A coach in your pocket

On chronic cancer-related fatigue and physical behavior

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ON CHRONIC CANCER–RELATED FATIGUE AND PHYSICAL BEHAVIOR

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General introduction

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Cancer related fatigue and physical behavior

Outline

Cancer-related fatigue and physical behavior

Fatigue is a common and distressing long-term consequence of cancer [1]. Cancer-related fatigue affects work ability [2], hampers in maintaining social relations, and impacts patients' well-being [3]. If fatigue continues three months after treatment, it is unlikely to decrease of its own accord [4]. With growing incidence of cancer and improved life expectancy [5], there is a strong need for effective and accessible treatments of such chronic cancer-related fatigue (CCRF).

Most treatments for CCRF somehow involve physical behavior change [6]. By means of exercise interventions [7–9], graded activity as part of cognitive behavior therapy [10] or energy conservation interventions [11], different dimensions of physical behavior are targeted in order to reduce fatigue.

Although consensus exists about the fact that being physically active has benefits for cancer survivors [12], much is currently unknown about the physical activity in relation to CCRF, and current findings are not always in line. Some examples. Lower fatigue level was predictive for becoming sufficient physically active after breast cancer [13] and increased physical activity level served a mediating role in reducing fatigue in exercise interventions [14], both implying a longitudinal association between fatigue and physical activity level. However, cancer survivors that suffered from fatigue were on average not less active than cancer survivors who did not report to be fatigued [15], which is unexpected given the former association.

In most studies performed so far physical activity is expressed as physical activity level, which is a general measure of how active a person has been in a certain period of time, for example a day or week. However, such a measure does not provide information on more specific behaviors (sitting, walking) or how the physical activity was accumulated throughout the day. However, considering the guidelines for healthy behavior, not only the physical activity level but also intensity and duration of physical behavior are relevant for accomplishing health benefits: thirty minutes of moderate or vigorous physical activity is suggested as a minimum [16]. With this in mind it is hypothesized that also **other physical behavior measures** than physical activity level could be relevant in the context of CCRF and should be studied in longitudinal research.

In addition, current treatments and research focus on the patients as a group of individuals with identical characteristics and behavior, however, **interindividual differences** are considered to be important to get more insight in physical activity in relation to CCRF. For example, Van der Werf et al [17] studied differences of physical activity level in chronic fatigue syndrome, and concluded that multiple groups could be distinct that would require different physical activity targets as their starting point for the intervention differed.

Changing physical activity does not concern a physical dimension only, also, cognitive factors likely play a role. Firstly, ***self-efficacy*** in the context of physical activity was found to be a mediator for reducing fatigue in an exercise intervention for cancer survivors [18]. In addition, ***perceptions about physical activity*** are expected to play a role in reducing fatigue [19,20], which is in line with Heins et al [21] who found that perception of physical activity but not the physical activity level itself changed during cognitive behavior therapy in chronic fatigue syndrome. To increase understanding of behavioral interventions for CCRF, these factors should be targeted during the intervention and studied for its relation with fatigue change.

In 2012, the FNK (Dutch: 'Fitter na kanker') trial was set-up to further improve the knowledge about effectiveness, prognostic factors and workingsmechanisms of interventions for CCRF patients taking aforementioned aspects into account. In the FNK trial patients who suffer from CCRF are provided with new tools to reduce their fatigue The trial was designed to evaluate two online approaches: ambulant activity feedback therapy (AAF) and online mindfulness-based cognitive therapy (eMBCT).

It is expected that treatment from the home environment could be a welcome intervention for cancer survivors in stead of the current face to face treatments. It is expected that these online interventions provide various benefits for this patient group. Especially in the context of behavior change, the use of technology could support such a process by providing frequent prompts of the behavior change that a participant tried to establish: with continuous objective feedback throughout the day, by reinforcing current intended behavior directly, and by endorsing previously established behavior change.

This thesis will primarily focus on studying the AAF intervention. AAF is a novel mHealth intervention that is guided by a physiotherapist, following a nine week protocol that incorporates the use of an Activity Coach. The Activity Coach assembles an accelerometer, which is a hip-worn device that measures physical activity, and a smartphone application that provides real-time feedback. The use of accelerometers to track physical activity by means of internal smartphone sensors or external sensors is widely accessible (for example FitBit and MisFit), but definitely not commonly used in health care practice [22]. The Activity Coach hourly reviews the patient's personal activity goals. Physiotherapists remotely coach and monitor the progress of the patient, and set intervention goals that are translated to a reference line that can be targeted on the Activity Coach. Insights are gained about the potential, effectiveness, and working mechanisms of the AAF intervention by means of several studies that are performed as part of the FNK ('Fitter na kanker') trial that ran from 2012 to 2016 in The Netherlands.

Outline

The chapters of this thesis will gradually provide insights about the potential, effectiveness, and working mechanisms of the AAF, thereby addressing different aspects of physical activity behavior, interindividual differences and cognitive factors.

As a more thorough introduction, in Chapter 2, CCRF and its impact is further explained, along with the current state of the art of interventions for CCRF and the potential of Internet interventions for reducing CCRF. Both AAF and eMBCT will be shortly introduced. Also, the trial design is presented, including a stepwise analysis plan with accompanying hypotheses that are adopted in chapters 5 to 7.

Chapter 3 first focuses on the ambulant activity feedback therapy. The chapter presents a literature supported basis, and describes the development of the intervention protocol for the AAF.

The fourth chapter focuses on physical behavior patterns of the research sample. The activity coaching intervention assumes that this population is heterogeneous considering physical behavior profiles, and this assumption is studied in chapter four. Patterns of a set of nine measures of physical behavior are analyzed for their interrelatedness.

The last four chapters are results from the FNK trial and report on the effectiveness, and working mechanisms of the Internet interventions. Chapters 5 and 6 report on the effectiveness of both interventions. Trajectories of fatigue, mental health (Chapter 5), and perceived work ability (Chapter 6) of both experimental interventions are compared with the minimal intervention control group. Subsequently, it is studied whether the induced effects in the experimental conditions sustained (Chapter 6). Additionally, effect sizes, percentages of participants who changed reliably, and adherence are established for the first semester (Chapter 5), and correlations among changes of the outcome measures are calculated (Chapter 6).

Correlates of fatigue change are studied in Chapter 7 to find key components for effective behavioral treatment of CCRF. This is done by comparing the growth of potential working mechanisms for AAF with the growth of fatigue severity during the intervention, including measures of objective physical activity (physical activity level, MVPA, balance between physical activity level in the morning compared to the afternoon), measures of perceived physical activity, self-efficacy on physical activity, and sense of control over fatigue symptoms.

The results of the studies are integrated in Chapter 8, highlighting relevance for clinical practice as well as for future research.

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Chapter two
Design and analysis plan of the 'FNK trial'

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Abstract

Introduction. Internet interventions offer advantages that especially cancer survivors who suffer from fatigue could benefit from. Given the growing number of such patients, Internet interventions could supplement and strengthen currently available health care. This paper describes the design and analysis plan that will be used to study two Internet interventions aimed at reducing severe fatigue in cancer survivors: a mobile ambulant activity feedback therapy supported through a weekly email by a physiotherapist and a weekly Web- and mindfulness-based cognitive therapy supported online by a psychologist. The data resulting from this trial will be used to (1) investigate the effectiveness, (2) investigate potential mediators of these interventions, and (3) explore participant characteristics that can predict the effect of these interventions.

Methods. A three-armed randomized controlled trial is proposed that compares both Internet interventions with an active control condition that solely consists of receiving psycho-educational emails. The intervention period is nine weeks for all three conditions. Six months after baseline, participants in the control condition can choose to follow one of the two experimental Internet interventions. Outcomes are measured in terms of fatigue severity, mental health, and self-perceived work ability. All are Web-assessed at baseline, two weeks after the intervention period, and at 6 and 12 months after baseline. Fatigue severity, mindfulness, physical activity, expectations and credibility of the intervention, therapeutic working alliance, sleep quality, and sense of control over fatigue are assessed three times during the intervention period for identifying mediators of the interventions. A detailed analysis plan is described to address the research questions, which allows for individual variation, and fully exploits the longitudinal design.

Results. Recruitment started in April 2013 and will proceed until April 2015.

Conclusions. By publishing our hypotheses and analysis plan before completion of data collection, this paper is a first step in reporting on this trial comprehensively.

Introduction

Background

Behavioral interventions have shown to effectively relieve psychological and physical complaints in cancer survivors. However, the effect on the individual is less explicit, because patients differ greatly in the ways they experience and respond to such interventions. Therefore, when studying such an intervention, individual differences and temporal aspects need to be appreciated. This paper presents a detailed analysis plan for studying behavioral interventions that satisfies such needs.

The protocol of a 3-armed randomized controlled trial is described to study the effectiveness, mediators, and effect predictors of 2 different Internet interventions that share the same aim: reducing fatigue for cancer survivors. Due to its longitudinal design and multiple assessments during the intervention, the temporal development of relevant factors rather than pre-post differences can be studied. Latent growth analysis can be performed and mixture models can be run, which allow for individual variance in growth trajectories. Furthermore, full longitudinal mediation analyses can be performed on the most important potential mediators of both interventions, and differentiating effect predictors can be identified in order to allocate individuals to the most suitable intervention.

The goal of this paper is to present our trial design, hypotheses, and analysis plan. This paper will therefore be the basis for a number of papers that will present the results of the trial. We will first provide brief background information on the research population, the relevance of Internet interventions for this population, and introduce the 2 Internet interventions that are the subject of this trial. Next, the importance of identifying mediating and predicting factors for the intervention effect is discussed. In the remaining sections, we give a detailed description of the trial's design, our hypotheses, and the analysis plan for handling the data that the trial will collect. The analysis plan is written in general terms, in order to facilitate the use of this strategy in other contexts, and to keep this paper focused. Consequently, the extended background of—and reasoning for—the specific hypotheses will be presented in future papers that will focus on the results of the proposed analyses.

Chronic fatigue and cancer

Cancer-related fatigue is defined as "a persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and interferes with usual functioning" [1]. It is one of the most prevalent and distressing long-term consequences of cancer [2], interferes with the activities of daily living, work ability [3] and maintenance of social relations, and consequently impacts patients' well-being [4]. As the number of cancer survivors in the

Netherlands is expected to increase rapidly, with a growth of 50% in the 10-year prevalence between 2009 and 2020 [5], there is a strong need for effective and accessible treatments.

The etiology of cancer-related fatigue probably involves the deregulation of several interrelated physiological, biochemical and psychological systems [6]. There is no definite somatic explanation for the persistence of fatigue after cancer [7–9], and estimates of the proportion of cancer survivors who suffer from persistent fatigue vary widely [8,10]. However, research has shown that if fatigue continues three months after treatment, it is unlikely to decrease of its own accord [8]. The term chronic cancer-related fatigue (CCRF) will be used in this paper for severe fatigue that sustains for three months or longer after completing cancer treatment.

Management of chronic cancer-related fatigue

Currently, both pharmacological treatments and non-pharmacological treatments are applied to the effective management of CCRF; see the overview articles published by Ahlberg et al. [9] and Koornstra et al. [11]. Guidelines state that if no primary association can be found for the persistence of fatigue with a somatic condition, behavioral interventions should also be considered [1]. The previously reported effects of non-pharmacological interventions on fatigue vary widely, as can be seen in the overview of recent meta-analyses in Table 1. Effect sizes tend to be higher when the intervention targets fatigue, and when increased fatigue was an inclusion criterion for the study. Not all studies that were included in the meta-analyses primarily targeted fatigue, therefore effect sizes might not be representative for nonpharmacological interventions that target fatigue.

Behavioral interventions are often based on energy balance models and/or stress coping models [12,19]. In energy balance models, CCRF is seen as a consequence of deconditioning and prolonged inactivity during cancer and its treatment. Secondary fatigue arises as a result of detraining and can lead to a downward spiral. In stress coping models, CCRF is conceptualized as a result of ineffective coping strategies and prolonged stress response [20]. Cognitive behavioral treatments that are based on these theories include physical activity interventions, exercise interventions [14,17,21,15,22], and mindfulness-based cognitive interventions [23–26] and have been shown to help reduce CCRF in previous studies [12,13]. However, all these interventions require the patient to travel to a health care facility, which can be a burden to the patient. Therefore,introducing effective interventions in a home-based setting could improve the health care options for this group.

Table 1. Ten recent meta-analyses considering non-pharmacological interventions for cancer patients that included off-treatment fatigue

Meta-analyses (off treatment)	Intervention type	ES (95% CI)	Fatigue reduced (*P*-value)
Jacobsen 2007 (k = 4%)	Psychological	$d = 0.10$ (0.02 − 0.18)	Yes (<.05) [12]
Jacobsen 2007 (k = 29%)	Activity-based	$d = 0.05$ (-0.08 − 0.19)	ns [12]
Kangas 2008 (100%)	Psychological	WMES (r) = 0.51 (0.10 − 0.92)	Yes (.015) [13]
Kangas 2008 (100%)	Exercise	WMES (r) = 0.13 (-0.77 − 1.02)	ns (.784) [13]
Speck 2010 (100%)	Exercise	WMES (r) = 0.54 (0.19 − 0.90)	Yes (.003) [14]
Brown 2011 (*k* = 54%)	Exercise	WMES (r) = 0.31 (0.22 − 0.40)	Yes [15]
Duijts 2011 (*n* = 31%)	Behavioral techniques	SMD (f) = 0.16 (0.08 − 0.23)	Yes (<.001) [16]
Duijts 2011 (*n* = 42%)	Exercise	SMD (r) = 0.315 (0.10 − 0.53)	Yes (.004) [16]
Cramp 2012 (100%)	Exercise	SMD = 0.37 (0.18 − 0.55)	Yes [17]
Tomlinson 2014 (100%)	Exercise	SMD (r) = 0.61 (0.33 − 0.88)	Yes [18]

Note. Effect size values are positive when the intervention was able to reduce fatigue more compared to the control condition. Abbreviations: *n* (percentage of participants), *k* (percentage of studies), *d* (Cohen's *d)*, WMES (weighted means effect size), SMD (standardized mean difference), r (random effects), f (fixed effects).

Potential benefits of Internet interventions

Internet interventions offer advantages that cancer survivors who suffer from fatigue could especially benefit from. They have been found to be as effective as face-to-face therapies for a wide range of disorders, such as posttraumatic stress disorder, burnout or chronic stress, and depression [27–32]. Internet interventions have the ability to reach a wider range of patients compared to face-to-face interventions, especially severely fatigued patients, those with limited mobility, or patients in rural or even remote areas. Also, patients may benefit from the home-based setting of Internet interventions as these patients can practice more often, are less bound to the availability of care professionals, and can incorporate the intended behavioral change directly into their daily routine. Moreover, visiting a health care facility may no longer be desirable for some cancer survivors due to negative associations with the disease process or because they no longer want to be identified as a cancer patient and prefer the anonymity of their own environment.

Internet interventions for fatigue

Overview

In the Netherlands, to our best knowledge there are currently three Internet interventions that aim to reduce chronic fatigue: (1) an experimental mobile intervention aimed at changing physical activity behavior for participants with chronic fatigue syndrome [33], (2) the Web-based mindfulness-based cognitive therapy "Minder Moe Bij Kanker" [34], and (3) a Web-based cognitive behavior therapy for severely fatigued breast cancer survivors, which is the subject of the current CHANGE study (trial registration NTR4309) [35].

This paper describes the design and analysis plan that studies the first two of these Internet interventions in a randomized controlled trial. Each of these two interventions is described below.

Mobile activity management intervention: ambulant activity feedback therapy (AAF)

The ambulant activity feedback therapy (AAF) is a mobile intervention that utilizes an ambulant activity coaching system, supported weekly by a physiotherapist through e-mail [33]. The activity coaching system has been developed by Roessingh Research and Development (Enschede, The Netherlands) and consists of a smartphone and an accelerometer (Supplementary materials 1) that communicate through BlueTooth [33].

In this intervention, the patient works to meet personal activity goals and subgoals that will be defined together with the therapist. The coaching system supports this process by showing real-time feedback about the accumulated activity of the patient relative to a personalized line of reference and tailored hourly feedback messages. Both the line of reference and the set of feedback messages of the activity coaching system can be adjusted by the therapist through a Web portal (see Figure 1 and Supplementary materials 1). Patients also have access to a Web portal where they can monitor their past personal activity records. Consequently, patients are expected to gain insight in their activity pattern and on how to increase or balance their daily activity in a way that improves their energy levels. More information is given in Chapter 3.
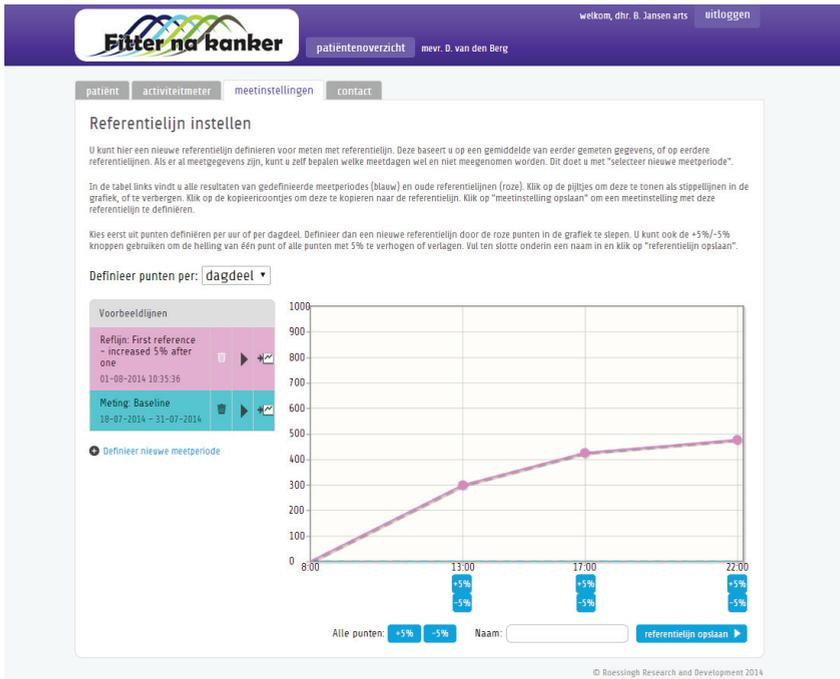
**Figure 1.** Screenshot of the web-portal for the activity management intervention (Dutch).
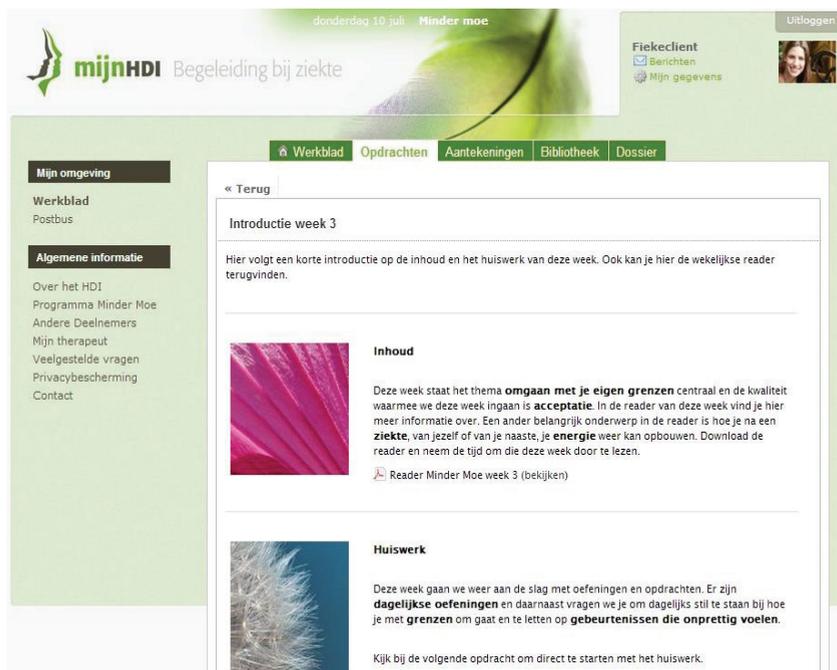
Figure 2. Screenshot of the web-portal for eMBCT (Dutch).

Web-based mindfulness-based cognitive therapy: eMBCT

Mindfulness-based cognitive therapy (MBCT) [36] adds elements of cognitive therapy to the mindfulness-based stress reduction program that was originally developed by John Kabat-Zinn [37]. The Helen Dowling Institute (Bilthoven, the Netherlands) developed a nine-week Web-based, therapist-guided, individual MBCT (eMBCT) specifically designed to reduce CCRF [23]. On a personal Web-page, (see Figure 2 and Supplementary materials 3), each patient can download audio files with mindfulness exercises and read information about a specific mindfulness theme each week. Patients write down their experiences of following the mindfulness exercises in a log. On an agreed day of the week, the therapist replies to this log, thereby guiding the patient through the program. It is hypothesized that by learning to raise awareness of the present experience non-judgmentally and openly, the patient can become aware of potentially ineffective coping strategies that prolong stress and fatigue [38,39]. Patients learn to use a detached perspective as a skill to prevent the escalation of automatic negative thinking patterns. MBCT also teaches patients how to accept fatigue, physical limitations, or pain. The protocol of the eMBCT is discussed more extensively in the article by Bruggeman-Everts et al. [34].

