separate from any documentation that could identify the participant. Additionally, for the safety of the participant, if clinical measures were indicative of requiring treatment, the participants named GP or gastroenterologist was informed. A complete back up of the electronic database was performed once a month, via a password protected hard drive, this storage device was stored off-site. Incremental data back-ups were performed daily. Passwords were changed on a regular basis.

4.7 Harms

Adverse event (AE) reporting was conducted in accordance with Northumbria University (Sponsor) AE reporting procedures. The principal investigator, or clinical co-investigator, was responsible for determining the causality and seriousness of AE and ensuring that appropriate action was taken. Information about AE's were collected (Appendix 4l) from the beginning and procedures were in place to deal with participant change of status (Appendix 4m). For the purpose of this thesis, this is defined as the point at which written informed consent is given by the participant. The AE reporting period stopped at the participant's final trial contact.

All serious adverse events (SAE) were reported and recorded, as well as all non-SAE that were either deemed to be related to participation in the research or to result in withdrawal

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from the study. SAE's were defined as any untoward medical occurrence that fell into one of the following criteria: results in death; is life threatening; requires unplanned or prolonged hospitalisation; persistent or significant disability or incapacity. Non-SAE were defined as any untoward medical occurrence that does not fulfil any of the SAE criteria.

CHAPTER

5

Test-retest reliability of bone mineral density
and muscular function measures

5.1 Introduction

A growing body of evidence, suggests that individuals with CD are at an increased risk of muscle dysfunction and reduced BMD, potentially resulting in further disability (Miheller et al., 2013; Lima et al., 2017). Given the importance of maintaining muscular function and preserving BMD, the reliable assessment of these variables is important to monitor and evaluate changes for healthcare professionals and researchers.

One device used for evaluating muscular strength is the isokinetic dynamometer, considered the ‘gold standard’, valid and reliable tool to determine the force, or torque generated by a specific muscle group when undergoing a specific action. However, this tool is not universally accessible and rarely used due to costs, needed expertise and long testing protocols. Few studies have determined the test-retest reliability of an isokinetic dynamometer (Biodek system 4 Pro) which vary greatly in the number of limb repetitions completed, the angular velocity at which the repetition is completed and the position of the participant in the dynamometer chair. It is therefore, important to determine the test-retest reliability specific to the protocol of this study design. Similarly, handgrip dynamometer has been advocated as an alternate way to determine muscle strength due to its simplistic, quick and inexpensive nature (Trosclair et al., 2011). However, studies vary on how grip strength is undertaken, with some protocols holding the dynamometer above the head, some with a straight arm and some with the elbow at a 90° angle. The 30-s CST and 30-s BCT are appealing ways to determine muscular endurance, due to the ease of testing and its quick and non-invasive nature. However, study protocols vary in the way these measurements are undertaken and therefore it is important to determine reliability of these outcome measures when adhering to the study protocol. The DEXA is seen as the ‘gold standard’ for determining BMD. Although the DEXA has demonstrated a high degree of accuracy, high

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coefficients of variation and a high consistency (Zack et al., 2002; Small et al., 2005; Humadi et al., 2010), the precisions of the scans are essential in obtaining meaningful results which relies heavily on the expertise of the technical staff and positioning of the participant.

To ensure the appropriateness of a test, an understanding of its reliability needs to be established as often these outcome measures are applied before and/or after to evaluate change and facilitate the assessment and effectiveness of an intervention. To determine the consistency and reproducibility of these outcomes, prior to the implementation of an intervention, this study investigated the degree of test-retest reliability using the JAMAR Hydraulic, Biodex system 4 Pro, the 30-s CST, the 30-s BCT and Hologic Horizon W DEXA scanner to evaluate the change in grip strength, isokinetic muscular strength, muscular endurance and BMD, respectively.

5.2 Methods

Using the sample from Chapter 6, 33 self-reported healthy participants were required to attend two testing sessions, 7 days apart (+/-1 day) at similar times of the day. At present there is little evidence available to aid in the selection of the time interval between assessment visits for a test-retest reliability study. Due to the variation in the scope, nature and purpose of research, no ‘gold standard’ time interval exists. Therefore, the time interval for this test-retest reliability study was based on the current literature. Firstly, Marx et al (2003) compared the test-retest at 2 days and 2 weeks on subjective and objective outcomes, to determine if there was any statistically significant differences (ICC and limits of agreement statistics) for the two intervals. No clinically or significant differences were identified, thus an interval between 2 days and 2 weeks was deemed appropriate. Seven days between intervals was chosen as this duration was deemed long enough to ensure the participants

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would not likely remember or be influenced by their first assessment, but short enough to ensure lifestyle behavioural changes, which may occur after exercise testing, would not influence results.

Participants were asked to wear the same/similar clothing for both assessments, follow a similar routine the day of both tests (e.g. walking/driving or getting public transport to the assessment centre) and avoid any moderate to high intensity exercise prior to testing. To reduce the risk of any exercise testing-related injury and ensure the same/similar tasks were performed before each assessment visit. The eligibility criteria (section 6.2.1) and recruitment methods (section 6.2.2) from Chapter 6 apply to this study. Outcome measures included: BMD, muscular strength and endurance, detailed in Chapter 4.

5.3 Data Collection

All visits took place in the Neurophysiology and DEXA lab at Northumbria University. After written informed consent was gained, blood pressure and heart rate were assessed to deem it safe for the participant to conduct any exercise testing in accordance with the ASCM Guidelines (2017). Demographical and clinical characteristics such as age, stature, body mass and BMI were obtained. The same testing order was followed for session two. All assessments were performed by the same researcher.

5.4 Statistical Analysis

Differences between test and retest measures were analysed using the paired samples t test. To estimate the degree of test-retest reliability the intraclass correlation coefficient (ICC) was calculated. The ICC varies between 0 and 1, with 0 representing no reliability and 1

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indicating perfect reliability. According to Shrout's classification (1998), test-retest reliability is considered good when the ICC values range between 0.61 to 0.80 and excellent for values between 0.81 and 1.00. ICC for single measures was calculated using a two-way random effects model ($ICC_{2,1}$) of absolute agreement for the computation of ICC. The ICC is a well-accepted measure of relative reliability; however, it is difficult to interpret ICC values due to their high dependence on the variability of the group being assessed. Therefore, to determine the absolute reliability, the standard error of measurement (SEM) and the 95% limits of agreement (LOA) were calculated. Bland-Altman plots were utilised to examine the difference between test and retest against their mean (Bland and Altman, 1986). Variables were computed for each DEXA region (femoral neck, greater trochanter, lumbar spine [L2-L4], handgrip dynamometer, 30-s CST, 30-s BCT and MVIS parameters (60°/s and 120°/s for elbow scores and 60°/s and 180°/s for knee scores) for healthy participants.

5.5 Results

5.5.1 Descriptive Statistics

Demographic information and characteristics of study participants are summarised in table 6. A total of 33 participants volunteered to participate, 9 (27.3%) of whom were males and all of whom were of white ethnicity. Participants had a mean age of 50 years ($SD=13.2$), with a wide age range of 27 to 72 years and a mean BMI of 24.5 kg/m^2 ($SD=3.0$).

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Table 6.

Participant characteristics

	Men (n=9)	Women (n=24)	Total (n=33)
Age (years)	51.1 ± 12.8	50.5 ± 13.7	50.6 ± 13.2
Stature (cm)	172.3 ± 7.8	163.4 ± 6.3	166.3 ± 7.9
Body Mass (kg)	78.1 ± 9.1	63.0 ± 7.9	68.1 ± 11.4
BMI (kg/m^2)	26.3 ± 2.6	23.6 ± 2.7	24.5 ± 3.0

Mean \pm S.D are indicated for all columns unless stated.

5.5.1.1 BMD

BMD of the lumbar spine (L2-L4) scores ranged from 0.804 to $1.393 \text{ g}/\text{cm}^2$, with 0 (0%) participants in the osteoporotic range (T-score -2.5 and below) according to the WHO diagnostic criteria and 9 (27.3%) participants in the osteopenic range (T-score -1.0 to -2.5) and 0% in the osteoporotic range (T-score > -2.5). BMD of the femoral neck and greater trochanter scores ranged from 0.584 to $1.347 \text{ g}/\text{cm}^2$ and 0.524 to $0.956 \text{ g}/\text{cm}^2$, respectively, with 11 (33.3%) participants in the osteopenic range and 0% in the osteoporotic range. BMD values obtained at the first testing session were 1.058 ± 0.153 , 0.846 ± 0.222 and 0.713 ± 0.111 for the lumbar spine, femoral neck and greater trochanter, respectively and 1.059 ± 0.154 , 0.849 ± 0.223 and 0.714 ± 0.115 for the second session (figure 22). Although there seems to be a large difference in males test and retest scores at the lumbar spine, this may be apparent due to the small increments in the scale of the graph and therefore appearing larger than it is. In addition, differences in test and retest scores could have been as a result of the positioning of the participant, or the participant moving on the DEXA machine after being positioned.

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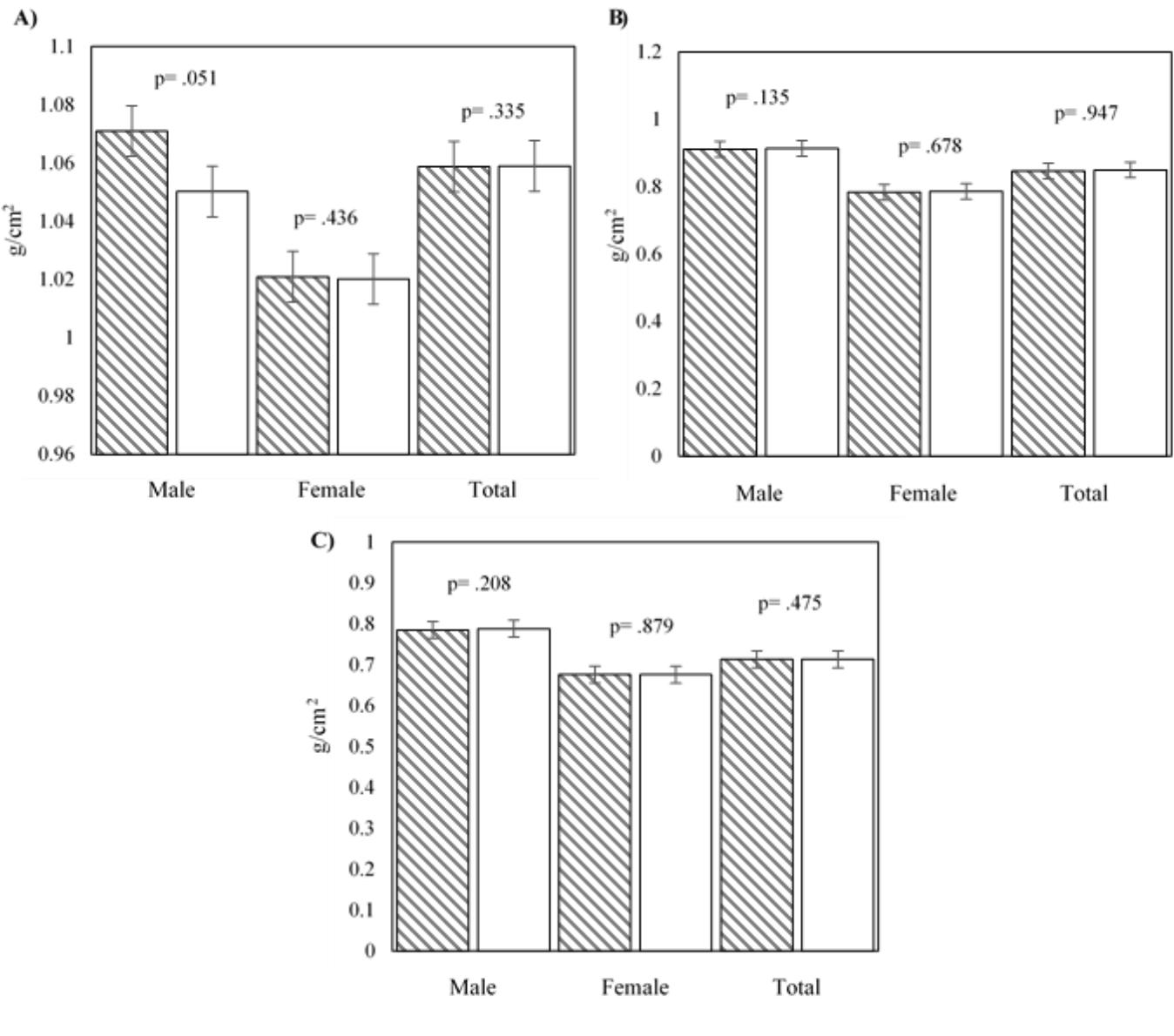


Figure 22. Test-retest reliability of BMD (g/cm^2) for males and females at the (a) lumbar spine (L2-L4) ($p= .335$), (b) femoral neck ($p= .947$) and (c) greater trochanter ($p= .475$) using the Hologic Horizon DEXA Scanner

■ Test □ Retest

5.5.1.2 Muscular Function

Knee extension and flexion scores, calculated separately, were computed as peak torque values averaged for both the left and right knee at $60^\circ/\text{s}$ and $180^\circ/\text{s}$ using extension and flexion values, respectively. Knee extension isokinetic strength measures obtained at the first

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session were 77.4 ± 40.4 Nm and 52.6 ± 22.2 Nm and knee flexion strength measures were 78.4 ± 38.0 Nm and 54.4 ± 20.2 Nm, respectively (figure 23). Elbow extension and flexion scores, calculated separately, were computed as peak torque values averaged for both the left and right elbow at $60^\circ/\text{s}$ and $120^\circ/\text{s}$ using extension and flexion values, respectively. Elbow extension isokinetic strength values for the first session were 35.7 ± 14.2 Nm and 24.1 ± 11.8 Nm and elbow flexion strength measures were 37.1 ± 14.8 Nm and 24.9 ± 11.5 Nm, respectively (figure 24). Maximum voluntary force obtained during visit one and visit two using the JAMAR Hydraulic handgrip dynamometer were 32.2 ± 16.3 kg and 32.7 ± 16.8 kg, respectively. All measures reflect a mild learning effect.

The 30-s CST and the 30-s BCT also reflected a mild learning effect. In the first session, participants performed 18 ± 4 chair stands and 19 ± 4 in the second session. Similarly, with bicep curls, 21 ± 4 were performed in the first session and 22 ± 3 in the second.

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Figure 23. Test-retest reliability of maximum voluntary isokinetic knee extension (A) and knee flexion (B) (Nm) strength, using the Biodex system 4 pro. Computed as peak torque values averaged for both legs at 60°/s and 180°/s

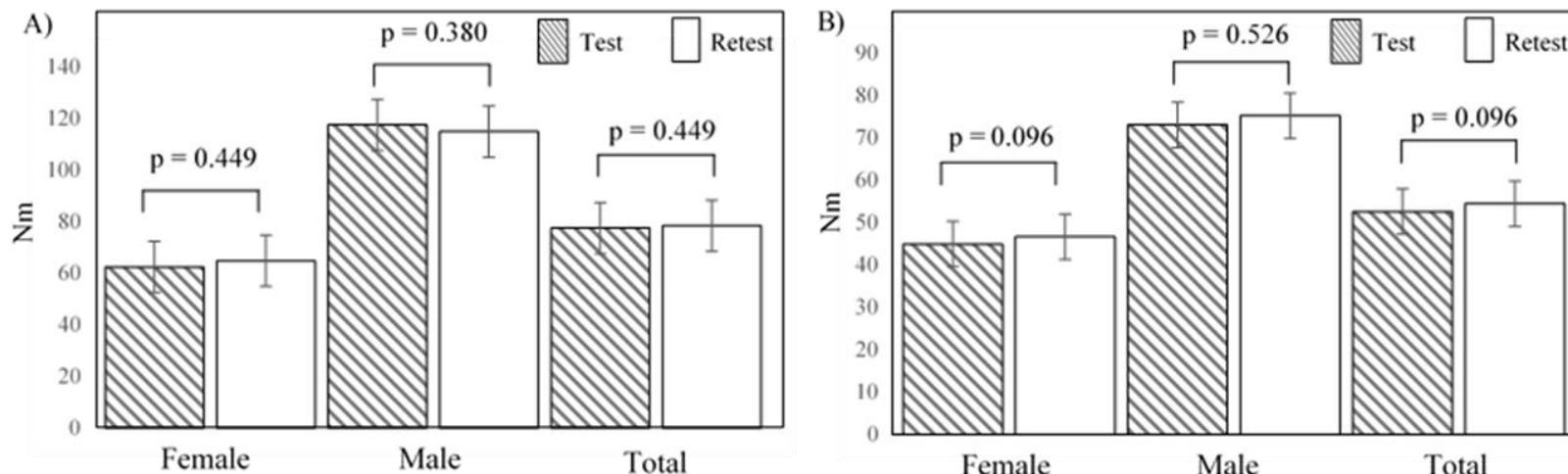
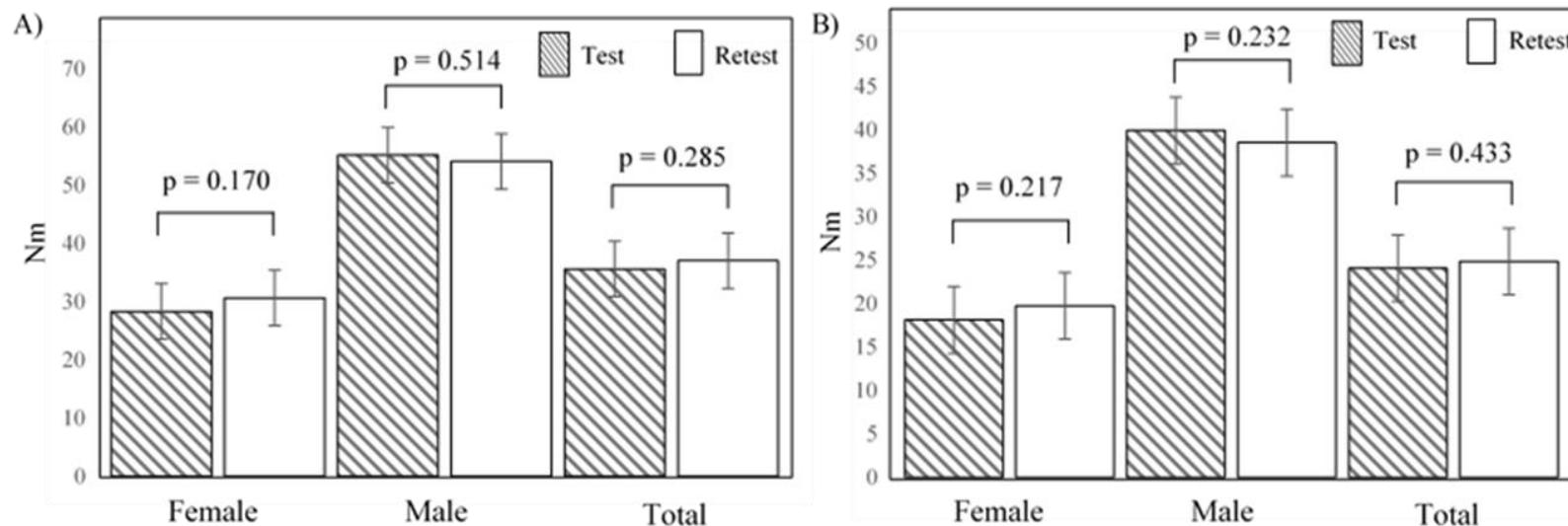


Figure 24. Test-retest reliability of maximum voluntary isokinetic elbow extension (A) and elbow flexion (B) (Nm) strength, using the Biodex system 4 pro. Computed as peak torque values averaged for both legs at 60°/s and 120°/s



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5.5.2 Reliability

Table 7 represents the test and retest values and index of relative and absolute reliability of BMD and muscular function measures.

Table 7.

Test and retest values of bone mineral density and muscular function

	Test	Retest	Bias	ICC (95% CI)	95% LOA	
					Lower	Upper
Lumbar Spine	1.06 ± 0.154	1.06 ± 0.155	0.00	0.998 (0.997-0.999)	-0.006	0.006
Femoral Neck	0.846 ± 0.22	0.849 ± 0.22	0.003	0.999 (0.998-0.999)	-0.015	0.015
Greater Trochanter	0.713 ± 0.11	0.714 ± 0.12	0.001	0.999 (0.997-0.999)	-0.015	0.014
Handgrip Strength	32.2 ± 16.3	32.7 ± 16.7	0.5	0.992 (0.984-0.996)	-3.78	4.08
Knee Extension	77.4 ± 40.4	78.4 ± 38.0	1.0	0.991 (0.982-0.996)	-15.43	13.46
Knee Flexion	52.6 ± 22.2	54.4 ± 20.2	1.8	0.978 (0.956-0.989)	-13.93	10.25
Elbow Extension	35.7 ± 14.2	37.1 ± 14.8	1.4	0.931 (0.860-0.966)	-15.86	13.07
Elbow Flexion	24.1 ± 11.8	24.9 ± 11.5	0.8	0.936 (0.870-0.968)	-11.97	10.40
30-s CST	18.4 ± 3.5	18.9 ± 3.6	0.5	0.881 (0.758-0.889)	-5.69	2.29
30-s BCT	20.8 ± 4.4	21.6 ± 2.7	0.8	0.875 (0.747-0.938)	-5.95	3.23

ICC, intraclass correlation; LOA, limits of agreement; CST, chair stand test; BCT, bicep curl test

5.5.2.1 BMD

Based on Shrout's classification, BMD at the lumbar spine, femoral neck and greater trochanter demonstrated excellent test-retest reliability, with $ICC_{2,1}$ values of 0.998 (95% CI 0.997-0.999, $p=0.335$), 0.999 (95% CI 0.998-0.999, $p=0.947$) and 0.999 (95% CI 0.997-0.999, $p=0.475$) respectively. SEM obtained in the first visit and second visit were the same at the lumbar spine (SEM_1 and SEM_2 0.03 g/cm²), femoral neck (SEM_1 and SEM_2 0.04 g/cm²) and greater trochanter (SEM_1 and SEM_2 0.02 g/cm²). Bland-Altman plot analysis illustrated the upper and lower LOA were -0.006 to 0.007 with a 0.00055 g/cm² mean

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difference at the lumbar spine (figure 25), -0.0154 to 0.0152 with a -0.00009 g/cm² mean difference at the femoral neck (figure 26) and -0.015 to 0.014 with a -0.00094 g/cm² mean difference at the greater trochanter (figure 27). Most of the points for BMD scores lie between the 95% LOA, suggesting a normal distribution of the differences.

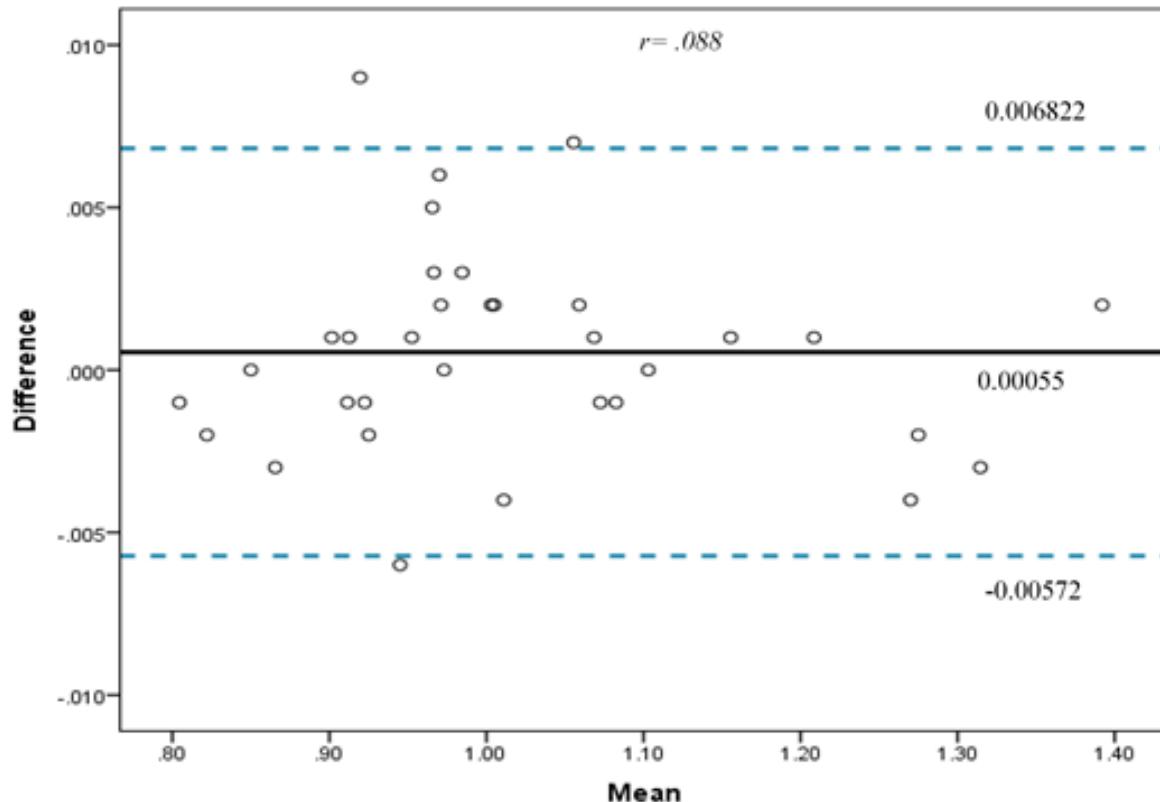


Figure 25. Bland-Altman plot for lumbar spine (L2-L4) BMD. The Y axis's shows the difference between test and retest BMD scores. The X axis shows the mean of test and retest BMD scores. The central line represents the mean difference (-0.00055). The upper and lower dashed lines represent the 95% LOA (0.006822, -0.00572). $r = .088$.

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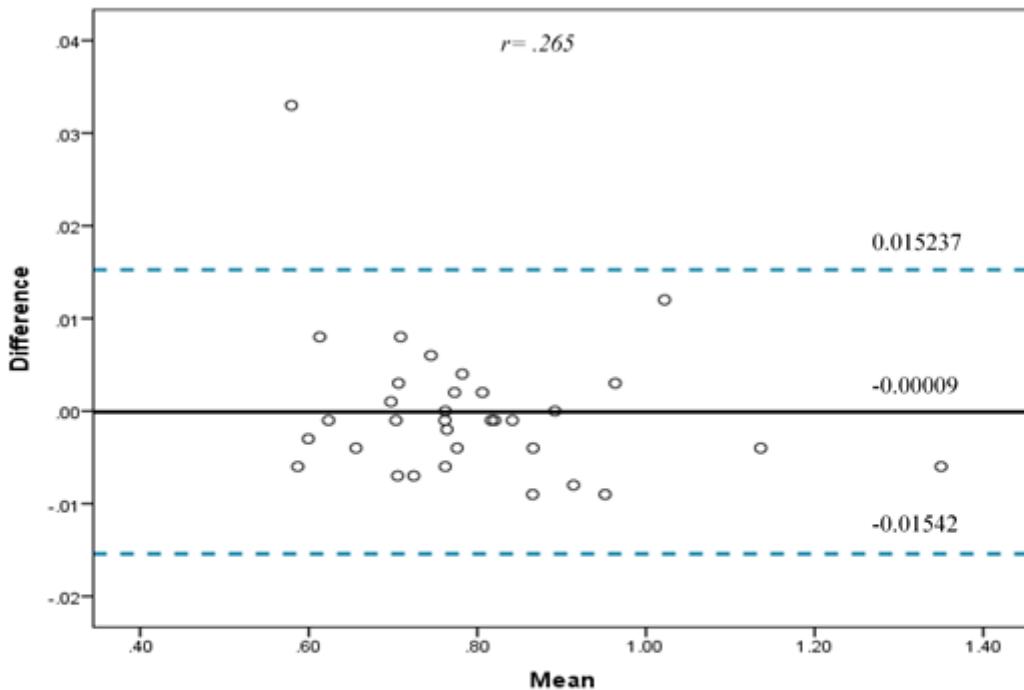


Figure 26. Bland- Altman plot for femoral neck BMD. The Y axis's shows the difference between test and retest BMD scores. The X axis's shows the mean of test and retest BMD scores. The central line represents the mean difference (-0.00009). The upper and lower dashed lines represent the 95% LOA (0.015237, -0.01542). $r= .265$.

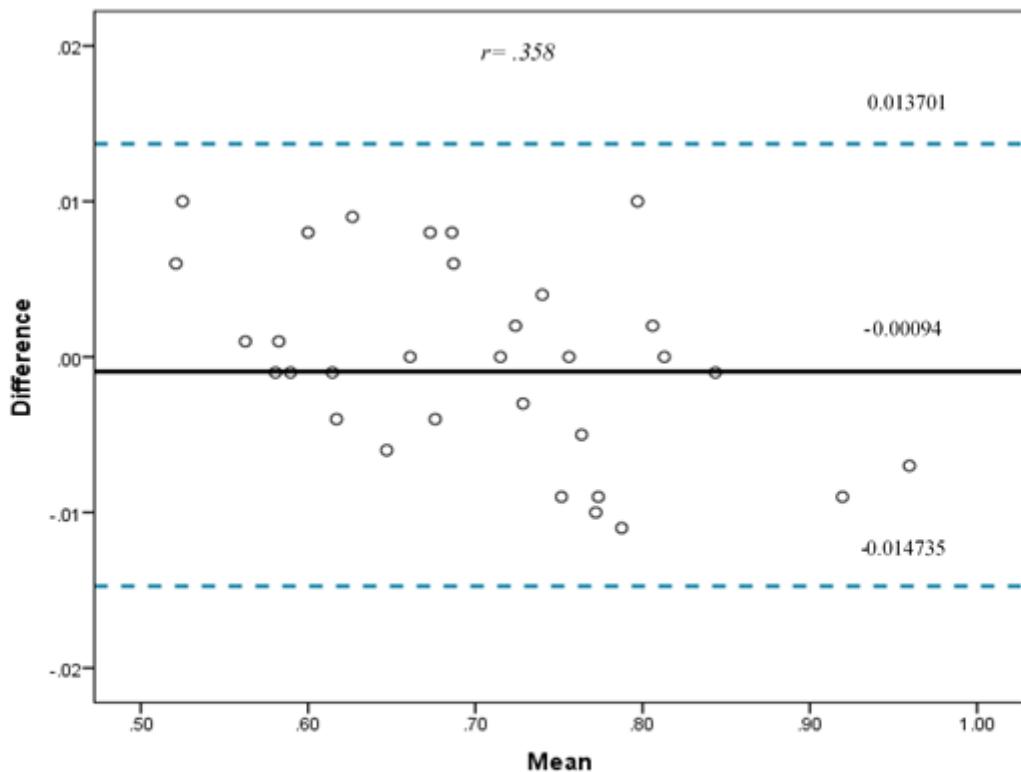


Figure 27. Bland- Altman plot for greater trochanter BMD. The Y axis's shows the difference between test and retest BMD scores. The X axis shows the mean of test and retest BMD scores. The central line represents the mean difference (-0.00094). The upper and lower dashed lines represent the 95% LOA (0.013701, -0.014735). $r= .358$.

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5.5.2.2 Muscular Function

Test-retest reliability was also excellent for upper and lower-limb isokinetic strength performances. Elbow extension and elbow flexion values, computed as peak torque averaged for both the left and right elbow at 60°/s and 120°/s, demonstrated an ICC_{2,1} of 0.931 (95% CI 0.860-0.966, p=0.285) and 0.936 (95% CI 0.870-0.968, p=0.433), respectively. SEM obtained in the first visit for elbow extension (SEM₁ 2.58) and elbow flexion (SEM₁ 2.05) were slightly lower in comparison to the second testing visit (SEM₂ 2.48 and 2.00, respectively). Bland-Altman plot analysis were conducted for further examination of the differences, upper and lower LOA were -15.86 to 13.07 and -11.97 to 10.40, with a mean difference of -1.3967 Nm and 0.7885 Nm, respectively. Most of the points fall between the 95% LOA suggesting a normal distribution of differences (figure 28)

Knee extension and knee flexion values, computed as peak torque averaged for the left and right knee at 60°/s and 180°/s, demonstrated an ICC_{2,1} of 0.991 (95% CI 0.982-0.996, p=0.449) and 0.978 (95% CI 0.956-0.989, p=0.096). SEM obtained in the first visit for knee extension (SEM₁ 7.03) and knee extension (SEM₁ 3.87) were lower in comparison to the second testing visit (SEM₂ 6.61 and 3.51, respectively). Bland-Altman plot analysis were conducted for further examination of the differences, upper and lower LOA were -15.43 to 13.46 and -13.93 to 10.25 with a mean difference of -0.9845 Nm and -1.84 Nm, respectively. Most of the points for lower limb strength scores lie between the 95% LOA, suggesting a normal distribution of the differences (figure 29).

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Figure 28. Bland-Altman plot. Y axis's represent the difference between maximum voluntary isokinetic strength of the upper limbs A) elbow extension and B) elbow flexion (Nm). Computed as peak torque values averaged for both arms at 60°/s and 120°/s. The central line represents the mean difference of both measurements. The upper and lower dashed lines represents the 95% LOA.

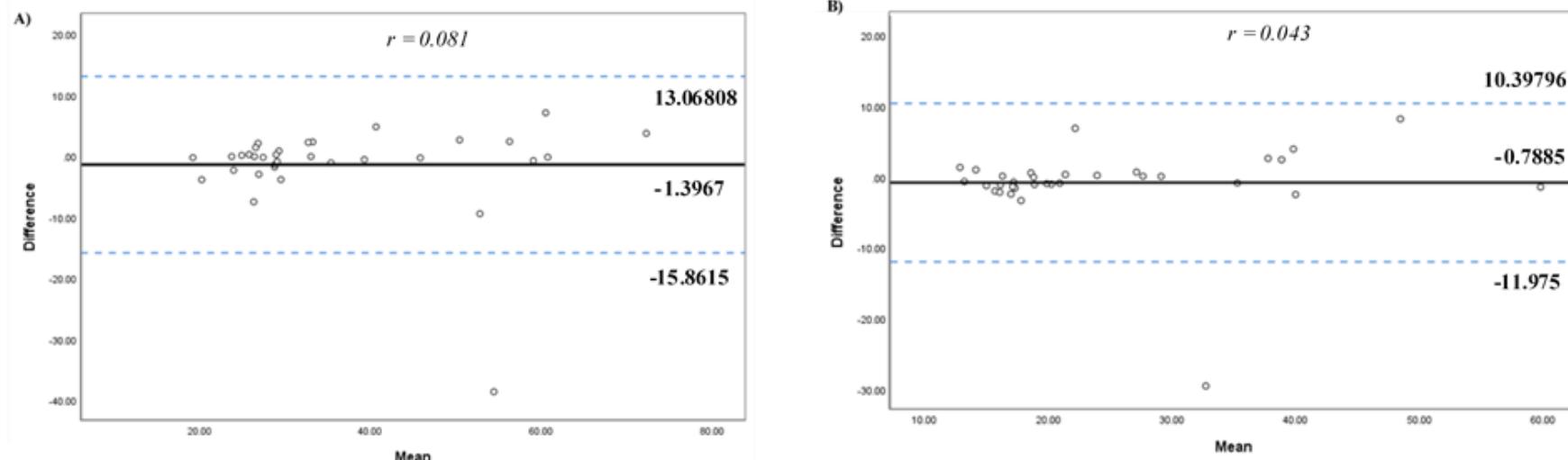
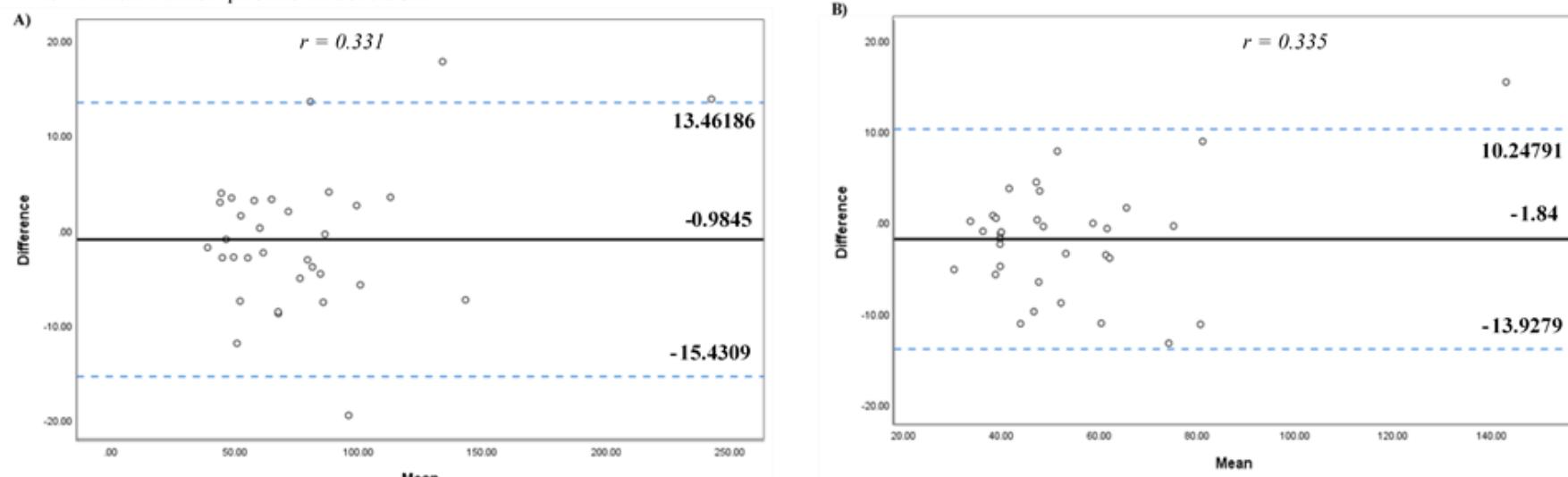


Figure 29. Bland- Altman plot. Y axis's represent the difference between maximum voluntary isokinetic strength of the lower limbs A) knee extension and B) knee flexion (Nm). Computed as peak torque values averaged for both legs at 60°/s and 180°/s. The central line represents the mean difference of both measurements. The upper and lower dashed lines represents the 95% LOA.



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Based on Shrout's classification, grip strength and muscular endurance measures: 30-s CST and 30-s BCT demonstrated excellent test-retest reliability ($ICC_{2,1}$ 0.992, 0.881 and 0.875, respectively). SEM obtained at the first was slightly higher for the grip strength measurement than the second visit ($SEM_1 = 1.98$, $SEM_2 = 1.92$), slightly higher for the 30-s CST ($SEM_1 = 0.57$, $SEM_2 = 0.51$) and lower for the 30-s BCT ($SEM_1 = 0.20$, $SEM_2 = 0.48$). Bland-Altman plot analysis illustrated the upper and lower LOA were -3.78 to 4.08 with a mean difference of 0.15 kg for grip strength (figure 30), -5.96 to 2.29 with a mean difference of -1.69 for the 30-s CST (figure 31a) and -5.95 to 3.23 with a mean difference of -1.36 for the 30-s BCT (figure 31b). Most of the points lie between the 95% LOA, suggesting a normal distribution of the differences.

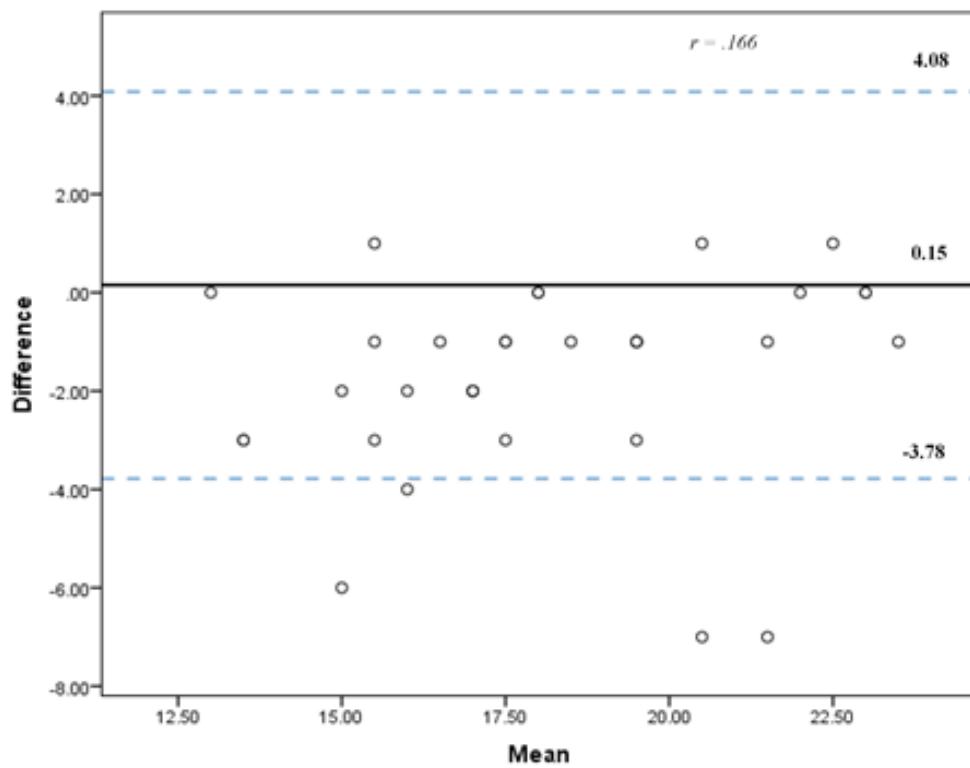


Figure 30. Bland- Altman plot. Y axis's represent the difference between both scores and the X axis's represent the mean of both scores for HGS. The central line represents the mean difference of both measurements. The upper and lower dashed lines represents the 95% LOA

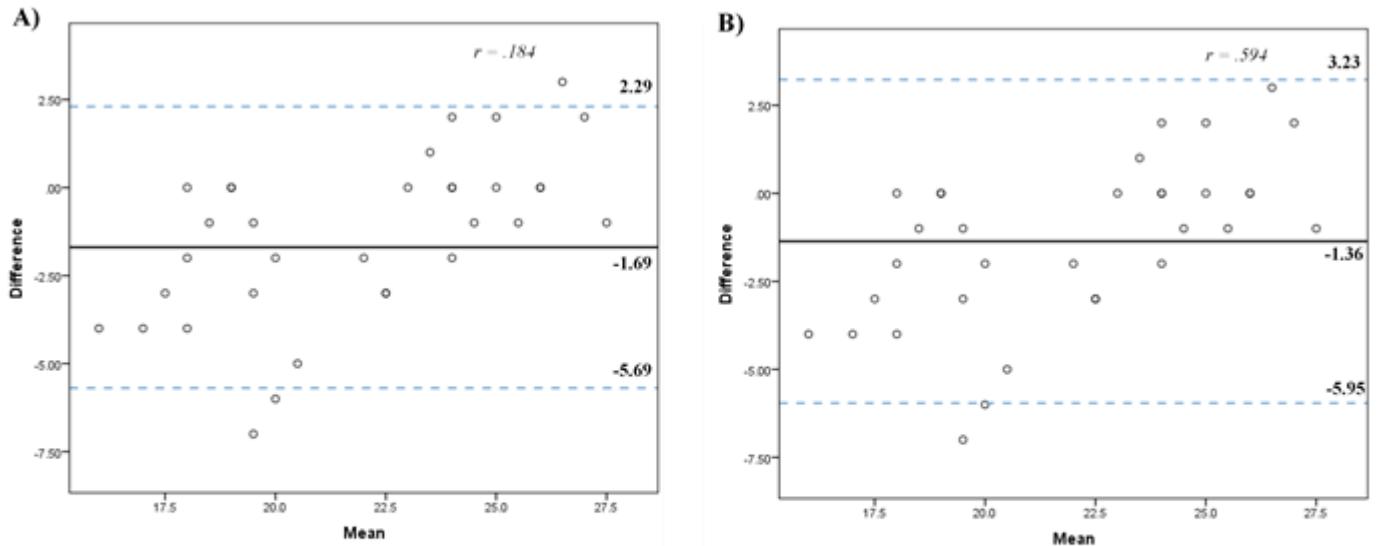


Figure 31. Bland- Altman plot. Y axis's represent the difference between both scores and the X axis's represent the mean of both scores for (a) CST and (b) BCT. The central line represents the mean difference of both measurements. The upper and lower dashed lines represents the 95% LOA

5.6 Discussion

Through a test-retest design, this study aimed to determine the reliability of grip strength, isokinetic muscular strength, muscular endurance and BMD, adopting the Bland-Altman plots to explore the relationship between measurement errors and outcome measures. Overall, these results demonstrate that the 30-s BCT, 30-s CST, HGS, MVIS of the knee extensors and elbow flexors and BMD at the lumbar spine, femoral neck and greater trochanter have excellent test-retest reliability.

5.6.1 BMD

Results from this study revealed excellent test-retest reliability for BMD at the lumbar spine, femoral neck and greater trochanter demonstrating $ICC_{2,1}$ values of 0.998 (95% CI 0.997-0.999, $p=0.335$), 0.999 (95% CI 0.998-0.999, $p=0.947$) and 0.999 (95% CI 0.997-0.999,

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$p=0.475$) respectively. Based on Shrout's classification, the 95% confidence interval of the $ICC_{2,1}$ reaffirmed that the test-retest reliability was excellent with lower and upper bounds remaining within the excellent scoring range at all sites, suggesting that these measures are reliable outcome measures, providing consistent and stable results.

The reproducibility of a DEXA scan is a key issue in clinical research as changes in BMD are small and gradual. Several studies have explored the reliability of DEXA scans, demonstrating a high degree of reliability with high coefficients of variation (CV%) at the lumbar spine 0.92%, total proximal femur 0.92%, total forearm 0.69% and whole body 0.73% and high consistency, with correlation coefficients ranging from 0.993 to 0.996 ($p<0.01$) (Zack et al., 2002; Small et al., 2005; Humadi et al., 2010). These ICC ranges are similar to those demonstrated in this study ($ICC_{2,1}>0.998$).

5.6.2 Muscular Strength

Results from this study revealed excellent test-retest reliability for HGS and upper and lower-limb isokinetic strength performances, obtaining $ICC_{2,1}$ values ranging from 0.931 to 0.992. The 95% confidence interval of the $ICC_{2,1}$ reaffirmed that the test-retest reliability was excellent with lower and upper bounds remaining within the excellent scoring range for HGS (0.984-0.996, respectively) and MVIS of the knee extensors (0.982-0.996), knee flexors (0.956-0.996), elbow extensors (0.860-0.966) and elbow flexors (0.870-0.968) in accordance with Shrout's Classification (1998), suggesting that these outcome measures are reliable, providing consistent and stable results.

These findings are consistent with those of previous studies. Firstly, HGS reliability has been determined in symptomatic and asymptomatic populations, including individuals with

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musculoskeletal disorder, shoulder injuries and cervical radiculopathy. Regardless of the population, both cohorts demonstrated excellent test-retest reliability. In the symptomatic populations, excellent levels of test-retest reliability ($ICC_{2,1}>0.91$) were identified, highlighting its potential as an outcome measure in clinical populations (Coldham et al., 2006; Savva et al., 2014; Villafane et al., 2015). Excellent test-retest reliability was also reported in the asymptomatic populations demonstrating $ICC_{2,1}$ measures ranging from 0.87 to 0.97 (Mathiowetz et al., 1984; Peolsson et al., 2001; Ng and Fan, 2001). However, most of these studies involving asymptomatic participants varied in the analysis method, some using a two-way random or fixed test and not reporting the measurement error, therefore not facilitating meaningful comparisons. Secondly, test-retest reliability of the MVIS of the knee extensors and elbow flexors has been determined in healthy, paediatric, elderly and clinical populations (Iga et al., 2006; Fagher et al., 2016; Van Driessche et al., 2018). All populations demonstrated an $ICC_{2,1}>0.87$. However, these studies differed greatly in the protocol of assessing muscular strength, with some opting for an isometric or isotonic mode, some only using a single repetition and others varying the angular velocity in which peak torque was determined. Three studies did, however, follow a similar protocol, estimating peak torque at an angular velocity of 60°/s and 180°/s for knee extension both demonstrating an $ICC_{2,1}>0.95$, although neither determined peak torque at the elbow flexors (Feiring et al., 1990; Kellis et al., 1999; Tsilos et al., 2011).

5.6.3 Muscular Endurance

The 30-s CST and the 30-s BCT demonstrated excellent test-retest reliability in this study ($ICC_{2,1}>0.88$). This finding was supported by Jones et al (1999) who demonstrated excellent test-retest reliability for values for the 30-s CST overall ($ICC_{2,1} 0.89$) and for males ($ICC_{2,1}$

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0.84) and females ($ICC_{2,1}$ 0.92). Similarly, excellent test-retest reliability for the 30-s BCT were reported in asymptomatic populations ($ICC_{2,1}$ 0.90) and in community-dwelling elderly people with cognitive impairment ($ICC_{2,1}$ 0.93) (Hesseberg et al., 2014). However, both studies differed in the instructions provided, with the later study providing verbal instruction and the study by Jones et al (1999) providing verbal instruction and a demonstration. Future studies should consider the instruction provided to participants to allow for direct comparison. In addition, the 95% confidence interval of the $ICC_{2,1}$ did not support the excellent test-retest reliability, with lower and upper bounds demonstrating a moderate to good reliability for both the 30-s BCT (0.747-0.938) and 30-s CST test (0.758-0.889). However, the SEM was low with only a small width of the 95% LOA in the Bland-Altman plot, reflecting a small variation in the differences between test 1 and test 2.

5.7 Limitations

There are limitations of this study that warrant discussion. Firstly, grip strength, isokinetic muscular strength and muscular endurance can be influenced by confounding variables e.g. the participants lifestyle (i.e. muscle soreness or fatigue caused by physical activity between the two testing sessions). Secondly, the health status of the healthy controls was self-reported and apparently healthy, and therefore ambulatory results may have limited applicability to the intervention in adults with CD. Lastly, only short-term reliability was assessed. Future research determining the long-term reliability of these outcome measures is important for healthcare professionals and researchers who require an awareness of the random error associated with each outcome measure over the time period of an intervention (Atkinson and Nevil, 1998).

5.8 Conclusion

In summary, the test-retest reliability of grip strength, isokinetic muscular strength, muscular endurance and BMD in a healthy adult population was excellent. This highlights these methods as reliable outcome measures to facilitate the assessment and effectiveness of an intervention.

CHAPTER

6

A case control study and correlates of bone
mineral density and muscle function in adults
with inactive or mildly active Crohn's disease

6.1 Introduction

Bone loss, reduced QOL, impaired muscle function and overwhelming tiredness are all recognised complications of IBD and especially of CD (Narula and Fedorak, 2008; Bilski et al., 2014). Although CD is an intestinal disorder, secondary disorders such as low BMD, muscle dysfunction, fatigue and impaired QOL may frequently occur and are important predictors of further disability.

As discussed in Chapter 2, the aetiology and the exact mechanisms that underpin the relationship between low BMD and CD are yet to be fully elucidated, however are likely to be multifactorial. Several hypothesised contributing factors are elevated pro-inflammatory cytokines, glucocorticoids, diet and malabsorption and surgical implications (Bernstein et al., 2003; Duggan et al., 2004; Mundy, 2007). These mechanisms have been shown to cause osteoclasts to differentiate and mature, impact the efficiency of intestinal absorption and increase renal excretion of calcium resulting in elevated levels of bone turnover and bone loss (Tilg et al., 2008; Targownik et al., 2013). These factors have also been hypothesised to contribute to muscle dysfunction in CD, with elevated and decreased levels of proinflammatory cytokines, suppression of protein synthesis and deficiencies in vitamin D thought to impair the regulation and preservation of muscle mass, growth and size (Cominelli, 2004; Spooren et al., 2015).

These cytokines-induced alterations also have a wide spectrum of peripheral central effects that contribute to the negative effects on energy, maintaining day-to-day activities and play an important role in the development of depression, anxiety and irritability (Miller and Timmie, 2009). With its chronic and unpredictable cyclical nature, and psychological and physiological comorbidities persisting even at times of remission, it is not surprising that

people with CD experience impaired QOL (Guthrie et al., 2002; Sainsbury and Heatley, 2005).

The occurrence of these disorders vary significantly depending on the study population (age, body weight, health status and other comorbidities), study location, study design (cross-sectional vs prospective), statistical power for determining effect and technique used to determine outcome. To date, few studies have characterised BMD and muscle function in CD participants in the UK. To increase our understanding and attempt to close the gap in identifying comorbidities that are associated with CD a case control design comparing CD participants to healthy controls (CON) was undertaken. Therefore, the objectives of this study were to a) evaluate BMD, muscular function and QOL in people with CD when matched for age, gender, BMI and physical activity habits to CON and b) identify possible risk factors associated with BMD in CD.

6.2 Methods

For this case control study, 33 healthy participants were matched according to age (+/-5 years), gender, physical activity status (*low* [no activity or some activity but not enough to meet categories moderate or highly active], *moderate* [5 or more days of at least 30 minutes of activity reported per day], *high* [1.5-2 hours of activities everyday]), BMI (grouped by category: underweight [<18.5], healthy [18.5-24.9], overweight [25-29.9] and obese [30-39.9]), ethnic origin and smoking status (group by: never smoked, previously smoked and currently smoking) to data already obtained on 33 CD participants (Chapter 7). Variables were selected based on their link in the development and risk of osteoporosis: older age, women, physical inactivity, low BMI, white and Asian women and smokers (National Institute of Arthritis and Musculoskeletal and Skin Disorders, 2018).

