Physical Activity and Fatigue in Multiple Sclerosis: Secondary Outcomes from a Double-blinded Randomized Controlled Trial of Cocoa Flavonoid Drinks

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Abstract

Fatigue is a common and pervasive symptom reducing physical activity in people with multiple sclerosis (pwMS). Exercise may reduce fatigue, although evidence to guide optimal prescription is limited. Specifically, supportive evidence for the timing of exercise for fatigue management or the impact of dietary supplements is unavailable. We performed intensive phenotyping of the interrelation of time of day, physical activity levels, and fatigue to evidence exercise prescription in 40 pwMS participating in a six week randomized controlled trial of morning flavonoid intake (n=19) or a control (n=21). Physical activity was measured over seven days by using an accelerometer at baseline, week three and week six. Participants self-reported their fatigue on a 1–10 rating scale at 10 am, 3 pm, and 8 pm daily. Physical activity levels were calculated for 2.5 h before and after fatigue was reported. Generalized estimating equations were used to explore the time of day fatigue profiles, the relationship of physical activity to fatigue, and the effect of morning flavonoids on this relationship. Participants experienced higher fatigue at 8 pm (4.64±2.29) than at 3 pm (4.39±2.28) and 10 am (3.90±2.10) (P<0.001). Higher fatigue was shown to predict subsequent lower physical activity behavior (P=0.015), but physical activity did not predict higher subsequent fatigue (P>0.05). Morning flavonoid cocoa consumption reduced the relationship of fatigue to physical activity (P=0.049) and fatigue to time of the day (P<0.001). Fatigue levels increased during the day and higher fatigue reduced physical activity in pwMS, but physical activity did not increase fatigue. In addition, morning cocoa reduced daytime fatigue and the relationship of fatigue to subsequent physical activity levels. Therefore, morning exercise prescription is indicated; in combination with dietary flavonoids, it may optimize exercise and physical activity potential in pwMS.

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Registration name: A study to determine whether the daily consumption of flavonoid-rich pure cocoa has the potential to reduce fatigue in people with relapsing-remitting multiple sclerosis (RRMS).

CONSORT Statement: In this study, we adhered to CONSORT guidelines. As this paper is a secondary analysis, we therefore did not repeat some parts in the methods, results, diagrams, or tables that have been published in the first paper authored by Coe et al. 2019.

Keywords: multiple sclerosis; physical activity; fatigue; flavonoid
Introduction

Multiple sclerosis (MS) affects around 85,000 to 100,000 people in the UK and an estimated 2.3 million people worldwide. Ample evidence from meta-analysis indicates that exercise has pleiotropic effects for people with MS (pwMS), being a safe intervention that improves physical fitness, functioning, fatigue, mood, and quality of life; early evidence suggests that it may also have disease-modifying effects. However, compared to healthy individuals, pwMS commonly report several non-motor symptoms including fatigue, pain, and cognitive dysfunction, which affect their ability to achieve a physically active lifestyle and participate in prescribed exercise. A recent study of 358 pwMS highlighted the impact of fatigue symptoms on life quality and life roles, with 47.8% of participants aged 18–65 years. Fatigue, occurring in up to 80% of pwMS, is one of the most common symptoms reported to reduce physical activity, with approximately two-thirds of people reporting daily tiredness as their most troubling symptom. Fatigue is commonly related to lower activity levels in pwMS, with a small number of studies describing higher levels of fatigue later in the day. However, these studies typically report activity and fatigue cross-sectionally at a single time point rather than by more regular measurement strategies. A systematic review and meta-analysis of 2434 pwMS supports that certain exercise programs can reduce fatigue, although a number of studies fail to report this effect. In addition, certain diet sources such as flavonoid rich cocoa have been shown to reduce fatigue in different chronic conditions and this could positively impact on exercise performance. Thus, we hypothesize that as fatigue reduces physical activity and exercise can reduce fatigue, a better understanding of the physical activity to fatigue relationship may be useful to inform exercise engagement and prescription. We set out to objectively confirm the relationship of physical activity to fatigue throughout the day. To date, supportive evidence to suggest optimal timing of exercise in pwMS is unavailable. We performed intensive phenotyping of the interrelationships of time of the day, physical activity levels, and fatigue to evidence exercise prescription within a clinical trial of flavonoid consumption previously found to improve exercise endurance and sports performance in athletes.

