Title: A feasibility study to determine whether the daily consumption of flavonoid-rich pure cocoa has the potential to reduce fatigue and fatigability in people with Parkinson's (pwP).

Authors: Coe, S*[1,2], Andreoli, D[3], George, M[1,2], Collett J[1], Reed, A,[3] Cossington J[1], Izadi, H[4], Dixon, A[1,2] Mansoubi, M[5] and Dawes H[5,6].

*Corresponding author: Dr Shelly Coe, Centre for Movement Occupational and Rehabilitation Sciences[1], Centre for Nutrition and Health[2], Oxford Brookes Centre for Nutrition and Health, Department of Sport Health Sciences and Social Work, Oxford Brookes University, Oxford, OX30BP. Email: scoe@brookes.ac.uk, Tel: + (0)1865 483839.

Affiliations: Centre for Movement Occupational and Rehabilitation Sciences[1], Centre for Nutrition and Health[2], Oxford Brookes Centre for Nutrition and Health, Department of Sport Health Sciences and Social Work, Oxford Brookes University, Oxford, OX30BP; European Parkinson Therapy Centre, Italy.[3]; School of Engineering, Computing and Mathematics Faculty of Technology, Design and Environment, Oxford Brookes Univeristy[4;] College of Medicine and Health, University of Exeter[5], Oxford Health BRC [6].

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Abbreviations: PIS, participant information sheet; PwP, people with Parkinson's

Abstract

Flavonoids, plant compounds found in certain foods, may have the ability to improve fatigue and fatigability. However, to date, no well-designed intervention studies assessing the role of flavonoid consumption for fatigue management in people with Parkinson's (pwP) have been performed.

Objectives: To determine the feasibility and estimate potential effect of flavonoid-rich cocoa on fatigue and fatigability in pwP.

Methods: This was a randomised (1:1) double-blind placebo controlled feasibility study in which 30 pwP were recruited from the European Parkinson Therapy Centre, Italy (trial registration: NCT03288155). During a six day intervention participants consumed a high (10.79mg/g) or low flavonoid cocoa (1.02mg/g) beverage (18 grams Cocoa with 200ml Rice milk) once daily. Potential effect on fatigue and fatigability was measured (baseline to day 6). Feasibility and fidelity were assessed through recruitment and retention, adherence and a process evaluation.

Results: From July 2017 to May 2018, 30 pwP were recruited and randomised and allocated to high (n=15) or low (n=15) flavonoid groups and included in analysis. Missing data was less than 5% and adherence to intervention of all allocated individuals was 97%. There was a small effect on fatigability (six minute walk test: ES 0.11 (95%CI=-0.11-0.26); Z=0.81).There were 2 adverse events (one in the control and one in the intervention group).

Conclusion: The consumption of cocoa is feasible and well received in pwP, and further investigation on the effect on fatigability is warranted.

Key words: Diet, Parkinson's, cocoa, flavonoid, fatigue

Highlights

1. Missing data was low and adherence to intervention of all allocated individuals was high.
2. There was a moderate effect on fatigability after high flavonoid cocoa consumption.
3. The consumption of cocoa is feasible and well received in people with Parkinson's, and further investigation on the effect on fatigability is warranted.

1. Introduction

There are currently limited supporting treatments for fatigue in Parkinson's(1). Dark cocoa, containing 70-85% cocoa solids has high antioxidant and flavonoid content, and consumption has been shown to improve fatigue in those with chronic fatigue syndrome (CFS) (2). Therefore, a simple dietary supplement could be implemented alongside other behavioural interventions early after diagnosis as an adjunctive therapeutic approach to support pwP to manage fatigue. Previously we performed a double blind placebo control feasibility trial of a high versus a control-low flavonoid drink for fatigue in 40 people with Multiple Sclerosis (MS) (3), finding a small effect potential on fatigability. The intervention trial demonstrated safety and feasibility as measured by recruitment rate, intervention adherence, acceptance and completion of outcome measures.