CHAPTER 6: CASE CONTROL AND CROSS-SECTIONAL STUDY

Using the data obtained on CD participants (Chapter 7), secondary objectives were evaluated using a cross-sectional design to identify the variables associated with BMD in 33 CD participants with an inactive to mildly active disease. In considering potential factors that may be bone-related, variables that have been linked to the development of osteoporosis, identified from both cross-sectional and longitudinal studies in healthy and chronic conditions and from the International Osteoporosis Foundation (2017) were included:

- Age: Older age increases the risk of low bone density, as with age bones become thinner and weaker (Xia et al., 2018).
- Alcohol intake: Excessive alcohol consumption increases the risk of bone loss, due to increased levels of cortisol which decreases bone formation and increases the breakdown of bone (Department of Health and Human Services, 2012).
- Physical activity habits: Inactivity or extended bed rest is related to weaker bones as a result of the lack of stress stimulated on the bone to initiate bone growth (Department of Health and Human Services, 2012).
- Gender: Women are at a greater risk as they have less bone tissue and bone loss is faster than men due to changes with menopause (Sun et al., 2014; Xia et al., 2018).
- Smoking status: Smokers are at a greater risk of bone loss, as the tobacco in smoking can cause an imbalance in bone turnover which can lead to lower BMD (Department of Health and Human Services, 2012).

The rationale for including the disease-specific variables such as disease duration, behaviour and surgical history were:

- Discussed in Chapter 2, elevated proinflammatory cytokines are present in CD and CS interferes with bone metabolism. It was thought, the longer the diagnosis the

longer this negative interaction occurs and the increased chance of accumulating a greater steroid usage and dosage.

- The effects of disease behaviour on BMD is sparse, moreover it was thought stricturing or penetrating behaviour may result in higher rates of malabsorption, as discussed in Chapter 2.
- Surgical interventions were also included due to malabsorption difficulties particularly in people who had undergone a resection(s), ileostomy or j-pouch surgery.

6.2.1 Eligibility Criteria

Healthy men and women aged 27-85 years of age, based on the age range of previously obtained data, were eligible to participate if they were able to provide written consent, complete study questionnaires and were able to travel to the research centre for assessments.

The following exclusions were also applied:

- Medical conditions or prescriptions such as, but not limited to: renal disease, thyroid disease, kidney disorders and auto-immune diseases who are/or have taken any steroid or anti-inflammatory drugs or have done previously for longer than 3 months. As these conditions and prescription medications can influence bone structure and muscular health.
- Self-reported history of falls and poor mobility. Falls are one of the largest risk factors for fractures, with 95% of hip fractures caused by falling, and a reduction in BMD is an independent risk factor for fractures (Parkkari et al., 1999; Edwards et al., 2013). Therefore reducing the potential of participants having underlying bone health issues.

- Absolute contraindications to exercise testing as defined by the ACSM (2017)

- Pregnant, due to radiation exposure
- Currently participating in >2 sessions/week of resistance exercise (self-reported) to match the exclusion criteria applied in Chapter 7

6.2.2 Recruitment

Healthy adult's (n=33) were identified and recruited from a non-clinical population on a volunteer basis by one of three methods:

1. Recruitment posters (Appendix 6a) placed around Northumbria University
2. Social media via twitter
3. Brain, Performance and Nutrition Research database, a database of participants who have consented to being contacted regarding future research studies. The database of 680 participants, as of March 2019, was screened and 378 potentially eligible participants were sent an email containing the recruitment poster.

Participants who expressed an interest were sent a participant information sheet (Appendix 6b) and an eligibility form (Appendix 6c), containing the SPAQ. Participants were asked to complete and return the form to assess suitability against the inclusion/exclusion criteria and to match the demographical and clinical characteristics to previously obtained CD data. The first 33 participants matching these criteria were recruited.

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6.2.3 Outcome Measures

6.2.3.1 Primary Outcome Measures

- BMD (g/cm^2) was assessed using a DEXA at the femoral neck, greater trochanter and lumbar spine (L2-L4)
- Muscular strength was determined using an isokinetic dynamometer (Biodek system 4 Pro) to measure maximum voluntary isokinetic strength (MVIS) of the knee extensors on both legs and elbow flexors on both arms. HGS was measured using a handgrip dynamometer (JAMAR Handgrip) on the nondominant forearm
- Lower and upper extremity muscle endurance was measured using the 30-s CST and 30-s BCT, respectively

6.2.3.2 Secondary Outcome Measures

- QOL was assessed using the EQ-5D-5L

6.2.4 Sample Size

The number of participants required in each group was powered based on the anticipated difference in BMD between CD participants and CON. This was on the basis of a cross-sectional population-based study (Jahnsen et al., 1997). Jahnsen et al (1997) compared BMD in people with CD, UC and healthy participants and identified a significant reduction in BMD in people with CD compared to CON with mean difference results as follows; lumbar spine $0.09\text{g}/\text{cm}^2$, femoral neck $0.07\text{g}/\text{cm}^2$ and total body $0.06\text{g}/\text{cm}^2$.

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The sample size calculation used methods of Noordzij et al (2010) assuming 80% power and a 5% alpha level (2-sided). Assuming a mean difference of 0.09g/cm^2 at the lumbar spine, based on the monitoring site suggested by the National Osteoporosis Foundation (NOF) (2008) and accounting for 10% attrition, the sample size required 66 participants (33 CON and 33 CD participants) to be recruited.

6.3 Data Collection

All visits took place in the Neurophysiology and DEXA lab at Northumbria University, within 10 days of confirming eligibility. After written informed consent (Appendix 6d) was gained, blood pressure and heart rate were assessed to determine if it was safe for the participant to undertake exercising test in accordance with ACSM guidelines (2017). A CRF (Appendix 6e) was used to obtain demographical information. Clinical characteristics such as stature and body mass were determined and outcome measures assessed (Chapter 4) in the same order for every participant: HGS, 30-s BCT, 30-s CST, EQ-5D-5L, MVIS and BMD.

6.4 Statistical Analysis

6.4.1 Case control study

The purpose of the analysis was to obtain estimates of difference in BMD and muscular function between individuals with CD and healthy participants. Data were collated, coded and inputted into Microsoft Excel. Following data entry checks by the outcome assessor, data were analysed using SPSS statistics version 26. To present the distribution of data, descriptive statistics such as graphs, measures of central tendency, interquartile ranges (IQR), standard deviations (SD), frequencies and percentages were applied in accordance with the

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user guidance of each questionnaire instrument. Analysis of covariance (ANCOVA) was implemented to compare the two data sets while adjusting for relevant covariates hypothesised to influence BMD and muscular function. The following variables were entered as covariates in the ANCOVA: age, gender, smoking status (current/previous/never) and physical activity habits.

To assess whether the covariates were not varied across the dependent variable, analysis of variance (ANOVA) was employed and no significant correlations were identified (BMI p=0.357; adjusted physical activity scores p=0.506 and smoking status p=0.192). To assess the residuals are normally distributed, Shapiro-Wilk was employed and the handgrip, computed knee at 60°/s and 180°/s, computed elbow at 60°/s and 120°/s and BMD at the femoral neck underwent transformation, to best approximate a normal distribution. Levene's test was carried out to determine the homogeneity of variances, all variables were p>0.05, therefore equal variances could be assumed. Scatterplots were applied to check the homoscedasticity of the data to explore residual distribution. Independency of residual errors were determined by the Durbin-Watson statistic. As results were between 1.5 and 2.5 it can be assumed that the data are not autocorrelated and that all assumptions for ANCOVA have been met. All tests were two-sided with a 5% significance level.

6.4.2 Cross-sectional study

The purpose of the analysis was to determine which factors best explain the variation in BMD levels in individuals with CD. Data were collated, coded and inputted into Microsoft Excel. Following data entry checks by the outcome assessor, data were analysed using SPSS statistics version 26. A backward, elimination log-linear regression model, a model incorporating all possible covariates and then sequentially eliminating variables based on the size of the t statistic, was implemented to assess the independent association of all variables

on BMD at the lumbar spine (L2-L4), femoral neck and greater trochanter, while allowing the retention of a large R-squared value.

To assess for the assumption of normality, Shapiro-Wilk was employed and the lumbar spine data (L2-L4) underwent logarithmic transformation. The transformation provided residuals that best approximate to a normal distribution with constant variance. In the case of BMD of the lumbar spine (L2-L4), following logarithmic transformation parameters, data were not statistically significant ($p=0.721$) confirming that a log transformation of BMD was near-optimal. Scatterplots were applied to check the homoscedasticity of the data to explore residual distribution. To test for multicollinearity, a variance inflation factor was computed for each independent variable. All values were below this threshold, suggesting the assumption has been met. Alpha was set at 0.05 for all statistical procedures.

6.5 Results

Recruitment took place between October 2018 to April 2019. Of the 106 healthy control participants who expressed interest, 87 returned the eligibility form and were assessed against the inclusion criteria. The first 33 participants matching the criteria were recruited. The most common reason for exclusion was not matching on BMI status ($n=21$). Other reasons included age ($n=12$), medical history that could influence BMD ($n=3$) or not eligible for a DEXA scan ($n=2$) (Figure 32).

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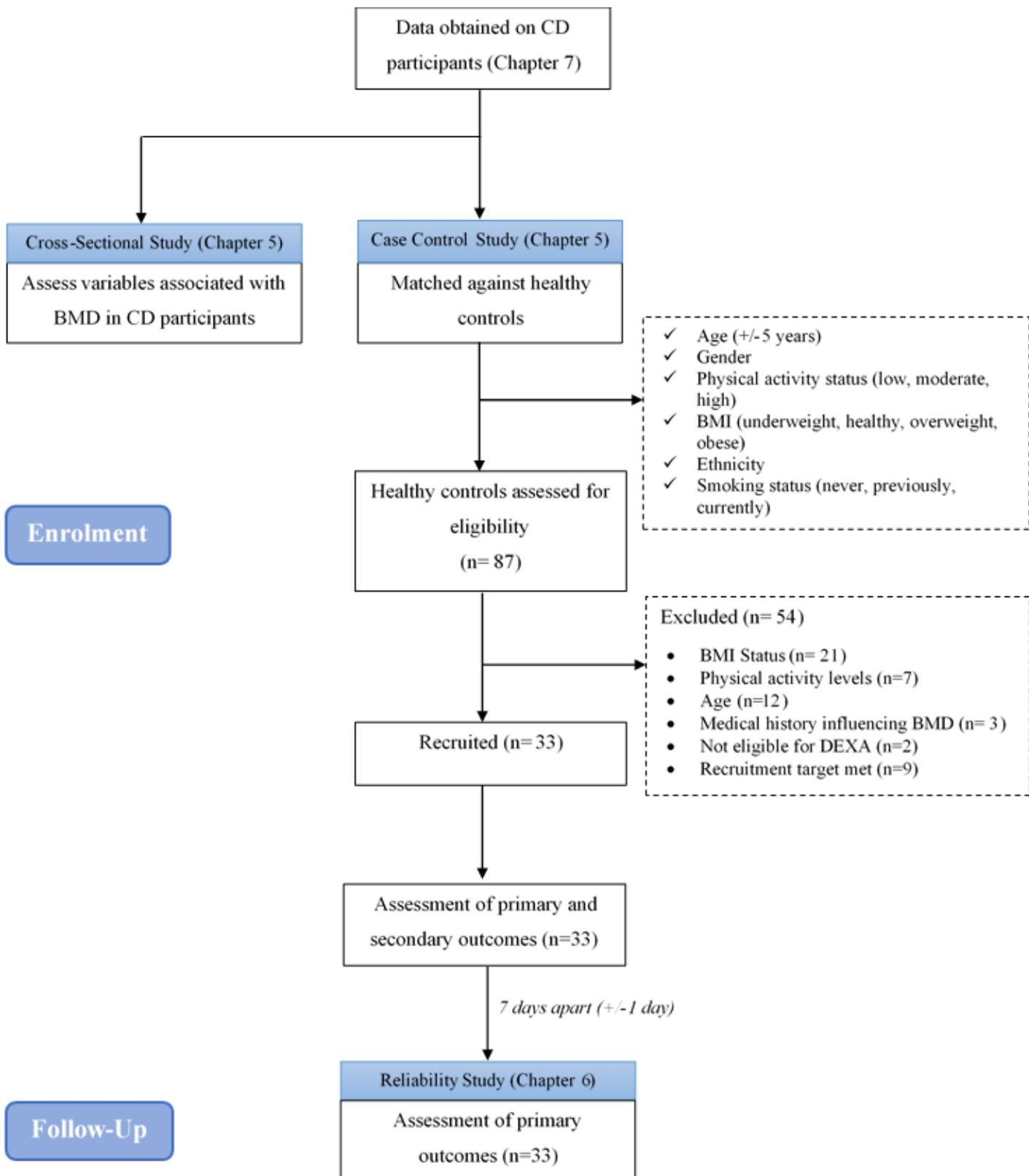


Figure 32. Participant Study Flowchart

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6.5.1 Descriptive Statistics

Demographic information and characteristics of study participants are summarised in table 8. Of the total sample, 18 (27.3%) were males and all participants were of white ethnicity. CON (n=33) had a mean age of 50 years (SD=13.2), with a wide age range from 27-72 years. Just over a third of participants (36.4%) were in full-time employment. The next largest groups were retired (33.3%) and part-time employment (18.2%). Most participants (75.8%) were non-smokers with an average alcohol intake of 6.2 (SD=7.2) units a week. The CON had a mean BMI of 24.5 kg/m² (SD=3.0), resting heart rate of 70 beats/min (SD=13) and resting blood pressure of 129 mmHg (SD=14.1)/ 74.4 (SD=10.4). CD participants (n=33) had a mean age of 49.9 years (SD=11.7), with a similarly wide age range of 27-71 years. Just less than half of participants (42.4%) were in full-time employment. The next largest groups were retired (21.2%) and unemployed (15.2%). Most participants (63.6%) were non-smokers with an average alcohol intake of 4.4 (SD=4.8) units a week. CD participants had a mean BMI of 25.2 kg/m² (SD=3.2), resting heart rate of 79 beats/min (SD=8) and resting blood pressure of 130 mmHg (SD=18.4)/ 76.2 (SD=10.4).

Table 9 illustrates participant characteristics at baseline. Median age at diagnosis was 30 years (IQR=21-36.3) with a diagnosis duration of 222 months (IQR=78-388). Most participants (45.5%) had ileocolonic CD that presented as non-stricturing and non-penetrating (72.7%). Disease activity (CDAI) and intestinal inflammation (FC) markers were 114 (SD=59.9) and 86.5 μ g/g (SD=59.5), respectively, with the majority of participants presenting with an inactive disease (60.6%). There were very few comorbidities (36.4%), of which included enteropathic arthritis (n=5), osteoporosis/ osteopenia (n=4), psoriasis (n=3), bile salt malabsorption (n=2), erythema nodosum (n=1), orofacial granulomatosis (n=1), ankylosing spondylitis (n=1), lymphoma/malignancy (n=1) and serious infections (n=1).

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Table 8.

Demographical and health characteristics of CD participants and controls

	CD (n=33)	CON (n=33)	p value ^a
Age, mean (SD), years	49.9 ± 11.7	50.6 ± 13.2	.219
Ethnicity, White British, n (%)	33(100)	33(100)	1.00 ^b
Employment Status, n (%)			.370 ^b
Employed-Full Time	14(42.4)	12(36.4)	
Employed-Part Time	3(9.1)	6(18.2)	
Self-Employed	4(12.1)	1(3.0)	
Unemployed	5(15.2)	0(0)	
Student	0(0)	3(9.1)	
Retired	7(21.2)	11(33.3)	
BMI, mean (SD), kg/m ²	25.2 ± 3.2	24.5 ± 3.0	.310
Body Mass, mean (SD), kg	72.5 ± 21.4	68.1 ± 11.4	.244
Stature, mean (SD), cm	161.9 ± 20.9	166.3 ± 7.9	.237
Resting Heart Rate, mean (SD), beats/min	79 ± 9	70 ± 13	.315
Blood Pressure, mean (SD), mmHg			
Systolic Blood Pressure	130 ± 18	129 ± 14	.838
Diastolic Blood Pressure	76 ± 10	74 ± 10	.525
Smoking Status, n (CS/ FS/ NS)	0/12/21	0/8/25	.254 ^b
Alcohol Intake, mean (SD), units	4.4 ± 4.8	6.2 ± 7.2	.213

CD, Crohn's Disease; CS, current smokers; FS, former smokers; NS, non-smokers. ^a indicates independent t-test, ^b indicates Chi-squared test

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Table 9.

CD Participant Characteristics

	Men (n=9)	Women (n=24)	Total (n=33)
Age at Diagnosis, median (IQR), years	31 (26.3-36.3)	30 (21-36.5)	30 (21-36.3)
Diagnosis Duration, median (IQR), months	246.5 (204.1-222)	216 (72-404)	222 (78-388)
Disease Location, n (Ileal/ Colonic/ Ileocolonic)	1/2/6	8/7/9	9/9/15
Number of surgical episodes, n	10	33	43
Disease Behaviour, n (N-S, N-P/ST/PE)	5/4/0	19/5/0	24/9/0
Current immunosuppressant use, n (%)	3(33.3)	12(50)	15(45.5)
Current anti-TNF use, n (%)	4(44.4)	7(29.2)	11(33.3)
Disease Activity, mean (SD)			
Faecal Calprotectin, µg/g	83.4(58.2)	90.0(60.1)	86.5(59.5)
CDAI	109.9(59.1)	116.4(60.9)	114.1(59.9)
CDAI Activity Status, n (%)			
Inactive	6(66.7)	14(58.3)	20(60.6)
Mildly Active	3(33.3)	10(41.7)	13(39.4)
Extra-intestinal Manifestations, n			
None	8	13	21
EA/ EN/ OG/ PS/ AS/ LY/ SI/ BSM/ OP	0/0/1/0/0/0/0/1	5/1/0/3/1/1/1/2/3	5/1/1/3/1/1/1/2/4

CD, Crohn's Disease; N-S, N-P, Non-Stricturing, Non-Penetrating; ST, Stricturing; PE, Penetrating; EA, Enteropathic Arthritis; EN, Erythema Nodosum; OG, Orofacial Granulomatosis; PS, Psoriasis; AS, Ankylosing Spondylitis; LY, Lymphoma/ Malignancy; SI, Serious Infections; BSM, Bile Salt Malabsorption; OP, Osteoporosis/ Osteopenia

6.5.2 Bone Mineral Density

The BMD data (in g/cm²) for CD participants and CON, are summarised in figure 33. CD participants showed significantly reduced values at the femoral neck (mean difference= -0.063; 95% CI 0.001-0.125; p=0.045) and lumbar spine (-0.063; 0.003-0.129; p=0.040), when adjusted for age, gender, smoking status and physical activity habits. No significant differences were identified at the greater trochanter (-0.031; -0.022-0.078; p=0.260).

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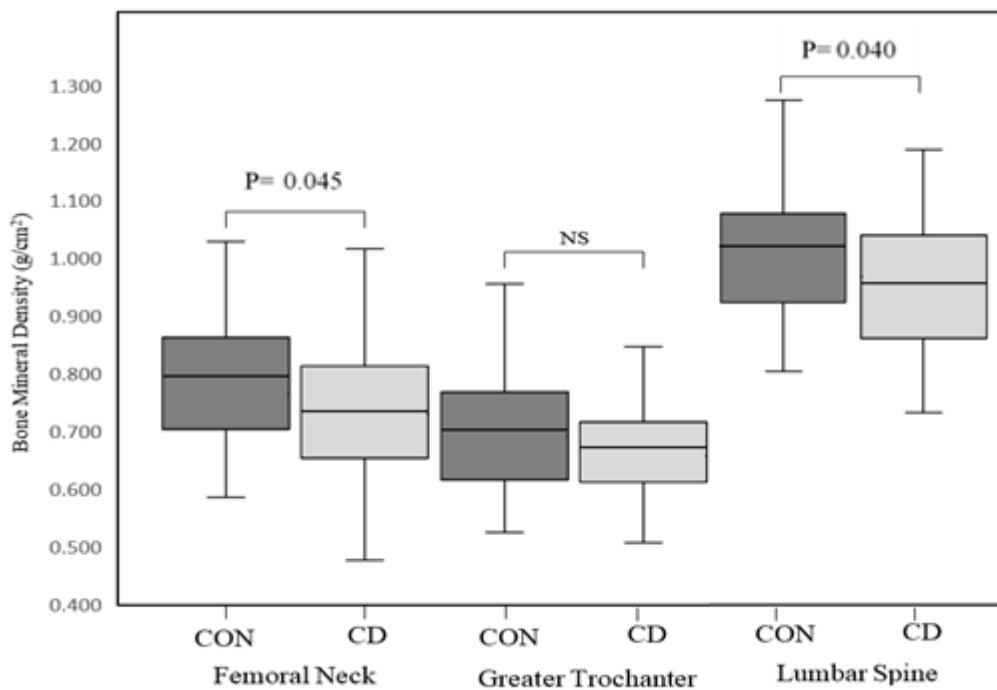


Figure 33. Bone mineral density in CD participants (n=33) compared to healthy controls (CON) (n=33)
 CON, Control; CD, Crohn's Disease; NS, Non-significant. The central line represents the median and the
 box illustrates the interquartile range

Mean BMD scores are presented in table 10. Following the analysis, according to WHO (Czerwinski et al., 2007) diagnostic criteria, 48.5% of CD participants were indicative of having osteopenia (T-score between -1.0 and -2.5) at the left hip and 6% of osteoporosis (T-score -2.5 and below) in comparison to 33.3% and 0% of CON, respectively. T-scores of the lumbar spine suggested osteopenia in 36.4% of people with CD and osteoporosis in 6% compared to 27.3% and 0% in CON, respectively.

Table 10. Bone mineral density (g/cm²) values. Data are presented as mean (SD)

	CD (n=33)	CON (n=33)	P value
Femoral Neck	0.734 ± 0.12	0.796 ± 0.16	0.045
Greater Trochanter	0.671 ± 0.11	0.702 ± 0.10	0.260
Lumbar Spine (L2-L4)	0.957 ± 0.12	1.020 ± 0.14	0.040

6.5.3 Muscular Function

Figure 34 demonstrates MVIS of the knee extensors on both legs at 60°/s and 180°/s (A) and elbow flexors on both arms at 60°/s and 120°/s (B). CD participants showed significantly reduced lower limb muscular strength compared to CON when performing isokinetic knee extension, working at angular velocities of 60°/s ($df = -22.0 \text{Nm}$, 95% CI 10.6-37.3; $p=0.001$) and 180°/s (-13.9Nm; 3.4 to 34.6; $p=0.011$). There were no significant differences between CD participants and CON when performing upper limb elbow flexion at velocities of 60°/s (-0.6Nm; -2.2-3.4; $p=0.664$) or 120°/s (-0.01Nm; -2.8-2.0; $p=0.747$). Negative differences in HGS were identified between CD participants and CON, however these were not significant ($df = -3.0 \text{ kg}$, $p=0.109$). Mean muscular strength scores are presented in table 11.

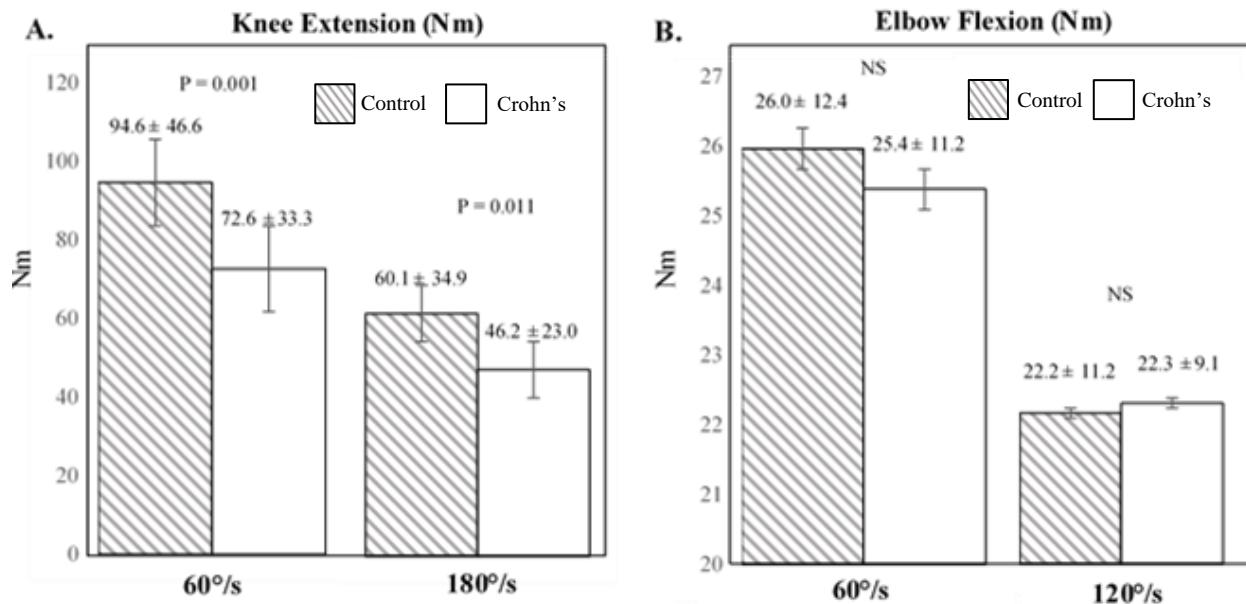


Figure 34.

Mean comparison of maximum voluntary isokinetic strength parameters (a: knee extension; b: elbow flexion) between CD participants and healthy controls. Error bars denote standard error.

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Mean muscular endurance results are presented in table 11. The 30-s CST and 30-s BCT results showed that people with CD completed fewer repetitions (both $p<0.01$), with an average difference of 5 repetitions and 4 repetitions for CST and BCT, respectively.

Table 11.

Muscular function variables of CD participants and controls

	CD (n=33)	CON (n=33)	P value
<i>Muscle Strength</i>			
Knee Extension-60°/s ^a	72.6 ± 33.3	94.6 ± 46.6	0.001
Knee Extension-180°/s ^a	46.2 ± 23.0	60.1 ± 34.9	0.011
Elbow Flexion-60°/s ^b	25.4 ± 11.2	26.0 ± 12.4	0.664
Elbow Flexion-120°/s ^b	22.3 ± 9.1	22.2 ± 11.2	0.747
HGS, kg	32.7 ± 11.3	35.7 ± 11.7	0.109
<i>Muscle Endurance</i>			
30-s CST, repetitions	13.4 ± 3.2	17.3 ± 3.3	<0.001
30-s BCT, repetitions	16.4 ± 3.5	21.2 ± 4.1	<0.001

HGS, Handgrip Strength; CST, Chair Stand Test; BCP, Bicep Curl Test; CD, Crohn's Disease; CON, Controls

Mean ± S.D are indicated for all columns unless stated.

^a Computed as average MVIS on both legs

^b Computed as average MVIS on both arms

6.5.4 Quality of life

Mean QOL scores determined using the EQ-5D-5L are illustrated in table 12. CD participants experienced a significantly reduced QOL in comparison to CON in the EQ VAS (mean df= -11.4; 95% CI -5.6 to -17.1, $p<0.001$) and in the ED-5Q-5L index scores (-0.098; -0.032 to -0.165; $p=0.004$).

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Table 12.

Quality of life data in CD participants and healthy controls

	CD (n=33)	CON (n=33)	Mean Difference (95% CI)	P value
<i>Quality of Life^a</i>				
EQ-5D-5L Index Scores (-0.285 to 1)	0.825 ± 0.16	0.935 ± 0.10	-0.098 (-0.032 to -0.165)	0.004
EQ-5D-5L VAS Scores (0 to 100)	76.7 ± 14.0	88.1 ± 9.0	-11.4 (-5.6 to -17.1)	<0.001

Mean \pm S.D are indicated for all columns unless stated.

^a Higher values represent better outcomes

6.5.5 Correlates of Bone Mineral Density

To identify factors associated with BMD at the lumbar spine, greater trochanter and femoral neck in adults with CD, a backwards stepwise regression analysis was performed. In this regression model, age, alcohol intake, disease behaviour, disease duration, physical activity habits, gender, smoking status and surgical history were included. The regression model accounted for 38.5% of variance (adjusted R²) in lumbar spine bone BMD scores, 16.1% of variance in the greater trochanter BMD scores and 31.3% of variance in the femoral neck BMD scores. Findings identified the variables significantly correlated in CD participants with a logarithmic transformed lumbar spine (L2-L4) BMD scores were disease duration ($b = -0.27$, $p=0.024$), physical activity habits ($b = 0.38$, $p<0.01$), gender ($b = -0.47$, $p<0.01$) and smoking status ($b = -0.26$, $p=0.033$) (Appendix 6f). Similarly, disease duration ($b = -0.34$, $p<0.01$), physical activity habits ($b = 0.36$, $p<0.01$) and gender ($b = -0.42$, $p<0.01$) were significant correlates of femoral neck BMD scores (Appendix 6g), while only physical activity habits ($b = 0.36$, $p=0.013$) were significant correlates of greater trochanter BMD scores (Appendix 6h). Table 13 illustrates the final multivariable linear regression model for BMD scores.

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Table 13.

Final multivariable linear regression models for bone mineral density scores

BMD Region	Unstandardised coefficients		Standardised coefficients		95% Confidence Interval for B			
	B	Std. Error	Beta	t	Sig	Upper Bound	Lower Bound	
Lumbar Spine ^a	Constant	.156	.084		1.862	.070	-.013	.326
	Disease Duration ^b	-.046	.020	-.273	-2.350	.024*	-.086	-.007
	PA Habits ^c	.062	.020	.375	3.125	.003**	.022	.101
	Gender	-.074	.019	-.471	-3.904	.000**	-.112	-.036
	Smoking Status	-.038	.017	-.259	-2.210	.033*	-.073	-.003
Femoral Neck	Constant	.910	.146		6.214	.000**	.615	1.206
	Disease Duration ^b	-.108	.039	-.341	-2.784	.008*	-.186	-.030
	PA Habits ^c	.110	.039	.360	2.843	.007*	.032	.187
	Gender	-.123	.037	-.423	-3.350	.002*	-.198	-.049
Greater Trochanter	Constant	.681	.129		5.286	.000**	.421	.940
	PA Habits ^c	.088	.034	.363	2.596	.013**	.020	.156

Note: The results presented here include only the variables that show significance in the final multivariate linear regression models

D, Disease; PA, Physical Activity; Adj, Adjusted

*. Correlation is significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

^aComputed as the total bone mineral density (g/cm²) at the lumbar spine (L2-L4) (logarithmic transformed)

^bPresented as total months (logarithmic transformed)

^cCombined total physical activity minutes, computed as the sum of leisure time + work time scores -/+ typical week minutes (logarithmic transformed)

6.6 Discussion

The present study identified that CD participants in remission or with a mildly active disease have a significantly reduced BMD at the lumbar spine and femoral neck, impaired lower limb muscular strength and endurance, impaired upper limb muscular endurance and reduced QOL when compared to healthy matched controls. Correlates of BMD in CD participants were explored and identified as disease duration, physical activity habits, gender and smoking status to be a significant predictor of BMD at the lumbar spine, disease duration, physical activity habits and gender at the femoral neck and physical activity habits at the greater trochanter.

6.6.1 Primary Outcomes

6.6.1.1 Bone Mineral Density

In this study significant reductions in BMD were identified at the lumbar spine and femoral neck, between CD participants and healthy matched controls, but not at the greater trochanter. This non-significant difference could be explained by the composition and microarchitecture of the greater trochanter, which has demonstrated significantly higher mineralisation (+2%, p<0.05) than the femoral neck (Turunen et al., 2013). It is interesting to observe that when age, BMI, gender and physical activity matched that significant differences at the femoral neck and lumbar spine were observed. A potential reason for this significance could be explained by numerous factors such as genetic abnormalities, premature menopause and/or nutritional deficiencies, particularly of vitamin D and calcium none of which were controlled for (Rockville, 2004).

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A frequency of 48.5% and 6% of CD participants were indicative of having osteopenia and osteoporosis, respectively at the left hip and 36.4% and 6% at the lumbar spine, supporting the rates reported by other observational studies in CD (Ghosh et al., 1994; Bjarnason et al., 1997; Ardizzone et al., 2000; Szathmari et al., 2002; Lima et al., 2017). The clinical significance of low BMD is the increased bone fragility and high propensity to fractures, contributing to poor QOL, increased morbidity and mortality and loss of independence (National Institutes of Health, 2014). The relative risk of sustaining a fracture for people with CD is 40% higher in comparison to the general population and is significantly increased at the spine (incidence rate ratio [IRR], 1.74 [95% CI=1.34-2.24]; p<0.001), hip (IRR, 1.59 [CI=1.27-2.00]; p<0.001), wrist/forearm (IRR, 1.33 [CI=1.11-1.58]; p=0.001) and ribs (IRR, 1.25 [CI=1.02-1.52]; p=0.03) (Bernstein et al., 2000). These results lend support to CD being a risk factor for low BMD.

Silvennoinen et al (1995) and Jahnsen et al (1997) also reported similar reductions in BMD in adults with CD at the femoral neck and lumbar spine when compared to CON. However, mean BMD (g/cm^2) scores reported at the femoral neck (0.948; 0.910) and spine (1.177; 1.140) by both studies, respectively, were considerably higher than the mean scores reported in this study (0.957; 0.734, respectively). Potential reasons for this variation could be explained by the use of older equipment used to assess BMD due to the age of the publications, since then modifications have been made that have resulted in better image quality, use of different software and type of scanning beam used, all of which are known to affect results (Genton et al., 2002). In contrast to the current findings, another observational study between 68 newly diagnosed (<6 months) IBD participants and healthy controls reported no significant group differences (Schoon et al., 2000). Suggesting that disease-related factors seem to be responsible for the development of reduced BMD and thus, the

potential differences could also be explained by the variation in participant clinical characteristics. Findings were further supported by a more recent cross-sectional study of 1230 IBD (CD=719, UC=511) participants, who identified adults with CD to be nearly 50% more likely to develop osteoporosis than CON (Targownik et al., 2013).

However, comparisons and conclusions are difficult to deduce due to the variability in participant selection, statistical analysis method and the method of measurement. Studies comparing healthy controls to people with CD and identifying possible risk factors associated with low BMD are crucial.

6.6.1.1 Correlates of Bone Mineral Density

Statistically significant correlates of BMD in CD at the lumbar spine were disease duration, physical activity habits, gender and smoking status. Disease duration, physical activity habits and gender were identified as significant correlates at the femoral neck and physical activity at the greater trochanter. However, these coefficients only account for 16.1-38.5% of the variability and further evaluation of the potential association between BMD and 1) perianal disease, associated to higher disease recurrences and younger age of disease onset (Choi et al., 2015; Schule et al., 2016), 2) disease activity, associated to malabsorption and increased levels of proinflammatory cytokines that interfere in bone metabolism pathway (Sgambato et al., 2019), and 3) medication type, particularly corticosteroids which are associated with decreased serum markers of bone remodelling (Miheller et al., 2007).

Several previous studies have explored whether gender affects BMD in CD, however with no definite answer. In this study, being female was a significant correlate at the lumbar spine and femoral neck. This is in line with published data from an earlier study. Andreassen et al's

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(1999) case control study matched 113 CD participants for gender, age and body weight identifying female sex as an independent risk for BMD. This was confirmed by Targownik et al's (2013) study of 1230 IBD participants (n=719 CD; n=511 UC), who after controlling for age, gender, BMI, hormone replacement therapy, osteoprotective medications, and corticosteroid use identified female sex as risk factor for BMD. Women are thought to be at a greater risk as a result of hormonal changes. Oestrogen plays an important role in bone growth and maturation as well as in the regulation of bone turnover, levels of which decrease during and after menopause. As a result of oestrogen deficiencies, disturbed architecture and reduced bone mass and bone strength are induced (Riggs, 2000; Eastell et al., 2016; NHS, 2019). Moreover, chances of developing osteoporosis are increased further if they have undergone a hysterectomy, partially when the ovaries are also removed due to the lack of oestrogen being produced (Eastell et al., 2016; NHS, 2019). However, contrary to the current study's findings, males have also been identified as significant independent risk factor for low BMD in people with CD (Bartram et al., 2006; Lima et al., 2017). The exact cause of osteoporosis in males is unknown, however is thought to be linked to testosterone levels, made by dehydroepiandrosterone sulphate (DHEAS) (NHS, 2019). A study of 45 males with IBD (UC=25; CD=20) explored DHEAS levels in relation to BMD, identifying 23 participants who had significantly reduced DHEAS levels and consequently lower lumbar spine and femoral neck BMD T-scores than participants within a normal DHEAS range (Szathmari et al., 2002), which may explain the variation in findings.

Non-stricturing/ non-penetrating, stricturing and penetrating disease behaviour was not identified as a risk factor for low BMD at any site, contradicting the findings of Lima et al (2017). This cross-sectional prevalence study of 165 participants (60 with CD, 68 with UC and 67 CON) identified through multiple correspondence analysis that penetrating behaviour

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was associated with low BMD. One possible reason for this difference could be that no participants in the current study presented with a penetrating disease behaviour, compared to 30% in Lima et al's (2017) study. In the current study, surgical history and alcohol intake were not identified as risk factors of low BMD in people with CD. However, there are inconsistent findings about the association of surgery with BMD and whether the association is influenced by the type of surgery. For example, initially it was thought that proctocolectomy with ileal pouch-anastomosis would benefit BMD, possibly due to the discontinuation of corticosteroids, improved nutritional intake and reduced cytokine release due to the removal of the diseased colon (Gupta and Shen, 2013). However, the anatomy and function of the small-intestine is altered in ileal pouch surgery, reducing the absorption of bile salts, thus reducing the absorption of vitamin D. In addition, inflammation of the ileal pouch has been shown to increase inflammatory cytokines IL-1, IL-6 and TNF- α , stimulators of osteoclast activity, which promotes bone loss (Gupta et al., 2014). Therefore, it remains unclear as to whether these metabolic consequences of surgery provide benefits or detriments to BMD. Longitudinal studies identifying BMD before and after surgery is needed to better evaluate the effect of the type of surgery on bone loss.

Moderate to vigorous physical activity was identified as a correlate of BMD at the lumbar spine, femoral neck and greater trochanter. Supporting the positive relationship between physical activity and BMD identified in Nobile et al's (2018) cross-sectional study of 216 paediatric IBD participants. Without physical activity as a loading stimulus, sedentary behaviour promotes the activity of osteoclasts, which re-absorb bone tissue, and impairs IGF-1 and TGF-beta (TGF- β) signalling involved in maintaining bone strength (Troy et al., 2018). Conversely, physical activity has shown a positive correlation with increased BMD in healthy individuals and as a treatment or prevention in metabolic diseases such as diabetes,

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osteoporosis and lupus (Todd and Robinson, 2003; Vainionpaa et al., 2005; Pineau et al., 2004). An osteogenic stimulus occurs during exercise, in which bone is subjected to forces induced by gravitational loading and muscle loading. This osteogenic stimulus initiates an adaptive response involving osteocytes that transduce the energy from the mechanical forces into biological signals that impact bone formation and resorption. This elicits bone deformation, stimulating the stretch-activated ion channel on osteocytes and triggers the expression of genes that mediate bone growth and increase the threshold of stress tolerance, thus eliciting an architectural modification (Zagdsuren, 2014).

However, the strength of the relationship observed between physical activity and BMD in the current study may be impacted by the measurement tool used to quantify activity levels. The SPAQ does not take into consideration the type of activity performed, therefore participants could have reported being highly active but undertook no bone loading activities. Future research exploring this association using objective measures or questionnaires that quantify the type of exercise are needed.

Disease duration was a significant predictor of BMD at the lumbar spine and femoral neck, supporting the findings of Pollak et al (1998) and Schulte et al (1998). However, due to the unknown pathogenesis of osteoporosis, it remains unclear at what phase BMD starts to decrease in CD. Sakellariou et al's (2006) prospective study of 32 CD participants identified that participants with a disease duration of >6 months had a lower BMD when compared to those with a diagnosis of less than 6 months. Fifteen newly diagnosed CD participants were also identified as having a lower BMD (Ghosh et al., 1994). Ghosh et al (1994) determined BMD using Z-scores, a value comparing BMD to what is normal in someone of the same age and body size. However, it is thought that Z-scores can be misleading and, in accordance with the NOF, a diagnosis of osteoporosis using Z-scores should not be used in younger men,

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premenopausal women and children (NOF, 2013). Therefore, deductions are difficult to make. A cross-sectional study observed 79 newly-diagnosed IBD participants, who had never used glucocorticoids, but had a low BMD (Bjarnason et al., 1997). One hypothesised explanation for this could be due to the disease itself, IL-1 (α and β), IL-6, IL-11, IL-15, and IL-17, TNF- α and prostaglandin E2 in IBD, are elevated in IBD. These proinflammatory cytokines interfere in the pathway involved in bone metabolism, known as RANK-RANKL-OPG, and thus change the rate of bone formation, bone resorption and overall bone homeostasis (Bernstein and Leslie, 2003; Bernstein et al., 2005; Mundy, 2007).

In this study, no correlations were identified between BMD and age at the lumbar spine, femoral neck or greater trochanter, contrary to previous findings (Ghosh et al., 1994; Bjarnason et al., 1997; Bartram et al., 2006). However, methodological limitations and differences in participant characteristics could explain these variations. Ghosh et al's (1994) study was significantly limited by the recruitment of participants aged 14 and determining BMD through Z scores, as Z scores are not possible to apply to individuals under 20 years of age due to growth and development (NOF, 2013). Moreover, the average score for disease activity determined using the CDAI was 196, suggesting participants were only representative of having a mildly active disease, compared to the CDAI of 114 identified in this study. No participants in the present study were taking glucocorticoids, compared to 19 participants in Bjarnason et al's (1997) study. The use of glucocorticoids has been suggested to induce bone loss, by impairing osteoblast function and the synthesis of osteoprotegerin, allowing an interaction that causes osteoclasts to differentiate and mature resulting in bone loss (Ali et al., 2010). Additionally, in Bjarnason et al's (1997) study and Bartram et al's (2006) study, 15.2-32.2% participants, respectively, were current smokers, a determinant of BMD, compared to 0% in this study.

However, comparisons are difficult to make and it is more likely that these inconsistencies are due to the variability in participant selection/ characteristics (e.g. age, body weight, health status, other comorbidities), study design (cross-sectional vs prospective), statistical power for determining effect and technique used to determine outcome. Nevertheless, all studies reported a reduction in BMD, thus suggesting that people with CD are at an increased risk of osteopenia or osteoporosis.

6.6.1.2 Muscular Function

The findings of this study identified that people with CD have a significantly impaired lower limb muscle strength and impaired upper and lower limb muscle endurance than healthy matched controls. In regards to maximal isokinetic lower limb strength, our results partially contradict those of Geerling et al (1998) who reported a significantly lower hamstring peak torque in CD participants but similar quadriceps torque to CON at velocities of 60°/s and 180°/s. These variances may be explained by the age and disease duration of study participants compared to the present study. Geerling et al (1998) reported a median age of 40 and a median disease duration of 16 years compared to 51 and 21, respectively in this study. Moreover, 41% of participants in Geerling et al's (1998) study were receiving prednisone treatment, perhaps because 47% were suggestive of having an CDAI>150. The use of glucocorticoids has been suggested to induce loss of skeletal muscle mass and muscle weakness, contributing to a reduction in muscular strength and endurance (Sato et al., 2017). As muscles are a large site of protein, it is thought this deterioration occurs due to the suppression of protein synthesis, the naturally occurring process in which protein is produced to repair muscle damage, by glucocorticoids (Al-Jaouni et al., 2002). This causes a protein imbalance resulting in muscle wasting. However, whole-body and muscle protein

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metabolism, such as muscle strength and muscle mitochondrial function is not adversely affected by short term low doses of glucocorticoids as it uses epinephrine to mobilise energy and deliver it to the muscles, thus promoting energy replenishment (Short et al., 2004). It is therefore thought that chronic use or high dosage of GC administration is associated with muscle wasting. Our results are similar to those of Brevinge et al (1995) and Wiroth et al (2005) who both identified significant lower limb muscular strength in people with CD compared to CON. Brevinge et al (1995) found significantly reduced working capacity in CD participants while undertaking maximal exercise on a cycle ergometer involving extensor muscles of the lower limb. Wiroth et al's (2005) study assessed strength parameters in 41 CD participants in clinical remission, with findings demonstrating a significant reduction in maximal isometric strength (-24.6%, p<0.001) and endurance (-25.8%, p<0.001) of the leg extensors.

Upper limb isokinetic strength and HGS were similar in people with CD and controls, suggesting that upper limb strength is preserved in people with CD. This finding is consistent with those of Wiroth et al (2005) and Cabalzar et al (2017) who found no significant difference in either parameters. Interestingly, Zaltman et al's (2014) study assessing upper and lower limb muscle strength in UC participants also reported significantly decreased maximal quadriceps strength ($d= -6\%$; $p=0.012$), but not in HGS ($p=0.362$). A similar pattern is often observed within the elderly, where upper limb strength is preserved while lower body function is often decreased (Izquierdo et al., 1999). This is thought to result from sedentary behaviour, alternating behaviours such as avoiding climbing stairs, or individuals with weaker limbs supplementing lower body movements with arm muscles, such as rising from a chair (Macaluso and Devito, 2004). This constant sedentary behaviour can negatively influence muscular performance, by adversely affecting the recruitment of fast twitch muscle

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fibres, reduce glycogen stores and suppress the ability to produce enough energy

(Minderhoud et al., 2003; Wiroth et al., 2005).

Impaired nutritional status as a result of poor food intake, impaired digestion and absorption, medication side effects, surgical intervention or systemic inflammation due to active disease could explain the variation in impaired muscle function (Ispas et al., 2015; Spooren et al., 2015). IGF-1 is a marker for the nutritional state, with low level concentrations a sign of malabsorption. IGF-1 is a hormone that stimulates the proliferation of muscle progenitor cells and their integration with existing muscle fibres during the muscle repair process, and the elevation of TBARS is a marker of oxidative stress (Machida and Booth, 2004). The combination of these changes will decrease the PI3K/AKT signalling pathway that is involved in inducing skeletal muscle hypertrophy. Therefore, it is thought to play a role in the reduction in muscle mass and muscle CSA in CD (Cominelli, 2004). This was supported by the findings from a cross-sectional study that obtained muscle biopsies from 27 CD participants and compared them to CON. Results demonstrated a 37% reduction in IGF-1 ($p<0.01$), a 54% lower phosphorylated:total Akt ratio ($p<0.05$) and increased serum TBARS ($p<0.05$), suggesting impaired activation of muscle protein IGF-1-Akt pathway plays a role in the regulation and reduction of skeletal muscle growth (van Langenberg et al., 2014). This rationale would therefore support the findings of Valentini et al's (2008) study in 94 CD participants, of whom 23.7% showed signs of malnutrition and demonstrated a significantly reduced HGS when compared to CON (23.1kg, 20.8–28.7, $p=0.021$). These variables could also provide an explanation for the impaired muscular endurance values.

Similar reductions in muscular endurance were identified in Wiroth et al's (2005) study which assessed muscular endurance using the 12-repetition sit-up test (-25.1%, $p<0.001$) and in Zaltman et al's (2014) study of UC participants, using the sit-up test ($d= -32\%$; $p=0.00001$)

and gait speeds ($d = -17\%$; $p=0.0004$). These tests reflect tasks of daily living and therefore highlighting the importance of introducing interventions to increase muscular strength and endurance prior to the development of musculoskeletal EIM's.

6.6.2 Secondary Outcomes

6.6.2.1 Quality of Life

Quality of life, determined using the EQ-5D-5L was impaired in people with CD compared with CON. Five studies have measured QOL in CD participants compared with that in CON, two utilizing the IBDQ (Love et al., 1992; Casellas et al., 2000), one using the German KINDL and IMPACT III questionnaires (Werkstetter et al., 2012), one using the Sickness Impact Profile (Drossman et al., 1989), and one using the SF-36 (Cabalzar et al., 2017). Regardless of the questionnaire used, all studies found QOL scores to be worse in people with CD. However, none of these studies took into consideration the disease state of the participant which remains the most significant predictor of physical and mental HRQOL in IBD, with strong correlations identified between the CAI ($r = -0.623$, $p=0.0003$), Endoscopic Activity Index ($r = -0.511$, $p=0.005$), CDAI ($r = -0.506$, $p<0.001$) and HBI ($r = -0.600$, $p<0.001$) with disease-specific, self-assessed QOL questionnaire (Kim et al., 1999; Zahn et al., 2006). Although, disease activity does not explain the decrements in QOL completely, with more than 30% of asymptomatic individuals reporting an impaired QOL, so other correlates of QOL in CD such as stress (Mawdsley and Rampton, 2005), sleep (Graff et al., 2011), surgical history or disease duration (Haapamaki, 2011) should be adjusted for. Nevertheless, with the variability between active and quiescent disease states, medical and surgical side effects, disease-specific complications and social, psychological and financial

repercussions it is not surprising that people with IBD have an impaired QOL (Bernklev et al., 2005; Moradkhani et al., 2013).

6.7 Strengths and Limitations

One of the strengths of this study was the matching of confounding factors (age, gender, BMI, smoking status and physical activity status) of CD participants with CON, this reduces the effect of the confounding factors on the variable investigated. CD participants were also randomly recruited from a clinical population and therefore considered to be more representative of the target population regarding age, gender, disease location and duration, treatment history/management and surgical implications. Lastly, this study also involved a comprehensive assessment of health outcomes, allowing for a detailed comparison of the participants health status.

The study did have some limitations that are worth noting. Firstly, cytokines were not ascertained. Proinflammatory cytokines such as TNF- α and IL-6 have been shown to interfere with the pathway involved in bone metabolism and to impair muscle function through reducing secretions of IGF-1, important for muscular strength, mass and endurance (Barbieri et al., 2013). Future studies should consider studying inflammatory cytokines to better understand their role in muscle dysfunction and bone loss. Secondly, medications were not adjusted for. Anti-TNF therapies and immunosuppressants are commonly used as a treatment in CD and may influence the cytokine production, and thereby potentially positively impacting BMD and muscular function. Infliximab, an anti-TNF drug, was administered to 45 CD participants over a period of 22 months and this treatment showed a significant increase in BMD at the lumbar spine, independent of nutritional status, from baseline to 22

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months when compared to CD participants who had never had infliximab ($p<0.01$) (8.13% ± 7.7) (Mauro et al., 2007). A retrospective study of 59 CD participants analysed the effects of azathioprine on BMD, finding that although azathioprine does not positively or negatively impact BMD itself, it seems to preserve BMD in people with CD (Floren et al., 1998). However, given the small sample size, it was unfeasible to adjust analysis according to medication type, particularly as many participants were currently taking both treatments, making it difficult to distinguish the impact of each. Moreover, many participants had been on these medication types in the past and the duration of these potentially preserving effects is unknown.

Thirdly, nutritional state was not determined. Although participants included in this sample were in clinical remission or mildly active, impaired nutritional status was estimated in 65-75% of people with CD, resulting in deficiencies in vitamin D and calcium (Ispas et al., 2015; Spooren et al., 2015). These deficiencies are inversely associated with elevated levels of markers of bone turnover and increased concentrations of uncarboxylated osteocalcin, a predictor of risk fracture and premature and accelerated development of low muscle mass, strength and physical performance (Greenland and Nair, 2003; Duggan et al., 2004). Given the effects of malnutrition on bone and muscle health, it is important that this is incorporated into future studies to better understand the effect of this risk factor. In addition, steroid history was not obtained due to recal problems. Glucocorticoid usage, particularly of long duration and high concentration has been suggested to induce loss of skeletal muscle mass and muscle weakness and impair osteoblast function causing an increased activity, proliferation and maturation of osteoclasts (Bernstein et al., 2003; Sato et al., 2017).

Lastly, the use of a cross-sectional design to determine the correlates of BMD was also a limitation of this study as correlation does not necessarily imply causation, therefore further research would be needed to determine a causal relationship.

6.8 Conclusion

Although the results of these studies do not provide novel findings, they strengthen the evidence base that adults with CD are at an increased risk of osteopenia or osteoporosis and provides support to the correlations associated with BMD, which might facilitate the decision in regards to BMD testing. Adults with CD in clinical remission or with a mildly active disease also show a reduced lower muscular strength and upper and lower muscular endurance when compared to CON. Consequently, these are two important predictors of future disability. Interestingly, upper muscular strength scores were similar in CD and healthy controls, suggesting upper limb strength is preserved. As discussed previously, this is thought to be as a result of sedentary behaviour and supplementing lower body movements with arm movements such as rising from a chair. Nevertheless, a complete evaluation of participants BMD and muscular performance should be assessed as part of routine clinical care and specific pharmacological and non-pharmacological therapeutic strategies should aim at preventing, treating or avoiding further deterioration of these secondary complications.

The potential role of non-pharmacological therapies in CD remains poorly understood. However, until the aetiology of the exact mechanisms of bone loss and muscle dysfunction is understood it is believed a combined impact and resistance training programme focusing on bone and muscle parameters may reduce the deleterious effects on CD while enhancing fatigue and QOL, as demonstrated in osteoporosis, sarcopenia and postmenopausal women.

CHAPTER

7

Effects of a 6-month practical resistance-training
programme on muscle function and bone mineral
density in adults with inactive or mildly active
Crohn's disease

7.1 Introduction

A growing body of evidence suggests that individuals with CD are at an increased risk of muscle dysfunction and reduced BMD, potentially resulting in further disability. Despite pharmacological advances, the prevalence of these disorders remains high (Wiroth et al., 2005; Ali et al., 2009). The aetiology and exact mechanisms that may under-pin the relationship between bone and muscle loss in CD are yet to be fully elucidated. However, they are likely to be multifactorial including proinflammatory cytokines, glucocorticoid usage and malnutrition (Bryant et al., 2015; Lima et al., 2017). Nevertheless, measures to treat these secondary complications in this high-risk group have not yet been well established.

