A randomised controlled pilot study investigating the effect of increasing physical activity and/or omega-3 supplementation on fatigue in patients with inflammatory bowel disease

Short title/Running head: Lifestyle changes in IBD-related fatigue

ABSTRACT

Objective: Fatigue is frequently reported by patients with inflammatory bowel disease (IBD), irrespective of disease activity; however, evidence regarding fatigue management is limited. This study tested the effect of individualised advice to increase physical activity and/or omega-3 fatty acids supplementation on fatigue in inactive IBD.

Methods: Patients in remission were recruited to a pilot study utilising a randomised controlled 2x2 factorial design (four groups) comparing baseline and post-intervention fatigue scores. Study interventions (12 weeks): individualised exercise advice (15-minute consultation) and/or supplementation (omega-3 fatty acids, 2970mg/day). Control interventions: general health discussion and/or placebo supplement. Primary outcome was fatigue measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale score; secondary outcomes included change in Inflammatory Bowel Disease-Fatigue (IBD-F) scale score.

Results: From n=656 screened patients, n=74 who met the eligibility criteria (designed to remove confounding factors) were randomised, n=60 commenced, and n=52 completed the study. The primary outcome, fatigue measured with FACIT-F score, was worse with omega-3 supplementation (95%CI:-8.6-(-0.7);p=0.02), and unchanged with exercise advice (p=0.38). Fatigue, measured by IBD-F score, was reduced with exercise

advice (95%CI:-3.8-(-0.2);p=0.03). One treatment-related adverse event (musculoskeletal pain) was reported with exercise.

Conclusions: Advice to increase physical activity and omega-3 supplementation, singly or in combination, were shown to be well-tolerated in IBD patients in remission. There was no evidence of exercise-related adverse effects on gut symptoms. Fatigue (IBD-F score) was reduced with exercise advice, but fatigue (FACIT-F score) was unchanged. Increasing fatigue with omega-3 supplementation is unexplained. Regular exercise may be a self-management option in IBD-related fatigue.

Keywords: IBD-Fatigue; Nutrition; Omega-3 supplementation; Physical Activity.

INTRODUCTION

Fatigue is a predominant feature of inflammatory bowel disease (IBD), irrespective of disease activity[1]. While high fatigue prevalence (86%) is observed in active disease (characterised by symptoms including diarrhoea; abdominal pain, cramping and bloating; fever), fatigue levels are still high (41-48%) in disease remission (periods of asymptomatic inactive disease)[1]. Fatigue is reported as a major concern for IBD patients[2, 3], with negative impact on health-related quality of life (HRQOL)[4]. Several physical and psychological factors, such as disease activity and depression, have been suggested to influence IBD-related fatigue, although inconsistencies in these reports prevent firm conclusions being drawn[1, 5]. Results from randomised controlled trials (RCTs) on IBD-related fatigue have reported reductions of fatigue with infliximab or adalimumab[6, 7, 8], and benefits from a stress management programme[9] and solution-focused therapy[10]. However, few studies identify fatigue as their primary endpoint[11], or compare fatigue occurring in the two types of IBD (Crohn's Disease [CD] and Ulcerative Colitis [UC]); in addition, the management of fatigue in remission has received limited attention, despite the fact that focusing specifically on the inactive disease phase allows investigation of IBD-related fatigue unrelated to gut symptoms. This pilot RCT aimed to test the effectiveness and acceptability of two interventions (i) individual advice to increase PA and/or (ii) supplementation with ω-3 FAs, on fatigue in patients with inactive IBD.

Fatigue features in diseases involving the immune system, e.g. cancer, rheumatoid arthritis, and multiple sclerosis. Recent evidence suggests similarities in fatigue

between different conditions[12, 13], though it is unclear which elements of fatigue co-exist. Although physical activity (PA) has been suggested to be appropriate for adults and children with IBD[14, 15], patients may raise concerns regarding exercise-related exacerbation of their symptoms [16].