Effectiveness

Our primary question is whether both interventions are effective in reducing fatigue. Therefore, both interventions will be compared to an active control group in a randomized controlled trial. The advantage of this design, as compared to a waiting-list control group, is that we can control for non-specific influences of the trial, such as receiving attention. Also, we expect that in an active control group, fewer participants drop out than in a waiting-list control group.

Usually, results of interventions are presented in terms of an average improvement of the relevant outcome measure. However, practice shows that individuals benefit differently from interventions [40]. Therefore, the proposed trial will aim to identify individual fatigue trajectories, since that seems to be more informative and helpful in improving health care provisions for CCRF-patients than just presenting averages.

Mediators

To optimize interventions in terms of efficiency and effectiveness, treatment-specific and nonspecific working mechanisms should be identified that account for each intervention's effect on fatigue. Knowledge about these mechanisms is an important prerequisite for improving the efficiency of interventions by shifting focus or shortening the intervention. Also, effectiveness can be increased by improving and tailoring the relevant items, subjects, or exercises, as well as improving the way these are embedded in the intervention.

Therefore, the second objective of this study will be to identify the working mechanisms underpinning the interventions.

By using a three-armed randomized design, it is possible to study both treatment-specific (differentiating) and nonspecific working mechanisms. Also, by assessing important factors multiple times during the intervention, important time-specific information can be acquired.

Effect predictors

Although we expect that, in general, both interventions are effective, personal factors, medical factors, and demographics may determine the effect that each intervention has on fatigue [40]. We do not expect all individuals to benefit similarly from the interventions. Therefore, studying potential predictors of each intervention's effect will give us important input to inform both patients and caregivers and allow them to set reasonable expectations.

CCRF has a multifactorial character (eg, physical, cognitive, motivation); therefore, studying the effect predictors of two theoretically differing interventions simultaneously, might also reveal differentiating predictors for both therapies. By applying such knowledge carefully, the overall effectiveness of interventions that aim to reduce CCRF can be increased.

Methods

Design

A randomized controlled trial is performed including 3 parallel conditions: 2 experimental conditions (AAF and eMBCT) and a minimal intervention control condition. The intervention period is 9 weeks for all 3 conditions. Both experimental conditions are made as similar as possible in terms of time-investment and contact intensity with the therapist. Outcomes are self-reported and are Web-assessed at baseline (T0), 2 weeks post-intervention (T1), and at 6 months (T2) and 12 months (T3) after baseline. Figure 3 shows a schematic summary of the trial design.

The baseline assessment consists of 3 time-points: (1) T0a, the assessment to check eligibility; (2) T0b, the main baseline assessment taken after the eligibility check and informed consent, but naive of condition; and (3) T0c, directly after randomization for assessing the participant's credibility and expectancy about the condition. All participants are invited to fill out short questionnaires in weeks 1, 2, 3, 4, 6, and 9 (Mi) of the intervention period in order to study mediation of the interventions.
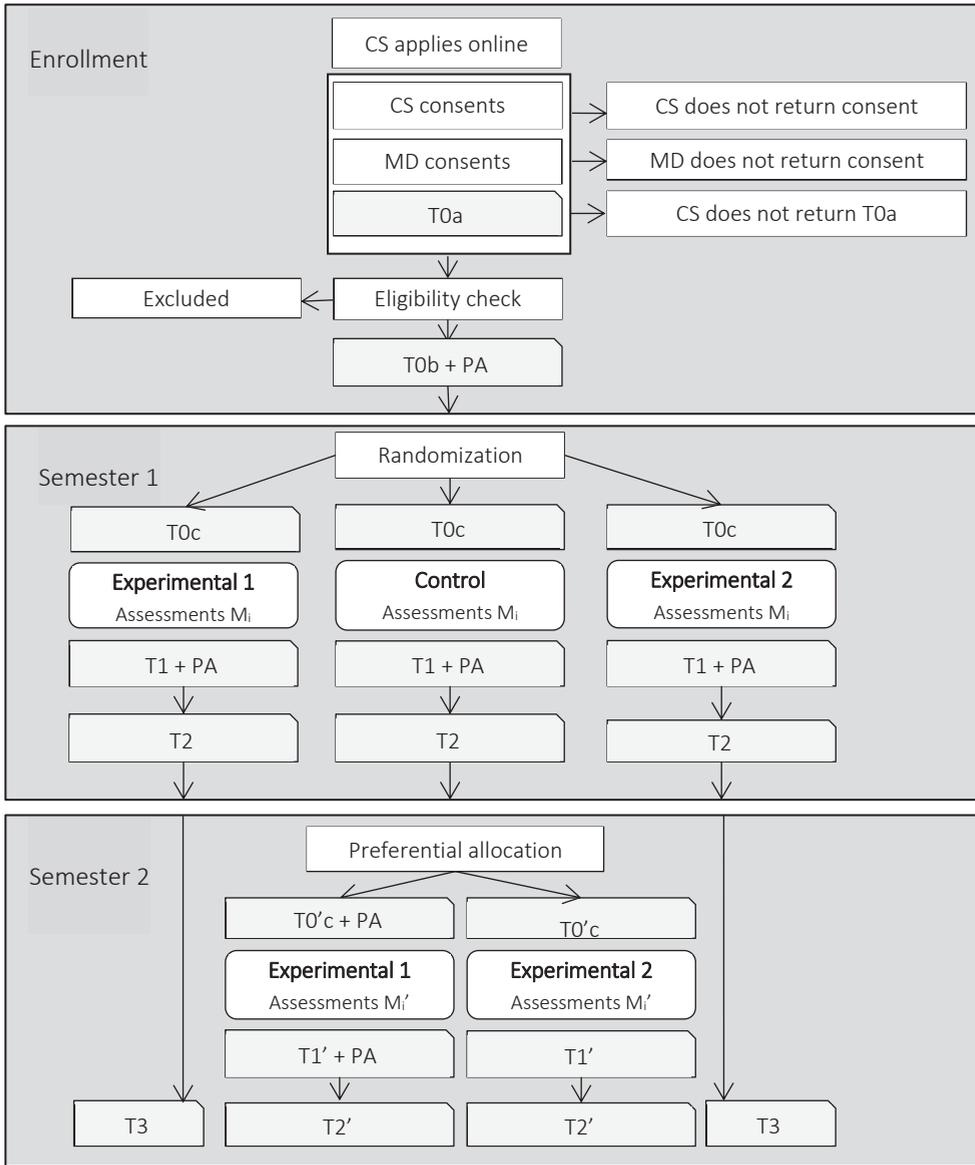
Figure 2. Flow chart of trial design. CS (cancer survivor), MD (medical doctor), PA (physical activity). T0(a-c)-T3 are the main assessments. Mi and Mi′ represent assessments in week i =1,2,3,4,6,9 of the intervention. For addressing the primary research questions on effectiveness, only data from the first semester will be used.

After T2, patients in the control condition are offered 1 of the 2 experimental interventions, again in a research setting. Please note that the first 4 participants of this trial were randomized to 1 of the experimental conditions for the second semester, but to minimize dropout, all other patients will be allocated based on their own preference. During this second intervention period, these participants will again be assessed in weeks 1, 2, 3, 4, 6, and 9 (Mi'), the second week after the intervention (T1'), and 6 months after the second allocation (T2'). Participants in the control condition that are preferentially allocated to eMBCT after T2 do not wear the accelerometer during the second semester.

The protocol allows delay within the intervention period of a maximum of 2 weeks in case of, for example, illness or holiday. For all participants, the duration of their participation is approximately 12 months. Additional qualitative feedback will be obtained through explorative interviews with a subset of participants in the experimental condition shortly after T1 or T1'.

This trial was approved by the Twente Medical Ethical Committee (Enschede, the Netherlands) under number P12-26 and has been registered at The Netherlands National Trial Register under number NTR3483 [42].

Eligibility

The following criteria are used to check eligibility for participation in the trial:

- Completion of a curative-intent treatment for cancer at least three months ago (checked by participant's medical doctor). For this study, surgery, chemotherapy, radiotherapy, immunotherapy, and/or stem cell transplantation are considered treatment.However, the us of anti-inflammatories, and monitoring visits are not considered treatment for this study.
- Patient has been suffering from severe fatigue for at least three months.
- Patient scores 35 or higher on the fatigue severity subscale of the Checklist Individual Strength.
- Aged 19 years old or older.
- At least 18 years old at disease onset.
- Capable of reading and writing in the Dutch language and of using the Internet (implicit eligibility criterion accounted for during registration, but not checked explicitly).

In addition to the mentioned exclusion criteria, please note that:

- Mild depression is not an exclusion criterion. A score of 20 points or higher on the Hospital Anxiety and Depression Scale (HADS) during baseline is considered indicative of depression [47]. Therefore, if the patient scores 20 points or higher,

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- Comorbid somatic diseases—such as cardiovascular diseases, cerebrovascular diseases, diabetes, hypertension, and arthritis that are not treatable but are a possible cause of fatigue—are not exclusion criteria but will be registered during the study. Although this choice will probably lead to an underestimated effect size compared to studies that do exclude patients with comorbidities, we expect that such a sample will lead to a better representation of the CCRF population.
- Participants are requested not to take part in any other therapy directed at overcoming fatigue during the study.
- Data of participants who report pregnancy or recurrence of cancer during the course of the study will be excluded from analysis since the fatigue they experience cannot be considered to be of a chronic character according to our definitions. However, if requested, these patients will be allowed to finish the intervention.

Procedures

Participants apply for inclusion in the study at the project website [48,49].

Informed consent

After online registration, participants receive the patient information and informed consent form by direct mail. They are requested to sign and return the informed consent in a prepaid envelope. Also, they receive a registration confirmation by email with login details for the participant's Web portal on the project website. Participants are requested to complete assessment T0a as a check on eligibility. Also, the participant's medical doctor is consulted to check three of the eligibility criteria: finished curative-intent treatment for cancer more than three months ago, no current signs of cancer activity, absence of current or former major psychiatric disease.

Randomization

If the eligibility-criteria are met, the researcher confirms the participant's enrollment. Subsequently, the activity sensor is given to the participant and its setup is explained in a face-to-face meeting in the participant's home or another mutually convenient location. The second baseline assessment starts (T0b), followed by randomization of the participant to 1 of the 3 conditions by a script embedded in the researchers' Web portal and uses the random function of php (rand(1,3)) [50]. The researchers can neither influence nor predict the outcome of the randomization process. Subsequently, the researcher emails the participant about the outcome of randomization, requests the participant to complete the third baseline assessment (T0c), and assigns the participant to a therapist in case the participant has been randomized to an experimental condition. Participants who do not fill out T0c are considered as not being included. The allocation of a therapist is based on current availability of the therapists who are involved in the trial.

Research conditions

Both experimental conditions are described in the Introduction and will be described more extensively in an article on eMBCT by Bruggeman-Everts et al. [34], and in Chapter 3.

Active control condition

Patients who are assigned to the control condition receive weekly emails containing standard psycho-educational texts about CCRF in order to minimize the dropout rate, following the design of Postel et al [51]. An example of the information that is offered in this minimal intervention control condition is given in Supplementary materials 4 and overlaps completely with the information that is given during both experimental interventions. This condition controls for receiving information on CCRF and for being involved in eHealth research.

Non-adherence and withdrawal

Participants who do not adhere to, or withdraw from, the study or the intervention are contacted by phone and asked for the reason for nonadherence or withdrawal. Participants who want to stop with the intervention are asked to complete a post-intervention assessment at T1 and follow-up assessments at T2 and T3. Participants who withdraw from the study are asked to answer the questions of the fatigue severity subscale of the CIS online or during a telephone conversation.

Assessments

All self-reported questionnaires are Web-assessed via a Web portal on the project website [48,49], developed by Roessingh Research and Development. Participants receive an email when an assessment becomes available and can log in to the Web portal to complete the questionnaires. During the intervention period, each assessment is available for 1 week, but can stay open longer if therapy is postponed due to, for example, illness or holiday. If a participant has not completed it within 6 days, he or she is reminded by email at least once to complete the questionnaire. Within each assessment, the questionnaires are grouped on the basis of importance and subject. Item sequences of the questionnaires for the mediating factors and outcome measures differ between the assessments. Personal data is stored separately from the research data. An overview of all the assessments is shown in Tables 2 and 3.

Physical activity data is collected using the same device as that used for the ambulant activity feedback therapy: a 3D-accelerometer (ProMove 3D) combined with a mobile phone that collects the accelerometer data and sends it to a secured Web server at

Table 2. Assessments of outcome measures and potentially mediating factors.

Parameter	Instrument	T0*	Mᵢ/Mᵢ'	T1/T1'	T2/T2'	T3
Primary outcome						
Fatigue severity	*Checklist Individual Strength*; subscale fatigue severity: 8 items on a 7-pt. Likert scale.	a, b	3,6,9	x	x	x
Secondary outcomes						
Other dimensions of fatigue	*Checklist Individual Strength*; physical and cognitive fatigue and motivation subscales: 4 items for each subscale, all on a 7-pt. Likert scale.	b		x	x	x
Affect	Positive And Negative Affect Scale: 20 items on a 5-pt. Likert scale.	a		x	x	x
Psychological distress	Hospital Anxiety and Depression Scale: 14 items on a 4-pt scale.	a		x	x	x
Self-perceived ability to work	*Work Ability score*: 1 item on a 0-10 numeric rating scale (NRS).	b		x	x	x
Return to work and working hours	Adapted questions of the *Trimbos and iMTA questionnaire on costs associated with psychiatric illness*.	b			x	x
Primary mediating factors						
Mindfulness	*Freiburg Mindfulness Inventory short form* [65,66]: 14 items on a 4-pt Likert scale.	b	3,6,9	x	x	x
Physical activity	Accelerometry: ProMove 3D [52]. Both summative PA and daily PA decline will be considered.	b	3,9**	x		

Construct	Description					
Sleep quality	*Subjective Sleep Quality Scale* [67,68]:15 items (yes/no), and one self-conceptualized item (yes/no) that translates into: "Did you use sleep medication?"	b	3,6,9	x	x	x
Sense of control over fatigue	*Self-Efficacy Scale* [56]: 7 items on a 4-pt Likert scale.	b	3,6,9	x	x	x
Credibility and expectancy	*Credibility and Expectancy Questionnaire* [69]: 6 items of which 4 are on a 9-pt. Likert scale, and 2 items on a 0-100 NRS.	c/c'	1,2,4	x		
Working alliance	*Working Alliance Inventory short form* [70,71]: 12 items on 5-pt scale, subscales: goal, task, bond.		1,2,4	x		
Secondary mediating factors						
Perceived physical activity	Four self-conceptualized questions on perceived activity volume, comparative volume and satisfaction with volume.	b		x	x	x
Self-efficacy on activities	Selected items from the self-efficacy scales of Bandura [72] and Rodgers [73,74]: 13 items on a 0-100 NRS, subscales: planning and coping.	b		x		
Catastrophizing	*Fatigue Catastrophizing Scale* [75,76] 9 selected items on a 5-pt. Likert scale.	b		x		
Fear of cancer recurrence	Two selected items on a 7-pt. Likert scale [77].	b		x		
Causal attributions	One self-conceptualized open answer question that translates into: "What do you consider as the cause of your fatigue?"	b		x		

*) Baseline assessment T0 consists of three time-points: T0a: before eligibility check; T0b: after inclusion and T0c: after randomization. T0c' is assessed after preferential allocation. **) All physical activity measurements are blind, except for the experimental activity feedback condition at M_3, M_6, and M_9. In the second semester, M_3', M_6', and M_9' do not include a physical activity measurement in the mindfulness condition. Abbreviations: NRS (numeric rating scale); pt (point); PA (physical activity); M_i and M_i' (assessments at week (i =) 1, 2, 3, 4, 6, 9 of the intervention

2

Roessingh Research and Development [52]. However, the mobile phone does not give feedback on activity, but does state whether the system is working properly and sends an error message if the connection to the sensor fails. Participants are reminded by email to wear the accelerometer on the day before the start of the week in which they will be using it.

Outcome Measures

Fatigue Fatigue severity will be assessed with the CIS, which consists of 20 items that score on a 7-point Likert scale [53,54]. The CIS has 4 subscales (fatigue severity, motivation, concentration, and physical fatigue) of which the fatigue severity subscale will be used as the primary outcome (8 items, range: 8-56 points). The CIS has shown good discriminative validity in a working population [55], is sensitive to changes in the chronic fatigue syndrome population [56], and has previously been used with cancer survivors [7,57]. The CIS strongly resembles the Multidimensional Fatigue Inventory, which is often used in international studies [54]. Fatigue severity will be assessed at T0a, T0b, M3, M6, M9, T1, T2, and T3. However, the other 3 subscales will only be assessed at T0b, T1, T2, and T3.

Mental Health

Mental health will be assessed from the results of 2 questionnaires: the Positive and Negative Affect Scale (PANAS [52]) and the HADS [58], both of which are included in an item bank for cancer survivors [59]. The PANAS consists of 20 items that score on a 5-point Likert scale and has 2 subscales: positive and negative affect. The HADS consists of 14 items on a 4-point scale, has been validated for a Dutch-speaking population [60], and has previously been used to assess psychological distress in cancer patients [61]. Mental health will be assessed at T0a, T1, T2, and T3.

Perceived Ability to Work

The work ability score, which is assessed with the first question of the work ability index [62,63], will also be used as an outcome parameter. It asks: "Imagine that your working ability in the best period of your life is rated 10 points. How would you rate your working ability at the present moment?" It is assessed at T0b, T1, T2, and T3.

Working hours and the level of absenteeism are assessed with questions from the Trimbos and iMTA questionnaire on costs associated with psychiatric illness (TiC-P) [64]). These will be assessed at T0b, T2, and T3.

Mediating Factors

Several categories of mediators will be considered: intervention-specific mediators for either eMBCT (eg, mindfulness, catastrophizing, and fear of cancer recurrence) or AAF (eg, physical activity, perceived physical activity, and self-efficacy on physical activity), and generic mediators (eg, sleep quality, sense of control over fatigue, credibility, expectancy,

working alliance, and causal attributions). Furthermore, a distinction is made between primary and secondary mediating factors: primary factors are assessed at multiple occasions during the intervention in order to study the timely development of those factors; secondary factors are not assessed during the intervention. A complete overview of all assessments on mediating factors is given in Table 2.

Demographics, medical history, and control factors

Several other factors are assessed, including demographics, medical history, and control factors. All are listed in Table 3.

Table 3. Other assessments.

Demographics, medical history, and control factors	T0*	T1/T1'	T2/T2'	T3
Age, gender, education, family status, nationality, time since diagnosis, time since previous treatment, fatigue duration, psychological counseling in the past, comorbidity.	a			
Cancer type, cancer treatment, perceived life threat of cancer (7-pt. Likert scale), known heredity of cancer (yes/ no/ don't know), former experience with attention focusing exercise (yes/no), religious beliefs, perceived social support (*Multidimensional Scale of Perceived Social Support* [78]: 12 items on a 7-pt. Likert scale).	b			
Medication use, substance use (caffeine, nicotine, alcohol, drugs), quality of life (1 item on a 0 -10 numeric rating scale (NRS)).	a	x	x	x
Pain intensity and limitations by pain (2 items on a 7-pt. Likert scale), body mass index.	b	x	x	x
Life events since previous assessment, professional help received for fatigue outside the scope of the study protocol.		x	x	x
Perceived effectiveness of the intervention (5 items of which 1 item 0-10 NRS and 2 yes/no questions), perceived social support in following the intervention (1-10 NRS).		x		
Social desirability: 6 selected items from the *Balanced Inventory of Desirable Responding* [79] on 5-pt. Likert scale.			x	

Abbreviations: NRS (numeric rating scale), pt (point), PA (physical activity). *Baseline assessment T0 consists of three time-points: T0a: before eligibility check; T0b: after inclusion; and T0c: after randomization.

Analysis plan

Overview

SPSS software will be used for data management and Mplus [80], which is latent variable modeling program, for the subsequent analyses. The exact versions of the software used will be reported in the future papers.

Pre-analysis

Power analyses

The sample size for analyses for data relating to the primary objective has been calculated for a repeated measures analysis of variance: based on an alpha of .05, a minimal detectable effect size of f2 = .15, and a power of .80, a total number of 55 participants [81] is required in each group to answer the primary research question of this study in a statistically valid manner.

We expect to be able to include 330 eligible participants within a period of 2 years, based on a mean of 3.7 intakes per week for the eMBCT of the Helen Dowling Institute in 2011. An estimated attrition of 30% of the participants during both experimental interventions and 15% during the minimal intervention control condition [51] would leave us with 77 participants in each experimental group and 94 participants in the control group at T2. Again, we expect a dropout rate of 30% during the second semester. Such a dropout would leave a total of 110 participants completing each experimental intervention. Ten percent of the participants may have to be excluded from the analyses because of recurrence or diagnosis of metastasis. That would result in 198 participants that complete the full trial. We expect that this number will be enough for testing the 6 mediating factors or effect predictors: A classical, conservative power calculation (analysis of variance for testing 6 mediators or effect predictors with an intermediate effect size (f2 = .08), corrected according to Bonferroni (alpha = .05/6), and at a power of .80 [81]) would result in approximately 254 participants being needed. We expect that the actual power when including 198 participants, and not the required 254 participants, will be great enough to detect up to 6 mediators or effect predictors with the use of Bayesian statistics [76]. Bayesian statistics allow analysis on small sample sizes [76,77], as more power can be generated with the use of prior information which is incorporated in the model that is being tested. Various papers describe comparisons between traditional null hypothesis testing and Bayesian estimation [82-85]. For this study, prior knowledge is available for many parameters, such as the effects of mindfulness in cancer survivors [23,25,66,86] and the role of working alliance in online interventions [87]. Examples of these methods can be found in both applied psychology and social science articles [88-92].

