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

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The manuscript, including related data, figures and tables has not been previously published and it is not under consideration elsewhere. A summary of this data was presented at the Digestive Disease Federation meeting, London, June 2015, and at the European Crohn’s and Colitis Organisation meeting, Amsterdam, March 2016.

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 IBD-related fatigue.

Methods: A pilot study in patients with inactive IBD, utilising a randomised controlled 2x2 factorial design (four groups) compared baseline and post-intervention fatigue scores. Study interventions: individualised exercise advice (15 minute consultation) and/or supplementation (omega-3 fatty acids, 2970mg/day) for 12 weeks. Control interventions: general health discussion and/or placebo supplement. All patients received follow-up support. 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 selection criteria were randomised, n=60 commenced, and n=52 completed the study. tThe primary outcome fatigue, measured with FACIT-F, showed slight worsening in the omega-3 supplementation group (95%CI:-8.6-(-0.7);p=0.02), and no change in the exercise advice group (p=0.38). Reduced fatigue, measured by IBD-F score, was identified in the exercise group (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 safe and generally well-tolerated. There was no

evidence of exercise-related adverse effects on gut-related symptoms, and some evidence of improvement in fatigue. The slight worsening of fatigue with omega-3 supplementation is unexplained. Regular moderate to vigorous exercise may be a self-management option in IBD-related fatigue.

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

INTRODUCTION

Fatigue is predominantly a feature of active inflammatory bowel disease (IBD), but remains a problem for some patients even during remission, with a prevalence of 41-48%(1). With negative impact on health-related quality of life (HRQOL)(2), fatigue is consistently reported as a major concern for IBD patients (3, 4). Several physical and psychological factors, such as disease activity and depression, have been reported to influence fatigue in IBD, 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(6-8), and benefits from a stress management programme(9) and solution-focused therapy(10). However, few studies identify fatigue as their primary endpoint(11), and there is no consensus regarding mechanisms driving fatigue or suggestions for treatment.

Fatigue appears in diseases involving the immune system, e.g. cancer, rheumatoid arthritis (RA), and multiple sclerosis (MS). 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(21). There are no evidence-based guidelines or recommendations regarding type, duration and intensity of exercise for IBD patients(16). A few small cohort studies testing PA in IBD patients have reported exercise to be well-tolerated(17-20). Patients with Crohn's Disease (CD) tolerated

cycling at low (60%) oxygen consumption(17). (18). Need to say what this means – ie low O2 consumption means physiologically well tolerated

Improvements in HRQOL and psychological benefits were reported in CD patients (with no/mild-moderate disease activity) undergoing low to moderate intensity PA programmes insert 18, 20, 22 (19, 21, 22). 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(23). Self-reported fatigue and skeletal muscle fatigue were significantly correlated in CD patients and non-IBD controls (24). It has been suggested that anti-inflammatory peptides released by exercising muscle could reduce muscle fatigue(25). This mechanism may have potential for reducing IBD-related fatigue.

Exercise interventions have been tested for fatigue management in other chronic disorders. A Cochrane review of the effects of exercise on fatigue in patients with advanced progressive illnesses, such as cancer and MS, reported a benefit from exercise (26). However, review of studies in RA reported only limited benefit from exercise on fatigue (27).

Several characteristics of omega-3 fatty acids (ω-3 FAs, also known as omega-3 fish oils) suggest a potential beneficial role in the management of IBD-related fatigue, with positive effects on muscle strength and/or reduced muscle fatigue (32), decreased inflammation and improved mood(28). Eicosapentaenoic acid (EPA) was reported to be particularly beneficial for treating mild depression(29), 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(30, 31). (32).

A study of breast cancer survivors reported that higher intake of ω-3 FAs was significantly associated with reduced physical parameters of fatigue(33). In advanced lung cancer, supplementation with ω-3 FAs (amongst other treatments) reduced fatigue and inflammation significantly(34). However neither study measured cancer-related fatigue as the primary endpoint. Systematic reviews of the effect of ω-3 FAs on the maintenance of IBD remission have found insufficient evidence to recommend a change in clinical practice(35-37), although further interventional studies were recommended. Many previous studies have used IBD populations with mixed disease activity, precluding generalisation of results to patients either with active disease or those in remission. Studies in participants with defined disease activity may provide greater clarity regarding effects of interventions.