A few small cohort studies testing PA in IBD patients have reported exercise to be well-tolerated[17, 18, 19, 20]. Low intensity exercise (cycling) was tolerated in patients with CD [17]; improvements in HRQOL and psychological benefits were reported in CD patients (with no/mild-moderate disease activity) undergoing low-moderate intensity PA programmes[16, 18, 19, 20, 21]. Greater impairments in physical fitness (assessed by cardiorespiratory fitness, 6-minute walk distance, and isokinetic muscle strength) and PA levels were reported in fatigued compared with non-fatigued IBD patients, and these were ameliorated by exercise[22]. Self-reported fatigue and skeletal muscle fatigue were significantly correlated in CD patients and non-IBD controls[23]. It has been suggested that anti-inflammatory peptides released by exercising muscle could reduce muscle fatigue[24]. This mechanism may have potential for reducing IBD-related fatigue.

Omega-3 fatty acids (ω-3 FAs, also known as omega-3 fish oils) are polyunsaturated fatty acids essential for normal physiological function in humans, and include the long-chain ω-3 FAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Several characteristics of ω-3 FAs suggest a potential beneficial role in the management of IBD-related fatigue, with positive effects on muscle strength and/or reduced muscle fatigue[25], decreased inflammation and improved mood[26]. EPA

was reported to be particularly beneficial for treating mild depression[27], suggesting that ω-3 FAs might improve mood and HRQOL in IBD patients through the release of cytokines, neuropeptides and eicosanoids in the gut, hence influencing brain function[28, 29].

Given there are no evidence-based guidelines or recommendations regarding type, duration and intensity of exercise for IBD patients[30], we selected an individualised 'Treat-to-Target' strategy for the exercise advice intervention, aiming to initiate a ≥30% increase in PA levels[31]. The regime for the ω-3 FA intervention was comparable with the dose and frequency of regimes used in studies on the effect of ω-3 FA on IBD disease activity [1, 32].

METHODS

A pilot RCT with a 2x2 factorial design was used to test the effect of PA and/or ω-3 FAs on fatigue. The active interventions consisted of: i) Personalised exercise advice to increase PA by 30% and ii) Oral ω-3 FA capsule supplementation. Participants were randomised to one of four groups (See Table I):

1) Exercise advice with ω-3 FAs supplement capsule

2) Exercise advice with placebo capsule

3) ω-3 FAs supplement capsule with exercise placebo

4) Placebo capsule with exercise placebo

Researchers were blinded to capsule type, but not to consultation type; participants were blinded to capsule type and objective PA accelerometer readout, but not to their own level of PA. Block randomisation with computer-generated random numbers allotted participants to one of the four study groups at the first appointment, ensuring similar characteristics and number of participants per group. A schedule of three visits, baseline measures, initiation, and completion of the intervention, were required for participation in the study (see Figure 1 and Supplementary Data, Methods). All patients received follow-up support via email or telephone. The study was approved by the Dulwich Research Ethics Committee (REC 12/LO/1856;13/12/2012). All data were coded prior to analysis to ensure participants' confidentiality and anonymity.

Study Participants

Prospective study participants were approached at tertiary referral hospital IBD out-patient clinics. Those willing to participate were recruited if they met the eligibility criteria of: clinically confirmed CD or ulcerative colitis in remission [C-reactive protein (CRP) <5mg/dl; Harvey-Bradshaw Index (HBI) <5 [33] or Simple Clinical Colitis Index (SCCI) <3 [34]]; self-diagnosed fatigue; ≥18 years old; willing to increase their current activity levels; and able to take medication with ingredients derived from animal/fish sources.

Patients were excluded if they had any comorbidities likely to be confounders for fatigue: anaemia, depression, multiple sclerosis, unstable respiratory or cardiovascular disease, uncontrolled hypertension, mental illness, cognitive dysfunction, reduced mobility, Chronic Fatigue Syndrome or Myalgic Encephalopathy. Patients were also

excluded if they were currently pregnant, taking anticoagulant medications, consumed oily fish ≥ twice per week or 8 times per month, took ω-3 FA supplements during the 12 weeks before screening, performed ≥60 minutes of moderate to vigorous exercise weekly, or were currently participating in another RCT.

