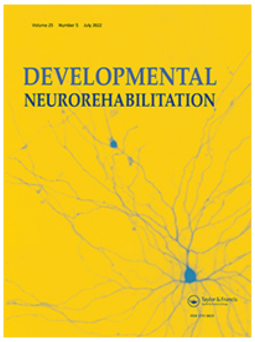

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Reducing fatigue following acquired brain injury: A feasibility study of high intensity interval training for young adults

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ABSTRACT

The aim was to evaluate feasibility of high-intensity interval training (HIIT) in fatigued adults (20–40 years old) with acquired brain injury (ABI). A prospective pre-post single-arm intervention trial was conducted, including 6–8 months follow-up assessment and interview. Intervention was 18 sessions of intermittent exercise on a cycle ergometer over six weeks. Six out of ten participants without motor impairments completed the intervention (all females, mean age = 30.2 years, months post-injury = 22). On average, participants attended 88% of sessions and achieved high intensity (93% of max heart rate). VO_{2max} improved by 0.53 l/min (*SD* = 0.29), and participants continued exercising post-intervention. All participants were satisfied with HIIT, were more inclined to exercise, and reported positive effects of exercising for self-management of fatigue. Three sessions a week were demanding to some participants. Findings support feasibility of HIIT as a promising intervention for young adults with post-ABI fatigue.

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Acquired brain injury; fatigue; HIIT; exercise; young adults

Introduction

Fatigue is a common, debilitating, and often persistent sequela of acquired brain injury (ABI). Self-reported fatigue is associated with increased mortality,[1] lower quality of life,[2,3] disability, and limited social participation.[4–8] Further, fatigue is a barrier to keeping a job after ABI and a predictor of not returning to work.[9–11]

To young adults, who are in the midst of their active working and family life, fatigue may have longstanding and pronounced detrimental effects on functional outcome following stroke.[12] Among adolescents and young adults (15–30 years old) with ABI, the prevalence of fatigue has been estimated at 73% using the Multidimensional Fatigue Inventory (MFI-20).[13] This proportion was significantly higher than in age-matched healthy controls (29%) with an adjusted prevalence proportion ratio of 2.7, 95% CI [2.1, 3.5]. Further, more severe fatigue in young adults with ABI has been associated with symptoms of depression,[14] limited participation, and lower quality of life.[15,16]

The etiology of post-ABI fatigue is not clear and no consistent findings indicate associations of fatigue with lesion characteristics such as location and severity.[17–19] Fatigue is likely to be multifactorial with biological, psychological, behavioral, and social factors contributing to the development and persistence of fatigue.[20–26] Some studies in traumatic brain injury (TBI) suggest associations with attentional deficits, e.g. selective attention[27,28] and vigilance performance,[29] and fatigue may be caused by compensatory efforts for cognitive impairments.[24] A few studies in post-stroke fatigue have also found associations with cognitive deficits,[30,31] but current evidence of this relationship is ambiguous.[32] Several treatment strategies have been trialed, including pharmacological treatment, cognitive-behavioral therapy, and physical exercise, without strong evidence on the effects of any treatment.[33,34] A randomized-controlled trial on persistent post-stroke fatigue (> 4 months) found additional effects of graded activity training when combined with cognitive therapy compared to cognitive therapy only.[35]

Benefits of exercise are multifaceted in healthy populations,[36] and physical activity may be a promising therapeutic target for alleviating fatigue following ABI.[37] Reduced physical activity and cardiorespiratory deconditioning are common after both stroke and TBI.[38,39] Deconditioning may exacerbate fatigue, and exercise may interrupt such mechanisms. However, evidence is insufficient to establish associations of activity and fitness with self-reported fatigue following ABI.[40–42] Benefits of exercise in relation to fatigue are also uncertain in other patient groups, in which fatigue is a major complaint, such as cancer.[43] Regarding cancer-related fatigue, hypothesized mechanisms of exercise include i) improving psychological well-being and physical fitness, ii) decreasing inflammation, iii) improving autonomic nervous system functioning, and iv) promoting neurotrophic factors.[44] One or more of these hypotheses may also apply to fatigue following ABI, depending on whether mechanisms of fatigue and benefits of exercise are generic or disease-specific.[45,46]

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Despite the potential benefits of exercise, knowledge is lacking on the barriers and drivers of engaging in aerobic exercise programs for young adults suffering from fatigue after ABI. The primary aim of this study was to investigate feasibility of an intensive intermittent exercise protocol on a cycle ergometer, high-intensity interval training (HIIT), for young adults (20–40 years old) reporting debilitating fatigue following mild-to-moderate ABI. More specifically, objectives were to evaluate *i*) attendance and retention rates, *ii*) adherence to workout intensity, and *iii*) acceptability (i.e., satisfaction with HIIT). The secondary aim was to explore short- and long-term changes in self-reported fatigue, cardiorespiratory fitness, cognitive performance, and exercise behavior.

Materials and Methods

Trial Design

This feasibility study was designed prospectively as a pre-post single arm intervention trial including a 6–8 months follow-up assessment and interview. The study was approved by the Danish Data Protection Agency (j.no.: 2012–58-0004) and was conducted in accordance with the Declaration of Helsinki. Study participants provided informed consent and were offered reimbursement of traveling expenses. No changes to methods were made after trial commencement.