Methods

A total of 43 pwMS were recruited as part of a larger study. The trial registration is ISRCTN69897291 and full details can be found in Coe et al. (2019). Participants were recruited from the Oxford University Hospitals NHS Trust (John Radcliffe Hospital site), Milton Keynes Hospital, Royal Berkshire Hospital, or Buckingham Hospital through a list of those who have consented to be contacted. Totally 40 participants (69.2% female and 30.8% male) completed the study (Fig. 1). Potentially eligible participants, who were interested in the study, had their contact details shared with the research team; then, they received further information about the study. All potential participants were screened against the eligibility criteria. The process of screening for eligibility and gaining informed consent was undertaken by the researcher. Checking eligibility was performed over the phone, and at the first assessment, written consent was obtained. Ethical approval was obtained from the National Research Ethics Service (Solihull, West Midlands) reference: 199515.
Measurement of fatigue
Numerical rating scale (NRS): Participants rated their level of fatigue at 10 am, 3 pm, and 8 pm, respectively. They were asked to reply to the text message with a score of fatigue from 1–10 (1=lowest, 10=highest). On assessment days at the University, participants arrived fasted before measurements were administered.

Measurement of physical activity
A wristband accelerometer (Axivity AX3) was worn by every patient prior to intervention (at the baseline) and during weeks three and six (3×7 days; sampling rate at 100 hertz) throughout the intervention. Participants were reminded to initiate wearing the accelerometers by the lead researcher.

The daily amount of sedentary behavior and physical activity time were measured using the Axivity AX3, a ‘wrist-worn’ tri-axial accelerometer designed by Open Lab, Newcastle University, UK. AX3 data were downloaded and processed using OMMGUI software (open movement [V.1.0.0.37]). Physical activity data were processed and analyzed in one-minute epochs by using Philips cut points: right wrist (Sedentary: < 6, Light: 6–21, Moderate: 22–56, Vigorous: >56) and left wrist (Sedentary: < 7, Light: 7–19, Moderate: 20–60, Vigorous: > 60). The minimum valid wear time for inclusion in the analysis was at least 10 h per day on at least three weekdays and one weekend day for any data collection. Sleep time was classified from the data for each day between 10 pm and 6 am. All participants followed the monitoring protocol and provided at least three weekdays and one weekend day of AX3 data during each measurement period. Any days with missing data were treated as missing data, and the mean time and proportion of time spent in each classification were calculated from the remaining data.

The result provided the absolute and proportion of each behavior (to control for the differences in accelerometer wear time in participants) of physical activity levels. The activity level was calculated for 2.5 h before and after the fatigue level was recorded.

Cocoa intervention protocol
Participants were asked to consume a cocoa drink in their homes, after an overnight fast at the same time each morning. After consumption of a cocoa drink, they had to wait for 30 min before they could consume any other food or beverage. They were instructed to take their medication and follow their diet as usual. After consumption of the cocoa drink, participants...
rated their level of fatigue on an NRS, followed by two additional measures of fatigue recorded at 3 pm and 8 pm. On assessment days at the University, participants arrived fasted and did not consume the cocoa drink on that day. The cocoa drinks (for both intervention and control groups) had been designed to differ only in flavonoid content (low versus high flavonoid content, 18 g). The flavonoid-rich pure cocoa drink was matched to the control drink for macronutrients (low flavonoid: 192 Calories (Kcal), 37.5 g carbohydrate, 3 g fat, 1.2 g protein; high flavonoid: 177 Kcal, 28.9 g carbohydrate, 4 g fat, 4.2 g protein), theobromine (both drinks: 283 mg), and caffeine (59.4 mg) and was identical, as much as possible, in appearance and taste to ensure double-blinding\textsuperscript{13}. Cocoa powder for both groups was provided in airtight individual sachets; the contents were added to a mug, and heated rice milk was added to the drink prior to consumption. Instruction on preparation was provided to ensure all participants followed the same protocol\textsuperscript{13}.