Description of interventions

Interventions were delivered over a 12 week period.

i) Exercise Advice: An individual 15-minute consultation with a personal trainer and researcher (AM) was provided at week 1. Advice consisted of personalised goal setting using the treatment paradigm of 'Treat-to-Target' to initiate a ≥30% increase in PA levels[31]. This is in line with current recommendations of 30-60 min of dynamic exercise of the large muscles, three to four times per week [35]. Personal PA goals and achievements were recorded in a diary kept by participants for the study duration. A positive approach to the PA advice provided was encouraged by initiating and maintaining motivation. This utilised techniques of imagery, goal setting (for each week and the whole programme), and overcoming barriers to exercise (e.g. physical limitations and fears of worsening IBD symptoms). The exercise trainer assessed participants' mobility, and from their self-reported clinical and exercise history (frequency, duration and intensity of exercise), suggested a type of activity enabling an increase in exercise levels. Examples of PA for less active individuals included initiation of walking, swimming and simple gym routines. For those already undertaking some exercise, the trainer suggested activities enabling them to extend their personal goals, e.g. training for a 5km - 10km run.

ii) ω-3 FA Supplement Capsules: A total daily oral dose comprised 2970mg pharmaceutical grade ω-3 FAs (EPA, 2250mg; DHA, 150mg; "Take Omega-3"©, Edinburgh, UK) in three capsules. Current guidelines suggest that doses up to 3g per day of marine derived ω-3 FAs are safe [36]; a high EPA:DHA ratio is thought to be preferable [27, 37, 38].

iii) Exercise Placebo: A 15-minute conversation with the researcher (AM) about the participant's' current dietary habits and general health was undertaken at week 1, including questions such as: 'Can you tell me about your current diet?', 'Did you have to change your diet following the diagnosis of IBD?', and 'In what way has IBD affected your general health?' No advice was given by the researcher regarding exercise.

iv) Placebo Capsule: Similar appearing capsules to the ω-3 FA supplement capsules contained placebo (capric and caprylic acid).

Participants in all groups were contacted by the researcher (AM) via telephone or email on six occasions during the intervention, a week following commencement of the interventions and then approximately every two weeks. Topics of conversation covered their well-being, whether they were taking the capsules as instructed, and the occurrence of any adverse effects. In addition, those receiving exercise advice were asked about progress towards set goals during that period. The exercise goals were reinforced and renegotiated (if necessary), and any adverse effects or barriers to activity were discussed. Participants were also reminded not to eat ≥2 portions of oily fish/week or 8 portions per month, and not to take additional ω-3 FA supplements during the intervention period.

Compliance to ω-3 FA supplement intake was assessed via self-report diary, kept by all study participants, in which they recorded their capsule intake, levels of dietary sources of ω-3 FAs, and possible treatment-related adverse effects. Participants returned left-over capsules, which were counted to assess the number of capsules missed. Compliance to increased exercise during the intervention period was assessed by comparison of goals set and achievements recorded in the self-report diaries.

Study Outcomes and Measurement Tools

The primary study outcome was fatigue, measured with the Functional Assessment of Chronic Illness Therapy – Fatigue scale (FACIT-F)[39]. Other fatigue scales were used as secondary outcome measures: the Multidimensional Fatigue Inventory (MFI)[40] and the Inflammatory Bowel Disease-Fatigue (IBD-F) scale [41]. The rationale for using these different scales is provided in Table II. In addition, HRQOL was assessed with the Inflammatory Bowel Disease Quality of Life questionnaire (IBDQ)[42], and anxiety and depression with the Hospital Anxiety and Depression Scale (HADS)[43]. Physical activity levels were recorded daily for up to seven non-contiguous days (incorporating two weekend days and at least four weekdays), using a bi-axial accelerometer GT1M (Actigraph, Pensacola, US)[44]. A valid PA assessment was defined as wear-time ≥11 hours per day, and data were analysed using Actilife data analysis software version 6.5. All outcomes were assessed at baseline and at the end of the treatment. Participants' demographic data and other variables (see Table II) were also collected.