Participants

Young adults with mild-to-moderate ABI were sequentially approached for recruitment between May 2016 and February 2017 at an outpatient clinic and at municipal neurorehabilitation centers in the capital region of Denmark. For a detailed description of settings, please see Norup et al.[13] Inclusion criteria were: 1) 20–40 years old; 2) diagnosis of mild-to-moderate ABI and three months to five years post-injury; 3) fatigued, defined as ≥ 12 on the General Fatigue subscale of MFI-20; 4) ability to walk without walking aids; 5) no progressive ABI; 6) no or only limited physical limitations, defined as 0 or 1 on item 5 “motor arm” or item 6 “motor leg” on The National Institute of Health Stroke Scale.[47] Participants were excluded if they had 1) severe cognitive deficits, i.e. not able to understand and/or participate in testing and intervention (assessed by a physician and, in case of doubt, a neuropsychologist); 2) any health risks associated with performing high intensity fitness training (evaluated by a physician); 3) depression or anxiety requiring treatment (evaluated by a physician using the Major Depression Inventory[48] and the Beck Anxiety Inventory,[49] if relevant); 4) active treatment with beta blockers; and 5) regular use of sedative medicine, defined as more than twice a week for at least four weeks. Sedative medicine was defined as medication with fatigue or drowsiness as a common (0–10%) or very common (> 10%) side effect.

Table 1. Procedures of the high intensity interval training program.

Contents of sessions		Week 1–2		Week 3–4		Week 5–6	
Set	Intensity [a]	No.	Min.	No.	Min.	No.	Min.
Warm-up	Low	1	5	1	5	1	5
Warm-up	Medium	1	5	1	5	1	5
“All-out” intervals	High	4	0.5	5	0.5	6	0.5
Breaks in-between intervals	Low	3	4	4	3.5	5	3.5
Cool-down, optional	Low	0–1	2	0–1	2	0–1	2

Note. Sessions were repeated three times a week for six weeks. Each session was introduced by a 10 min. warm-up followed by an increasing number of intermittent high intensity intervals. Watt, pulse, and Borg measures were recorded at each set to guide load adjustments. No. = number of sets per session; min. = minutes (per each number of set).

[a]Low = 45–55% of watt max; Medium = 55–60% of watt max; High = ≥ 90% of watt max.

Intervention

Intervention was a six-week HIIT program for fatigue following ABI. The HIIT protocol was designed by a trained physiotherapist (author MB), experienced in neurorehabilitation, based on the Wingate test[50] and the program described by Løppenthin et al.[51] The program was provided individually over six weeks and consisted of 18 sessions of intensive intermittent exercise on a cycle ergometer (three sessions a week). Each session lasted for 30 min and included 30-s intervals of high intensity workout. Workout sequences for each session, including program progression, are described in Table 1. Sessions were scheduled based on the preference of participants to ease their planning of sessions in relation to work/study, family, diurnal variations in energy levels, etc. To extent possible, sessions were planned in opening hours and were not planned three days in a row on account of restitution. Participants could choose to do sessions at the regional outpatient clinic or at the local rehabilitation center.

Sessions were supervised by a physiotherapist trained in neurorehabilitation. Initial exercise workload (watt) was individualized based on a maximal incremental cycle ergometer test (watt-max test) at baseline. During intervention, the supervising physiotherapist adjusted the workload based on feedback measures of heart rate (primary) and self-reports of perceived exertion (secondary). Heart rate was monitored using a pulse watch (pulsometer) and perceived exertion was measured using the Borg scale.[52] On the Borg scale, respondents rate how hard they feel they are working from 6 (no feeling of exertion) to 20 (very, very hard). A strong correlation between the Borg scale and heart rate (r = .85) has been reported previously.[52] Feedback measures were recorded during every high intensity interval and every break, and watt was adjusted accordingly to ensure high intensity during intervals, i.e. ≥ 90% of maximum heart rate.

No other materials than those described were necessary for carrying out the intervention, and no modifications to the intervention program were performed during the study period.

Outcomes

Indicators of Feasibility

Recruitment and retention rates, including reasons for dropout, were monitored to estimate participation and completion percentages. Training adherence was assessed using intervention logs, which were completed each session to monitor the number of sessions provided as planned and achieved workout intensity. The following indicators were used to assess workout intensity: heart rate, ratings of perceived exertion on the Borg scale, and workload (watt). All indicators were recorded repeatedly at each 'all-out' interval. Participants were expected to participate in at least 14 out of 18 sessions and to achieve an average ≥ 90% of baseline maximum heart rate.

A custom-made evaluation form was administered by the therapist following the last session to evaluate satisfaction with the HIIT program. The evaluation form included five items addressing satisfaction with the i) intensity, ii) frequency, and iii) mode of exercise, and experiences with iv) positive and v) negative effects of exercising. Items were rated dichotomously (yes/no) with optional comments.

Effect Outcomes

Fatigue, fitness, cognitive performance, and physical activity in leisure time were assessed at baseline (within one week before commencement of intervention), post-intervention (within one week after intervention), and follow-up (6–8 months after intervention).

Self-reported fatigue was assessed with MFI-20,[53,54] which consists of 20 items evenly distributed on five subscales: General Fatigue (GF), Physical Fatigue (PF), Reduced Activity (RA), Reduced Motivation (RM) and Mental Fatigue (MF). Each item is a statement rated on a five-point Likert scale ranging from 1 (yes, that is true) to 5 (no, that is not true). Negatively worded items are reverse-scored, and items are summed in subscale scores that range from 4 (no fatigue) to 20 (maximum fatigue). MFI-20 has demonstrated good internal consistency in various clinical samples with Cronbach's alpha ranging from .68–.92.[55,56] The Reduced Motivation subscale demonstrated low internal consistency in young patients with ABI ($\alpha = 0.53$)[13] and has demonstrated psychometric issues previously.[53,57] Scores were compared to reference data on a Danish sample of healthy adolescents and young adults (age 15–30).[13]