**Data analysis**

All data were coded anonymously. The Shapiro–Wilk test confirmed that all data were normally distributed. The main research questions were to what extent can physical activity predict fatigue levels in pwMS, to what extent can fatigue levels predict physical activity time in pwMS, and to what extent can time of the day predict fatigue levels. To address these questions, physical activity levels, calculated for 2.5 h before and after fatigue levels were recorded (10 am, 3 pm, and 8 pm), and generalized estimating equations (GEEs) were used to analyze the data. Another aim of this study was to determine the impact of a flavonoid-rich dark cocoa drink intervention on physical activity and fatigue relationships in pwMS. All statistical analyses were performed using SPSS version 26 (IBM SPSS Statistics). Data are displayed as mean ±SD, \(P\) values, effect sizes, and mean (95% CI) in the text and (or) tables.

**Results**

A total of 40 participants completed the study. Participants were allocated using computer-generated randomization balanced for age and gender and assigned into either a control group (\(n=21\), age= 46±8, 74% female) or an intervention group (\(n=19\), age= 41±11, 76% female). A minimum of 17 participants was required per group (intervention and control groups) based on the assumption that \(1-\beta=0.90\), \(\alpha=0.05\), and effect size \(|\rho|=0.50\)\textsuperscript{21}. A demographic table and clinical characteristics have been reported by Coe et al. (2019)\textsuperscript{13}. Also, this data is available in Table 1.

**Predictability of physical activity and fatigue in pwMS**

GEEs showed that physical activity time did not predict fatigue levels in pwMS \((P>0.169)\). However, the fatigue level was shown to significantly predict physical activity time in pwMS \((P<0.015)\) (Table 2).

| Demographic information at baseline for both groups |
|-----------------------------------------------------|
| Demographic data | Intervention \((n=19)\) | Control \((n=21)\) |
|------------------|--------------------------|------------------|
| Age (years)      | 41±11                    | 46±8             |
| Women            | 14 (74%)                 | 16 (76%)         |
| BMI (kg/m\textsuperscript{2}) | 26±7                    | 25±6             |
| Treatment naïve  | 7/19 (37%)               | 6/21 (29%)       |

**Medications**

| Medications                      | Intervention \((n=19)\) | Control \((n=21)\) |
|----------------------------------|--------------------------|------------------|
| Antidepressants/anti-anxietytics | 6                         | 6                |
| Anticonvulsants/antispastics     | 3                         | 6                |
| Sedating analgesics              | 0                         | 1                |
| Other sedating agents            | 2                         | 7                |
| Others (excluding DMTs)          | 25                        | 24               |
| Smokers                          | 0 (0%)                    | 2 (10%)          |
| Uses assistive device            | 2 (11%)                   | 6 (29%)          |
| Reported food allergy            | 2 (11%)                   | 2 (10%)          |
| Reported food intolerance        | 6 (32%)                   | 5 (24%)          |
| Reported taking special diet     | 4 (21%)                   | 2 (10%)          |
| Fatigue Severity Scale (FSS) total | 5±2                    | 5±3              |
| Barthel Index (BI) total         | 20±2                      | 19±8             |
| Physical Activity for the Elderly (PASE) total | 90±32                   | 102±31           |

Values are presented as mean ± SD, or total number of people in () considering the percentage of the total sample population. FSS and Barthel Index totals are reported as medi- ans ± ranges. An independent \(t\) test was used to compare means for age, BMI and PASE. A Mann-Witney \(U\) test was used to compare medians for FSS and BI for non-parametric measures to determine differences between the intervention groups. A \(x^2\) test was used to compare means for nominal data. There were no significant differences between groups for any baseline measures \((P>0.05)\). BMI, body mass index; DMTs, disease modifying treatments. (The same diagram has been presented in the first published paper of the study by Coe et al, 2019\textsuperscript{13}).
Impact of cocoa intervention on the predictability of physical activity and fatigue in pwMS