Statistical Methods

Categorical variables were analysed with Fisher's exact test. Normally distributed continuous variables were analysed using analysis of variance (ANOVA), whilst the Kruskal-Wallis test was used for non-normally distributed continuous variables. Continuous outcomes were analysed using analysis of covariance (ANCOVA), with a log scale used for non-normally distributed data. Binary outcomes were analysed by logistic regression. The baseline value of each outcome was used as a covariate in the analysis. A p-value ≤0.01 was deemed statistically significant for all outcomes since multiple measurements were collected.

RESULTS

Study Participants

Recruitment took place over a period of 13 months, and 656 patients with confirmed or suspected IBD were screened. Seventy-four eligible participants received the Patient Information Sheet before informed consent was obtained, 60 were randomised and commenced the intervention, and 52 completed the protocol. Study flow, and reasons for exclusion and withdrawal of participants are shown in Figure 2.

Data were analysed on an intention-to-treat basis; however, results did not differ from those following per protocol analysis.

Baseline variables

Patient demographics and baseline values of variables in the four study groups were comparable in relation to disease type, location, activity scores, treatment received (Table III), and scores for fatigue scales, Health-Related Quality of Life, and PA

(Supplementary data, Table SI). The only difference between groups at baseline was for depression (p=0.04), highest in the group receiving ω-3 FAs and exercise placebo, which was adjusted for in subsequent analyses.

Outcome variables

There were no interactions (at p-value <0.01) between the effects of exercise advice and those of ω-3 FAs on fatigue (Table IV). In this circumstance, the 2x2 factorial study design enables analysis as two rather than four groups. Hence, fatigue levels could be compared for participants receiving exercise advice (n=26) versus exercise placebo (n=26) (regardless of whether they took ω-3 FAs); and fatigue levels could be compared for participants receiving ω-3 FA supplement (n=25) versus placebo supplement (n=27) (regardless of whether they had received exercise advice), adjusted for the baseline difference in depression between groups (Table I).

There was no significant difference in fatigue measured by FACIT-F score between those receiving exercise advice and exercise placebo (p=0.38). However, a small but statistically insignificant difference was shown between mean FACIT-F scores for those receiving the ω-3 FA supplement compared to those receiving placebo capsules (mean (95% CI):-4.6(-8.6,-0.7);p=0.02): Patients receiving ω-3 FA supplements had average scores 4.6 units lower (worse fatigue) than patients receiving placebo.

Fatigue severity, measured by the IBD-F scale as a secondary outcome, was lower in patients receiving exercise advice than in those receiving exercise placebo (mean (95% CI):-2.0(-3.8,-0.2);p=0.03). However, there was no observed effect of ω-3 FAs on the

IBD-F scale scores (Table IV). No statistically significant changes for any of the other secondary outcomes (disease activity scores, other fatigue scale scores, and anxiety and depression scores) were found between exercise advice, ω-3 FAs, or placebo groups (at p-value <0.01) (Table IV).

Satisfactory compliance of all groups to low levels of dietary sources of ω-3 FAs, and correct capsule intake were reported (Table IV). Diary entries from the exercise groups indicated broad compliance with the goals set, although no changes in PA levels were documented following the intervention period (Table IV).

Adverse events

There were no differences in the number of adverse events (gastrointestinal, musculoskeletal, and dermatological) reported between the four treatment groups (Figure 3), indicating that the adverse effects reported were unlikely to be linked to the interventions. The Odds Ratios (CI 95%) for a patient experiencing an adverse event following receipt of exercise advice or ω-3 FA were 1.14(CI 0.35-3.67) and 0.67(CI 0.21-2.18) (p=0.51), respectively. None of the adverse events were considered serious, with only one case of musculoskeletal pain possibly related to treatment resulting in cessation of exercise. The most frequently reported symptoms of diarrhoea (three cases) or epigastric discomfort (five cases) were reported across all four patient groups (Figure 3). No patient discontinued the supplements due to adverse effects.