Maximal oxygen uptake per minute (VO_{2max}) was estimated as an indicator of cardiorespiratory fitness using the watt-max test. The watt-max test is a cycle ergometer test measuring the maximal power output (watt-max), which is used as an indirect measure of VO_{2max}. The watt-max test was administered using a standardized protocol described by Andersen for adolescents and young adults.[58] First, participants warm up for 7 min at a load of 69 watts for women and 103 watts for men. Participants are instructed to keep a cadence of 70 pedal stroke revolutions per minute throughout the test. After the warm-up period, the load increases by 35 watts every two minutes. The workload (watt) continues to increase until the participant reaches exhaustion. Then, watt-max is calculated by adding *i*) the highest number of watts completed for two full minutes (before the last increase in workload) with *ii*) 35 times the proportion of two minutes completed on the highest load before exhaustion. Based on watt-max, VO_{2max} was predicted using the linear regression formula reported by Andersen[58]:

$$VO_{2max}\ (\mathrm{l}\ O_2/\mathrm{min}) = (0.0117 \times \text{watt-max}) + 0.16$$

Andersen reported excellent test-retest reliability of the watt-max measure ($r = 0.95$) and high validity with a direct measure of VO_{2max} ($r = 0.88$).[58]

Trail Making Test (TMT) part A and B[59] and Symbol Digit Modalities Test (SDMT)[60] were administered as measures of cognitive functioning. In TMT, participants are instructed to connect a series of circles scattered over a sheet of paper as fast as possible. Part A has a series of numbers from one to 25, and part B has a series of alternating numbers and letters. Performance (seconds to completion) requires visual scanning, processing speed, mental flexibility, and executive functions.[61] Both TMT A and B were found to have high test-retest reliability in two diverse samples: r = .76–.79 and .82–.86 for part A and B, respectively. The first sample included community-dwelling residents (60–90 years old) and the second adults with depression (20–65 years old).[62,63]

SDMT is a simple substitution task. Using a reference key with pairs of numbers and figures, participants must pair as many figures as possible in 90 s.[64,65] Performance (number of correct pairs) requires attention, visual scanning, and motor speed. Test-retest reliability was found to range between r = .74–.91 in young athletes[66,67] and r = .84–.93 in healthy adults.[68–70]

Self-reported levels of physical activity was assessed using a questionnaire with three items addressing the number of weekly hours and minutes spent at *i*) easy, *ii*) moderate, and *iii*) hard physical activity and exercise in leisure time.

Statistical Methods

Participant characteristics and indicators of feasibility were analyzed using descriptive statistics. Effect sizes of mean differences in outcomes were estimated using Cohen's *d* for paired comparisons.[71] Analyses were performed using R version 4.0.3[72] using *psych*[73] for descriptive statistics, *effsize*[74] for effect sizes, and *ggplot2*[75] for graphics.

Interviews

Semi-structured interviews were conducted at 6–8 months follow-up to explore perspectives on fatigue, experiences with HIIT, and previous and current exercise routines. An interview guide was developed based on the following topics:

(1) Facilitating factors and barriers to HIIT, e.g. "what do you think about HIIT?"
(2) Exercise behavior, e.g. "do you exercise as much as you did during the intervention?"
(3) The effect on fatigue, e.g. "describe in your own words the effect of the intervention on your experience with fatigue"

Interviews were conducted individually by a psychologist, who had not been involved in provision of intervention or assessment of outcomes. Interviews took about 30 min to complete and were audio recorded and transcribed verbatim. Transcripts were coded with respect to the research questions defined in the interview guide, and results were summarized and reported for each of the three topics above. Analysis was conducted using NVivo 12 Pro.[76]

Results

Recruitment and Retention

A total of 21 young adults with ABI were approached for recruitment. Five individuals declined due to logistics (*n* = 2) and lack of energy to manage additional activities in daily life (*n* = 3). Consequently, 16 individuals were assessed for eligibility. Five individuals did not meet the criteria, and another withdrew right before enrollment due to initiation of a physiotherapy program in community rehabilitation. The remaining 10 eligible individuals all consented to participate in the trial.

Of those enrolled in the trial (*n* = 10), four participants (40%) were withdrawn or discontinued the intervention. First, one was excluded after baseline assessment but prior to intervention due to an episode of epilepsy and need for medications. Second, one was withdrawn after completing 11/11 sessions due to a new stroke. Third, one discontinued the program after completing the first two sessions and failing to complete another two due to interfering pain when cycling, which required GP referral. Finally, one participant did not turn up after completing 3/3 sessions and did not return calls. This left a total of six participants (60%) completing the intervention. Figure 1 shows a flowchart of recruitment and retention for the study.