Exercise for up to 2.5 hours a week in PwP has been shown to have a moderate long term effect on disease progression, even when implemented early (4). However the use of other interventions alongside exercise may prove more beneficial than a single intervention alone. Pure cocoa has anti-inflammatory effects (5) and inflammation is increased in chronic conditions and is associated with fatigue (6). Flavonoid rich cocoa has also been shown to increase cerebral blood flow which may increase ability to perform specific movement tasks (7), and therefore may have benefits on fatigue and fatigability in PwP.

We therefore predict that the intervention has the potential to improve fatigue and fatigability in people with Parkinson's. This study is designed to inform a fully powered, targeted, well controlled, cost effective intervention study in pwP. It is therefore proposed that a flavonoid approach for managing Parkinson's related fatigue may be moderately effective, inexpensive, and safe (8). The hypothesis is that the consumption of a flavonoid-rich pure cocoa beverage will have the potential to reduce fatigue and fatigability in pwP. The

following key objectives will be assessed from results of this study: 1) The acceptance of the diet intervention by participants; 2) Monitoring recruitment rate, adherence to the protocol and reasons for non-recruitment and loss to follow up; 3) Efficiency of data collection methods; 4) To determine effect sizes to inform future trials.

2. Methods

This was a parallel randomised double blind placebo controlled trial to assess feasibility and estimate effect potential (clinicaltrials.gov: NCT03288155). The study received University Ethical approval (161036) and was conducted in accordance with the Declaration of Helsinki.

2.1 Recruitment and consent

PwP were recruited from the European Parkinson Therapy Centre (EPTC), Italy, who were commencing a 6-day rehabilitation program. Researchers at the Centre responsible for the admissions of new clients performed an initial eligibility check to assess for potential participants. Those selected were sent a participant information sheet (PIS) by email to see if they were interested in the study. All potential participants were given at least 24 hours to decide if they would like to take part. The process of screening for eligibility and gaining informed consent was undertaken by the researchers at the Centre, and confirmed by the researchers at Oxford Brookes University (OBU). Checking eligibility took place over the phone, and written consent was obtained immediate prior to the baseline assessment.

2.2 Setting

Assessments took place between 7:30 and 10 am at the EPTC, at baseline and on day 6. The intervention was self-administered and took place at the participant's accommodation over 6 consecutive days.

2.3 Randomisation and allocation

Participants were allocated the next available study number by the blinded assessor. The study number related to a computer-generated randomisation list held by the principal investigator and randomised individuals (1:1) into either intervention or control groups. The

randomisation list used minimisation to balance groups for gender and if individuals were on levodopa containing medication. The list provided a three digit code that matched a code on identical pre-packaged sachets (made up by a co-investigator), containing either intervention or control cocoa. Participants were assessed at baseline on enrolment into the trial by a member of clinical staff at the Centre. Group allocation was performed following the baseline assessment, sachets were dispensed to the participant by the lead researcher at the Centre, and intervention delivery began immediately after the assessment. Group allocation was concealed throughout the study and analysis. Participants were reassessed at day 6 following baseline assessment and in accordance with the rehabilitation program at the EPTC.

2.4 Eligibility

Participants were considered eligible for the study if they met the following criteria:
Male and females 18 years + with a clinical diagnosis of Parkinson's who are attending the EPTC; No contraindications tolerating the cocoa drink; No other conditions that may be associated with fatigue, e.g. anaemia; No change in medication for the previous week of the trial and no expected change during; No known psychiatric disorder; Sufficient mental capacity to consent; Score of 1-2 on Hoehn and Yahr scale; Not pregnant or lactating.

2.5 Intervention

This was a 6 day nutrition intervention and the nutritional content of the cocoa is shown in table 1. Participants consumed the drink after an overnight fast at the same time each morning. On the first day of the study however, participants consumed the drink at the Centre after the baseline assessment. They were instructed to take their medication and to follow their diet as usual. Participants were given 6 x 18g doses of cocoa powder, individually contained in silver air tight sachets (identical in appearance for control and

intervention) and instructed to consume with 200ml of rice milk (also provided) at their hotel each morning on an empty stomach, at least 15-30 minutes before any food or drink consumption. These cocoa sachets contents were made at OBU in the Oxford Brookes Centre for Nutrition and Health (OxBCNH) kitchen, which has a food hygiene certificate in order to prepare food used in research studies. The cocoa drinks (intervention and control) were designed to differ only in flavonoid content (low versus high flavonoid content). The flavonoid-rich pure cocoa drink was matched to the control drink for: macronutrients, theobromine and caffeine and were as identical as possible in appearance and taste. Unused cocoa was be saved and documented by the researcher.