DISCUSSION

This single site, pilot RCT tested the effect of advice to increase exercise, alone or in combination with ω-3 FA supplementation, on fatigue levels in inactive IBD. The interventions were shown to be generally well-tolerated, with only one possible treatment-related adverse event (musculoskeletal pain) resulting in discontinuation of the exercise intervention.

This is the first study in IBD patients providing individually-prescribed advice relating to non-supervised PA on a Treat-to-Target basis[31], aiming to increase each individual participant's PA by 30%. There was some indication that exercise advice improved IBD-related fatigue. This was demonstrated by lower scores from the secondary outcome measure IBD-F – an IBD-fatigue specific scale - although this effect was not apparent from other fatigue scales, notably from the primary measure (FACIT-F scale). This raises the possibility that different scales detect different facets of fatigue (see Table II) - possibly occurring at varying frequencies in CD and UC patients - justifying further investigation. Advantages of the Treat-to-Target approach include promoting engagement in non-supervised exercise by previous non-exercisers: reports from participants receiving the exercise advice ranged from expressions of initial enthusiasm to life-changing positive experiences.

Studies investigating the effect of exercise on symptoms of chronic disease including fatigue, have reported on similar intervention periods of 12 weeks or less [45, 46]. A recent RCT investigating the effect of a 10-week PA program in 30 cases of mild-moderate IBD has reported a non-significant increase in HRQOL, predominantly through effects on the IBD-Q social subscale[21]. Thus, larger studies investigating the

effect of exercise on IBD-related fatigue, possibly including longer intervention periods, are warranted.

In the ω-3 FA group, the finding of worsening of fatigue as measured by the FACIT-F scale was not statistically significant, and not observed with any of the other fatigue scales utilised; hence, results from this study do not provide evidence to support the effectiveness of ω-3 FA supplements on IBD-related fatigue.

The effect of ω-3 FA on fatigue in IBD has not been studied previously. Results from RCTs in healthy individuals have shown varied effects of ω-3 FA supplementation (up to 12 weeks) on cognitive function and mood[37, 38, 47], and a 6-week intervention including ω-3 FA significantly reduced fatigue in patients with lung cancer[48]. However, in our study a 12-week period of ω-3 FA supplementation, did not appear sufficient to show a reduction in IBD-related fatigue.

Previous studies using 1800mg-7000mg ω-3 FA per day (compared to the 2970mg daily dose in this study), showed positive effects on maintenance of IBD activity remission[1, 49], although beneficial effects on IBD-related fatigue may require different dosage regimes. Omega-3 FA supplementation at lower dose (up to 690mg per day) and for a shorter period (8 weeks) than in the present study, significantly increased levels of blood erythrocyte ω-3 FAs [50], suggesting that the dosage and intervention period used in this study did produce biologically active levels of ω-3 FAs.

Exercise has proven beneficial in healthy individuals[35]. Potential positive benefits were also reported in studies with IBD patients, including muscle mass gain[51], and increased bone mineral density and HRQOL[16]. Symptoms of IBD, such as diarrhoea,

especially if accompanied by fears of incontinence, may create barriers to exercise[52]. Evidence to date suggests that individuals with IBD should benefit from increased exercise[15, 22, 23, 53, 54], and in particular, that low-moderate intensity PA is safe[19, 55]. The results from our study support these findings: no serious adverse effects related to exercise were reported. Clinicians' reluctance to prescribe exercise because of the fear of symptom exacerbation can now be largely dispelled[16].