Therefore, this pilot RCT aimed to test the safety and effectiveness of two interventions (i) individual advice to increase PA and/or (ii) supplementation with ω-3 FAs, on fatigue in patients with inactive IBD.

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 FAs capsule supplementation. Participants were randomised to one of four groups (See Table 1):

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, 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;). 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 UC in remission [C-reactive protein (CRP) <5mg/dl; Harvey-Bradshaw Index (HBI) <5 (38) or Simple Clinical Colitis Index (SCCI) <3 (39)]; 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 of the confounding comorbidities: anaemia, depression, MS???, 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-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 individualised goal setting using the treatment paradigm of 'Treat-to-Target'(40) to initiate a ≥30% increase in PA levels. This is in line with current recommendations of 30-60 min of dynamic exercise of the large muscles, three to four times per week (41). 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 FAs Supplement Capsules: A total daily oral dose comprised 2970mg 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 (42); a high EPA:DHA ratio is thought to be preferable (29, 43, 44).

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 a healthy lifestyle.

iv) Capsule Placebo: Similar appearing capsules to the ω-3 FAs 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, specific to the participants' group allocation, 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)(45). Other fatigue scales were used as secondary outcome measures: the Multidimensional Fatigue Inventory (MFI)(46) and the Inflammatory Bowel Disease-Fatigue (IBD-F) scale (47). In addition, HRQOL was assessed with the Inflammatory Bowel Disease Quality of Life questionnaire (IBDQ)(48), and anxiety and depression with the Hospital Anxiety and Depression Scale (HADS)(49). 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)(50). 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 2) were also collected.

Statistical Methods

Categorical variables were analysed with Fisher's exact test. Continuous variables found to be normally distributed were analysed using analysis of variance (ANOVA), whilst continuous variables not found to be normally distributed were analysed using the Kruskal-Wallis test.

Continuous outcomes were analysed using analysis of covariance (ANCOVA). Non-normally distributed data were analysed on a log scale. 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 were screened. Those eligible for the study received the Patient Information Sheet before informed consent was obtained. Seventy-four participants were randomised, 60 commenced the intervention and 52 completed the protocol. Study flow and reasons for withdrawal and exclusion of patients 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

Baseline values of variables in the four study groups were comparable in relation to disease type, location, activity scores, treatment received (Table 3), and fatigue scale scores and PA (Supplementary data, Table S1). 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 4), enabling analysis as two rather than four groups. Hence, data from all patients was used to evaluate both interventions: for exercise advice (n=26) versus exercise placebo (n=26); and for ω-3 FA supplement (n=25) versus placebo supplement (n=27), adjusted for the baseline difference in depression between groups (Table 1).

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 not statistically significant 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 4). 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 FA, or placebo groups (at p-value <0.01) (Table 4).

Satisfactory compliance of all groups to low levels of dietary sources of ω-3 FAs, and correct capsule intake were reported (Table 4). 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 4).

Adverse events

Seventeen adverse events were reported, including gastrointestinal, musculoskeletal, and dermatological side effects (Figure 3), with no differences between the four treatment groups (p=0.51). The Odds Ratios (CI 95%) for a patient experiencing an adverse event following receipt of exercise advice or ω-3 FAs 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 (considered as likely to have been related to treatment) resulting in cessation of exercise. The most frequently reported symptoms, of diarrhoea or epigastric discomfort, both common in IBD, were no more apparent in exercisers or those taking ω-3 FAs. 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 in IBD patients. The interventions were shown to be safe and generally well-tolerated. This is the first study in IBD patients providing individually-prescribed advice relating to non-supervised PA on a Treat-to-Target basis (40), aiming to increase each individual participant's PA by 30%. This approach also promotes 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. Improvement in fatigue was only demonstrable with the secondary outcome measure (IBD-F), and not from the primary measure (FACIT-F). In the ω-3 FAs group, a slight worsening of fatigue as measured by the FACIT-F scale was not statistically significant.