[Table 1 at back]

2.6 Outcomes

The primary aim was to assess safety and feasibility of the dietary intervention in terms of recruitment rate, adherence to the protocol and loss to follow up, and perform process evaluation. Adverse events (AEs) were documented. Duration of participation and dropout from the intervention were also recorded. Appropriateness of data collection methods was determined through completion of questionnaires and missing data. Estimates of effect {effect sizes (ES) and confidence intervals (CI)} were calculated based on Z scores, and were calculated for measures and demographics were collected at baseline. Demographic information including age, gender and BMI (kg/m2) and the fatigue severity scale (FSS), Barthel index (BI), Physical Activity for the Elderly (PASE) and the UDPRS I non-motor were collected.

2.7 Fatigue/ fatigability

Throughout the six day intervention participants were asked via text message to rate their level of fatigue on a numerical rating scale (NRS) at 10:00, 15:00 and 20:00 every day, rating their fatigue between 1-10. They replied to the text message 'On a scale from 1-10, with 1 being no/ little fatigue and 10 being the worst fatigue you have experienced, how fatigued are you at the current time?'. Fatigability was measured at baseline and week 6 using the 6MWT (9). Participants were asked to walk as fast as possible for 6 minutes in a rectangular path. They walked anti clockwise initially, and at 3 minutes they were asked to change direction; at the 2nd, 4th, and 6th minutes the rate of perceived exertion (RPE) was recorded.

The Adult Memory and Information Processing Battery (AMIBP) (10) was used to measure cognitive fatigue. The AMIPB required the second highest number in each row to be circled, with 15 rows of five double digit numbers. Participants had two minutes and their attempts were timed, with incorrect answers being noted.

2.8 Covariates

Physical activity was monitored over the 6 days using wrist accelerometers (AX3, Axivity) and were worn by every patient throughout the intervention. Two 24 hour dietary recalls were administered by a trained researcher at the Centre to provide information about the diet of each participant and to determine any changes that may take place throughout the study. A series of questionnaires were also performed throughout the trial, some of which were already performed as part of the rehabilitation program at the Centre. The Centre was already delivering a rehabilitation program, and therefore this may have confounder some of the results. However both the control and intervention group were under this program by the Centre.

2.9 Process evaluation

Upon exiting the study at day 6, each participant was interviewed about queries regarding the intervention process, ease of adherence, tolerance and acceptability of the flavonoid drink and the collection of outcome measures.

2.10 Statistical analysis

A sample size of 30 pwP was deemed feasible based on a 6 month recruitment period, and was used in order to determine suitability of the outcome measures and thus estimate power for a full study. Feasibility was analysed through evaluation of eligibility, recruitment and retention (11). Completeness of outcome measures was reported and 80% was considered appropriate. Retention was measured by the proportion of participants who were lost to follow-up. Successful adherence to the intervention was defined as at least 75% of the participants having completed cocoa consumption. Further aspects of adherence were measured by the percentage of fatigue NRS completed by participants. Primary analysis followed the intention to treat principal and utilised the complete case data set. Results were presented using point estimates and 95% confidence intervals. A GEE method was implemented using SAS/STAT 14.3. An independent t-test was used to compare means for continuous variables. A Mann-Witney U test was used to compare medians for non-parametric measures to determine differences between the intervention groups. A chi-squared test was used to compare means for nominal data. Estimates of effects {effect sizes (ES) and confidence intervals (CI)} were calculated for the measures and demographics were collected at baseline. The effect sizes were calculated based on Z.