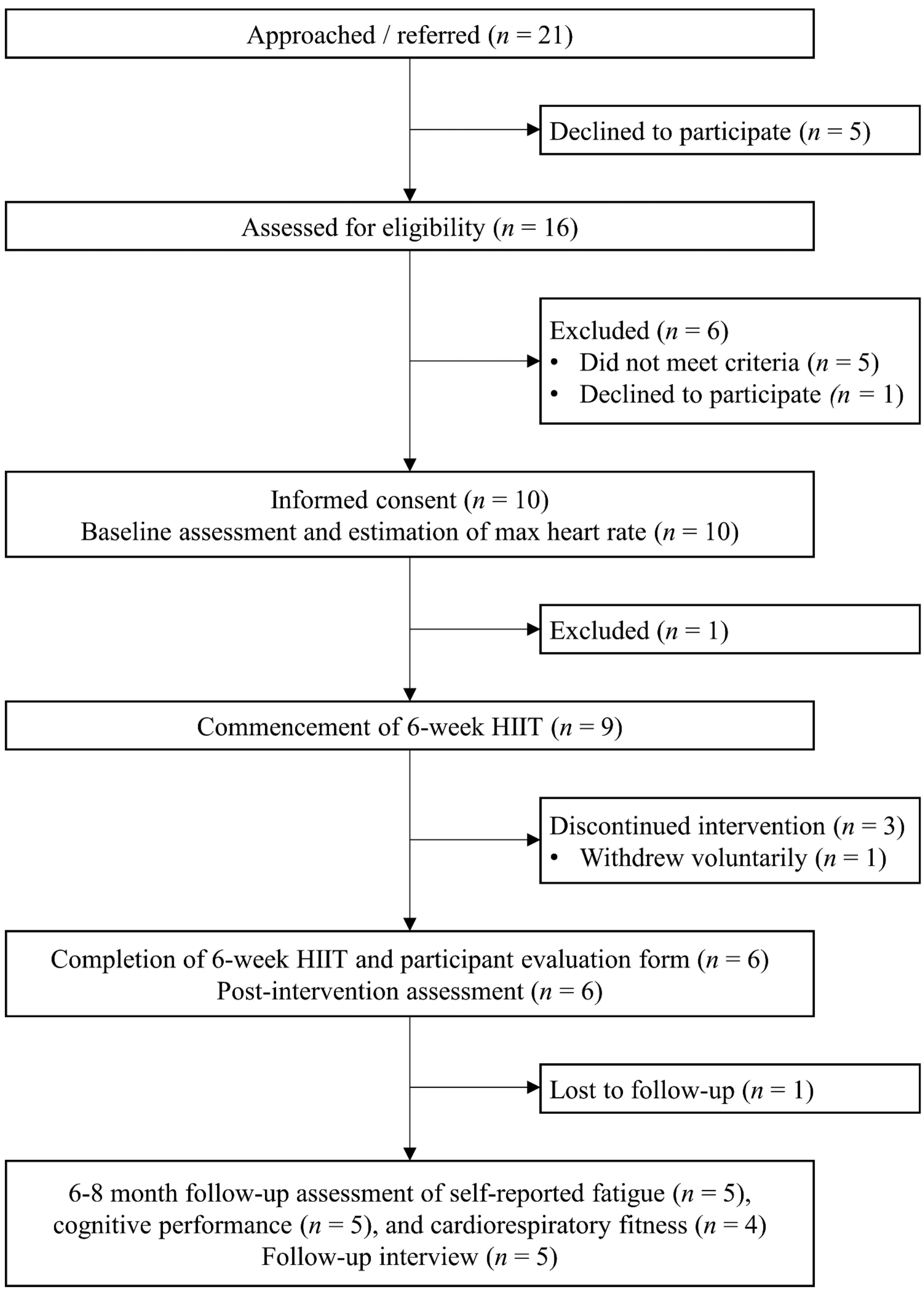

Figure 1. Flowchart of participants.

All six participants completing the intervention were assessed at baseline and post-intervention. One participant was lost to the 6–8 months follow-up assessment due to health condition (unrelated to the intervention). Consequently, five participants completed the follow-up assessment and interview. However, one of these was not eligible for the watt-max test due to pregnancy.

Sample Characteristics

Participants completing the intervention were all female and had a mean age of 30.2 years (SD = 6.9; range 22–40). Half the sample had acquired a TBI, and the mean time since injury was 22 months (SD = 18.9; range 4–55). One was working/studying on normal conditions. The majority (66.7%) were living alone. Four participants did not engage in hard exercise or tiring sports prior to intervention, and two did for about one hour a week. Characteristics of participants are summarized in Table 2, and Table 3 shows physical activity and exercise across the study period.

Table 2. Baseline characteristics.

Variable	Completed intervention (*n* = 6)	Discontinued intervention (*n* = 4)
Age, mean (*SD*)	30 (7.0)	23 (2.7)
Sex, *n*		
Male	0	3
Female	6	1
Occupation, *n*		
Work/study (normal conditions)	1	2
Work/study (special conditions)	3	0
Sick leave	2	1
Unemployed	0	1
Living arrangement, *n* (%)		
Cohabitation	1	1
Married	1	0
Living with parents	0	2
Living alone	4	1
Highest educational level		
Elementary	1	3
9–12 years	3	1
> 12 years	2	0
Type of injury		
Traumatic brain injury	3	1
Stroke	1	2
Tumor	1	1
Meningitis	1	0
Months since injury, mean (*SD*) [a]	22.0 (18.9)	33.3 (39.8)
Body mass (kg), mean (*SD*)	66.4 (1.6)	86.3 (13.5)
Smoker, *n* (%)	2 (33)	2 (50)

Note.
[a]If tumor, the date of injury was defined as the day of neurosurgery.

Training Adherence: Attendance and Workout Intensity

All participants completing the intervention attended ≥ 14 sessions (please see Figure 2A). On average, participants completed 16 out of 18 planned sessions (SD = 1), equal to 88%. Participants achieved high intensity during 'all-out' intervals at an average of 93% of maximum heart rate (Figure 2B). All participants had a mean heart rate ≥ 90% of maximum, indicating adherence to exercise instructions. In addition, perceived exertion ratings and workload were high during intervals (Figure 2C & D).

Evaluation Form on HIIT

All participants reported that the exercise was adequate in terms of intensity, frequency, and mode (i.e. biking). Two participants elaborated: "If the intervention continued for more than six weeks, three times a week, it would be a bit too much" and "if the intervention had been longer than six weeks, then two times a week would be better due to little flexibility." One participant reported that "the first week and a half was too tough with nausea and dizziness, but it was alright afterwards."