Missing data handling

Missing data will be analyzed considering their pattern and randomness following guidelines proposed by Schafer and Graham [93]. Bias due to systematic missing data will be managed according to guidelines proposed by Asendorpf et al [94].

Descriptives

Quantitative analyses will be conducted on an intention-to-treat basis. A flow diagram following the CONSORT guidelines will be included. Descriptive statistics will be calculated and presented. Independent samples' *t*-tests and χ2 tests will be performed to check for baseline differences between the respective experimental conditions and the control condition with respect to demographic variables (eg, family status, age, gender, and level of education), time since end of treatment, and baseline levels of the outcome variables. If we find statistically significant differences in the mean of fatigue severity across baseline descriptives, dummy variables will be added to the model as covariates to control for these differences.

Core analysis

Effectiveness

Overview

Five steps will be taken to evaluate the effectiveness of both interventions, which are explained here in a generic way. The specific hypotheses on the effectiveness of the interventions in our study are shown in Textbox 1.

Step 1

Overall effectiveness will be tested in an intention-to-treat analysis by a multiple group latent growth model [79] using data from the first semester. This technique allows individuals to have an individual growth trajectory over time and compensates for missing data in an elegant way.

Since different growth patterns are expected for the pre-intervention period, the intervention period, and the post-intervention period, we will apply piecewise growth modeling so that a slope factor will be estimated for each of the 3 periods (Figure 4). Initial intercepts will be configured to represent the T0b score. This intercept and the pre-intervention slope factor will be constrained to be equal between all three conditions (and this assumption will be checked), whereas the subsequent slope factors will be estimated separately for the three conditions.

The fit of the piecewise model will be compared with a quadratic model. In the quadratic model, the entire first semester is modeled with one slope factor and one quadratic factor for each of the three conditions and an intercept that represents T0b and is constrained similarly to the piecewise model.

Both models will be run both with and without using time-varying loadings in order to check whether corrections should be made for differences in timings between the questionnaires. Growth factor estimates and model fits for all four models will be reported (Table 4).

Textbox 1. Hypotheses on effectiveness.

2

Primary outcome

In both experimental conditions,
- fatigue severity
  - decreases during the intervention, and
  - remains decreased after 6 months,
- after 6 months, fatigue severity has decreased significantly more compared to the control condition.
- after 6 months, more participants show a clinically relevant reduction of fatigue severity compared to the control condition. A patient is considered clinically improved if he or she has a reliable change index of more than 1.96, according to the reliable change index, and the end score has to be within the normal range, that is a score < 1 standard deviation above the mean of a normative group [95], i.e. a score < 30.4 on CIS fatigue severity [51].

Secondary outcomes

For both interventions we expect that:
- After 6 months, mental health and work ability have improved more than in the control condition.
- After 12 months, fatigue severity, work ability and mental health remain improved in both interventions groups.
- Improvements in mental health and work ability after 6 and 12 months are related to reductions in fatigue severity.

Return to work and reduced absenteeism will be studied as explorative outcomes.

Neither the participants nor the researchers (FBE and MW) are blinded to allocation. Therefore, an independent statistician (RvdS) who is blind to the allocation will test the primary hypothesis.

The same procedure will be followed for the secondary outcomes, except that the initial intercept of mental health will represent T0a, rather than T0b, because T0b does not include an assessment of mental health.

Results of frequentist analyses will be reported by P-values (significant in case <.05) and with 95% confidence intervals. Parameter estimates of models by means of Bayesian estimators will be reported with 95% central credibility intervals.

Step 2

The effect size of both experimental interventions will be calculated according to recommendations in Feingold (2009) [96] for both primary and secondary outcomes.

Step 3

The proportion of participants who make clinically relevant progress on the primary outcome will be calculated for all three conditions; again, in an intention-to-treat analysis. Percentages and standard deviations of the reliable change index will be presented.

Step 4

A latent growth model will be built of the primary outcome, in which the outcome measures that have been measured at T3 will also be included, as distal outcomes of changes in the primary outcome during the first semester.
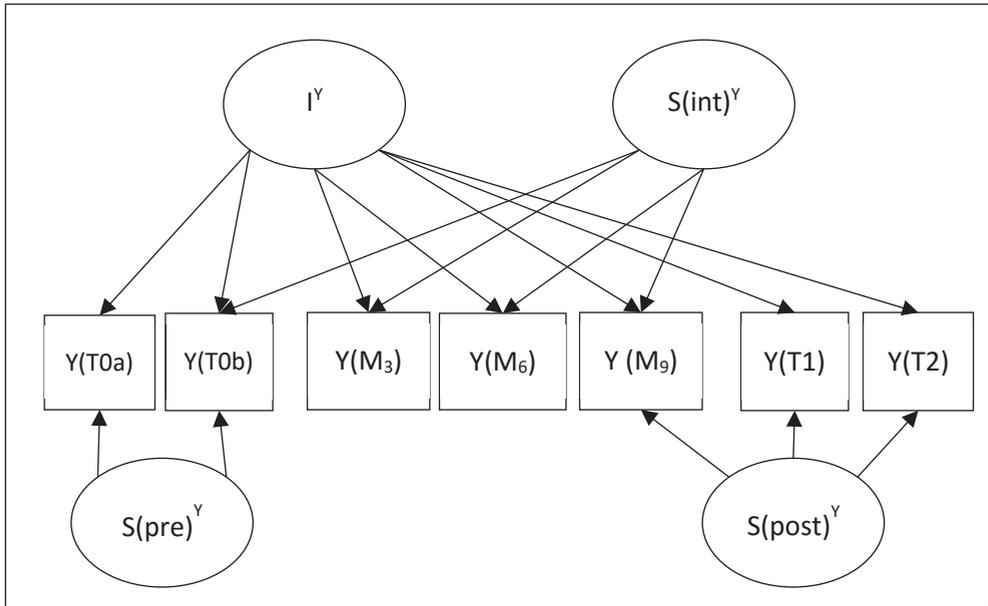
Figure 3. Simplified representation of a piecewise linear latent growth model, with latent intercept factor (I^Y), latent slope factors pre-intervention ($S(pre)^Y$), during the intervention ($S(int)^Y$), and post-intervention ($S(post)^Y$), and seven indicators Y. Error terms, correlation coefficients, and covariances are left out.

Table 4. Growth factor estimates of four different latent growth models.

	Fixed loadings	Time-varying loadings
Piecewise, linear	Mean: I, S(pre), S(int), S(post)	Mean: I, S(pre), S(int), S(post)
	Variance: I, S(pre), S(int), S(post)	Variance: I, S(pre), S(int), S(post)
Quadratic	Mean: I, S, Q	Mean: I, S, Q
	Variance: I, S, Q	Variance: I, S, Q

Abbreviations: I (intercept), S (linear slope), Q (quadratic slope).

Step 5

A growth mixture model (GMM) will be used to further explore differences between individuals, and more specifically to identify subpopulations (latent classes) with homogeneous growth trajectories of the primary outcome within the experimental groups. The Bayesian information criterion will be used for model selection [96].

If convergence considerations allow, this model will be adjusted to allow covariance of the growth factors in order to acknowledge individual variation around the estimated growth trajectories. The trace plots will be inspected to check whether the models have converged to global solutions and a set of diverse starting values will be used. For more information on these analyses, we refer to an introduction to GMM and latent class growth analysis by Jung and Wickrama [97] and examples of similar analyses in the field of Internet interventions [98] and cancer patients [41].

Mediators

Overview

The analysis of the mediators of the experimental conditions can be roughly subdivided into two steps: first analyze the primary factors individually for their longitudinal correlations with the outcome (Step 6), then combine the relevant factors in a multivariate analysis (Step 7). The specific hypothesis on the mediating factors of the interventions in this study are shown in Textbox 2.

Step 6

For analyzing the mediators of the experimental conditions, first we want to see whether there is a correlation between the growth trajectories of our outcome parameter and the potential mediator over time. The hypotheses considering mediators are shown in Textbox 2. The combined data from the participants in the first semester and data from the preferentially assigned participants in the second semester will be used.

Textbox 2. Hypotheses on mediators

We expect that, for AAF, increasing mean cumulative daily PA and reductions of daily PA decline are specific mediators.

We expect that, for eMBCT, developing mindfulness skills is a specific mediator.

We expect that sleep quality, working alliance, sense of control over fatigue, credibility, and expectancy are generic mediators for both e-therapies.

The mediating role of the following factors will be explored: number of sessions completed, changes in causal attributions [99], decreased catastrophizing thoughts about fatigue [8], decreased fear of cancer recurrence [100,101], changes in perceived activity [102], increased self-efficacy on physical activity [103].
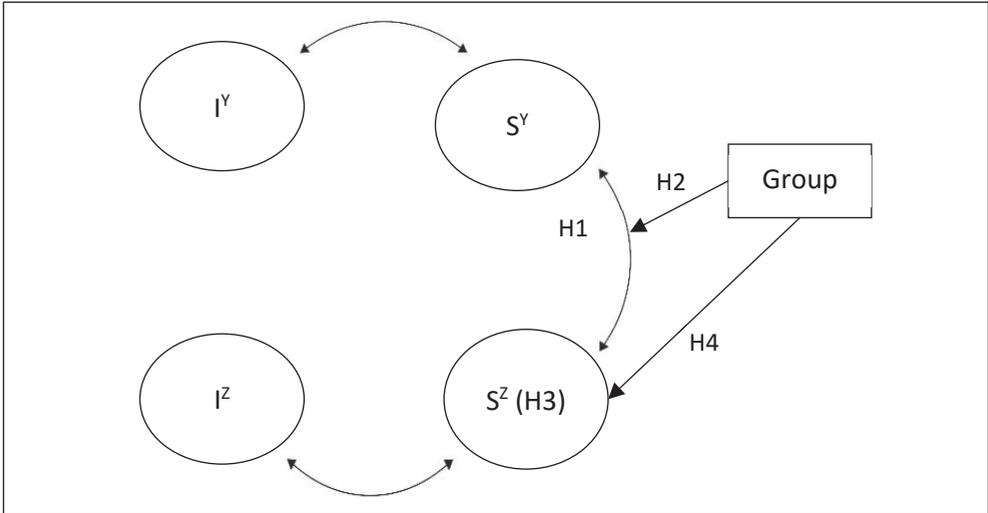
Figure 4. Strongly simplified representation of a correlated growth model in which I^Y and S^Y represent the intercept and slope factors of the latent growth model of the outcome parameter, and I^Z and S^Z represent the latent growth factors of the mediator. H1-4 represent the four sub-hypotheses of Step 6. All indicators have been left out for clarity.
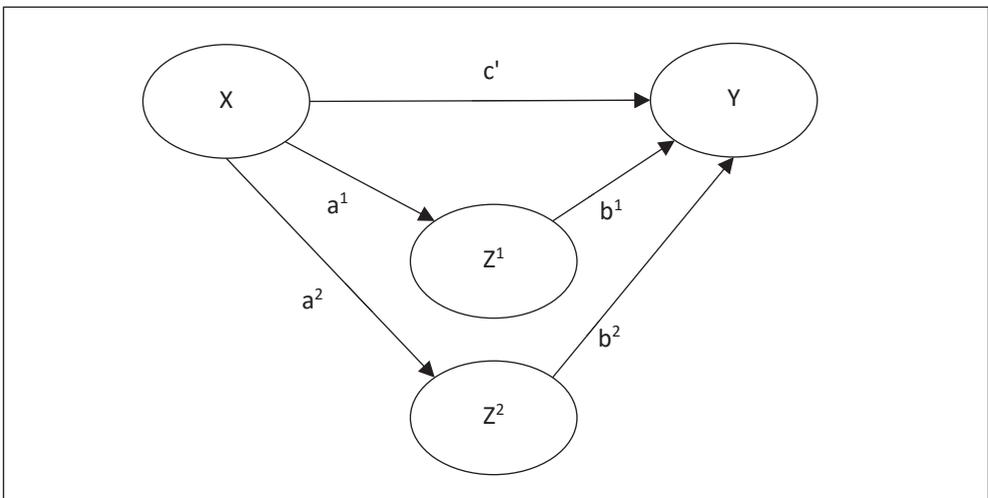
Figure 5. Multiple mediation model with independent variable (X), dependent variable (Y), and two mediators (Z). Direct effect (c'), and indirect effects (a x b) are shown.

The following subhypotheses will be tested for each primary mediator (these are also shown in Figure 5):

- Is the growth of the primary outcome (Sy) for the entire study population correlated with growth of the potential mediator (Sz)?
- Is such correlation independent of group?
- Does the potential mediator change over time in the specific group, so is the slope factor (Sz) substantially unequal to zero?
- Is the slope factor in the specific group substantially greater than the slope factors in the other groups?

In these 4 subhypotheses, the first is congruent with testing the "conceptual theory" in classical mediation analysis, and subhypothesis 3 with testing the "action theory." If subhypotheses 1-4 all are true, the factor will be considered a specific mediator for that intervention. If subhypotheses 1, 2, and 3—but not 4—are true, the factor will be considered a general mediator for fatigue severity. If either subhypothesis 1 (conceptual theory) or 3 (action theory) is false, the factor will not be considered a mediator.

Step 7

The next step in studying potential working mechanisms is a single-step, multiple-mediation analysis using structural equation modeling [104-106]. By estimating such a model, we expect to obtain a comprehensive model for all the working mechanisms of the intervention. It should be noted that this model assumes that an intervention works in the same way for all participants in a particular group [107]. Again, data from both semesters will be used.

A separate model will be tested for each intervention. Each model will have the following paths (Figure 6), where X = independent variable (1/0 for specific intervention vs control group), Y = outcome variable (difference score T2-T0b of the primary outcome measure), and Z = mediator:

- *a*: X regressed on Z.
- *b*: Z regressed on Y;
- *c'*: direct effect of X on Y.

For each experimental intervention, the starting model will consist of all the significant primary mediators of Step 6 that have also been assessed in the control group. In other words, the factors that have shown to be mediators in the correlated growth model will be the starting point for this model. The models will then be complemented with the secondary mediating factors described of Textbox 2. Mediating factors for which the

indirect effect ($a \times b$) is insignificant will be removed stepwise, after which a final model will be created.

Model fit, standardized path coefficients - including indirect effects -, and the total effect of at least the first and final models will be reported with 95% confidence intervals.

Effect predictors

Overview

Two complementing approaches for analyzing the effect predictors are addressed in steps 8 and 9 of this analysis plan. The specific hypotheses on the effect predictors for both interventions in this particular study are shown in Textbox 3.

Step 8

To find out which participants benefit most from each intervention, the final model of fatigue severity of Step 1 will be extended with potential effect predictors (Textbox 3) that load on the latent growth factors "linear slope" (the "post randomization" linear slope in case of the piecewise model) and, if applicable, "quadratic slope". As the regression coefficients of all potential effect predictors on the development of fatigue severity will be freely estimated across the three intervention groups, this is also called a moderation effect of intervention.

Factor loadings of all hypothesized effect predictors will be reported. Those with the highest loadings will be compared between the conditions in order to find differential effect predictors.

Step 9

To identify common effect predictors of homogeneous subpopulations within the heterogeneous population, rather than identifying effect predictors for individual growth patterns, the final step will consist of regressing predictors on latent classes. Therefore, the final model of Step 5, namely the unconditional GMM, will be extended. Again, several potential effect predictors will be regressed onto this model, but this time on the latent class factor, instead of on the latent growth factors. The three-step procedure proposed by Vermunt [109] will be used for model selection. This step will be carried out separately for each experimental condition. Factor loadings of all hypothesized effect predictors will be reported. Those with the highest loadings will be compared between the conditions in order to find differential effect predictors.

Textbox 3. Hypotheses on effect predictors

> We expect that for AAF, low perceived physical activity predicts reduction of fatigue severity.
>
> We expect that for eMBCT, low perceived concentration, previous experience with mediation exercises, high perceived life threat from cancer, and a high education level predict reduction of fatigue severity.
>
> In general, we expect that low perceived social support, longer time since last treatment, suffering from more comorbidities [108], and having strong somatic attributions [57] predict small effects on fatigue severity in both interventions. We expect that high sense of control and good sleep quality predict large effects in both experimental conditions.
>
> Other factors will be included for explorative research.

Results

Recruitment for the trial started in March 2013 and is expected to continue until April 2015. No major changes have been made to the protocol. However, due to an error in the randomization algorithm between January 14, 2014, and July 15, 2014, allocation was dependent on the number of participants who were allocated at once. This in turn was completely random. Consequently, 10 participants were allocated directly to the AAF group; four other participants were divided equally between the two experimental interventions; and 15 accounts (of which, one was a dummy account) were equally divided between the three groups. None of the researchers were aware of this error, as this allocation could very well have simply been the result of the "roll the dice" scenario that should have been applied. How many participants were allocated at once was not the subject of the researchers' decision-making. Therefore, we argue that allocation has still been random and, accordingly, data for all considered participants will be processed as originally planned.

At the time of this writing in January 2015, 269 patients have registered at the project website. Of these, 111 have been officially included in the study, 50 were excluded from participation, and 35 withdrew before their eligibility was checked. The remaining patients are still in the enrollment phase. The main reason for exclusion so far has been a score lower than 35 on the CIS fatigue severity subscale (60%). Furthermore 11% did not meet the psychiatric stability requirement, 8% were younger than 18 at the time of cancer diagnosis, and 8% were still receiving cancer treatment.

Current group sizes as of January 2015 for participants in the first semester are 36 (AAF), 24 (eMBCT), and 32 (control). However, 19 participants have not yet been randomized. Initial responses to the primary research question are expected to be available by the end of 2015.

Discussion

Principle findings

This paper has described the design, hypotheses and analysis plan of a randomized controlled trial in order to study the effectiveness, mediation, and effect predictors of two Internet-based interventions for CCRF. Although recruitment and inclusion have already started, publishing the analysis plan is of great value because it will help to prevent outcome reporting bias [110] and adds validity information to the final studies [111].

By using multiple assessments during the intervention, the proposed trial design is suitable for studying the chronological development of both potential mediators and fatigue. That has two main advantages. Firstly, the data will be suitable for analyses that allow for variation in the individual fatigue trajectories. We do not expect that either of the interventions that have been included in the trial will be beneficial for all participants: our study sample will be highly heterogeneous considering for example tumor and treatment types. Therefore, the analyses on individual growth trajectories can acknowledge that expectation and test that hypothesis. This will substantiate the interpretation of the results on effectiveness and will be an important first step in identifying what works for whom. Secondly, this study design enables us to use a fully longitudinal mediation analysis, at least for the most important factors, rather than using indirect effects analysis in cross-sectional mediation analysis.

Another important feature of the proposed design is that by comparing two different interventions with an active control group, therapy-specific elements of the interventions can be distilled from the data acquired during this trial. This advantage counts for both the effect predictors and the mediators. Knowledge about such differentiating factors can and should be used to better inform patients with CCRF and to improve allocation of patients with CCRF to suitable interventions. As a result, an increase in the overall effectiveness of relevant interventions can be established.

In this paper, we have presented the trial design, our hypotheses, and a detailed analysis plan. In accordance with good clinical practice, and to avoid outcome reporting bias, this paper was submitted before any of the data was analyzed. All methods are now openly predetermined, therefore any future publication describing this trial can be valued reliably on its quality.

Limitations

A limitation of the current paper is that for most instruments, this paper does not include information on its properties or a thorough rationale for its choice. More extensive

information on the actual instruments will be reported in subsequent papers on the results of the various research questions posed in this trial.

Conclusion

Given the growing number of patients suffering from CCRF, the availability of effective Internet interventions potentially strengthens current health care for this population substantially. We have proposed a design to study two Internet interventions in order to gain insight into their effectiveness, mediators, and effect predictors, which fully acknowledges differences between individual patients and differences in the way they respond to each intervention. Results on the effectiveness and mediators will give useful information for improving both the quality and availability of such interventions. Also, identifying effect predictors for positive intervention effects will improve the referral of patients to relevant interventions. By presenting our hypotheses and analytic strategy before completion of data collection, this paper is a first step in carefully reporting on this comprehensive trial.

Supplementary materials

https://progress.rrdweb.nl/39/

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Chapter three
An mHealth intervention strategy for physical activity coaching in cancer survivors

3

Abstract

Introduction. Many cancer survivors experience severe fatigue long after they have finished curative treatment. The aim of this study was to develop an intervention strategy that aims to decrease cancer-related fatigue by integrating a physical activity coaching system in primary care physiotherapy.