Despite the mechanical properties of weight-bearing exercises and its widespread clinical use in osteoporosis, sarcopenia and postmenopausal women to increase muscular strength, muscular endurance and BMD (Palombaro et al, 2013; Hong and Kim, 2018), little is known about the beneficial effects in people with CD. To our knowledge no studies have explored the potential for weight-bearing and impact training to minimise or reverse muscle strength or endurance impairments or improve BMD in people with CD. One RCT has explored the potential of a home-based resistance training programme as an adjunct therapy for BMD in CD, demonstrating that those participants who were fully compliant with the programme showed greater improvements at the femoral neck, lumbar spine and greater trochanter. This suggests that improvements in BMD are related to the amount of exercise performed and that a home-based resistance training programme is feasible in adults with CD. To address the lack of research in this area, this RCT aims to assess the effects of a 6-month combined impact and resistance training programme on BMD, muscle strength and muscular endurance in adults with CD. With a hypothesis that the implementation of a combined impact and resistance training programme improves primary outcomes 1) BMD and 2) muscular function in adults with inactive to mildly active CD.

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7.1.1 Study Objectives

Primary Objective

1. To investigate the effects of a 6-month combined impact and resistance intervention on muscle function and BMD in adults with inactive or mildly active CD

Secondary Objectives

2. To examine the possible benefits on fatigue, HRQOL and disease activity
3. To explore acceptability and safety of a 6-month combined impact and resistance intervention
4. To evaluate the feasibility of conducting a larger, multi-centre RCT

7.2 Methods

There was one deviation from protocol. It was planned to use the Florence Telehealth App to act as a motivational support to exercise participants, however this method was unavailable. Participants were instead contacted every 4 weeks by the intervention facilitator via their preferred method of contact.

7.2.1 Study Design

PROTECT (PROgressive resistance Training Exercise and Crohn's disease Trial) was a single centre, two arm, parallel-group, RCT. Following baseline assessments participants were randomly allocated 1:1 to either usual care plus a 6-month combined impact and resistance training programme or a control group, who received usual care alone. Study

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outcomes were conducted at baseline, 3 and 6 months following randomisation. The study flowchart is shown in figure 35.

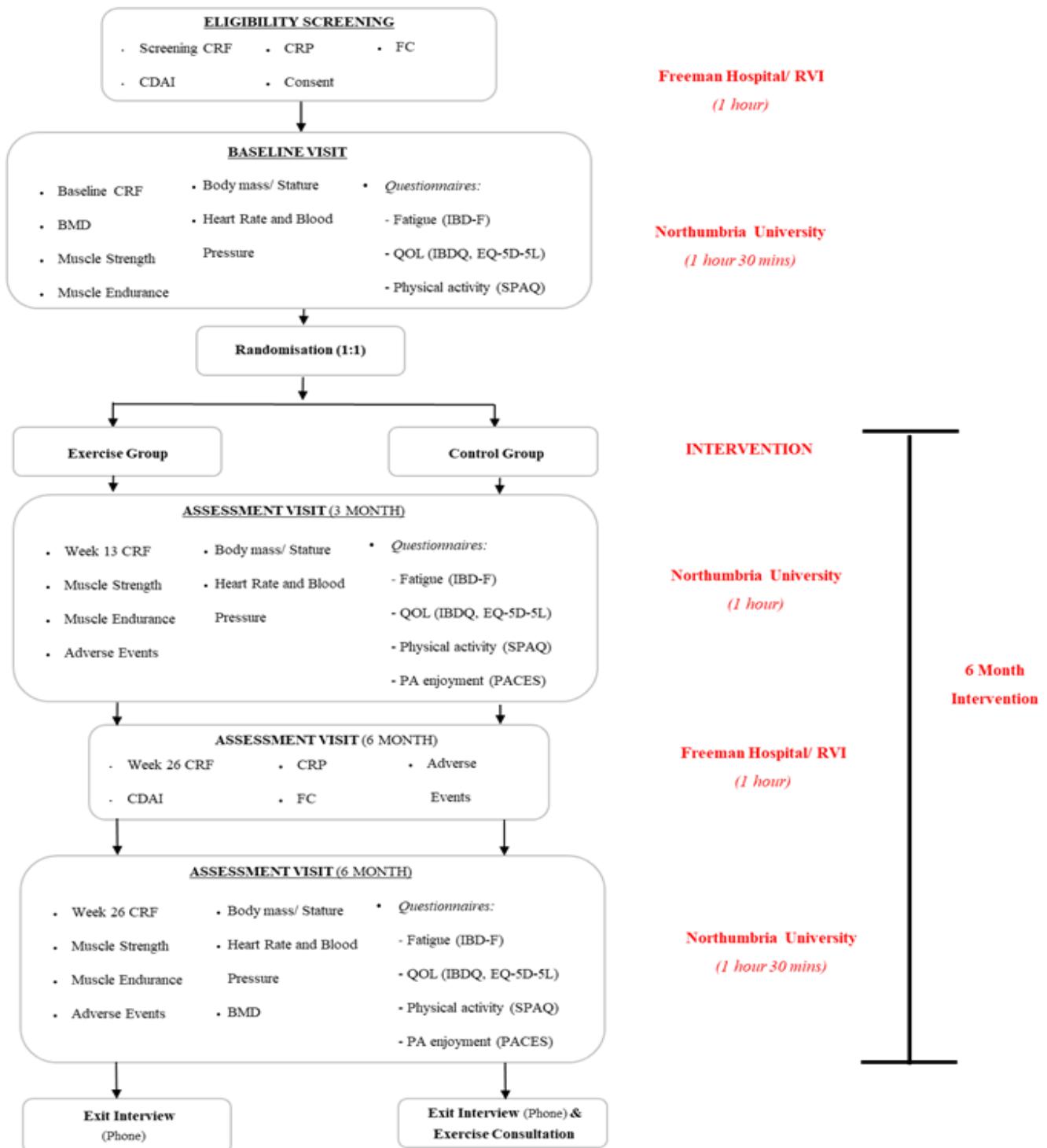


Figure 35. Study Flowchart.

CRF, Case Report Form; CDAI, Crohn's Disease Activity Index; FC, Faecal Calprotectin; CRP, C-reactive Protein; BMD, Bone Mineral Density; QOL, Quality of Life

7.2.2 Study Setting

Adults with CD were recruited from a clinical population within NUTH Trust sites (The Royal Victoria Infirmary or the Freeman Hospital). Baseline, week 13, week 26 visits and exercise sessions were delivered at the University of Northumbria at Newcastle.

7.2.3 Eligibility Criteria

Men and women aged ≥ 16 years were eligible to participate if they were able to provide written consent, were able to travel to the research centre and had a verified (radiologically, histologically and endoscopically) diagnosis of CD of at least 4 weeks duration. This duration was applied to allow medications to be adjusted, symptoms to be better controlled and to allow time for individuals to educate themselves and manage their new diagnosis. The following exclusion were applied:

- Adults with UC or IBD-U. Due to osteoporosis and osteopenia occurring more frequently in CD than UC or IBD-U.
- Medication changes 4 weeks prior to the screening visit, or if the individual presented with an active disease determined, within 4 weeks, using the CDAI (>220) and FC (>250 mcg/g). These exclusions were applied due to these determinants indicating active inflammation. As nothing or little is known about the safety of exercise in people with a moderately or severely active disease, people with CD who presented with inflammatory markers above the threshold were excluded for safety reasons.
- Deemed unsuitable to undertake resistance exercise (assessed by gastroenterologist/physician).
- Participation in another clinical trial for which concurrent participation was deemed inappropriate and likely to influence the results of either study.

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- Current participation in >2 sessions/week of resistance exercise (self-reported). This exclusion was applied as it would be difficult, if not impossible, to distinguish between the effects as a result of the intervention prescribed or the current training the participant was undertaking
- Absolute contraindications to exercise testing and training as defined by the ACSM (2017) (Appendix 7a), for the safety of the participant and the potential risks of exercise testing outweighing the benefits.
- Pregnant, female planning pregnancy or planned major surgery within 6 months after randomisation, due to the intervention type and radiation exposure.

7.2.4 Recruitment

Adults were recruited on a volunteer basis by one of four methods. Recruiting from a clinical population enabled the evaluation of interventions feasibility, acceptability and effectiveness when applied to a realistic, real-life, routine practice conditions to provide the best level of evidence-based care.

1. IBD-specific database (Bioresource, United Kingdom) at the Newcastle Centre of Bowel Disease Research. A database of individuals who have consented to being contacted regarding future trials. The database of 786 CD, as of November 2018, was screened and potentially eligible participants were identified. If the inclusion/exclusion criteria appeared satisfactory, individuals were sent an information pack prior to attending the gastroenterology department for their routine appointment. This information pack contained a recruitment letter (Appendix 7b), participant information sheet (Appendix 7c), disease activity diary (Appendix 7d) and an example informed consent form. Interested potential participants were asked to

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contact the study co-ordinator 24 hours after reading the information via phone or email for further information, to answer any questions and/or to arrange an eligibility visit. Arranged the same day as an upcoming appointment or at a date/time convenient.

2. Recruitment posters (Appendix 7e) advertising the research study were placed in the gastroenterology waiting areas.
3. Study posters (Appendix 7f) were also placed in examination rooms to act as a reminder to staff. Participants identified by their gastroenterologist were directed to see the study co-ordinator and an information pack provided. Those wishing to participate were asked to wait 24 hours before contacting a member of the research team.
4. Social media and networking sites, the details of the study were uploaded and hashtags such as #Crohn's and #IBD were used to generate interest.

7.2.4.1 Eligibility Assessment

Prior to attending the eligibility assessment, potential participants were asked to complete a 7-day disease activity diary, contained in their information pack, and bring this along with them to their appointment. If lost/thrown away another copy was sent out via post. The disease diary recorded parameters such as number of liquid stools, abdominal pain and general well-being, information used towards assessing disease activity using the CDAI. During the eligibility assessment, the study was explained in more detail, any questions were answered and informed consent (Appendix 7g), participant contact details and GP details (Appendix 7h) were obtained. To assess eligibility a CRF was completed (Appendix 7i), acquiring demographical and clinical information established from self-reports and medical

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records. Objective and subjective measures of disease activity were also assessed using FC markers, CRP and the CDAI. For the latter measure, body mass, extra-intestinal complications, anti-diarrhoeal medication, haematocrit and an abdominal examination to exclude the presence of an abdominal mass were assessed by a direct care team member.

On the return of disease activity parameters, participants were contacted via their preferred method and eligible participants invited to attend a baseline assessment. Appointed gastroenterologists were informed of any inflammatory measures that came back suggestive of an active disease. Eligibility CRF's were signed by the clinical principal investigator and a copy placed in medical records.

7.2.5 Outcome Measures

7.2.5.1 Primary Outcomes

- BMD (g/cm^2) was determined at baseline and 6 months using a DEXA (Hologic Horizon W DEXA scanner). Measurement sites included the femoral neck and greater trochanter of the left hip and lumbar spine (L2-L4)
- An isokinetic dynamometer (Biodex system 4 Pro) was used to assess lower limb and upper limb muscle strength (Nm) at baseline, 3 and 6 months. Maximum voluntary isokinetic strength (MVIS) of the knee extensors on both legs and elbow flexors on both arms were evaluated. Handgrip strength (HGS) was measured using a handgrip dynamometer (JAMAR Hydraulic), taken from the nondominant forearm.
- Muscle endurance was determined at baseline, 3 and 6 months. Lower extremity muscle endurance was assessed using the 30-s CST, upper extremity muscle

endurance was established using the 30-s BCT, conducted from the nondominant forearm

7.2.5.2 Secondary Outcomes

- The IBD-F was used to determine fatigue at baseline, 3 and 6 months
- QOL was evaluated using the IBDQ and EQ-5D-5L at baseline, 3 and 6 months
- Disease activity was assessed at baseline and 6 months using the CDAI
- Intestinal inflammation was determined by measuring FC at baseline and 6 months
- CRP was used to measure inflammatory markers in the body at baseline and 6 months
- Physical activity habits were assessed using the SPAQ at baseline, 3 and 6 months

7.2.5.3 Feasibility and Acceptability Outcomes

Trial acceptability outcomes were assessed by recruitment rates and examining reasons for dropout in discontinuing participants and comparing attrition rates between the two study groups and between participants who did and did not receive their preferred group allocation, assessed at baseline and prior to randomisation. The acceptability of the exercise programme was determined by exercise adherence rates, measures of exercise enjoyment established by the Physical Activity Enjoyment Scale (PACES) at 3 and 6 months, and participant feedback via exit telephone interviews following 6-month assessments. Attrition rates were also established at discontinuation of intervention and loss to follow-up measurement for all groups.

Trial feasibility outcomes were determined by examining and evaluating the suitability of outcome measurements, based on completion rates and rates of missing data. The safety of

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exercise training was assessed by exploring rates of relapse at 3 months, through self-report, and at 6 months, defined by an increase in CDAI of ≥ 100 points to a score ≥ 150 . Reasons for dropout from the exercise programme and the number and type of AE that occurred in each group were recorded.

7.2.6 Data Collection

Appendix 7j demonstrates the participant timeline of enrolment, interventions and assessments. All visits took place in the Neurophysiology and DEXA lab at Northumbria University. In accordance with ACSM guidelines (2017), for the safety of the participants, blood pressure and heart rate were determined prior to any exercise testing.

7.2.6.1 Baseline Assessment

Baseline assessments, conducted within 4 weeks of receiving disease activity results, were completed and a baseline CRF (Appendix 7k) gathered information on intervention preference, body mass, stature, resting heart rate and resting blood pressure. Outcome measures were recorded and obtained in the same order for every participant: HGS, 30-s BCT, 30-s CST, questionnaires (IBDQ, EQ-5D-5L, IBD-F, SPAQ), MVIS and BMD. A GP letter (Appendix 7l) was sent following randomisation.

7.2.6.2 Randomisation and allocation

Following the baseline assessment participants were randomly assigned 1:1 to either a 6-month combined resistance and impact training programme plus usual care or a control group

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who received usual care alone. An online randomisation programme (www.randomization.com) was used by a researcher, not involved in the recruitment process, to generate the randomisation sequence. Participants were randomly allocated by block-randomisation with varying block size to ensure concealment, stratified by gender (male/female) and disease activity (inactive [CDAI <150]/mildly active [CDAI 150-219]). Control group participants were notified by letter (Appendix 7m).

7.2.7 Interventions

7.2.7.1 Combined impact and resistance training

Participants allocated to the exercise group were provided with latex-free TheraBand equipment, skipping ropes and an exercise information booklet (Appendix 7n) and invited to complete three sessions of exercise a week on non-consecutive days for 6 months. The study co-ordinator went through the booklet in detail and answered any questions, participants were then asked to read the information on participation, monitoring, TheraBand care and safety, travel information and contact information at home. Sessions were primarily unsupervised and home-based with 12 supervised support sessions tapered over time:

1. 2 sessions a week for 2 weeks (week 1 and week 2) =4 sessions
2. 1 session a week for 2 weeks (week 3 and week 4) =2 sessions
3. 2 fortnightly sessions (week 5/6 and week 7/8) =2 sessions
4. 4 monthly visits (week 9 onwards) =4 sessions

To facilitate attendance, sessions were offered in early mornings, evenings and weekends. The supervised sessions were conducted to provide participants with motivation, knowledge

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and support regarding technique, posture and body alignment. Lasting approximately 60 minutes, each session began with a 5-minute warm-up consisting of pulse raising dynamic exercises and stretches. Followed by 5 minutes of initial rope skipping. Participants then progressed to 10-15 minutes of plyometric jumping involving 2-3 sets, 10-15 reps of 5 multidirectional jumps.

Participants were instructed to perform these jumps explosively, quickly with maximum power and speed with 30-s rest after each rep. The main body of the programme involved 2-3 sets, 10-15 reps of 10 high intensity exercises targeting the upper body, lower body and midsection using a resistance TheraBand. The session ended with a 5 minute cool down consisting of pulse lowering dynamic and static stretches.

Each supervised session was delivered by the study co-ordinator who was trained in delivering the exercise protocol, CPR and automated external defibrillation. A maximum of three participants were trained per session. Prior to the exercise session and 10 minutes post exercise, heart rate and blood pressure were recorded to ensure the safety of the participant. An exercise CRF (Appendix 7o), monitoring heart rate, blood pressure and exercise difficulty (Resistance Intensity Scale for Exercise [RISE]) self-reported by participants were completed for each session with notes made regarding any serious or non-SAE that occurred.

7.2.7.2 Exercise Progression

The RISE (Figure 36) was used to rate perceived exertion to dose appropriate level of resistance, as recommended by the ACSM (2004). The RISE has demonstrated high validity coefficients for the active muscle ($r^2=0.87$) and overall body ($r^2=0.76$ to 0.85) (Colado et al., 2014). Following each exercise session, participants were asked to rate (easy to maximal) on

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the scale how hard they found the session and progression to the next band level occurred when the participant was able to complete 3 sets of 15 repetitions easily (Table 14).

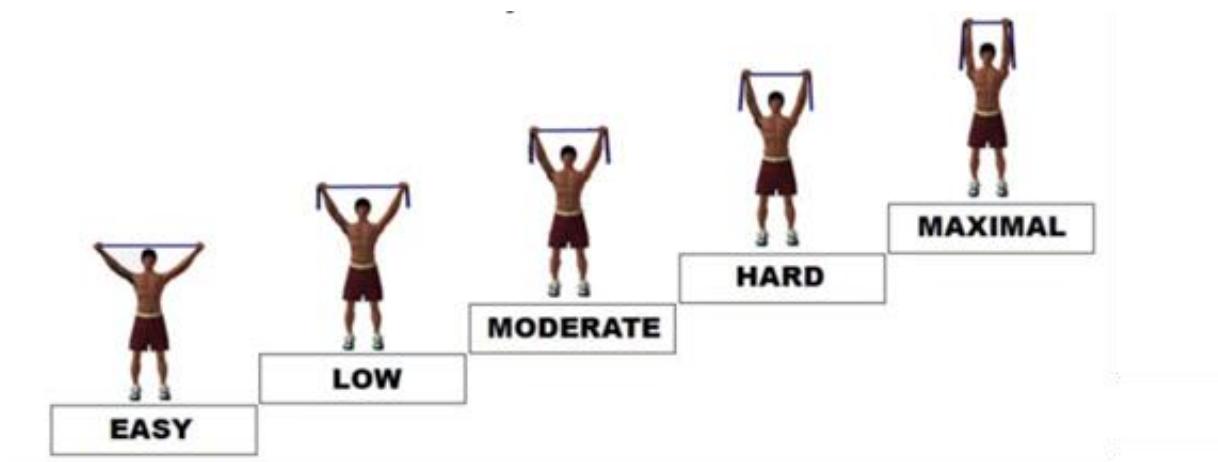


Figure 36. Resistance Intensity Scale for Exercise (RISE)

Based on plyometric jump training criteria (Hansen and Kennelly, 2017), the skipping and jumping phase were progressed on the principles that they were performed pain-free with no difficulty, such as muscle soreness or fatigue and the correct technique was performed. With the latter focusing on the landing/force absorption, distribution of landing, quick concentric movement with complete control while demonstrating good landing mechanics. Often performed within three weeks into the training cycle.

Table 14. Exercise Progression

JUMP TRAINING						
Step One	Step Two	Step Three	Step Four	Step Five	Step Six	Step Seven
Double Leg Skipping	Alternate Leg Skipping	15-30's Single Leg Skipping	2 Sets, 10 reps	2 Sets, 15 reps	3 Sets, 10 reps	3 Sets, 15 reps
5 minutes each			Squat Jumps, Power Skips, 1 Legged Forward Jumps, Broad Jumps, Scissor Jumps			
RESISTANCE TRAINING						
Start: Yellow TheraBand	Step One	Step Two	Step Three	Step Four	Progression: Red TheraBand (repeat steps 1-4) Green TheraBand (repeat steps 1-4) Blue TheraBand (repeat steps 1-4)	
	2 Sets, 10 reps	2 Sets, 15 reps	3 Sets, 10 reps	3 Sets, 15 reps		

7.2.7.3 Discontinuation

Throughout the trial, participants were encouraged to contact the study co-ordinator should they experience any problems in completing the exercise sessions or if any changes in their condition or medical history occurred. The criteria for discontinuing the intervention included any participant who experienced a disease flare-up requiring hospitalisation or a course of steroids, if the participant was unwilling/unable to comply with study procedures or if the investigator deemed it unsafe. Participants were also instructed to stop the exercise programme if they experienced chest pain or any other distressing symptoms and to contact emergency services. SAE and AE were reported in accordance with Northumbria University's procedures (Chapter 4, Section 4.8).

7.2.7.4 Compliance and adherence

Exercise participants received 12 supervised sessions at the Northumbria University to allow for familiarisation and exercise progression. However, to promote long-term adherence, the frequency of these supervised sessions was tapered over time, with an increasing emphasis on home-based, unsupervised training. Increasing self-efficacy is a recognised and critical psychological determinant considered necessary for preparing the participant to adopt and maintain an exercise programme (Dijkstra et al., 2003). Significant support has accumulated in favour of exercise interventions targeting increasing self-efficacy with the use of behavioural techniques such as goal setting, self-monitoring and social support (Bandura, 1997; Rovniak et al., 2002). These specific techniques have demonstrated an 80% improvement to adhering to exercise and maintaining and eliciting lifestyle behavioural changes post intervention (McAuley, 1993; Trost et al., 2002; Perri and Corsica, 2002). As adults with CD have been shown not to meet the recommend daily exercise guidelines it is

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important to include these techniques to facilitate a transition in behavioural change (Mack et al., 2011; Chan et al., 2013; Tew et al., 2016). Strategies to improve and monitor adherence were employed throughout the study:

- Goal setting: planning weekly specific, quantifiable and realistic goals following SMART guidelines (Doran, 1981). Goals were made, discussed at the next supervised session and addressed at completion
- Support contact: participants were contacted via preferred method every 4 weeks, to provide a motivational climate through the delivery of personalised motivation and support
- Self-monitoring: through a diary/log recording the completion of home-based sessions, whether each phase was managed, the perceived exertion based on RISE and any comments to be discussed, via support contact or at the next supervised session

7.2.7.5 Intervention Rationale

This RCT integrated a high-load resistance with high-impact exercises, to maximise the potential bone loading effects, based on a meta-analysis of 24 clinical trials on the preservation of BMD (Zhao et al., 2015). Results demonstrated that a combined protocol, integrating high-load resistance training with high-impact exercises, appeared more effective in improving BMD at the femoral neck ($SMD=0.411$, 95% CI 0.176–0.645, $p=0.001$) and lumbar spine ($SMD=0.431$, 95% CI 0.159–0.702, $p=0.002$), compared to resistance training alone which only produced a nonsignificant positive effect. Furthermore, similar training modes have shown to be safe and effective in other clinical populations such as diabetes, osteoarthritis and multiple sclerosis (Sabapathy et al., 2011; Latham and Liu, 2013).

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Latex free resistance TheraBands were used in the exercise intervention. They came in a range of precisely calibrated strengths and lengths (figure 37), allowing participants to reach an exercise overload effect regardless of initial fitness levels. They are light, easily stored and transported which simplifies the integration of a home-based exercise programme into the lifestyle of the participant. TheraBands have shown to be easier on the joints and less likely to cause injury in comparison to weights (Page and Ellenbecker, 2010; TheraBand, 2016), thus better for people with CD who can experience symptoms of joint pain (Crohn's and Colitis Foundation, 2015).

Thera-Band® Band/Tubing Color	Increase from Preceding Color at 100% Elongation	Resistance In Pounds at:	
		100% Elongation	200% Elongation
Thera-Band Tan	-	2.4	3.4
Thera-Band Yellow	25%	3.0	4.3
Thera-Band Red	25%	3.7	5.5
Thera-Band Green	25%	4.6	6.7
Thera-Band Blue	25%	5.8	8.6
Thera-Band Black	25%	7.3	10.2
Thera-Band Silver	40%	10.2	15.3
Thera-Band Gold	40%	14.2	21.3

BEGINNER
↓
ADVANCED

Figure 37. TheraBand progression scale

The frequency and duration of the intervention were based on 8 systematic reviews, of which 3 included a meta-analysis, that explored the effects of strength and/or impact training in young and older adults, post-menopausal and premenopausal women on BMD (Zehnacker and Bemis-Dougherty, 2007; Martyn-St James and Carroll, 2009; Nikander et al., 2010; Babatunde et al., 2012; Gomez-Cabello et al., 2012; Bielemann et al., 2013; Bolam et al., 2013; Vieira et al., 2013). Strength training programmes alone demonstrated more favourable changes in BMD in programmes of a longer duration (>6 months) with the majority delivering sessions 2 to 3 times a week. However, results of a combined programme demonstrated that a shorter intervention, from 4 months, generated significant improvements

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in BMD. With the majority of the studies delivering sessions 3-4 times a week. Taking these systematic reviews into consideration and a pragmatic approach to the 3-year duration of the PhD, a programme of 6 month, 3 times a week was thought to be sufficient to produce significant gains in BMD.

7.2.7.6 Usual Care

Participants allocated to the control group received usual care only, comprised of high level evidence-based medical treatment. As part of the trial, participants did not receive any supervised exercise or any specific exercise recommendations. However, to minimise the potential for resentful demoralisation that may occur through control group allocation (Torgerson and Sibbald, 1998) following the completion of the 6-month outcome assessment participants were offered a one-to-one exercise consultation with the study co-ordinator. Exercise benefits, barriers, facilitators and guidelines were discussed and guidance on incorporating physical activity into their lifestyle was provided.

7.2.7.7 Three month assessment

A follow-up assessment was carried out at week 13, allowing a \pm 2 week window for the completion. A 13-week CRF (Appendix 7p) was used to record medication changes, body mass, stature, resting heart rate, blood pressure and the occurrence of any AE. Outcome measures (Chapter 4) were also recorded.

7.2.7.8 Six month assessment

At 6 months, follow-up visits at Northumbria University and NUTH Trust sites were completed, with the allowance of a \pm 6 week window for the completion of both visits. A 6-month CRF (Appendix 7q) was completed to record medication changes, body mass, stature, resting heart rate, blood pressure and the occurrence of any AE. Outcome measures (Chapter 4) were also recorded. At this visit participants were given a 7-day disease activity diary to complete prior to their 6-month hospital assessment.

At the 6-month hospital assessment, changes in medications or medical history were obtained and disease activity assessed through the FC, CRP and CDAI. For the latter measure, body mass, extra-intestinal complications, anti-diarrhoeal medication, haematocrit and a physical examination of abdominal mass were assessed by a direct care team member. Results were recorded in a 6-month hospital CRF (Appendix 7r) and signed when completed by the medical principal investigator and a copy placed in medical records. Following the conclusion of the study, participants were provided with an end of study information sheet (Appendix 7s) and debrief sheet (Appendix 7t) explaining the nature of the research, how they could withdraw their data and how they could find out about the results of the study.

7.2.7.9 Exit Interview and Exercise Consultation

Prior to the 6-month assessments, to enable the recording of the exit interviews, participants were sent an audio recording invitation letter (Appendix 7u), an audio recording informed consent form (Appendix 7v) and a pre-paid envelope. If participants gave their permission to be recorded they were asked to return the completed written consent form and post it back in the pre-paid envelope.

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The exit interview and exercise consultation occurred following the completion of both 6-month assessments, a window of 6 weeks was allowed for the completion of the telephone follow-up activities. All exit interviews adhered to a script (Appendix 7w), covering perceived benefits and negative consequences from participating in the study, feedback regarding specific study design features (exercise/assessment procedures), and perceptions of barriers and facilitators to intervention participation. The interviews took no longer than 30 minutes and were audio-recorded if written informed consent was obtained.

7.2.8 Sample Size and Statistical Analysis

As the minimally clinical important difference has not been established for BMD measures in people with CD, a distribution-based approach was used to calculate sample size. A superiority design, which aims to demonstrate the superiority of a new therapy compared to an established therapy or placebo, was proposed to observe an effect size of 0.4 (i.e. a small-to-moderate effect). This was based upon the effect size observed at the femoral neck in a meta-analysis of 24 clinical trials examining the effects of combined resistance training interventions on the preservation of BMD in postmenopausal women (Zhao et al., 2015). Using the sample size calculation methods of Borm et al (2007), and assuming 80% power, a 5% alpha level (2-sided), and a correlation between pre and post femoral neck BMD measures of $r=0.9$, a total of 19 participants per group were required to detect a respective group difference. Accounting for a potential loss of power as a result of dropouts, after allowing for 20% attrition, it was planned to include at least 50 participants in total (25 intervention, 25 control).

Descriptive statistics such as percentages, means and SD were used to present participant and disease-related characteristics. All statistical tests were two-sided at the 5% significance

level. To determine whether the covariates varied across the dependent variable, ANOVA was employed and no significant correlations were identified. Intervention effects were evaluated using separate covariance models for outcomes at months 3 and 6. These models were adjusted for baseline value of the dependent variable, gender, and baseline disease status. Adjusted mean differences, 95% confidence intervals and p values between treatment groups at 3 and 6 months were extracted from the models.

The key strength of an RCT design is the random allocation of participants and, if there are enough participants, similar baseline characteristics which is critical for avoiding selection bias and establishing causation. Therefore to maintain this baseline comparability and to better inform clinical implementations, where individuals do not always comply with treatment, all analyses were based on an intention-to-treat basis. Missing outcomes however, may seriously comprise the validity and ability to make correct inferences from the trial. However, due to low rates of missing data, primary analysis were conducted using a modified intention-to-treat population that included all randomised participants who had both baseline and follow-up outcome data (i.e. complete-case analysis). Although multiple imputation is generally viewed as the preferred analytical approach to preserve sample size, for low rates of missing data at random or completely at random, a complete case method has demonstrated estimates to generally remain unbiased and achieve similar to or better precision results to a multiple imputation method (Mukaka et al., 2016). Best-case and worst-case sensitivity analyses were also performed to explore the impact of missing data for primary outcomes. Assuming that all participants lost to follow-up in one group had a ‘beneficial outcome’ and all those with missing outcomes in the other group had a ‘harmful outcome’, the dataset was generated by using the group mean plus 1 standard deviation of the group mean as a ‘beneficial outcome’ and the group mean minus 1 standard deviation of the group mean as a ‘harmful outcome’ (Jakobsen et al., 2014).

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All analyses were performed using the IBM Statistical Package for the Social Sciences software version 24 (IBM Corporation, UK).

7.2.9 Blinding

Due to the nature of the intervention, both the intervention facilitators and participants were aware of their group allocation. However, to reduce the risk of detection bias a blinded outcome assessor conducted the 3 and 6-month assessments. Participants were asked to conceal their intervention arm to the outcome assessor, which was adhered to by all participants.

7.3 Results

Recruitment took place between February 2018 to March 2019, with all follow-up data completed by October 2019. Of those who expressed interest, 129 requested further study information, 18 would have liked to have taken part however could not due to travel constraints (n=9), current health status (n=6), work responsibilities (n=2) or family commitments (n=1). From the PROTECT trial log, 35 (74.5%) participants were recruited and randomised from the IBDBioresource Database, 1 (2.1%) from social media, 10 (21.3%) from outpatient clinics and 1 (2.1%) from recruitment posters.

Out of 76 participants, 48 met the eligibility criteria and 47 were randomised into the exercise (n=23) or control (n=24) group (figure 38). The reasons for exclusion were elevated FC ≥ 250 mcg/g (n=24), CDAI >220 (n=2) and unavailable FC result (n=2). Three participants had to repeat FC biomarkers as a result of falling outside the 4-week window to attend the baseline visit, due to family bereavement (n=2) and family illness (n=1). Prior to randomisation the

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resistance exercise intervention was the group preference for 40 (85.1%) participants and 7 (14.9%) participants stated that they did not have a preference on group allocation.

Three participants formally withdrew from the study, due to self-reported acute flare (n=1) and an allergic reaction to infliximab (n=1) not trial related and one from the exercise group due to family commitments. One participant in the control group was also lost to the 3-month follow-up due to being uncontactable.

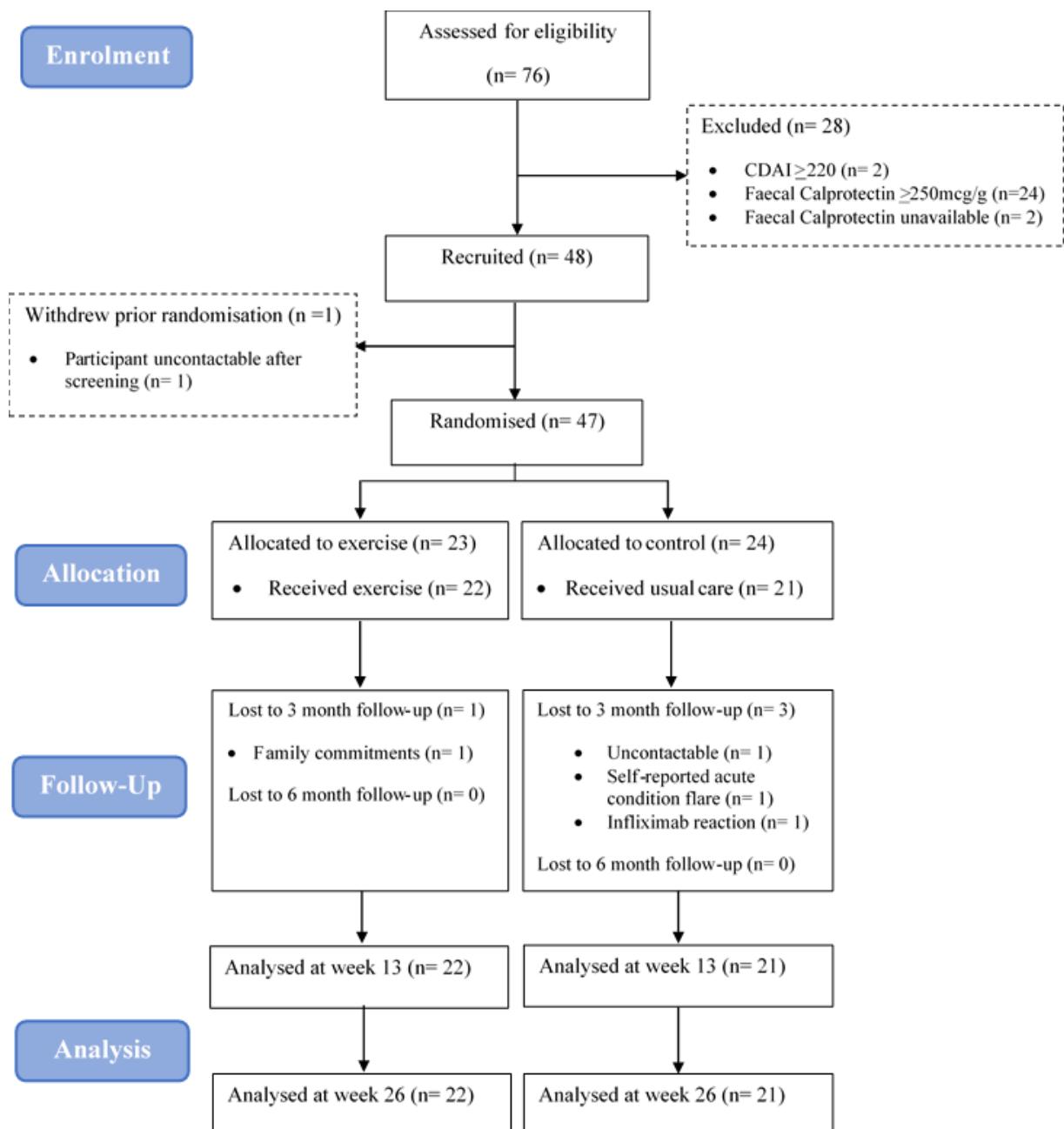


Figure 38. Participant study flowchart at each stage and reasons for exclusion from the trial

7.3.1 Participant Characteristics

Demographic information and disease characteristics of study participants are summarised in table 15. Of the 47 eligible participants, 15 (31.9%) were males, all participants were of white ethnicity with a mean age of 49.3 (SD=13.0), with a wide age range from 25-85 years. Most participants were in full-time employment (40.4%). The next largest groups were retired (19.1%), part-time employment (14.9%), self-employed (12.8%) and unemployed (12.8%). Almost 60% of participants had never smoked before and had an average alcohol intake of 4.5 (SD=4.7) units per week. Median age at diagnosis was 31 years, ranging from 11-56 years and had a median diagnosis duration of 216 months (18 years), ranging from 12 (1 year) to 660 months (55 years). A longer duration of disease was seen in the exercise group (216 months) than the control group (204 months). Inflammatory markers suggested that most participants had an inactive disease (66.0%), with a mean FC of 86.5 (SD=59.5) and CDAI of 114.1 (SD=59.5).

Appendix 7x illustrates clinical characteristics at baseline. CD were located in the ileum and colon in 18 (38.3%) participants, in the ileum alone in 15 (31.9%) participants, in the colon alone in 12 (25.5%) participants and in both the ileum, colon and upper gastrointestinal tract in 2 (4.3%) participants. The disease presented itself as non-stricturing and non-penetrating in most participants (66.0%) with 13 (27.7%) of participants affected by perianal CD.

Immunosuppressants (42.6%), anti-TNF treatment (40.4%) and vitamin D supplementation (25.5%) were the most commonly used medications. The most common surgical procedures were right hemicolectomy/ileocecal resection (40.5%), ileal/jejunal resection or stricturoplasty (25.5%) and colectomy and ileostomy (14.9%). Almost one third of participants, in addition to their CD, experienced an EIM, such as enteropathic arthritis (12.8%), psoriasis (8.5%), osteoporosis/osteopenia (8.5%), ankylosing spondylitis (6.4%),

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bile salt malabsorption (4.3%), lymphoma/malignancy (4.3%), iritis/uveitis (4.3%), erythema nodosum (2.1%), orofacial granulomatosis (2.1%) or serious infections (2.1%).

Table 15.

Baseline demographic information and disease variables

	Exercise [n=23]	Control [n=24]	Total [n=47]	P value ^a
Age, mean (SD), years	46.1 ± 11.9	52.3 ± 13.6	49.3 ± 13.0	.293
Gender, n (%)				.653 ^b
Female, n (%)	16(69.6)	16(66.7)	32(68.1)	-
Male, n (%)	7(30.4)	8(33.3)	15(31.9)	-
White Ethnicity, n (%)	23(100)	24(100)	47(100)	1.00 ^b
Employment Status, n (%)				.650 ^b
Employed Full-Time	10(43.5)	9(37.5)	19(40.4)	-
Employed Part-Time	1(4.3)	6(25.0)	7(14.9)	-
Self-employed	4(17.4)	2(8.3)	6(12.8)	-
Unemployed	3(13.0)	3(12.5)	6(12.8)	-
Retired	5(21.7)	4(16.7)	9(19.1)	-
Smoking Status, n (%)				.715 ^b
Previously	9(39.1)	11(45.8)	20(42.6)	-
Never	14(60.9)	13(54.2)	27(57.4)	-
Alcohol Intake, mean (SD), units	5.1 ± 5.4	3.9 ± 3.9	4.5 ± 4.7	.041
Age at Diagnosis, median (IQR), years	27(21-35)	31(27-41)	31(22-37)	.999
Duration of Diagnosis, median (IQR), months	216(96-288)	204(60-396)	216(63-386)	.121
Disease Activity, mean (SD)				-
Faecal Calprotectin, µg/g	55.9 ± 28.9	113.3 ± 66.9	86.5 ± 59.5	.030
CDAI	104.7 ± 57.6	123.1 ± 61.9	114.1 ± 59.9	.575
CDAI Activity Status, n (%)				.653 ^b
Inactive	15(65.2)	16(66.7)	31(66.0)	-
Mildly Active	8(34.8)	8(33.3)	16(34.0)	-

CDAI, Crohn's Disease Activity Index; ^aindicates independent t-test, ^b indicates Chi-squared test

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These participant characteristics are similar to UK epidemiological data of 4546 CD participants across 21 centres (Bardhan et al., 2010). Median age at diagnosis was 30 years, and median disease duration ranged from 1 to 801 months. Disease extent was fairly even across all locations and resections were reported in 37-41% of participants. The use of biologics were not routinely used over ten years ago and therefore comparisons are unable to be made. However, in comparison to recent exercise interventions in CD, Cronin et al (2019) and Tew et al (2019) identified similar use of immunosuppressants, but not in biologics. It is therefore thought this is not atypical in a group of individuals presenting with an inactive to mildly active disease.

7.3.2 BMD

BMD (g/cm^2) results are presented in figure 39. Following analysis, according to WHO diagnostic criteria, 21.3% of CD participants were indicative of having osteopenia (T-score between -1.0 and -2.5) at the lumbar spine and 4.3%, of osteoporosis (T-score -2.5 and below). T-scores of the left hip suggested osteoporosis in 6.3% and osteopenia in 38.3% of CD participants (figure 40).

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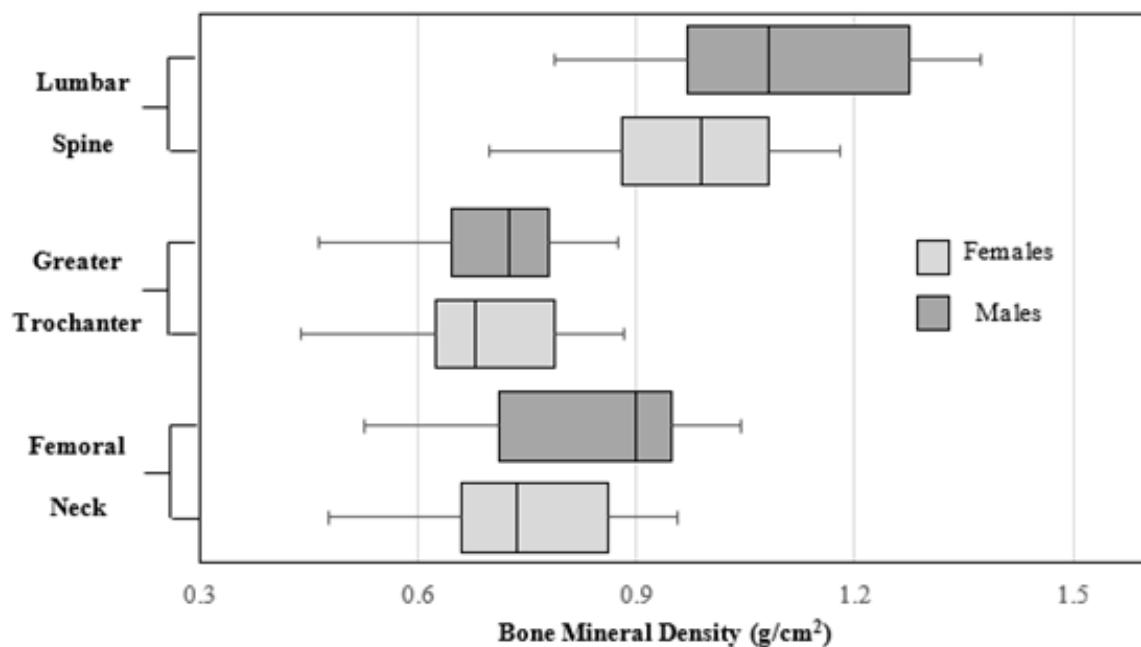


Figure 39. Baseline bone mineral density scores (g/cm^2) of the lumbar spine (L2-L4), greater trochanter and femoral neck in CD participants. Minimum, median, interquartile (Q1-Q3) and maximum values are indicated.

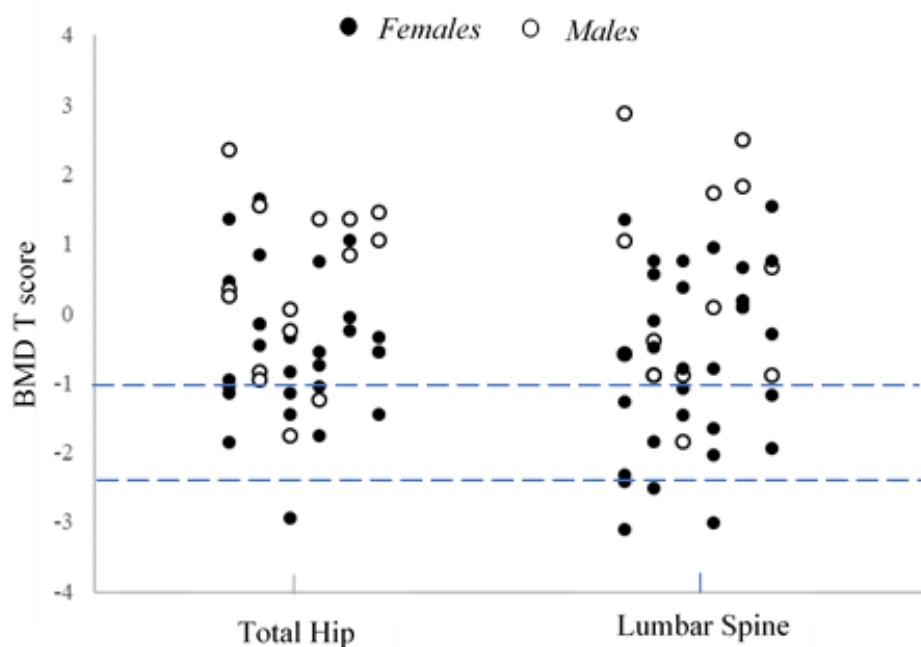


Figure 40. Baseline T-scores of the total hip (Greater Trochanter, Femoral Neck and Wards Triangle) and lumbar spine (L2-L4) in participants with CD

— — — — — Osteopenia: T-score between -1.0 and -2.5; Osteoporosis: T-score -2.5 and below

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Intervention changes in BMD are presented in table 16. At 6 months, the exercise group demonstrated favourable and statistically significant between group differences at the lumbar spine (adjusted mean df=0.036g/cm²; 95% CI 0.024-0.048; p<0.001) and femoral neck (0.018g/cm²; 95% CI 0.001-0.035; p=0.039), but not at the greater trochanter (0.013 g/cm²; 95% CI -0.019-0.045; p=0.415).

Table 16. Means, adjusted means and group differences in BMD (g/cm²) from baseline to 6-month

		Baseline ^a	6 Months ^b	Adjusted Mean (95% CI)	Difference (95% CI)	p value
Lumbar Spine	IG	1.068 ± 0.16	1.111 ± 0.15	1.091 (1.082-1.099)	0.036 (0.024-	<0.001
	CG	1.037 ± 0.22	1.032 ± 0.24	1.055 (1.046-1.063)	0.048)	
Greater Trochanter	IG	0.728 ± 0.11	0.737 ± 0.11	0.713 (0.691-0.735)	0.013 (-0.019 to	0.415
	CG	0.678 ± 0.10	0.676 ± 0.11	0.700 (0.678-0.723)	0.045)	
Femoral Neck	IG	0.812 ± 0.14	0.845 ± 0.15	0.812 (0.800-0.823)	0.018 (0.001-	0.039
	CG	0.753 ± 0.13	0.759 ± 0.13	0.794 (0.782-0.806)	0.035)	

Mean ± S.D are indicated for all columns unless stated

IG, Intervention Group; CG, Control Group

^a IG n=23, CG n=24; ^b IG n=22, CG n=21

Percent changes in BMD from baseline to 6 months are presented in figure 41. In the exercise group percentage changes ranged from 0.4%-4.1% (2.3%; p=0.018) at the femoral neck, -2.2%-5.1% (1.4%; p=0.426) at the greater trochanter and 2.6%-5.1% (3.8%; p<0.001) at the lumbar spine. In the control group, the lumbar spine increased by an average of 0.79%, while the femoral neck and greater trochanter decreased by 0.29% and 0.48%, respectively.

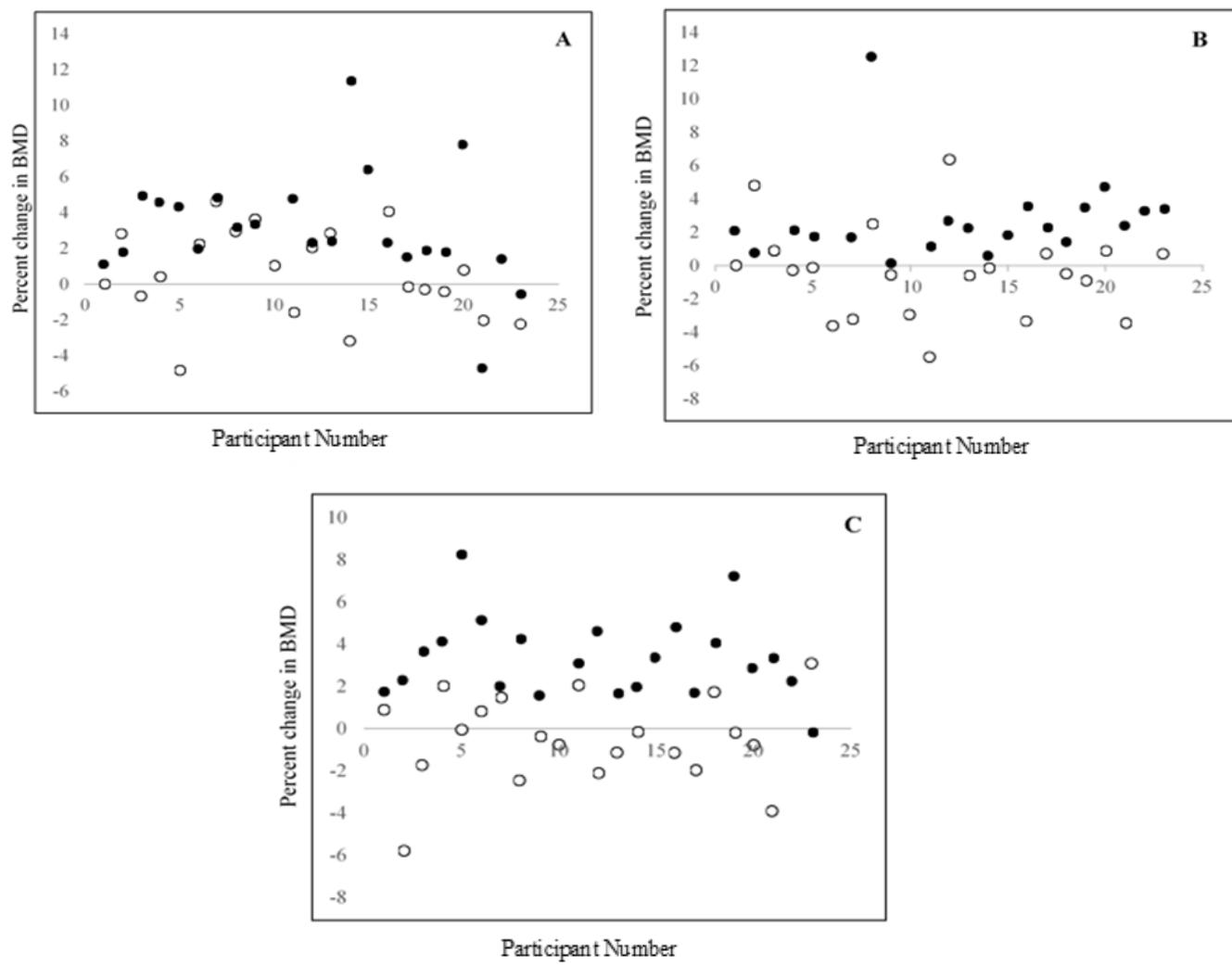


Figure 41. Percent changes in BMD from baseline to 6 months at the femoral neck (A), greater trochanter (B)

and lumbar spine (C) ● Exercise Group ○ Control Group

7.3.3 Muscle Strength

Table 17 demonstrates maximum voluntary isokinetic strength (MVIS) of the knee extensors and elbow flexors. Exercise participants experienced more favourable changes in muscular strength than the control group at week 13 and 26. When working lower limbs at a velocity of 60°/s (figure 42a), statistically significant group differences were identified at week 13 (adjusted mean df=12.9 Nm; 95% CI 2.5-23.3; p=0.16) and sustained at week 26 (22.4 Nm; 95% CI 12.1-32.8; p<0.001). Isokinetic knee extension at a velocity of 180°/s (figure 42b) also demonstrated significant between group differences at week 13 (10.1 Nm; 95% CI 3.6-

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16.7; $p=0.003$) and 26 weeks (16.8 Nm; 95% CI 9.0-24.5; $p<0.001$). Statistically significant between group differences in the upper limbs at an angular velocity of 60°/s were identified at week 13 (5.2 Nm; 95% CI 2.8-7.6; $p<0.001$) and sustained at week 26 (6.8 Nm; 95% CI 3.9-9.6; $p<0.001$) (figure 42c). Significant changes were also seen at an angular velocity of 120°/s at 13 weeks (5.8 Nm; 95% CI 3.5-8.1; $p<0.001$) and 26 weeks (6.3 Nm; 95% CI 3.3-9.3; $p<0.001$) (figure 42d).