All participants reported positive effects of exercising, including feeling more clear-minded and less stressed, being in a better mood, and having more energy. One participant reported negative effects and explained that "if the session was too early in the day, I felt physically tired the rest of the day."

Changes in Self-reported Fatigue, Cardiorespiratory Fitness, and Cognitive Performance

Trajectories in fatigue varied across participants as some improved over the course of study, while others reported stable or greater levels of fatigue (see Figure 3). Mean scores on MFI-20 improved from baseline vs. post-intervention (range: 1.3–4.0 points) and vs. 6–8 months follow-up (range: 1.8–4.0 points; see Table 4). Five out of six

Table 3. Minutes of weekly physical activity and exercise in the study period.

	Baseline			Post-intervention			Follow-up			
ID	Easy	Moderate	Hard	Easy	Moderate	Hard	Easy	Moderate	Hard	Type of exercise [a]
2	630	60	60	480	390	90	300	90	120	Running
5	720	300	0	570	360	90	-	-	-	-
6	240	0	60	420	0	240	150	90	210	Running & cycling
7	1260	840	0	1260	0	90	900	0	0	None
9	1680	420	0	600	120	90	600	120	60	Running
10	300	180	0	360	0	90	360	180	0	Fitness training
Total	4830	1800	120	3690	870	690	-	-	-	-

Note. Examples of easy physical activity included walks, easy cleaning, sweeping and raking in the garden, and easy exercise such as yoga, bowling, etc.; Moderate physical activity included gardening, carrying something up the stairs, and moderate exercise such as gymnastics, swimming, cycling, weightlifting, etc.; Hard physical activity included tiring sports and exercise such as running, jogging, football, tennis, aerobic, etc.
[a]Information on current exercise behavior was collected during follow-up interviews.

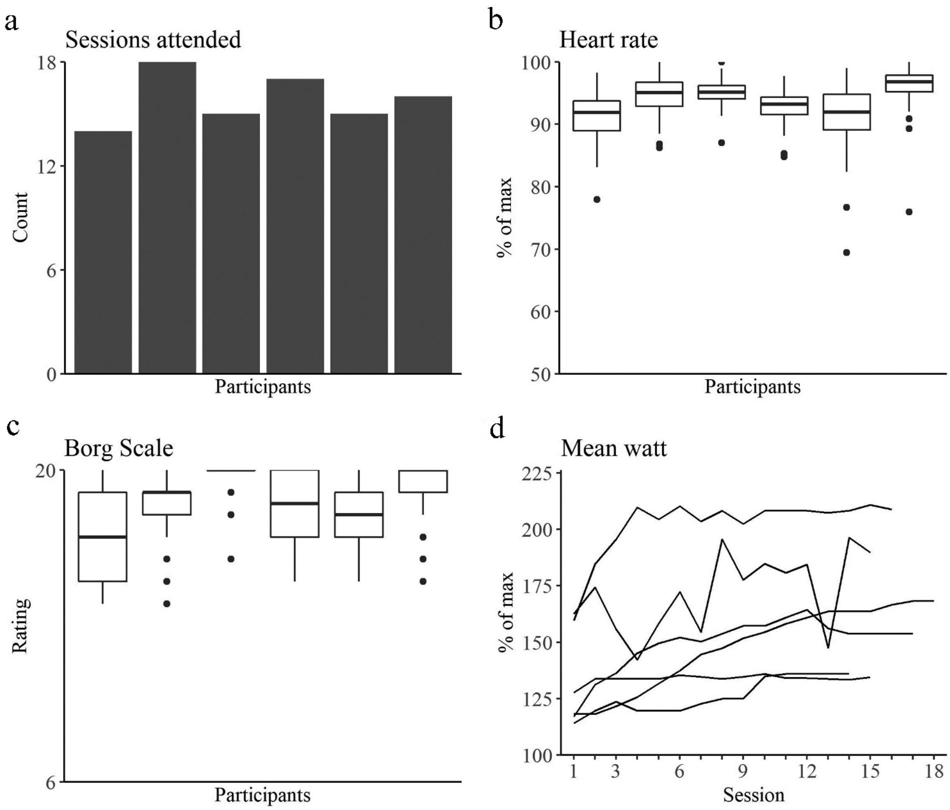

Figure 2. Indicators of feasibility and adherence during high intensity interval training. Note. Part B, C, and D shows data recorded at high intensity intervals only. Boxes extend to the first and third quartiles, and the horizontal line corresponds to the median. Whiskers extend to the largest and smallest value within 1.5 times the interquartile range. Dots correspond to values beyond the range of the whiskers (outliers). Regarding part B and D, max heart rate and max watt, respectively, were determined at the baseline watt-max test.

participants continued to meet the criterion for pathological fatigue (i.e., ≥12 on General Fatigue) at post-intervention and follow-up assessments.

VO_{2max} improved by 0.53 l/min from baseline (M = 2.11, SD = 0.46) to post-intervention (M = 2.64, SD = 0.62), d = 0.82. The improvement had attenuated at follow-up (M = 2.34, SD = 0.43), d = 0.68. Average performance on neuropsychological tests improved from baseline to post-intervention, and improvements attenuated at follow-up (see Table 4).

Follow-up Interview

Five participants completed follow-up interviews. They were all satisfied with the intervention and had a positive experience with HIIT overall. Two participants described that they were pleased to experience benefits of exercising as an alternative to pharmacological treatment.