Methods. This development started from the current state of the art. Therefore, firstly, an overview is given about physical activity goals for cancer-related fatigue, relevant cognitive behavioral change factors in this context, and recommendations for using mobile Health applications. Subsequently, interviews with five experienced health professionals were held to define recommendations for the first draft intervention strategy. Via an iterative process with two physiotherapists and a patient, the final intervention strategy was developed.

Results and conclusions. The final result is a 9-week intervention strategy that could benefit a large variety of patients with chronic cancer-related fatigue, that has the potential to be integrated successfully in current primary health care, and is currently evaluated in a large randomized controlled trial.

Introduction

Chronic cancer-related fatigue

Fatigue is a frequent and debilitating residual symptom of cancer and its treatment. It is estimated that more than 20% of cancer survivors report severe fatigue one year after treatment [1]. Survival rates and life expectancies of cancer patients are rising, and cancer is increasingly often considered a chronic disease. The 10-year prevalence of cancer patients in the Netherlands is expected to grow by 40% between 2011 and 2020 [2]. As a result, the number of patients suffering from cancer-related fatigue will increase rapidly.

Currently, cognitive behavioral therapy, multidisciplinary rehabilitation programs, exercise, and energy conservation interventions seem effective in reducing fatigue. The Dutch Cancer Society recommends to partially shift such oncological aftercare to primary care, and to encourage patients' self-management with respect to their health problems. It is expected that this will make health care accessible to a larger group of patients, and is more cost-effective. In order to achieve the necessary changes, new treatment strategies for the primary care need to be developed.

Physical activity coaching

Physical activity is considered an important element in treatments of chronic cancer-related fatigue. An upcoming trend to achieve changes in physical activity is the use of Mobile Health (mHealth) applications [3], such as UbiFit Garden [4] and Fish`n`Steps [5]. Such systems use information from accelerometers or pedometers to send text messages to subjects in order to encourage physical activity, based on personalized step goals. Another example is the Activity Coach, which has been developed by Roessingh Research and Development (RRD, Enschede, The Netherlands) [6]. Previous research showed that subjects with chronic fatigue syndrome and chronic obstructive pulmonary disease were able to increase their daily physical activity by using this system [7,8]. Based on this, it is expected that patients with chronic cancer-related fatigue might benefit from using this system as well.

However, despite the short term effectiveness of the use of such mHealth systems, current research shows that adherence and longer term effects are often still limited. One reason could be that mHealth systems are often deployed as a standalone tool: It is hypothesized that the use of mHealth systems should be better integrated in the everyday care practice [9]. A motivating role of the health professional in using mHealth systems will enhance a patient to generate insight in the usefulness and rationale of its use, which will promote compliance. Also, the mHealth system can be used in a much more personalized way, and behavior change processes can be supported more effectively. Conversely, by using mHealth technology, the professional can monitor and stimulate behavioral change in a

patient's home environment. Therefore, the aim of this work was to develop an mHealth intervention strategy for patients who suffer from chronic cancer-related fatigue that utilizes the Activity Coach, integrated in primary care physiotherapy.

Background

The next paragraphs describe the starting points for the development of the intervention strategy. First, the activity coaching system is described in more detail. Without trying to give a complete systematic review, the three subsequent paragraphs describe the state of the art considering physical activity, behavioral change principles, and experiences in the context of cancer-related fatigue with the use of mHealth systems.
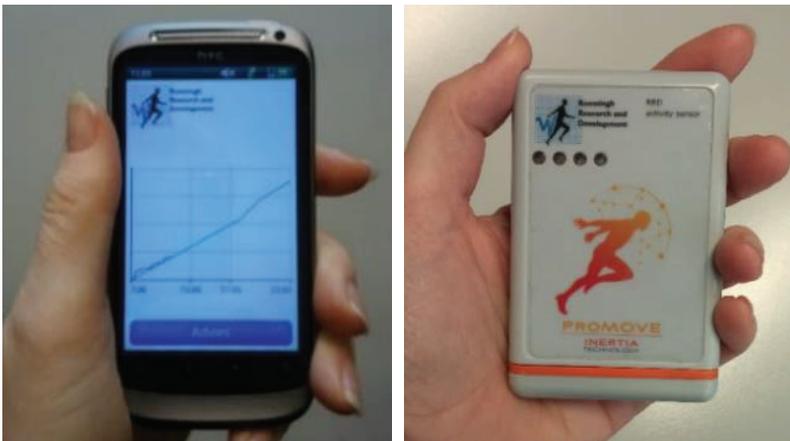
Figure 1. The Activity Coach. Left: Smartphone (HTC Corporation, Taiwan) showing the application. Right: ProMove 3D accelerometer (Inertia Technology, The Netherlands).

The Activity Coach

The Activity Coach consists of a smartphone and a 3d-accelerometer (ProMove3D, Inertia Technology B.V., Enschede), shown in Figure 1. The sensor is worn on the hip by means of an elastic belt or clipped onto the waistband. Both devices communicate with each other real time through Bluetooth.

The accelerometer converts the accelerometer data into IMA's, Integral of the Modulus of the Accelerometer output, as described by Boerema et al. [10], which can be used as a measure of physical activity and correlates well with energy expenditure as measured with oxygen consumption for many activities [11]. The smartphone displays a real time visual of the patient's cumulative activity, relative to a line of reference, and generates automated feedback messages about the patient's current activity level relative to that line of reference. The smartphone uses its wireless internet connection to send the converted data

to a database, so that the data can be retrieved on a web portal. The level and shape of the reference line, the content of the feedback messages, and functionalities on the web portal were subject to change in the development of this intervention strategy.

Physical activity

Many behavioral change interventions that target fatigue in cancer survivors use physical activity goals such as increasing physical activity and/or physical exercise [12–16]. Walking programs, aerobic training, and resistance training have shown to be beneficial. For example meta-analyses by Brown et al. (2011) [15] suggest that intensity of exercise is strongly related to the effect of the intervention on cancer-related fatigue. Two other reviews on the effects of exercise interventions are more cautious in their conclusions, but acknowledge positive effects of strength training on physical functioning [17,18]. In addition, Jacobsen et al. [19] did not find significant effect sizes of physical activity interventions on fatigue outcomes in their meta-analysis. Multiple activity types and intensities were included. However, they did find that home interventions more often had a positive effect when compared to supervised interventions.

Other examples of goals that target physical behavior to reduce fatigue in cancer survivors could include balancing activity throughout the day, or energy conservation [20,21]. This would include the management of opportunistic activities, which are activities that a patient incorporates in their daily life, such as cycling to work and taking the stairs.

So, despite contradictory results from various meta-analyses, relevant goals for patients with chronic cancer-related fatigue could be adjusting their physical behavior by increasing the amount of opportunistic activities and the volume of aerobic or strength training. However, energy conservation seems to be a promising focus for this population too.

Cognitive behavioral change principles

Exercise interventions seem more effective in reducing fatigue in cancer survivors when they are guided by behavioral change or adaptation theory [15]. One of the relevant factors in this context is improving self-efficacy over physical activity [22,23], as it seems to be one of the most important mediators of exercise interventions on fatigue in cancer survivors. This can be achieved by (1) setting realistic but challenging sub-goals and giving the possibility to monitor progress easily, so make sure the patient experiences 'he can do it', (2) social comparison: make sure the patient knows that comparable patients before him have been able to make comparable adjustments of behavior, (3) verbal persuasion per e-mail. Learning to formulate implementation intentions could help patients to change their physical behavior [24] in order to attain the goals that they have set. The use of text messages in mHealth interventions can help remind people of their implementation intentions [25].

Also, the patient's stage of change should be acknowledged throughout the intervention in order to decide on (when to change the) the focus of the intervention: i.e. informing and raising awareness, motivating or maintenance [26]. The Activity Coach could be used to give insight in the patient's progression in order to increase the perceived behavioral control.

Servaes et al. [27] reported on other cognitive elements that are associated with cancer-related fatigue: Patients with low sense of control over fatigue symptoms (and high anxiety and high impairments in role functioning) are more likely to suffer from persistent fatigue after cancer treatment. Therefore, targeting such cognitions could increase the effect of interventions for fatigue. The involvement of a health professional in the intervention could provide in this need, and make sure the patient is guided and coached in a personalized manner.

mHealth recommendations

A patients compliance can make or break a behavioral therapy, whether or not mHealth technology is utilized. However, the use of mHealth brings new challenges considering this topic, of which some are closely related to the previously mentioned cognitive aspects. According to Fogg [28], persuasive technologies should keep in mind three factors in order to be successful in their aim: motivation, ability, trigger. His framework gives useful support for utilizing the Activity Coach. Consolvo et al. [29] formulated recommendations more specifically for activity coaching applications successfully: 1) give users proper credit for activities, 2) provide personal awareness of activity level, 3) support social influence, and 4) consider the practical constraints of users' lifestyles. Moreover, varying and personalizing feedback messages could make it more interesting to use the system and therefore learn from it [8,30]. It also possibly extends the patient's use of, and compliance with, this system. Also, activity goals, when using a reference line in an mHealth application, should be based on a the individual patient's baseline activity pattern rather than on for example a "healthy" norm value of physical activity [7].

Finally, "increased interaction with a counselor, more frequent intended usage, more frequent updates and more extensive employment of dialogue support significantly predicted better adherence" [31].

Methods

Taking into consideration the existing system and background knowledge, the development of the intervention strategy started. In order to do so, the guidelines published by Huis in 't Veld et al. were used [32]. These guidelines suggest, as we did, to start from current state of the art and evidence based medicine, and work in close co-operation with the intended users: both professionals and patients. In order to do so, first, semi-structured interviews

were held with five health professionals in the field and with one patient. The interviews allowed plenty space for discussing new ideas and followed the personal interests and concerns of the specific interviewee. The activity coaching system was presented and discussed in these sessions in order to get first ideas about how this system could be utilized successfully in their current practice. Ideas and recommendations were pooled and summarized. Then, a first version of the intervention strategy was drafted.

Secondly, an iterative process of discussions and testing with two other physiotherapists was performed. This was completed with a test session with a patient, after which the intervention strategy was finalized.

Results

Step 1: Insights from health professionals

One psychotherapist, three physiotherapists, and an occupational therapist of the multidisciplinary cancer-rehabilitation team of Rehabilitation Centre Roessingh (Enschede, The Netherlands) were approached for interviews, and all agreed to cooperate. The health professionals were all very experienced with treating patients that suffer from either chronic fatigue syndrome or chronic cancer-related fatigue, and two of them also had prior experience with using a previous version of the activity coaching system. These semi-structured interviews focused on three aspects: "How would you use the activity coaching system in an intervention for chronic cancer-related fatigue", "Given the fact that such an intervention takes place at home solely, would e-mail be an appropriate means of communication?", and "What would enable the system to be incorporated successfully in current primary health care?" The following issues arose:

1. E-mail was generally considered an efficient and effective medium to communicate between patient and health professional.
2. In the Netherlands, complementary health insurance packages for physiotherapy often cover up to nine consults, this should be taken into account.
3. Two therapists would recommend at least one face-to-face contact.
4. One therapist was concerned about whether patients would like to be monitored all over again, and questioned if patients would appreciate to wear the system.
5. There should be weeks planned in which the patient does not have to wear the system. In that way, the patient will have to translate what he has learned to daily living and compliance to the system in the other weeks might increase.
6. Personalized and well-justified goals are easier to attain than acting upon a standard, "healthy" reference line, so a therapist should be able to adjust that line.

In that way, the end goal can be divided into sub-goals and adjusted throughout the intervention in order to support the patient in a flexible manner.

7. Large inter-individual differences exist in baseline activity patterns and personal goals should be set, which requires tailoring of the automated feedback.

Draft of the intervention strategy after Step 1

Based on the background knowledge and the results of the interviews, a first draft of the intervention strategy was developed with as main characteristics that it includes a theoretical framework, weekly instructions, e-mail examples, and guidelines for the incorporation and use of the activity coaching system.

The Activity Coach

Adjustments to the technology were made to the web portal and the software on the smartphone that generates the feedback messages.

Web portal

The therapist enters the web portal at the home page, which shows a "traffic light"-visual of each patient's compliance to wearing the accelerometer of the current week. More detailed information on each patient is shown in three tabs:

1. "Patient": a summary of demographics and contact details of the patient;
2. "Activity monitor": tab on which different graphs of the patient's activity are shown in line charts that show either the cumulative (Figure 2) or raw IMA data from each day, or in a bar plot that represent the three day-parts or separate days.
3. "Measurement settings": tab in which the Activity Coach can be set up for patients: level and shape of the reference line and the content of the feedback messages on the smartphone.

Feedback scenarios

In order to create flexibility for the therapist, and acknowledging the great inter-individual differences between patients, three different feedback scenarios were created. They differ from each other in terms of content of the feedback messages. The first scenario is for persons who are prone to being not physically active enough (activate). The second scenario is meant for patients who are used to push their boundaries, and could use encouragement of taking rest above a certain point (temper). The third scenario (balance) is the most neutral scenario, and can be used for patients who require to balance their activities throughout the day, and especially to conserve energy in the morning. Figure 3 shows a visual of the classification of the three scenarios. The messages differ on three scales.
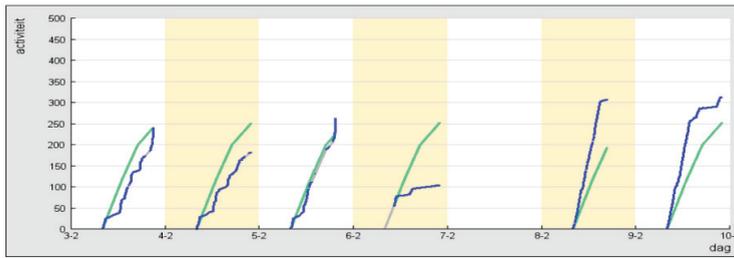
Figure 2. Screenshot of the activity viewer on the therapist portal, showing the reference line (green) and the actual cumulative activity (blue). Grey segments represent missing data, which are inter- or extrapolations of the reference line.

Firstly, the goal of the feedback message can be to reward or acknowledge the physical behavior (green), or to stimulate the patient to change the physical behavior (yellow, orange, red). These messages differ in rigorousness of the feedback or the proposed behavior (for example "a nice stroll" (yellow) versus "a brisk walk" (red)), as can be seen in the intensity of the colors in Figure 3. Boundaries for all three scenarios are set at a deviation of respectively +/-10 and +/-20% from the reference line. Secondly, the messages can either be suggestive or imposing, for example "Is there any chance that you can plan a brisk walk this afternoon?" or "Is your current activity in line with your intentions?" versus "Time for a brisk walk".
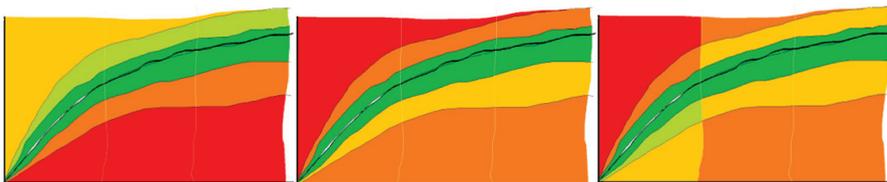
Figure 3. Visual representation of the feedback scenarios. Left: activate, middle: temper, right: balance. The black line in the middle of the green strip represents the reference line.

Process guidelines

The intervention strategy starts as the patient completes an intake questionnaire about demographics, medical condition, and fatigue complaints. Questionnaires can be administered online, and the hardware can be sent by direct mail easily. The patient wears the system for a week to create a baseline activity measurement. In this week, the smartphone does not display any feedback about the patient's activity. However, the therapist should keep in mind that the simple act of wearing the device might influence the results of this measurement.

After the baseline week, the therapist logs into the web portal to see the results of the baseline measurement, and to change the settings of the Activity Coach. The therapist selects a reference line that is equal to, or is based on the patient's average daily activity

during the baseline week. In that way, the patient can get used to using the Activity Coach. Subsequently, the therapist approaches the patient through e-mail, gives an introduction about himself and the intervention, and gives a rough planning for the upcoming 9 weeks. The patient is asked to introduce himself too and to use the system for a minimum of three days to get used to the feedback scenario.

For the patient, the first feedback period now starts. Each hour, a feedback message is selected and pops up at the smartphone. The patient can retrieve the message the entire hour, until another message is generated.

In the second week, by phone contact, the patient and the therapist set personal goals for the upcoming eight weeks, and define and plan tasks to accomplish these goals. Goals and sub-goals can vary from "doing groceries independently by bike in week 9" to "Being able to take effective rest moments during the week". Accordingly, the therapist translates sub-goals into a set of reference activity patterns that will be adjusted throughout the nine weeks of intervention. When desired, also the feedback scenario can be adjusted by the therapist.

The intervention strategy suggests to change the reference activity pattern of the Activity Coach in at least three steps throughout the 9-week intervention. This likely stimulates the use of feasible goals and consequently increases the self-efficacy of the patient. The therapist supports and coaches the patient with weekly e-mails during nine weeks. The intervention strategy suggests that in week 7, the patient is asked to not wear the system, and the patient is stimulated to translate his experiences and future goals in terms that relate to day-to-day activities and planning. Exercises that could be used in this week include keeping a fatigue or energy diary. The intervention is concluded by evaluating the progress of the patient, the benefits and difficult parts of the intervention, and setting goals for the future.

Step 2: Feedback from the iterative test phase

The first draft of the intervention strategy was presented, explained, and discussed extensively with two physiotherapists (PMI Rembrandt, Veenendaal, The Netherlands), after which it was tested and evaluated with these therapists and a patient.

The most important results from the therapists are that it is difficult to formulate goals and tasks for the intervention, and to explain the use of the system by e-mail. Also, it was recommended that the patient should get access to an online environment in which he can look up his past physical behavior in order to monitor and evaluate his own progress. Finally, it was suggested that a normative reference line could support the therapist to value a patient's activity level.

The patient's feedback was that the system is bulky and can be bothering to wear during exercise. Also, it is sometimes short of power for an entire day. Furthermore, more information about the reasoning behind the suggested activities in the automated feedback messages would be considered useful. The informative feedback messages were preferred over the direct messages. Finally, the lacking recognition of activities, and underestimations of certain physical activities was sometimes frustrating for them.

Adjustments to the draft intervention strategy after Step 2

The Activity Coach

Power-saving software adjustments were made to ensure that the battery of both devices will last an entire day. However, no adjustments to address the bulkiness of the system were made, because the choice for hardware was among the starting points for this study. Also, the system was not adapted to recognize activities. It is expected that this issue will be only a minor limitation in the current intervention, because individual goals are based on patients' own baseline activity patterns, which likely incorporate a constant underestimation throughout the intervention.

Web portal

In order to support the decision making of the therapist, a normative reference line was incorporated in the portal. It represents the average daily activity pattern of twenty patients who suffered from severe chronic cancer-related fatigue, and wore the activity coaching system for one week consecutively. This reference line is shown when the therapist reviews the baseline activity of the patient.

Patients were also enabled to have access to a web portal. For patients, it consists of an 'activity viewer' that is similar to the one that is shown in the therapist portal, but without plots of the raw data.

Feedback scenarios

The content of the messages was not further adjusted as a reaction to the patient's feedback. We hypothesize that such preferences are likely dependent on for example the stage of change of the patient, learning style, and personality. Adjusting the system to tailor the set of feedback messages for each individual was not technically feasible for this project. A mixed approach was therefore maintained.

Process guidelines.

A phone-call was implemented in the protocol during the second week in order to set goals. Also, the intervention strategy now suggests introducing the patient to the portal from the fifth week on. It is expected that from that moment on, patients are used to wearing and using the Activity Coach, and can interpret the line charts properly. The use of this portal

creates an evaluation moment, and goals can be adapted accordingly if necessary. Also, example exercises were added to the intervention strategy that review earlier physical behavior and achievements during the intervention, thereby using the patient portal.

As the Activity Coach is known to underestimate the intensity of certain activities, caution should be taken when interpreting absolute IMA counts, and (any change of) type of activity should be kept in mind when doing so. The intervention strategy therefore now includes thorough recommendations for the therapist on informing patients explicitly about the possibilities, strengths and weaknesses of the system.

3

Discussion

This paper has described the development of an mHealth intervention strategy that targets chronic cancer-related fatigue. Feedback was obtained by involving potential end-users with various backgrounds in all phases of the development process. Such development was intended to result in a highly accepted intervention, contrasting technology-driven approaches that often do not come beyond the pilot stage [32].

The added value of this work is mostly the explicit involvement of a health professional for deploying the mHealth technology. Although this seems to be an obvious improvement, to our best knowledge, other examples of such use of activity coaching systems have not been published so far [33,34]. By involving a health professional, more subtle and tailored physical behavior goals can be attained, such as creating awareness and improving energy conservation. Being able to set flexible goals is a huge advantage for the targeted population because of the population's heterogeneous character.

Another important feature of this intervention is that it is directed at opportunistic physical activities and at low-to-moderate intensity exercise, rather than high-intensity exercise. This serves two goals: to accommodate the diverse nature of the population, and to establish safety of the patient; physical tests cannot be performed because no face-to-face sessions were incorporated. However, we are confident that increasing the volume of opportunistic activities and actively managing their daily activities will have beneficial health outcomes for many patients. This could be strengthened by improving cognitions about physical behavior: Some argue that perceived amount of physical activity or the self-efficacy over physical activity is even more important than the amount of the physical activity itself [35]. Future research that focusses on the role of physical activity in interventions for fatigue should therefore also focus on cognitions and on other dimensions of physical behavior than just the objective daily amount.