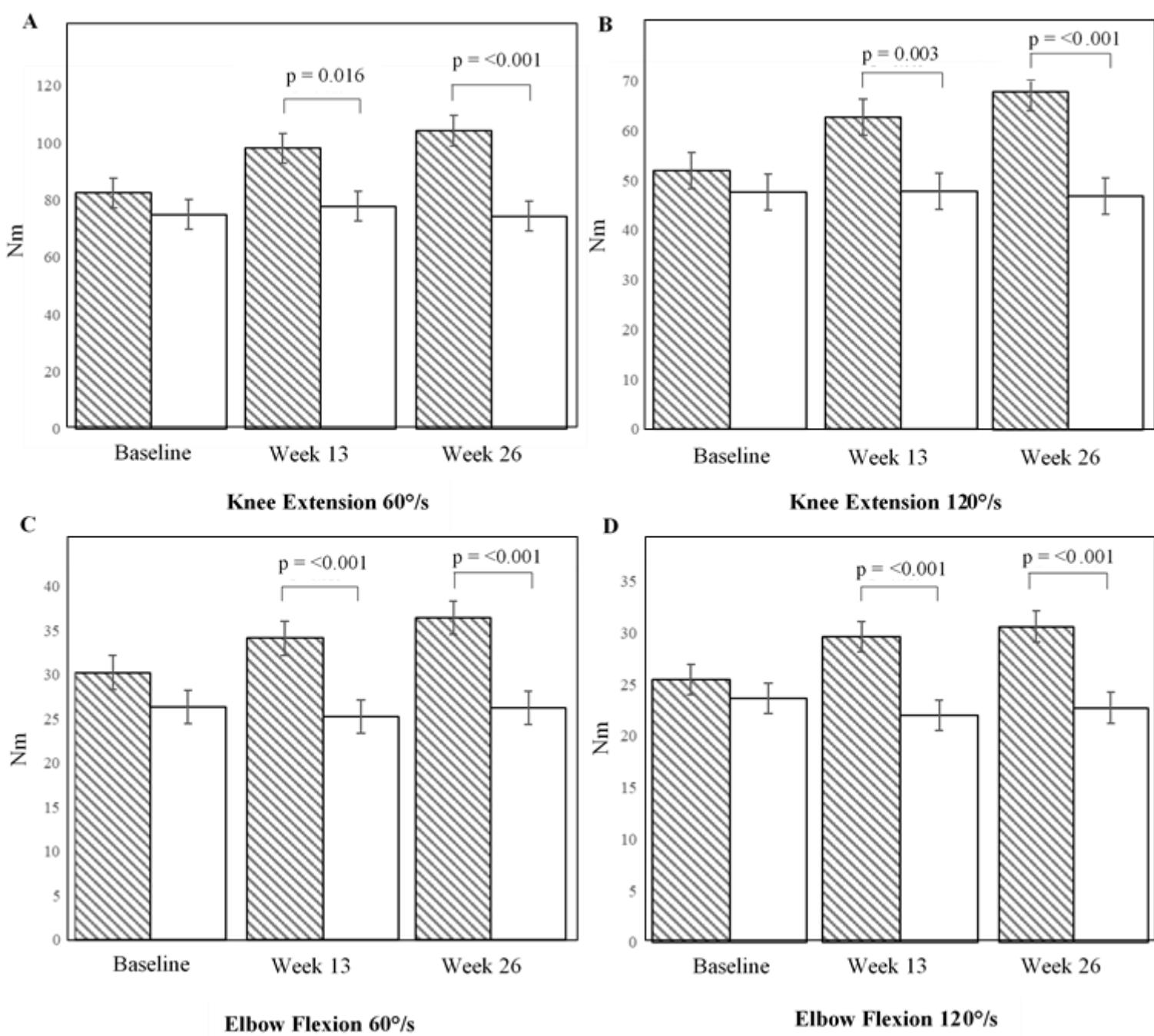


Figure 42. Adjusted mean differences of the knee extension at angular velocities of 60°/s (A) and 180°/s (B) and elbow flexion at angular velocities of 60°/s (C) and 120°/s (D)

Favourable significant between group differences in HGS, determined using the JAMAR Hydraulic dynamometer, were identified in the exercise group at week 13 (adjusted mean df=4.0 kg; 95% CI 2.1-5.9; p<0.001) and 26 weeks (8.3 kg; 95% CI 6.2-10.5; p<0.001) (table 17).

7.3.4 Muscle Endurance

During the course of the 6-month study, upper and lower limb muscular endurance significantly improved in the exercise group at week 13, and were sustained at week 26 (table 17) when compared to the control group. Significant upper muscular endurance between group differences were identified at 13 weeks (adjusted mean df= 3 reps; 95% CI 1-5; p<0.001) and 26 weeks (7 reps; 95% CI 5-8; p<0.001) (Figure 43a). Significant improvements were also identified in lower muscular endurance at week 13 (3 reps; 95% CI 1-4; p<0.001) and 26 weeks (4 reps; 95% CI 3-6; p<0.001) (Figure 43b) in the exercise group when compared to the control group.

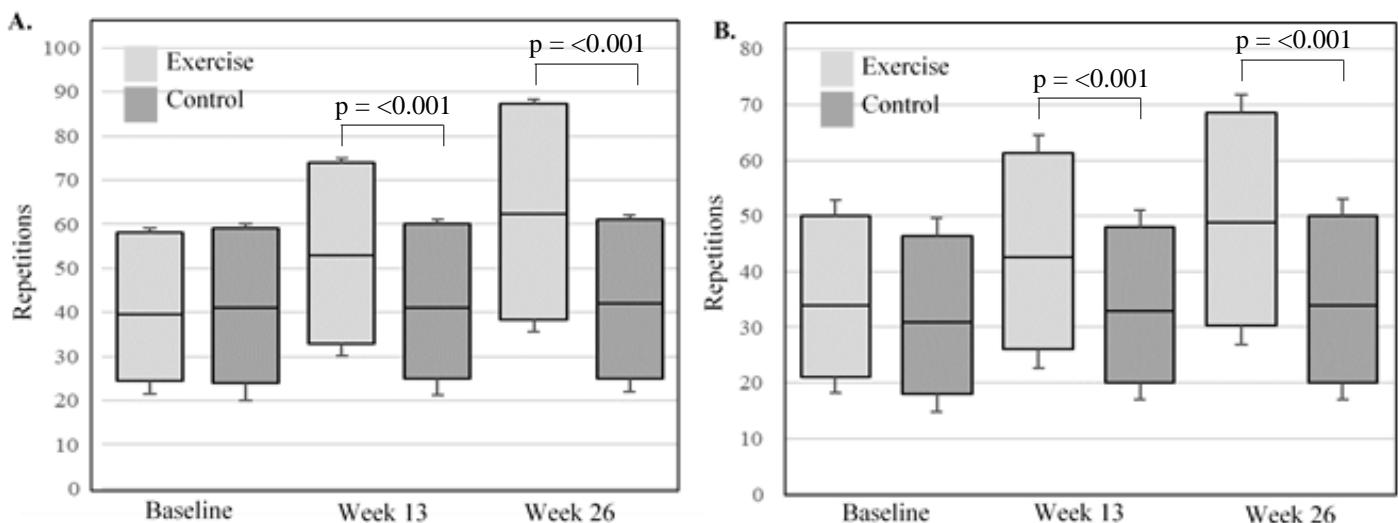


Figure 43. Changes in bicep curl (A) and chair stand test (B) (repetitions) scores at baseline, week 13 and week 26. Minimum, median, interquartile (Q1-Q3) and maximum values are indicated.

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Table 17. Change in muscular function variables from baseline, 3 and 6 month

Group Allocation	Baseline	3 Months	Adjusted Mean 3 Months (95% CI)	Mean Difference (95% CI)	P value	6 months	Adjusted Mean 6 Months (95% CI)	Mean Difference (95% CI)	P value	
<i>Muscle Endurance</i>										
30-s CST	IG	13.6 ± 2.8	16.5 ± 3.4	16 (15-17)	3 (1-4)	<0.001	18.6 ± 3.3	18 (17-20)	4 (3-6)	<0.001
	CG	13.5 ± 3.5	13.6 ± 3.0	14 (13-15)			14.3 ± 3.1	14 (13-16)		
30-s BCT	IG	16.1 ± 3.0	20.0 ± 2.80	20 (19-21)	3 (1-5)	<0.001	23.5 ± 2.7	23 (22-25)	7 (5-8)	<0.001
	CG	16.6 ± 4.1	16.8 ± 3.7	17 (16-18)			16.6 ± 3.1	17 (15-18)		
<i>Muscle Strength</i>										
HGS	IG	36.4 ± 13.1	39.4 ± 12.1	37.7 (36.4-39.0)	4.0 (2.1-5.9)	<0.001	42.4 ± 12.6	40.9 (39.4-42.4)	8.3 (6.2-10.5)	<0.001
	CG	32.2 ± 12.2	31.8 ± 10.8	33.6 (32.3-35.0)				32.5 (31.0-34.1)		
Isokinetic Knee Extension-60°/s ^a	IG	82.5 ± 44.0	98.2 ± 47.5	94.6 (87.4-101.8)	12.9 (2.5-23.3)	0.016	104.3 ± 52.6	100.7 (93.4-107.9)	22.4 (12.1-32.8)	<0.001
CG	74.9 ± 36.2	77.9 ± 38.4	81.7 (74.3-89.1)					78.2 (70.8-85.6)		
Isokinetic Knee Extension-180°/s ^a	IG	51.9 ± 32.7	62.7 ± 34.6	60.4 (55.8-65.0)	10.1 (3.6-16.7)	0.003	67.8 ± 34.2	65.8 (60.4-71.2)	16.8 (9.0-24.5)	<0.001
CG	47.6 ± 23.1	47.8 ± 26.4	50.3 (45.6-54.9)					49.1 (43.5-54.6)		
Isokinetic Elbow Flexion-60°/s ^b	IG	30.2 ± 16.0	34.1 ± 16.4	32.3 (30.7-34.0)	5.2 (2.8-7.6)	<0.001	36.5 ± 16.5	34.8 (32.8-36.7)	6.8 (3.9-9.6)	<0.001
CG	26.4 ± 10.9	25.3 ± 11.3	27.1 (25.4-28.8)					28.0 (26.0-30.0)		
Isokinetic Elbow Flexion-120°/s ^b	IG	25.5 ± 12.1	29.6 ± 14.9	28.7 (27.1-30.4)	5.8 (3.5-8.1)	<0.001	30.6 ± 14.0	29.8 (27.8-31.9)	6.3 (3.3-9.3)	<0.001
CG	23.6 ± 10.0	22.0 ± 10.1	23.0 (27.1-24.6)					23.6 (21.4-25.7)		

Mean ± S.D are indicated for all columns unless stated.

IG, Intervention Group; CG, Control Group; CST, Chair Stand Test; BCT, Bicep Curl Test; HGS, Hand Grip Strength

^aComputed as average MVIS of both legs

^bComputed as average MVIS of both arms

7.3.5 QOL

7.3.5.1 EQ-5D-5L

Assessed using the EQ-5D-5L, the descriptive system comprised of five dimensions, illustrated that 19.1%, 6.4%, 29.8%, 51.1% and 51.1% of CD reported that their QOL was impacted by mobility problems, self-care problems, usual activities, pain/discomfort and anxiety/depression, respectively. The self-assessed visual analogue scale, indicated that participants aged 18-29 reported the poorest health and participants aged 50-59 and 70+ reporting the best health (figure 44).

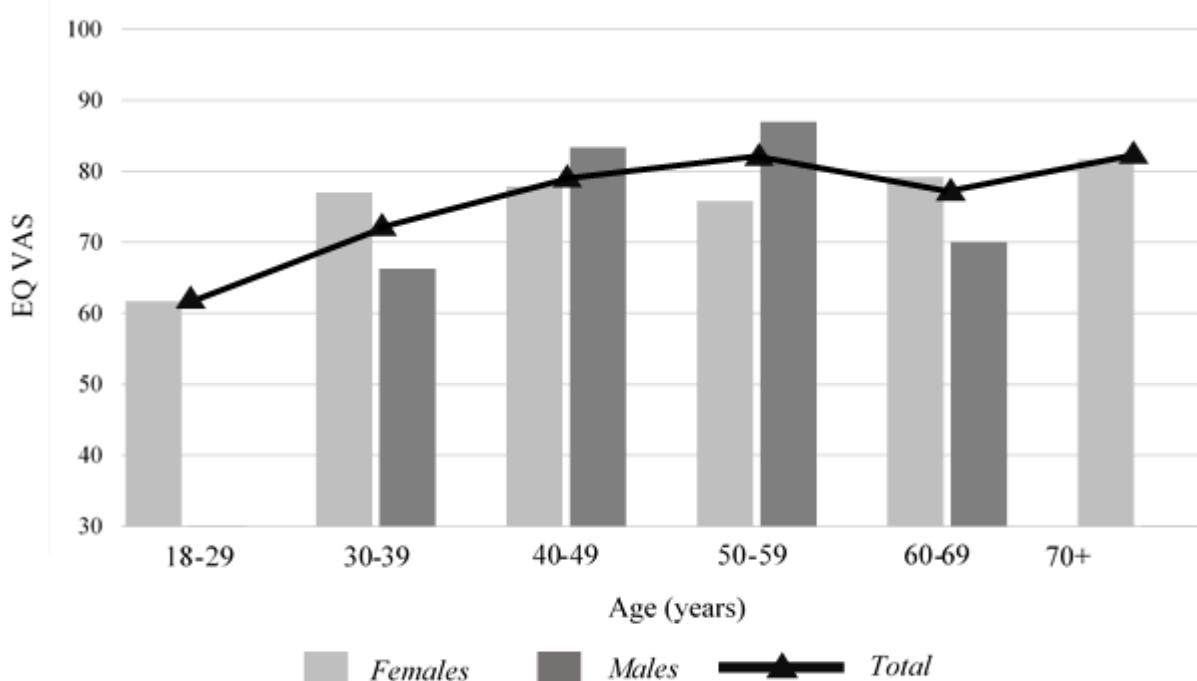


Figure 44. Baseline mean EQ VAS scores in CD participants by age and group

Intervention changes on the five descriptive domains are identified in table 18. In the exercise group, mobility, self-care, usual activities and pain/discomfort remained stable throughout the intervention. Five participants reported experiencing fewer feelings of anxiety/depression. Control group participants reported experiencing more problems in mobility, self-care and

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pain/discomfort from baseline to week 26 with usual activities and anxiety/depression remaining stable.

Table 18.

Frequency (n) of QOL^a values for CD participants by EQ-5D-5L dimension at baseline, 3-month and 6-month (n=43)

EQ-5D Dimension		Exercise Group			Control Group		
		Baseline	Week 13	Week 26	Baseline	Week 13	Week 26
Mobility	No problems	18	20	19	17	12	12
	Problems	4	2	3	4	9	9
Self-Care	No problems	21	21	21	20	21	18
	Problems	1	1	1	1	0	3
Usual Activity	No problems	20	19	20	12	9	12
	Problems	2	3	2	9	12	9
Pain/Discomfort	No problems	13	12	13	9	4	5
	Problems	9	10	9	12	17	16
Anxiety/Depression	No problems	15	17	20	8	9	8
	Problems	7	5	2	13	12	13

^a ‘No problems’ dichotomised as level 1 and ‘problems’ as levels 2 to 5

Table 19 demonstrates intervention changes in QOL data. Statistically significant between group differences were identified in the EQ-5D-5L utility index scores at 13 weeks (adjusted mean df=0.117; 95% CI 0.023- 0.211; p=0.016) and 26 weeks (0.109; 95% CI 0.038-0.181; p=0.004). Estimated marginal means in the EQ VAS scores demonstrated no significant between group differences at 3 month (10.4; 95% CI 1.4-19.4; p=0.24) or 6 months (8.3; 95% CI -1.5 to 18.3; p=0.095).

7.3.5.2 IBDQ

Intervention changes in IBDQ data are presented in table 19. Estimated marginal means from week 1 to week 13 demonstrated that the total IBDQ score increased from 182 ± 23 to 191 ± 20 ($\Delta=9$) in the exercise group and decreased from 166 ± 25 to 162 ± 26 ($\Delta= -4$) in the control group, resulting in a significant adjusted between group difference of 17 (95% CI 7 to 26; $p=0.001$). However this was not sustained at week 26 (6; 95% CI 3-15; $p=0.175$). All IBDQ subscales illustrated significant between group differences at 13 weeks: bowel symptoms (5.4; 95% CI 1.4 to 9.3; $p=0.010$), systemic systems (3.2; 95% CI 1.0-5.3; $p=0.006$), emotional health (4.5; 95% CI 0.6-8.5; $p=0.024$) and social function (3.6; 95% CI 1.5-5.6; $p=0.001$). However, these between group differences were only sustained at 6-month in the subscale social function (3.1; 95% CI 1.2-4.9; $p=0.002$).

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Table 19. Change in QOL indices from baseline, 3 and 6-month

	Group Allocation	Baseline	3 Months	Adjusted Mean 3 Months (95% CI)	Mean Difference (95% CI)	P value	6 months	Adjusted Mean 6 Months (95% CI)	Mean Difference (95% CI)	P value
<i>EQ-5D-5L^a</i>										
Index-scores (-0.285 to 1)	IG	0.856 ± 0.12	0.872 ± 0.12	0.859 (0.793-0.925)	0.117 (0.023-0.211)	0.016	0.885 ± 0.13	0.875 (0.825-0.924)	0.109 (0.038-0.181)	0.004
	CG	0.810 ± 0.113	0.729 ± 0.19	0.742 (0.677-0.808)			0.749 ± 0.14	0.765 (0.715-0.816)		
VAS-scores (0 to 100)	IG	80.0 ± 14.6	84.5 ± 9.4	83.0 (76.9-89.2)	10.4 (1.4-19.4)	0.024	85.0 ± 14.4	82.8 (76.0-89.6)	8.3 (-1.5 to 18.3)	0.095
	CG	73.5 ± 14.7	71.1 ± 19.0	72.6 (66.3-79.0)			72.2 ± 21.2	74.5 (67.5-81.4)		
<i>IBDQ^a</i>										
Total (32 to 224)	IG	182 ± 23.0	191 ± 20.0	185 (179-191)	17 (7-26)	0.001	187 ± 23.0	180 (174-186)	6 (-3 to 15)	0.175
	CG	166 ± 25.0	162 ± 26.0	169 (162-175)			166 ± 29.0	174 (167-180)		
Bowel Symptoms (10 to 70)	IG	57.9 ± 8.6	59.6 ± 9.2	57.7 (55.0-60.4)	5.4 (1.4-9.3)	0.010	58.6 ± 9.3	56.4 (54.2-58.6)	3.1 (0.5-10.6)	0.084
	CG	52.1 ± 9.8	50.3 ± 8.8	52.3 (49.5-55.1)			51.2 ± 8.8	53.5 (51.2-55.8)		
Systemic Systems (5 to 35)	IG	24.0 ± 4.8	26.1 ± 4.3	25.6 (24.0-27.1)	3.2 (1.0-5.3)	0.006	24.5 ± 6.1	24.0 (22.1-25.8)	1.2 (-2.0 to 4.5)	0.405
	CG	21.9 ± 5.6	21.8 ± 5.1	22.4 (20.9-24.0)			22.1 ± 4.8	22.8 (20.9-24.8)		
Emotional Health (12 to 84)	IG	67.9 ± 10.2	71.6 ± 7.2	68.7 (66.0-71.4)	4.5 (0.6-8.5)	0.024	70.3 ± 10.7	66.8 (63.7-69.9)	0.2 (-2.3 to 12.0)	0.927
	CG	59.8 ± 12.4	61.1 ± 13.1	64.2 (61.4-66.9)			63.0 ± 13.9	66.6 (63.5-69.7)		
Social Function (5 to 35)	IG	32.4 ± 3.7	33.8 ± 1.8	33.3 (31.9-34.7)	3.6 (1.5-5.6)	0.001	33.6 ± 2.1	33.1 (31.8-34.4)	3.1 (1.2-4.9)	0.002
	CG	30.4 ± 4.4	29.2 ± 5.1	29.7 (28.3-31.2)			29.5 ± 4.7	30.0 (28.7-31.3)		

Mean ± S.D are indicated for all columns unless stated.

IG, Intervention Group; CG, Control Group; EQ-5D-5L, EuroQol; IBDQ, Inflammatory Bowel Disease QOL Questionnaire; VAS, Visual Analogue Scale

^aHigher scores represent a better quality of life

7.3.6 Fatigue

Severity, frequency and duration of fatigue was higher at baseline in females (8.3 ± 4.4) than males (7.3 ± 3.7). Reports of experiencing no fatigue were reported in 2 (4.6%) participants, slight to moderate in 30 (62.8%) participants and severe in 15 (32.6%) participants. The perceived impact of fatigue on daily activities in the past two weeks was reported as having no effect in 4 (8.5%) participants, a moderate effect in 35 (74.5%) participants and a severe effect in 8 (17%) participants. Perceived effects of fatigue on daily activities at baseline were higher in males (26.2 ± 22.1) than females (25.6 ± 25.9). Figure 45 identifies the main causes of fatigue. The main causes identified were poor sleep/sleep quality (34%), work/travelling to work (26%), secondary complications (15%) and poor nutrition (13%). Figure 46 identifies the factors reported by participants that help reduce fatigue. The main alleviants identified were resting/napping/sleeping (34%) and exercise (12.8%). 29.8% of participants stated nothing reduced their fatigue.

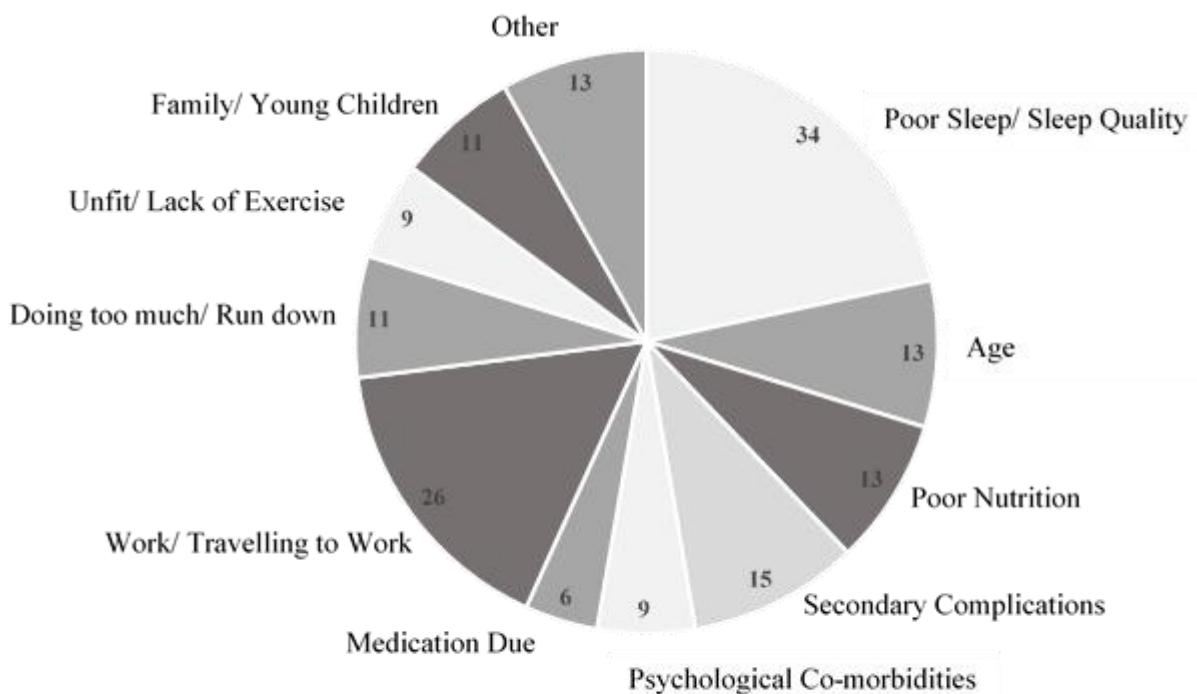


Figure 45. Main causes of fatigue identified by 47 Crohn's Disease participants. Percentages are presented. Multiple answers possible

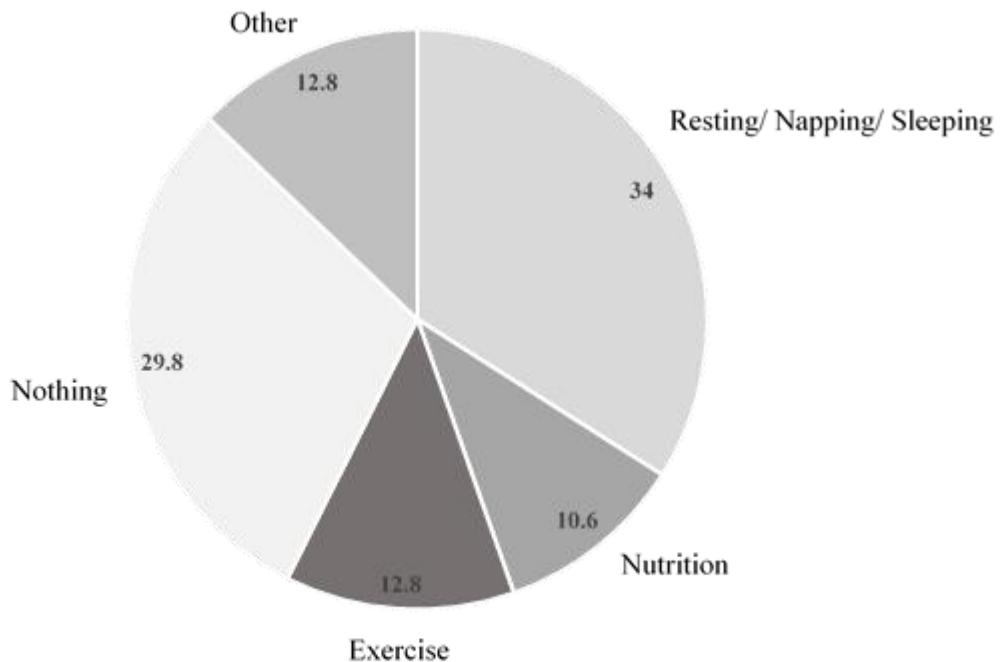


Figure 46. Factors identified to reduce fatigue by 47 Crohn's Disease participants.
Percentages are presented. Multiple answers possible

During the course of the study the exercise group reported reduced feelings of fatigue, assessed using the IBD-F, in both subcategories: assessment (Severity, frequency and duration) and perceived impact (table 20). In the assessment fatigue subcategory, 2 (8.7%) participants reported feeling no fatigue at baseline, week 13 and week 26. Slight to moderate fatigue was reported in 16 (69.6%) participants at baseline, 17 (72.7%) at week 13 and 19 (86.4%) at week 26. Although numbers increased in this category, they decreased in the severe fatigue category with 5 (21.7%) reporting severe fatigue at baseline, 3 (13.6%) at week 13 and 1 (4.5%) at week 26. Suggesting that participants did feel some benefits of exercising on fatigue levels. However, no significant between group differences were identified at 13 weeks (adjusted mean df= -1; 95% CI -3 to 1; p=0.249), but statistically significant between group differences were achieved at 26 weeks (-2; 95% CI -4 to -1; p=0.005).

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In the perceived impact fatigue subcategory, 4 (17.4%) participants reported fatigue having no effect on daily activities at baseline, 5 (22.7%) at week 13 and 3 (13.6%) at week 26. A moderate effect on daily activities was reported in 16 (69.9%) participants at baseline, 16 (72.7%) at week 13 and 18 (81.8%) at week 26. Although numbers increased in this category, they decreased in the severe impact on daily activities with 3 (13%) reporting fatigue having a severe impact on daily activities at baseline and only 1 (4.5%) participant at week 13 and week 26. Although no significant between group differences were identified at week 13 (-6.5; 95% CI -13.4 to 0.5; p=0.068), significant between group differences were seen at week 26 (-6.8; 95% CI -13.0 to -0.619; p=0.032) (table 20). By week 26, 4 (18.2%) exercise participants reported their fatigued change from being constant to intermittent.

7.3.7 Physical Activity

No significant between group differences in physical activity levels were identified at week 13 (p=0.077) or week 26 (p=0.930) (table 20). Larger between group differences were seen between baseline and 3 months (adjusted mean df= 414 minutes; 95% CI -47 to 875) than baseline to 6 months (-21 minutes; 95% CI -499 to 457). On average, in the exercise group, leisure physical activity time increased by 120 minutes from baseline to 13 weeks and decreased by 27 minutes at 26 weeks. On the other hand, the control group saw a decrease of 72 minutes from baseline to week 13 and an increase of 71 minutes at week 26. Total work physical activity time, including only participants who worked, the exercise group saw an increase of 99 minutes from baseline to 13 weeks and a decrease of 37 minutes at week 26. Likewise, the control group decreased by 22 minutes of work physical activity by week 13, however by week 26 physical activity at work increased by 310 minutes.

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Table 20. Change in questionnaire variables from baseline, 3 and 6-month

	Group Allocation	Baseline	3 Months	Adjusted Mean 3 Months (95% CI)	Mean Difference (95% CI)	P value	6 months	Adjusted Mean 6 Months (95% CI)	Mean Difference (95% CI)	P value
<i>Fatigue^a</i>										
Assessment (0-20)	IG	6.0 ± 4.0	6.0 ± 4.0	7 (5-8)	-1 (-3 to 1)	0.249	5.0 ± 3.0	6 (5-7)	-2 (-4 to -1)	0.005
	CG	9 ± 4.0	9 ± 4.0	8 (7-9)			10 ± 5.0	8 (7-10)		
Impact (0-120)	IG	17.7 ± 21.7	12.2 ± 14.1	16.4 (11.6-21.2)	-6.5 (-13.4 to 0.5)	0.068	12.1 ± 15.9	17.0 (12.8-21.2)	-6.8 (-13.0 to -.619)	0.032
	CG	33.6 ± 25.0	27.2 ± 21.3	22.9 (18.0-27.7)			28.9 ± 22.3	23.8 (19.5-28.1)		
Physical Activity	IG	1498 ± 1049	1544 ± 1057	1348 (1037-1658)	414 (-47 to 875)	0.077	1456 ± 924	1239 (917-1561)	-21 (-499 to 457)	0.930
Habits (min/week)	CG	794 ± 782	728 ± 621	934 (616-1253)			1032 ± 917	1260 (929-1590)		

Mean ± S.D are indicated for all columns unless stated.

IG, Intervention Group; CG, Control Group

^aLower scores represent better reported fatigue levels

7.3.8 Disease Activity

To ensure participants did not flare up during the intervention, disease activity was assessed at baseline and at 6 months using the CDAI and FC. Baseline CDAI and FC scores in the exercise group were 104.7 ± 57.6 and 55.9 ± 28.9 , respectively. At week 26, out of 22 participants in the exercise group, 21 had completed all CDAI parameters (7-day disease activity diary unavailable n=1) and 17 had submitted a stool sample for FC testing. Mean CDAI scores had decreased to 77.8 ± 48.2 , but FC scores had increased to 115.3 ± 121.4 . In the control group, baseline CDAI and FC scores were 123.1 ± 61.9 and 113.3 ± 66.9 , respectively. Out of the 21 participants in the control group, 20 had completed all CDAI parameters (7-day disease activity unavailable n=1) and 18 had submitted a stool sample for FC testing. Mean CDAI scores had decreased to 128.5 ± 69.1 , but FC scores had increased to 202.1 ± 154.1 .

7.3.9 Anthropometrics

Significant between group differences in resting heart rate were identified at week 13 (adjusted mean df= -5 beats per minute (bpm); 95% CI -10 to 0; p=0.032) and week 26 (-6 bpm; 95% CI -12 to -1; p=0.032). No between group differences were identified in BMI or blood pressure, systolic or diastolic at week 13 or week 26 (Appendix 7y).

7.3.10 Best-case and Worst-case Sensitivity Analysis

Effect sizes and significant values for muscular function outcomes did not substantially alter, however BMD outcomes appeared to be more sensitive to missing data (Appendix 7z). Best-case sensitivity analysis identified an increase in effect size for the lumbar spine (adjusted

mean $\text{df} = 0.085 \text{ g/cm}^2$; 95% CI 0.027 to 0.124; $p=0.005$), femoral neck (0.052 g/cm^2 ; 95% CI 0.010 to 0.095; $p=0.017$) and greater trochanter (0.036 g/cm^2 ; 95% CI -0.002 to 0.074; $p=0.065$). In contrast, effect sizes were reduced in the worst-case sensitivity analyses for the lumbar spine (adjusted mean $\text{df} = 0.014 \text{ g/cm}^2$; 95% CI -0.030 to 0.059; $p=0.521$), femoral neck (0.006 g/cm^2 ; 95% CI -0.026 to 0.037; $p=0.704$) and greater trochanter (-0.002 g/cm^2 ; 95% CI -0.035 to 0.032; $p=0.928$).

7.3.11 Compliance and exercise enjoyment

Participants in the exercise group attended 214 ± 2.1 (81.1%) out of 264 supervised sessions and completed 843 ± 14.4 (58.1%) out of 1452 unsupervised sessions. From the total 1716 exercise sessions offered, 1057 ± 15.0 (61.6%) were completed. A median (IQR) of 10 (8-12) supervised sessions were completed by each participant, 39 (24-48) out of 66 for unsupervised sessions and 50 (36-59) out of 78 for total number of exercise sessions.

Exercise enjoyment was determined at 3 (figure 47) and 6 months (figure 48) using the PACES questionnaire. At 3 months the mean (SD) enjoyment score was 104 ± 13 out of a possible 126, with a median (IQR) of 107 (96-114) scored for each participant. Enjoyment scores were sustained at 6 months, with a mean (SD) score of 103 ± 15 out of a possible 126 and a median (IQR) of 109 (92-114).

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Figure 47. Physical activity enjoyment scores (1-7) pre to 3 months in the exercise training group (n=21). Mean (SD) values presented. Higher scores reflect greater levels of enjoyment.

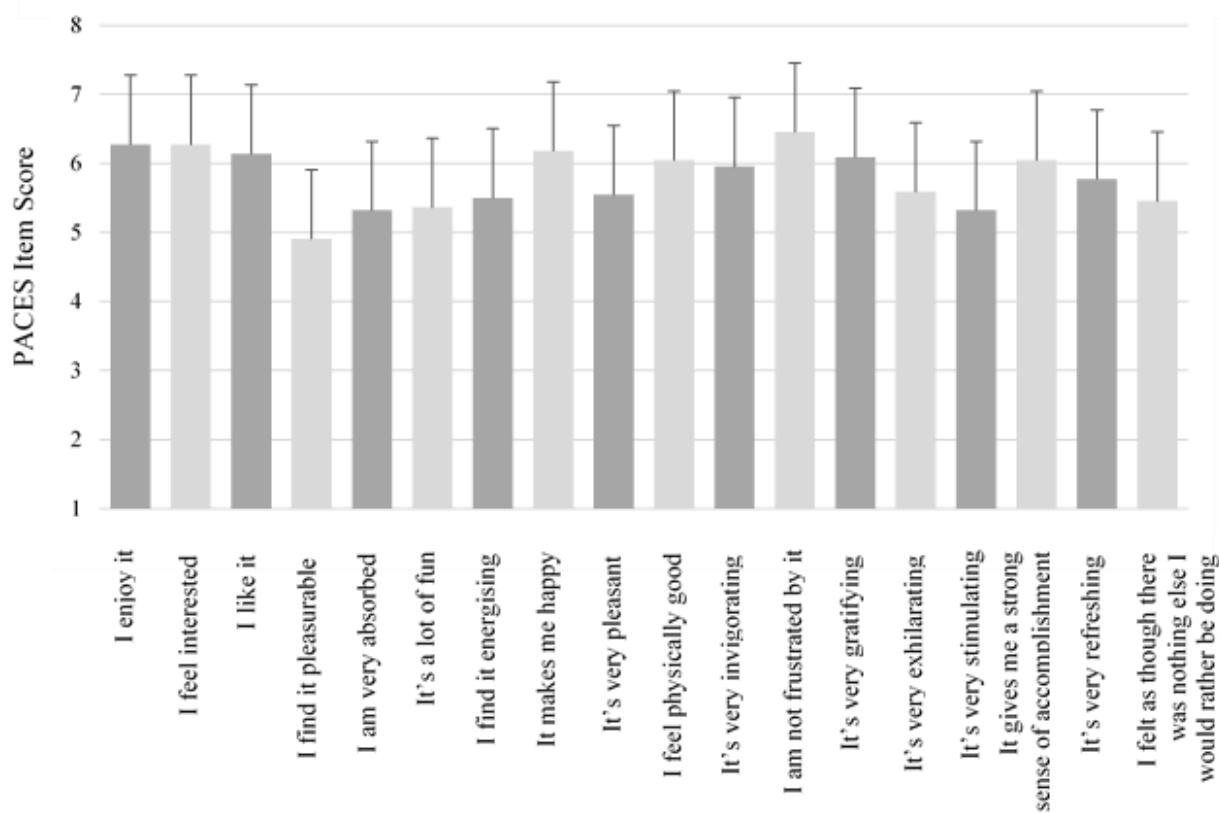
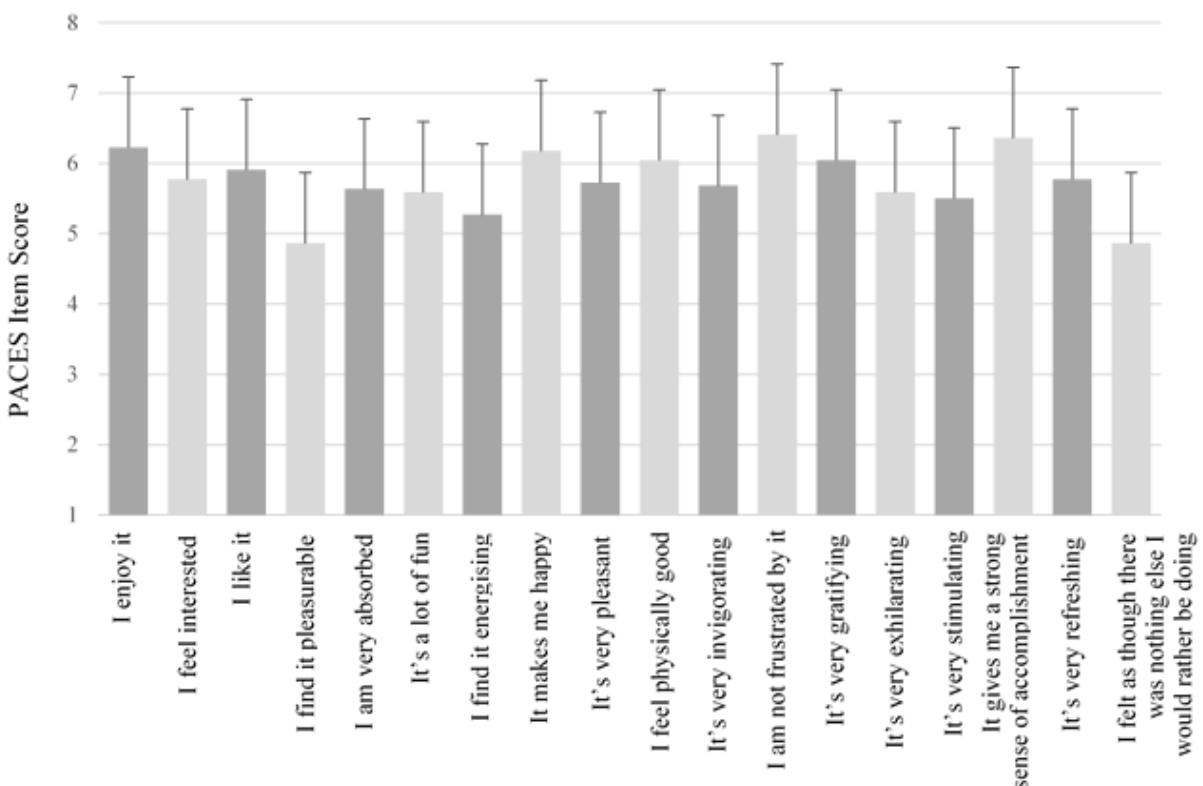


Figure 48. Physical activity enjoyment scores (1-7) 3 months to 6 months in the exercise training group (n=21) . Mean (SD) values presented. Higher scores reflect greater levels of enjoyment.



7.3.12 Adverse Events

A total of six AE were recorded, three exercise-related and three deemed unrelated to the research. The three exercise-related events recorded were: two instances of light-headedness due to lack of food during the day; and one instance of nausea as a result of the participant immediately eating prior to exercise. On all occasions the exercise was stopped and participants advised about appropriate dietary habits in relation to exercise. The three AE deemed unrelated to the research were: a transient ischaemic attack by a participant in the exercise group, the medical PI deemed this unrelated to the research; a self-reported disease flare by a participant in the control group and an allergic reaction to infliximab from a participant in the control group, the latter two resulted in both participants being withdrawn from the study. One control participant experienced disease relapse between baseline and 6 months, defined by an increase in CDAI of ≥ 100 to a score ≥ 150 , increasing from 46 at baseline to 175 at 6 months.

7.4 Discussion

To our knowledge, this is the first RCT to evaluate a combined impact and resistance training programme in adults with inactive to mildly active CD. Our results illustrate that a largely (85%) unsupervised 6-month intervention led to significant improvements in BMD, muscular strength, muscular endurance and fatigue at 6 months and without any deterioration in disease activity. Although the intervention group experienced significant improvements in QOL, determined using the IBDQ (total and subdomains) and EQ-5D-5L (VAS and index) at 3 months, these improvements were only sustained in the EQ-5D-5L index scores and the IBDQ subdomain social function at 6 months. Given the significant pressure within the NHS to control expenditure and the secondary burdening complications associated with CD, the

implementation of these findings not only provide NHS clinicians, stakeholders and clinical commissioning groups but people with CD additional management options. Additionally, providing an essential step in the development of providing evidence-based exercise guidelines for individuals with CD to improve health and care outcomes, a primary aim of the NHS.

7.4.1 Bone Mineral Density

The results of this study show that a 6-month resistance and impact training programme has favourable improvements in BMD at the lumbar spine and femoral neck in adults with CD. To the best of our knowledge, only one published RCT so far has investigated the effects of resistance exercise on BMD in adults with CD (Robinson et al., 1998). Following the conclusion of this 12-month low-impact resistance-training programme, improvements in BMD were identified in the exercise group at the greater trochanter, femoral neck and lumbar spine in comparison to the control group. Although these differences did not reach statistical significance, after analysis of the fully compliant participants only, significant differences were seen at the greater trochanter, and greater improvements identified at the femoral neck and lumbar spine, suggesting that increased BMD is positively related to the amount of exercise performed. These findings partially contradict the results of the current study, which found significant improvements at the lumbar spine and femoral neck but not at the greater trochanter. Disease activity may explain this variation, with the current study only including participants in clinical remission or with a mildly active disease while Robinson et al (1998) included a more heterogeneous sample, which may explain why only 52% of participants were compliant with the exercise programme. Proinflammatory cytokines that correlate with disease activity such as IL-1 (α and β), IL-6, IL-17 and TNF- α , also activate osteoclasts that interfere with the pathway involved in bone metabolism, known as RANK-RANKL-OPG and

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thus changing the rate of bone formation, bone resorption and overall bone homeostasis (Bernstein and Leslie, 2003; Bernstein et al., 2005; Mundy, 2007). RANKL (receptor activator of NF- κ B ligand) stimulates mature osteoclasts to resorb bone by binding to OPG, which is produced by osteoblasts and responsible for blocking the interaction between RANK and RANKL, an interaction that causes osteoclasts to differentiate and mature resulting in bone loss (Wei et al., 2001; Ali et al., 2009). Another explanation could be the intensity of the intervention and lack of impact exercises, with Robinson and colleagues opting for a low intensity resistance programme alone involving twice-weekly, 12 floor-based exercises.

Further unpublished randomised controlled trials have investigated the effects of a multimodal intervention (weight-bearing exercise and supplementation) and found effects partly in line with those of the current study. Sanges et al (2013) assessed the impact of prescribing 1g of calcium carbonate and 800 IU vitamin D with and without a thrice-weekly muscular training programme. Although improvements in BMD after 12 months were identified in both groups, greater improvements were seen in the exercise group at the lumbar spine and femoral neck ($p<0.05$), suggesting that supplementation alone is not as effective than a combination approach including exercise. However, analysis at 12 weeks of a 24-week progressive resistance-training programme alongside calcium and vitamin D supplementation did not significantly improve BMD and week 24 results remain unreported (Ponich et al., 2003). However, this study was significantly limited by the unclear methods of randomisation, lack of control group and lack of a priori sample size calculation. Although these findings do suggest that to elicit significant and beneficial changes in BMD, a longer training intervention is required.

The findings of the current study indicate that regular combined impact and resistance training can help improve BMD in adults with CD, significantly at the lumbar spine and femoral neck but not at the greater trochanter. This exercise programme was designed to load

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the musculoskeletal system slowly, while providing enough time for bone growth and adaptation before incorporating small increases over an extended period. Although the optimum frequency and duration of exercise required to increase BMD has not yet been established, the greatest improvements in BMD have been reported in exercise interventions combining resistance exercise and high-impact jump training, which this study included and was based upon. In post-menopausal women, a meta-analysis of 24 RCT's combining impact and resistance training interventions between 6 and 24 months illustrated mean changes of 0.431 (1.8%) (95% CI 0.159 to 0.702; p=0.002) at the lumbar spine and 0.411 (2.4%) (95% CI 0.176 to 0.645; p=0.001) at the femoral neck (Zhao et al., 2015). A more recent 8 month, twice-weekly, high-intensity resistance and impact training RCT of 101 postmenopausal women with low bone mass found superior changes at the lumbar spine ($2.9 \pm 2.8\%$) and femoral neck ($0.3 \pm 3.0\%$) (Watson et al., 2017). Interestingly, none of these studies aforementioned measured the greater trochanter. Another systematic review of 43 RCT's, identified 10 studies that examined combination exercise interventions, two of which measured the greater trochanter. These two studies identified mean change improvements of 1.31% (95% CI 0.69 to 1.92), however the results of a meta-analysis showed that there was a statistically significant effect in favour of control in percentage change in BMD at the hip. A potential reason for this non-significance could be explained by the composition and microarchitecture of the greater trochanter, which has demonstrated significantly higher mineralisation (+2%, p<0.05) than the femoral neck (Turunen et al., 2013). Nevertheless, the mean percentage changes echo those of the current study indicate that bone density at the lumbar spine increased by 3.8% (95% CI 2.6 to 5.1), 2.3% (95% CI 0.4 to 4.1) at the femoral neck and 1.4% (95% CI -2.2 to 5.1) at the greater trochanter after 6 months compared to the control group.

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The most important question is this of clinical importance. Bisphosphates remain the most common treatment for treating osteoporosis and are thought to induce an average increase between 7 to 8% at the spine and 5 to 7% at the hip following daily treatment over a three-year period (Chestnut et al., 2004). Although the changes in this study do not meet the level of bisphosphonate treatment, the changes in this study occurred from a thrice-weekly 6-month intervention and not following daily treatment for three years. However, recent meta-regression analysis indicated that a 2% improvement in BMD to be associated with a 28% reduction in vertebral fracture risk and a 15-22% reduction in hip fracture risk (Bouxsein et al, 2019). Thus, could be considered clinically relevant. Given the relative risk of sustaining a fracture in CD is 40% higher in comparison to the general population, contributing to poor QOL, increased morbidity and mortality and loss of independence. The potential implications and importance of encouraging adults with CD to remain active and incorporate impact and weight-bearing exercises is essential to preserve BMD, improve person centred care and to support the effective use of NHS resources.

7.4.2 Muscular Function

7.4.2.1 Muscular Strength

The findings of this study indicate that regular combined impact and resistance training can help significantly improve HGS and isokinetic knee-extension and elbow-flexion force in CD participants at 13 and 26 weeks. These statistically significant improvements were independent of covariates such as gender, baseline value and disease activity status. Despite aerobic exercise having the most well-known health benefits, the findings of this study support the ACSM (2012), NHS (2019b) and WHO (2020) recommendations that resistance training and jump training elicit gains in muscular strength. Although a predictor of future

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disability, to date only two studies have assessed the impact of resistance exercise on muscular strength in CD, despite its widespread clinical use in sarcopenia, rheumatoid arthritis and aging (Santilli et al., 2014).

The improvements in knee-extension force were in line with previous findings (Candow et al., 2002; De Souza-Tajiri et al., 2014). Both studies, one letter to the editor and one unpublished, found significant improvements in lower strength muscle indices following a 8 and 12 weeks of PRT, respectively. The mean improvement in isokinetic knee extension force was greater in this sample than in the two previous studies, an explanation for this might be the type of intervention delivered of these studies which were resistance training only compared to a combination (impact and resistance) intervention in the current study. Interestingly, mean improvements in upper body strength were smaller than those identified in Candow et al's (2002) quasi-experimental design study, who demonstrated a 21% improvement in upper body strength compared to 7-13% in the current study at 3 months. Reasons for this variation in improvement may be related to differences in the measurement equipment, population characteristics and disease activity. In addition, the intervention of the current study focused on impact training involving the lower body and did not include impact exercises for the upper-limbs, which could explain why there was a difference in upper and lower limb mean improvements. Future research should include a combination of upper and lower limb impact training.

To our knowledge this is the first study to explore the benefits of exercise on HGS and find significant improvements in adults with CD. Further trials in other populations and chronic conditions, presenting similar symptoms as CD, have assessed the impact of resistance exercise on HGS. Statistically significant improvements were also reported in elderly hypertensive participants (n=12) following a 14-week PRT programme (Nascimento et al., 2014), in 17 people with type 2 diabetes mellitus following a 12-week PRT programme

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(Geirdottir et al., 2012), in elderly adults (n=198) following a 12-week PRT programme (Geirdottir et al., 2012) and after a 16-week PRT programme in 24 people with rheumatoid arthritis (Flint-Wagner et al., 2009). Contrary to the current findings, no improvements in HGS were identified in healthy older adults (n=40) following 8-week resistance training programme (Martins et al., 2015), in older men and women (n=12) after a 4-week PRT intervention (Cegielski et al., 2017) and after a 8-week resistance training programme in people with multiple sclerosis (n=16) (Sabapathy et al., 2011). Although there is evidence to suggest that a longer intervention period elicits gains in skeletal muscle hypertrophy and thereby muscle mass, CSA and working capacity. Adaptations in structural, metabolic, hormonal, neural and molecular composition that in turn increase the force and power exerted and sustained by the muscle depend greatly on the type, intensity, duration and frequency of the exercise stimuli. More research employing high-quality methodological designs are warranted to confirm and expand on these findings to provide an evidence-based rationale for using combination training as a therapy for people with CD.

7.4.2.2 Muscular Endurance

The findings of this study showed that a 6-month combination exercise programme improved upper and lower limb muscular endurance in adults with CD. To our knowledge this is the first study to explore and demonstrate statistically significant improvements in muscular endurance in the CD population. The results are in broad agreement with similar previous intervention trials. A 17% and 32% increase in the 30-s CST from baseline to 3 month and to 6 months, respectively, is consistent with previous research in older adults, which found following a 12-week combined exercise intervention improvements of 13.5% and 20%, respectively (Cao et al., 2007; Islam et al., 2004). Larger improvements of 54.7% and 66%

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were also identified by two other research groups following a 10-week resistance training intervention in older adults, however exercises were focused on lower-body resistance training only (Hruda et al., 2003; Zhuang et al., 2014).

A 24% and 42% increase in the 30-s BCT from baseline to 3 months and to 6 months, respectively, is consistent with previous research in older adults. With results demonstrating that after a 24-week resistance training programme, a 10-week combination intervention and a 4-month multicomponent intervention upper muscular endurance improved by 35%, 26% and 15%, respectively (Minges et al., 2011; Crandall et al., 2015; Belza et al., 2016). A potential reason why the shorter intervention period elicited more favourable results could be explained by the exercise type delivered. Belza et al's (2016) 10-week exercise intervention incorporated moderate intensity aerobic, strength, flexibility and balance training, compared to Crandall et al's (2015) bingocize programme involved walking in place, stretches, balance and strengthening exercises. During aerobic exercise, the metabolic stress stimulates an increase in mitochondrial content and respiratory capacity of muscle fibres, which, when repeated can accumulate into adaptations in mitochondrial function (Jacobs and Lunby, 2013). These adaptations play an important role in the ability to perform prolonged strenuous exercise that occurs during physical activity. Further research is required to understand the cellular and molecular mechanisms responsible for the protective effect of regular combined impact and resistance training on skeletal muscle in CD.

Muscle-strengthening activities, such as weight lifting, at least twice a week is recommended for the prevention of loss of muscle mass and impaired physical function in the aging population (Nelson et al., 2007). However, given the impaired muscular function parameters identified in people with CD, as demonstrated in Chapter 6, it could be argued that the prevention of loss of muscle mass and physical function is just as important in this population. Given the benefits of regular combined impact and resistance training on muscle

function parameters demonstrated in this study implies that it is a safe and effective option in the management of CD.

7.4.3 Quality of life

7.4.3.1 EQ-5D-5L

In this RCT, a 6-month combination intervention induced more favourable improvements in QOL in adults with CD compared to the usual care group. Determined using the EQ VAS and EQ-5D index scores, the intervention group demonstrated superior QOL at 3 months compared with the control group. Significant group differences in the EQ-5D index scores were also demonstrated at 6 months, but not in the EQ VAS. Elsenbruh et al's (2005) 10-week mind-body therapy observed effects in line with those of the current study. This RCT involving stress management, moderate exercise, Mediterranean diet, behavioural techniques and self-care strategies in UC participants found significant improvements in QOL, assessed using the Short Form 36 (SF36). However, the results contradict those of Cronin et al (2019) who found no significant changes in QOL, determined using the SF36, following an 8-week combined aerobic and resistance training programme. However, while it assessed QOL, using a different QOL scale to the current study, the study's main focus was on body composition. Moreover, the study had a number of major flaws including the crossover design, making it difficult to determine the estimates separately, and the small sample size that may have been underpowered to detect meaningful changes.