Facilitating Factors and Barriers in Relation to HIIT

Three participants mentioned supervised training as an important driver. They were motivated to get going by the fact that somebody was waiting for them, and they were encouraged to push harder during intervals. The flexibility in scheduling sessions and the short duration (30 min) were also mentioned as facilitating factors. Two participants described that three sessions a week was too time-consuming in everyday life, and one of them could not do much else the rest of the day after exercising. This participant would prefer fewer but longer sessions. No other barriers were mentioned.

Exercise Behavior

All participants continued exercising after completing the intervention, and most (4/5) exercised regularly at follow-up. No one were using the HIIT program for exercising, but a few continued using interval training in other types of exercise such as running or fitness training (Table 3 shows types of exercise at follow-up). All participants described that participation in the study had made them more aware of the benefits of exercise in relation to wellbeing, and they were more inclined to engage in physical activity. Two participants described that improvements in cardiorespiratory fitness following HIIT had encouraged them to keep exercising after intervention to maintain the benefits.

Effect on Fatigue

No participant felt that the experience of fatigue per se had changed. However, two participants described that the intensity of fatigue was reduced. Both were exercising regularly at follow-up, and they experienced that exercise contributes to a better mood and more reserves of energy (mentally) to manage daily activities. One of them described that she was recovering already, when she enrolled in the program, but felt like HIIT accelerated the process.

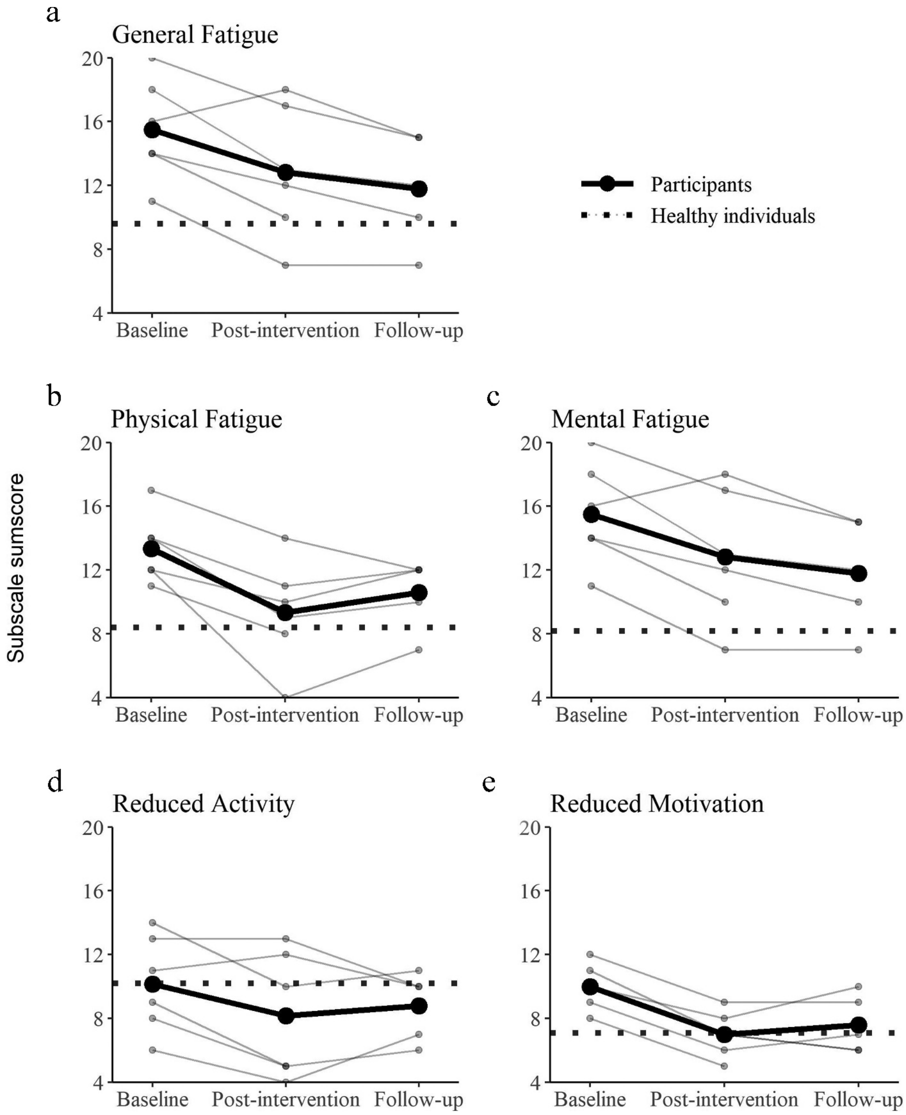

Figure 3. Raw and mean scores on the multidimensional fatigue inventory. Note. Straight lines indicate raw (transparent) and mean (bold) scores of participants on subscales of the Multidimensional Fatigue Inventory at i) baseline, ii) completion of High Intensity Interval Training (HIIT), and iii) 6–8 months after completion of HIIT. Dashed lines indicate mean scores of healthy individuals (*N* = 168, age range = 15–30 years), provided by Norup et al.[13] One participant was lost to follow-up.

Table 4. Changes in study outcomes of six individuals with acquired brain injury receiving high intensity interval training.