Although the current employment of the Activity Coach was realized by extensive collaboration with experts and based on a broad spectrum of literature, many of the

features have not been optimized so far. Firstly, the bulky hardware can be an important bias for the effectiveness of this intervention strategy. Also, personalizing the feedback messages to the subject's stage of change or learning style, and the way that the boundaries are set within the feedback scenarios have not been subject of this work, but could be an interesting topic for subsequent studies. Currently, the system is being adjusted to generate tailored motivational feedback messages considering for example timing and content [36]. Also, the visual representation of the activity measurement on both the smartphone and the web portal should be improved and personalized. The current visualization is rather simplistic, however, ideally they should explicitly support the goals they serve: visualize the longitudinal change or highlight improvement of the patient in order to strengthen self-efficacy and sense of control. Relevant examples for comparable goals yet exist [37]. Finally, the current experiments are limited due to the small number of patients that were involved, and the limited structure of the interviews.

Conclusion

This paper is a first step in order to develop an mHealth intervention to support patients who suffer from chronic cancer-related fatigue. The intervention strategy succeeds in meeting many of the recommendations that were extracted from relevant literature or formulated by health professionals in the field. However, the actual usefulness, acceptability, and effectiveness of the final intervention strategy have not been established yet. A randomized controlled trial (The Netherlands Trial Register, number NTR3483) is conducted currently to study the effectiveness, working mechanisms, and effect predictors of the intervention within the target group.

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Chapter four
Physical behavior profiles in chronic cancer-related fatigue

4

Abstract

Purpose. Increasing physical activity level is a generally effective intervention goal for patients who suffer from chronic cancer-related fatigue (CCRF). However, it is unlikely that patients benefit equally from these interventions, as their behavioral starting points might vary substantially. Therefore, we explored patterns of physical behavior of participants who suffer from CCRF.

Methods. The baseline data of a randomized controlled trial were used for a latent profiles analyses on nine accelerometer-derived physical behavior measures, describing levels and patterns of physical activity, moderate-to-vigorous intensity physical activity (MVPA), and sedentary behavior. Participant characteristics were analyzed for predictive properties.

Results. Three latent profiles were distinguished that differed most on physical activity level and total time spent in MVPA. 88% of all participants was assigned to a profile with a probability higher than .8. Age, and perceiving limitations by comorbid conditions and pain were predictive of profile membership.

Conclusions. We distinguished three physical behavior profiles. The differences between the patterns indicate that the heterogeneity of this sample requires patients to have substantially different treatment goals. Further research should test the applicability of these profiles in clinical practice.

Implications for cancer survivors. These physical behavior profiles can be used for optimizing and personalizing physical behavior oriented treatment goals for reducing CCRF.

Background

Fatigue is a common and debilitating side effect of cancer and its treatment, that often persists well beyond active cancer treatment [1,2]. Chronic cancer-related fatigue (CCRF) prevents patients to have 'a normal life' [3] and hampers in performing daily activities [4]. Vice-versa, behavioral interventions that try to reduce fatigue mostly aim at increasing level of physical activity by means of exercise or graded activity [5–9]. Behavioral interventions have shown to be generally effective in reducing fatigue [5–10], but should be adapted to individual physiological differences [11] to be fully appreciated. Presumably, effective intervention goals correspondingly depend on the individual's starting point in terms of physical behavior. Therefore, it is needed to consider the heterogeneity of patients' physical behavior, and to explore what patient characteristics relate to these behaviors.

Heterogeneity in physical behavior has been scarcely considered in behavioral intervention studies. One example is a study by Van der Werf et al. who aimed at revealing heterogeneity of physical behavior in patients who suffer from chronic fatigue syndrome [12]: Patients were labeled pervasively passive, active, or moderately active based on their total amounts of physical activity. Such 'sub-typing' can aid in personalizing interventions and defining helpful and realistic treatment goals.

However, other, more specific physical behavior measures are increasingly acknowledged as being important and clinically relevant, thus focusing solely on total amounts of physical activity might be on a level that is to generic. Firstly, the benefits of exercising or performing higher intensity activities are substantiated for cancer survivors [8]. Secondly, deteriorating effects of high amounts of sedentary behavior are increasingly acknowledged [13,14], and described in many guidelines for cancer survivors [11]. Thirdly, measures that quantify distributions of these dimensions of behaviors over time [15–17] were able to differentiate patients with chronic health conditions comparable to CCRF from healthy subjects independently of the total amounts of these physical behaviors.

To acknowledge the relevance of different measures of physical behavior, Thompson et al. advocate the use of profiles in describing individuals on physical activity [18]. This imminently leads to the research question in the current paper: What physical behavior profiles are prominent in persons who suffer from CCRF? With that, we explicitly focus on the interrelatedness of a range of physical behavior measures, which is novel in this field.

Secondly, this paper will explore if the physical behavior profiles are related to participant characteristics. Therefore, demographic and clinical factors (age, sex, education, body mass index (BMI), working hours, cancer treatment types, time since last cancer treatment, and limitations due to pain or comorbidities) and fatigue, distress, and perceived work-ability are studied for their predictive value for the physical behavior profiles.

Methods

Design

This study is a cross-sectional analysis of the baseline data of a randomized controlled trial to study Internet interventions for CCRF (approved by the Twente Medical Ethical Committee, Enschede, the Netherlands under number P12-26 and registered at The Netherlands National Trial Register (NTR3483, http://www.webcitation.org/6NWZqon3o). Data was assessed online during the registration process (T0a), and after eligibility was confirmed (T0b). At T0b, participants were asked to wear a hip-worn accelerometer for 7 consecutive days, during waking hours, starting on a Friday, and to keep activity diaries for the periods that they did not wear the accelerometer. Extensive information about the trial design in Chapter 2 [19].

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Participants

Of 179 patients who started the FNK-trial, 7 did not provide sufficient accelerometer data, leaving 172 participants for the analyses (see Supplementary Figure 1 for a flow chart). Participants were mostly women (72%), on average 56 years of age (between 21 and 82), and 53% acquired a college degree or higher. Most participants had breast cancer (46%) or hematological malignancies (17%). 9.4% had experienced recurrence of cancer, and 14% had metastasized cancer. Eight have reported cancer recurrence at the moment of submitting this paper.

Measures

Physical behavior measures

Accelerometer data preprocessing

We focused on three dimensions of physical behavior: overall levels of physical activity, sedentary behavior (SB), and moderate-to-vigorous intensity physical activity (MVPA). These dimensions were operationalized as total amount measures, bout duration measures, and day part distribution measures. An overview is presented in Supplementary Table 1.

The accelerometer (ProMove 3D, Inertia Technology, Enschede, The Netherlands, well-described elsewhere [20]) outputs 'integral of the modulus of acceleration' per minute in metric units (10^{-3} m/s^2), which in this paper is referred to as counts per minute (cpm). The accelerometer data were scanned and processed in Matlab version R2013b (The MathWorks Inc., Boston, MA, USA). Non-wear was removed only when agreement was reached between two researchers (no agreement was reached in <1 % of all measurement days). Reasons for missing accelerometer data were diverse (forgetting to charge or wear the system, aesthetic objections, performing non-accelerometer-compatible activities such as swimming or sleeping, and various technical failures) but, unfortunately, sparsely provided in the activity diaries.

A measurement day was considered valid if it consisted of >600 minutes of data. Three day parts were distinguished (05h00 to 12h00 (morning), 12h00 to 18h00 (afternoon), 18h00 to 00h00 (evening)), which were considered valid if they consisted of >120 minutes of data. An average of at least 4 valid days or day part combinations was required for analysis.

Amount measures

Physical activity level (PAL [cpm]) was calculated by averaging all cpm values per day [21]. **SB time** [%] was the percentage of the total measurement time spent below 1303 cpm. This value captured 95% of the distribution of SB in a lab-study [22] and is well below walking at a comfortable speed (z = -1.97) [20] and performing active office tasks (z = -2.58) [22]. **MVPA time** [%] was the percentage of the total measurement time spent above 2588 cpm. This value is the right 95% confidence interval of treadmill walking at 6 kilometers per hour (2418 ± 275 cpm, n = 10) [20]. It corresponds with a z-score of 0.36 of walking at a comfortable speed, and a z-score of -0.32 of active office tasks.

Bout duration measures

Time of prolonged SB bouts [min] was the total SB time that was accumulated in bouts of 30 minutes and longer [23]. **Time of prolonged MVPA bouts** [min] was the total MVPA time that was accumulated in bouts of 10 minutes and longer [23].

Day part distribution measures

For the **day part difference of PAL** (dPAL), the change score of the average PALs of two consecutive day parts was divided by the average PAL of the afternoon to correct for absolute difference of daily PALs between participants:

$$dPAL1 = (\overline{PAL}_{afternoon} - \overline{PAL}_{morning})/ \overline{PAL}_{afternoon}$$

$$dPAL2 = (\overline{PAL}_{evening} - \overline{PAL}_{afternoon})/ PAL_{afternoon}$$

For the **day part difference of SB time** (dSB), change scores between two consecutive day parts were calculated from the fractions (F) of the time of each day part that was spent sedentary:

$$dSB1 = F_{afternoon} - F_{morning}$$

$$dSB2 = F_{evening} - F_{afternoon}$$

Predictor variables

Fifteen factors were used as predictor variables, among which **age, sex, BMI** (calculated from self-reported height and weight), **education** (seven answers possible, dichotomized as accomplished college degree or higher), **weeks since last primary cancer treatment** (logtransformed to account for skewness), and **work status** (dichotomized as working more than eight hours per week). **Cancer treatments** were reduced to chemotherapy, radiotherapy, and/or stem cell transplant. **Comorbid conditions** were reduced to seven categories (lung, cardiovascular, musculoskeletal, neurologic, and organ disease, back and neck pain and trauma(tic) injuries, and 'other comorbidities' (mainly sleep apnea)), and counted. **Limitations by comorbid conditions** were assessed: '*How limiting are these complaints or disease(s) currently for you?*' Answers ranged from '*not at all*' (1) to '*very limiting*' (4), and were dichotomized (≥3). **Limitations by pain** was assessed: '*In the past week, to what extend did you feel limited in performing daily physical activities because of pain?*' Answers ranged from '*not at all limited*' (1) to '*extremely limited*' (7), and were dichotomized (≥4).

Fatigue was assessed at T0b (Cronbach's α = .839, N = 170) with the subscale fatigue severity of the Checklist Individual Strength [24,25]. The sum score has been used in cancer survivors [1,26], and has shown good internal consistency and discriminative validity [27]. **Distress** was assessed at T0a (Cronbach's α = .883, N = 172) with the Hospital Anxiety and Depression Scale. The sum score has been validated thoroughly [28], and has been used in cancer survivor populations [29–32]. **Perceived work-ability** was assessed at T0b with the work ability index [33]: one question "*Imagine that your working ability in the best period of your life is rated 10 points. How would you rate your working ability at the present moment?*" that is answered on a scale from 0 (*'not being able to work at all'*) to 10.

Missing predictor data

Predictor variables were missing for BMI (18 observations missing), and weeks since last treatment (one observation missing). Furthermore, one participant did not finish the T0b assessment. Between samples *t*-tests and chi-square tests revealed that participants with missing BMI's reported lower perceived work ability (95% confidence interval of the difference [-1.694 -0.001]), but were comparable on the other predictor variables.

Statistical analyses

The primary research question was answered with latent profiles analysis with robust – full information – maximum loglikelihood estimation in Mplus version 7.4 (Muthén and Muthén, Los Angeles, CA, USA). The indicators were z-scores of the physical behavior measures.

Model checking

Three model series (models A_k, B_k, C_k) were compared to decide how to deal best with theoretical pre-established overlap among the indicators (PAL with SB, pSB, MVPA, and pMVPA; MVPA with pMVPA; SB with pSB; dPAL1 with dSB1; and dPAL2 with dSB2), while acknowledging the distribution of pMVPA (left-skewed, 35 zero-observations). In each series, an ascending number of profiles was imposed (K = 2 - 5). In models A_k, pMVPA was modeled as a left-censored variable, thus covariances with pMVPA were ignored. In models B_k, pMVPA was log-transformed. In models C_k, overlap between the indicator variables was captured in four latent factors. Diagrams (Supplementary Figure 2) and Mplus syntax (Supplementary Table 2) are provided for all three model series.

Latent profiles analysis

The results of the final model series were reported with Bayesian information criteria (BIC), class proportions, entropy, bootstrapped likelihood ratio tests, and Lo-Mendel-Rubin likelihood ratio tests. The best model from this series was established by evaluating the BIC [34], and reported by the profile means, standard deviations, and posterior probabilities for each profile.

Predictive factors

The relation between the physical behavior profiles and participant characteristics was explored by means of Vermunt's three-step approach [35], currently only available with list-wise deletion. The factor 'stem cell transplant' had only one observation in one profile, and therefore was left out. A backward elimination strategy was used: In each step, the factor with highest *p*-values of all lowest *p*-values per factor was removed until only factors with a lowest *p*-value below .01 remained. Leaving out BMI resulted in the same final model.

Results

Model checking

Not all models converged convincingly. Models A_4 and A_5 had no stable solutions, even when running 200.000 starts, and resulted in multiple errors and small profiles. Only one model (B_2) from the B series, and none from the C series resulted in stable solutions. The logtransformation was not sufficient to specify pMVPA correctly in model B, and model C

was too complex for the amount of data. Therefore we proceeded with the model A series that converged adequately up to three classes.

Table 1. Model results of the Ak series.

K	BIC	Entropy	LMR (p-value)	BLRT (p-value)	Profile proportions (N)
1	3435.299	n.a.	n.a.	n.a.	172
2	3269.204	0.804	261.23 (.02)	<.001	72; 100
3	3218.251	0.848	147.25 (.23)	<.001	28; 71; 73
4[a]	n.a.	0.869	n.a.	n.a.	7; 49; 55; 61
5[a]	n.a.	0.901	n.a.	n.a.	4; 19; 40; 46; 63

Abbreviations: K (number of imposed profiles), BIC (Bayesian information criterion), LMR (Lo-Mendel-Rubin likelihood ratio test), BLRT (bootstrapped likelihood ratio test). N.a. (not available). aNo stable models were estimated; the models with best loglikelihoods after 200,000 random starts are reported.

Latent profiles analysis

The results for the model A series are presented in Table 1. Model A_3 was selected because that model had a lower BIC than the two-profile model. The A_3 model resulted in profiles of 28, 71, and 73 participants in each profile, and most participants were allocated convincingly: 88% of the participants were allocated to a profile with probability higher than 0.8.
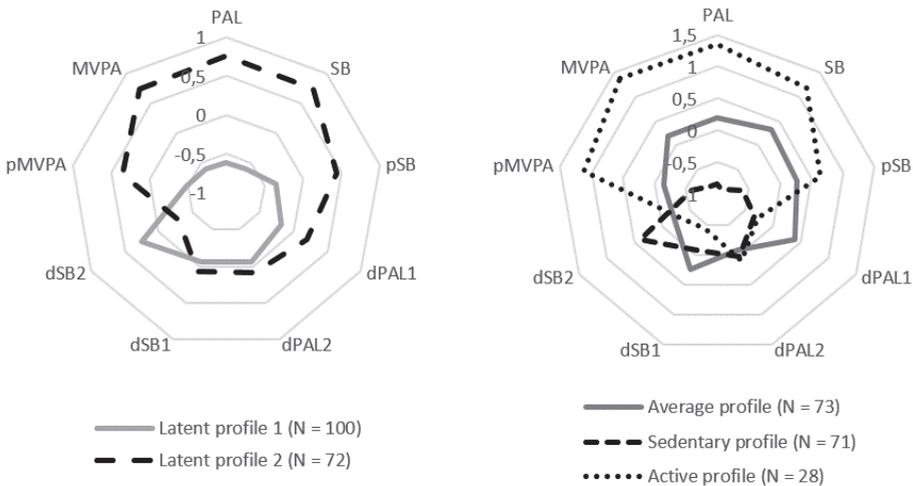
Figure 1. Standardized profile means [z-scores] of models A2 (left) and A3 (right). SB, dSB1 and dSB2 have switched signs, thus are defined 'higher is better'. Abbreviations: PAL (physical activity level), MVPA (moderate-to-vigorous intensity physical activity time), pMVPA: prolonged bouts of MVPA), SB (sedentary behavior time), pSB (prolonged bouts of SB), dPAL and dSB (day part difference (1: morning to afternoon, 2: afternoon to evening)).

The profile means for model A_3 (and for completeness also A_2), standardized to Z-scores of the total sample, are shown in Figure 1, and presented with standard deviations in Supplementary Table 6. Raw profile means and standard deviations, and posterior probabilities are presented in Table 2. To improve readability, the A_3 profiles are labeled 'active', 'average' and 'sedentary'. The right panel of Figure 1Error! Reference source not ound. shows that the mean scores of the average profile are similar to the sample mean scores (z < |0.5|) for all indicators. The sedentary and active profile can be distinguished best from the average profile by PAL and MVPA. However, differences between profiles are also captured in the mean scores of other measures. For example, decline of physical activity from morning to afternoon was lowest (so high dPAL1) in the average profile. By contrast, dPAL2 is not distinctive at all. Supplementary Figure 3 shows histograms of the sample profile distributions, which provide further insight into the distinctive character of the individual measures.

Predictive factors

Exploration of the relation between the physical behavior profiles and participant characteristics showed that participants in the sedentary profile were older and less likely to report limitations by comorbid conditions compared to the average profile, and were more likely to have limitations by pain compared to participants in the active profile. The results are presented in Table 3.

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Table 2. Model results of the A3 model.

	Total sample[c]		Sedentary		Average		Active	
N (%)	.936		71 (41%)		73 (42%)		28 (16%)	
Profile posterior probabilities[b], mean (lowest)			.926 (.50)		.944 (.59)		.943 (.66)	
Profile posterior probabilities <.8, N (%)	20 (12%)		11 (15%)		7 (10%)		2 (7%)	
	mean	SD	mean	SD	mean	SD	mean	SD
Physical activity level [cpm][d]	790.3	217.0	609.7	71.0	834.1	43.6	1081.5	103.7
MVPA [%][d]	6.22	3.47	0.10	0.62	13.06	1.38	27.94	2.43
Prolonged bouts of MVPA [min][a,d]	10.64[a]	12.62	3.14	5.36	8.87	8.77	24.82	28.35
Sedentary behavior time [%][d]	78.36	7.21	84.84	2.09	76.02	2.39	69.85	4.18
Prolonged bouts of SB [min][d]	325.6	110.6	391.3	88.7	295.8	84.7	254.5	56.8
dPAL1 [%-pt] (N=148)	-17.47	35.07	-28.83	41.70	-3.72	17.7	-27.15	30.5
dPAL2 [%-pt] (N=166)	-28.80	22.49	-28.21	26.36	30.30	20.0	-26.32	21.60
dSB1 [%-pt] (N=148)	2.1	8.4	2.8	5.0	0.1	9.4	5.7	10.1
dSB2 [%-pt] (N=166)	10.2	7.1	7.5	4.38	11.8	6.7	12.3	8.3

Abbreviations: SD (standard deviation), MVPA (moderate-to-vigorous intensity physical activity time), dPAL and dSB (day part difference (1: morning to afternoon, 2: afternoon to evening)). [a]Skewness = 2.13; kurtosis = 6.66; median = 6.57. 15% of the total sample ($n = 25$) accrued > 21 minutes of pMVPA per day, thus potentially accrues 150 minutes of pMVPA per week. [b]The profile mean (of those participants who were actually assigned to this specific profile) of the posterior probabilities for each profile. Between brackets is the lowest posterior probability with which a participant was assigned to that profile. [c]Supplementary Table 4 shows the bivariate covariances matrix and modeled covariances on the overall level of models A_1 and A_3. [d]$n = 165$.

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Table 3. Predictive value of participant characteristics of the three-profile model.

	Total sample	Eliminated in step	Average vs sedentary[a]	Active vs sedentary[a]	Active vs average[a]
		Step # (lowest *p*-value)	Logodds (*p*-value)	Logodds (*p*-value)	Logodds (*p*-value)
Age [years]	55.8 (10.2)		-0.070 (.001)*	-0.047 (.105)	-0.024 (.372)
Sex (male)	28%	2 (.698)			
Education (≥ college degree)	52.9%	3 (.581)			
Work status (> 8 h/week)	53.8%	6 (.423)			
Body mass index [kg/m²]	26.4 (5.1)	9 (.061)			
Weeks since last treatment[b]	206 (236)	7 (.248)			
Comorbid conditions (≥2)	14.0%	4 (.465)			
Limitations by comorbid condition (≥3/4)	37.8%		1.496 (.002)*	1.480 (.011)	0.015 (.977)
Limitations by pain (≥4/7)	32.8%		-0.923 (.046)	-1.959 (.006)*	1.035 (.136)
Treatment: chemo	69.6%	8 (.27)			
Treatment: radiotherapy	59.7%	1 (.717)			
Treatment: stem cell transplant	6.4%	0[c]			
Fatigue [8-56]	42.0 (8.0)	11 (.010)			
Distress [0-42]	14.3 (6.8)	5 (.474)			
Work ability [0-10]	1.2 (1.7)	10 (.035)			

[a]Logodds > 0 indicate that the risk of the outcome falling in the comparison profile relative to the risk of the outcome falling in the referent profile increases as the variable increases. Univariate results are presented in the Supplementary Table 5. [b]Median: 126 weeks. [c]In the active profile only one participant had experienced a stem cell transplant, therefore this factor was excluded from the analyses. [c]n = 154. * p < .01.