3. Results

Between June 2017 and May 2018, 30 pwP were recruited from the EPTC.

Figure 1 shows participant flow (11).

[Figure 1 at back]

3.1 Feasibility

58 people showed an initial interest in the trial, however 22 were not eligible and 6 decided not to take part due to: changing medications, cognitive inability or not wanting to consume the cocoa. Adherence to intervention overall was 96% for the intervention group and the 100% control group. Missing data from NRS was less than 5% of total responses. Overall missing data for outcome measures was less than 5%. There were two AEs during the trial, due to digestive discomfort (intervention) and an anxiety disorder (control), and the AE in the intervention group discontinued consuming the cocoa yet still continued with the rest of the trial. There were no incidences of un-blinding of the researcher or participant. Demographic and clinical data are shown in Table 2. There were no significant differences for demographics between the groups at baseline ($p>0.05$).

[Table 2 at back]

3.2 Outcome measures

Between group effect sizes were considered from both assessments points. Efficacy potential of fatigue and feasibility was determined. There was a small effect on fatigability (six minute walk test: ES 0.11 (CI -0.1092-0.2645); Z=0.81; Table 3). A breakdown of the outcome

measures is shown in Table 3. Axivity measures and dietary intake over the 6 days is shown in Table 4 and 5. NRS fatigue results at 10:00, 15:00 and 20:00 are presented in figures 2a, 2b and 2c, with no significant difference between means for the intervention versus control group (p=0.34).

[Tables 3,4,5 at back]

[Figures 2a, b, c at back]

3.3 Process evaluation

Taste of the cocoa:

In the control group everybody said that they liked the cocoa overall. The only negative comments were that there was too much sugar in the cocoa, and some would prefer it to have been less sweet. Three people said that there was a "good quantity". In the intervention group, 8 of the 14 people said that it tasted good/ acceptable. Negative comments included: lumpy and it had a few clots (3); the drink had too much liquid to drink in such a small time (1); too much at the start, but then they got used to it (1); the drink was too bitter and strong (4).

Continue to drink the cocoa

In the control group, 13 of the 15 people said that they would continue the consumption. One person said that he would only continue to drink the drink if he knew the ingredients in them and the other if it showed any benefits. In the intervention group, 11 of the 14 people said that they would continue to drink however; some specified that they would only consume it if it was proven to be beneficial to them.

Dietary Impact:

Out of all 30, 24 people said that they experienced no changes to their diet. Seven people in the intervention group said they ate less at breakfast and three people in the control group ate less because the cocoa filled them up. Two people in the intervention group and one in the control didn't have their usual tea/ coffee in the morning.

4. Discussion

A flavonoid rich cocoa intervention in pwP over a 6 day period, was feasible and tolerated, and showed some potential for improving symptoms including fatigability although responses demonstrated heterogeneity. Considering the limited treatment options for fatigue further investigation is now warranted. Indeed this simple cheap and accessible intervention can be easily implemented within a healthy lifestyle and alongside medication, and may help in improving quality of life.

4.1 Feasibility and process evaluation

Adherence was high and both cocoa drink interventions were well tolerated and accepted in a sample of pwP. In addition, missing data was low and the intervention and outcome measures were well received. Diet interventions have been shown to be successful in pwP with high adherence and benefits on motor and non-motor symptoms (12). The process evaluation in the current study showed overall positive feedback, with most people liking and/ or accepting both cocoa beverages. A majority from both groups also indicated that they would continue to consume the cocoa, and they were more likely to do this if the results of the study showed benefit. Also, positive effects were seen on reducing food intake especially at breakfast. Being overweight and obese may increase the risk of developing Parkinson's (13), and medication use including dopamine agonists in Parkinson's has been associated with increased eating/ weight gain (14), and therefore balancing food intake may be important to reduce risk of obesity and comorbidities. A reduction of food intake in the current study was also shown in the 24 hour diet recall data, and although there was no significance, the intervention group had a reduced energy, carbohydrate, protein and fat intake at day six compared to baseline. The BMI reported in each group was borderline overweight in the control group (25 (3.6)) and overweight in the intervention group (28 (5.8)). Therefore a

larger sample size or a longer intervention period may have shown results in favour of the intervention group having an overall reduced food intake.