The effect of ω-3 FAs on fatigue in IBD has not been studied previously. Results from RCTs in healthy individuals have shown beneficial effects of ω-3 FA supplementation for weeks on cognitive function and mood(43, 44, 51). A 6-week intervention including ω-3 FAs significantly reduced fatigue in patients with lung cancer(34), and an ongoing randomised trial of ω-3 FAs in breast cancer-related fatigue is also using a 6-week treatment period (https://clinicaltrials.gov/ct2/show/NCT02352779). In our study on IBD patients, a 12-week period of ω-3 FA supplementation, did not show positive effects on fatigue, although it is possible that a longer period of supplementation may reduce IBD-related fatigue (47, 52).

Previous studies using 1800mg-7000mg ω-3 FAs per day (compared to the 2970mg daily dose in this study), showed positive effects on remission maintenance in IBD patients (1, 35), 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 (53). This further suggests that the 12-week period in this study should be sufficient to show positive effects on fatigue from ω-3 FAs supplementation if such an effect exists.

There was some indication that exercise advice improved IBD-related fatigue. This was demonstrated by lower scores from the IBD-specific fatigue scale, although this effect was not apparent from other fatigue scales. Studies investigating the effect of exercise on symptoms of chronic disease, including fatigue, have reported on intervention periods of 12 weeks or less (26, 27). 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(22). Thus, larger and possibly longer studies investigating the effect of exercise on IBD-related fatigue are needed(22, 54, 55).

Exercise has proven beneficial in healthy individuals(41). Potential positive benefits were also reported in studies with IBD patients, including muscle mass gain(56), and increased bone mineral density and HRQOL(21). Symptoms of IBD, such as diarrhoea,especially if accompanied by fears of incontinence, may create barriers to exercise(57). Evidence to date suggests that individuals with IBD should benefit from

increased exercise(15, 23, 24, 58, 59), and in particular, that low-moderate PA is safe(19, 60). 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(21).

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 could be analysed with two groups (n=25-27). The relatively small sample size may be seen as a limitation, although this can be justified given the trial's pilot status. Despite the large numbers of patients screened, many were excluded because of the stringent eligibility criteria used to remove confounding factors, (e.g. fatigue-related comorbidities (131/656 ; 20%), or else because of their non-availability (147/656; 23%). A variety of variables were measured; however in the future, additional variables including faecal calprotectin, body composition analysis, baseline serum levels of vitamin B12 and ferritin, plus post-interventional serum concentrations of ω-3 FAs, could be determined to add to the understanding and interpretation of the results. 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 consumption bias. I too don't know what this means

4.2 Conclusions

This was the first study assessing the effect of exercise advice and/or ω-3 FA supplementation in IBD patients, and the results demonstrate that these interventions are generally well-tolerated. 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. 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 moderate-vigorous physical activity may provide a safe and 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 capsule placebo (n=15):**

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

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

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

4) **Capsule placebo with exercise placebo (n=12)**

   Consultation with researcher; diet diary; capsule placebo

Table 1: 2x2 Trial Design and Details of Treatment Groups.

ω-3 FA: Omega-3 Fatty Acids.

Outcome variable	Scale/Assessment	Outcome	Rationale
Fatigue score	Functional Assessment of Chronic Illness Therapy – Fatigue scale(45)	Primary	Scale validated in IBD patients by correlation with inflammatory markers
Fatigue score	Multiple Fatigue Inventory scale(46)	Secondary	Widely-used scale; inclusion allows comparison with other fatigued populations
Fatigue score	Inflammatory Bowel Disease-Fatigue scale(47)	Secondary	Newly-developed scale, validated for use with IBD patients
Quality of Life score	Inflammatory Bowel Disease – Quality of Life scale(48)	Secondary	Health-related quality of life scale validated for use with IBD patients
Depression score	Hospital Anxiety and Depression scale(49)	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)(50)	Secondary	Objective measure of physical activity
Disease activity score	Harvey-Bradshaw Index(38) and Simple Clinical Colitis Index(39)	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 2: 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 3: Demographics and Baseline Values 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 4: 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.