Discussion

In this study we collected multiple physical behavior measures to exhibit heterogeneity of patients who suffer from CCRF by means of physical behavior profiles. This resulted in three profiles: a sedentary, active, and average profile. Furthermore, we investigated participant characteristics as predictors of these profiles, to increase knowledge on and enhance personalization of interventions that somehow target physical behavior in this population.

The three profiles were most distinguishable by the measures PAL and MVPA time. Compared to the sedentary profile, participants in the active profile were roughly twice as active in terms of PAL, and almost seven times longer in a prolonged state of MVPA. Time spent in prolonged bouts of SB also differed between profiles: means were 4h15m in the active profile, compared to 6h31m in the sedentary profile. The average profile had the lowest (almost no) decline of PAL between morning and afternoon. These results show that persons who suffer from CCRF form a very heterogeneous group in terms of physical behaviors, who require diverse intervention goals when focusing on physical behavior All three profiles provide potential focus for intervening on physical behavior. Obvious goals – and currently widely accepted [11] – are increasing PAL and prolonged MVPA time, which apply to participants in the sedentary and average profile. In the active profile, increasing PAL will generally be less effective compared to the other profiles. However, patients who have an active profile might benefit from reducing the time of pronged SB or from better dividing physical activities throughout the day by energy conservation strategies [36]. Indeed, a patient in the active profile may actually be helped by reducing PAL before increasing it gradually in order to match the patient's physical behavior to his or her capacity. This assumption is supported by a study in breast cancer survivors in which self-reported physical activity measures showed that psychological outcomes were poor for the quartile of patients with the highest durations of physical activity [37]. However, much is unknown about the relation between specific dimensions of physical behavior and the effects on health and fatigue, therefore research in this area is important.

Our sample is comparable to a sample of long term colon cancer survivors [23], in terms of prolonged MVPA. 14% compared to 15% in the current sample meets clinical guidelines, operationalized as spending 150 minutes per week on MVPA in bouts of 10 minutes or longer. However, MVPA time (6.2%) differed greatly from samples of breast cancer survivors: 1.9% [14] and 1.1% [13], and SB time (78.4% in our sample) differed from breast cancer survivors (61.3% [38], 66.3% [13], and 78.2% [14]) and from colon cancer survivors (60.7% [23]). Prolonged SB differed even more: 152.9 minutes of prolonged SB [23] versus 325.6 minutes in the current sample. Differences could relate to choices for cut-off values, as well as to clinical status: the comparison samples were not necessarily fatigued and consisted of homogeneous groups of cancer types.

This study also studied predictors of these profiles. Participants who reported stronger limitations by pain were more likely to have a sedentary profile compared to an active profile. This result highlights the relevance of pain management in the context of physical activity interventions. Older participants and participants who reported weaker limitations due to comorbid conditions were more likely to have a sedentary profile compared to an average profile. The results on age are supported by studies with – not necessarily fatigued – breast cancer survivors [39]. The result on limitations by comorbid conditions seems contradictory to the findings on limitations by pain. An explanation might be that comorbid conditions are perceived as less limiting for those who are engaged in a sedentary lifestyle, although it should be noted that the question that assesses limitations due to comorbid conditions did not explicitly mention physical activities.

Our study has a number of limitations. Firstly, all participants were willing to follow an intervention in a trial called 'Fitter after cancer', and were aware that physical activity was measured. Both properties could provide bias by overestimating PAL compared to the general population of CCRF. Secondly, generalizability might be hampered because our sample experienced varying cancer types and treatments. Thirdly, evaluating one minute measurement intervals, although generally used [40], cause real life data points to represent a mixture of behaviors. Therefore absolute values of SB and MVPA measures should be interpreted cautiously. Finally, in order to come to the set of physical behavior measures, some choices in selecting measures and cut-off values for time or cpm lack evidence or were chosen arbitrarily. However, by describing these choices transparently, we feel that the results of this study are valuable nevertheless.

Conclusions

We distinguished three profiles of physical behavior in a sample of severely fatigued cancer survivors, showing the heterogeneous character of the sample. The results indicate that optimal support might require substantially different treatment goals for different patients. These profiles demonstrate an opportunity for personalizing physical behavior oriented treatment goals, but further research should test the applicability of these profiles in clinical practice.

Supplementary materials

https://progress.rrdweb.nl/39/

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Chapter five
Effectiveness of two Internet interventions for chronic cancer-related fatigue

Abstract

Purpose. The current paper reports on the results of a three-armed randomized controlled trial investigating the clinical effectiveness of two different guided internet interventions for reducing chronic cancer-related fatigue (CCRF).

Patients and Methods. Severely fatigued cancer survivors were recruited via online and offline channels, and self-registered on an open-access website. After eligibility checks, 167 participants were randomized into: (1) physiotherapist-guided ambulant activity feedback therapy encompassing the use of an accelerometer (AAF) ($n = 62$); (2) psychologist guided Web-based mindfulness-based cognitive therapy (eMBCT) ($n = 55$); or (3) an active minimal intervention control condition receiving psycho-educational e-mails (PE) ($n = 50$). All interventions lasted nine weeks. Fatigue severity was assessed six times from baseline ($T0_b$) to six months (T2) (Checklist Individual Strength – fatigue severity subscale; primary outcome). Mental health (Hospital Anxiety and Depression Scale and Positive and Negative Affect Schedule; secondary outcome) was assessed three times. Non- adherence to treatment was investigated.

Results. Multiple group latent growth curve analysis, corrected for individual time between assessments, showed that fatigue severity decreased significantly more in AAF and eMBCT compared to PE. The analyses were checked by a researcher who was blind to allocation. Reliable improved fatigue severity was observed in 66% ($n = 41$) in AAF, 49% ($n = 27$) in eMBCT and 12% ($n = 6$) in PE. Effect sizes (d) were high, namely 1.18 in AAF and 0.94 in eMBCT, compared to PE. Mental health improved significantly in all three conditions. Non-adherence was 18% ($n = 11$) in AAF, mainly due to hindrance caused by the accelerometer, and 38% ($n = 21$) in eMBCT, mainly due to perceived high intensity of the program.

Conclusions. Both the AAF and eMBCT are effective for managing fatigue severity compared to receiving psycho-educational e-mails.

Introduction

Cancer-related fatigue (CRF) is 'a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning' [1]. In approximately 30% of the patients who have been successfully treated for cancer, severe fatigue persists for months or even years [2]. This persistent fatigue, termed chronic CRF (CCRF) is often accompanied by distress and affects the patients' mental health [1,3].

Physical activity interventions and psychosocial interventions specifically designed to reduce CCRF have been shown to be effective [4–9]. As readily accessible interventions are needed for patients who do not have the energy or time to travel to a specialized healthcare institute, we have developed two different Web-based interventions aimed at reducing CCRF: (1) a psychotherapist-guided Ambulant Activity Feedback (AAF, Chapter 3) and (2) a psychologist-guided Web-based Mindfulness-Based Cognitive Therapy (eMBCT) [11].

The overall aim of the project 'Fitter na kanker' was to study the effectiveness, effect predictors and mediators of AAF and eMBCT [12] (Chapter 2). The current paper reports on the clinical effectiveness of these interventions in reducing fatigue severity and improving mental health in severely fatigued cancer survivors compared to patients in an active control condition.

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Patients and methods

Patients and setting

In our previous article [12] (Chapter 2) we provide a detailed description of the Methods of the *Fitter na kanker* trial. Severely fatigued cancer survivors were recruited via both online and offline channels, inviting them to follow a web-based intervention in a research setting for their fatigue and could register on an open-access website (www.fitternakanker.nl [13,14]). However, to recruit a varied group of participants, we did not specify the exact content of the interventions in the advertisements.

Participants – all cancer types included – had finished curative-intent cancer treatment (with the exception of hormonal treatment as this often is low intensive and may last up to five years) at least three months previously, and had been suffering from severe fatigue ever since ($\geq$ 35 on the Checklist Individual Strength – fatigue severity subscale (CIS-FS) [7,15]). They had no current or former severe psychiatric morbidity such as suicidal ideation, psychosis, or schizophrenia, were > 19 years old, and at least 18 years old at disease onset. For external validity purpose, non-treatable comorbid somatic diseases that were possible

causes for fatigue (such as rheumatoid arthritis, diabetes, myocardial damage) were not exclusion criterion, but were registered during the study.

We aimed to include 360 participants so as to be able to study working mechanisms in addition to effectiveness of the interventions. Despite persistent recruitment efforts and an extension of the recruitment period by three months, this number proved infeasible as we had to exclude more patients than anticipated. However, we continued recruiting until we had enough participants to study the effectiveness with enough power, namely 55 participants per condition [12].

Trial design

Participants were randomized in one of three conditions by a computerized tool [12]: two experimental conditions: (1) AAF and (2) eMBCT, or (3) an active control condition in which participants received psycho-educational information (PE). The intervention period was nine weeks for all three conditions. The primary outcome was self-perceived fatigue severity measured after the eligibility check (T0$_b$: baseline), three times during the intervention (M3, M6, M9), two weeks after completion of the interventions (T1), and six months after baseline (T2: primary outcome). Secondary outcome was mental health, measured at recruitment (T0$_a$), T1 and T2. In the current paper, we report on Steps 1, 2, 3, and 5 of the original analysis plan [12]. All outcomes were self-reported and Web-assessed. Non-adherent participants were interviewed by telephone by the first and second authors to enquire about their reasons for non-adherence.

Interventions

The eMBCT is a web-based psychologist guided intervention, which follows the MBCT protocol specifically designed for CCRF [16,17]. It aims to change the behavioral and cognitive reactions of the patient to cancer-related stressors including fatigue itself [5,16,18]. Bruggeman-Everts et al [11] have published a pilot study on the effectiveness of eMBCT and a detailed description of the eMBCT protocol and setting.

The AAF consists of a home-based physiotherapist-guided protocol in which participants use an accelerometer to gain insight in their physical activity pattern, and increase or balance their daily activities in ways that improve their energy levels [5,19]. See Chapter 3 [10] for a detailed description of the development of AAF.

Patients in the PE condition received psycho-educational e-mails describing possible causes of fatigue, sleep hygiene, balancing energy during the day, and how to cope with worrying thoughts. This psycho-education was derived from the eMBCT protocol for CCRF [11,16], and was also included in the AAF.

Measures

Fatigue severity was measured using the CIS-FS [7,15], which consists of eight items that are rated on a seven-point Likert scale (range 8-56, Cronbach's α = 0.84). The CIS closely resembles the Multidimensional Fatigue Inventory (MFI) [20,21].

The secondary outcome was the concept of 'mental health' measured using both negatively and positively framed questionnaires [22]: The Positive and Negative Affect Schedule (PANAS) [23,24] was used to measure Positive Affect (PA, range 10-50, α = 0.90) and Negative Affect (NA, range 10-50, α = 0.89), and the Hospital Anxiety and Depression Scale (HADS) [25–27] (range 0-42, α = .88) was used to measure distress.

Baseline characteristics demographic – such as demographics, medical history and help received in the past – were assessed.

Data analyses

First, analyses of variance (ANOVA) and χ^2-tests were performed to: (1) check for differences in baseline characteristics between all conditions; and (2) check whether baseline variables correlated with missing data patterns to check if data was randomly missing. The significance level was set at $p < .01$ to correct for multiple testing. This resulted in no auxiliary variables or covariates being included in the model. Outcome measures were checked for normality and outliers and resulted in no modifications being made. These analyses were performed in SPSS Version 23 for Windows package (SPSS Inc, Chicago, IL).

Second, we tested which model best fitted the longitudinal data of the outcome measures (CIS-FS, HADS and PANAS) using Mplus version 7.31 [28]: (1) a linear or linear and quadratic slope, (2): one slope or a piece-wise model with two slopes (piece-wise only for CIS-FS); and (3) with or without individual timescores (the exact time points when a participant filled in the assessment). See Supplementary Materials A for the procedure of selecting the best fitting model for CIS-FS. Next, we tested whether the trajectories of the best fitting model significantly differed between the three conditions by applying Wald testing (for linear slopes) or χ^2 difference testing (for linear and quadratic slopes). This was done on an intention-to-treat (ITT) basis and we checked whether the results for CIS-FS changed when only including adherent participants. An independent statistician (RvdS) who was blind to allocation checked all analyses.

Third, to measure strength of change in AAF and eMBCT compared to PE, the effect sizes of the CIS-FS, HADS and PANAS were calculated according to the method proposed by Feingold [29]. As reliable methods to calculate effect sizes of non-linear growth models still need to be developed and validated [30], we calculated the effect size based on a linear model, while including timescores and on an ITT basis. The effect size calculations are presented in Supplementary Materials B.

Fourth, to measure the clinical importance in addition to statistical significance, the proportion of participants who were clinically relevantly changed on CIS-FS was calculated for each condition, using the reliable change index (RCI) [31,32]. The calculations of the proportion of clinically relevantly changed participants is presented in Supplementary Materials C. We used a clinical cut-off score of a normative group (CIS-FS < 28.0 [33]) which consisted of non-fatigued breast cancer survivors [33]. The proportions of participants who had *recovered* (passed both the cut-off score of the normative group and the RCI criteria), *improved* (passed the RCI criteria in the direction of fatigue reduction), and *unchanged* (passed neither the RCI criteria, nor the cut-off score), or *deteriorated* (passed the RCI in the direction of fatigue increase) were all calculated.

Finally, notes of and quotations from the telephone interviews with non-adherent participants were analyzed by close reading, followed by clustering of emerging themes concerning reasons for non-adherence. ANOVA and χ^2-tests were performed to identify differences between adherent and non-adherent participants. The proportion of non-adherent participants was calculated.

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Results

Patients

Between March 2013 and June 2015, 360 persons applied on the website to participate (see Figure 1 for flowchart). See Supplementary Materials D for details about the recruitment over the course of time.

We excluded 24% (*n* = 86) of the applicants (*M* age = 56.3, *SD* = 13.3, 59% women) for the reasons given in Figure 1, and another 26% (*n* = 95) declined to participate (*M* age=58.0; *SD*= 12.7, 68% women) before the eligibility criteria were checked.

Eventually, 179 participants were included (see Table 1 for baseline characteristics). Of these, four participants dropped out before filling in $T0_b$, and eight participants were excluded from analyses due to cancer recurrence during the study, leaving 167 participants for the analyses.

Participants were randomized in one of the three conditions: (1) AAF (*n* = 62), (2) eMBCT (*n* = 55), or (3) PE (*n* = 50).
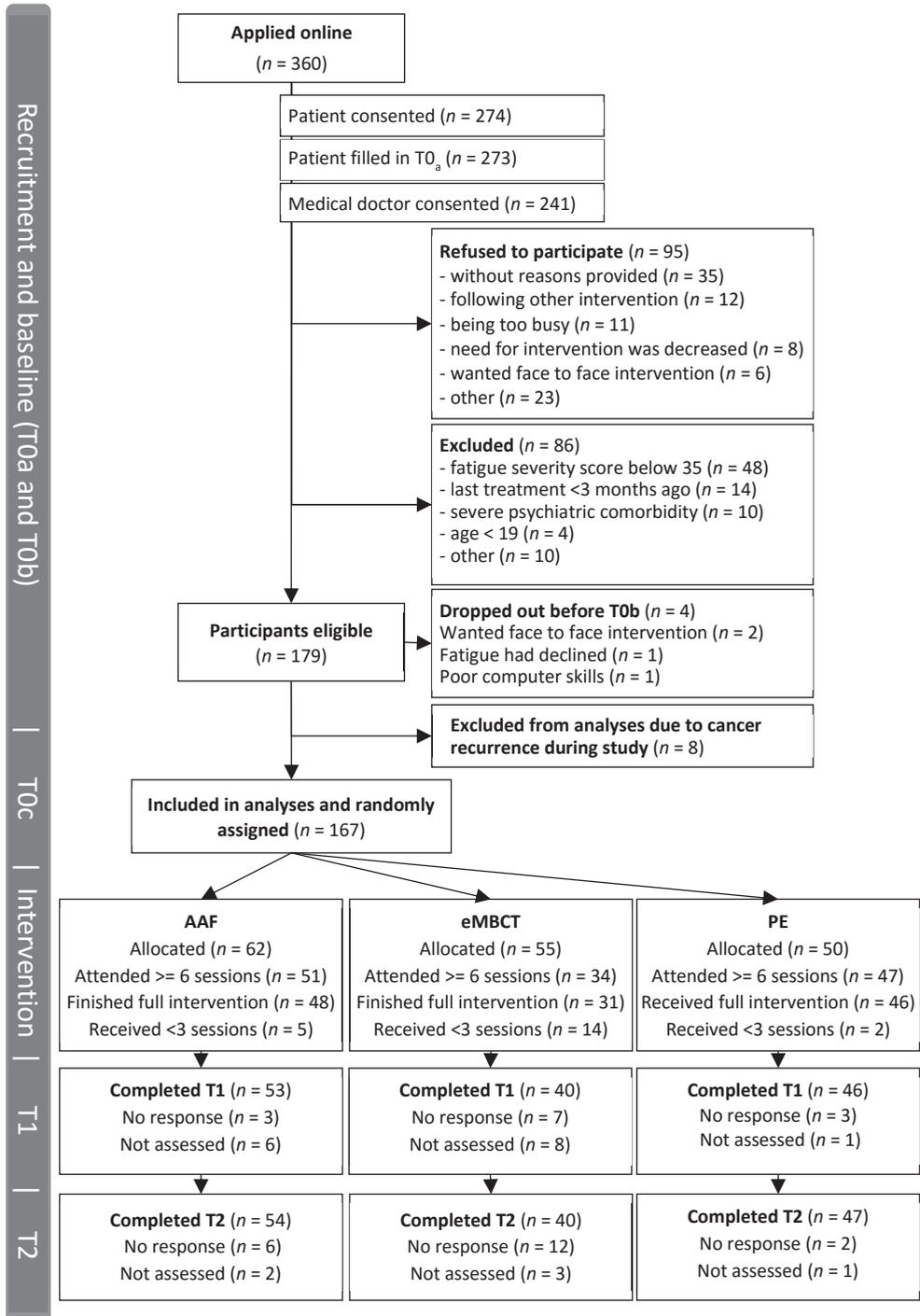
Figure 1. Flowchart Fitter na kanker trial. Of the 360 applicants involved in the study, 179 participants were randomized, of whom 167 were included in the analysis. Participants reported as 'not assessed' at T1 and T2 were not sent the questionnaire because they were still in the trial at time of analysis.

Table 1. Baseline characteristics of included participants (N = 179)

Demographics	Mean (SD) / % (n)
Age (years)	55.1 (10.1)
Women	72.6 (*n* = 130)
Dutch nationality	98.9 (*n* = 177)
Living with partner and/or children	86.6 (*n* = 155)
Religious beliefs	
No	61.5 (*n* = 110)
Christian	25.7 (*n* = 46)
Other	12.8 (*n* = 23)
Education	
Low	3.4 (*n* = 6)
Middle	32.4 (*n* = 58)
High	64.2 (*n* = 115)
Employment	
Paid job	41.9 (*n* = 75)
Absent from work	24.6 (*n* = 44)
Medical history	
Cancer diagnosis	
Breast	*n* = 81
Blood, bone marrow, Hodgkin's	*n* = 27
Reproductive organs	*n* = 27
Digestive system	*n* = 18
Head and neck	*n* = 11
Urinary tract	*n* = 9
Leukemia	*n* = 8
Other	*n* = 24
Cancer recurrence in the past	8.9 (*n* = 16)
Hereditary form of cancer	3.4 (*n* = 6)
Lymph nodes affected	40.8 (*n* = 73)
Metastases	13.9 (*n* = 24)
Time since first cancer diagnosis	
<1 yr	2.3 (*n* = 4)
1-2 yr	21.4 (*n* = 37)
2-5 yr	35.3 (*n* = 61)
> 5 yr	41.0 (*n* = 71)
Time since final cancer treatment	
< 6 months	1.7 (*n* = 3)
6 months - 1 year	14.5 (*n* = 25)
1-2 year	25.6 (*n* = 44)

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2-5 year	33.1 ($n = 57$)
> 5 year	25.0 ($n = 43$)
Type of cancer treatment [a]	
Surgery	76.5 ($n = 137$)
Chemotherapy	68.7 ($n = 123$)
Radiotherapy	58.1 ($n = 104$)
Hormonal therapy	29.6 ($n = 53$)
Immunotherapy	7.3 ($n = 13$)
Stem cell or bone marrow transplantation	6.1 ($n = 11$)
Other	1.7 ($n = 3$)
Operation only	8.9 ($n = 16$)
Operation, radiotherapy, and chemo	34.1 ($n = 61$)
Comorbidity	
No comorbidity	49.2 ($n = 88$)
One comorbidity	33.5 ($n = 60$)
More than one comorbidity	17.3 ($n = 31$)
Medication use between T0b and T2	
Hormone therapy	21.8 ($n = 38$)
Changed hormone therapy use	$n = 5$
Antidepressants	4.5 ($n = 7$)
Changed antidepressants use	$n = 1$
Help received	
Psychological counseling in the past	49.2 ($n = 88$)
Has received help to cope with cancer in the past	68.2 ($n = 122$)
No experience with attention-focused exercises, such as meditation or yoga	44.1 ($n = 79$)
Followed other form of psychological care for fatigue at baseline	8.4 ($n = 15$)
Fatigue	
Score on CIS-FS at T0a	45.5 (5.4)
Score on CIS-FS at T0b	42.0 (7.9)
Duration 0 - 1 year	21.3 ($n = 38$)
Duration 1 - 5 years	46.6 ($n = 83$)
Duration > 5 years	31.0 ($n = 57$)
Mental health	
Total score on *Positive and Negative Affect Schedule*	50.9 (7.0)
Negative affect	21.1 (7.9)
Positive affect	29.8 (7.3)
Total score on *Hospital Anxiety and Depression Scale*	14.3 (7.0)
≥20 at baseline	22.3 ($n = 40$)

[a] Numbers do not sum to $n = 179$ as some participants had undergone multiple cancer treatments.