4.2 *Outcome measures*

Fatigability, measured through metres walked, decreased in the intervention group from day 1 to 6 with a small effect, with smaller improvements seen in the control group. Fatigue in Parkinson's is poorly understood and there are several mechanisms that might explain this potential improvement in fatigability. Energy metabolism has now been recognised as a contributing pathomechanism in neurological disease, and PwP have found to have mitochondrial dysfunction (15). Flavonoids have been shown to improve dysfunction of mitochondria via several potential mechanisms (16). Also, fatigue correlates with a decrease of physical endurance (17) and walking speed (18), therefore flavonoid rich cocoa may be effective at improving walking and mobility through mechanisms associated with reducing fatigue.

There was a small effect size for change in reaction time and visual processing. This finding is corroborated by Field et al., (19), who examined the effect of cocoa flavonoids on choice reaction time and visual spatial memory in healthy individuals. The results suggested an improvement in choice reaction time by eight milliseconds, yet this was not significant ($p=0.19$). Despite these findings coming from participants who do not have Parkinson's disease, these findings suggest that the short-term improvement of cocoa flavonoids in unlikely. In acute studies on flavonoids and cognitive performance, improvements in reaction time were seen with inconsistent findings on other cognitive measures(20). This is in line with the current study where reaction time improved in the intervention group, however this did not reach significance. Therefore, to observe the cognitive performance improvements as

a result of flavonoid supplementation the observation time of the study would have to be extended beyond six days.

Although it is difficult to report anything conclusive from the NRS fatigue figures, there is a pattern for reduced fatigue from day 1 to day 6, especially in the intervention group. Fatigue generally worsens throughout the day and therefore cocoa may help to mediate the worsen effects of Parkinson's later in the day (21).

4.3 Limitations

This feasibility study was conducted on a sample of people attending the EPTC. Therefore, the follow-up periods were shortened to fit with the Centres treatment period and therefore a longer follow-up period may be required to measure the true effect of the flavonoid-rich cocoa on cognitive and physical ability improvements. Also, the participants were assessed over an active six day period in which they were performing rehabilitation under the guidance of the Centre. We observed potential improvements in fatigability and not fatigue. The study did not capture engagement with rehabilitation in individuals, which may have influenced fatigue results, as previous studies have shown that individuals tend to increase activity in response to interventions that reduce fatigue, resulting in no change in fatigue levels. We recruited from individuals attending rehabilitation, and thus our study findings may not translate to the general population of pwP in a free living situation. The sample only incorporates subjects with a Hoen Yahr scale between 1 and 3, and therefore individuals with an increased severity of Parkinson's were not represented. However, as this was a feasibility study, a full proposal assessing the impact of flavonoid-rich cocoa consumption in individuals with Parkinson's may show promise.

4.4 Conclusion

Flavonoid rich pure cocoa was well received, tolerated and accepted by a sample of pwP during a rehabilitation program. AEs were not severe and were resolved, and missing data was scarce. Fatigue is prevalent in pwP and a cost effective simple dietary supplement may be used in addition to other rehabilitation and disease modifying treatments to reduce the debilitating symptom of fatigue and fatigability and to increase quality of life. We propose that further studies are warranted to explore this effect in a larger more representative sample of pwP with a longer intervention and follow up period, considering physical activity interventions with careful monitoring of activity and rehabilitation.

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Author contributions

Coe, S: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

Andreoli, D: Conceptualization; Data curation; Methodology; Project administration; Resources; Software; Supervision; Writing - review & editing.

George, M: Conceptualization; Data curation; Methodology; Project administration; Software; Supervision; Writing - review & editing.

Collett J: Conceptualization; Formal analysis; Investigation; Methodology; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

Reed, A: Conceptualization; Methodology; Project administration; Resources; Software; Writing - review & editing.

Cossington J: Data curation; Project administration; Software; Writing - review & editing.

Izadi, H: Data curation; Formal analysis; Writing - review & editing.