Two GEE models were developed. The first one evaluated the impact of the intervention on the predictability of fatigue by physical activity, and the second model investigated the predictability of physical activity by fatigue. Therefore, both groups (intervention and control) were added as a predictor factor into the model. The first model result showed that the intervention had no significant impact on the predictability of fatigue by physical activity \( (P=0.962) \). Furthermore, the interaction of the groups had no significant impact on the predictability of fatigue by physical activity \( (P=0.346) \) (Table 3). The second model showed that both the intervention and control groups could not significantly predict physical activity \( (P=0.049) \) when interacting with fatigue (Table 4).

Table 3 Differences in the predictability of fatigue by physical activity (PA) between intervention and control groups

| Parameters | B     | Standard error | 95% Wald confidence interval | Hypothesis test | Wald Chi-Square | df | P value |
|------------|-------|----------------|----------------------------|-----------------|----------------|----|---------|
| ( Intercept) | 4.586 | 0.579          | 3.451 − 5.721              |                 | 62.671         | 1  | < 0.001 |
| [Group = Intervention]  | 0.040 | 0.840          | -1.606 − 1.686             |                 | 0.002          | 1  | 0.962   |
| [Group = Control]  | 0*    | Referent       | Referent                   | Referent        | Referent       | Referent Referent Referent Referent |
| [Fatigue predictability by PA (Intervention)] | -0.011 | 0.009          | -0.027 − 0.006             |                 | 1.571          | 1  | 0.210   |
| [Fatigue predictability by PA (Control)] | -0.007 | 0.009          | -0.024 − 0.011             |                 | 0.549          | 1  | 0.459   |
| (Scale) | 4.998 |                |                            |                 |                |    |         |

Dependent variable: PA; Model: ( Intercept), Group, (Group∗Fatigue); * Set to zero because this parameter is redundant. \( (*) = \) Interaction.

Predictability of fatigue by the time of the day in pwMS

Fatigue and time of the day for both the control and intervention groups were calculated and reported in Table 5 and Fig. 2. GEEs showed that the time of the day can significantly predict fatigue levels \( (P<0.001) \) (Table 6). Comparison between different time points showed that pwMS felt significantly less fatigued at 10 am \( (P<0.001) \) compared with at 8 pm (Table 7).

Table 4 Differences in the predictability of physical activity (PA) by fatigue between control and intervention groups

| Parameters | B     | Standard error | 95% Wald confidence interval | Hypothesis test | Wald Chi-Square | df | P value |
|------------|-------|----------------|----------------------------|-----------------|----------------|----|---------|
| ( Intercept) | 39.610 | 6.183          | 27.492 − 51.729            |                 | 41.040         | 1  | < 0.001 |
| [Group = Intervention]  | -2.192 | 8.435          | -18.725 − 14.341           |                 | 0.068          | 1  | 0.795   |
| [Group = Control]  | 0*    | Referent       | Referent                   | Referent        | Referent       | Referent Referent Referent Referent |
| [Fatigue]  | -1.827 | 0.976          | -3.740 − 0.086             |                 | 3.503          | 1  | 0.061   |
| (Scale) | 670.592 |                |                            |                 |                |    |         |

Dependent variable: PA; Model: ( Intercept), Group, (Group∗Fatigue); * Set to zero because this parameter is redundant. \( (*) = \) Interaction.