	Mean (*SD*)			Mean difference (*SD*)		Cohen's *d*	
Outcome	Pre	Post	FU [a]	Pre – Post	Pre – FU [a]	Pre–Post	Pre–FU [a]
MFI-20							
General Fatigue	17.0 (2.2)	15.7 (2.4)	14.0 (3.3)	1.3 (2.4)	3.0 (2.1)	0.58	0.96
Reduced Motivation	10.0 (1.4)	7.0 (1.4)	7.6 (1.8)	3.0 (0.6)	2.8 (1.9)	2.12	1.82
Mental Fatigue	15.5 (3.2)	12.8 (4.2)	11.8 (3.4)	2.7 (2.5)	4.0 (1.9)	0.67	1.16
Reduced Activity	10.2 (3.1)	8.2 (4.0)	8.8 (2.2)	2.0 (2.1)	1.8 (1.8)	0.52	0.55
Physical Fatigue	13.3 (2.2)	9.3 (3.3)	10.6 (2.2)	4.0 (2.2)	3.2 (2.2)	1.26	1.51
Cardiorespiratory fitness							
VO_{2max}, l/min	2.11 (0.46)	2.64 (0.62)	2.34 (0.43)	−0.53 (0.29)	−0.24 (0.40)	−0.82	−0.68
Neuropsychological test							
TMT-A, sec.	25.7 (8.8)	19.2 (6.6)	21.0 (8.3)	6.5 (4.2)	3.6 (3.5)	0.73	0.39
TMT-B, sec.	65.5 (22.4)	53.5 (16.0)	53.0 (20.6)	12.0 (16.9)	7.6 (8.6)	0.59	0.36
SDMT, score	50.8 (8.1)	55.5 (8.9)	55.4 (10.5)	−4.7 (2.6)	−4.4 (2.9)	−0.52	−0.39

Note. Pre = baseline; Post = post-intervention; FU = 6–8 months follow-up; MFI-20 = Multidimensional Fatigue Inventory; VO_{2max} = maximal oxygen uptake; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; SDMT = Symbol Digit Modalities Test.
[a]At follow-up, *n* = 5 on MFI-20 and neuropsychological test, and *n* = 4 on cardiorespiratory fitness. Cases with missing data was excluded by analysis.

The remaining three participants did not experience changes in fatigue or the impact of fatigue in everyday life. All of them described positive effects of exercising, however, and one of them was using exercise as an alternative to rest to help clear the mind and to get physically fatigued instead of mentally.

Discussion

This study investigated feasibility of an intensive intermittent exercise program on a cycle ergometer for young adults with debilitating fatigue following ABI. The six participants completing HIIT attended most sessions (88%), exercised at high intensity (93% of max heart rate), and were satisfied with HIIT. They reported subjective benefits of exercising such as increased energy levels and improved mood. Four participants dropped out, of which three were withdrawn involuntarily due to medical complications unrelated to HIIT.

Feasibility of the HIIT Program

Participants reported that intensity and frequency of sessions were adequate, although the exercise program was comprehensive and tough. Additional weeks of training or more sessions a week would have been overwhelming to some participants, and one participant reported nausea and dizziness in the beginning of the program. Nevertheless, those completing HIIT adhered to the training program and achieved high intensity workout. They were satisfied with HIIT and reported perceived benefits of exercising. Five of the 21 adults approached for recruitment declined to participate in the trial, as it was challenging to manage additional activities or the amount of traveling needed to attend sessions. Further, one participant did not show up after three sessions. This patient group of young adults may struggle to reengage in employment/study, to cope with demands of daily life, and to make sparse energy resources count. In this context, three sessions a week can be very demanding for some adults to manage in addition to other daily activities. Consequently, those completing HIIT may represent a subgroup of the more motivated and capable patients, and the positive findings on feasibility may not generalize to patients with worse functional outcome. It would also be inappropriate to generalize results to older adults (> 40 years old) with ABI without considering differences in patient characteristics that may influence feasibility.

Testing adaptations to the program that would make it less demanding and more accessible to a larger part of the patient group may have promising prospects, although such changes may compromise any efficacy. The optimal dose-response ratio is unclear,[50] and further research is needed to determine whether any effects of the program are maintained using a less comprehensive exercise protocol, e.g. fewer sessions per week or fewer weeks of exercise. Future research may also consider alternative training structures such as group-based training or tele-health approaches to reduce costs associated with having a supervising physiotherapist present at each session for each participant. In this trial, HIIT was administered individually to ensure adequate workout intensity and progression. For group-based training, technological solutions may be used for feedback measures and adjustment of workload and being part of a group may be an additional motivational factor for participants to attend sessions.

Participant perspectives revealed that supervised training was an important motivational factor, and supervision may be critical for the attendance rate and achieved workout intensity. Many participants reported feeling responsible for attending the training sessions, because the physiotherapist was waiting for them. One participant received regular reminders to attend sessions, either by phone call or e-mail, and most participants scheduled sessions according to their preference. These procedures could likely be contributing to high attendance and adherence.

Only one participant reported an adverse effect (dizziness and nausea), but this effect resolved after the first week. One participant ceased to show up without reporting any reason, and the other dropouts were unrelated to the intervention. These results are consistent with previous findings suggesting that fitness training is safe to perform after TBI and stroke.[38,39] However, any health risks associated with high intensity workout need to be evaluated before administering HIIT. In this trial, one adult screened for eligibility was excluded based on health risks.

Cardiorespiratory Fitness and Exercise Behavior

Baseline fitness was poor compared to the healthy population. Loe et al. reported mean VO_{2max} at 2.78 (*SD* = 0.46) among 20–29 years old women and 2.75 (*SD* = 0.48) among 30–39.[77] In comparison, baseline VO_{2max} was 2.11 l/min (*SD* = 0.46) on average. After intervention, mean VO_{2max} had increased to 2.64 l/min, indicating that six-week HIIT was sufficient to improve exercise capacity in consistency with previous findings in healthy young individuals[50] and patients with coronary artery disease.[78] HIIT is very intensive but has a low training volume and is therefore not very time consuming compared to endurance training.[50] The time-efficiency of HIIT could be important for long-term adherence to young adults with ABI, as they may have few energy resources and greater fatigability.