The strength of this study lies in its 2x2 factorial design; in the absence of interaction between the effects of exercise advice and ω-3 FA supplements on IBD-related fatigue, data from all participants could be analysed in two groups for each intervention (n=25-27). The relatively small sample size may be seen as a limitation (and precluded comparison of CD and UC cases), although this can be justified given the trial's pilot status. The large numbers of patients excluded relates to the stringent eligibility criteria used to remove potential effects from confounding factors (e.g. fatigue-related comorbidities, 131/656;20%; pre-existing exercise or ω-3 FAs intake, 43/656; 7%), or else because of patients' non-availability for the full study period (147/656;23%). Whilst the self-report diaries used in this study may be useful tools to confirm adherence to protocols, they have known limitations since their veracity cannot be proven. However, careful review of the completed diaries suggested contemporaneous completion without systemic bias regarding nutritional intake.

Conclusions

This was the first study assessing the effect of exercise advice and/or ω-3 FA supplementation in IBD patients with inactive disease: the results demonstrate that

these interventions are generally well-tolerated, and suggest that patients with IBD-related fatigue could safely increase levels of PA. There is a need for further investigation in a larger sample to derive recommendations and specific practice-based guidelines; in addition, the use of IBD-F, a population-specific disease scale, should be considered in future studies. Omega-3 FA supplementation did not produce positive results on IBD-related fatigue, although there were no serious adverse effects related to its intake. It is possible that regular PA may provide an effective self-management option in IBD-related fatigue.

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Statement of Authorship

The following authors have made substantial contributions to the following:

(1)The conception and design of the study - AM, IN, MM, CN, GG, FB, WCD, SB, MG, MD, HT, AF

Acquisition of data - AM, IN, MM, FB, MD

Analysis and interpretation of data - AM, IN, MM, GG, CN, FB, WCD, SB, MG, MD, HT, AF

(2)Drafting the article or revising it critically for important intellectual content: AM, IN, MM, CN, GG, WCD, HT, AF

(3)Final approval of the version to be submitted - AM, IN, MM, GG, CN, FB, WCD, SB, MG, MD, HT, AF

Statistical analysis was performed by Paul Bassett, Statsconsultancy Ltd, http://www.statsconsultancy.co.uk

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TABLES

		Exercise Advice	
		Yes	**No**
Omega-3 Fatty Acids	**Yes**	Exercise advice + ω-3 FAs (Group 1)	ω-3 FAs (Group 3)
	No	Exercise advice (Group 2)	Neither (Group 4)

Treatment Groups:

1) **Exercise advice with ω-3 FAs supplement capsule (n=11):**

   Consultation with personal trainer; activity and diet diary; omega-3 fatty acid capusles

2) **Exercise advice with placebo capsule (n=15):**

   Consultation with personal trainer; activity and diet diary; placebo capsule

3) **ω-3 FA supplement capsule with exercise placebo (n=14)**

   Consultation with researcher; diet diary; omega-3 fatty acid capusles

4) **Placebo capsule with exercise placebo (n=12)**

   Consultation with researcher; diet diary; placebo capsule

Table I: 2x2 Trial Design and Details of Treatment Groups.

ω-3 FAs: Omega-3 Fatty Acids.

Outcome variable	Scale/Assessment	Outcome	Rationale
Fatigue score	Functional Assessment of Chronic Illness Therapy – Fatigue scale[39]	Primary	The only fatigue scale validated in IBD patients at the time of the study design
Fatigue score	Multiple Fatigue Inventory scale[40]	Secondary	The most frequently-used scale in studies of IBD fatigue (but not validated in the IBD population)
Fatigue score	Inflammatory Bowel Disease-Fatigue scale[41]	Secondary	Scale developed and tested in the IBD population; used in

			this study to further test its validity
Quality of Life score	Inflammatory Bowel Disease – Quality of Life scale[42]	Secondary	Health-related quality of life scale validated for use with IBD patients
Depression score	Hospital Anxiety and Depression scale[43]	Secondary	Scale assessing role of anxiety and depression in influencing fatigue levels
Activity counts per minute; Time spent in Moderate-Vigorous Physical Activity; Daily steps	Accelerometer, GT1M (Actigraph)[44]	Secondary	Objective measure of physical activity
Disease activity score	Harvey-Bradshaw Index[33] and Simple Clinical Colitis Index[34]	Secondary	Validated scales indicating level of disease activity
Height and weight measurement	Procedure	Secondary	To indicate change in body composition
Haemoglobin measurement	Procedure - blood test	Secondary	To determine iron status
C-Reactive Protein measurement	Procedure - blood test	Secondary	As a marker of inflammation

Table II: Details of Assessment Tools Used for Data Collection.