Table 5 Fatigue means for control and intervention groups at different times of the day

| Time of the day | Groups | Fatigue means | Standard deviation |
|----------------|--------|---------------|--------------------|
| 10 am−12:30 pm | Intervention | 3.90          | 1.954              |
| Control | 3.90          | 2.240          |
| Total | 3.90          | 2.103          |
| 3 pm−5:30 pm | Intervention | 4.42          | 2.302              |
| Control | 4.35          | 2.259          |
| Total | 4.39          | 2.277          |
| 8 pm−10:30 pm | Intervention | 4.49          | 2.299              |
| Control | 4.78          | 2.280          |
| Total | 4.64          | 2.291          |
| Total | 4.27          | 2.202          |
| Control | 4.34          | 2.284          |
| Total | 4.31          | 2.244          |
Discussion

We observed that pwMS had higher levels of fatigue later in the day which was unaffected by the amount of physical activity during the day. Fatigue reduced subsequent physical activity behavior, but physical activity did not relate to an increase in subsequent fatigue. Thus, our findings alongside the evidence that exercise reduces fatigue support the investigation of mor-

Table 8  Impact of group (intervention and control) on the predictability of fatigue by the time of the day

| Source | Type III Wald Chi-Square | df | P value |
|--------|-------------------------|----|--------|
| (Intercept) | 196.482 | 1 | < 0.001 |
| Time of the day* Group | 24.985 | 5 | < 0.001 |

Dependent variable: Fatigue; Model: (Intercept), Time of the day* Group. (*) = Interaction.

Table 9  Differences in the impact of the group (intervention and control) on the predictability of fatigue by the time of the day

| Parameters | B | Standard error | 95% Wald confidence interval Lower | Upper | Wald Chi-Square | df | P value |
|------------|---|----------------|-------------------------------|-------|----------------|----|--------|
| (Intercept) | 4.783 | 0.418 | 3.963 - 5.602 | 130.803 | 1 | < 0.001 |
| [Time of the day =10 am−12:30 pm ] * | -0.883 | 0.605 | -2.068 - 0.302 | 2.131 | 1 | 0.144 |
| [Group=intervention] | | | | | | |
| [Time of the day =10 am−12:30 pm ] * | -0.883 | 0.237 | -1.347 - 0.420 | 13.940 | 1 | < 0.001 |
| [Group=Control] | | | | | | |
| [Time of the day =3 pm−5:30 pm ] * | -0.358 | 0.627 | -1.586 - 0.870 | 0.327 | 1 | 0.567 |
| [Group=intervention] | | | | | | |
| [Time of the day =3 pm−5:30 pm ] * | -0.432 | 0.206 | -0.835 - 0.028 | 4.401 | 1 | 0.036 |
| [Group=Control] | | | | | | |
| [Time of the day =8 pm−10:30 pm ] * | -0.289 | 0.657 | -1.576 - 0.998 | 0.194 | 1 | 0.660 |
| [Group=intervention] | | | | | | |
| [Time of the day =8 pm−10:30 pm ] * | 0* | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent | Referent 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Impact of cocoa on the predictability of fatigue by the time of the day (morning, afternoon, and evening) in pwMS

The GEE result showed that being in either the intervention group or control group could significantly impact the predictability of fatigue by the time of the day (P<0.001) (Table 8). Differences between the impact of control and intervention groups on the predictability of fatigue by the time of the day are shown in Table 9.
ning exercise interventions as a strategy to optimize engagement in exercise and simultaneously reduce fatigue in pwMS. Morning high flavonoid cocoa intake reduced daytime fatigue and the relationship of fatigue to subsequent physical activity levels. Thus, we propose that specific morning dietary and exercise prescription combinations have the potential to increase physical activity and reduce fatigue in pwMS. Our findings are novel and important because this study is the first to highlight a proactive strategy to increase physical activity in pwMS through the timing of exercise and dietary supplementation. We suggest the potential for non-pharmacological dietary approaches to be combined with physical interventions, considering the importance of achieving a physically active lifestyle and the effect of exercise interventions for health and well-being in pwMS.