Improved physical fitness, physical health, self-confidence, cognitive function and alleviating symptoms of anxiety, depression and stress are contributors of physical activity (Berger and Tobar, 2007; Gillison et al., 2009). Brain biochemistry changes as a result of physical activity, reducing the levels of stress hormones, adrenaline and cortisol while stimulating the

release neurotransmitters such as dopamine, norepinephrine and serotone that play an important part in regulating mood (Nabkasorn et al., 2005). Although disease-specific QOL questionnaires have been developed they tend to focus on an individual's perception of their current health status, rather than assessing their life satisfaction i.e how satisfied are they with their health, as individuals may appreciate their health may not be perfect, they still express high life satisfaction. Understanding these perspective when it comes to exercise interventions in people with CD is imperative and therefore future studies should consider the use of both QOL and HRQOL questionnaires when determining the effectiveness of an intervention.

7.4.3.2 IBDQ

The exercise intervention resulted in a profound impact on HRQOL and clinically relevant improvements, defined as an increase of 16 points or more and an total IBDQ score of 170 points or more, in 6 participants from baseline to 3 months. Inspection of the separate sub dimensions at 3 months of the HRQOL scale revealed significant improvements in bowel symptoms, emotional health, systemic systems and social function. One unanticipated finding was that improvements in total HRQOL or in sub-dimensions: bowel symptoms, emotional health or systemic systems dimension were not sustained at 6 months. This non-significant result may be explained by the fact that at pre-intervention IBDQ scores were higher than those reported in other IBD exercise interventions (De Souza-Tajiri et al., 2014; Klare et al., 2015; Cramer et al., 2017), which left not much potential for improvement. Another reason for this unanticipated finding maybe as a result of exercise adherence. Males have been found to have higher adherence rates in studies examining changes in physical activity (Simmons et al., 2010; Pavey et al., 2012), given this study was largely female based (68.1%) this could

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have contributed to this non-significant result. In addition, lower exercise adherence rates have been reported towards the end of the programme (Kallings et al., 2009; Leijon et al., 2010; Pavey et al., 2012). Therefore, to maintain improvements, strategies targeting enhancing adherence towards the end of an intervention should be employed. However, at 6 months the mean change in social function dimension of HRQOL was significantly higher for the exercise group when compared to the control group, suggesting a beneficial effect of regular exercise on social well-being in adults with CD.

Further trials have assessed the impact of exercise on HRQOL in IBD and found effects partly in line with those of the current study. In one uncontrolled trial, Loudon et al (1999) reported significant improvements in overall HRQOL, determined using the IBDQ, following a thrice-weekly three-month low intensity progressive walking programme in mildly active CD participants. Ng et al (2007) built on this preliminary work and incorporated a control group, which Loudon et al's (1999) study lacked. Improvements in total and sub dimensions of IBDQ were also observed in Klare et al's (2015) 10-week thrice-weekly running programme in inactive to moderately active adults with CD, but only through performing within group analysis. Significant differences between the intervention and control group only occurred in the social function domain, a finding similar to that of the current study. However, this finding is contrary to a recent finding from Cramer et al (2017), who observed no significant improvement in the IBDQ domain social function following a 24-week yoga intervention. On the other hand, Cramer and colleagues did observe a significant improvement in total IBDQ and sub dimensions bowel symptoms, systemic systems and emotional health. These variances may be explained by the disease state of the participants, with Cramer et al's (2017) study only including participants in clinical remission while the present study and Klare et al's (2015) study included inactive to mildly active participants. A major determinant of HRQOL is disease activity that remains the most significant predictor

of mental and physical HRQOL, because of the medical and surgical side effects, social, psychological and financial repercussions that are more prevalent during active periods.

Nevertheless, disease activity does not explain the decrements in HRQOL completely, with more than 30% of asymptomatic individuals reporting an impaired QOL, suggesting a role for other determinants (Sajadinejad et al., 2012; Theede et al., 2015). Moreover, the participants in Cramer et al's (2017) study had UC, which is associated with lower rates of surgery and inversely higher rates of HRQOL than CD, which could also explain the variation (Haapamaki, 2011).

Based on these preliminary studies, exercise may be a useful adjunct to CD therapy to elicit psychological changes. However, further research is needed to explore optimal exercise prescription in regards to type, intensity, duration and frequency tailored to meet the physical and psychological needs of the individual, that involve larger cohorts and different disease states, particularly those with a more moderate to severe disease.

7.4.4 Fatigue

In this randomised clinical trial, a 6-month combined impact and resistance training programme induced a reduction in fatigue in adults with CD compared to the usual care group. However, the self-reported severity and frequency of fatigue and the impact of fatigue on daily activities only demonstrated significant reductions at 26 weeks. No significant group differences in either domain were identified at 13 weeks. However self-reported fatigue severity, frequency and day-to-day impact ratings by participants in this study were relatively lower to those reported by others (Chan et al., 2014; Tew et al., 2016). One explanation for which could be selection bias, with participants volunteering to participate in a thrice-weekly exercise intervention more likely to be at the lower end of the fatigue spectrum. Furthermore,

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included study participants presented with an inactive or mildly active disease, disease states that are associated with experiencing fewer fatigue symptoms than those with a moderate to severely active disease (Levenstein et al., 2001; Romkens et al., 2011; Czuber-Dochan et al., 2015).

Further trials in other chronic conditions, presenting similar symptoms as CD, have assessed the impact of exercise on fatigue. Contrary to current findings, a meta-analysis of 28 RCT's of at least 4 weeks duration demonstrated significant improvements in fatigue in people with fibromyalgia (-0.22; 95% CI -0.3 to -0.05; p=0.009) (Hauser et al., 2010). Similar findings were reported in people with multiple sclerosis following an 8 to 12-week intervention (Klefbeck and Nedjad, 2003; Roehers and Karst, 2004; Briken et al., 2014; Pilutti et al., 2011). However, all these findings of shorter exercise durations were from moderate to high intensity aerobic interventions. Plausible explanation for this is the hypothesised theory is the relationship between fatigue and aerobic capacity. Aerobic capacity and muscular strength were assessed in 10 participants with quiescent IBD with self-reported fatigue, assessed using the CIS-fatigue (>35), and compared to gender and age matched (± 5 years) to a non-fatigued group with IBD. Fatigued individuals displayed an impaired aerobic capacity and muscle strength in comparison to non-fatigued individuals, suggesting that fatigued individuals may benefit from an aerobic exercise programme. A potential explanation for this could be as a result of physical inactivity due to the release of IL-15 during skeletal muscle contraction which induces a direct anti-inflammatory effect (DeFilippis et al., 2016). Another explanation could be the enhanced presence of inflammatory cytokines such as TNF- α , IFN- γ , IL-6, IL-10, IL-12 present in fatigued IBD participants (Vogelaar et al., 2017). A comparison between an aerobic vs resistance exercise intervention demonstrated a significant post intervention reduction in TNF- α , IL-6 and IL-10 in the aerobic intervention and no significant differences in the resistance intervention (Kader and Shreef, 2018). Suggesting that aerobic exercise is

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more appropriate in modulating the immune system, thus symptoms of fatigue, than resistance exercise.

Contrary to findings reported in other chronic conditions, Tew et al's (2019) HIIT and MICT intervention observed similar findings to that of the current study. Observing mean improvements in the severity and frequency of fatigue reported by adults with CD at 6 months, but not at 3 months. Although improvement in mean change in Tew et al's (2019) feasibility study was small from baseline to 6 months, it is valuable for people with CD who describe fatigue as impacting their psychological, physiological, social and behavioural aspects of life and that continues to impair their QOL (Vogelaar et al., 2015). The variation between reported fatigue levels in CD and in other chronic conditions could be explained due to the heterogeneity in how the symptom presents itself and the proinflammatory cytokines present during quiescent states of inflammation. In addition, both the current and Tew et al's (2019) study used a disease-specific fatigue questionnaire, in comparison to the previous studies mentioned who used generic fatigue measures such as the Fatigue Severity Scale or Fatigue Visual Analogue Scale. The two tools measure non-overlapping aspects of fatigue and therefore the comparison between the two are difficult to deduce due to the variability in the questions asked.

Progressive resistance training, in other chronic conditions has also demonstrated significant improvements in self-reported fatigue. In people with fibromyalgia significant improvements in fatigue were reported after a 21-week (Hakkinen et al., 2000) and 15-week (Ericsson et al., 2016) strength training programme working at 40-80% of 1-RM. Strength training programmes of a shorter duration, however, identified no significant improvements in fatigue. A systematic review of exercise therapy for the treatment of fatigue in multiple sclerosis identified three RCT's with a duration of 8, 10 and 12 weeks comparing progressive resistance training with controls, identified no significant improvement in fatigue (Heine et

al., 2015). Suggesting that resistance-training programmes may need a longer duration in order to elicit these improvements. Interestingly a recent RCT in adults with rheumatoid arthritis, demonstrated significant improvements in physical and mental fatigue at 20 weeks following a resistance training intervention (Kucharski et al., 2019). However, following a 52-week follow-up the end of the 20-week supervised intervention, resulted in the loss of the significant improvements in both physical and mental fatigue. Future research is warranted to establish what duration for the type of exercise performed is required to induce improvements in fatigue and evaluate if these are sustained after the intervention period.

Overall, there are important methodological limitations future research need to overcome to better understand the exact mechanisms as to how exercise helps fatigue. These include high-quality trials that are sufficiently powered and specifically aimed at fatigue, exploring different types, durations, frequencies and intensity of exercise and investigating the immune response to responders versus non-responders.

7.4.5 Disease Activity

A combination home-based intervention is feasible in inactive to mildly active CD and without CDAI or FC measures indicating a moderate to severely active disease. This is particular importance for individuals wanting to do unsupervised interventions. Our findings are similar to previous reports that exercise did not exacerbate symptoms (Loudon et al., 1999; Candow et al., 2002; Ng et al., 2007; Klare et al., 2015; Sharma et al., 2015; Cramer et al., 2017; Cronin et al., 2019; Tew et al., 2019) and therefore it is possible that exercise has anti-inflammatory properties in people with CD. Despite the importance of TNF- α , IL-1 β , IL-6, IL-10 demonstrating protective anti-inflammatory effects of exercise in IBD mice studies and in other health conditions such as cancer and type two diabetes, little is known about

these immune parameters in adults with CD in relation to exercise (Lee et al., 1997; Thune et al., 2001; Lamonte et al., 2005; Hoffman-Goetz et al., 2008). Nevertheless, it is promising for people with CD as TNF-*a* is a major pathological marker that correlates with intestinal inflammation (Muzes et al., 2012; Levin et al., 2016). Therefore, future research needs to explore the frequency, intensity, duration and type of exercise needed to induce the release of these cytokines in CD.

7.5 Strengths and Limitations

7.5.1 Strengths

The strengths of this study include the randomised controlled design and block randomisation of participants, minimising confounding due to unequal distribution of prognostic factors and making groups comparable to confounding factors which are both known and unknown, thus decreasing allocation and selection bias. The use of a blinded outcome assessor was also a strength of this study, minimising performance bias. Another strength of this study was the statistical reliability, through an adequately powered sample size and achieving statistical power and therefore avoiding the null hypothesis incorrectly being rejected or accepted. The study also included a well-defined population, including participants with different surgical history and on different treatment types. By including a well-defined population allows for findings to be applicable and acceptable to clinical practice. Moreover, the low rates of missing data and use of validated self-reported questionnaires and objective laboratory parameters are also strengths of this study.

7.5.2 Limitations

There are a number of limitations in this study. Firstly, although participants were randomly allocated 1:1 to receive either the exercise intervention or usual care, participants in the latter group may have experienced some disheartening of their group allocation knowing their counterparts were doing exercise and may have become more physically active. It therefore cannot be ruled out that the differences between groups may have been influenced by the increase in physical activity at 6 months performed by the control group, who performed on average an additional 71 minutes of leisure time activity, and 310 minutes of work time activity compared to baseline. In addition, the lack of participant blinding to group allocation could also make the participant-reported outcomes susceptible to bias (Moustgaard et al., 2020). Thirdly, the study was also limited to participants in clinical remission or with a mildly active disease and thus not reflective of the changes that may occur in participants with a moderate or severely active disease. Future studies should be extended to those with a more active disease, who may benefit from an exercise intervention.

Although the use of laboratory measures such as FC and CRP were a strength of this study, there was an inconsistency between these markers and the CDAI when it came to screening potentially eligible participants. Potential participants were excluded for presenting with a $FC > 250 \mu\text{g/g}$, however they presented with no symptoms and scored < 149 in the CDAI which is suggestive of an inactive disease. Likewise, potential participants were excluded because they reported being symptomatic and scored > 220 on the CDAI, however had a $FC < 250 \mu\text{g/g}$. Therefore, future studies should consider endoscopies or imaging techniques such as MRI, CT or small intestine ultrasonography (SICUS) with or without contrast against to assess the extent and severity of CD.

Another limitation was the use a self-reported physical activity questionnaire and the lack of controlled exercise environment when participants were exercising at home, variables that may have been susceptible to social desirability bias. Future studies should consider using objective measures such as accelerometers, to reduce the risk of bias. The study was also limited to a single site and the homogeneity of the cohort in regards to ethnicity makes application of the results difficult. Nutritional intake, although important for bone health, was not taken into consideration. This was primarily due to the complexity of recording food intake for a prolonged period and the inability to determine absorption rates between individuals. Future research is needed to determine the potential influence of a nutritional intervention alongside different modes of exercise.

Lack of follow-up post intervention was also a limitation and therefore it is unknown whether these improvements are sustained, and if so how long were they sustained for. In addition, although BMD is used to monitor osteoporosis, it only accounts for 60-70% of bone strength and therefore future research should consider using serum bone turnover markers. Lastly, the trial had several primary outcome measures, as one single measure would not sufficiently capture the range of clinically relevant intervention benefits and no adjustments were made for multiplicity. However, following Bonferroni adjustment (Bland and Altman, 1995), eight out of the ten outcomes would remain statistically significant supporting the beneficial effects of the intervention.

7.6 Conclusion

In view of these results, a resistance and impact training programme is a potent stimulator for skeletal growth, structure and maintenance to enhance BMD, and can induce statistically significant improvements in QOL, muscular function and fatigue in adults with CD compared

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to usual care. The intervention not only represents an inexpensive strategy for the prevention and treatment of CD-related complications but it also appeared safe, without any deterioration in disease activity and with few AE and SAE reported that were equally balanced between groups. The exercises were simple, required little equipment, minimal instruction and were able to be performed by participants aged between 27-85 of varying fitness abilities. Adults with CD should also be reassured that resistance and impact training did not exacerbate symptoms in those with an inactive or mildly active disease. Although the intervention demonstrated statistically significant improvements in BMD, it is unknown whether these improvements have been sustained after the intervention and for how long. In addition, moderately or severely active CD was not addressed in this research study and therefore caution should be applied before advising individuals who are presenting with a more active disease. It should also be highlighted that this research explores some of the unknowns relating to exercise in CD, and therefore more research is needed before conclusive statements and exercise guidelines can be established.

CHAPTER

8

Discussion

8.1 Overview

Overall, this thesis explored the benefits and harms of exercise interventions in IBD (Chapter 3), determined the test-retest reliability of outcome measures (Chapter 5), assessed bone and muscle health and identified possible risk factors associated with BMD in CD (Chapter 6), and investigated the effects of a combined impact and resistance training programme on BMD and muscle function in adults with CD (Chapter 7).

8.2 Summary of Key Findings

The systematic review described in Chapter 3 identified the effects of all modes of exercise interventions in adults with IBD and provided preliminary evidence that exercise is safe, feasible and acceptable in adults with an inactive to mildly disease. However, these studies were limited by their small cohort size, lack of blinded outcome assessor and follow-up. In addition, the majority of these studies involved exercise modalities, such as yoga or walking that are not optimal for improving bone health.

The reliability study described in Chapter 5 illustrated excellent test-retest reliability of the outcome measures used to evaluate and facilitate the assessment and effectiveness of an intervention. Interestingly, largely studies have focused on assessing reliability using an isometric or isotonic mode. This is one of a few studies that has used an isokinetic mode, using the Biodex System 4 Pro at different angular velocities (60°/s, 120°/s and 180°/s).

Moreover, the case control study (Chapter 6) provided novel findings as the first study to assess and identify reduced muscular endurance in adults with an inactive to mildly active CD. In addition to strengthening the evidence that adults with CD in the UK had a significantly reduced BMD, lower muscular strength and QOL when compared to matched

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healthy controls. This study was also the first to match adults with CD to healthy controls on physical activity habits.

Chapter 6 also demonstrated, through a cross-sectional design, that longer disease duration, low physical activity habits, being female and current smokers were correlated to BMD in CD. Supporting the current literature that gender, disease duration and smoking status were independent risk factors for BMD in CD participants. This study was also the second study to support the findings that identified a positive relationship between physical activity and BMD. However, the previous study (Nobile et al., 2018) included all IBD disease types whereas this one solely focused on CD. Results of this cross-sectional study also contraindicated the findings in disease behaviour, therefore more research in this area is needed to identify the potential risks different disease behaviours have upon BMD.

These studies aided in the design of an RCT (Chapter 7), which was then conducted to evaluate the effects of a 6-month combined exercise intervention on primary outcomes of BMD and muscular function. This study provided novel findings, demonstrating that a combined impact and resistance home-based training programme is a feasible and effective method to elicit significant improvements in lower and upper muscular endurance, handgrip strength and BMD at the lumbar spine and femoral neck. Although findings support the significant improvement identified in upper and lower muscular strength, this was the first intervention to demonstrate that, using resistance TheraBands and not weighted machines. Another novel finding was a statistically significant improvement in fatigue at 6 months. Although one of two studies that included fatigue as an outcome measure, the previous MICT and HIIT intervention was a feasibility study (Tew et al., 2019) with an intentionally small sample size and therefore underpowered to detect effect. The combined intervention was also safe for CD participants, with no serious adverse events related to the intervention recorded. Furthermore, the utilisation of behavioural change techniques employed such as goal setting,

support contact and self-monitoring resulted in good adherence rates (62%) and low drop-out rates (n=3 control, n=1 exercise) for an exercise intervention study. Supported by the use of a home-based programme and the use of accessible equipment. Lastly, this is one of only two exercise interventions in adults with CD to employ a physical activity enjoyment scale, supporting the ‘enjoyment’ participants reported following the exercise sessions.

8.3 Implications for Clinical Practice

The current guidelines around screening for osteoporosis in this high-risk group differs depending on the organisation. However, the ECCO, the American College of Gastroenterology, the American Gastroenterological Association and the British Society of Gastroenterology all agree that individuals who are repeatedly exposed to steroids and/or have a persistently active disease should have a DEXA scan (Scott et al., 2000; Bernstein et al., 2003; Lichtenstein et al., 2009; Van-Assche et al., 2013). However, the results of the cross-sectional study, described in Chapter 6, identified those with a longer disease duration, less physically active, females and current smokers were also potential risk factors. Findings that will increase clinician awareness and help identify individuals who should be monitored closely. In addition, Chapter 6 also identified adults with inactive to mildly active CD, via a case control study, show a reduced muscle strength and endurance when compared to matched healthy controls. While more research is clearly needed in this area, these results suggest the assessment of muscle function should be integrated into clinical practice and interventions put in place to prevent the development of musculoskeletal EIM’s.

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Although consensus from the ECCO (Harboard et al., 2016) addresses that weight-bearing or resistive exercises should be implemented to prevent bone loss, there are no specific guidelines for clinicians regarding the type, duration, frequency or intensity of exercise that is most appropriate to elicit favourable changes in adults with CD. With recommendations based largely on the general population who do not experience the same barriers to exercise such as fatigue, joint pain and abdominal pain as someone with CD. Thus, it is not surprising that exercise is infrequently discussed by gastroenterologists, GP's and other healthcare professionals (Lambdin et al., 2018).

The results of the RCT, described in Chapter 7, provide novel data on the efficacy of a combined intervention to elicit positive changes in BMD, muscular function, fatigue and QOL in this high-risk population. The current NICE pathway, following diagnosis and discussions about the disease, involves guidelines on smoking cessation, medication adherence, fertility, prognosis, cancer risk, surgery, diet and nutrition. Implementation of exercise guidelines would be best integrated into the clinical pathway at this stage, to educate individuals about alternative methods of managing and preventing the secondary complications associated with their condition while giving the individual an active role in their treatment. By also supporting and educating the CD multidisciplinary team on disease-specific exercise guidelines will enable them to discuss and recommend exercise to optimise health outcomes. The RCT also supports using behavioural change strategies to improve self-efficacy can achieve good levels of exercise adherence (Bandura, 1997; Rovniak et al., 2002). It is, however, important to stress that from a medical perspective exercise does not necessarily alter the disease course, it is intended as a complementary holistic approach in the management of CD and not to replace pharmacological treatment.

8.4 Limitations

Specific study limitations are presented in each chapter, however there are some limitations which reoccur between studies. Firstly, the studies in this thesis focused primarily on adults with an inactive to mildly active CD and therefore results may not be generalisable to people with other forms and severities of IBD. A further limitation is the use of the SPAQ to determine physical activity habits, in Chapters 5 and 7. Many participants had some issues with recalling physical activity performed over the last 7 days and understanding the inclusion of moderate to vigorous activity only, which may have led to under or over-reporting. Lastly, primarily due to time constraints, training requirements and additional costs, proinflammatory cytokines and nutritional state of individuals were not ascertained for Chapter 6 or 7. As discussed previously proinflammatory cytokines, particularly TNF- α and IL-6, and deficiencies, particularly in vitamin D and calcium, interfere with bone metabolism and muscular function (Duggan et al., 2004; Barbieri et al., 2013). Given the influence these variables can have on bone and muscle health, it is important that they are incorporated into future studies to better understand this relationship.

8.5 Future Directions

With individuals looking for alternative modalities, a series of larger-scale multi-centre RCT's are needed focusing on different training regimens in regards to type, duration, frequency and intensity, particularly higher intensities, to refine optimal exercise prescription. Involving different participant sub-groups in regards to disease type (i.e. CD and/or UC) and disease states, particularly those with a moderate to severe disease. While addressing the incorporation of different support strategies and follow-ups examining whether the

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participant is still exercising post intervention and whether improvements are sustained, and if so for how long. Future studies should also consider involving larger cohorts with a primary focus on the least researched areas including fatigue, cardiorespiratory fitness and immune function, particularly focusing on TNF- α and IL-6 which has demonstrated protective anti-inflammatory effects while exercising.

Given the benefits of aerobic exercise in the general population, and the evidence indicating that it improves immune function and aerobic capacity and helps reduce fatigue in other chronic conditions (Oldervoll et al, 2004; Cramp and Byron-Daniel, 2012). It would be beneficial to explore the benefits of an aerobic programme alongside an impact/resistance intervention to determine whether this multi-component intervention has superior physiological and psychological effects. In addition, to incorporating nutritional aspects from the input of nutritionists/dietitians and exploring the cost effectiveness, with the aid of health economists, to support the implementation of this within the NHS.

8.6 Conclusion

The findings arising from this thesis have demonstrated that:

- Aerobic and resistance exercise is safe and feasible in adults with inactive to mildly active CD and can potentially counteract some disease-specific complications.
- CD is linked to the development of osteoporosis/osteopenia and contributes to an individual's chance of developing muscular function and QOL impairments
- BMD was correlated to disease duration, physical activity habits, gender and smoking status in participants with an inactive to mildly active CD

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- Combined impact and resistance training of 3-6 months is a safe and effective mode of exercise for adults with inactive to mildly active CD, eliciting improvements in BMD, muscular strength and endurance, QOL and fatigue. Integration of impact and resistance exercise into the clinical pathway as a means of reducing risk of fractures and physical disability in this high-risk population is needed.

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Appendix 2a: Breakdown of UK costs per patient per year for CD and UC

A breakdown of UK Costs per patient per year for CD and UC

Treatment	Cost	Adverse Event	Cost	Complication	Cost
Pentasa	£517	Blood Test ^a	£152	Cancer	£10,514
Asacol	£823	Pancreatitis ^a	£2043.19	Uveitis	£125.66
Azathioprine	£95.88	Myelotoxicity ^a	£2036.14	Iritis	£125.66
6- mercaptopurine	£540.96	Hepatotoxicity ^a	£1209.81	Pyoderma gangrenosum	£463.04
Oral prednisolone	£78.88	Osteopenia ^b	£1134	Primary Sclerosing Cholangitis	£2099.25
Infliximab	£12,584	Osteoporosis ^b	£2267		
Adalimumab	£10,368	Mild Neuropsychiatric ^b	£1384		
Surgery for UC	£16,226.23	Severe Neuropsychiatric ^b	£2778		
Hospital bed day	£440	Serious Infection ^c	£4095.65		
Outpatient consultation	£128	Bleeding ^d	£561.48		

^a from thiopurine use, ^b from steroids, ^c from biological treatment, ^d from balloon dilatation

Appendix 3a: Deviations from systematic review study protocol

Protocol Method	Deviation from protocol method, with justification
Planned to include RCTs only	<p>Initial reviewing of including only RCTs failed to identify any studies of interest. Following the search non-randomised controlled trials were included as another study of inclusion as a means to expand the volume of research evidence. To comply to this change, the risk of bias tool ROBINS-I was added to include non RCTs.</p> <p>Type of deviation: Addition</p>
Planned to only include outcome measures on bone mineral density and muscular function	<p>Again, due to limited available research in this field following the initial review more primary outcomes such as quality of life, psychological well-being, disease activity, physical activity levels, body composition measures, cardiopulmonary measures, immunological outcomes and fatigue were included.</p> <p>Type of deviation: Addition</p>

Appendix 3b: Systematic review detailed outcome measures

1. Bone health outcomes- determined using validated standardised clinical measures (e.g. bone densitometry, ultrasound, calipers):
 - Bone mineral content (BMC) (g) of total body
 - BMD (g/cm^2) (areal and volumetric) of total body at the lumbar spine, femoral neck and/ or total hip
 - Bone metabolism biomarkers including: bone alkaline phosphate, alkaline phosphatase, serum osteocalcin, albumin, carboxy-terminal collagen type 1 crosslinks, N-telopeptide collagen type 1 cross linked, deoxypyridinoline, bone specific alkaline phosphate, N-terminal propeptides of type I procollagen, C-terminal propeptides of type I procollagen, pyridinoline, bone sialoprotein and isoform 5b of tartrate-resistant acid phosphatase.
 - Fractures at any site
 - Osteoporosis, osteopenia and osteomalacia
2. Muscle function of lower and upper extremities including muscle mass, endurance, strength, flexibility and physical performance determined using validated standardised clinical tools (e.g. handgrip dynamometer, timed chair stands, isokinetic dynamometry, gait speed, timed up and go)
3. QOL - including general measures (e.g. 36-item short form survey and EQ-5D) and disease-specific measures (e.g. Inflammatory Bowel Disease QOL questionnaire [IBDQ]) of HRQOL determined using validated standardised clinical tools
4. Psychological well-being such as depression, anxiety or stress determined using validated standardised clinical tools (e.g. Hospital Anxiety and Depression Scale [HADS], PHQ-9, perceived stress scale and State Trait Anxiety Inventory [STAI]):

5. Disease Activity - determined using validated standardised clinical measures (e.g. FC, CDAI, HBI, CRP and CAI)
6. Physical Activity Levels - determined using validated standardised clinical measures (e.g. accelerometer, pedometer and International Physical Activity Questionnaire)
7. Body Composition- determined using validated standardised clinical tools (e.g. DEXA, circumference and girth measures, bodpod, CT or MRI scans, bioelectrical impedance):
 - BMI (kg/m^2)
 - Lean and fat mass (kg) (%)
 - Skeletal mass (%) and muscle mass (%)
 - Cross-sectional muscle area (mm^2)
 - Percentage body fat (%)
 - Total body water (lt, %), potassium, nitrogen
8. Cardiopulmonary outcomes - determined using validated standardised clinical tools (e.g. exercise stress test, cardiopulmonary exercise test, submaximal treadmill test and incremental shuttle walk test):
 - Maximal and peak oxygen consumption ($\dot{V}\text{O}_2 \text{ max}$) ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)
 - Peak aerobic and anaerobic mechanical power (Wpeak) ($\text{W}\cdot\text{kg}^{-1}$)
 - Oxygen pulse
 - Maximum, peak and resting heart rate (beats per min)
 - Maximum tidal volume
 - Respiratory exchange ratio
9. Immune markers such as leukocytes, lymphocytes, granulocytes, monocytes and neutrophils determined using validated standardised clinical tools (e.g. endocrinological blood samples, inflammatory cytokines and immunotoxicity)
10. Fatigue- determined using validated standardised clinical measures (e.g. Inflammatory

Bowel Disease- Fatigue Scale [IBD-F], fatigue severity scale, multidimensional assessment of fatigue and blood tests such as ferritin and haemoglobin)

11. Safety: Exercise-related adverse events

12. Feasibility and acceptability will be assessed using attrition, compliance and adherence rates to the intervention

Appendix 3c: Systematic review search strategy

MEDLINE

1. exp Crohn disease/ or crohn*.mp.
2. indeterminate colitis.mp.
3. (colitis and ulcerat*).mp.
4. ulcerative colitis.mp. or exp ulcerative colitis/ or colitis, ulcerative/
5. (inflammatory bowel disease* or IBD).mp.
6. or/1-5
7. exp exercise/
8. exp exercise therapy/
9. (exercise* or exercising).mp.
10. exp sports/
11. ((resist* or weight* or strength* or endurance or circuit* or aerobic* or cardio* or jump* or anaerobic or balance or interval or muscl* or isokinetic or isometric) adj2 training).mp.
12. ('walking' or 'running' or 'sprinting' or 'jogging' or 'swimming' or 'cycling' or 'rowing' or 'dancing' or 'yoga' or 'boxing' or 'skipping' or 'pilates' or 'aqua').mp.
13. Or/7-12
14. 6 and 13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 not 15
17. 16 [Limit to English Language]

EMBASE

1. exp Crohn disease/ or crohn*.mp.
2. indeterminate colitis.mp.
3. (colitis and ulcerat*).mp.
4. ulcerative colitis.mp. or exp ulcerative colitis/ or colitis, ulcerative/
5. (inflammatory bowel disease* or IBD).mp.
6. or/1-5
7. exp exercise/
8. exp exercise therapy/
9. (exercise* or exercising).mp.
10. exp sports/

11. ((resist* or weight* or strength* or endurance or circuit* or aerobic* or cardio* or jump* or anaerobic or balance or interval or muscl* or isokinetic or isometric) adj2 training).mp.
12. ('walking' or 'running' or 'sprinting' or 'jogging' or 'swimming' or 'cycling' or 'rowing' or 'dancing' or 'yoga' or 'boxing' or 'skipping' or 'pilates' or 'aqua').mp.
13. Or/7-12
14. 6 and 13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 not 15
17. 16 [Limit to English Language]

CINAHL

1. ((MH "inflammatory bowel diseases") or (MH "colitis, ulcerative") or (MH "crohn disease"))
2. TI ((inflammatory bowel disease or IBD or Crohn* or ulcerative colitis or colitis* or indeterminate colitis) OR AB (inflammatory bowel disease or IBD or Crohn* or ulcerative colitis or colitis* or indeterminate colitis))
3. 1 or 2
4. ((MH "exercise") or (MH "exercise therapy") or (MH "sports"))
5. TI ((resist* or weight* or strength* or endurance or circuit* or aerobic* or cardio* or jump* or anaerobic or balance or interval or muscl* or isokinetic or isometric) N2 training) OR AB ((resist* or weight* or strength* or endurance or circuit* or aerobic* or cardio* or jump* or anaerobic or balance or interval or muscl* or isokinetic or isometric) N2 training)
6. TI ("walking" or "running" or "sprinting" or "jogging" or "swimming" or "cycling" or "rowing" or "dancing" or "yoga" or "boxing" or "skipping" or "pilates" or "aqua") OR AB ("walking" or "running" or "sprinting" or "jogging" or "swimming" or "cycling" or "rowing" or "dancing" or "yoga" or "boxing" or "skipping" or "pilates" or "aqua")
7. 3 or 4 or 5
8. 3 and 7
9. 8 [Limit to English Language]
10. 9 [Limit to Human]

Cochrane Central Register of Controlled Trials (CENTRAL)

1. MeSH descriptor: [inflammatory bowel disease] explode all trees
2. TI ((IBD or Crohn* or ulcerative colitis or indeterminate colitis) or AB (IBD or Crohn* or ulcerative colitis or indeterminate colitis))

3. #1 or #2 or #3 or #4
4. MeSH descriptor [exercise] explode all trees
5. MeSH descriptor [exercise therapy] explode all trees
6. MeSH descriptor [sports] explode all trees
7. ((resist* or weight* or strength* or endurance or circuit* or aerobic* or cardio* or jump* or anaerobic or balance or interval or muscl* or isokinetic or isometric) near/2 (training))
8. ‘walking’ or ‘running’ or ‘sprinting’ or ‘jogging’ or ‘swimming’ or ‘cycling’ or ‘rowing’ or ‘dancing’ or ‘yoga’ or ‘boxing’ or ‘skipping’ or ‘pilates’ or ‘aqua’
9. #6 or #7 or #8 or #9 or #10
10. #5 and #11

SPORTDiscus

1. “inflammatory bowel disease*”
2. TI ((inflammatory bowel disease or IBD or Crohn* or ulcerative colitis or colitis* or indeterminate colitis) OR AB (inflammatory bowel disease or IBD or Crohn* or ulcerative colitis or colitis* or indeterminate colitis))
3. 1 or 2
4. "exercis*" or “exercise therapy” or “sports”
5. TI ((resist* or weight* or strength* or endurance or circuit* or aerobic* or cardio* or jump* or anaerobic or balance or interval or muscl* or isokinetic or isometric) N2 training) OR AB ((resist* or weight* or strength* or endurance or circuit* or aerobic* or cardio* or jump* or anaerobic or balance or interval or muscl* or isokinetic or isometric) N2 training)
6. TI (“walking” or “running” or “sprinting” or “jogging” or “swimming” or “cycling” or “rowing” or “dancing” or “yoga” or “boxing” or “skipping” or “pilates” or “aqua”) OR AB (“walking” or “running” or “sprinting” or “jogging” or “swimming” or “cycling” or “rowing” or “dancing” or “yoga” or “boxing” or “skipping” or “pilates” or “aqua”)
7. 4 or 5 or 6
8. 3 and 7
9. 8 [Limit to English Language]

Appendix 4a: Eligibility bone health assessment form

Criteria for Body Composition and Bone Health Assessment using Dual-energy X-ray Absorptiometry

All information provided on this form will be kept confidential

Name of GP _____

Name of GP surgery _____

Section 1. Primary criteria

Please tick the answer that applies to you.

Are you younger than 18 years of age?

YES

NO

Are you / is there a possibility that you could you be pregnant?

YES

NO

Have you had or are you currently undergoing radiation therapy?

YES

NO

Have you had a significant radiation dose in the last 12 months?

YES

NO

Section 2. Factors that may influence the result (Please note, deformities and implants will be visible on the DXA scan image)

Have you had a major bone fracture that has not healed correctly?

YES

NO

If yes, please give further details:

Do you have any medical implants such as a pacemaker, any surgical pins or plates, or any synthetic joints e.g. knee or hip replacement?

YES

NO

For use by the operational user:

Section 1.

The DXA scan must be refused if the answer is yes to any question in section 1.

Section 2.

If the participant/patient has a significant fracture deformity, the operator must assess if the scan is justified for the measurement required.

Appendix 4b: GP letter of bone health result



Dr Ian Walshe
Laboratory Director
Senior Lecturer in Health and
Exercise Sciences

Northumbria University
Northumberland Building
Newcastle upon Tyne
NE1 8ST

DATE

Dear Dr _____,

I am writing to inform you that it has come to our attention during a recent research study that your patient, _____, has been estimated to have low / high (**please delete**) bone mineral content (compared to the normal values expected for an individual of their age). The study in which they were participating utilises dual-energy x-ray absorptiometry (DXA) scanning equipment to estimate the body composition of an individual (fat mass, lean mass and bone mineral content). The patient gave their consent prior to participation in the study that if such results were found regarding their bone mineral content then their G.P should be notified. It is highly recommended that such findings are followed up and the appropriate care and advice is provided to the patient.

I have attached the DXA scan report of _____. If you need any further information, please feel free to contact me.

Yours faithfully,

Dr Ian Walshe
Senior Lecturer in Health and Exercise Sciences

Appendix 4c: EQ-5D-5L Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- | | |
|---|--------------------------|
| I have no problems in walking about | <input type="checkbox"/> |
| I have slight problems in walking about | <input type="checkbox"/> |
| I have moderate problems in walking about | <input type="checkbox"/> |
| I have severe problems in walking about | <input type="checkbox"/> |
| I am unable to walk about | <input type="checkbox"/> |

SELF-CARE

- | | |
|---|--------------------------|
| I have no problems washing or dressing myself | <input type="checkbox"/> |
| I have slight problems washing or dressing myself | <input type="checkbox"/> |
| I have moderate problems washing or dressing myself | <input type="checkbox"/> |
| I have severe problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself | <input type="checkbox"/> |

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- | | |
|--|--------------------------|
| I have no problems doing my usual activities | <input type="checkbox"/> |
| I have slight problems doing my usual activities | <input type="checkbox"/> |
| I have moderate problems doing my usual activities | <input type="checkbox"/> |
| I have severe problems doing my usual activities | <input type="checkbox"/> |
| I am unable to do my usual activities | <input type="checkbox"/> |

PAIN / DISCOMFORT

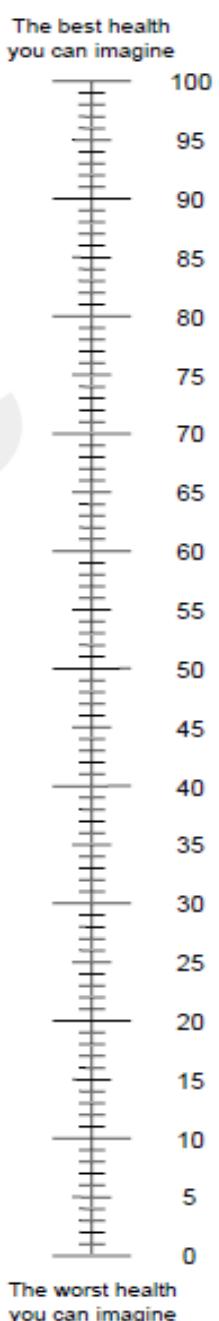
- | | |
|------------------------------------|--------------------------|
| I have no pain or discomfort | <input type="checkbox"/> |
| I have slight pain or discomfort | <input type="checkbox"/> |
| I have moderate pain or discomfort | <input type="checkbox"/> |
| I have severe pain or discomfort | <input type="checkbox"/> |
| I have extreme pain or discomfort | <input type="checkbox"/> |

ANXIETY / DEPRESSION

- I am not anxious or depressed
 - I am slightly anxious or depressed
 - I am moderately anxious or depressed
 - I am severely anxious or depressed
 - I am extremely anxious or depressed



- We would like to know how good or bad your health is TODAY.
 - This scale is numbered from 0 to 100.
 - 100 means the best health you can imagine.
0 means the worst health you can imagine.
 - Mark an X on the scale to indicate how your health is TODAY.
 - Now, please write the number you marked on the scale in the box.



YOUR HEALTH TODAY =

Appendix 4d: IBDQ and IBDQ-Stoma

[Questions in bold are for IBDQ-Stoma, which replaced IBDQ questions and completed by patients who presented with an colostomy or ileostomy]

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from
 1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
 2. EXTREMELY FREQUENT
 3. VERY FREQUENT
 4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

1. **How frequent have you had to empty your colostomy or ileostomy appliance during the last two weeks? Please indicate how frequent your stomal output has been during the last two weeks by picking one of the options from**
 1. AS OR MORE FREQUENT THAN EVER
 2. EXTREMELY FREQUENT
 3. VERY FREQUENT
 4. MODERATE INCREASE IN FREQUENCY OF EMPTYING
 5. SOME INCREASE IN FREQUENCY OF EMPTYING
 6. SLIGHT INCREASE IN FREQUENCY OF EMPTYING
 7. NORMAL, NO INCREASE IN FREQUENCY OF EMPTYING

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from
 1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
4. How often during the last 2 weeks have you been unable to attend school or do you work because of your bowel problem? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
5. **How much of the time during the last 2 weeks have your stoma output been looser than normal? Please choose an option from**
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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6. How much energy have you had during the last 2 weeks? Please choose an option from
1. NO ENERGY AT ALL
 2. VERY LITTLE ENERGY
 3. A LITTLE ENERGY
 4. SOME ENERGY
 5. A MODERATE AMOUNT OF ENERGY
 6. A LOT OF ENERGY
 7. FULL OF ENERGY
7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from
1. A GREAT DEAL OF DIFFICULTY, ACTIVITIES MADE IMPOSSIBLE
 2. A LOT OF DIFFICULTY
 3. A FAIR BIT OF DIFFICULTY
 4. SOME DIFFICULTY
 5. A LITTLE DIFFICULTY
 6. HARDLY ANY DIFFICULTY
 7. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES
13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from
1. A MAJOR PROBLEM
 2. A BIG PROBLEM
 3. A SIGNIFICANT PROBLEM
 4. SOME TROUBLE
 5. A LITTLE TROUBLE
 6. HARDLY ANY TROUBLE
 7. NO TROUBLE

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17. Overall, in the last 2 weeks, how much of a problem have you had with your stomal appliance filling up with large amounts of gas? Please choose an option from
1. A MAJOR PROBLEM
 2. A BIG PROBLEM
 3. A SIGNIFICANT PROBLEM
 4. SOME TROUBLE
 5. A LITTLE TROUBLE
 6. HARDLY ANY TROUBLE
 7. NO TROUBLE
18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from
1. A MAJOR PROBLEM
 2. A BIG PROBLEM
 3. A SIGNIFICANT PROBLEM
 4. SOME TROUBLE
 5. A LITTLE TROUBLE
 6. HARDLY ANY TROUBLE
 7. NO TROUBLE
19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from
1. NONE OF THE TIME
 2. A LITTLE OF THE TIME
 3. SOME OF THE TIME
 4. A GOOD BIT OF THE TIME
 5. MOST OF THE TIME
 6. ALMOST ALL OF THE TIME
 7. ALL OF THE TIME
22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
- 22. How much of the time during the last 2 weeks have you had a problem with blood in your stomal output or blood from the rectum? Please choose an option from**
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
24. **How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom to empty your rectum, even though you have a stoma?**
Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your clothing or bedding because of leaking from your stomal appliance? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from
1. NO SEX AS A RESULT OF BOWEL DISEASE
 2. MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
 3. MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
 4. SOME LIMITATION AS A RESULT OF BOWEL DISEASE
 5. A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
 6. HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
 7. NO LIMITATION AS A RESULT OF BOWEL DISEASE
29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE BIT OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from
1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
 2. GENERALLY DISSATISFIED, UNHAPPY
 3. SOMEWHAT DISSATISFIED, UNHAPPY
 4. GENERALLY SATISFIED, PLEASED
 5. SATISFIED MOST OF THE TIME, HAPPY
 6. VERY SATISFIED MOST OF THE TIME, HAPPY
 7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

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Appendix 4e: IBD Fatigue Self-assessment Scale (IBD-F)

Date: Time:

SECTION I - Fatigue Assessment Scale

This section of the questionnaire will identify fatigue, its severity, frequency and duration.

Sometimes people with inflammatory bowel disease feel fatigued. The term 'fatigue' is used throughout the questionnaire. Fatigue has been defined as a sense of continuing tiredness, with periods of sudden and overwhelming lack of energy or feeling of exhaustion that is not relieved following rest or sleep

Please tick ONE number for each question		Score from 0 – 4 with				
		0 = no fatigue			Severe fatigue = 4	
1.	What is your fatigue level right NOW	0	1	2	3	4
2.	What was your HIGHEST fatigue level in the past two weeks	0	1	2	3	4
3.	What was your LOWEST fatigue level in the past two weeks	0	1	2	3	4
4.	What was your AVERAGE fatigue level in the past two weeks	0	1	2	3	4
5.	How much of your waking time have you felt fatigued in the past two weeks	0 None of the time	1 Some of the time	2 Often	3 Most of the time	4 All the time

SECTION II - IBD-Fatigue Impact on Daily Activities Scale

This section assesses the perceived impact of fatigue on your daily activities in the past two weeks.

Please answer all the questions. The possible answers to the questions are:

None of the time - 0; Some of the time – 1; Often - 2; Most of the time - 3; All of the time - 4.

If a particular activity does not apply to you, for example you do not drive, please select N/A.

Please tick <u>only ONE</u> answer for each question reflecting on the past two weeks	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
1. I had to nap during the day because of fatigue	0	1	2	3	4	
2. Fatigue stopped me from going out to social events	0	1	2	3	4	
3. I was not able to go to work or college because of fatigue	0	1	2	3	4	N/A
4. My performance at work or education was affected by fatigue	0	1	2	3	4	N/A
5. I had problems concentrating because of fatigue	0	1	2	3	4	
6. I had difficulty motivating myself because of fatigue	0	1	2	3	4	
7. I could not wash and dress myself because of fatigue	0	1	2	3	4	
8. I had difficulty with walking because of fatigue	0	1	2	3	4	
9. I was unable to drive as much as I need to because of fatigue	0	1	2	3	4	N/A
10. I was not able to do as much physical exercise as I wanted to because of fatigue	0	1	2	3	4	

Please tick only ONE answer for each question reflecting on the past two weeks	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
11. I had difficulty continuing with my hobbies/interests because of fatigue	0	1	2	3	4	
12. My emotional relationship with my partner was affected by fatigue	0	1	2	3	4	N/A
13. My sexual relationship with my partner was affected by fatigue	0	1	2	3	4	N/A
14. My relationship with my children was affected by fatigue	0	1	2	3	4	N/A
15. I was low in mood because of fatigue	0	1	2	3	4	
16. I felt isolated because of fatigue	0	1	2	3	4	
17. My memory was affected because of fatigue	0	1	2	3	4	
18. I made mistakes because of fatigue	0	1	2	3	4	
19. Fatigue made me irritable	0	1	2	3	4	
20. Fatigue made me frustrated	0	1	2	3	4	
21. I got words mixed up because of fatigue	0	1	2	3	4	
22. Fatigue stopped me from enjoying life	0	1	2	3	4	
23. Fatigue stopped me from having a fulfilling life	0	1	2	3	4	
24. My self-esteem was affected by fatigue	0	1	2	3	4	
25. Fatigue affected by confidence	0	1	2	3	4	

Please tick only ONE answer for each question reflecting on the past two weeks	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
26. Fatigue made me feel unhappy	0	1	2	3	4	
27. I had difficulties sleeping at night because of fatigue	0	1	2	3	4	
28. Fatigue affected my ability to do all my normal household activities	0	1	2	3	4	
29. I had to ask others for help because of fatigue	0	1	2	3	4	
30. Quality of my life was affected by fatigue	0	1	2	3	4	

SECTION III – Additional Questions about your Fatigue

1. What do you think is the main cause of your fatigue apart from IBD?
.....
2. What do you think are the other causes of your fatigue?
.....
3. Have you found anything that helps with your fatigue?
.....
4. How long have you experienced fatigue? Years Months
5. During this time has your fatigue been:

a) Constant	b) Intermittent
-------------	-----------------

Appendix 4f: Scottish Physical Activity Questionnaire (SPAQ)

The following questions relate to your physical activity over the **previous week**. Please mark in the appropriate box the number of minutes spent doing a particular activity. Please try and think carefully and be as accurate as possible with your answers and only include activities of either **moderate or vigorous** intensity.
Examples are given of what should and should not be included.

<input checked="" type="checkbox"/>	LIGHT INTENSITY - Your heart rate and breathing rate are no different from what they are when you are standing, sitting etc
<input checked="" type="checkbox"/>	MODERATE INTENSITY - Your heart rate and breathing rate are faster than normal. You may also sweat a little. Brisk walking or sweeping and mopping are good examples of how you might feel
<input checked="" type="checkbox"/>	VIGOROUS INTENSITY – Your heart rate is much faster and you have to breathe deeper and faster than normal. You will probably sweat. Playing football or squash are good examples of how you might feel

LEISURE TIME PHYSICAL ACTIVTIY- remember, do not include light intensity activities

In the past week how many minutes did you spend each day:	MON	TUE	WED	THUR	FRI	SAT	SUN	TOTAL
Walking outside of work? <i>Include ✓ e.g walking to the shops, walking to work, walking the dog or stair walking✓ Do NOT Include ✗ e.g standing, sitting, driving, walking whilst at work ✗</i>								
Manual labour outside of work? <i>Include ✓ e.g cutting the grass, decorating, washing the car, DIY, digging ✓ Do NOT Include ✗ e.g weeding, planting, pruning ✗</i>								
Active housework? <i>Include ✓ e.g vacuuming, scrubbing floors, bed making, hanging out washing ✓ Do NOT Include ✗ e.g. sewing, dusting, washing dishes, preparing food ✗</i>								
Dancing? <i>Include ✓ e.g only include time actually spent dancing: disco, line, country ✓ Do NOT Include ✗ e.g time spent not actually dancing ✗</i>								
Participating in a sport, leisure activity or training? <i>Include ✓ e.g. exercise classes, cycling, football, swimming, golf, jogging, athletics ✓ Do NOT Include ✗ e.g darts, snooker/pool, fishing, playing a musical instrument ✗</i>								

Other Physical Activity if not already covered (please write in)								
								TOTAL

PHYSICAL ACTIVITY AT WORK- (Only complete if you are currently employed and remember not to include light intensity activities)

In the past week how many minutes did you spend each day:

	MON	TUE	WED	THUR	FRI	SAT	SUN	TOTAL
Walking whilst at work? <i>Include ✓ e.g walking up or down stairs, to and from your desk, 'doing the rounds' ✓ Do NOT Include ✗ e.g. standing, sitting at desk, time spent not actually walking ✗</i>								
Manual labour whilst at work? <i>Include ✓ e.g. lifting, stacking shelves, climbing ladders, building work, cleaning ✓ Do NOT Include ✗ e.g sitting at desk, answering telephone, driving, check-out operation ✗</i>								

Was last week typical of the amount of physical activity you already do?

YES					
No- I usually do more		Normally, how much more?		Of which activity?	
No- I usually do less		Normally, how much less?		Of which activity?	

Appendix 4g: Crohn's Disease Activity Index (CDAI)

Parameter									Factor	Subtotal			
Liquid stools (total over last 7 days)	M	T	W	T	F	S	S	Sum =	x 2				
Abdominal pain † (total over last 7 days)	M	T	W	T	F	S	S	Sum =	x 5				
General wellbeing * (total over last 7 days)	M	T	W	T	F	S	S	Sum =	x 7				
Extra-Intestinal													
Arthritis/arthritis	None = 0				Score =			x 20					
	Yes = 1												
Iritis/uveitis	None = 0				Score =			x 20					
	Yes = 1												
Skin/mouth lesions	None = 0				Score =			x 20					
	Yes = 1												
Peri-anal disease	None = 0				Score =			x 20					
	Yes = 1												
Other fistula	None = 0				Score =			x 20					
	Yes = 1												
Fever > 37.8°C	None = 0				Score =			x 20					
	Yes = 1												
Anti-diarrhoeals	None = 0				Score =			x 30					
	Yes = 1												
Abdominal mass	None = 0				Score =			x 10					
	Questionable = 2												
	Definite = 5												
Haematocrit (Hct)	Males (47- Hct)				Score =		%	(Typical – Current)					
	Females (42- Hct)							x 6					
Weight +	Standard kg				kg		100 x (1 - <u>Current</u>)						
	Current kg						kg		Standard				

KEY	Abdominal pain †	General wellbeing *	Weight +
	None = 0 Intermediate = 1 or 2 Severe = 3	Well = 0 Intermediate = 1, 2 or 3 Terrible = 4	Skip this section (0) unless weight changes related to Crohn's are known. Maximum deduction of -10 for overweight patients)

Appendix 4h: Standard weight chart

RESISTANCE TRAINING IN ADULTS WITH CROHN'S DISEASE

This document is to accompany Q8 on the CDAI calculation form. **RECOMMENDATION:** Unless weight changes related to Crohn's are known, skip this section. Maximum deduction of -10 for overweight patients.