Dixon, A: Data curation; Methodology; Project administration; Software; Writing - review & editing.

Mansoubi M: Data curation; Formal analysis; Methodology; Software.

Dawes H: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

Declaration of interest

Co-author Alex Reed is the Director and Founder of the European Parkinson Therapy Centre, where the research testing/ data collection took place. He did not take part in the data collection or data analysis, nor did he provide significant input into the results. Daria Andreoli is an employee at the European Parkinson Therapy Centre.

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Table 1. Nutritional information for low-flavanol and high-flavanol cocoa drinks

	Low-flavanol cocoa drink	High-flavanol cocoa drink
Ingredients		
Cocoa powder (g)	18	18
Rice milk (ml)	200	200
Sugar (g)	6.5	6.5
Caffeine (mg)	59.4	59.4
Theobromine (mg)	283	283
Macronutrient composition	**Quantity**	**Quantity**
Energy (kcal)	192	177
Carbohydrate (g)	37.5	28.9
Fat (g)	3.0	4.0
Protein (g)	1.2	4.2
Cocoa Flavanols	**mg/g**	**mg/g**
Catechins	0.99	8.00
DP2	0.03	0.73
DP3	0.00	0.59
DP4	0.00	0.58
DP5	0.00	0.36
DP6	0.00	0.26
DP7	0.00	0.19
DP8	0.00	0.09
Total Flavanols	1.02	10.79

DP, Procyanidin oligomers. Rice milk was Alpro brand.

Table 2. Demographic information at baseline for both groups

Demographic data	Intervention (n = 15)	Control (n = 15)
Age (years)	66.2 (10)	62.13 (13.2)
Women	7	5
BMI (kg/m2)	28 (5.8)	25.0 (3.6)
Fatigue Severity Scale (FSS) Total	3 (5)	4 (5)
Barthel Index (BI) Total	20 (3)	20 (2)
Physical Activity for the Elderly (PASE) Total	115.8	121.3
UDPRS I non-motor Total	10 (13)	9 (27)

Values are means ± standard deviations, or total number of people with in () percentage of the total sample population. FSS, UPDRS total and Barthel Index totals are reported as medians ± ranges. An independent t-test was used to compare means for age, BMI, PASE. A Mann-Witney U test was used to compare medians for FSS, UPDRS and BI for non-parametric measures to determine differences between the intervention groups. A chi-squared test was used to compare means for nominal data. There were no significant differences between groups for any baseline measures ($p>0.05$).

Table 3. Results for outcome measures at baseline, and day 6 of the intervention.

	Intervention (n=15)		Control (n=15)		Z	Effect size
	Baseline	Day 6	Baseline	Day 6		
Fatigability						
AMIPB						
Incorrect	0.7 (1.0)	1.1 (2.4)	1.6 (2.3)	1.6 (3.0)	0.54	0.07
Time (secs)	108.5 (68.3)	71.4 (32.3)	71.6 (19.8)	70.8 (35.4)	-0.29	-0.04
6 minute walk (metres)	360.1 (105.6)	387.2 (121.6)*	405.6 (113.2)	418.1 (94.3)	0.81	0.11
RPE (0-10)	6.2 (2.2)	6.5 (2.4)	5.4 (2.0)	6.3 (2.4)	-0.04	-0.01

Vales are means ± standard error for normally distributed values and medians ± ranges (1st to 3rd quartile) for categorical data. *significant difference between baseline and day 6, a GEE method was implemented using SAS/STAT 14.3., $p<0.05$. AMIPB, adult memory and information processing battery; RPE, reps per minute.

Table 4. Activity levels of participants over the 6 day period.

	Control day	Control night	Intervention day	Intervention night
Activity Sedentary	421.6 (39.9)	426.2 (6.5)	371.1 (49.9)	423.5 (6.0)
Light	230.4 (25.1)	36.2 (3.2)	248.9 (25.6)	40.8 (4.0)
Moderate	261.1 (39.0)	17.5 (5.6)	287.4 (38.9)	15.7 (2.4)
MVPA	255.0 (34.0)	17.0 (4.8)	274 (31.1)	14.7 (2.3)
Vigorous	1.5 (0.7)	0	3.0 (2.0)	0

Activity was measured using an axivity wrist watch for 6 days throughout the intervention period. MVPA, moderate to vigorous physical activity. Values are reported as means +/- standard deviation.