All participants at follow-up continued exercising after the intervention, but not all were exercising as much as they did during intervention, and average fitness had decreased compared to end of trial. Most of them were running, as this was an easy and time-efficient way of exercising. The HIIT program may influence long-term exercise behavior and physical activity, as participants had positive experiences with exercising and described being more inclined to engage in physical exercise than before. It may be worthwhile to design and investigate effects of a post-intervention program for those in need of guidance, structure, and motivation to keep exercising and to establish exercise habits in everyday life. Previous studies on behavioral interventions for fatigue following ABI have included components to facilitate exercise and physical activity.[35,79,80] Besides being a potential target for alleviating fatigue, physical activity and aerobic training reduces the risk of chronic diseases and conditions, including cardiovascular disease,[36,81] which emphasizes the need to evaluate physical activity and exercise interventions such as HIIT for young adults with ABI.

Fatigue and Cognitive Performance

Results on self-reported fatigue and cognitive performance were promising but need to be interpreted with caution, as the primary aim was to investigate feasibility. Thus, the trial was exploratory in nature and had no control group, and sample size was small (n = 6). This limits the inferences that can be drawn from results on effect outcomes, as considerable risks of bias are introduced, e.g. improvements may be due to natural recovery or practice effects (on neuropsychological tests), and they may not generalize to other subgroups of the population. Further, the trial did not have adequate statistical power to identify even substantial effect sizes.

Recognizing these limitations, results were promising as all mean scores on effect outcomes improved by medium-to-large standardized effects (d ranging from 0.52 to 2.12). These findings warrant further research using more methodological rigorous designs to investigate effectiveness of HIIT. Previous intervention studies have suggested that exercise may have a positive impact on fatigue, but only few have evaluated a physical training program outside the context of other simultaneous interventions.[33]

Interestingly, average performance on neuropsychological tests improved from baseline to post-intervention by medium standardized effects (d ranging from 0.52 to 0.73), and improvements had attenuated at follow-up. However, there might be a learning effect on TMT,[82] which needs to be taken into account when interpreting pre-post results. The possible impact of physical exercise on cognitive performance following ABI is an interesting avenue for future research.

Methodological Considerations

There are several methodological considerations related to this feasibility study. First, the study design (pre-post single arm trial) does not support inferences about the effect of HIIT on fatigue due to risks of bias and the small sample.

Second, recruitment of participants was challenging, and this aspect needs to be considered in future trials. Fatigue impacts everyday life and the capability of individuals to participate in activities, including rehabilitation and interventions. Many individuals approached for recruitment were already struggling to manage everyday activities such as study and work because of fatigue, and they found it difficult to manage additional activities. Further, some individuals were interested in participating but did not meet eligibility criteria due to comorbidities or use of medications with fatigue or tiredness as a potential side effect. In addition, four out of ten participants recruited for the trial did not complete the intervention. Three of these were withdrawn involuntarily due to new health complications, while one ceased to show up. Consequently, the sample may represent individuals with more resources and a better functional outcome compared to the target population, introducing a risk of bias. The intervention was feasible to the six participants completing the trial, but a relatively large group of young adults were either excluded or declined to participate, and it is unknown whether HIIT would be feasible to these individuals. This limitation needs consideration in interpretation of results. Further, future trials need to consider recruitment procedures, accommodating needs of participants as far as possible and planning adequate recruitment periods.

Third, both quantitative and qualitative methods were used to assess multiple aspects of feasibility, including attendance, adherence to instructions, achievement of intervention targets, satisfaction with the intervention and perceived effects, facilitating factors, and barriers. Thus, results reflect many aspects that are important to successfully delivering the intervention and may guide modifications to improve feasibility.

Fourth, there is no standard measure of fatigue, and the MFI-20 was not developed for individuals with ABI. In the present study, MFI-20 was chosen as effect outcome because of its multidimensional aspects, which are important for understanding fatigue.[8,54] However, validity is not well documented in ABI populations, and MFI-20 may risk addressing other symptoms associated with brain injury such as cognitive deficits or paresis. The Dutch Multifactor Fatigue Scale has been developed specifically for post-ABI fatigue,[83] and may be a better option for future research. Further, ideally a direct maximum fitness test should have been used, which could provide a more exact result of VO_{2max}. However, this is difficult given that the equipment for a direct maximum fitness test is expensive and requires qualified and trained staff.[84]

Finally, findings on effect sizes should be interpreted with caution given the small sample size and the lack of control group and blinding. Although physical activity was assessed before and after intervention, extraneous activities during intervention such as exercise and treatment was not monitored. While this limits causality inferences regarding effect outcomes, it should not be a concern for inferences on the feasibility of HIIT.

Conclusion

Findings support feasibility of HIIT for physically able young individuals with fatigue following ABI, but recruitment (10/21) and retention (6/10) was challenging in this population. Consequently, adaptations to the exercise program and recruitment procedures need to be considered in future research and clinical applications. Participants completing intervention were satisfied with the program and reported that exercise was helpful in relation to fatigue. To some participants, three sessions a week was challenging to manage in addition to other activities in everyday life, considering the few energy resources available. Attendance rates and workout intensity during intervals were high. Effect outcomes on fatigue, fitness, and cognitive performance were promising. Exercise behavior varied across participants at 6–8 months follow-up, but all participants continued to exercise after intervention and were more inclined to exercise than before.

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MB, AN, HF, and ST contributed to conception and design of the study; MB and AN organized the database; FD, MB, and AN performed the qualitative and statistical analyses; FD, MB, and AN wrote the first draft of the manuscript; MB, AN, FD, HF, and ST wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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