Actual Height CM (Inches)	Standard Weight- MEN KG (Pounds)	Standard Weight- WOMEN KG (Pounds)
147.3 (58.0)		52.2 (115.0)
148.6 (58.5)		52.6 (116.0)
149.9 (59.0)		53.1 (117.0)
151.1 (59.5)		53.6 (118.3)
152.4 (60.0)		54.2 (119.5)
153.7 (60.5)		54.8 (120.8)
154.9 (61.0)		55.3 (122.0)
156.2 (61.5)		56.0 (123.5)
157.5 (62.0)	61.7 (136.0)	56.7 (125.0)
158.8 (62.5)	62.1 (137.0)	57.4 (126.5)
160.0 (63.0)	62.6 (138.0)	58.0 (128.0)
161.3 (63.5)	63.0 (139.0)	58.7 (129.5)
162.6 (64.0)	63.5 (140.0)	59.4 (131.0)
163.8 (64.5)	64.1 (141.3)	60.1 (132.5)
165.1 (65.0)	64.6 (142.5)	60.8 (134.0)
166.4 (65.5)	65.2 (143.6)	61.4 (135.5)
167.6 (66.0)	65.8 (145.0)	62.1 (137.0)
168.9 (66.5)	66.4 (146.5)	62.8 (138.5)
170.2 (67.0)	67.1 (148.0)	63.5 (140.0)
171.5 (67.5)	67.8 (149.5)	64.2 (141.5)
172.7 (68.0)	68.5 (151.0)	64.9 (143.0)
174.0 (68.5)	69.2 (152.5)	65.5 (144.5)
175.3 (69.0)	69.8 (154.0)	66.2 (146.0)
176.5 (69.5)	70.5 (155.5)	66.9 (147.5)
177.8 (70.0)	71.2 (157.0)	67.6 (149.0)
179.1 (70.5)	71.9 (158.5)	68.3 (150.5)
180.3 (71.0)	72.6 (160.0)	68.9 (152.0)
181.6 (71.5)	73.4 (161.8)	69.9 (153.5)
182.9 (72.0)	74.1 (163.5)	70.3 (155.0)
184.2 (72.5)	75.0 (165.3)	
185.4 (73.0)	75.7 (167.0)	
186.7 (73.5)	76.6 (169.0)	
188.0 (74.0)	77.5 (171.0)	
189.2 (74.5)	78.4 (172.8)	
190.5 (75.0)	79.1 (174.5)	
191.8 (75.5)	80.2 (176.8)	
193.0 (76.0)	81.2 (179.0)	

- Height in shoes with one-inch heels
- Indoor clothing weight 5 pounds for men and 3 pounds for women
- Centimetres x 0.3937 = inches
- Pounds x 0.4535 = kilograms

Appendix 4i: HRA approval



Dr Garry Tew
Associate Professor of Exercise and Health Sciences/Director of Enterprise and Engagement
University of Northumbria University at Newcastle
431 Northumberland Building
Northumbria University
Newcastle
NE1 8ST

Email: hra.approval@nhs.net

17 November 2017

Dear

Letter of HRA Approval

Study title: Effects of a 6-month practical resistance training programme on muscle function and bone mineral density in adults with inactive or mildly active Crohn's disease: Study protocol for a randomised controlled trial
IRAS project ID: 226369
REC reference: 17/NE/0308
Sponsor University of Northumbria at Newcastle

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. Please read Appendix B carefully, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Appendix 4j: REC approval



Health Research Authority

North East - Tyne & Wear South Research Ethics Committee

HRA Jarrow
Jarrow Business Centre
Room 001
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0207 104 8084

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

17 November 2017

Dr Garry Tew
Associate Professor of Exercise & Health Sciences/
Director of Enterprise and Engagement
University of Northumbria at Newcastle
431 Northumberland Building
Northumbria University
Newcastle upon Tyne
NE1 8ST

Dear Dr Tew

Study title: Effects of a 6-month practical resistance training programme on muscle function and bone mineral density in adults with inactive or mildly active Crohn's disease: Study protocol for a randomised controlled trial
REC reference: 17/NE/0308
IRAS project ID: 226369

Thank you for your letter of , responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a Favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised], subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the

A Research Ethics Committee established by the Health Research Authority

Appendix 4k: NUTH R&D approval

From: Clark, Ayesha
Sent: 06 February 2018 14:17
To: Speight, Richard
Cc: samantha.king@northumbria.ac.uk; Scott, Julia (Clinical Trials); Finance Research and Development Team; McShane, Lesley
Subject: 8488 - Confirmation of Capacity and Capability

Dear Dr Speight

[Confirmation of Capacity and Capability at The Newcastle upon Tyne Hospitals NHS Foundation Trust](#)

-
Study Title: Effects of a 6-month practical resistance training programme on muscle function and bone mineral density in adults with inactive or mildly active Crohn's disease: Study protocol for a randomised controlled trial
IRAS ID: 226369
R&D Ref: 8488
Site for Recruitment to CPMS: Freeman Hospital RTD01

This email confirms that The Newcastle upon Tyne Hospitals NHS Foundation Trust has the capacity and capability to deliver the above referenced study. You now may begin work on this study.

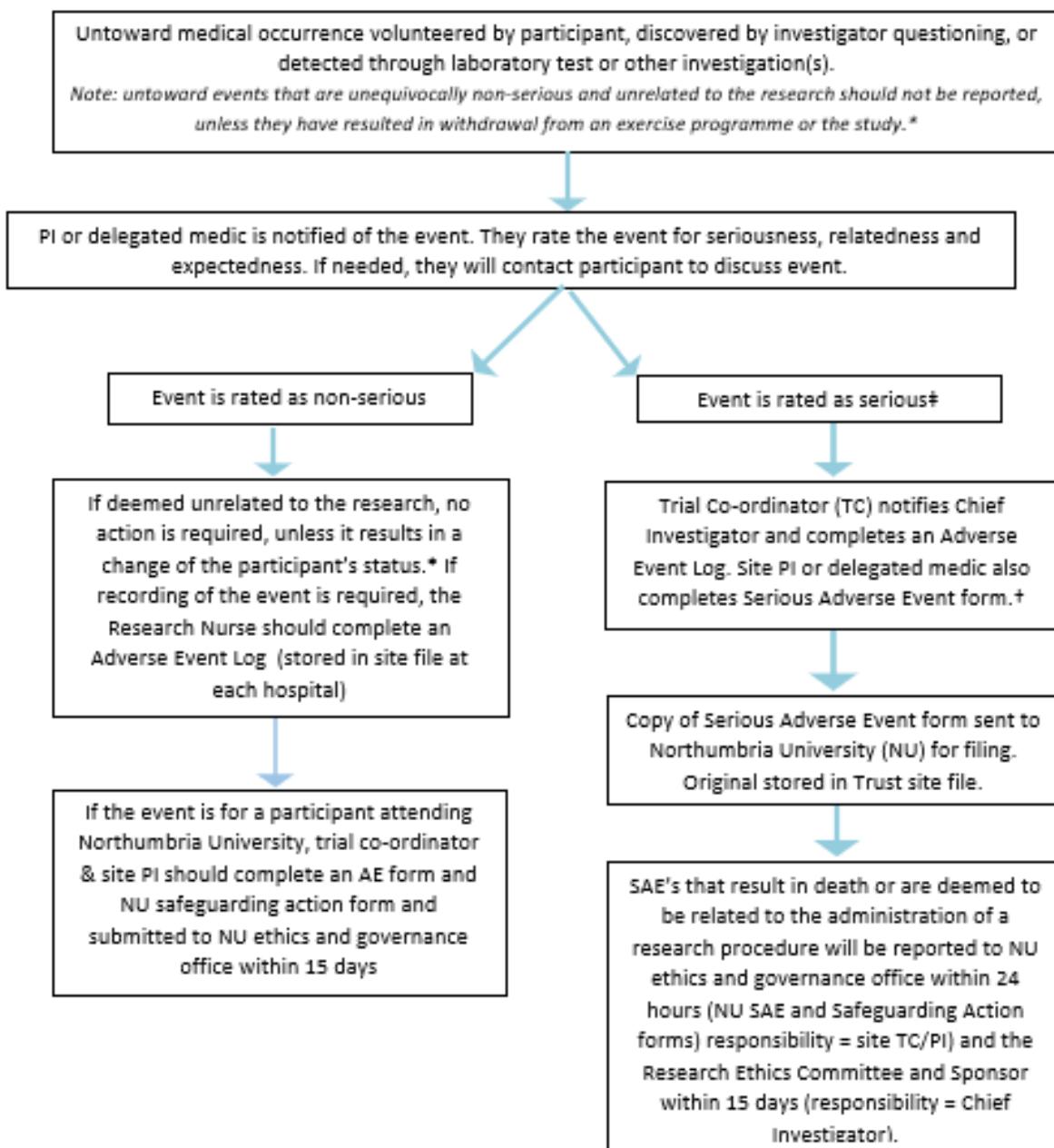
Best Wishes

Ayesha

Ayesha Clark
Research & Development Officer

Appendix 4l: Adverse and serious adverse events procedure and reporting form

Reporting an adverse event (AE)/ serious adverse event (SAE)



* If the event results in a change of participant's status, follow the change of trial procedure (stored in trial master file)

‡ Serious adverse events are defined as any untoward medical occurrence that fall in one of the following criteria: results in death, is life threatening, requires unplanned or prolonged hospitalisation, results in persistent or significant disability or incapacity or results in a congenital abnormality or birth defect

† Each SAE should be recorded on separate forms, even when events occur concurrently

Adverse Event (AE) /Serious Adverse Event (SAE) Form

STUDY TITLE: PROTECT- Progressive Resistance Training Exercise and Crohn's Disease Trial	
SPONSOR: University of Northumbria at Newcastle	CHIEF INVESTIGATOR: Dr Garry Tew

Adverse Event OR Serious Adverse Event

Initial OR Follow-up no _____

Participant identification number: Today's Date: ____/____/_____

Participant DoB: ____/____/_____ Male Female

Main Event	Outcome

Location and Description of event:

Start date: / / Duration if less than 24 hours

Stop date: / / (hrs:mins):

Classification of Serious Adverse Event (please cross one box only):

- | | | |
|--|--|--|
| <input type="checkbox"/> Death | <input type="checkbox"/> Prolonged hospitalisation | <input type="checkbox"/> Life Threatening |
| <input type="checkbox"/> Persistent or significant disability/incapacity | <input type="checkbox"/> Required hospitalisation | <input type="checkbox"/> Congenital anomaly/birth defect |
| <input type="checkbox"/> Other medically important condition | | |

Please state outcome of event at time of this report

Resolved

Date resolved

Resolved with sequelae (specify below & give date)

Ongoing with sequelae (specify below)

Ongoing

Died

Date of death:

/ /

Cause of death

Action taken:

None

Therapy prescribed/ other likely action

Study treatment interrupted/ halted

Discontinued treatment

Other (please specify):

Relationship of event to any of the research procedures

Not related

Unlikely to be related

Possibly related

Probably related

Definitely related

Is this event expected?

Yes

No

Researcher's name

Researcher's signature

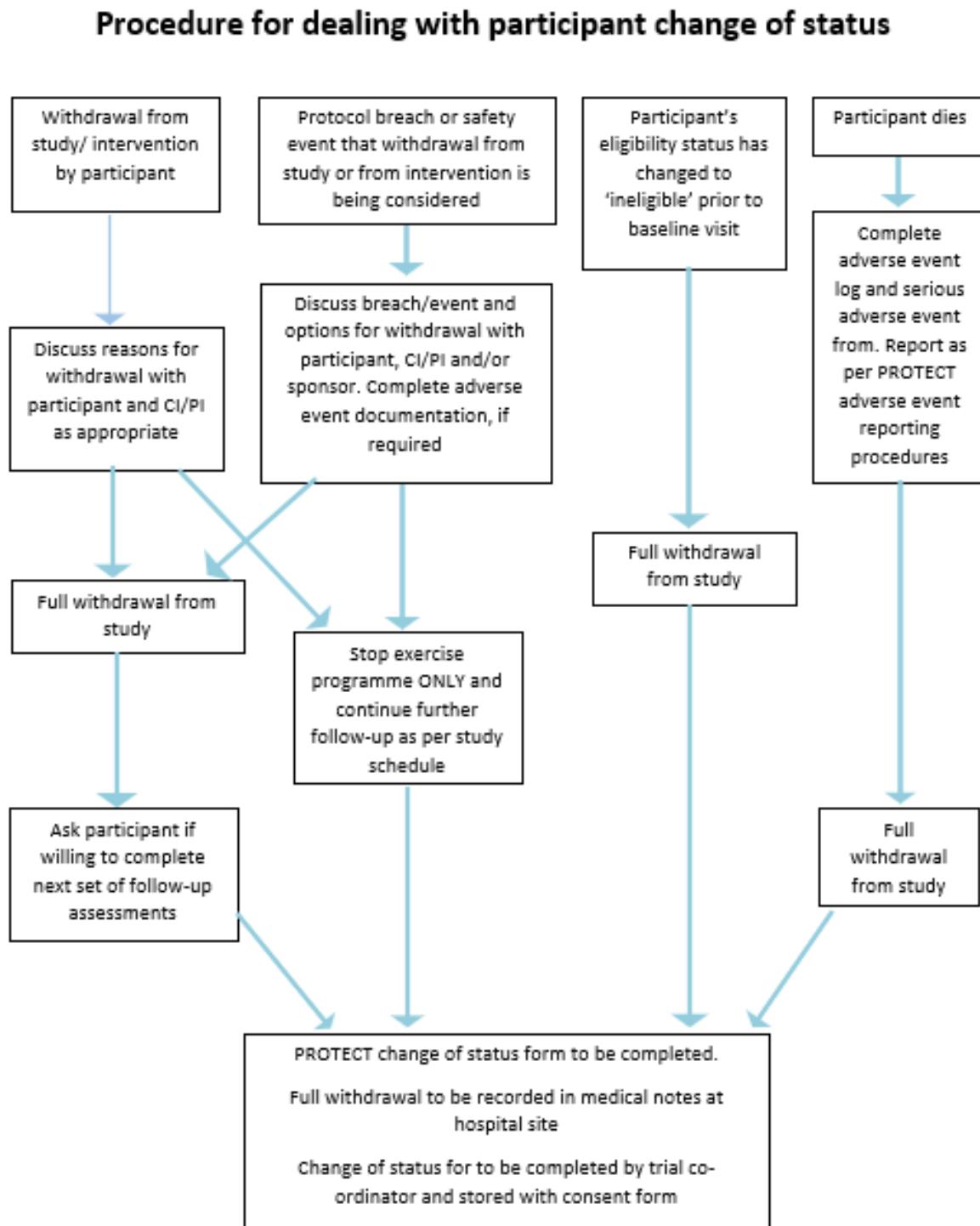
Date (dd/mm/yyyy)

CI or delegated medic- name

CI or delegated medic signature

Date (dd/mm/yyyy)

Appendix 4m: Participant change of status procedure and form



Participant Change of Status Form

STUDY TITLE: PROTECT- Progressive Resistance Training Exercise and Crohn's Disease Trial	SPONSOR: University of Northumbria at Newcastle	CHIEF INVESTIGATOR: Dr Garry Tew
---	--	---

Please complete this form when there is a change in the status of a participant

Participant identification number:

Date of change in status: / /
DAY MONTH YEAR

Reason(s) for change in patient follow-up (cross the appropriate box):

- Participant is being withdrawn from exercise training and agrees to further follow up

Participant is being fully withdraw from the study

Patient agrees to complete next study visit: Yes _____ No _____

Participant eligibility status has changed prior to baseline visit:

Participant has died

A serious adverse event form has been completed: Yes No

Date of death / /
 DAY MONTH YEAR

Please provide further information for change in status:

Name of person completing form: _____

Signature of person completing form:

Date: / /

Appendix 6a: Recruitment poster



Participants WANTED!

To assess **Bone Mineral Density (DXA)** and
Muscle Function measurements



Why?

To assess bone and muscle health and evaluate possible differences between Crohn's disease patients and healthy participants.

What's involved:

- 2 Assessment visits (approx. 1 hr each), 7 days apart. Both involving:
 - A bone mineral density scan (DXA) of your hip and spine
 - A muscle strength test on both arms and legs
 - A muscle endurance test on upper and lower extremities

Who? You can take part if:

- You are over 18
- You are healthy: have no medical conditions that can cause or contribute to bone and muscle deficiencies. *If unsure contact the researcher below*
- You are not currently pregnant
- You have no history of falls or poor mobility
- You participate in no more than 2 sessions of resistance exercise a week
- You have not previously taken any steroid or anti-inflammatory medication lasting longer than 3 months

This study has received ethical approval from the Faculty of Health and Life Sciences Ethics Committee at Northumbria University

What Next?

For more information or you are interested in taking part, please contact katherine.jones@northumbria.ac.uk and arrange your 2 visits at a time and day convenient for you.

Appendix 6b: Participant information sheet



Bone mineral density and muscle function in adults with inactive and mildly active Crohn's disease: A case control study

PARTICIPANT INFORMATION SHEET

You have been invited to take part in a research study. Before you decide whether or not to participate it is important for you to understand why the research is being carried out and what it will involve.

Please take time to read the information carefully, discuss it with others and ask any questions you may have.

1. What is the purpose of the study?

We are inviting healthy participants to take part in this research study to enable us to assess bone and muscle biomarkers and possible differences between a healthy population in comparison to Crohn's disease patients. Crohn's disease (CD) is an autoimmune lifelong disorder in which parts of the digestive system become inflamed and ulcerated causing abdominal pain, diarrhoea, fatigue, anaemia and weight loss. These symptoms are traditionally maintained with medical and surgical treatments, however problems outside the digestive system such as reduced bone and muscle health continue to reduce a person's quality of life. It is thought that up to 60% of CD patients have a depletion in muscle mass, muscle strength and endurance, factors which are strongly associated with the onset of osteopenia and osteoporosis, skeletal disorders characterised by weakening of the bones.

Therefore, it is important to assess bone and muscle health in Crohn's disease patients and evaluate possible differences between the patient groups and healthy participants to identify concerns before the diagnosis of extraintestinal complications such as osteoporosis or osteopenia. In addition to assessing the prevalence, it's also important to determine the test-retest reliability of the measures determining bone mineral density and muscle function to ensure consistency and reproducibility.

2. Who can take part?

Healthy male and female participants who match according to BMI group and physical activity habits to data previously obtained from patients with Crohn's disease. However, you should not take part if:

- You are under the age of 18

- Have a medical condition or currently take any medication (anti-inflammatory or steroid drugs) that can cause or contribute to bone and muscle deficiencies. Please contact the researcher if you are unsure about a specific condition
- Pregnant
- Currently participating in 2 or more sessions a week of resistance exercise (i.e. weight training)
- You have a history of falls or have poor mobility
- Currently undergoing radiation therapy or had a significant amount of radiation in the last 12 months
- Have previously taken anti-inflammatory or steroid medication for 3 months or more

3. Do I have to take part?

You are under no obligation to take part and you will not experience any loss of benefit or penalty if you choose not to participate, this information sheet is to help you make that decision. If you do decide to take part you are free to withdraw at any time with no reason required, just inform the researcher (contact details below) as soon as possible. They will facilitate your withdrawal and discuss how you would like your data to be treated. Unless you object the data collected up to that point of treatment will still be kept, as this is valuable to the study however as all data is anonymous your individual data will not be identifiable in any way.

4. What would taking part involve?

After you have consented to participate in this study you will be required to complete a short online form lasting approximately 5 minutes. Information such as your age, gender, weight, height and email address will be required and you will be asked to complete a short questionnaire based on your physical activity habits in the previous week.

After completion, eligible participants will be contacted via the email address provided and invited to book in for two assessment visits, a week apart of each other at your soonest convenience (i.e Monday 16th and Monday 23rd). Details of each visit can be found in the table below. Participants who aren't eligible will also be contacted via the email address provided to inform them that their participation at present is not required. However, ineligible participants may be contacted up to 3 months after initial interest if this changes.

Visit One	Location: Northumbria University Northumberland Building, Floor 4	Time: 1hr 45 mins
During this you will be asked to answer a series of questions, complete a questionnaire and perform a series of physical assessments:		
<ol style="list-style-type: none"> 1. Demographical information- smoking history, past medical history, past surgical history, fracture history and a record of any medications you are taking will be collected 2. Height and weight 3. Heart rate and blood pressure 4. Questionnaire- Quality of Life and Fatigue 5. Bone Mineral Density- lying flat and still on an X-ray table while a scanning arm is passed over your body (Figure 1) 6. Muscle Strength- Warm up session. Strapped (like a seatbelt) onto a chair and required to kick your leg and arm at different speeds with force applied (Figure 2) 		

- | |
|---|
| <p>7. Grip Strength- Squeeze a handle with as much force as you can (Figure 3)</p> <p>8. Muscle endurance- complete as many chair rises to standing in 30 seconds. Complete as many arm curls in 30 seconds</p> |
|---|

Visit Two	Location: Northumbria University Northumberland Building, Floor 4	Time: 1hr 45 mins
<p>During this you will be asked to answer a series of questions, complete a questionnaire and perform a series of physical assessments:</p> <ol style="list-style-type: none"> 1. Demographical information update- any changes to medications or any medical events since the previous visit 2. Height and weight 3. Heart rate and blood pressure 4. Questionnaire- Quality of Life and Fatigue 5. Bone Mineral Density- lying flat and still on an X-ray table while a scanning arm is passed over your body (Figure 1) 6. Muscle Strength- Warm up session. Strapped (like a seatbelt) onto a chair and required to kick your leg and arm at different speeds with force applied (Figure 2) 7. Grip Strength- Squeeze a handle with as much force as you can (Figure 3) 8. Muscle endurance- complete as many chair rises to standing in 30 seconds. Complete as many arm curls in 30 seconds 		



Figure 1. Bone mineral density



Figure 2. Muscle Strength



Figure 3. Grip Strength

5. Are there any expenses of payments involved?

Unfortunately there are no payments involved for taking part in this research study and we are unable to reimburse you for any travel expenses incurred. However, free on-site car parking is available at the University of Northumbria at Newcastle.

6. If I decide to participate, will my GP be notified?

Your named general practitioner, with your consent and for your safety will be notified if your results are indicative of requiring treatment. If any serious health problems are detected and require immediate attention, you will be referred to the nearest hospital.

7. What are the possible benefits, disadvantages, risks or discomfort of taking part?

The findings of this study may have an impact upon the screening guidelines for CD patients with low bone density and muscle deficiencies in the UK, while increasing physician awareness.

All the procedures used throughout this study are well established clinical assessment measures which are routinely used throughout research and health care. However, like with many procedures there

are very small risks involved. The bone mineral density assessment (DEXA scan) uses x-rays to produce pictures and information from of inside the body. If you take part in this study you will have two of these scans which will be extra to those that you would have if you did not take part. The x-rays are a form of ionising radiation which can cause cell damage that may after many years or decades turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about half of the people in the population at some point in their life. Taking part in this study will add only a very small chance of this happening to you.

You may also experience muscular fatigue or soreness as a result from the muscular performance testing, however, this is a completely normal short term experience but may cause slight discomfort.

The researcher is trained in first aid procedures.

8. How will my information be kept confidential? How will my data be stored?

All data collected in this study will be fully anonymised using numerical coding to maintain confidentiality. Only the researcher will have access to any identifiable information which will be kept separate from any data that can identify you. All data will be stored on a password-protected computer in accordance with university guidelines and the Data Protection Act (2018). At no point will your personal information or data be revealed unless forced to do so by the courts.

9. What if I change my mind about taking part during the study? Can I withdraw?

If you do decide to take part during or after the study you are still free to withdraw at any time with no reason required. Inform the researcher as soon as possible (contact details provided below) and they will facilitate your withdrawal and discuss how you would like your data to be treated. We would like to use all your data collected up to this point to help with analysis, however if you would prefer your data not be used you may request it to be removed from the study. If you do complete the study, after one month of competition it may not be possible to withdraw your individual data as the results may have already been published. However, as all data are anonymous, your individual data will not be identifiable in any way.

11. What will happen to the results of the study?

The results will be used in the formation of a PhD thesis that will be examined as part of a postgraduate degree. Occasionally, some results might be reported in a scientific journal or presented at a research conference, however the data will always remain anonymous unless specific consent is obtained beforehand. Findings may also be shared with other organisations/ institutions that have been involved with the study. A summary of the study's findings can be provided to you if the researcher is emailed, details found above and at the end of this document.

All information and data gathered during this research will be stored in line with the Data Protection Act (2018).

12. Who is funding the study?

This study has not received any funding.

13. What happens if I have a complaint?

If you are unhappy about the way you have been approached or treated before, during or after your participation, the researcher should be contacted. However, if you feel this is not appropriate you should contact the Chair of ethics for Sport, Exercise and Rehabilitation Dr Nick Neave, Email: nick.neave@northumbria.ac.uk.

14. Who has reviewed this study?

This study has received full ethical approval from the organisation Northumbria university, Department of Sport, Exercise and Rehabilitation postgraduate ethics committee. If you require confirmation of this please contact the chair of ethics committee using the details below, please state the full title of this project and the principle investigator.

Dr Nick Neave

Faculty Director of Ethics and Chair of Faculty Research Ethics Committee

Northumbria University

Northumberland Road

Newcastle-upon-Tyne

NE1 8ST

nick.neave@northumbria.ac.uk

Contact Information

For further information please contact:

Katherine Jones (Study Co-ordinator):

Email: katherine.jones@northumbria.ac.uk, **Tel:** 07434668536

◦ **Chief Investigator:** Dr Garry Tew,

Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle

Email: garry.tew@northumbria.ac.uk

◦ **Academic Supervisor:** Dr Katherine Baker,

Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle

Email: katherine.baker@northumbria.ac.uk

Appendix 6c: Participant eligibility form

Eligibility Information <i>(delete or highlight as appropriate)</i>			
1. Please state your date of birth as MM/YYYY (e.g. 11/1980)			
2. What is your gender?	MALE	FEMALE	
3. How tall are you (e.g. 5ft 9"/ 179.8cm) <i>please be as accurate as possible</i>			
4. How much do you weigh (e.g. 9st 4lbs/ 59.6kg) <i>please be as accurate as possible</i>			
5. Is there a possibility you may be pregnant?	N/A	YES	NO
6. Have you or are you currently undergoing radiation therapy?	YES	NO	
7. Have you had a significant radiation dose in the last 12 months?	YES	NO	
8. Have you had a major bone fracture that has no healed correctly?	YES	NO	
9. Do you have any medical implants? E.g. plates, pins	YES	NO	

Appendix 6d: Informed consent



**Northumbria
University**
NEWCASTLE
Faculty of Health and Life Sciences

Informed Consent Form Version 1.0: 01/07/2018

Participant ID Number:.....

Bone mineral density and muscle function in adults with inactive and mildly active Crohn's disease: A case control study

INFORMED CONSENT FORM

(Initial)

1. I confirm that I have read and understood the participation information sheet provided for the above study. I have had the opportunity to consider and discuss the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and I am free to withdraw from the study at any time, without having to give any reason and without prejudice
3. I understand that any personal information collected during this study will be anonymised and may be used to support other future research
4. I agree to my General Practitioner (GP) being informed of any results that are indicative of requiring treatment
5. I understand that my participation in this research study involves exposure to radiation in addition to what I may receive as part of my standard care
6. I understand that if I would like to receive feedback on the overall results of the study I must contact the researcher at: katherine.jones@northumbria.ac.uk
7. I agree to take part in the above study

.....
Name of Participant

.....
Date

.....
Signature

Statement by the person taking consent

I can confirm that the participant was given the information sheet and the opportunity to ask any questions or queries related to this study. All the questions asked by the participant have been answered correctly and to the best of my ability the participant understands what they are required to do. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

.....
Name of person taking consent

.....
Date

.....
Signature

Appendix 6e: Case control study case report form

CRF Version 1.0: 10/11/2018



**Northumbria
University**
NEWCASTLE

Faculty of Health and Life Sciences

CASE CONTROL STUDY

Case Report Form

Participant ID:

Visit Date: / /
DAY MONTH YEAR

Section A: Demographical Data

PERSONAL DETAILS

1. Date of birth / / YEAR
DAY MONTH YEAR

2. Gender Male Female

LIFESTYLE FACTORS

3. Smoking status Current Previous Never

How many _____

Stopped for _____

How many _____

4. Alcohol intake (units per week)



5. On average over the last month, how many resistance-type exercise sessions (e.g weight lifting/ bearing- free weights and weight machines) has the patient undertaken?

EMPLOYMENT HISTORY

6. Primary employment status

Employed
 Self-employed
 Unemployed
 Student
 Retired
 Any other employment group (*please specify*)

If employed: Full time

Part time

CURRENT MEDICATIONS

Provide details in the table below of all the prescribed medication, over-the-counter medication and supplements/ nutraceuticals that the participant is currently taking.

Medication Name	Dose and Route	Start Date (dd/mm/yyyy)

STERIOD USE

7. Have you ever taken any steroids- anabolic or corticosteroids?

YES NO

8. If 'YES', complete the table below

Steroid Type and Form (Tablet, IV, Inhaler)	Reason for Steroid Use	When	How Long for

MEDICAL CONDITIONS

9. Medical History:

.....

.....

.....

.....

SURGICAL TREATMENT

10. Has the participant ever had any surgery? YES NO

11. If 'YES', please indicate the type of surgery and date of the procedure:

Procedure	Date (Format mm/yyyy)

FRACTURE HISTORY

1. Has the participant had any fractures? YES NO

2. If 'YES', please indicate the fracture, date and treatment

Fracture Location	Date (Format mm/yyyy)	Treatment (Cast, Splint) and for how long

Section B: Physical Measurements

1. Body Mass (kg to 1 decimal place): .

2. Stature (cm to 1 decimal place): .

3. Resting Heart Rate (beats/minute):

4. Resting Blood Pressure (mmHG): /
SYSTOLIC DIASTOLIC

Use this space for any other comments about the physical measurements.

Section C: Questionnaires

1. Has the participant completed the EQ-5D-5L? Yes No

2. Has the participant completed the IBD-F? Yes No

If 'No' to Q1-5, state the reason(s) in the box below. Use this space for any other comments about the questionnaires.

Section D: Muscle Performance Testing

Follow the study-specific procedure for muscle performance testing and complete the assessment testing data collection sheet contained within this case report form.

1. Has the patient completed the lower muscle strength test? Yes No

2. Has the patient completed the upper muscle strength test? Yes No

3. Has the patient completed the 30's chair stand test? Yes No

4. Has the patient completed the 30's arm curl test? Yes No

5. Has the patient completed the grip strength? Yes No

If 'No', state the reason(s) in the box below. Use this space for any other comments about muscle performance testing.

Section E: Bone Health Assessment

Follow the study-specific procedure for muscle performance testing and complete the exercise testing data collection sheet contained within this case report form.

1. Has a DXA scan on the patient been carried out?

Yes

No

If 'No', state the reason(s) in the box below. Use this space for any other comments about the bone health assessment.

Section F: Check List and Investigator Sign-off

1. Have all sections of this case report been completed?

Yes

No

2. Any adverse events reported, or has the participant confirmed that no adverse events have occurred?

Yes

No

3. Form completed by:

Signature:

Print name:

Date: / /

DAY

MONTH

YEAR

Use the box below for any further comments regarding this visit.

Appendix 6f: Backwards stepwise logistic regression model for lumbar spine

Table 7.

Summary of backward stepwise logistic regression model for Lumbar Spine^a

Predictors	B	Std. Error	Beta	t	Sig	Adj R ²
Step 1						.373
Constant	.051	.104		.489	.628	
Age	.001	.001	.167	.894	.377	
Alcohol Intake	-.001	.002	-.040	-.285	.778	
D Behaviour	.015	.014	.138	1.058	.297	
D Duration ^b	-.054	.031	-.317	-1.718	.094	
PA Habits ^c	.067	.022	.407	2.988	.005	
Gender	-.077	.022	-.491	-3.467	.001	
Smoking Status	-.035	.019	-.233	-1.863	.070	
Surgical History	.018	.014	.174	1.248	.220	
Step 2						.388
Constant	.056	.101		.554	.583	
Age	.001	.001	.145	.862	.394	
D Behaviour	.015	.014	.137	1.061	.295	
D Duration ^b	-.052	.030	-.303	-1.725	.092	
PA Habits ^c	.064	.020	.391	3.178	.003	
Gender	-.075	.021	-.477	-3.638	.001	
Smoking Status	-.036	.018	-.240	-1.985	.054	
Surgical History	.018	.014	.171	1.246	.220	
Step 3						.392
Constant	.082	.096		.854	.398	
D Behaviour	.011	.013	.104	.847	.402	
D Duration ^b	-.034	.022	-.201	-1.554	.128	
PA Habits ^c	.061	.020	.372	3.082	.004	
Gender	-.077	.020	-.489	-3.757	.001	
Smoking Status	-.039	.017	-.267	-2.284	.028	
Surgical History	.019	.014	.189	1.399	.170	
Step 4						.396
Constant	.101	.093		1.088	.283	
D Duration ^b	-.033	.022	-.196	-1.521	.136	
PA Habits ^c	.063	.020	.385	3.234	.002	
Gender	-.081	.020	-.518	-4.152	.000	
Smoking Status	-.040	.017	-.269	-2.313	.026	
Surgical History	.018	.014	.177	1.322	.193	
Step 5						.385
Constant	.156	.084		1.862	.070	
D Duration ^b	-.046	.020	-.273	-2.350	.024	
PA Habits ^c	.062	.020	.375	3.125	.003	
Gender	-.074	.019	-.471	-3.904	.000	
Smoking Status	-.038	.017	-.259	-2.210	.033	

D, Disease; PA, Physical Activity; Adj, Adjusted; P-values significant at the <0.05 threshold are in bold

^aComputed as the total bone mineral density (g/cm²) at the lumbar spine (L2-L4) (logarithmic transformed)

^bPresented as total months (logarithmic transformed)

^cCombined total physical activity minutes, computed as the sum of leisure time + work time scores -/+ typical week minutes (logarithmic transformed)

Appendix 6g: Backwards stepwise logistic regression model for femoral neck

Table 8.

Summary of backward stepwise logistic regression model for Femoral Neck

Predictors	B	Std. Error	Beta	t	Sig	Adj R ²
Step 1						.280
Constant	.894	.206		4.331	.000	
Age	-.001	.002	-.136	-.680	.500	
Alcohol Intake	.004	.004	.131	.866	.392	
D Behaviour	.035	.028	.174	1.246	.220	
D Duration ^b	-.079	.062	-.250	-1.261	.215	
PA Habits ^c	.084	.044	.277	1.900	.065	
Gender	-.096	.044	-.330	-2.176	.036	
Smoking Status	-.013	.037	-.047	-.352	.727	
Surgical History	.008	.029	.041	.278	.783	
Step 2						.297
Constant	.917	.188		4.880	.000	
Age	-.001	.002	-.130	-.662	.512	
Alcohol Intake	.004	.004	.134	.899	.374	
D Behaviour	.034	.028	.172	1.248	.220	
D Duration ^b	-.086	.057	-.271	1.504	.141	
PA Habits ^c	.084	.044	.275	1.911	.063	
Gender	-.093	.042	-.319	-2.208	.033	
Smoking Status	-.012	.036	-.044	-.334	.740	
Step 3						.313
Constant	.884	.159		5.554	.000	
Age	-.001	.002	-.110	-.595	.555	
Alcohol Intake	.004	.004	.123	.857	.396	
D Behaviour	.035	.027	.177	1.306	.199	
D Duration ^b	-.090	.055	-.284	-1.631	.111	
PA Habits ^c	.085	.043	.279	.1966	.056	
Gender	-.095	.041	-.327	-2.317	.026	
Step 4						.323
Constant	.854	.150		5.710	.000	
Alcohol Intake	.003	.004	.091	.687	.496	
D Behaviour	.040	.026	.199	1.540	.131	
D Duration ^b	-.113	.039	-.357	-2.918	.006	
PA Habits ^c	.093	.041	.306	2.289	.027	
Gender	-.096	.041	-.331	-2.364	.023	
Step 5						.332
Constant	.861	.148		5.809	.000	
D Behaviour	.038	.026	.190	1.485	.145	
D Duration ^b	-.114	.038	-.360	-2.964	.005	
PA Habits ^c	.102	.038	.334	2.652	.011	
Gender	-.106	.038	-.362	-2.764	.008	
Step 6						.313
Constant	.910	.146		6.214	.000	
D Duration ^b	-.108	.039	-.341	-2.784	.008	
PA Habits ^c	.110	.039	.360	2.843	.007	
Gender	-.123	.037	-.423	-3.350	.002	

D, Disease; PA, Physical Activity; Adj, Adjusted; P-values significant at the <0.05 threshold are in bold

^aPresented as total months (logarithmic transformed) ^b Combined total physical activity minutes, computed as the sum of leisure time + work time scores -/+ typical week minutes (logarithmic transformed)

Appendix 6h: Backwards stepwise logistic regression model for greater trochanter

Table 9.

Summary of backward stepwise logistic regression model for Greater Trochanter^a

Predictors	B	Std. Error	Beta	t	Sig	Adj R ²
Step 1						.078
Constant	.578	.186		3.109	.004	
Age	.000	.002	.040	.177	.861	
Alcohol Intake	-.002	.004	-.096	-.562	.578	
D Behaviour	.016	.025	.098	.623	.537	
D Duration ^b	-.057	.056	-.229	-1.021	.314	
PA Habits ^c	.094	.040	.389	2.355	.024	
Gender	-.068	.040	-.295	-1.720	.094	
Smoking Status	.013	.033	.060	.393	.696	
Surgical History	.016	.026	.102	.607	.547	
Step 2						.101
Constant	.589	.173		3.414	.002	
Alcohol Intake	-.002	.004	-.084	-.543	.590	
D Behaviour	.014	.024	.090	.605	.549	
D Duration ^b	-.050	.039	-.201	-1.277	.209	
PA Habits ^c	.092	.037	.379	2.455	.019	
Gender	-.068	.039	-.294	-1.734	.091	
Smoking Status	.011	.031	.051	.361	.720	
Surgical History	.016	.025	.106	.639	.527	
Step 3						.120
Constant	.612	.158		3.868	.000	
Alcohol Intake	-.002	.004	-.079	-.519	.607	
D Behaviour	.014	.024	.090	.606	.548	
D Duration ^b	-.050	.039	-.200	-1.286	.206	
PA Habits ^c	.092	.037	.381	2.492	.017	
Gender	-.066	.039	-.286	-1.722	.093	
Surgical History	.017	.025	.109	.666	.509	
Step 4						.136
Constant	.613	.157		3.908	.000	
D Behaviour	.015	.023	.097	.662	.511	
D Duration ^b	-.051	.039	-.202	-1.312	.197	
PA Habits ^c	.086	.035	.355	2.477	.017	
Gender	-.059	.036	-.256	-1.659	.105	
Surgical History	.015	.024	.097	.607	.547	
Step 5						.149
Constant	.663	.133		4.979	.000	
D Behaviour	.014	.023	.087	.606	.548	
D Duration ^b	-.061	.034	-.244	-1.775	.083	
PA Habits ^c	.085	.034	.351	2.469	.018	
Gender	-.054	.034	-.232	-1.567	.125	
Step 6						.161
Constant	.681	.129		5.286	.000	
D Duration ^b	-.059	.034	-.235	-1.734	.090	
PA Habits ^c	.088	.034	.363	2.596	.013	
Gender	-.060	.032	-.260	-1.863	.069	

D, Disease; PA, Physical Activity; Adj, Adjusted; P-values significant at the <0.05 threshold are in bold

^aPresented as total months (logarithmic transformed) ^bCombined total physical activity minutes, computed as the sum of leisure time + work time scores -/+ typical week minutes (logarithmic transformed)

Appendix 7a: ACSM absolute contraindications to exercise testing

American College of Sports Medicine (ACSM) exercise contraindications

- Recent significant change in resting electrocardiogram which may suggest significant ischemia, myocardial infarction or other acute cardiac event
- Unstable angina
- Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
- Suspected or known dissecting aneurysm
- Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands

Appendix 7b: Recruitment letter

[Version one- Sent to patients on the IBD database]



The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Resistance training in adults with Crohn's disease

Chief Investigator: Dr Garry Tew

Dear Patient

We are undertaking a research study that aims to investigate the effects of a 6 month home based exercise programme on fatigue, muscle strength, bone mineral density, quality of life and disease activity in adults with inactive or mildly active Crohn's disease.

You have been identified as being potentially suitable for this study having previously consented to be contacted regarding future IBD research through the IBD database at Newcastle Hospitals.

Enclosed is a participant information sheet explaining the study in further detail, please take your time to read this information. If you are interested in participating please complete the disease activity diary enclosed 7 days before your next gastroenterology appointment.

If you have any questions or would like to discuss anything further please contact Katherine Jones (Study Co-ordinator) at katherine.jones@northumbria.ac.uk or on 07434668536 (Mon-Sat 9am-6pm).

PLEASE NOTE: Choosing not to participate in this study will **NOT** affect your existing gastroenterology appointment or the quality of care you will receive.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Garry Tew".

Dr Garry Tew, PhD, CSci

Chief Investigator

[Version two- Sent to patients identified in clinics]



The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Resistance training in adults with Crohn's disease

Chief Investigator: Dr Garry Tew

Dear Patient

We are undertaking a research study that aims to investigate the effects of a 6 month home based training programme on fatigue, muscle strength, bone mineral density, quality of life and disease activity in adults with inactive or mildly active Crohn's disease.

You have been identified as being potentially suitable for this study following your recent gastroenterology appointment at Newcastle Hospitals.

Enclosed is a participation information sheet explaining the study in further detail, please take your time to read this information. If you have any questions or would like to discuss anything further please contact Katherine Jones (Study Co-ordinator) at katherine.jones@northumbria.ac.uk or on 07434668536 (Mon-Sat 9am-6pm).

Yours sincerely,

A handwritten signature in black ink, appearing to read "Garry Tew".

Dr Garry Tew, PhD, CSci

Chief Investigator

Appendix 7c: Participant information sheet



The Newcastle upon Tyne Hospitals **NHS**
NHS Foundation Trust

Resistance training in adults with Crohn's disease

PARTICIPANT INFORMATION SHEET

IRAS ID: 226369

Centre Number:.....

Study Number:.....

You have been invited to take part in a research study. Before you decide whether or not to participate it is important for you to understand why the research is being carried out and what it will involve.

Please take time to read the information carefully, discuss it with others and ask any questions you may have.

1. What is the purpose of the study?

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract causing symptoms such as fatigue, abdominal pain, blood loss and diarrhoea. These symptoms are traditionally maintained with medical and surgical treatments, however problems with reduced muscle and bone health persist which can be just as debilitating as CD. Although not part of routine treatment, regular exercise has demonstrated improvements in fatigue, disease activity, psychological health, quality of life and bone and muscle health. Despite these potential benefits, the role of exercise in CD has not been well studied and remains poorly understood with research primarily focusing on the potential of aerobic exercise programmes (e.g. running, cycling).

However, growing evidence in other chronic conditions has shown that resistance (strength) training may have a better effect on bone health, muscle strength and endurance than aerobic exercise. Despite this, little information exists around the potential of resistance training in CD patients. With the debilitating nature of this disease, further research is needed as these findings may have a significant impact upon management in the CD population by providing physical activity solutions instead of or alongside current treatments.

Therefore, the purpose of this study is to investigate the effects of a 6 month resistance training programme on muscle function, bone mineral density, fatigue, quality of life and disease activity in adults with CD.

2. Why have I been invited to take part?

You have been invited to participate in this research study as you have been diagnosed with CD for longer than 4 weeks and are currently in a state of inactive or mildly active disease. However, you should *not* partake in this study if:

- You have any other medical conditions that would make it unsuitable and unsafe to undertake resistance exercise
- You are pregnant or planning pregnancy within the next 6 months
- You currently participate in more than 2 sessions a week of resistance exercise, such as weight lifting
- You are currently participating in another clinical trial where the two trials may influence each other (if unsure please discuss with us)
- You are under the age of 16
- You have a moderate or severely active CD
- You have had or are planned to have major surgery within the first 6 months of the study
- Your medications have not been stable for at least 4 weeks prior to enrolment

3. Do I have to take part?

You are under no obligation to take part and you will not experience any loss of benefit or penalty if you choose not to participate, this information sheet is to help you make that decision. If you do decide to take part you are free to withdraw at any time with no reason required, just inform the researcher (contact details below) as soon as possible. They will facilitate your withdrawal and discuss how you would like your data to be treated. Unless you object the data collected up to that point of treatment will still be kept, as this is valuable to the study however as all data is anonymous your individual data will not be identifiable in any way. If you do not wish to take part in this study it will not affect the ongoing standard care you receive in any way from the NHS.

4. What would taking part involve?

After you read this information sheet if you are happy to take part, contact Katherine Jones, study co-ordinator on 07434668536 (Mon-Sat 9am-6pm). The study co-ordinator will invite you to attend a screening visit and ask you to keep a disease activity diary for 7 days, recording number of liquid stools, abdominal pain (between none and severe) and general well-being (between well and terrible).

Screening Visit	Location: Freeman Hospital/ RVI	Time: 1 Hour
You will be asked to bring your 7 day disease activity diary to this screening. During this eligibility screening visit the study will be explained in more detail and any questions you may have will be answered. If you're happy with this, you will be asked to sign a consent form indicating you understand the study, what is involved and have had the opportunity to ask questions. A copy of this consent form will be given to you along		

with this participant information sheet. A direct care team member will then assess eligibility in more detail and medical records may need to be accessed:

1. Demographical information (age, gender, smoking history) and information on your medical history, surgical history and medications will be collected
2. A physical examination of your abdomen- consisting of a visual examination (inspection), listening to bowel sounds (auscultation) and feeling for abdominal tenderness (palpations)
3. You will also be required to provide a stool and blood sample, unless this has been performed within the previous 4 weeks

If the results from the screening visit confirm you are eligible to take part in the study, you will be telephoned and invited to attend a baseline visit. If it is confirmed that you are not eligible you will be contacted letting you know your participation is not required.

Baseline Visit	Location: Northumbria University	Time: 1 hr 30 mins
During this visit, you will be asked to complete a series of questionnaires and perform a series of physical assessments:		
<ol style="list-style-type: none"> 1. Height 2. Weight 3. Heart rate and Blood pressure 4. Questionnaire- Fatigue 5. Questionnaire- Quality of Life (x2) 6. Questionnaire- Physical Activity 7. Bone mineral density- lying flat and still on an X-ray table while a scanning arm is passed over your body (Figure 1) 8. Muscle strength- 10 minute warm up session. Strapped (like a seatbelt) onto a chair and required to kick your leg and arm at different speeds with force applied (Figure 2). 9. Grip strength- squeeze a handle with as much force as you can (Figure 3) 10. Muscle endurance- complete as many chair rises to standing in 30 seconds. Complete as many arm curls in 30 seconds 		



Figure 1. Bone mineral density



Figure 2. Muscle Strength



Figure 3. Grip Strength

After completing the baseline assessment visit you will have an equal chance of being assigned to one of two groups, however both groups will undergo the same measurements and are required to attend the two assessment visits:

- Group One: Half of patients will be enrolled to receive usual care plus a 6 month resistance training programme. Patients allocated to this group will be invited to complete three sessions a week for 60 minutes on non-consecutive days (e.g Monday, Wednesday and Friday). The majority of these sessions will be unsupervised and carried out in the comfort of your own home with the equipment provided. However to monitor your progress and to provide you with support, 12 supervised exercise sessions will be conducted at the University of Northumbria at Newcastle over the 26 weeks. These supervised sessions will gradually decrease over time. A breakdown of these supervised and unsupervised sessions is illustrated below:

Week	Supervised Session	Unsupervised Session	Total	Week	Supervised Session	Unsupervised Session	Total
1	2	1	3	14	1*	2 or 3	3
2	2	1	3	15		2 or 3	3
3	1	2	3	16		2 or 3	3
4	1	2	3	17		2 or 3	3
5	1*	2 or 3	3	18	1*	2 or 3	3
6		2 or 3	3	19		2 or 3	3
7	1*	2 or 3	3	20		2 or 3	3
8		2 or 3	3	21		2 or 3	3
9	1*	2 or 3	3	22	1*	2 or 3	3
10		2 or 3	3	23		2 or 3	3
11		2 or 3	3	24		2 or 3	3
12		2 or 3	3	25		2 or 3	3
13	Assessment Visit	3	3	26	Assessment Visit	3	3

* You decide which week you would like to schedule your supervised session, at your soonest convenience.

- Group Two: Half of patients will be enrolled to receive usual care from The Newcastle Upon Tyne Hospitals NHS Foundation Trust. Participants allocated to this group will be required to attend assessment visits at week 13 and 26 of the study, details below.

Week 13	Assessment Visit	Location: Northumbria University	Time: 1 Hour
Similar to the baseline visit above, height, weight, heart rate and blood pressure, fatigue, quality of life, physical activity, muscle strength, grip strength and muscle endurance will be assessed. In addition:			
<ol style="list-style-type: none"> 1. Information on your medications will be updated 2. You will also be questioned regarding any medical events 3. Questionnaire- physical activity enjoyment 			

Prior to the final assessment visit you will be asked to keep a disease activity diary for 7 days, recording number of liquid stools, abdominal pain (between none and severe) and general well-being (between well and terrible).

Week 26	Assessment Visit	Location: Freeman Hospital/RVI	Time: 1 hr
You will be asked to bring your 7 day disease activity diary to this assessment. Similar to the screening visit above. A direct care team member will assess: <ol style="list-style-type: none">1. Information on your medical history and medications will be collected2. A physical examination of your abdomen- consisting of a visual examination (inspection), listening to bowel sounds (auscultation) and feeling for abdominal tenderness (palpations)3. You will also be required to provide a stool and blood sample, unless this has been performed within the previous 4 weeks			

Week 26	Assessment Visit	Location: Northumbria University	Time: 1 hr 45 mins
Similar to the baseline and assessment visit above, height, weight, fatigue, quality of life, physical activity, bone mineral density, muscle strength, grip strength, muscle endurance and physical activity enjoyment will assessed.			

Following these assessments we would also like to contact you regarding some follow up questions about your experience in the study and your thoughts on the intervention you received. This telephone interview will last approximately 30 minutes.

Following completion of the study, participants in group two will receive another phone call offering an exercise consultation from the researcher. During this call the benefits and guidelines of exercise will be discussed and a personalised action plan for developing and achieving your exercise goals will be established.

5. Are there any expenses or payments involved?

Unfortunately there are no payments involved for taking part in this research study and we are unable to reimburse you for any travel expenses incurred. However participants in group one will be allowed to keep the exercise equipment (e.g. resistance bands) used at home, while participants in group two will be offered a one-to-one exercise consultation, discussing personal goals, guidelines and action plans. In addition, free on-site car parking is available at the University of Northumbria at Newcastle.

6. If I decide to participate, will my GP be notified?

Your general practitioner, with your consent will be notified that you are taking part in this study and for your safety a record will be kept regarding your involvement.

7. What are the possible benefits, disadvantages, risks or discomfort of taking part?

The findings of this study may have a significant impact upon management in the CD population by providing physical activity solutions instead of or alongside current treatments. By participating in this study you will help develop a greater understanding into this disease, raise awareness and encourage further research. As the role of exercise in CD has not been well studied and remains poorly understood, we cannot say what benefits you will gain from taking part or whether you will benefit. However, previous CD studies have demonstrated improvements in bone mineral density, symptoms, psychological health, fatigue and quality of life.

All the procedures used throughout this study are well established clinical assessment measures which are routinely used throughout research and health care. However, like with many procedures there are very small risks involved.

The bone mineral density assessment (DEXA scan) uses x-rays to produce pictures and information from of inside the body. If you take part in this study you will have two of these scans which will be extra to those that you would have if you did not take part. The x-rays are a form of ionising radiation which can cause cell damage that may after many years or decades turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about half of the people in the population at some point in their life. Taking part in this study will add only a very small chance of this happening to you.

You may also experience muscular fatigue or soreness as a result from the muscular performance testing or from the resistance exercise. However, this is a completely normal short term experience but may cause slight discomfort.

For your safety you will be monitored at various points throughout the programme, as mentioned before and at least one researcher will be trained in first aid procedures during all supervised exercise sessions.

8. How will my information be kept confidential? How will my data be stored?

All data collected in this study will be fully anonymised using numerical coding to maintain confidentiality. With exception of the healthcare professionals only the researcher will have access to any identifiable information which will be kept separate from any data that can identify you. In addition, for your safety if clinical measures are indicative of requiring treatment the patients named gastroenterologist and GP will be informed. If any serious health problems are detected and require immediate attention, you will be referred to the nearest hospital. All data will be stored on a password-protected computer in accordance with university guidelines and the Data Protection Act (1998) and destroyed after 2 years following the conclusion of the study. Some results might be reported in a scientific journal, presented at a research conference or shared within other organisations/ institutions, however the data will always remain anonymous unless specific consent is obtained beforehand. At no point will your personal information or data be revealed unless forced to do so by the courts.

9. What if I do not wish to take part?

If you do not wish to take part in this study it will not affect the ongoing standard care you receive in any way from the NHS.

10. What if I change my mind about taking part during the study? Can I withdraw?

If you do decide to take part during or after the study you are still free to withdraw at any time with no reason required. Inform the researcher as soon as possible (contact details provided below) and they will facilitate your withdrawal and discuss how you would like your data to be treated. We would like to use all your data collected up to this point to help with analysis, however if you would prefer your data not be used you may request it to be removed from the study. If you do complete the study, after one month of competition it may not be possible to withdraw your individual data as the results may have already been published. However, as all data are anonymous, your individual data will not be identifiable in any way. The care you receive will not be affected in anyway by your withdrawal.

11. What will happen to the results of the study?

The results will be used in the formation of a PhD thesis that will be examined as part of a postgraduate degree. Occasionally, some results might be reported in a scientific journal or presented at a research conference, however the data will always remain anonymous unless specific consent is obtained beforehand. Findings may also be shared with other organisations/ institutions that have been involved with the study. A summary of the study's findings can be provided to you if the researcher is emailed, details found above and at the end of this document. All information and data gathered during this research will be stored in line with the Data Protection Act (1998) and will be destroyed after 2 years following the conclusion of the study.

12. What if there is a problem?

If a problem occurs before, during or after the study you should contact the researcher who will do their best to answer your queries. If you feel this is not appropriate, a formal complaint can be made through the NHS Complaints Procedure by contacting the local clinical commissioning group (CCG), Tel: 0191 217 2996, Email: ngccg.enquiries@nhs.net.

13. Who is Organising and Funding the study?

This study has been funded by PROcare LTD and the University of Northumbria at Newcastle. The University of Northumbria at Newcastle is responsible for the conduct of the study.