Table 5. Macronutrient intake at baseline and day 6 using a 24 hour dietary recall.

	Control		**Intervention**	
	Baseline	**Day 6**	**Baseline**	**Day 6**
Energy (kcal)	1963 ± 469	2127 ± 487	1948 ± 600	1910 ± 443
Carbohydrates (g)	177 ± 62	213 ± 55	200 ± 65	200 ± 62
Protein (g)	84 ± 21	92 ± 14	92 ± 40	88 ± 29
Fat (g)	84 ± 21	82 ± 36	78 ± 37	75 ± 24

kcal, kilocalorie. Values are +/- standard deviation. An independent t test was performed on each nutrient for each intervention, at baseline compared to day 6. Significance was set at $p<0.05$.

Figure 1 Flow diagram of recruitment

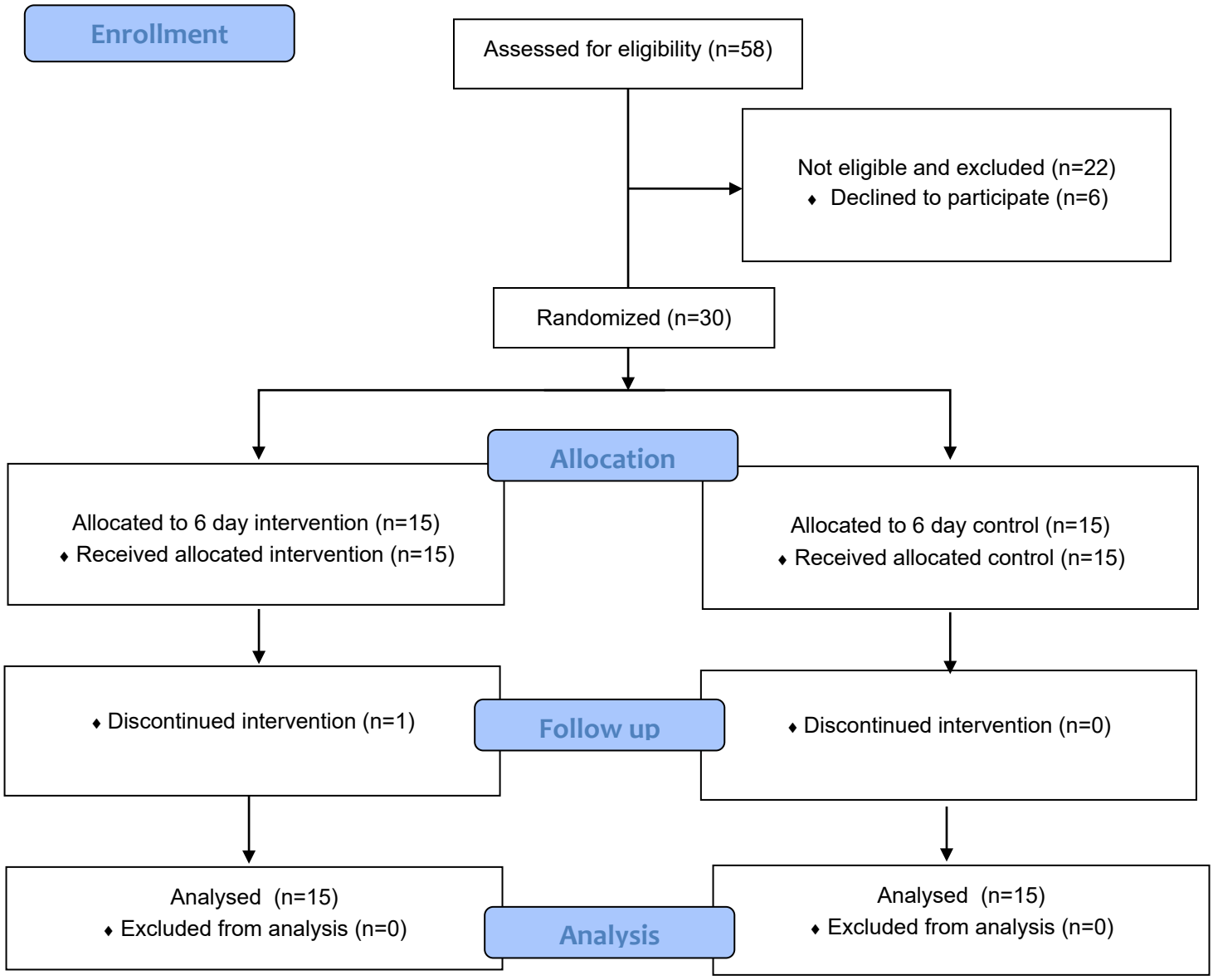

Figure 2a. Mean fatigue over 6 days measured at 10:00, using a visual analogue scale from 1-10, 1= no/ little fatigue and 10= high fatigue.

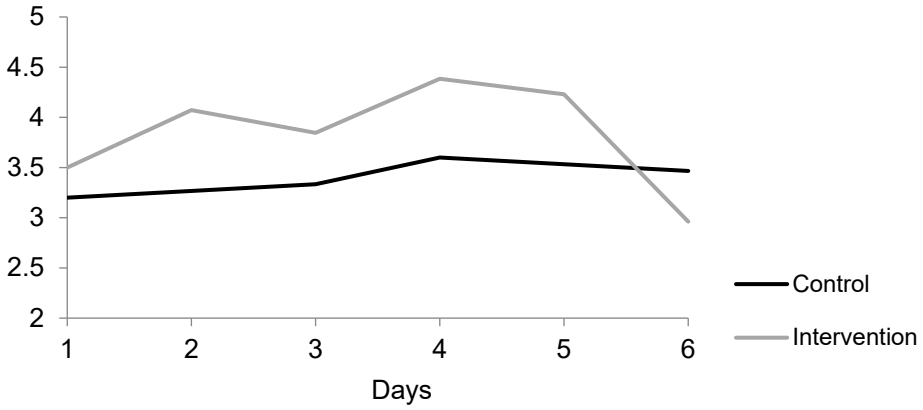

Figure 2b. Mean fatigue over 6 days measured at 15:00, using a visual analogue scale from 1-10, 1= no/ little fatigue and 10= high fatigue.

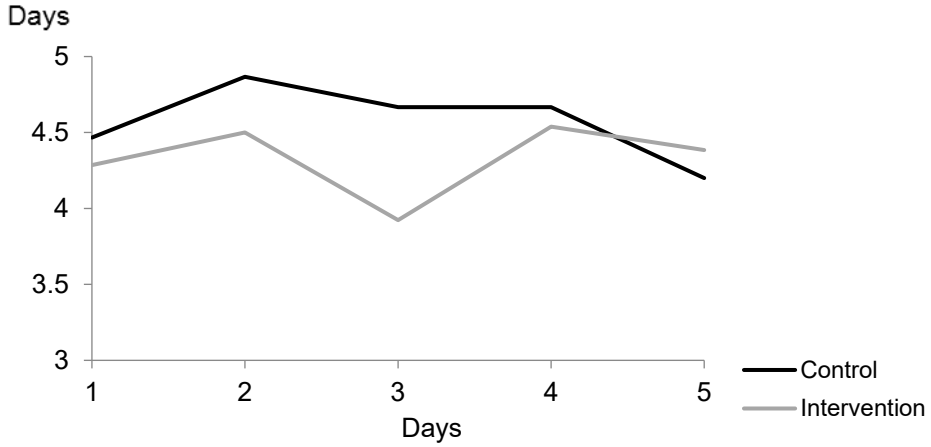

Figure 2c Mean fatigue over 6 days measured at 20:00, using a visual analogue scale from 1-10, 1= no/ little fatigue and 10= high fatigue.