IBD: Inflammatory bowel disease

Variable	**Placebo**		**Omega-3 Fish Oils**		**p-value**
	No Exercise (n=12)	Exercise (n=15)	No Exercise (n=14)	Exercise (n=11)	
Age [a]	31 (27, 51)	35 (28, 43)	45 (36, 51)	31 (29, 55)	0.52
Gender - Male	4 (33%)	8 (53%)	7 (50%)	6 (55%)	0.74

Ethnicity - White	9 (75%)	10 (67%)	14 (100%)	9 (82%)	0.11
- Other	3 (25%)	5 (33%)	0 (0%)	2 (18%)	
Smoker - No	11 (92%)	14 (93%)	13 (93%)	9 (82%)	0.80
Haemoglobin [b]	13.7 (1.7)	13.6 (1.4)	13.5 (0.9)	13.8 (1.4)	0.96
CRP [a]	1.6 (0.7, 2.7)	1.0 (0.6, 3.3)	1.2 (0.7, 3.2)	2.4 (1.2, 6.2)	0.29
BMI (kg/m^2) [b]	24.9 (4.5)	23.9 (4.2)	25.7 (3.9)	26.3 (3.1)	0.46
Diagnosis - CD	6 (50%)	6 (40%)	7 (50%)	6 (55%)	0.99
- UC	6 (50%)	8 (53%)	7 (50%)	5 (45%)	
- IBD unclassified	0 (0%)	1 (7%)	0 (0%)	0 (0%)	
Surgery	3 (25%)	5 (33%)	5 (36%)	3 (27%)	0.93
Stoma	0 (0%)	1 (7%)	2 (14%)	0 (0%)	0.54
SCCI [c]	5.0 (2.9)	5.6 (1.7)	4.9 (0.9)	5.0 (2.2)	0.90
HBI [d]	4.8 (2.7)	4.9 (3.1)	6.0 (2.8)	5.3 (4.3)	0.90

Table III: Demographics and Baseline Variables of the Study Participants.

[a] Median (inter-quartile range) reported. [b] Mean (standard deviation) reported. [c] Figures for patients with ulcerative colitis and unclassified inflammatory bowel disease. [d] Figures for patients with Crohn's disease and unclassified inflammatory bowel disease. P-value ≤0.01 indicates a statistically significant difference between the four groups. CRP: C - reactive protein;

BMI: Body Mass Index; CD: Crohn's disease; UC: Ulcerative Colitis; IBD: Inflammatory Bowel Disease; SCCI: Simple Clinical Colitis Index; HBI: Harvey Bradshaw Index.

Variable	Interaction[e]	Exercise Advice (n=26)		Omega-3 Fish Oils (n=25)	
	p-value	Mean (95% CI)	p-value	Mean (95% CI)	p-value
FACIT-F	0.24	1.8 (-2.3, 5.8)	0.38	-4.6 (-8.6, -0.7)	0.02