14. What happens if I have a complaint?

If you are unhappy about the way you have been approached or treated before, during or after your participation, the researcher should be contacted. However, if you feel this is not appropriate you should contact the Chair of ethics for Sport, Exercise and Rehabilitation Dr

Nick Neave, Email: nick.neave@northumbria.ac.uk. Alternatively you can use the normal hospital complaints procedure through the Patient Advice and Liaison Service (PALS), Freephone: 0800 0320202, Email: northoftynepals@nhct.nhs.uk, Txt/ SMS: 01670511098

15. Who has reviewed this study?

This study has received full ethical approval from the NHS Health Research Authority (HRA) and been reviewed by the REC committee, reference number: 17/NE/0308 and from the organisation Northumbria university, Department of Sport, Exercise and Rehabilitation postgraduate ethics committee, reference: 656.

Contact Information

If you would like to participate in the study, are interested but request further information please contact:

Katherine Jones (Study Co-ordinator) on Tel: 07434668536(Mon-Sat 9am-6pm)

- **Chief Investigator:** Dr Garry Tew,

Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle

Tel: 0191 243 7556, **Email:** garry.tew@northumbria.ac.uk

- **Supervisor to Study Co-ordinator:** Dr Katherine Baker

Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle

Tel: 0191 215 6723, **Email:** katherine.baker@northumbria.ac.uk

- **Research Nurse:** Elaine Stephenson

Gastroenterology Department, The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Tel: 0191 282 6596, **Email:** elaine.stephenson@nuth.nhs.uk

- **Research Nurse:** Mary Doona

Gastroenterology Department, The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Tel: 0191 244 8915, **Email:** mary.doona@nuth.nhs.uk

- **Hospital Co- Investigator:** Dr Nick Thompson

Gastrointestinal and Liver Services, Newcastle Upon Tyne Hospitals NHS Foundation Trust

Tel: 0191 233 7209

- **Hospital Principal Investigator:** Dr Ally Speight

Gastrointestinal and Liver Services, Newcastle Upon Tyne Hospitals NHS Foundation Trust

Tel: 0191 213 9785

If you have any other questions or for further independent information about being involved in a research study please contact the Patient Advice and Liaison Service (PALS), Freephone: 0800 0320202, Email: northoftynepals@nhct.nhs.uk, Txt/ SMS: 01670511098.

Thank you for your time and consideration!

Appendix 7d: Disease Activity Diary

[Version one: sent to patients on the IBD Database who had an upcoming appointment]



Patient Disease Activity Diary Version 1.0: 18/12/2017

The Newcastle upon Tyne Hospitals NHS Foundation Trust

DISEASE ACTIVITY DIARY

PLEASE BRING THIS ALONG TO YOUR GASTROENTEROLOGY APPOINTMENT

Complete this form every night before you go to sleep, starting 7 days before your next appointment (i.e. if your appointment was on 15th January start this diary on 8th January).

	Day One	Day Two	Day Three	Day Four	Day Five	Day Six	Day Seven
Liquid Stools (number of)							
Abdominal Pain 0 = None 1 = Mild 2 = Moderate 3 = Severe							
General Well-Being 0 = Well 1 = Slightly below 2 = Poor 3 = Very poor 4 = Terrible							

[Version two: sent to patients identified in clinic]



Patient Disease Activity Diary Version 1.0: 30/07/2017

The Newcastle upon Tyne Hospitals **NHS**
NHS Foundation Trust

DISEASE ACTIVITY DIARY

PLEASE BRING THIS ALONG TO YOUR SCREENING VISIT APPOINTMENT

Complete this form every night before you go to sleep, starting 7 days before your next appointment (i.e. if your appointment was on 15th January start this diary on 8th January).

	Day One	Day Two	Day Three	Day Four	Day Five	Day Six	Day Seven
Liquid Stools (number of)							
Abdominal Pain 0 = None 1 = Mild 2 = Moderate 3 = Severe							
General Well-Being 0 = Well 1 = Slightly below 2 = Poor 3 = Very poor 4 = Terrible							

Appendix 7e: Recruitment poster

Hospital Poster for Patients Version 1.0: 30/07/2017



The Newcastle upon Tyne Hospitals **NHS**
NHS Foundation Trust

Adults with Crohn's disease WANTED!

Does exercise improve bone mineral density, fatigue, quality of life, muscle function and disease activity in Crohn's Disease patients?

HELP US FIND OUT



We are currently **recruiting** participants to take part in a home based exercise programme.

If you are interested, or would like further information:

Simply ask your gastroenterologist

Or contact:

Katherine Jones (Study Co-ordinator)

Tel: 07434668536 (Mon-Sat 9am-6pm)

This study has been HRA approved, reviewed by the NHS REC Committee (Ref: 17/NE/0308) and approved by the organisation University of Northumbria at Newcastle postgraduate ethics committee (Ref: 656). This study has been funded by PROcare LTD and the University of Northumbria at Newcastle.

IRAS ID: 226369

Appendix 7f: Staff study poster

Hospital Poster for Staff Version 1.0: 30/07/2017



The Newcastle upon Tyne Hospitals **NHS**
NHS Foundation Trust

Resistance training in adults with Crohn's disease

A randomised controlled trial investigating the effects of a 6 month resistance training programme on muscle function, bone mineral density, fatigue, quality of life and disease activity

Inclusion Criteria

- ≥ 16 years
- Clinical diagnosis of CD for at least 4 weeks before screening visit
- Inactive (<150 on Crohn's Disease Activity Index [CDAI]) or mildly active (150-219 on CDAI) CD assessed no greater than 4 weeks before screening visit
- Stable medications for at least 4 weeks before screening visit
- Able to provide written informed consent and complete the study questionnaires
- Able to travel to the research centre for assessment visits and exercise sessions

Exclusion Criteria

- Current participation in >2 sessions/week of resistance exercise
- Planned major surgery within 6 months
- Patient is pregnant or planning pregnancy within 6 months
- Unsuitable/ unable to undertake resistance exercise
- Co-existing serious autoimmune disorders (e.g. rheumatoid arthritis)



CONTACTS

Katherine Jones (Study Co-ordinator) on Tel: 07434668536 (Mon-Sat 9am-6pm)

This study has been HRA approved, reviewed by the NHS REC Committee (Ref: 17/NE/0308) and approved by the organisation University of Northumbria at Newcastle postgraduate ethics committee (Ref: 656). This study has been funded by PROcare LTD and the University of Northumbria at Newcastle. IRAS ID: 226369

Appendix 7g: Informed consent form



Informed Consent Form Version 1.0: 30/07/2017

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Resistance training in adults with Crohn's disease INFORMED CONSENT FORM

IRAS ID: 226369
Centre Number.....
Participant ID Number.....
Study Number.....

(Initial)

1. I confirm that I have read and understood the participation information sheet dated (version.....) for the above study. I have had the opportunity to consider and discuss the information, ask questions and have had these answered satisfactory.

2. I understand that my participation is voluntary and I am free to withdraw from the study at anytime, without having to give any reason and without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Northumbria at Newcastle, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

5. I agree to my General Practitioner (GP) being informed of my participation in the study

6. I understand that the data collected may be used to inform my gastroenterologist about my health status

7. I understand that if I would like to receive feedback on the overall results of the study I must contact the researcher at: katherine.jones@northumbria.ac.uk

8. I agree to take part in the above study

Name of Participant	Date	Signature
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Statement by the person taking consent

I can confirm that the participant was given the information sheet and the opportunity to ask any questions or queries related to this study. All the questions asked by the participant have been answered correctly and to the best of my ability the participant understands what they are required to do. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Name of person taking consent	Date	Signature
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When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes

Appendix 7h: Participant and GP contact details form



Participant contact Details Form Version 1.0: 30/07/2017

The Newcastle upon Tyne Hospitals **NHS**
NHS Foundation Trust

Resistance training in adults with Crohn's disease

PARTICIPANT CONTACT DETAILS

Participant ID Number: _____

To be completed after informed consent is gained during first screening visit

DO NOT FILE WITH ANY IDENTIFIABLE DATA

Title: First Name: Surname:

Address:.....

..... Postcode:

Email:.....

Telephone (Home): Telephone (Work):

Telephone (Mobile):

Preferred method of contact (Tick all that applies):

Email Tel (Work) Tel (Home) Tel (Mobile)

Preferred time of contact:

.....

Print Name

Date (dd/mm/yyyy)

Signature

Resistance training in adults with Crohn's disease

PARTICIPANT GP DETAILS

Participant ID Number:

GP Practice: **Dr's Name:**

GP Address:.....

..... **Postcode:**

Telephone:

PROTECT

Progressive Resistance Training Exercise and Crohn's Disease Trial

Screening Case Report Form

Participant ID:

Visit Date: / /
DAY MONTH YEAR

Instructions for completing the screening case report form:

These questions and assessments, performed by the hospital principal investigator (PI) or a delegated member of the staff listed on the PROTECT Delegation log, are designed to screen participants for participation in the PROTECT trial.

PLEASE NOTE: Details on this form and eligibility MUST be confirmed by the PI or delegated medic, who sign and date section H. Informed consent must be obtained prior to any screening procedure, including the completion of this form

Please complete all sections in this form, using the spaces provided and only skipping sections if the text directs you to do so. If the patient is deemed ineligible at any section within this form it is important that the reasons are recorded and Sections F and G are completed.

If you have any questions, please do not hesitate to contact the Chief Investigator (Dr Garry Tew; garry.tew@northumbria.ac.uk) or Study Trial Coordinator (Katherine Jones; Katherine.jones@northumbria.ac.uk).

When complete, please make a paper copy of:

- This case report form
- Consent form (3 copies required- 1 copy for the patient, 1 to be kept in the patient's medical notes and one to be sent to the study researcher, Katherine Jones, who is conducting the baseline visit
- Patient 7-day diary for CDAI
- Contact details form

Original signed consent form and contact details need to be filed in the investigator site file at the hospital. Originals of this screening case report form and the patient 7-day diary for CDAI should be sent to the researcher separately to ensure the data remains anonymised, with copies made and stored in the patients study file at the hospital.

Section A: Demographical Data

PERSONAL DETAILS

1. Date of birth / / YEAR
 DAY MONTH YEAR

NOTE: If aged ≤ 16 , the patient is ineligible for participation. Please proceed directly to Sections F and G and complete as appropriate.

2. Gender Male Female

3. Ethnicity- please cross one box

White		
British <input type="checkbox"/>	Irish <input type="checkbox"/>	Any other white background <input type="checkbox"/>
Mixed		
White and Black Caribbean <input type="checkbox"/>	White and Black African <input type="checkbox"/>	White and Asian <input type="checkbox"/>
Any other mixed background <input type="checkbox"/>		
Asian or Asian background		
Indian <input type="checkbox"/>	Pakistani <input type="checkbox"/>	Bangladeshi <input type="checkbox"/>
Any other Asian background <input type="checkbox"/>		
Black or Black British		
Caribbean <input type="checkbox"/>	African <input type="checkbox"/>	Any other Black background <input type="checkbox"/>
Chinese or Other Ethnic Group		
Chinese <input type="checkbox"/>	Any other ethnic group (please specify) <input type="text"/>	Not stated <input type="checkbox"/>

LIFESTYLE FACTORS

4. Smoking status Current Previous Never

5. Alcohol intake (units per week)

Examples of units in common drinks



6. On average over the last month, how many resistance-type exercise sessions (e.g weight lifting/ bearing- free weights and weight machines) has the patient undertaken?

NOTE: If the patient participates in 2 or more sessions of resistance exercise a week they are ineligible for participation. Please proceed directly to Sections F and G and complete as appropriate.

EMPLOYMENT HISTORY

7. Primary employment status

Employed

If employed: Full time

Self-employed

Part time

Unemployed

Student

Retired

Any other employment group (*please specify*)

Section B: Assessment for Pregnancy

If the patient is male, please proceed to Section C

1. Is there any chance the patient could be pregnant?

Yes

No

NOTE: If 'Yes', the patient is ineligible to participate. Please proceed to Sections F and G and complete as appropriate.

2. Is the patient planning pregnancy within the next 6 months following the anticipated baseline visit?

Yes

No

NOTE: If 'Yes', the patient is ineligible to participate. Please proceed to Sections F and G and complete as appropriate.

Section C: Diagnosis and Classification of Crohn's Disease

1. Date of diagnosis of Crohn's disease

/ / YEAR

NOTE: If the date is less than 4 weeks before this screening visit, the patient is ineligible for participation. Please proceed directly to Sections F and G and complete as appropriate.

CLASSIFICATION OF CROHN'S DISEASE

2. Age at diagnosis	4. Disease Behaviour
16 years or younger <input type="checkbox"/>	Non-stricturing, non-penetrating <input type="checkbox"/>
Between 17 and 40 years old <input type="checkbox"/>	Stricturing <input type="checkbox"/>
Above 40 years old <input type="checkbox"/>	Penetrating <input type="checkbox"/>
Unknown age at diagnosis <input type="checkbox"/>	
3. Location of disease	5. Disease Modifier
Ileal Crohn's <input type="checkbox"/>	Perianal Disease <input type="checkbox"/>
Colonic Crohn's <input type="checkbox"/>	
Ileocolonic Crohn's <input type="checkbox"/>	
Isolated upper GI disease <input type="checkbox"/>	
Ileal Crohn's and upper GI disease <input type="checkbox"/>	
Colonic Crohn's and upper GI disease <input type="checkbox"/>	
Ileocolonic Crohn's and upper GI disease <input type="checkbox"/>	
Disease location unknown <input type="checkbox"/>	

CROHN'S DISEASE ACTIVITY INDEX (CDAI)

Ahead of the screening visit , the patient should have been given a CDAI diary to complete for 7 days. Please state the date the patient started completing this diary:

/ /

DAY

MONTH

YEAR

Use the CDAI calculation form on the next page to calculate the CDAI score.

Parameter	M	T	W	T	F	S	S		Factor	Subtotal
Liquid stools (total over last 7 days)								Sum =	x 2	
Abdominal pain † (total over last 7 days)								Sum =	x 5	
General wellbeing * (total over last 7 days)								Sum =	x 7	
Extra-Intestinal										
Arthritis/arthralgia				None = 0				Score =	x 20	
				Yes = 1						
Iritis/uveitis				None = 0				Score =	x 20	
				Yes = 1						
Skin/mouth lesions				None = 0				Score =	x 20	
				Yes = 1						
Peri-anal disease				None = 0				Score =	x 20	
				Yes = 1						
Other fistula				None = 0				Score =	x 20	
				Yes = 1						
Fever > 37.8°C				None = 0				Score =	x 20	
				Yes = 1						
Anti-diarrhoeals				None = 0				Score =	x 30	
				Yes = 1						
Abdominal mass				None = 0				Score =	x 10	
				Questionable = 2						
				Definite = 5						
Haematocrit (Hct)				Males (47- Hct)				Score = %	(Typical – Current) x 6	
Weight +				Standard kg			kg		100 x (1 - <u>Current</u>)	
				Current kg			kg		Standard	

KEY	Abdominal pain † None = 0 Intermediate = 1 or 2 Severe = 3	General wellbeing * Well = 0 Intermediate = 1, 2 or 3 Terrible = 4	Weight + Skip this section (0) unless weight changes related to Crohn's are known. Maximum deduction of -10 for overweight patients)
------------	--	--	--

6. CDAI score (cumulative score)

NOTE: If the CDAI is **>220**, the patient is ineligible for participation. Please proceed directly to Sections F and G and complete as appropriate.

FAECAL CALPROTECTIN

For the faecal calprotectin test, previous values may be used as long as they have been performed within 4 weeks of this screening visit. If previous values cannot be used, please collect a new sample from the patient. Please state the date of the stool sample used here:

<input type="text"/> <input type="text"/>	/	<input type="text"/> <input type="text"/>	/	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	YEAR
DAY	MONTH	YEAR			

2. Faecal calprotectin result ($\mu\text{g/g}$)

<input type="text"/> <input type="text"/> <input type="text"/>
--

NOTE: If the faecal calprotectin is $\geq 250 \mu\text{g/g}$, the patient is ineligible for participation. Please proceed directly to Sections F and G and complete as appropriate.

BLOOD MARKERS OF INFLAMMATION

For the C-Reactive Protein, previous values may be used as long as they have been performed within 4 weeks of this visit. If previous values cannot be used, please collect a new sample from the patient.

Please state the date of the blood sample used here:

<input type="text"/> <input type="text"/>	/	<input type="text"/> <input type="text"/>	/	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	YEAR
DAY	MONTH	YEAR			

1. CRP result (mg/L)

<input type="text"/> <input type="text"/> <input type="text"/>
--

SURGICAL TREATMENT OF CROHN'S DISEASE

3. Has the patient ever had any surgery for Crohn's disease?

Yes No

4. If 'Yes', please indicate the type of surgery and date of procedure in the list below:

Procedure	Date (format: dd/ mm/ yyyy)
<input type="checkbox"/> Anterior resection	
<input type="checkbox"/> Appendicectomy	
<input type="checkbox"/> Cholecystectomy	
<input type="checkbox"/> Colectomy and ileostomy	
<input type="checkbox"/> Creation of rectal mucous fistula	
<input type="checkbox"/> Defunctioning ileostomy	
<input type="checkbox"/> Drainage of abscess	
<input type="checkbox"/> Disease location unknown	

<input type="checkbox"/> Excision of fistula	
<input type="checkbox"/> Extended right hemicolectomy	
<input type="checkbox"/> Ileal/jejunal resection or stricturoplasty	
<input type="checkbox"/> Ileectomy and anastomosis of ileum to colon	
<input type="checkbox"/> Ileectomy and anastomosis of ileum to ileum	
<input type="checkbox"/> Left hemicolectomy	
<input type="checkbox"/> Panproctocolectomy and ileostomy	
<input type="checkbox"/> Partial jejunectomy and anastomosis of jejunum to ileum	
<input type="checkbox"/> Partial laying open of fistula/insertion of seton	
<input type="checkbox"/> Perianal surgery	
<input type="checkbox"/> Right hemicolectomy/ileocaecal resection	
<input type="checkbox"/> Sigmoid colectomy and anastomosis	
<input type="checkbox"/> Small bowel resection with end to end anastomosis	
<input type="checkbox"/> Strictureplasty	
<input type="checkbox"/> Subtotal colectomy and primary anastomosis	
<input type="checkbox"/> Total colectomy and ileorectal anastomosis	
<input type="checkbox"/> Other (please list) [Redacted] [Redacted]	

5. Does the patient have any major surgery planned within the first 6 months after randomisation?

Yes No, proceed to Section D

NOTE: If 'Yes', the patient is ineligible for participation. Please proceed directly to Sections F and G and complete as appropriate.

Section D: Current Medications

Provide details in the table below of all the prescribed medication, over-the-counter medication and supplements/ nutraceuticals that the patient is currently taking.

NOTE: If the patient has not had stable/unchanged medication for at least 4 weeks before the screening visit, the patient is ineligible for participation. Please proceed directly to Sections F and G and complete as appropriate.

Section E: Comorbidities

1. Absolute contraindications and comorbidities to exercise training and testing:

- | | |
|--|--|
| <input type="checkbox"/> Recent (48 hrs) ECG suggestive of ischaemia, acute myocardial infarction or other acute cardiac event | <input type="checkbox"/> Symptomatic severe aortic stenosis |
| <input type="checkbox"/> Aortic dissection | <input type="checkbox"/> Acute pulmonary embolus or pulmonary infarction |
| <input type="checkbox"/> Symptomatic heart failure | <input type="checkbox"/> Acute myocarditis or pericarditis |
| <input type="checkbox"/> Unstable angina not controlled by medical therapy | <input type="checkbox"/> Deep venous thrombosis |
| <input type="checkbox"/> Presence of potentially serious arrhythmias | <input type="checkbox"/> Suspected or known dissecting aortic aneurysm |
| <input type="checkbox"/> Acute systemic infections (influenza, rhinovirus) | <input type="checkbox"/> Endocarditis |
| <input type="checkbox"/> Insufficiently controlled arrhythmias which may cause hemodynamic compromise | |

NOTE: If the patient has any absolute contraindications listed above, then they are ineligible for participation. Please complete the question below (Q3) and then proceed directly to Sections F and G.

2. Relative contraindications to exercise training and testing:

- | | |
|---|---|
| <input type="checkbox"/> Left main coronary artery stenosis | <input type="checkbox"/> High degree AV block |
| <input type="checkbox"/> Moderate stenotic valvular heart disease | <input type="checkbox"/> Ventricular aneurysm |
| <input type="checkbox"/> Electrolyte abnormalities (hypokalemia, hypomagnesemia) | <input type="checkbox"/> Uncontrolled metabolic disease (diabetes) |
| <input type="checkbox"/> Severe hypertension (>200 mm Hg/ 110 mm Hg at rest) | <input type="checkbox"/> Chronic infectious disease (hepatitis, AIDS) |
| <input type="checkbox"/> Tacharrhythmias or bradyarrhythmias | <input type="checkbox"/> Severe hyperthyroidism |
| <input type="checkbox"/> Hypertrophic cardiomyopathy/ tract obstruction | |
| <input type="checkbox"/> Neuromuscular, musculoskeletal or rheumatoid disorders exacerbated by exercise | |

NOTE: If the patient has any relative contraindications listed above, then participation needs to be confirmed by the patients consultant.

Coexisting Medical conditions/ relative contraindications not deemed suitable to exercise by consultant:

3. Medical History, other conditions not listed above:

.....
.....
.....
.....

Do any comorbidities warrant exclusion from the trial?

Yes

No

COMMENTS (Please give details on the current status of medical conditions reported above)

Section F: Inclusion Criteria

The following criteria MUST all be answered YES for the patient to be include in the trial		YES	NO
1.	Is the patient aged 16 and over?		
2.	Has the patient had a clinical disease of Crohn's disease 4 weeks prior to this screening visit?		
3.	Does the patient have a CDAI score of lower than 220		
4.	Does the patient have a faecal calprotectin score no greater than 250 µg/g		
5.	Have the patients medication been stable/unchanged for at least 4 weeks before the screening visit		
6.	Is the patient able to provide written informed consent?		
7.	Is the patient capable of completing the study questionnaires?		
8.	Is the patient able and willing to travel to the research sites for assessment visits and exercise sessions?		

Section G: Exclusion Criteria

The following criteria MUST all be answered NO for the patient to be include in the trial		YES	NO
1.	Does the patient have any absolute contraindications to exercise testing and training?		
2.	Does the patient have any other coexisting medical condition listed in Section E		
3.	Does the patient have major surgery planned within the first 6 months after randomisation		
4.	Is the patient pregnant?		
5.	Is the patient female and planning pregnancy within the first 6 months after randomisation		
6.	Is the patient currently participating in another clinical trial for which concurrent participation is deemed inappropriate		
7.	Has the participant been deemed unsuitable by the gastroenterologist/assessor to undertake resistance exercise training		
8.	Is the patient current participating in 2 or more sessions of resistance exercise training a week		

Section H: Eligibility and Sign-off

1. Have all the inclusion criteria been answered **YES**? Yes No

2. Have all the exclusion criteria been answered **NO**? Yes No

3. Patient status, in Section H:

If Q1 and Q2 have both or individually been answered as '**No**',
the patient is to be excluded. Proceed to Q4 below.

In Section H, if Q1 and Q2 have both been answered as '**Yes**',
the patient is to be included. Proceed to Q4 below.

In Section H, if Q1 and Q2 have both been answered as '**Yes**',
but the patient is to be excluded. State in the box below why and proceed to Q4.

4. Consent form has been signed and dated (version _____) By patient
By investigator

5. Form completed by: (if different than medic assessor in item 6)

Signature:

Print name:

Date: / /
 DAY MONTH YEAR

6. Eligibility confirmed by medic assessor:

Signature:

Print name:

Date: / /
 DAY MONTH YEAR

If the individual(s) completing this screening form have any further comments regarding this screening visit, please enter them here:

A large, empty rectangular box with a thin black border, intended for the individual(s) to enter any further comments regarding the screening visit.

Appendix 7j: Participant timeline of enrolment, interventions and assessments

Schedule of enrolment, interventions and assessments

TIME FRAME			Within 4 weeks of Screening		Within 1 week of randomisation				±2 week window			±6 week window				
	PRE-EXERCISE				STUDY PERIOD									POST-EXERCISE		
	Enrolment	Screening Visit-Hospital	Baseline Visit-University	Randomisation (1:1)	Supervised Sessions- University				Assessment Visit-University	Supervised Sessions-University			Assessment Visit		Exit interview	Exercise consultation and interview
TIMEPOINT					Week 1-2	Week 3-4	Week 5-8	Week 9-12	Week 13 (3 months)	Week 14-17	Week 18-21	Week 22-25	Week 26 (6 months)			
Participant information sheet	X															
Eligibility screen- inclusion/ exclusion	X	X														
Disease Activity (CDAI and FC)		→												X		
Informed consent		X														
Participant ID number		X	X													
DATA COLLECTION																
Demographics		X														
Disease Variables (Medical history, medications)		X							X					X		

Stature: Stadiometer		X					X				X			
Body mass: Avery Scales		X					X				X			
Bone mineral density: Dual-Energy X-ray Absorptiometry		X									X			
Muscle strength: Isokinetic Dynamometer and Handgrip dynamometer		X					X				X			
Muscle Endurance: 30-s chair stand test and 30-s arm curl test		X					X				X			
Fatigue: (IBD-F)		X					X				X			
Quality of Life: (ED-5Q-5L and IBD-Q)		X					X				X			
C-reactive Protein (CRP)	X											X		
Heart Rate and Blood Pressure		X		X	X		X	X	X	X				
Physical Activity Levels (SPAQ)		X					X				X			
Adverse event monitoring							X				X	X		

Physical activity enjoyment (PACES)								X				X				
INTERVENTION																
Exercise plus usual care ^a				X	X (4)	X (2)	X (4)	X (1)		X (1)	X (1)	X (1)			X	
Usual care group only				X												X

^a Numbers in brackets represent the number of exercise sessions that week(s)

PROTECT

Progressive Resistance Training Exercise and Crohn's Disease Trial

Baseline Case Report Form

Participant ID:

Visit Date: / /
DAY MONTH YEAR

Instructions for the baseline case report form:

File this case report in the participants anonymised study file. A contact details form should also be completed at the Baseline visit and stored separately to the participants anonymised study documents.

Please contact the Chief Investigator (Dr Garry Tew; garry.tew@northumbria.ac.uk) or Trial Coordinator (Katherine Jones; Katherine.jones@northumbria.ac.uk) if you have any questions.

- Has the patient provided written informed consent for the PROTECT trial?

Yes No

If 'Yes', indicate the date on the patients consent form:

/ / YEAR
DAY MONTH YEAR

- Is the patient still eligible for recruitment?

(Review the screening CRF before responding)

Yes No

If 'No', state the reason(s) in the box and then proceed directly to the sign-off section of this form

If 'Yes', please indicate the date on the Screening CRF that is to be used for this:

/ / YEAR
DAY MONTH YEAR

If the screening date provided is less than 4 weeks this baseline visit,
cross the box and proceed to section A.

If the screening date is more than 4 weeks, then the patient needs to be
re-screened before a baseline visit can be completed. Cross the box and sign-off
section of this form.

Section A: Group Preference

Inform the patient of the following:

In this trial, you will be allocated to either a resistance training programme plus usual care or a control group, who will receive usual care only. The study investigators have no influence over the treatment you will receive, this is done completely by random, for example tossing a coin by an independent statistician.

Before we find out which study group you will be allocated to, we would like to know if you have a particular preference on one of the groups? Expressing a preference will not affect the group you will be allocated.

Indicate the patients group preference:

- Resistance training
- Usual care
- No preference

Section B: Physical Measurements

5. Body Mass (kg to 1 decimal place): .

6. Stature (cm to 1 decimal place): .

7. Resting Heart Rate (beats/minute):

8. Resting Blood Pressure (mmHG): / mmHg

Use this space for any other comments about the physical measurements

10. The following table shows the results of a survey of 1000 people regarding their favorite type of music. Complete the table by calculating the percentages for each category.

Section C: Questionnaires

Provide the participant with the set of questionnaires contained within this case report form and a black/blue pen. Ask the participant to complete the questionnaires. The only help you may provide is to read out the question(s) and possible responses as stated in the questionnaires. Do not rephrase questions or provide an interpretation of what a question means. Check that the participant has completed all sections of each questionnaire before progressing to the next section.

3. Has the participant completed the IBDQ? Yes No
4. Has the participant completed the EQ-5D-5L? Yes No
5. Has the participant completed the IBD-F? Yes No
6. Has the participant completed the SPAQ? Yes No

If 'No' to Q1-5, state the reason(s) in the box below. Use this space for any other comments about the questionnaires.

Section D: Muscle Performance Testing

Follow the study-specific procedure for muscle performance testing and complete the assessment testing data collection sheet contained within this case report form.

6. Has the patient completed the lower muscle strength test? Yes No
7. Has the patient completed the upper muscle strength test? Yes No
8. Has the patient completed the 30's chair stand test? Yes No
9. Has the patient completed the 30's arm curl test? Yes No
10. Has the patient completed the grip strength? Yes No

If 'No', state the reason(s) in the box below. Use this space for any other comments about muscle performance testing.

Section E: Bone Health Assessment

Follow the study-specific procedure for muscle performance testing and complete the exercise testing data collection sheet contained within this case report form.

2. Has a DXA scan on the patient been carried out? Yes No

If 'No', state the reason(s) in the box below. Use this space for any other comments about the bone health assessment.

Section F: Check List and Investigator Sign-off

4. Have all sections of this case report been completed? Yes No

5. Any adverse events reported, or has the participant confirmed that no adverse events have occurred? Yes No

6. Form completed by:

Signature:

Print name:

Date: / /
DAY MONTH YEAR

Use the box below for any further comments regarding this visit.

Appendix 7l: GP letter

GP Letter Version 1.0: 30/07/2017



The Newcastle upon Tyne Hospitals **NHS**
NHS Foundation Trust

**Effects of a 6-month practical resistance training programme on
muscle function and bone mineral density in adults with inactive or
mildly active Crohn's disease: a randomised controlled trial**

Patient Details:

000-.....

NHS Number:.....

Dear Doctor

I am writing to inform you that your patient, has agreed to take part in the research study above.

This study is a randomised controlled trial investigating the effects of a 6-month resistance programme on muscle function, bone mineral density, fatigue, disease activity and quality of life. If the inclusion and exclusion criteria appear satisfactory and consent is gained, the participant will be randomly assigned to one of two groups: (1) a 6-month resistance training programme plus usual care, or (2) a usual-care control group.

The exercise programme involves three, 60 minute sessions of resistance exercise on non-consecutive days each week. The majority of these sessions will be unsupervised and carried out in the participant's home, with equipment provided. However to monitor progress and to provide support, 12 supervised exercise sessions will be conducted at the University of Northumbria at Newcastle over the 26 weeks. These supervised sessions will gradually decrease over time.

All participants will be reviewed by their gastroenterologist or a direct care team member and monitored by exercise and health professionals with appropriate experience. Participants will be required to undertake various health and fitness objective and subjective measures:

- At the eligibility screening and 26 weeks after randomisation- Crohn's disease activity index (CDAI), C-reactive protein and faecal calprotectin
- At baseline visit, 13 weeks and 26 weeks after randomisation- Body mass, stature, heart rate, blood pressure, muscle strength, muscle endurance, bone mineral density, questionnaire in fatigue, questionnaire in quality of life (x2) and questionnaire in physical activity levels.

After the 26-week assessment, participants will be interviewed about their experience in the study and their thoughts on the intervention they received. If you know for any reason why the patient should not be included in this research study or if you wish to obtain further information, please do not hesitate to contact: katherine.jones@northumbria.ac.uk (Trial Co-ordinator). For the safety of the patient please keep this as a permanent record regarding their involvement in the study.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Garry Tew".

Dr Garry Tew, PhD, CSci

Chief Investigator

Associate Professor of Exercise and Health Sciences
Department of Sport, Exercise and Rehabilitation
Northumbria University, Newcastle, NE1 8ST

IRAS ID: 226369

1 | Page

Appendix 7m: Control group letter



The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Dear [INSERT NAME]

Thank you once again from agreeing to take part in this research study regarding resistance training in adults with Crohn's disease.

The group you have been randomly assigned to is Group Two, the control group. This means you will not receive any exercise sessions and will carry on receiving usual standard care from The Newcastle Upon Tyne NHS Hospitals for the next 6 months. Your participation in the comparison group is vital as it will help us establish an understanding of the role of resistance training for adults with Crohn's disease.

The researcher will contact you at week 13 and week 26 to arrange for you to attend an assessment visit at the University of Northumbria at Newcastle at a time and date convenient for you. A reminder of what these assessment visits will involve:

Week 13	Assessment Visit	Location: Northumbria University	Time: 1 Hour
Similar to the measures you had taken at your baseline visit at Northumbria University. Your height, weight, fatigue (questionnaire), quality of life (questionnaires), physical activity (questionnaire), muscle strength (required to move your legs and arms at different speeds with force applied; squeeze a handle with as much force as possible), muscle endurance (complete as many chair rises to standing in 30 seconds; complete as many arm curls in 30 seconds). In addition: <ol style="list-style-type: none">4. Information on your medications will be updated5. You will also be questioned regarding any medical events (issues with your health since the previous baseline assessment)			

Before your assessment at the Freeman hospital (week 26) you will be asked to keep a disease activity diary recording number of liquid stools, abdominal pain and general well-being. This diary can be found in your pack – if lost contact the researcher:

katherine.jones@northumbria.ac.uk and another copy can be sent out.

Week 26	Assessment Visit	Location: Freeman Hospital/RVI	Time: 1 hr
You will be asked to bring your 7 day disease activity diary to this assessment. Similar to the screening visit you attended at the Freeman Hospital. A direct care team member will assess: <ol style="list-style-type: none">4. Information on your medical history, surgical history and medications will be collected			

- | | |
|--|---|
| | <p>5. A physical examination of your abdomen- consisting of a visual examination (inspection), listening to bowel sounds (auscultation) and feeling for abdominal tenderness (palpations)</p> <p>6. You will also be required to provide a stool and blood sample, unless this has been performed within the previous 4 weeks</p> |
|--|---|

Week 26	Assessment Visit	Location: Northumbria University	Time: 1 hr 45 mins
----------------	------------------	---	---------------------------

<p>During this time we will assess all measures previously been done: height, weight, fatigue (questionnaire), quality of life (questionnaires), physical activity (questionnaire), bone mineral density, muscle strength, grip strength, muscle endurance and physical activity enjoyment will assessed. No new measures will be introduced.</p>



When attending assessment visits, for your safety and the safety
of others please ensure to wear suitable exercise clothing.

Following these assessments we would also like to have a brief telephone conversation with you regarding some follow up questions about your experience in the study, any medical events and your thoughts on being in the control group, who does not receive exercise. This telephone interview will last approximately 30 minutes. After completion of the study, you will receive another phone call offering an exercise consultation from the researcher. During this call the benefits and guidelines of exercise will be discussed and a personalised action plan for developing and achieving your exercise goals will be established.

If you have any questions, please contact the researcher Katherine Jones at Email:
katherine.jones@northumbria.ac.uk

Many thanks for your help.

Yours sincerely

Dr Garry Tew (Chief Investigator)

Appendix 7n: Exercise and information booklet



The Newcastle Upon
Tyne Hospitals
NHS Foundation Trust

Resistance Training in Adults with Crohn's Disease

Exercise Booklet



ANY QUESTIONS OR PROBLEMS CONTACT:

Study Coordinator: Katherine Jones
Department of Sport, Exercise and Rehabilitation
University of Northumbria at Newcastle
Tel: 07434668536
Email: katherine.jones@northumbria.ac.uk

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General Information



Please take your time to read and refer to this exercise booklet as part of your participation in the PROTECT study. Your involvement is important to help develop a greater understanding into this disease and may have a significant impact upon management in the Crohn's disease population.

Exercise Information

Before each session it is important to ensure that you are fit to exercise, if you experience any of the following please inform the study coordinator:

1. Illness or fever including coughs, colds and tummy upsets
2. Increased breathlessness
3. Chest pain
4. Palpitations or irregular heart beat
5. Dizzy spells
6. Persistent back pain
7. Swollen ankles or feet
8. Joint and muscle problems



How long and often should I train?

The whole training programme should take 60 minutes to complete, 20 minutes for the jump training, 30 minutes for the resistance training and the remainder for the warm up and cool-down. Ideally the programme should be completed 3 times a week on non-consecutive days (e.g. Mon, Wed, Fri).

How do I know if I am exercising at the correct effort level?

The trainer will advise you on what exercises to do and stage to start at and progress to. Each stage will detail how many times exercises should be performed (repetitions) and how many sets of these exercises will be completed. For the jump training, exercises should be performed explosively, quickly with maximum power and speed. For the resistance training you will be given a coloured band of a certain resistance (light to heavy), when you progress this band will change colour as will the resistance. Please familiarise yourself with the exercise tips and directions for using the bands found on page 21 and 22. The aim is to find a exercises that makes your muscles feel moderately fatigued after 10-15 repetitions.

How should I monitor my exercise?

Please use the physical activity diary on page 14-16 to document your exercise session, including how hard you found it using the scale (measured between: easy to maximal)

3



ALWAYS complete the warm up and cool down and wear suitable clothing for exercise

Warm Up

Complete exercises 1- 7 (page 4-5) for the specified time before moving onto the main exercise programme.

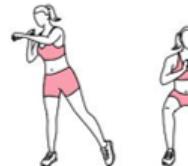
1. Marching



1. Start off marching on the spot, then after 45 seconds march forwards and backwards
2. Pump your arms up and down in the rhythm with your steps keeping your elbows bent, fists soft and knees high

Complete: 2 minutes

2. Boxer Squat Punch



1. Legs shoulder width apart, arms and hands in front of your face and chest (boxing stance)
2. Punch the air across your body, then squat
3. Return to standing position and punch the air across your body with the alternative arm

Complete: 60 Seconds

3. Arm Swings



1. Legs slightly wider than shoulder width apart
2. Extend your arms out fully to either side, with your palms facing down
3. In a crossing action, swing both arms across your chest. Return arms to either side and repeat

Complete: 30 Seconds

4

Warm Up

4. Leg Swings



1. If needed, hold onto the wall for support
2. Keep your back straight and arm slightly bent at your side
3. Begin to raise your leg forward and backwards, in a swinging motion. Repeat again on alternative leg.

Complete: 30's (15's Left, 15's Right)

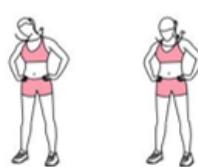
5. Big Arm Swings



1. Legs shoulder width apart, arms placed at either side of your body, slightly away from your hips
2. Begin to lift your arms forward, in a circle motion past your head and around your back.
3. Then return to starting position and repeat action

Complete: 30's (15's Forward, 15's Backward)

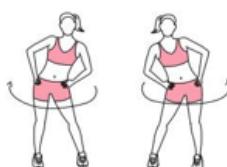
6. Neck Rolls



1. Legs shoulder width apart and place your hands on your hips
2. Keep your back straight and begin to roll your neck around to the left and right in small circles. Avoid rolling your neck backwards

Complete: 15 seconds

7. Hip Circles



1. Legs slightly wider than shoulder width apart, place your hands on your hips
2. While keeping your back straight begin to make big circles with your hips (like you would if you were hula-hooping)
3. After a few circles, change direction

Complete: 15 seconds

5

Exercise Programme

Jump Training

Perform Jumps explosively, quickly with maximum power and speed. Complete the recommended stage (e.g. stage one) as directed by the trainer. **DO NOT** progress to the next stage until instructed by the trainer.

Stage One

If you can't manage 5 minutes of skipping try:

- 1 min skipping, 30's rest etc until 5 mins is reached in total
- 2 minutes skipping, 30's rest until comfortable to complete 5 minutes

Exercise	Duration	Equipment
1a. Double leg skipping	5 minutes in total	Skipping Rope

Progress to 1B when instructed by the trainer

1b. Alternate leg skipping	5 minutes in total	Skipping Rope
----------------------------	--------------------	---------------

Progress to 1C when instructed by the trainer

1c. Single leg skipping	5 minutes in total (alternate leg every 15-30s)	Skipping Rope
-------------------------	---	---------------

Progress to STAGE 2 when instructed by the trainer

1. Skipping



1. Hold the skipping rope handles at either side of your waist.

Swing the rope in a circular motion

2. Lightly bend knees and jump 1 to 2 inches off the floor, keep your elbows close to your sides

Double leg skipping

3. Land with both feet as quietly as possible

Alternate leg skipping

3. Land on one foot as lightly as possible, alternating the leg you land on



Complete: 5 minutes

6

Jump Training

Stage Two		
Exercise	Duration	Equipment
Squat Jumps		
Power Skips	Sets: 2, Repetitions: 10-15	
1 Legged Forward Jumps		
Broad Jumps		
Scissor Jumps		

Progress to STAGE THREE when instructed by the trainer		
Stage Three		
Exercise	Duration	Equipment
Squat Jumps		
Power Skips	Sets: 3, Repetitions: 10-15	
1 Legged Forward Jumps		
Broad Jumps		
Scissor Jumps		

2. Squat Jumps



- 1, Stand with your feet shoulder-width apart, arms placed at your side
- 2, Bend knees at a 90 degree angle, keep arms extended at the waist and jump explosively up extending your arms above your head
- 4, When you land, lower your body back into the squat position. Land as quietly as possible.

Complete: 10-15 squat jumps then 30's rest

3. Power Skips

- 1, Leading with your right leg, skip as high as you can by raising your right knee to hip height and at the same time extending your left arm straight overhead
- 2, Your left leg should remain straight and your right elbow slightly bent at your side.
- 3, When you land, land on the ball of your foot. Repeat the skipping motion with your opposite arm and leg.

Complete: 10-15 power skips then 30's rest



7

Jump Training

4. One Legged Forward Jumps



1, Begin in a hop stance, knee slightly bent behind and arms at a 90 degree angle above your waist

2, When ready, explosively hop forward, swinging your arms forward and extending the none bent knee as much as possible.

3, Land on the same foot you took off with. Repeat again with opposite leg

Complete: 10-15 one legged forward jumps then 30's rest

5. Broad Jumps

1, Place your feet shoulder width apart, toes pointed forward. Stretch your arms above your head with your hips extended and rise up onto the balls of your feet

2, Bend your knees and hips and bring your arms behind you. Slowly prepare to jump by completing steps one and two once or twice.



3, After this in a half squat position explosively drive forward and up as powerfully as you can off the ground while simultaneously throwing your arms forward.

4, When in the air, extend your hips and drive your feet forward.
5, Land flat footed and use your arms to help you keep balance

Complete: 10-15 broad jumps then 30's rest

6. Scissor Jumps

1, Assume a lunge stance with one foot forward and the other knee slightly bent. Assume a full lunge position if you feel comfortable to perform the jump. Or a half lunge position if you don't

2, Ensure your front knee is over the midline of your foot.

3, Extend both legs and explosively push off the ground while swinging your arms to gain lift

4, As you explosively jump, switch the positions of your legs moving your front leg to the back and your back leg to the front



5, As you land, absorb the impact through your legs by adopting the lunge position. Repeat with the opposite leg forward.

Complete: 10-15 scissor jumps then 30's rest

8

Exercise Programme

Resistance Training

Please familiarise yourself with the exercise tips and directions for using the bands found on page 21 and 22. Complete the recommended stage as directed by the trainer. **DO NOT** progress to the next stage until instructed by the trainer.

Stage	Resistance Exercises	Duration	Equipment
1	Squat Lunge Press-Up	Rest for 30's between each type of theraband exercise. Rest for 2 minutes before repeating the stage again. Sets: 2, Repetitions: 10-15	Latex free resistance band
2	Cross Body Reach Reverse Fly Lateral Raise Biceps Curl Triceps Extension Frontal Raise	Rest for 30's between each type of theraband exercise. Rest for 2 minutes before repeating the stage again. Sets: 2, Repetitions: 15	Latex free resistance band
3	Bridge	Rest for 30's between each type of theraband exercise. Rest for 2 minutes before repeating the stage twice. Sets: 3, Repetitions: 10-15	Latex free resistance band

1. Squat



- 1, Stand in the middle of the band with both feet, grasping both ends of the TheraBand in a normal standing position
- 2, Arms should be at approximately 90 degrees with your palms facing outwards/forwards
- 3, Perform a squat with your arms in this position, keeping your back straight, knees pointing forward. Hold and slowly return to the starting position.

Complete: 10-15, then 30's rest

9

Resistance Training

2. Lunge

- 1, Stand with one foot on the middle of the band, grasping both ends.
- 2, Bend your elbows towards your chest, in a pray like position
- 3, Place your other leg behind with the knee slightly bent
- 4, Keeping your trunk and back up straight, bend your front knee and lowering the body straight down. Hold for a few seconds and return to the upright position against the band. Alternate legs.



Complete: 10-15, then 30's rest



3. Press -Ups

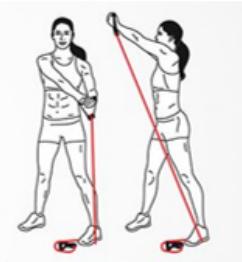
- 1, Grasp each end of the resistance band tightly around both of your fists
- 2, Assume a push up position, with the resistance band placed over your upper back. If you struggle with completing a press up, place your knees on the floor and cross your feet. Ensure your hands are below your shoulders and shoulder width apart.

- 3, Ensure the band is tight enough, squeeze your bum and try and keep your bum below your shoulders.

Complete: 10-15, then 30's rest

4. Double Handed Cross Body Reach

- 1, Standing shoulder width apart, place the theraband under your right foot. Grasp the other end of the theraband with both hands in a fist like shape
- 2, Start with both your arms stretched out above your right foot. Slightly above your hips.
- 3, When ready stretch your arms across your body at head height and above your left leg. Complete 5-7 on each side before alternating leg and arm

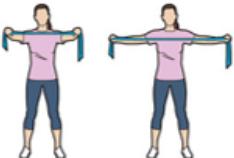


Complete: 10-15, then 30's rest

10

Resistance Training

5. Reverse Fly



- 1, Standing shoulder width apart, hold the band in its relaxed form with both hands
- 2, Extend your arms at shoulder level, keeping your elbows straight, head and trunk upright and stretch the band outwards
- 3, Hold and slowly return to the starting position

Complete: 10-15, then 30's rest

6. Lateral Raise

- 1, Stand on the resistance band, so that the band is about even on both sides.
- 2, Grasp the resistance band, so your palms are facing your thighs. Keeping your back straight, extend your arms out so they are parallel to your shoulders or as far as you are comfortable in going
- 3, Hold it for a few seconds and return slow to the starting position.



Complete: 10-15, then 30's rest

7. Biceps Curl



- 1, Standing straight, feet shoulder width apart. Place the resistance band under both feet
- 2, Hold the band with arms straight by your sides and palms facing out
- 3, Keeping your stomach flat slowly bend from the elbow raising your fists to your shoulders
- 4, Keep your elbows tucked in, slowly lower the band down and repeat

Complete: 10-15, then 30's rest

11

Resistance Training

8. Triceps Extension

- 1, Standing shoulder width apart, grab one end of the resistance band and raise your arm so that your elbow is pointing towards the ceiling and the band is handing down your back
- 2, Grab the other end of the band with your available hand just above your hips/ middle of your back and so your palm is facing away from your back.
- 3, With your top hand, extend your arm towards the ceiling. Keep your arm as straight as possible. Hold and then begin to lower to the starting position. Complete 5-7 on each side before alternating arm.



Complete: 10-15, then 30's rest

9. Frontal Raise



- 1, Stand on the resistance band, so that the band is about even on both sides.
- 2, Grasp each end of the band with the opposite hand, e.g. grab the left side with your right hand.
- 3, Bring the band up at waist level in front of you and raise your arms forward. Keep your elbows and back straight and abdomen tight.
- 4, Do not go above shoulder level. Hold and slowly return to the starting position

Complete: 10-15, then 30's rest

10. Bridge

- 1, Lie face up with both knees bent and feet flexed.
- 2, Place the band across the pelvis, pressing the ends into the floor by the sides of your hips
- 3, Brace abs tight, squeeze glutes and lift hips up into a bridge.
- 4, Hold and slowly lower over 3 seconds



Complete: 10-15, then 30's rest

12

Cool Down

Hold each exercise for: 10-15 Seconds. This cool down should take about 5 minutes.
Spend more time on the exercises if needed

Lower Body

1. Hamstring Stretch

- 1, Lying on the floor, lift one leg up towards your body
- 2, Hold the back of your leg with both hands to keep it in place
- 3, Keep your leg straight. Repeat with the opposite leg, then begin exercise again



2. Calf Stretch



- 1, Step your right leg forward, keeping it bent lean forwards slightly
- 2, For support use a wall
- 3, Keep your left leg straight and keep both heels flat to the ground
- 4, Hold and repeat with the opposite leg

3. Quads Stretch

- 1, Standing shoulder width apart, bring one leg up to your bum
- 2, Support your leg by holding the front of your foot, hold then return your leg to the starting position and repeat with opposite leg



Now complete the upper body cool down on page 14

13

Upper Body Cool Down

Hold each exercise for: 10-15 Seconds. This cool down should take about 5 minutes.
Spend more time on the exercises if needed

4. Chest Stretch



- 1, Standing shoulder width apart, back straight
- 2, Bring both arms behind your body and interlock your fingers
- 3, Gently push your arms up while pulling your shoulder blades together.

5. Upper Back Stretch



- 1, Round your upper back, extend arms in front of you and clasp your hands together palms facing in.
- 2, Drop your head slightly and focus on increasing the gap between your chest and hands, feel the stretch across your upper back.

6. Tricep Stretch

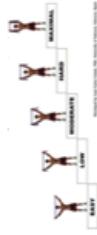


- 1, Place your hand on your upper back with your elbow bent upwards beside your head.
- 2, Use your other hand to support your arm and feel the stretch.
- 3, Keep your back straight and don't hold the elbow joint, just below. Repeat using opposite arm

14

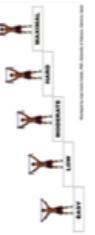
Physical Activity Diary

15



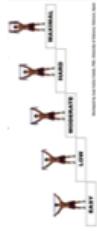
Physical Activity Diary

16



Physical Activity Diary

17



Attending Northumbria

Supervised Exercise Tracker

Session No.	Date	Time	Session No.	Date	Time
1			7		
2			8		
3			9		
4			10		
5			11		
6			12		

- The exercise sessions and assessment visits will be conducted at the University of Northumbria at Newcastle. You will be asked to meet the trainer at Café Central, on Northumberland Road NE1 8SU (Pictured)
 - Unfortunately we are unable to cover travel expenses however there is free onsite car parking at Northumbria, please contact the trial coordinator to arrange this.
 - If you are unable to attend or are running late, please contact the trial coordinator on 07434668536 or via email at
 - katherine.jones@northumbria.ac.uk
 - If you miss a session you may be contacted by a study member just to ensure everything is ok
 - If you wear glasses or hearing aids please wear them to the session



Supervised Exercise Sessions

- The exercise sessions will be one to one or in small groups (maximum of 3) and last around 60 minutes.
 - Please ensure you wear suitable clothing for exercising, changing facilities and toilets are available at Northumbria University

Warm Up	Jump and Resistance Training	Cool Down
To prepare your body, particularly your muscles , for the main training programme This last approximately 5 minutes	To help develop muscle endurance and strength and bone density. You will complete a series of jump and resistance exercises adjusted to suit you. This session will last approximately 50 minutes.	To allow your body to slowly return to its resting level while providing a period of recovery time. This last approximately 5 minutes.

18

Session Breakdown

When attending supervised sessions and assessment visits, for your safety and the safety of others please ensure to wear suitable exercise clothing.

Wk	Supervised	Unsupervised	Total	Completed	Wk	Supervised	Unsupervised	Total	Completed
1	2	1	3		14	1*	2/3	3	3
2	2	1	3		15		2/3	3	
3	1	2	3		16		2/3	3	
4	1	2	3		17		2/3	3	
5	1*	2/3	3		18	1*	2/3	3	
6		2/3	3		19		2/3	3	
7	1*	2/3	3		20		2/3	3	
8		2/3	3		21		2/3	3	
9	1*	2/3	3		22	1*	2/3	3	
10		2/3	3		23		2/3	3	
11		2/3	3		24		2/3	3	
12		2/3	3		25		2/3	3	
13	Assessment Visit				26	Assessment Visit			3
									3

* You decide which week you would like to schedule your supervised session, at your soonest convenience.

19

Assessment Visits

- The visit will be one to one and last approximately 30 mins- 1 hour 30 mins (see below)
- Please ensure you wear suitable clothing for testing, such as exercise gear or comfortable attire. **Avoid** wearing clothing that has metal or zippers, if this is not possible a gown will be provided when measuring bone mineral density (DXA scanner)

Wk 13	Assessment Visit	Location: Northumbria University	Time: 1 hr
1. Height 2. Weight 3. Questionnaire- Fatigue 4. Questionnaire -Quality of life (x2) 5. Muscle strength- 10 minute warm up session. Strapped (like a seatbelt) onto a chair and required to kick your leg and arm at different speeds with force applied 6. Grip strength- squeeze a handle with as much force as you can 7. Muscle endurance- complete as many chair rises to standing in 30 seconds. Complete as many arm curls in 30 seconds 8. Information on your medications will be updated 9. You will also be questioned regarding any medical events 10. Questionnaire- physical activity enjoyment			

Week 26	Assessment Visit	Locations: RVJ/Freeman	Time: 30 mins
You will be asked to bring your completed 7 day disease activity diary (below, pg 14) to this screening. 1. Information on your medical history medications will be collected 2. A physical examination of your abdomen- consisting of a visual examination (inspection), listening to bowel sounds (auscultation) and feeling for abdominal tenderness (palpations) 3. You will also be required to provide a stool and blood sample, unless this has been performed within the previous 4 weeks			

Wk 26	Assessment Visit	Location: Northumbria University	Time: 1 hr 30 mins
1. Height 2. Weight 3. Questionnaire- Fatigue 4. Questionnaire -Quality of life (x2) 5. Muscle strength- 10 minute warm up session. Strapped (like a seatbelt) onto a chair and required to kick your leg and arm at different speeds with force applied 6. Grip strength- squeeze a handle with as much force as you can 7. Muscle endurance- complete as many chair rises to standing in 30 seconds. Complete as many arm curls in 30 seconds 8. Information on your medications will be updated 9. You will also be questioned regarding any medical events 10. Questionnaire- physical activity enjoyment			

20

Directions for handling, connecting and securing elastic bands

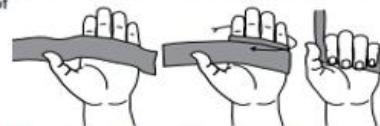
Always examine your band or tubing before use; discard and replace if you notice any tears or nicks. Protect the eyes during exercises that may cause the band or tubing to snap back toward the head. Check routinely for evidence of wear of the band or tubing at connection points and replace the band if evidence is found.