Our observations suggest the need to challenge the use of standard pacing of physical activity levels in fatigue management in pwMS. We suggest a more proactive strategy to alleviate fatigue in this condition. Initially, our observations of fatigue-mediating activity suggest the importance of exercise prescription at a time of the day when fatigue levels are low. We are not the first to observe the importance of fatigue on subsequent behavior, and our findings are broadly consistent with other studies including Kartz et al. (2019), which showed fatigue predicted physical activity in 107 pwMS, and Brown and Bray (2019), who observed that mental fatigue negatively affected physical activity and productivity. We acknowledge that the physiology and mechanisms of fatigue are complicated and may be moderated or predicted by other factors.

We further observed that for the majority of people, fatigue increased during the day from morning to afternoon, with pwMS experiencing higher levels of fatigue in the evening. These results are consistent with the study by Powell et al. (2017), in which fatigue impacted the quality of life to a greater extent than daily life stressors (assessed by an eight item questionnaire), mood, physical efforts, and quality of sleep in 1661 pwMS; the highest impact was observed in late afternoon. Furthermore, a review result by Chtourou et al. (2013) demonstrated that muscular fatigue was higher after an acute exercise in the evening compared to that in the morning. The study showed that biomarkers, which can cause cellular damage are higher in the evening, while antioxidant biomarkers are higher in the morning. These results show the importance of considering the time of day in designing optimal exercise prescription, with morning exercise likely to achieve better adherence in pwMS. Our findings support the need for intervention trials that explore timing of exercise interventions on adherence and subsequent physical activity levels.

Finally, the morning high flavonoid intervention group had less fatigue than the control group at the end of the day (Table 5). We propose that dietary supplements may offer benefits for increasing physical activity in pwMS. The current study has shown that cocoa intervention did not directly impact on physical activity. However, cocoa intervention did positively affect physical activity when an interaction with fatigue was shown. It also demonstrated that a high-content cocoa flavonoid supplement can be used to reduce the negative impact of fatigue on physical activity in pwMS. Previously, cocoa has been shown to reduce fatigue in fatiguing conditions, such as multiple sclerosis and chronic fatigue syndrome. The mechanisms are not fully understood, but it may be due to cocoa’s antiinflammatory and antioxidant properties, stimulation of cerebral blood flow, and its effect on improving cognition and mood, all of which may directly or indirectly reduce fatigue. Therefore, the effects of cocoa may be two-fold. Firstly, fatigue is worse as the day progresses in pwMS. Therefore, we propose consuming cocoa later in the day which may further help to combat evening fatigue. Secondly and importantly, the consumption of cocoa may allow increased physical activity at the same fatigue level and may be used to facilitate greater physical activity in pwMS.

Conclusion

In summary, we propose that it may be more beneficial for pwMS to do exercise in the morning rather than later in the day. Our data suggest that consuming high flavonoid cocoa in the morning may positively affect exercise prescription via interaction with the level of fatigue in pwMS. Given that fatigue levels affect subsequent physical activity, consideration of the use of dietary supplementation in combination with exercise prescription shows great potential as a novel approach to benefit health, quality of life, and well-being in pwMS. Certainly, further exploration of optimal timing and dosage of combined flavonoid and exercise prescription should be explored in this group.

The limitations of this study include having a small number of participants, limited access to participants’ social, economic status and educational level, and the use of subjective fatigue scores. Strengths include novel assessment of objectively measured physical activity as a predictor of fatigue and fatigue as a predictor of physical activity in pwMS. Other strengths include the use of cocoa intervention as a moderator.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets generated and (or) analyzed during the current study are not publicly available due to study ethical approval, but are available from the corresponding author on reasonable request.

Author contributions

Maedeh Mansoubi (MM), Shelly Coe (SC), Jo Cossington (JC1), Johnny Collet (JC2), Miriam Clegg (MC), Jacqueline Palace (JP), Ana Cavey (AC), Gabriele C DeLuca (JD), Martin Ovington (MO), Helen Dawes (HD), SC, MM and JC2 conceived the study and contributed towards its design. SC, MO and JC1 were responsible for the acquisition of data. MM and HD performed the statistical analysis and interpretation. MM, HD and SC were involved in drafting the manuscript. JC1, JC2, JP, JD, MC and AC revised the manuscript for important intellectual content. All authors gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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