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Effectiveness

Model selection for CIS-FS showed that a model with both linear and quadratic slopes, with individual timescores, freely estimated mean and slope variances, and with residual variances fixed to be equal between conditions, best fitted the data. Figure 2 shows the sample means of CIS-FS between $T0_b$ and T2 per condition.
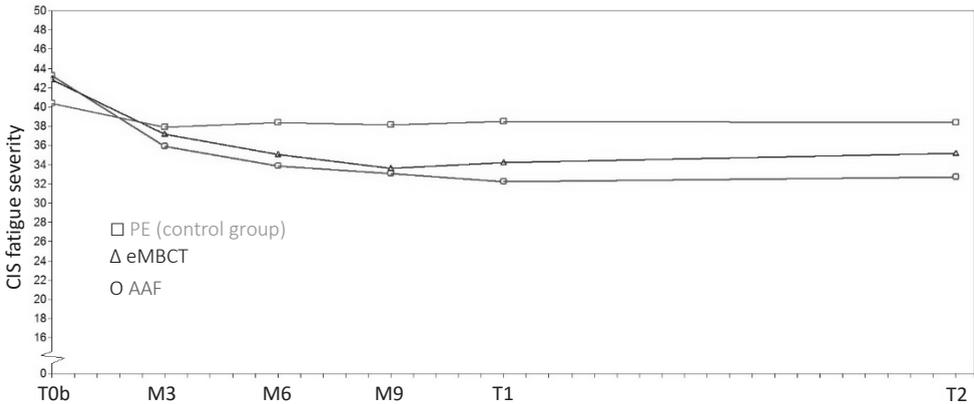
Figure 2. Sample means of fatigue severity (CIS) for all three conditions ($n = 167$).

χ^2-Square difference testing, with linear and quadratic slopes fixed to be equal between conditions, showed that the CIS-FS trajectories differed between all three conditions ($\chi^2(4)$ =27.63, $p < .001$). More specifically, the trajectories of AAF and PE differed ($\chi^2(2) = 28.28$, $p < .001$), and eMBCT and PE differed ($\chi^2(2) = 10.89$, $p = .004$), while the trajectories of AAF and eMBCT were equal ($\chi^2(2) = 2.19$, $p = .34$). When only adherent participants were included ($n = 132$), the results were similar: the slopes of AAF and eMBCT were equal ($\chi^2(2) = 0.991$, $p = .61$), while the slopes of PE and AAF differed ($\chi^2(2) = 28.11$, $p < .001$), and PE and eMBCT differed ($\chi^2(2) = 9.735$, $p = .008$). In conclusion, the slope estimates indicate that CIS-FS decreased significantly more in the AAF and eMBCT conditions compared to the PE condition.

The model fits for HADS, PA and NA were best for linear models with individual timescores and slope variances fixed at 0. As shown in Table 2, the slopes in all three conditions were significantly different from zero, HADS and NA decreased, and PA increased. Table 3 presents the results of Wald testing, and shows that there were no significant differences in slopes between the HADS, PA and NA between conditions.

Table 2. Model results of all outcome measurements. The mean intercepts and mean slope factors of all outcome measures with standard errors in brackets are presented.

Outcome	Condition	I	S	p^a	Q	p^b
Fatigue severity	AAF	42.838 (0.873)	-1.072 (0.162)	<.001	0.026 (0.005)	<.001
	eMBCT	42.752 (1.020)	-0.876 (0.178)	<.001	0.022 (0.006)	<.001
	PE	39.893 (1.243)	-0.208 (0.170)	0.22	0.006 (0.006)	0
Distress	AAF	13.237 (0.921)	-0.076 (0.017)	<.001	n.a.	n.a.
	eMBCT	13.903 (0.771)	-0.110 (0.022)	<.001	n.a.	n.a.
	PE	14.579 (1.012)	-0.083 (0.024)	<.001	n.a.	n.a.
Positive affect	AAF	31.762 (0.939)	0.101 (0.022)	<.001	n.a.	n.a.
	eMBCT	28.995 (0.932)	0.156 (0.026)	<.001	n.a.	n.a.
	PE	29.422 (1.091)	0.128 (0.027)	<.001	n.a.	n.a.
Negative affect	AAF	20.330 (0.931)	-0.068 (0.023)	0	n.a.	n.a.
	eMBCT	20.718 (0.914)	-0.071 (0.032)	0.03	n.a.	n.a.
	PE	20.805 (1.215)	-0.082 (0.029)	0	n.a.	n.a.

Abbreviations: AAF (Ambulant Activity Feedback), eMBCT (online Mindfulness-Based Cognitive Therapy), PE (Psycho-Education), n.a. (not applicable), I (intercept at T0b), S (linear slope factor), Q (quadratic slope factor). ^{a} two-tailed p-value of linear slope; ^{b} two-tailed p-value of quadratic slope.

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Table 3. Results of Wald testing for differences between conditions (HADS, PA, and NA).

	Wald test	Result
Distress	AAF = PE	0.067(1), *p* = .80
	eMBCT = PE	0.665(1), *p* = .41
	AAF = eMBCT	1.491(1), *p* = .22
Positive affect	AAF = PE	0.599(1), *p* = .44
	eMBCT = PE	0.573(1), *p* = .45
	AAF = eMBCT	2.640(1), *p* = .10
Negative affect	AAF = PE	0.148(1), *p* = .70
	eMBCT = PE	0.065(1), *p* = .80
	AAF = eMBCT	0.006(1), *p* = .94

Note. All Wald tests were nonsignificant, indicating that there was no significant difference between the slopes of the conditions. Abbreviations: AAF (Ambulant Activity Feedback), eMBCT (online Mindfulness-Based Cognitive Therapy), PE (Psycho-Education).

Effect size

AAF and eMBCT showed high effect sizes on CIS-FS compared to the PE condition: AAF = 1.18, and eMBCT = 0.94. Effect size for the secondary outcome measurements was not calculated as there was no significant effect observed between conditions.

Clinically relevant change

The proportion of *recovered* participants for AAF was 21% (*n* = 13), for eMBCT 9% (*n* = 5), and for PE 2% (*n* = 1). Of the adherent participants 26% (*n* = 13) recovered in the AAF condition, 6% (*n* = 2) in the eMBCT condition, and 2% (*n* = 1) in the PE condition. Figure 3 shows the proportion of *improved, unchanged*, or *deteriorated* participants per condition. In the AAF condition 66% (*n* = 41) was improved, in the eMBCT condition 49% (*n* = 27) and in the PE condition 12% (*n* = 6).

Treatment dropout

Treatment dropout was 18% (*n* = 11) in the AAF, 38% (*n* = 21) in the eMBCT condition, and 6% (*n* = 3) in the PE condition. No differences in baseline characteristics between adherent and non-adherent participants were found.

In both interventions, patients said they stopped using the intervention due to a lack of confidence the intervention would help them reducing fatigue. Another reason was that fatigue had reduced considerably thus treatment was no longer desired, or that they preferred face-to-face contact instead. Reasons for non-adherence in the AAF were mainly technical problems and poor usability of the accelerometer. Non-adherence of eMBCT was mainly because of high intensity of the program, the exercises were considered too woolly,

poor usability of the eMBCT portal, or difficulty in communicating in writing with the therapist.
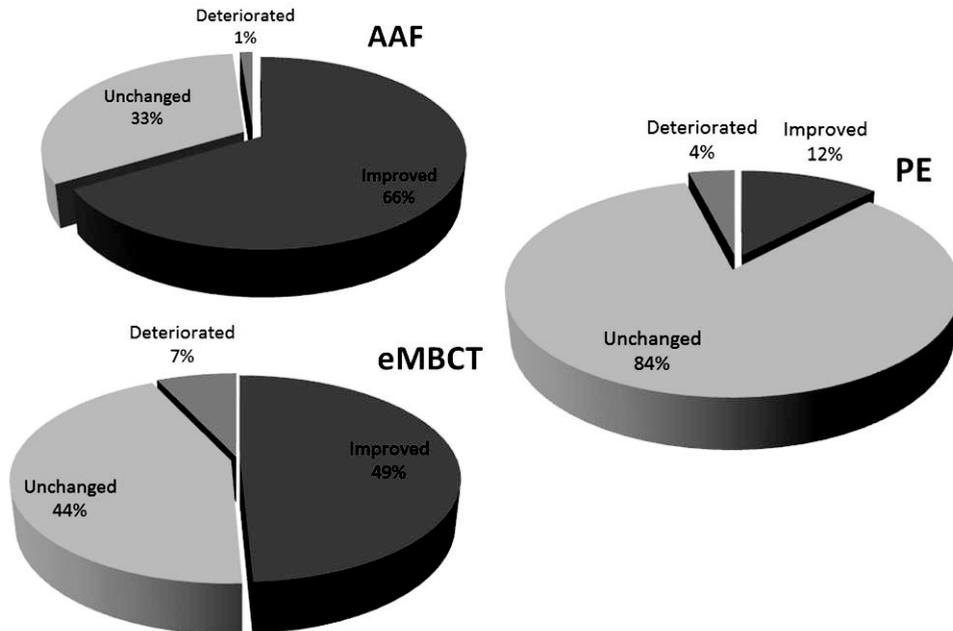
Figure 3. Proportion reliable change (improved, unchanged, deteriorated) for each condition (intent-to-treat). Abbreviations: AAF (Ambulant Activity Feedback), eMBCT (online Mindfulness-Based Cognitive Therapy), PE (Psycho-Education).

Discussion

Principal results

In this paper, we report on a 3-armed RCT that studies the effectiveness of two different guided Web-based interventions for reducing CCRF, compared to an active control condition in which participants received psycho-education (PE). These two interventions were: (1) Ambulant Activity Feedback (AAF); and (2) Web-based Mindfulness-Based Cognitive Therapy (eMBCT).

Using latent growth curve modeling, we found that AAF and eMBCT were significantly more effective in reducing fatigue severity than PE, with high effect sizes for both AAF and eMBCT compared to PE. The proportions of reliable fatigue improvement was 66% in the AAF condition, 49% in eMBCT, and 12% in the PE condition.

Treatment non-adherence was 18% in the AAF condition and 38% in the eMBCT condition. Reasons for non-adherence in AAF were technical problems with the accelerometer, and eMBCT was considered to be too intensive. As a result, we can conclude that both AAF and eMBCT are effective interventions for reducing fatigue severity.

Strengths and limitations

Our study design has several strengths. First, the longitudinal developmental fatigue trajectories (LGM) used, were assessed before, during, and after the intervention to study the effectiveness of the interventions. In contrast to ANOVA, LGM allows the study of individual longitudinal development instead of average group effects. Furthermore, it deals with missing data elegantly [34–36], and individual times between assessments can be included in the analysis.

Second, we used an active control condition that consisted of psycho-education. As psycho-education has been found to be effective for CCRF [37], comparing AAF and eMBCT to PE is a strict way of evaluating these interventions.

Third, as we wanted to study the intervention effect alone, we chose $T0_b$ (after the eligibility check) as our baseline measurement instead of $T0_a$ (at recruitment). As fatigue significantly reduced between $T0_a$ and $T0_b$ ($n = 174$, $t = 6.293$, $df = 173$, $p < .01$, $r = .548$), which was before any experimental intervention took place, choosing $T0_b$ as baseline assessment prevented overestimation of the intervention effect.

Fourth, to make these results relevant for healthcare practice, we chose not to exclude patients suffering from co-morbidities that may also explain fatigue. We also included all cancer types. In contrast, other researchers may choose exclusion criteria to limit confounding factors with the intervention effect to study the proof of concept. Though this decision is valid for research purposes, it consequently extends the gap between research findings and healthcare practice [38]. Therefore, we and others, e.g. Treweek and Zwarenstein [39], encourage researchers to study interventions that are intended to be applied in health care practice using a pragmatic RCT study design, thus with no strict exclusion criteria that extend the gap between research and healthcare practice.

In line with the arguments developed above, we want to make a general recommendation that clinicians and researchers should be cautious when comparing the effectivity results reported by different intervention studies (e.g. Gielissen et al. [7] and Abrahams et al. [40]), because assessment points, data analyses methods, and inclusion and exclusion criteria vary.

We noted several disadvantages of the RCT study design when evaluating these Web-based interventions. One limitation is that in an RCT design, the intervention is 'frozen' in time, while technical application evolve rapidly, resulting in the intervention being outdated

when the effectivity has been investigated. For example, the eMBCT webpage (developed in 2010) functioned poorly on a tablet, which lead to non-adherence of participants who used a tablet instead of a computer. Also, smaller and more elegant accelerometers have come to the market, which affected the credibility of the devices that were used in this study.

Another limitation was that we used a norm group to calculate the percentage of clinically relevant improved that was younger (norm group: age M = 45.9; SD = 6.3 [33] versus our study: age M = 55.1; SD = 10.1) and only consisted of breast cancer patients. Ideally we would have used a non-severely fatigued group of cancer survivors, of around the same age as our sample, but this was not available in literature.

In conclusion, this study has reported on the effectiveness of AAF and eMBCT six months after baseline compared to an active control condition. We are currently working on the results of a one year follow-up (Chapter 6). To improve the interventions we are also studying which baseline characteristics predict treatment outcome, study working mechanisms, and qualitatively analyze semi-structured interviews with participants about their experiences during the interventions [41] in order to improve the effectiveness of AAF and eMBCT.

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Supplementary materials

https://progress.rrdweb.nl/39/

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Chapter six
Long term effects of two Internet interventions

based on

Abstract

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Background. Severe, chronic fatigue of disease-free cancer survivors can be effectively reduced with Internet interventions: A mobile intervention in which participants used an activity coaching system, and a web-based mindfulness-based cognitive therapy. This study investigated their long-term effects on fatigue, mental health, and work ability. We expect that effects during the first six months (semester 1) sustained up to one year (so during semester 2), and that fatigue change correlates with change of mental health and work ability.

Methods. Data of a three-armed randomized controlled trial was used. Linear change during the second semester was studied with piecewise longitudinal growth models. Also, correlations were calculated between fatigue change and change of mental health and work ability. Bayesian estimation was used, which allows for analysis on small samples.

Results. During the second semester, outcome measures were on average constant. Reduced fatigue was associated with improved mental health, but reduced fatigue correlated stronger with increased positive affect in eMBCT and with decreased negative affect in AAF.

Conclusions. Internet interventions are effective in reducing severe, chronic fatigue in the long-term. Reduced fatigue was generally associated with improved mental health. Opposing associations between changed fatigue and affect probably reflect different working mechanisms.

Introduction

Fatigue is a common, distressing, and persistent effect of cancer and its treatment [1]. Internet interventions have the potential to reduce fatigue of persons who suffer from chronic cancer-related fatigue [2–4]. Two internet interventions were designed and tested for their effectiveness in reducing severe chronic cancer-related fatigue (CCRF) in a three-armed randomized controlled trial in which participants enrolled for one year: one intervention uses an activity coaching system and was guided by a physiotherapist [5] (Chapter 3), the other intervention is a mindfulness-based cognitive therapy guided by a psychologist [2]. Recently, the general effectiveness of both interventions was established for two outcomes: fatigue, and mental health [6] (Chapter 5).

For the first outcome, fatigue, both interventions were more effective in reducing severe fatigue up to 6 months after baseline (so during the first semester) compared to an active control group in which participants received weekly psycho-educational e-mails. In the experimental groups, 66.1 and 49.1% of the participants improved 'clinically relevantly' compared to 12% in the control group [6] (Chapter 5). As fatigue is a persistent complaint [7], the long term effects of both interventions are very relevant in assessing the value of both interventions. This study will therefore investigate the course of fatigue during the second semester of this trial.

The second outcome, mental health (operationalized with distress, and experience of positive and negative affect), also improved during the first semester, but not more in the experimental groups than in the control group [6][1]. Mental health has been suggested as a factor that is related with persistance of fatigue [8]. Accordingly, previous research showed that mental health and fatigue are strongly correlated outcomes in this population cross-sectionally [8,9]. Also, research involving breast cancer survivors showed that a combination of poor mental health and fatigue has a more persistent course over time compared to suffering from either poor mental health or fatigue alone [10]. The current study will test whether the intervention effects on mental health are maintained in both experimental groups, and to what extend fatigue and mental health are related over time.

Besides fatigue and mental health, work ability was assessed as a third outcome measure in this trial, but effects have thus far not been described. Perceived work ability is known to be affected by fatigue in cancer survivors [11], and is an important predictor for return to work in cancer survivors [12]. Yet, it is a more direct outcome than return to work itself, which depends on many more factors, such as the availability of suitable work, that are not

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[1] Modeled improvements over 6 months were [-1.9; -2.8; -2.2] on the Hospital Anxiety and Depression Scale (HADS), [2.6; 4.1; 3.3] on positive affect, and [-1.8; -1.8; -2.1] on negative affect (both PANAS) for AAF, eMBCT and PE respectively.

influenced by the interventions [13]. A natural recovery of work ability is often observed [13], but it is unclear to what extend recovery is related to reduced fatigue, and whether an intervention for fatigue also improves perceived work ability.

This paper thus aims to test the long term effectiveness of both interventions in terms of three outcomes. Hypotheses have been preregistered with the trial design and analysis plan [3], and are the following: (H1) During the first semester, work ability improved more in both experimental groups compared to the control group; (H2-4) Improvements in fatigue, work ability, and mental health during the first semester are maintained in the second semester in both experimental groups; (H5, H6) Improvements in work ability and mental health during the first semester, and (H7, H8) improvements in work ability and mental during the entire year are related to reductions of fatigue in the first semester.

Methods

Design

Data of the FNK-trial ('Fitter na kanker', Netherlands Trial Register NTR3483) was used to answer the research questions. All outcome measures, hypotheses, and methods were preregistered in the trial design paper (Chapter 2). A study on the effectiveness (hypotheses on primary outcomes, using step 1 to 3 of that paper) has been submitted for publication by Bruggeman-Everts et al [6] (Chapter 5). This study targets Step 4 and hypotheses on secondary outcomes of the published design. What follows is a reiteration of important features as well as alterations from the original plan.

Inclusion criteria involved having finished a curative-intend treatment for cancer, scoring 35 or higher on the fatigue severity subscale of the Checklist Individual Strength [14].

Research conditions

Participants were randomized into one of two experimental groups or the active control group and were requested to fill out multiple online questionnaires throughout the trial. The experimental conditions were (a) a mobile activity management intervention, Ambulant Activity Feedback (AAF), in which participants use an activity coaching application on a smartphone, guided by a physiotherapist [5], (b) a Web-based, psychologist-guided mindfulness-based cognitive therapy (eMBCT) in which participants do mindfulness exercises which they can download as MP3-files and readers [2], and (c) a minimal intervention control group in which participants received psycho-educational information about CCRF by weekly e-mails (PE) that was also given in both experimental interventions. The PE condition controls for receiving information on CCRF and for being involved in eHealth research. All three interventions are nine weeks and are described extensively

elsewhere [2,3,5]. Table 1 shows the participant characteristics of the sample that was included for the analyses of the present study (n = 167).

Assessments

Questionnaires were assessed online via the project web-page at baseline (T0a: before inclusion, T0b: after inclusion, yet before randomization), and at approximately three (T1), six (T2), and twelve months (T3) after randomization. Participants received prompts for the assessments by e-mail with a maximum of three reminders – by e-mail or phone – for each assessment. Fatigue was also assessed in weeks three, six, and nine of the intervention period (M3, M6, M9). Reminders for these questionnaires were only send once. The control group had no follow up measurement at T3, as they were invited to follow one of the two experimental interventions after finishing the T2 assessment.

Outcome measures

Fatigue

Fatigue was assessed with the Fatigue Severity subscale of the Checklist Individual Strength (CIS-FS), which consists of 8 items that score on a 7-point Likert scale (range: 8-56 points) [21,22]. It was assessed to check eligibility (T0a), but assessments at T0b (Cronbach's alpha = .845), M3, M6, M9, T1, T2, and T3 were used for the analysis. The CIS has repeatedly been used in Dutch cancer patients [17,23,24].