Handling the Bands

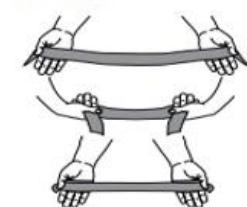
Your elastic band or tubing should be securely attached to your hand or foot before use to avoid slippage and possible injury. "Double wrapping" the band may help secure it to your hand or foot. Never exercise with the band or tubing unless it is secured properly.

Grip Wrap

Lay the band flat in your hand with the end toward your pinky finger. Wrap the long end of the band around the back of your hand. Repeat as needed. Firmly grasp.



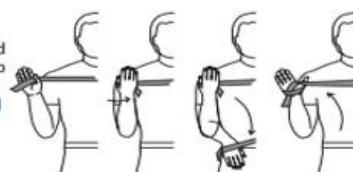
Palm Wrap



Begin with palms up and ends of band between the thumb and palm. Rotate your palms inward, bringing the band around the back of your hands. Repeat as needed. Firmly grasp.

Euro Wrap

Begin with your palm facing forward and the ends of the band between the thumb and palm. Rotate your arm inward. Turn your hand downward, bringing the band around the back of your hand. Return the palm facing forward, bringing the band between the thumb and fingers.



Creating Loops

Loops can be easily created for upper or lower body exercises.



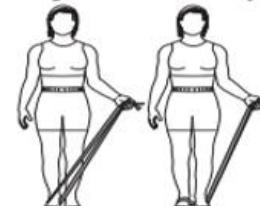
Short length loop: Tie each end into a square knot.



Long length loop: Tie ends together in a simple knot, leaving long loop.

21

Using Bands for Lower Body



Foot Loop: Stand on the middle of the band. Loop over the top of the foot and stabilize other ends with opposite foot.



Foot Wrap: Stand on the middle of the band. Wrap one end around the top of the foot.



Ankle Wrap: Place the back of your ankle in the middle of the band. Cross the ends in front of your ankle and bring them down on the sides of the ankle. Cross the ends under the foot and bring up around the sides.

Exercise Tips

- Always complete the warm up and cool down
- Use the band prescribed for the prescribed sets and repetitions. Rest between sets (1-2 minutes)
- With all exercises, posture and body alignment is critical. Keep the shoulders and hips aligned, tighten the abdominals, and relax the knees.
- Perform all exercises in a slow and controlled manner. At no time should you feel "out of control"; remember to control the band rather than allowing it to control you. Do not allow the band or tubing to snap back
- Avoid hyper extending or over-flexing joints when exercising. Don't lock the joints
- Breathe evenly while performing your exercises. Exhale during the more difficult phase of the repetition. Don't hold your breath

Caring for Elastic Bands

- Always examine the resistance band before use for small nicks, tears, or punctures that may cause the band to break. If you find any flaws, please contact the principal investigator.
- Store out of direct sunlight and away from extreme temperatures
- If the bands or tubing becomes sticky, clean with mild soap and water, dry flat, and then dust with talcum powder, baby powder or corn starch.

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Getting Here

By Road

City Campus Postcode: NE1 8ST. Car parks listed below are within a 5 minute walk from Northumbria University. For alternative parking please visit:
<https://www.newcastle.gov.uk/parking-roads-and-transport/parking/car-parks-and-on-street-parking>

- College Street (NE1 8JG)- 73 spaces, 5 disabled bays
Monday – Saturday (8am-6pm): £1.50 per hour, (6pm- 8am): FREE
Sunday (8am-6pm): £3.00 daily charge, (6pm-8am): FREE
- Ellison Place (NE1 8ST)- 119 spaces, 7 disabled bays
Monday – Saturday (8am-6pm): £1.40 per hour, (6pm- 8am): FREE
Sunday (8am-6pm): £3.00 daily charge, (6pm-8am): FREE
- Oxford Multi-storey (NE1 8AN)- 139 spaces
Monday – Saturday (8am-6pm): £1.30 per hour, (6pm- 8am): FREE
Sunday (8am-6pm): £3.00 daily charge, (6pm-8am): FREE
- Savile Place (NE1 8DQ)- 42 spaces, 3 disabled bays
Monday – Saturday (8am-6pm): £1.40 per hour, (6pm-8am): FREE
Sunday (8am-6pm): £3.00 daily charge, (6pm-8am): FREE

By Bus

Buses that stop at the civic ~~centre~~ opposite the university (Prices may vary slightly depending on your location):

- Stagecoach 1, 38 (Stagecoach ~~dayrider~~: £3.95)
- Go North East 57, 309, 310 (~~Buzzfare~~ day ticket: £5)
- Arriva 52, 306, 308 (Arriva Saver Ticket: £5.90)

PROTECT

Progressive Resistance Training Exercise and Crohn's Disease Trial

Exercise Session Form

Participant ID:

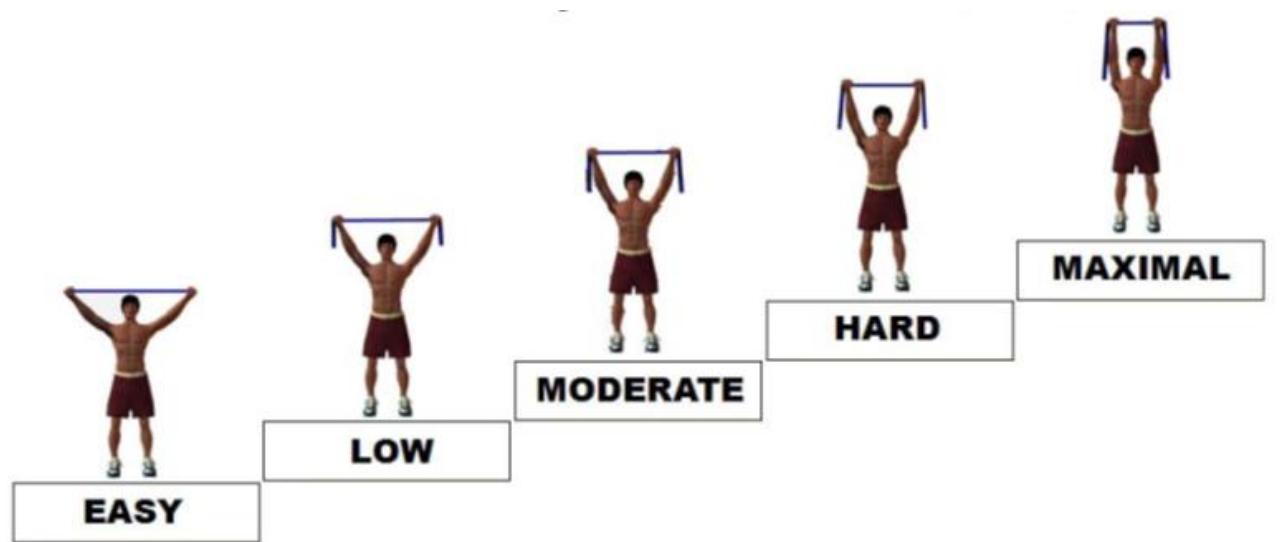
Section A: General Instructions

- Welcome the participant to the session, confirm their continuing consent and ask if anything has changed medically since their last visit
- Provide a reminder/ explain how the RISE scale works
- Check first aid equipment is immediately available
- Please make sure all sections of the CRF are completed
- If a session is missed, please state the reason why

Section B: Exercise Scales

RESISTANCE INTENSITY SCALE for EXERCISE

Using the scale below we would like you to rate your perception of exertion, that is how heavy and strenuous the physical task feels to you:



EXERCISE SESSIONParticipant Identification Number : Date of session (dd/mm/yyyy) : / / Session Number : TheraBand Colour: Jump Training Stage: Resistance Training Stage:

	Heart Rate (beats/min)	Blood Pressure (mm/Hg)	Number of Sets/repetitions/ exercises	RISE (Easy to Maximal)
Before warm up				
5 minute warm up				
Jumping training				
Resistance theraBand training				
3 minute cool down				
10 minutes post-exercise				

1. Was the session completed ? Yes No Please state why

2. Did any adverse events occur during this session?

Yes No

If 'Yes', please follow adverse event procedures and provide a brief description:

PROTECT

Progressive Resistance Training Exercise and Crohn's Disease Trial

13 Week University Case Report Form

Participant ID:

Visit Date: / /

Is the patient still eligible and willing to participate?

Yes

No

If 'Yes', complete all sections of this case report form.

If 'No', state the reason(s) in the box and then complete the sign-off section of this form

For more information about the study, please contact the study team at 1-800-258-4929 or visit www.cancer.gov.

Section A: Current Medications

Provide details of all prescribed medication, over-the-counter medication and supplements/nutraceuticals that the patient is currently taking.

Use the medication documented in the *Screening Case Report Form* to facilitate this process.

Medication Name	Dose and Route	Start Date (dd/mm/yyyy)

Section B: Physical Measurements

1. Body Mass (kg to 1 decimal place): .

2. Stature (cm to 1 decimal place): .

3. Resting Heart Rate (beats/minute):

4. Resting Blood Pressure (mmHG): /
 SYSTOLIC DIASTOLIC

Use this space for any other comments about the *physical measurements*.

For more information about the study, please contact Dr. John Smith at (555) 123-4567 or via email at john.smith@researchinstitute.org.

Section C: Questionnaires

Provide the participant with the set of questionnaires (page 8 onwards) and a blue or black pen. Ask the participant to complete the questionnaires.

NOTE: You may read out the question(s) and possible responses as stated in the questionnaire, however do not rephrase these questions or provide any interpretation of what the question means.

Check that the participant has completed all sections of each questionnaire before progressing to the next section.

- | | | |
|---|------------------------------|-----------------------------|
| 1. Has the participant completed the IBDQ? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 2. Has the participant completed the EQ-5D-5L? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 3. Has the participant completed the IBD-F? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 4. Has the participant completed the SPAQ? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 5. Has the participant completed the PACES?
(EXERCISE GROUP ONLY) | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

If 'No' to Q1-5, state the reason(s) in the box below. Use this space for any other comments about the questionnaires.

Section D: Muscle Performance Testing

Follow the study-specific procedure for muscle performance testing and complete the assessment data collection sheet contained within this case report form.

1. Has the patient completed the lower muscle strength test? Yes No
2. Has the patient completed the upper muscle strength test? Yes No
3. Has the patient completed the 30's chair stand test? Yes No
4. Has the patient completed the 30's arm curl test? Yes No
5. Has the patient completed the grip strength? Yes No

If 'No', state the reason(s) in the box below. Use this space for any other comments about muscle performance testing.

Section E: Check List and Investigator Sign-off

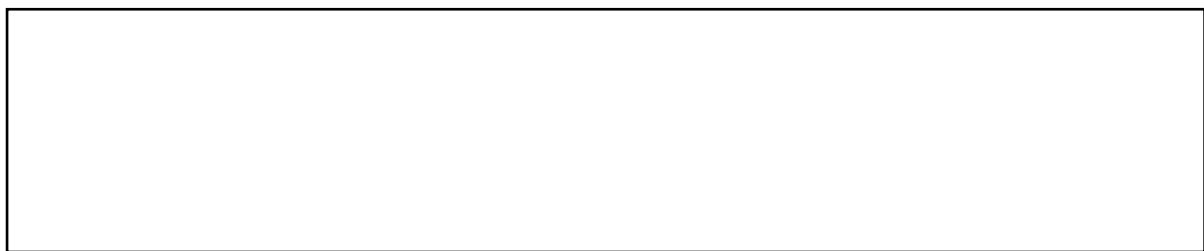
1. Have all sections of this case report been completed? Yes No
2. Any adverse events reported, or has the participant confirmed that no adverse events have occurred? Yes No
3. Form completed by:

Signature:

Print name:

Date: / /
 DAY MONTH YEAR

Use the box below for any further comments regarding this visit.

A large, empty rectangular box with a thin black border, intended for handwritten comments.

PROTECT

Progressive Resistance Training Exercise and Crohn's Disease Trial

26 Week University Case Report Form

Participant ID:

Visit Date: / /
DAY MONTH YEAR

Is the patient still eligible and willing to participate?

Yes

No

If 'Yes', complete all sections of this case report form.

If 'No', state the reason(s) in the box and then complete the sign-off section of this form

Section A: Current Medications

Provide details of all prescribed medication, over-the-counter medication and supplements/nutraceuticals that the patient is currently taking.

Use the medication documented in the *Screening Case Report Form* to facilitate this process.

Medication Name	Dose and Route	Start Date (dd/mm/yyyy)

Section B: Physical Measurements

5. Body Mass (kg to 1 decimal place): .

6. Stature (cm to 1 decimal place): .

7. Resting Heart Rate (beats/minute):

8. Resting Blood Pressure (mmHG): /
SYSTOLIC DIASTOLIC

Use this space for any other comments about the *physical measurements*.

Section C: Questionnaires

Provide the participant with the set of questionnaires (page 8 onwards) and a blue or black pen. Ask the participant to complete the questionnaires.

NOTE: You may read out the question(s) and possible responses as stated in the questionnaire, however do not rephrase these questions or provide any interpretation of what the question means.

Check that the participant has completed all sections of each questionnaire before progressing to the next section.

- | | | |
|--|------------------------------|-----------------------------|
| 6. Has the participant completed the IBDQ? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 7. Has the participant completed the EQ-5D-5L? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 8. Has the participant completed the IBD-F? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 9. Has the participant completed the SPAQ? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| 10. Has the participant completed the PACES?
(EXERCISE GROUP ONLY) | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

If 'No' to Q1-5, state the reason(s) in the box below. Use this space for any other comments about the questionnaires.

Section D: Muscle Performance Testing

Follow the study-specific procedure for muscle performance testing and complete the assessment data collection sheet contained within this case report form.

6. Has the patient completed the lower muscle strength test? Yes No
7. Has the patient completed the upper muscle strength test? Yes No
8. Has the patient completed the 30's chair stand test? Yes No
9. Has the patient completed the 30's arm curl test? Yes No
10. Has the patient completed the grip strength? Yes No

If 'No', state the reason(s) in the box below. Use this space for any other comments about muscle performance testing.

Section E: Bone Health Assessment

Follow the study-specific procedure for muscle performance testing and complete the exercise testing data collection sheet contained within this case report form.

1. Has a DXA scan on the patient been carried out? Yes No

If 'No', state the reason(s) in the box below. Use this space for any other comments about the bone health assessment.

Section E: Check List and Investigator Sign-off

4. Have all sections of this case report been completed? Yes No

5. Any adverse events reported, or has the participant confirmed that no adverse events have occurred? Yes No

6. Form completed by:

Signature:

Print name:

Date: / /
DAY MONTH YEAR

Use the box below for any further comments regarding this visit.

PROTECT

Progressive Resistance Training Exercise and Crohn's Disease Trial

26 Week Hospital Case Report Form

Participant ID:

Visit Date: / /

Instructions for completing the 26 week hospital case report form:

These questions and assessments are to be completed by the hospital principal investigator (PI) or delegated member of the staff listed on the PROTECT delegation log.

PLEASE NOTE: Details on this form MUST be confirmed by the PI or delegated medic, who sign and date section H.

Please complete all sections in this form. If you have any questions, please do not hesitate to contact the Chief Investigator (Dr Garry Tew; garry.tew@northumbria.ac.uk) or Study Trial Coordinator (Katherine Jones; Katherine.jones@northumbria.ac.uk).

When complete, please make a paper copy of:

- This case report form
- Patient 7-day diary for CDAI

Originals of this screening case report form and the patient 7-day diary for CDAI should be sent to the researcher separately to ensure the data remains anonymised, with copies made and stored in the patients study file at the hospital.

Is the patient still eligible and willing to participate?

Yes No

If 'Yes', complete all sections of this case report form.

If 'No', state the reason(s) in the box and then complete the sign-off section of this form

Section A: Current Medications and Medical History

Provide details of all prescribed medication, over-the-counter medication and supplements/nutraceuticals that the patient is currently taking.

Use the medication documented in the *Screening Case Report Form* to facilitate this process.

1. Has anything changed in regards to your medical history? Yes No, proceed to Section B

If 'Yes', please provide any details in the space provided

10. The following table summarizes the results of the study. The first column lists the variables, the second column lists the sample size, and the third column lists the estimated effect sizes.

Section B: Disease Activity Assessment

CROHN'S DISEASE ACTIVITY INDEX (CDAI)

Ahead of the screening visit, the patient should have been given a CDAI diary to complete for 7 days. Please state the date the patient started completing this diary:

/ /

DAY MONTH YEAR

Use the CDAI calculation form to calculate the CDAI score.

Parameter									Factor	Subtotal
Liquid stools (total over last 7 days)	M	T	W	T	F	S	S	Sum =	x 2	
Abdominal pain † (total over last 7 days)	M	T	W	T	F	S	S		Sum =	
General wellbeing * (total over last 7 days)	M	T	W	T	F	S	S	Sum =		x 7
Extra-Intestinal										
Arthritis/arthritis	None = 0							Score =	x 20	
	Yes = 1								x 20	
Iritis/uveitis	None = 0							Score =		x 20
	Yes = 1									
Skin/mouth lesions	None = 0							Score =	x 20	
	Yes = 1								x 20	
Peri-anal disease	None = 0							Score =		x 20
	Yes = 1									
Other fistula	None = 0							Score =	x 20	
	Yes = 1								x 20	
Fever > 37.8°C	None = 0							Score =		x 20
	Yes = 1									
Anti-diarrhoeals	None = 0							Score =	x 30	
	Yes = 1								x 30	
Abdominal mass	None = 0							Score =		x 10
	Questionable = 2									
	Definite = 5									
Haematocrit (Hct)	Males (47- Hct)							Score =	% (Typical – Current) x 6	
	Females (42- Hct)									
Weight +	Standard kg							kg	100 x (1 - $\frac{\text{Current}}{\text{Standard}}$)	
	Current kg									

KEY

Abdominal pain †
None = 0
Intermediate = 1 or 2
Severe = 3

General wellbeing *
Well = 0
Intermediate = 1, 2 or 3
Terrible = 4

Weight +
Skip this section (0) unless weight changes related to Crohn's are known. Maximum deduction of -10 for overweight patients)

6. CDAI score (cumulative score)

<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------

FAECAL CALPROTECTIN

For the faecal calprotectin test, previous values may be used as long as they have been performed within 4 weeks of this visit. If previous values cannot be used, please collect a new sample from the patient. Please state the date of the stool sample used here:

<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
DAY			MONTH			YEAR			

1. Faecal calprotectin result ($\mu\text{g/g}$)

BLOOD MARKERS OF INFLAMMATION

For the C-Reactive Protein, previous values may be used as long as they have been performed within 4 weeks of this visit. If previous values cannot be used, please collect a new sample from the patient. Please state the date of the blood sample used here:

<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
DAY			MONTH			YEAR			

1. CRP result (mg/L)

Section C: Eligibility and Sign-off

1. Have all sections of this case report been completed? Yes No

2. Any adverse events reported, or has the participant confirmed that no adverse events have occurred? Yes No

3. Form completed by: (if different than medic assessor in item 6)

Signature:
Print name:
Date: / /
DAY MONTH YEAR

4. Eligibility confirmed by medic assessor:

Signature:
Print name:
Date: / /
DAY MONTH YEAR

Use the box below for any further comments regarding this visit.

Appendix 7s: End of study information sheet

Resistance training in adults with Crohn's disease

END OF STUDY INFORMATION SHEET

Reference: *IRAS 226369; ISRCTN ISRCTN11470370; REC 17/NE/0308*

Q. Why

was this study important/ why was it needed?

Reduced bone mineral density and poor muscular strength and endurance are established complications of Crohn's disease (CD). Although not part of routine treatment, regular exercise has demonstrated improvements in fatigue, disease activity, psychological health, quality of life and bone and muscle health. Despite these potential benefits, the role of exercise in CD has not been well studied and remains poorly understood with research primarily focusing on the potential of aerobic exercise programmes (e.g. running, cycling).

However, growing evidence in other chronic conditions has shown that resistance (strength) training may have a better effect on bone health, muscle strength and endurance than aerobic exercise. Despite this, little information exists around the potential of resistance training in CD patients. With the debilitating nature of this disease, further research is needed as these findings may have a significant impact upon management in the CD population by providing physical activity solutions instead of or alongside current treatments.

Q. What was the main purpose of the study which I took part in?

The primary purpose of this study was to investigate the effects of a 6 month resistance training programme on muscle function and bone mineral density. We also assessed the impact it may have upon fatigue, disease activity and quality of life.

Q. Who was studied?

Between February 2018 and March 2019, 76 people with CD were screened for eligibility and after the eligibility assessment, 47 were recruited and randomised. Eligible participants were randomly (given an equal chance of being allocated to group one or group two) allocated to either the exercise group who completed three weekly, 60 minute sessions of impact and resistance training for 6 months, or to a control group who received usual care. Thirty-two participants were female and the average age was 49 years. Data collection commenced in October 2019.

Q. How was the study done?

All participants completed three assessment visits (baseline, at 3 months and 6 months) at the University of Northumbria at Newcastle. At each visit, participants completed a series of questionnaires regarding quality of life, fatigue and physical activity habits and completed a number of muscular strength and endurance measures. Bone mineral density was taken at baseline and 6 months only. Following the conclusion of the study, participants completed a telephone-based exit interview.

Q. What happens now the study has stopped?

Now the study has ended the data we collected will be stored on a password-protect computer in accordance with the Participant Information Sheet, University guidelines and Data Protection Act (1998). None of this information is identifiable. Any identifiable information collected throughout the study has been destroyed.

You will continue to receive the best possible care from the National Health Services.

Q. Invitation to take part in patient involvement

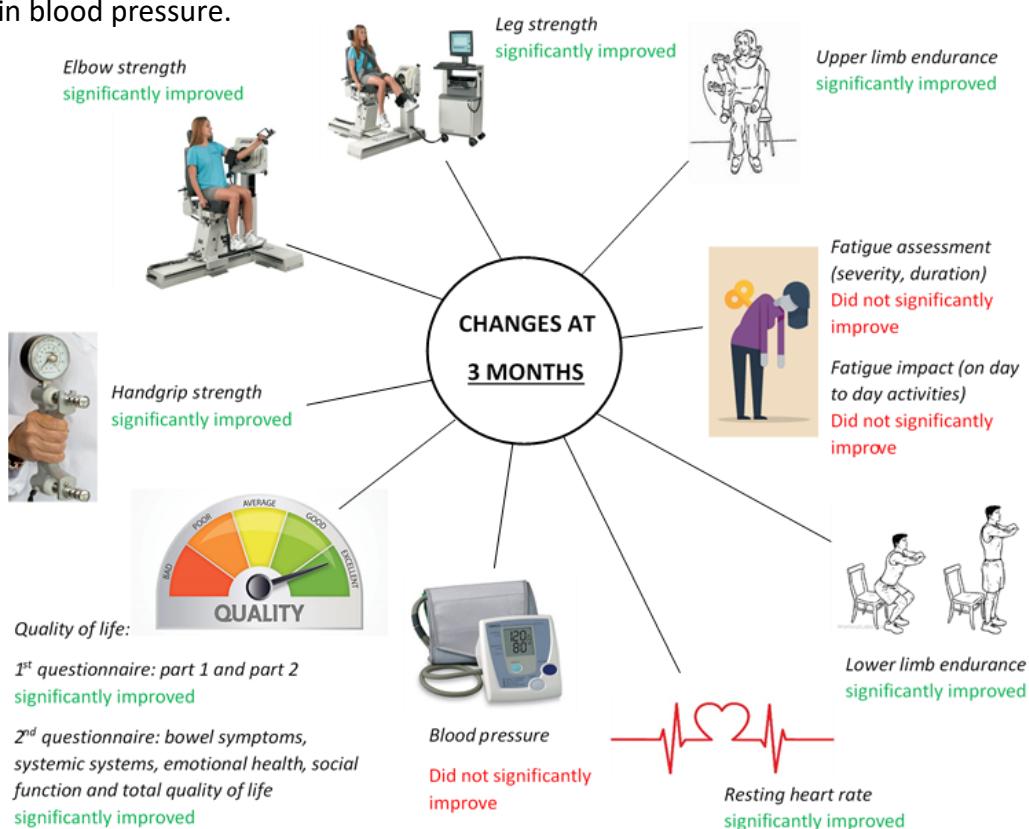
The IBD Bioresource is a national platform designed to research into Crohn's disease and ulcerative colitis and help develop new and better therapies. If you are not already part of the Bioresource and would like to be, please contact the NuTH IBD Research leads: Ashleigh Hogg at ashleigh.hogg@nhs.net or Lesley Jeffrey lesley.jeffrey1@nhs.net.

Q. How will the results of the research be made available to me?

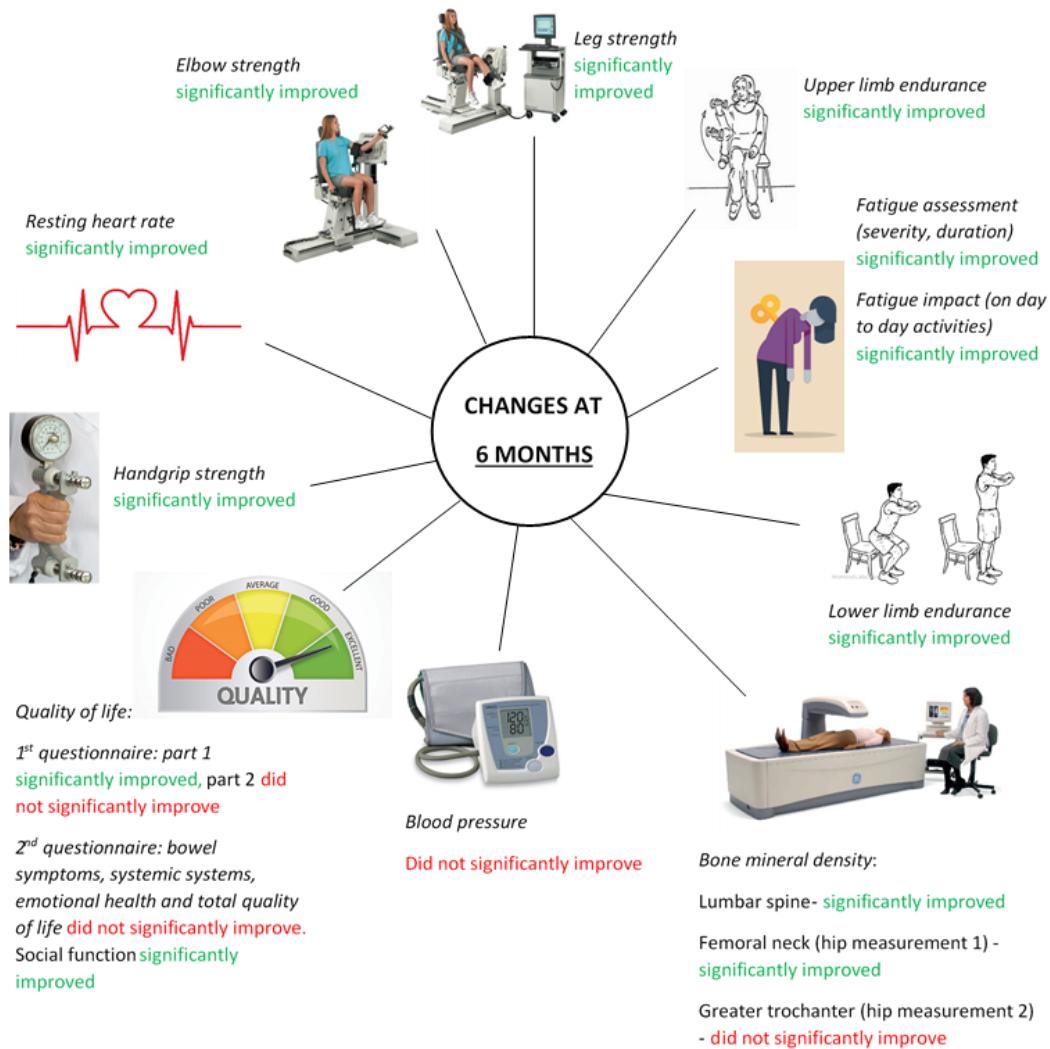
Please find below a summary of the findings. However, if you wish to access the results in more detail please contact one of the team members (contact details below) who can provide you with the information once available.

Q. What did we find?

Results from the 3-month assessment: At 3 months, we found a significant improvement in upper and lower limb strength and endurance measures. Handgrip strength significantly improved as did quality of life and resting heart rate. We found no significant improvements in fatigue severity, duration or impact or in blood pressure.



Results from the 6-month assessment: At 6 months, improvements were sustained in upper and lower limb strength and endurance measures, handgrip strength and resting heart rate. Fatigue severity, duration and impact significantly improved from baseline. Bone mineral density significantly improved at the lumbar spine and hip. Some aspects of quality of life were significantly improved (social function) but no significant improvements were shown in bowel symptoms, systemic systems, emotional health or total quality of life. Blood pressure did not significantly improve.



Q. What were the limitations of this study?

Nutritional intake, although important for bone health, were not taken into consideration. This was primarily due to the complexity of recording food intake for a prolonged period and the inability to determine absorption rates between patients. Future research is needed to determine the potential influence of a nutritional intervention alongside different modes of exercise.

Q. What are the implications of this study?

Our findings support the promotion of a combined impact and resistance-training programme to positively influence bone mineral density, muscle strength and muscle endurance in people with CD. Clinicians should consider asking and supporting their patients who are physically inactive.

Q. How do we let others know about this study?

We have submitted a short report of the study to the largest UK meeting of gastroenterologists, the BSG annual meeting – this will be held in Liverpool in June. We have also submitted a longer report for publication in a Clinical journal, this will need to be reviewed by others (peer-review) before a decision is made on whether the report is accepted for publication.

Thank You

On behalf of the PROTECT team members, University of Northumbria at Newcastle and The Newcastle Upon Tyne Hospitals NHS Foundation Trust we would like to take this opportunity to thank you for your interest and participation in the PROTECT (Resistance training in adults with Crohn's disease) study. We value your participation and the time and effort you committed to our research efforts. Your contribution will help others as a result of the knowledge gained from your participation.

Contact Details

For further information regarding the results of this study, please contact:

- Trial Coordinator: Katherine Jones

Department of Sport, Exercise and Rehabilitation, Northumbria University

Email: Katherine.jones@northumbria.ac.uk **Telephone:** 07434668536 (Mon- Fri 9am-5pm)

- Chief Investigator: Associate Professor Garry Tew

Department of Sport, Exercise and Rehabilitation, Northumbria University

Email: garry.tew@northumbria.ac.uk **Telephone:** 0191 243 7556

Appendix 7t: Debrief sheet

Resistance training in adults with Crohn's disease PARTICIPANT DEBRIEF SHEET

IRAS ID: 226369

Centre Number:.....

Participant ID Number:.....

Other Information:

1. What was the purpose of the project?

The purpose of this study was to investigate the effects of a 6 month resistance training programme on muscle function, bone mineral density, fatigue, quality of life and disease activity in adults with inactive or mildly active Crohn's disease (CD).

2. How will I find out about the results?

If you have requested to receive a summary of the findings the principal investigator will email you approximately 10 weeks after completion of the study.

3. Have I been deceived in any way during the project?

No, you have not been deceived at any point during or after this study.

4. If I change my mind and wish to withdraw the information I have provided, how do I do this?

If, for any reason you do wish to withdraw from this study, please inform the researcher as soon as possible (contact details below) within a month of your participation. They will facilitate your withdrawal and discuss how you would like your data to be treated. However, after this date it might not be possible to withdraw your individual data as the results may have already been published.

As this study may have caused some emotional discomfort, the details for counselling services that will provide support and guidance can be found below:

Crohn's and Colitis UK Support

Tel: 0121 7379931

Online Support: [http://s3-eu-west-](http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/counselling-for-IBD.pdf)

[1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/counselling-for-IBD.pdf](http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/counselling-for-IBD.pdf)

Other Organisations Suggested by CCUK:

British Association for Counselling and Psychotherapy

Tel: 01455 883300

United Kingdom Council for Psychotherapy

Tel: 020 7014 9955

British Association for Behavioural and Cognitive Psychotherapies

Online Support: www.babcp.com

Improving Access to Psychological Therapies

Online Support: www.iapt.nhs.uk

All data collected in this study will be fully anonymised using numerical coding to maintain

confidentiality. Only the principal investigator will have access to any identifiable information which will be kept separate from any data that can identify the participant. All data will be stored on a password-protected computer in accordance with university guidelines and the Data Protection Act

(1998) and destroyed within 2 years after the conclusion of the study. Some results might be reported

in a scientific journal, presented at a research conference or shared within other organisations/institutions, however the data will always remain anonymous unless specific consent is obtained beforehand. At no point will your personal information or data be revealed unless forced to do so by the courts.

If you wish to receive feedback about the findings of this research study then please contact the researcher at katherine.jones@northumbria.ac.uk.

This study and its protocol have received full ethical approval from the Faculty of Health and Life Sciences Research Ethics Committee. If you require confirmation of this, or if you have any concerns or worries concerning this research, or if you wish to register a complaint, please contact the Chair of this Committee (Dr Nick Neave: nick.neave@northumbria.ac.uk), stating the title of the research project and the name of the researcher.

Thank you for participating in this study

Appendix 7u: Audio recording invitation letter

Interview Recording Invitation Version 1.0: 28/01/201



Garry Tew
Northumbria University
Northumberland Building
Newcastle upon Tyne
NE1 8ST
Email: garry.tew@northumbria.ac.uk

DATE

Dear

Thank you for your ongoing participation in the PROTECT study (Resistance training in adults with Crohn's disease). Following the conclusion of the week 26 assessment the researcher will be in contact regarding some follow up questions about your experience in the study and your thoughts on the intervention you received.

We would like to be able to audio record this phone interview to help us gain an in depth knowledge and understanding of the perceptions, benefits and barriers of delivering an intervention like this to aid in the design of future research.

Enclosed is an audio recording consent form, if you are happy with everything on the consent form if you could sign, initial and date the relevant boxes to give your permission for this interview to be recorded. Once you have signed the consent form if you could post it back to us in the pre-paid envelope enclosed. Alternatively, if you do not wish for the interview to be recorded please do not complete the consent form, this will not affect your participation in the study.

We appreciate your help with this study and thank you for continuing to take part.

Yours sincerely

A handwritten signature in black ink, appearing to read "Garry Tew".

Dr Garry Tew, PhD, CSci

PROTECT Chief Investigator
Associate Professor of Exercise and Health Sciences

Appendix 7v: Audio recording informed consent



Faculty of Health and Life Sciences

Informed Consent Form Version 1.1: 20/02/2019

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Resistance training in adults with Crohn's disease

AUDIO RECORDING INFORMED CONSENT FORM

Chief Investigator: Dr Garry Tew

IRAS ID: 226369

Centre Number: RVI/Freeman

Participant ID Number: _____

Study Number: PROTECT

Recording	Purpose	Consent (Initial)
Voice Recording	To enable us to support future Crohn's disease research and to determine the views of participants opinions in regards to the current research study	

I hereby confirm that I give consent for the following recordings to be made, please initial:

1. I understand that the recording(s) may be used for teaching purposes, support future research and may be shared anonymously with other researchers
2. I understand that other individuals may be exposed to the recording(s) and asked to provide feedback. Personal information will never be associated with the recording(s)
3. I understand that once the recording(s) has been published/ in the public domain there may be no opportunity for the effective withdrawal of consent

Name of Participant	Date	Signature
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Name of researcher	Date	Signature
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When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes

Appendix 7w: Exit interview script

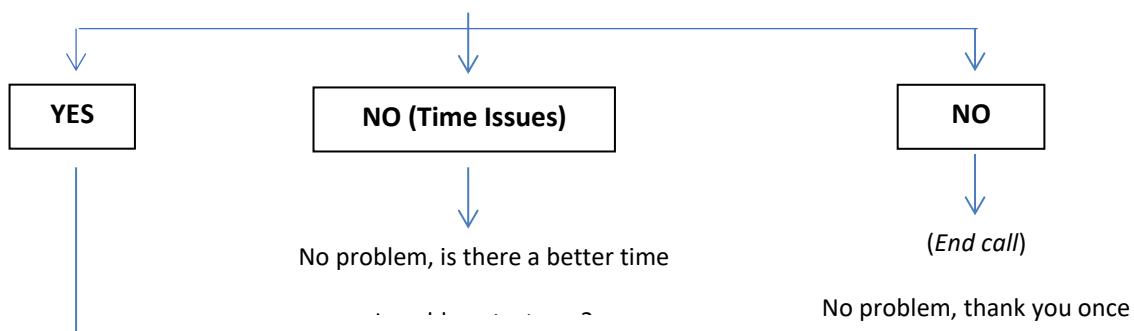
Resistance training in adults with Crohn's disease

EXIT INTERVIEW SCRIPT

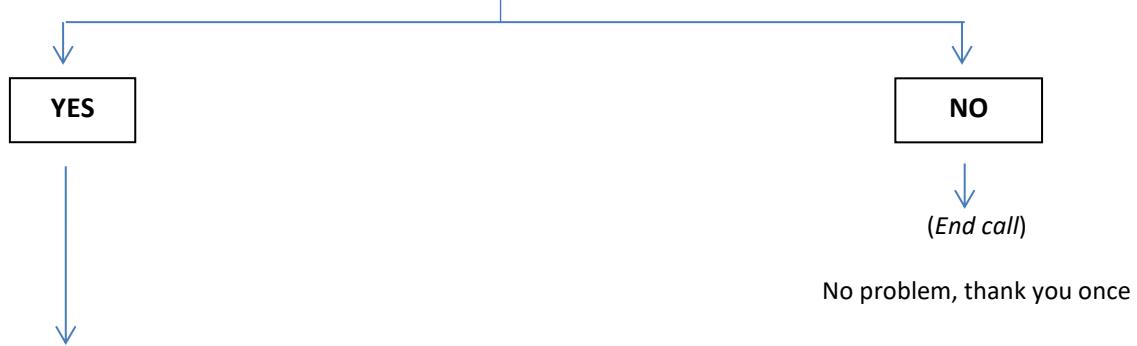
Introduction

Hello [INSERT], this is [INSERT]. I'm just calling in regards to the Resistance Training in adults with Crohn's disease study that you participated in. Thank you once again for taking part in this research study.

Q, At the beginning of the study, you agreed to someone ringing you after the exercise training had ended to ask you some questions regarding your experiences of the study. Please can you confirm you are happy to answer some questions, it should take no longer than 30 minutes?



Q, Before we begin, our discussion will be recorded as part of the research process and transcribed for analysis. Your personal details and everything you say will be anonymised and kept confidential so it cannot be identified. We will talk about your experiences and views of taking part in this study, are you happy to go ahead?



Q, Great, is there anything you would like to say or ask before I start the recorder?

Brief History

Q, Before we start talking about your experience participating in the research study, could you tell me a bit about your Crohn's disease? From when you were diagnosed up until taking part in the research:

- What were your presenting symptoms?
- When were you diagnosed? How long?
- How were you diagnosed?
- What is your history with Crohn's disease- flare ups, problems related to your condition
- What medications have you tried?

- Any surgical procedures?
- Have you tried anything yourself to manage your Crohn's disease?
- Has this method been successful? How?
- Do you experience abdominal pain or joint pain as a result of your condition? How long have you experienced this pain? Is there anything you do to reduce your pain? Is there anything you find makes it worse?

Research Questions

Q, The next few questions will be focused on your experience participating in the study. What were your thoughts when you heard about the research opportunity? How did you hear about the research?

Q, From the information you received which of the following was most important and relevant when deciding to participate:

1. Invitation letter
2. Participant information sheet
3. Organisation (location/timing of assessments)

Q, Was there any additional information you would have liked to receive that might have been helpful when you were deciding to participate?

Q, Why did you choose to participate in the research study?

Q, How did you find the study assessment at the hospital?

- What did you think about the setting at the hospital?
- How did you find the travel and length of the sessions?
- What was your relationship like with the research nurse and clinical investigators?
- How did you find the clinical assessments carried out at the hospital, such as the stool and blood samples and physical examination?

Q, How did you find the study assessments at the university?

- What did you think about the setting at the university?
- How did you find the travel and length of the sessions?
- What was your relationship like with the researcher and other investigators?
- How did you find the clinical assessments carried out at the university such as the bone mineral density scan, muscular performance tests and questionnaires

Intervention Experience (EXERCISE GROUP ONLY)

The next few questions are going to involve your experience in the group you were placed in. What was your initial preference, control or exercise? Why was this your preference?

Q, What did you think when you were allocated to the exercise group?

Q, What did you expect from the exercise programme before you began?

Q, Could you tell me what you thought about the design of the exercise programme?

- How did you feel about completing three sessions a week? (*too often, just right, not enough*)
- How did you find the intensity of the programme? (*too often, just right, not enough*)
- What did you think about the length of the session? (*too often, just right, not enough*)
- What are your thoughts regarding the length of the programme? (*too often, just right, not enough*)
- What are your thoughts on the type of exercise used? (*too often, just right, not enough*)

Q, What are your thoughts about the setting of the exercise programme? Was it appropriate? Could it have been better? If so, how?

Q, Was there anything that made it hard for you're to complete the exercise programme?

Q, What made you keep attending the sessions?

Q, Could you recommend are changes to the exercise programme if the study were to run again?

Q, In regards to the researcher delivering the exercise programme, can you tell me what your relationship was like? How did this relationship compare with your relationship with other healthcare professionals?

Q, Is there any aspect which could have been better? Do you think that the right sort of person delivered the intervention?

Outcomes

Q, Has the exercise intervention had any positive or negative changes on you, such as:

- Physical changes, anything you have noticed as a result of the exercise?
- Apart physical changes, how do you feel in yourself since completing the exercise programme?
- Do you see any changes in your condition after completing the exercise programme?
- Has it affected how you will manage you condition in the future?
- Has it changed your understanding of your condition?
- Do you see you condition differently than before?
- Abdominal pain, has the intervention affected the amount or severity of the abdominal pain you experienced before commencing the exercise programme?
- Joint pain, has the intervention affected the amount or severity of the abdominal pain you experienced before commencing the exercise programme?

Acceptability

The last few questions will focus on your thoughts of the acceptability of the exercise programme.

Q, How acceptable do you think the exercise programme was?

Q, Would you recommend this sort of exercise programme to other people with Crohn's disease? Why?

Q, Can you think of any reasons people with Crohn's disease may not want to participate in this type of exercise? Or research study?

Q, Do you think this type of exercise training should be offered on the NHS for people with Crohn's? If no, why not? If yes, what would the exercise training look like, what would you like to see?

Q, If exercise training wasn't available on the NHS, would you be willing to pay for it and if so much would you be willing to pay?

End

I think we have covered all necessary topics, is there anything you would like to discuss or add? Or do you have any questions?

(*End call*) Thank you very much for your time its greatly appreciated.

Appendix 7x: Clinical characteristics at baseline

Clinical Characteristics ^a

	Exercise [n= 23]	Control [n= 24]	Total [n= 47]
Disease Location, n (%)			
Ileal	5 (21.8)	10 (41.6)	15 (31.9)
Colonic	8 (34.8)	4 (16.7)	12 (25.5)
Ileocolonic	9 (39.1)	9 (37.5)	18 (38.3)
Ileocolonic Crohn's and upper GI disease	1 (4.3)	1 (4.2)	2 (4.3)
Disease Behaviour, n (%)			
Non-Stricturing, Non-Penetrating	14 (60.9)	17 (70.8)	31 (66.0)
Stricturing	5 (21.7)	6 (25)	11 (23.4)
Penetrating	4 (17.4)	1 (4.2)	5 (10.6)
Disease Modifier, n (%)			
Peri-anal Disease	6 (12.8)	7 (14.9)	13 (27.7)
Current Medication, n (%)			
Oral 5-Aminosalicylate	1 (4.3)	1 (4.2)	2 (4.3)
Anti-TNF Treatment	7 (30.4)	12 (50)	19 (40.4)
Immunosuppressants	13 (56.6)	7 (29.2)	20 (42.6)
Anti-diarrheals	3 (13.0)	7 (29.2)	10 (21.3)
Analgesics	2 (8.7)	5 (20.9)	7 (14.9)
Iron Supplements	2 (8.7)	2 (8.3)	4 (8.5)
Vitamin B12 Injections	7 (30.4)	4 (16.7)	11 (23.4)
Calcium Supplementation	4 (17.4)	5 (20.9)	9 (19.1)
Vitamin D Supplementation	5 (21.8)	7 (29.2)	12 (25.5)
Parenteral/ Enteral Nutrition	1 (4.3)	0 (0.0)	1 (2.1)
Folic Acid	6 (26.1)	4 (16.7)	10 (21.3)
Antiemetics	1 (4.3)	2 (8.3)	3 (6.4)
No Medication	1 (4.3)	2 (8.3)	3 (6.4)
Surgical History, n (%)			
Cholecystectomy	0 (0.0)	1 (4.2)	1 (2.1)
Colectomy and ileostomy	5 (21.7)	2 (8.3)	7 (14.9)
Defunctioning ileostomy	1 (4.3)	0 (0.0)	1 (2.1)
Drainage of abscess	0 (0.0)	2 (8.3)	2 (4.3)
Excision of fistula	1 (4.3)	0 (0.0)	1 (2.1)
Ileal/Jejunal resection or stricturoplasty	6 (26.1)	6 (25.0)	12 (25.5)

Ileectomy and anastomosis of ileum to colon	1 (4.3)	1 (4.2)	2 (4.3)
Panproctocolectomy and ileostomy	4 (17.4)	1 (4.2)	5 (10.6)
Perianal surgery	1 (4.3)	1 (4.2)	2 (4.3)
Right hemicolectomy/ ileocecal resection	9 (39.1)	10 (41.7)	19 (40.5)
Sigmoid colectomy and anastomosis	2 (8.7)	0 (0.0)	2 (4.3)
Small bowel resection with end to end anastomosis	2 (8.7)	1 (4.2)	1 (6.4)
Stricureplasty	2 (8.7)	1 (4.2)	3 (6.4)
Subtotal colectomy and primary anastomosis	2 (8.7)	0 (0.0)	2 (4.3)
No surgery	6 (26.1)	7 (29.2)	13 (27.7)
Extra-intestinal Manifestations, n (%)			
None	15 (65.2)	15 (62.5)	30 (63.4)
Enteropathic Arthritis	4 (17.4)	2 (8.3)	6 (12.8)
Erythema Nodosum	1 (4.3)	0 (0.0)	1 (2.1)
Iritis/ Uveitis	0 (0.0)	2 (8.3)	2 (4.3)
Orofacial Granulomatosis	1 (4.3)	0 (0.0)	1 (2.1)
Psoriasis	1 (4.3)	3 (12.5)	4 (8.5)
Ankylosing Spondylitis	1 (4.3)	2 (8.3)	3 (6.4)
Lymphoma/ Malignancy	1 (4.3)	1 (4.2)	2 (4.3)
Serious Infections	1 (4.3)	0 (0.0)	1 (2.1)
Bile Salt Malabsorption	1 (4.3)	1 (4.2)	2 (4.3)
Osteoporosis/ Osteopenia	1 (4.3)	3 (12.5)	4 (8.5)

^a Multiple answers possible

Appendix 7y: Clinical changes at 3 and 6 months

Change in clinical variables from baseline, 3 and 6 month

	Group Allocation	Baseline	3 Months	Adjusted Mean 3 Months (95% CI)	Mean Difference (95% CI)	P value	6 months	Adjusted Mean 6 Months (95% CI)	Mean Difference (95% CI)	P value
<i>Blood Pressure (mmHg)</i>										
Systolic	IG	136 ± 21	126 ± 15	125 (120 to 130)	-7 (-14 to 0)	0.060	129 ± 14	128 (122 to 133)	-1 (-9 to 8)	0.884
	CG	132 ± 20	131 ± 16	132 (127 to 137)			127 ± 18	128 (122 to 134)		
Diastolic	IG	81 ± 13	75 ± 11	73 (70-77)	-4 (-9 to 2)	0.178	76 ± 9	75 (71 to 78)	-3 (-8 to 2)	0.180
	CG	75 ± 9	76 ± 7	77 (73 to 81)			77 ± 10	78 (75 to 82)		
BMI	IG		27.7 ± 5.3	27.3 (26.3 to 28.3)	0.8 (-.555 to 2.3)	0.222	27.9 ± 5.3	27.6 (26.7 to 28.5)	0.9 (-.356 to 2.2)	0.151
	CG		26.1 ± 4.4	26.5 (25.4 to 27.5)			26.4 ± 3.7	26.7 (25.8 to 27.6)		
Resting Heart Rate (beats/min)	IG	79 ± 10	73 ± 8	74 (70 to 77)	-5 (-10 to 0)	0.032	75 ± 11	75 (71 to 79)	-6 (-12 to -1)	0.032
	CG	80 ± 11	79 ± 12	79 (75 to 82)			82 ± 11	82 (78 to 86)		

Mean ± S.D are indicated for all columns unless stated.

IG, Intervention Group; CG, Control Group; BMI, Body Mass Index

Appendix 7z: Best-case and worst-case sensitivity analysis

Best-case sensitivity analysis for primary outcomes at 6 months

	Exercise group (n=23)	Control group (n=24)	Difference	P value
<i>Bone Mineral Density (g/cm²)</i>				
Lumbar Spine	1.103 (1.062 to 1.144)	1.018 (0.978 to 1.058)	0.085 (0.027 to 0.142)	0.005
Greater Trochanter	0.720 (0.693 to 0.746)	0.684 (0.657 to 0.710)	0.036 (-0.002 to 0.074)	0.065
Femoral Neck	0.823 (0.793 to 0.853)	0.770 (0.741 to 0.800)	0.052 (0.010 to 0.095)	0.017
<i>Muscle Strength (Nm)</i>				
Knee Extension-60°/s ^a	104.9 (94.1 to 115.7)	71.6 (61.1 to 82.2)	33.2 (18.1 to 48.4)	<0.001
Knee Extension-180°/s ^a	68.0 (60.4 to 75.6)	44.0 (36.5 to 51.5)	24.0 (13.3 to 34.7)	<0.001
Elbow Flexion-60°/s ^b	36.1 (32.6 to 39.6)	25.8 (22.4 to 29.2)	10.3 (5.4 to 15.2)	<0.001
Elbow Flexion-120°/s ^b	30.8 (27.7 to 33.9)	21.7 (18.7 to 24.8)	9.0 (4.7 to 13.4)	<0.001
HGS (kg)	41.8 (38.9 to 44.6)	30.7 (27.8 to 33.5)	11.1 (7.0 to 15.2)	<0.001
<i>Muscle Endurance (repetitions)</i>				
30-s BCT	24 (23 to 25)	16 (15 to 17)	8 (6 to 9)	<0.001
30-s CST	19 (18 to 20)	14 (13 to 15)	5 (3 to 6)	<0.001

Data are mean and adjusted mean differences with 95% CI's in parentheses

Worst-case sensitivity analysis for primary outcomes at 6 months

	Exercise group (n=23)	Control group (n=24)	Difference	P value
<i>Bone Mineral Density (g/cm²)</i>				
Lumbar Spine	1·090 (1·059 to 1·122)	1·076 (1·045 to 1·107)	0·014 (-0·030 to 0·059)	0·521
Greater Trochanter	0·709 (0·686 to 0·733)	0·711 (0·688 to 0·734)	-0·002 (-0·035 to 0·032)	0·928
Femoral Neck	0·809 (0·787 to 0·831)	0·803 (0·781 to 0·825)	0·006 (-0·026 to 0·037)	0·704
<i>Muscle Strength (Nm)</i>				
Knee Extension-60°/s ^a	100·5 (92·7 to 108·3)	80·2 (72·6 to 87·8)	20·2 (9·3 to 31·2)	0·001
Knee Extension-180°/s ^a	65·4 (59·4 to 71·4)	52·2 (46·3 to 58·1)	13·2 (4·7 to 21·6)	0·003
Elbow Flexion-60°/s ^b	34·5 (32·2 to 36·8)	28·7 (26·4 to 30·9)	5·8 (2·5 to 9·1)	0·001
Elbow Flexion-120°/s ^b	29·7 (27·4 to 32·0)	24·4 (22·1 to 26·7)	5·3 (2·0 to 8·6)	0·002
HGS (kg)	40·8 (39·0 to 42·7)	33·4 (31·6 to 35·2)	7·4 (4·8 to 10·1)	<0·001
<i>Muscle Endurance (repetitions)</i>				
30-s BCT	24 (22 to 25)	17 (16 to 18)	7 (5 to 8)	<0·001
30-s CST	18 (17 to 19)	15 (14 to 16)	4 (2 to 5)	<0·001

Data are mean and adjusted mean differences with 95% CI's in parentheses