SCCI [a]	0.13	-0.6 (-1.8, 0.7)	0.37	-0.4 (-1.6, 0.9)	0.54
HBI [b]	0.77	-2.0 (-4.2, 0.2)	0.07	1.1 (-1.1, 3.3)	0.31
≥ 1 day's capsules missed [c]	0.30	0.70 (0.17, 2.96)	0.63	2.17 (0.52, 9.00)	0.29
Mean MVPA/day	0.80	-7.5 (-22.6, 7.6)	0.32	-9.9 (-25.1, 5.3)	0.20
CPM	0.78	57 (-153, 39)	0.24	-46 (-142, 51)	0.35
Steps/day	0.71	-443 (-2829, 1942)	0.71	-1212 (-3600, 1176)	0.31
Wear time/day	0.14	-0.8 (-3.1, 1.4)	0.46	0.0 (-2.3, 2.3)	0.97
Calendar days	0.47	-0.8 (-2.0, 0.4)	0.17	-0.2 (-1.4, 0.9)	0.71
Hemoglobin	0.04	-0.1 (-0.5, 0.3)	0.63	0.0 (-0.4, 0.4)	0.93
CRP [d]	0.47	0.76 (0.48, 1.20)	0.24	0.95 (0.59, 1.51)	0.81
Weight (kg)	0.76	0.3 (-1.1, 1.7)	0.69	-0.3 (-1.8, 1.1)	0.64
IBD-F Section I	0.48	-2.0 (-3.8, -0.2)	0.03	0.7 (-1.1, 2.5)	0.42
IBD-F Section II	0.33	-3.8 (-10.4, 2.7)	0.25	6.0 (-0.4, 12.3)	0.07
MFI general	0.53	-1.5 (-3.1, 0.1)	0.07	0.1 (-1.5, 1.7)	0.92
MFI physical	0.50	-0.9 (-2.6, 0.8)	0.30	1.1 (-0.5, 2.8)	0.18
MFI activity	0.70	-0.7 (-2.6, 1.3)	0.50	1.1 (-0.8, 3.0)	0.26
MFI motivation	0.35	-0.9 (-2.6, 0.8)	0.30	0.9 (-0.8, 2.6)	0.30
MFI mental	0.27	-0.60 (-2.4, 1.2)	0.50	-0.38 (-2.2, 1.4)	0.67
IBD-Q	0.83	3 (-7, 14)	0.56	2 (-9, 12)	0.74
HADS Anxiety	0.29	0.0 (-1.5, 1.6)	0.97	0.9 (-0.6, 2.4)	0.23
HADS Depression	0.55	0.1 (-1.3, 1.5)	0.86	1.0 (-0.4, 2.4)	0.16

Table IV: Comparisons of the effects of exercise advice and fish oil capsules compared with no exercise advice and placebo capsules respectively, on physical activity and fatigue assessments in patients with Inflammatory Bowel Disease.

[a] Figures for patients with UC and unclassified IBD; [b] Figures for patients with Crohn's disease and unclassified inflammatory bowel disease; [c] Odds Ratio (95% CI) reported; [d] Variable analyzed on log scale. Ratio (95% CI) reported; [e] Indicates whether the effects of exercise advice are independent from those of omega-3 fish oils. For all outcomes, $p \leq 0.01$ indicates a statistically significant difference between groups. Differences were adjusted for baseline differences between groups. FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue scale; SCCI: Simple Clinical Colitis Index; HBI: Harvey Bradshaw Index; MVPA: Moderate-vigorous physical activity; CPM: Counts per minute; CRP: C - reactive protein; IBD-F: Inflammatory Bowel Disease-Fatigue scale; MFI: Multidimensional Fatigue Inventory scale; IBD-Q: Inflammatory Bowel Disease – Quality of Life scale; HADS: Hospital Anxiety and Depression Scale.

FIGURES LEGENDS

Figure 1: Study Outline and Schedule

FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue scale; IBD-F: Inflammatory Bowel Disease - Fatigue scale; MFI: Multidimensional Fatigue Inventory scale; IBD-Q: Inflammatory Bowel Disease - Quality of Life scale; HADS: Hospital Anxiety and Depression Scale.

Figure 2: CONSORT Flowchart for Patients in Inflammatory Bowel Disease and Fatigue Study

Figure 3: Adverse Effects Reported during 12-week Intervention of Advice to Increase Physical Activity and/or Omega-3 Fatty Acids. IBD: inflammatory bowel disease.