Mental health

Mental health was assessed at T0a, T1, T2, and T3 with the Hospital Anxiety and Depression Scale (HADS, [25]) and with the positive and negative affect scales (PANAS, [52]). The HADS has previously been used in cancer patients [61], and has been validated for a Dutch-speaking population [60]. It consists of 14 statements that can be valued on a 4-point scale. Cronbach's alpha at baseline was .883. The PANAS [52] consists of two subscales: positive affect and negative affect. It asks to what extend a participant experienced certain feelings and emotions in the last two weeks: each subscale has 10 items that can be valued 1 (very little) to 5 (very much). Items on positive and negative affect were mixed. Cronbach's alpha at baseline was .900 for positive affect and .885 for negative affect.

Work ability

Participants' perceptions of their work ability was assessed with the first question of the work ability index, the work ability score (range: 0-10) [26,27] at T0a, T2, and T3. It asks: "Imagine that your working ability in the best period of your life is rated 10 points. How would you rate your working ability at the present moment?" This single question is a good alternative for assessing the entire work ability index (WAI) [28], as the WAI is known

Table 1. Characteristics of 167 participants in the analyses.

Participant characteristics	mean (SD) or % (n)
Age (years)	55.0 (10.3)
Female	74% (*n* = 123)
Living with partner and/or children	84% (*n* = 147)
Education: accomplished college degree or higher	52.7% (*n* = 88)
Employment (*n* = 166)	
Currently in paid employment	57.2% (*n* = 95)
of which on sick leave for > 4 weeks	32.6% (*n* = 31)
Currently in paid job (>8 hours per week)	54% (*n* = 90)
Currently in paid job (>32 hours per week)	19% (*n* = 31)
Social support [12-84][a]	66.6 (14.74)
Score ≥ 48	90.4% (*n* = 160)
Score ≥ 72	46.1% (*n* = 77)
Cancer cite[b]	
Breast	*n* = 77
Blood, bone marrow, (non) Hodgkin's disease	*n* = 30
Other or unknown	*n* = 74
Metastasized	13.2% (*n* = 22)
Time since first cancer diagnosis at T0b (*n* = 166)	
≤ 1 year	5.4% (*n* = 9)
> 5 years	41.0% (*n* = 68)
Time since last cancer treatment at T0b (*n* = 165)	
≤ 1 year	18.8% (*n* = 31)
> 5 years	23.6% (*n* = 39)
Type of cancer treatment	
Only surgery	*n* = 16
At least surgery, radiotherapy, and chemotherapy	*n* = 57
Pain and comorbid conditions	
No comorbid conditions reported (*n* = 166)	51% (*n* = 85)
More than 1 comorbid condition (*n* = 166)	14% (*n* = 23)
Felt limited by comorbid condition(s), score ≥ 3/4 (*n* = 166)	39% (*n* = 70)
Suffered from pain [1-7]	2.52 (1.46)
Score ≥ 5/7	13.2% (*n* = 22)
Felt limited due to pain [1-7]	2.75 (1.78)
Score ≥ 5/7	22.8% (*n* = 38)
BMI (kg/m^2)	26.3 (5.0)
Sleep quality [0-14][c]	8.27 (3.72)

Note. N = 167 unless stated otherwise due to missing data. Additional information can be found in Chapter 5. [a]Multidimensional Scale of Perceived Social Support [20]. [b]Percentages do not add up to 100% because multiple options are possible. [c]Sleep Quality Scale [18,19].

to consist of problematic items for adults on long-term sick leave. Correlation of the single item with the WAI was strong cross-sectionally (r = .87), and longitudinally over six months (r = .71) in a sample of 324 female workers on sick leave.

Preliminary analyses

Missing data

From 360 applicants, 179 participants were included in the trial. In total, 167 participants were included in the analyses, of which 117 participants were allocated to the experimental conditions (62 AAF and 55 EMBCT). To date, 75 participants (64%, n = 47 for AAF and n = 28 for eMBCT) provided T3 assessments for fatigue severity, 70 participants also provided mental health assessments at T3. 25 participants (21%) had not received the assessment at the moment of submitting this paper. A flowchart is provided in Figure 1.
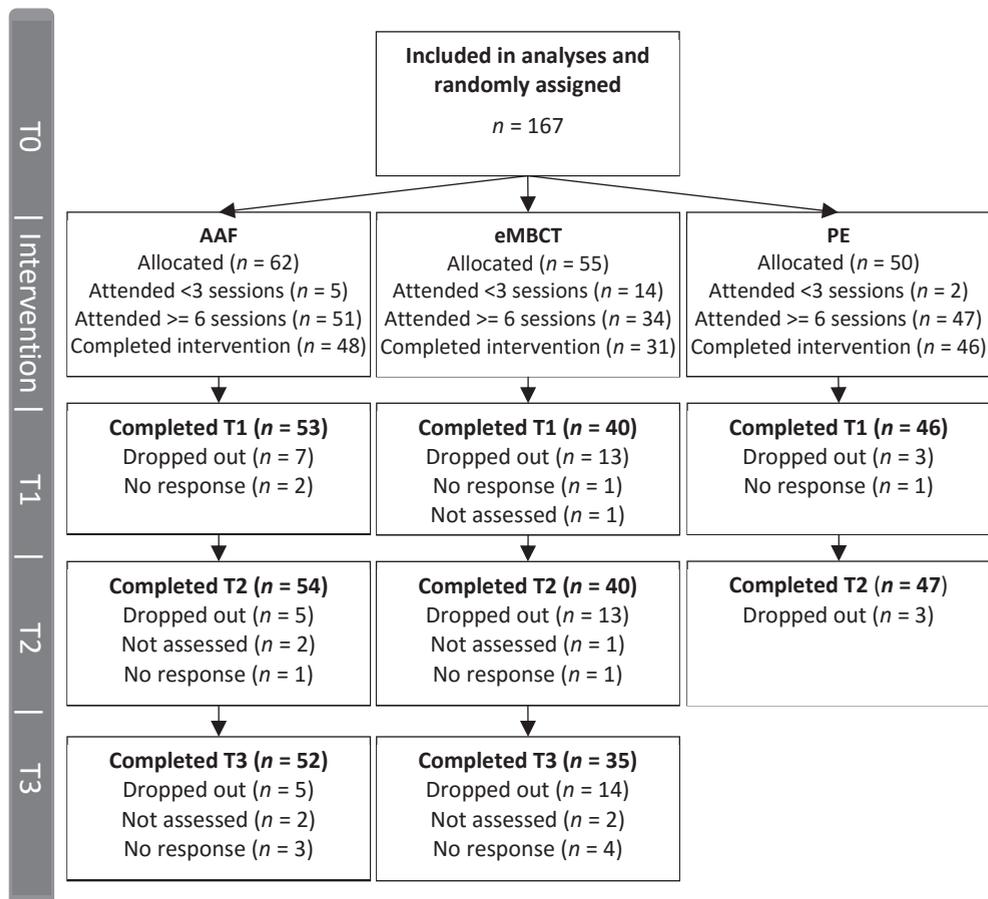

Figure 1. Flowchart of the FNK trial. Participants who 'attended' less then six sessions and did not respond were reported as 'Dropped out' in this flow chart.

For the flowchart on the recruitment and baseline phase, and for an analysis of missing data from the first semester, we refer to the effectiveness paper [6] (Chapter 5). Baseline scores of distress and fatigue, and fatigue change scores (T1-T0 and T2-T0) of participants who did and did not provide T3 assessments were compared: those who did not respond at T3 were slightly older and had a lower average change score of fatigue from T0 to T2, but comparable change scores from T0 to T1. Results are provided Supplementary materials 1.

Analytic strategy

All analyses were performed by means of Bayesian estimation. Bayesian estimation allows for the use of small samples [29,30] and often outperforms maximum likelihood estimation [31–33]. Contrasting maximum likelihood estimation, the default estimator for structural equation modeling, Bayesian estimation does not rely on asymptotic normality as posed int the central limit theorem [34], meaning that it does not require large samples [29,32][2]. Bayesian estimation results in posterior distributions rather than point estimates that directly account for uncertainty. Also, Bayesian 95% credible intervals – contrasting 'classical' frequentist confidence intervals – are intuitively interpreted as the probability that the parameter is in the specified interval.

Bayesian inference incorporates a prior distributions for every model estimate. In our study, we used vague, default priors. For the growth models that were used to analyze hypotheses 1 to 4, we used the default prior specifications of Mplus [35]. All prior distributions are reported in Supplementary materials 5, following guidelines reported in the WAMBS checklist [36]. This table also provides trace plots and posterior distribution plots for the final growth models to check whether convergence of these growth models was appropriate. For the analysis of hypotheses 5 to 8, we used JAPS (JASP Team (2016) JASP version 0.7.5.6 [Computer software]), and used the default prior on the correlation coefficient.

Latent growth curve modeling

Timing of assessments

For modeling time in the growth models, we used the averages of the actual timing [3], defined as the difference from the T0c assessment (baseline measurement following randomisation) in months, so [T0a T0b M3 M6 M9 T1 T2 T3] were assessed on average at [-2.08 -0.32 1.49 2.25 2.92 3.56 6.18 12.13] months after T0c. Density plots of the actual

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[2] An illustrative introduction to Bayesian estimation is given in [41].

[3] In the trial design paper, we proposed the use of time-varying factor loadings, but that was not possible when using Bayesian estimation in Mplus.

timing of the assessments, showing variance that was therefore ignored, are provided in the attachments (Supplementary materials 2).

First semester outcomes

To test the first hypothesis on development of work ability in the first semester, second order multiple group latent growth models were estimated for work ability, so posterior distributions were estimated for intercepts, linear growth, and quadratic growth parameters (see Supplementary materials 2 for a schematic and Mplus syntax). To test similarities and differences among study groups, we combined the three study groups in all five possible ways (see Table 2), and estimated models for all combinations. Convergence of these models was established visually with trace plots. Deviance Information Criteria (DICs), a Bayesian model comparison criterion comparable to the Akaike or Schwarz information criterion that are used for maximum likelihood estimation, were compared to test H1; lower DIC values indicate more favorable models. For the final model, growth parameter estimates and 95% credible intervals were reported.

Second semester outcomes

To test hypotheses H2-H4, on stability of improved outcomes during the second semester of the trial, a multiple group, piecewise model was tested, again by means of Bayesian estimation. In this model, second order growth models for the first semester (the first piece) were complemented with a linear slope for the second semester (the second piece)[4]. Both experimental groups were modeled separately, and residual variances were fixed to be equal among the different assessments of the outcome measures, yet variance of all growth estimates was allowed. In Supplementary materials 2, a schematic presentation of such a piecewise model and Mplus syntax is provided. Growth parameter estimates of the second semester piece are reported with 95% credible intervals and posterior predictive *p*-values (PPPs). The hypotheses are supported when these intervals of the slope from the second semester capture zero. As first semester growth models on fatigue and mental health have yet been published in Bruggeman-Everts et al. [6], albeit with some differences[5], the growth

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[4] Please note that because growth of work ability and fatigue severity in the first semester were best described by second order models, it was not possible to test H2 and H3 by having T3 scores as distal outcomes of first semester growth, which we proposed in the trial design [3].

[5] The first semester models differ on two aspects, which relate to the use of Bayesian estimation in this paper compared to maximum likelihood estimation in the first semester effectiveness paper [6]. First, in that previous paper individual time scores (time-varying indicators) were used for modeling fatigue severity and mental health to account for varying intervals between the assessments. This feature was not available in MPlus for Bayesian estimation, therefore the indicators were modeled as time-invariant, thereby ignoring differences in timing between participants. Second, in the previous paper growth of mental health outcomes was modeled linearly, because second order models (models with linear and quadratic growth factors) could not be estimated as results showed negative variances. With

parameter estimates of the first semester pieces as well as the covariance coefficients are attached in Supplementary materials 3.

Longitudinal relations

Finally, relations between changes in fatigue and changes in distress and work ability were studied to answer hypotheses 5 to 8. Change scores of the first semester (T0-T2), second semester (T2-T3), and entire year (T0-T3) of distress and work ability were correlated to change scores of fatigue within the first semester and second semester. Pearson's r's and Bayes factors (BF) were reported for each experimental group separately and combined, with and without the PE group. Bayes factors present the relative probability of one model over an alternative model, given that both models were equally likely a priori, and given the data at hand. For the current analysis, the alternative model depicts that the correlation is zero, thus a BF below one provides direct support for the absence of a correlation and a BF of 11 would mean that the existence of a certain correlation is 11 times as likely as a correlation of zero.

Results

Latent growth curve modeling

First semester outcomes

The first hypothesis, which states that growth of work ability was larger in the experimental groups compared with the control group, should be rejected: Table 2 shows that DIC was lowest for the model in which work ability of all three groups were modeled as one. Model results of models 1a and 1b are shown in Table 2. Model 1b is shown in Figure 2.

Second semester outcomes

All outcome measures were generally stable during the second semester: credible intervals of the linear slope mean included zero, so hypotheses H2 to H4, on the outcome measures in the second semester, were all supported by the data. However, it should be noted that variance of the second semester slopes were of considerable size, meaning that although outcomes were stable on a group level, subsets of participants had also increased or reduced in fatigue, work ability, and mental health during the second semester. For example, the estimated second semester change of fatigue of an imaginary participant in the eMBCT group at one standard deviation from the mean ($Z = 1$) would be 9.1, whereas a change of 4.1 was considered 'reliable change' for this measure [6]. Credible intervals of the

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Bayesian estimation, variance is forced to be positive by means of the prior distributions. Therefore, in the current paper, the use of Bayesian estimation allowed the second order models to converge nicely and showed to fit the data better than the linear model.

variance estimates of all outcomes overlapped, thus variance was similar for AAF and eMBCT. All second semester model estimates are presented in Table 3. Estimated trajectories (for completeness, starting from baseline) and individual observed trajectories are shown in Figure 3.
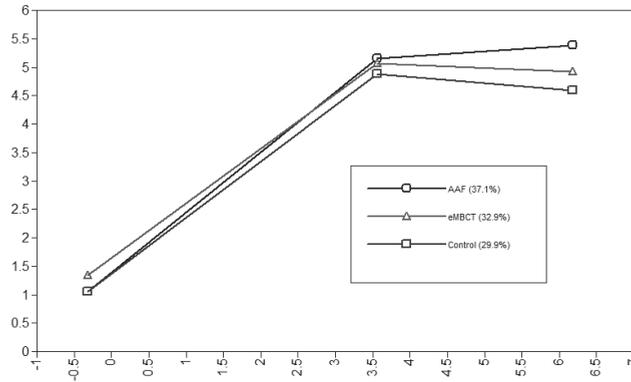

Figure 2. Results of model 1b in which AAF, eMBCT and control participants were modeled separately. Model comparison showed that the trajectories were not significantly different.

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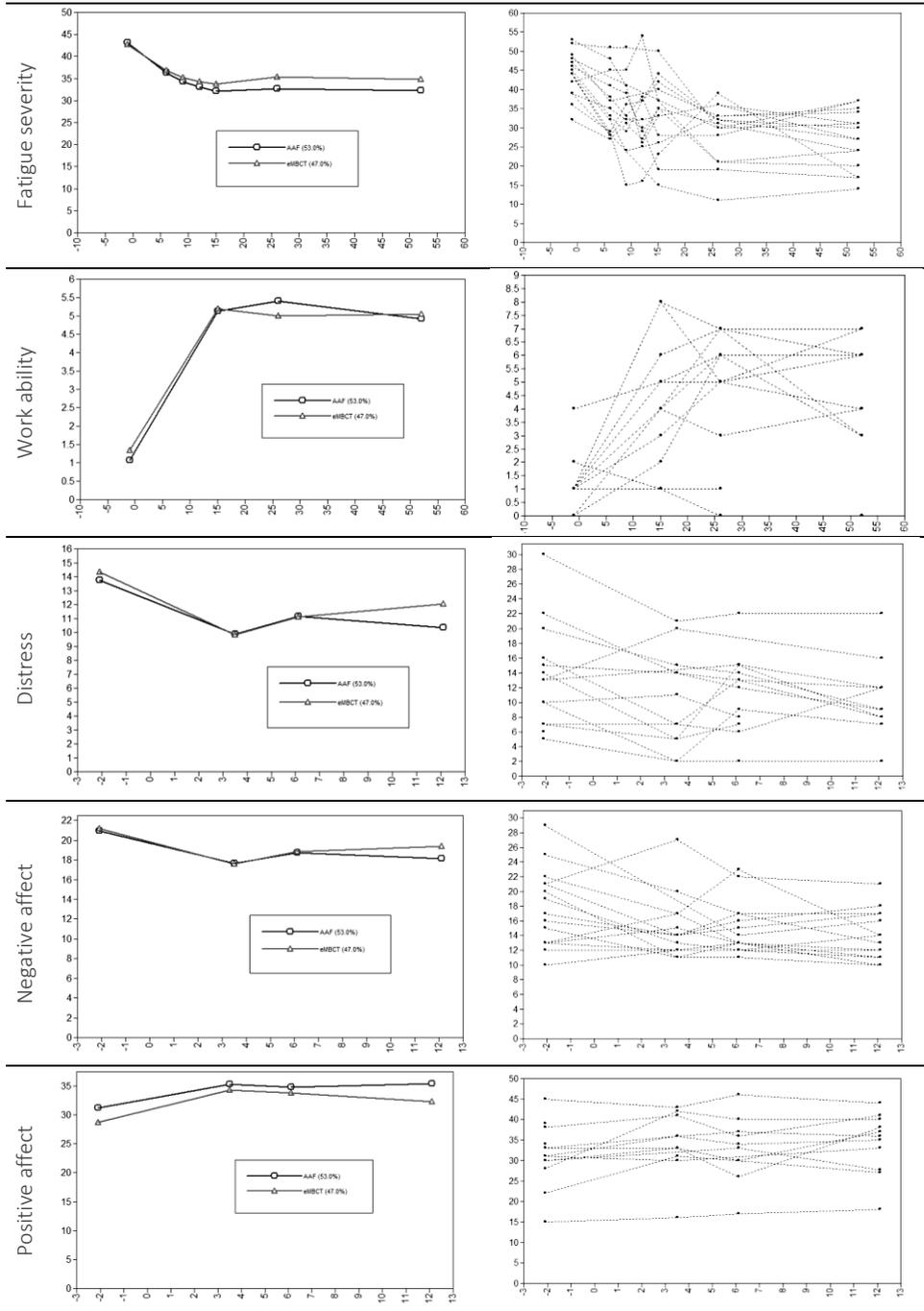
Figure 3. Modeled mean trajectories (O AAF; Δ eMBCT) and 15 observed individual trajectories.

Table 2. Posterior model results of latent growth models 1a and 1b on work ability (H1).

Model	DIC (PPP)	Group	I(M) M [CI]	I (var) M [CI]	S (M) M [CI]	S (var) M [CI]	Q (M) M [CI]	Q (var) M [CI]
1a: AAF = eMBCT = PE	1833.529 (0.478)	All	1.656 [1.397 1.914]	2.189 [1.221 3.166]	1.517 [1.304 1.728]	1.177 [0.627 1.790]	-0.158 [-0.189 -0.127]	0.022 [0.009 0.037]
1b: AAF; eMBCT; PE	1845.955 (0.370)							
		AAF	1.559 [1.189 1.932]	1.617 [0.713 2.778]	1.535 [1.188 1.879]	1.309 [0.650 2.252]	-0.148 [-0.202 -0.095]	0.029 [0.012 0.052]
		eMBCT	1.830 [1.247 2.422]	4.149 [2.460 6.829]	1.469 [1.012 1.911]	1.591 [0.778 3.006]	-0.157 [-0.222 -0.090]	0.031 [0.012 0.061]
		PE	1.565 [1.111 2.026]	2.119 [1.027 3.693]	1.530 [1.121 1.941]	1.620 [0.868 2.841]	-0.168 [-0.225 -0.111]	0.028 [0.012 0.053]
1c: PE; AAF = eMBCT	1840.841 (0.408)							
1d: AAF; eMBCT = PE	1836.690 (0.431)							
1e: eMBCT; AAF = PE	1838.962 (0.425)							

Abbreviations: AAF (ambulant activity feedback intervention), eMBCT (mindfulness based cognitive therapy), PE (psycho-educational information - control group), DIC (deviance information criterion), CI (95% credible interval), PPP (posterior predictive p-value), I (intercept), S (linear slope), Q (quadratic slope), var (variance).

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Table 3. Posterior linear growth estimates in the second semester (H2-H4).

Outcome measure	Group	Linear slope mean [95% CI]ᵃ	Linear slope variance [95% CI]	Modeled total growth for Z = 1ᵇ	Posterior predictive *p*-value
Fatigue	AAF	-0.074 [-0.474 0.320]	0.661 [0.170 1.672]	4.804	0.116
	eMBCT	-0.097 [-0.77 0.557]	2.354 [0.822 5.530]	9.109	0.483
Work ability	AAF	-0.082 [-0.170 0.006]	0.078 [0.031 0.142]	1.594	0.393
	eMBCT	0.009 [-0.109 0.134]	0.103 [0.042 0.212]	1.935	0.376
Distress	AAF	-0.135 [-0.402 0.132]	0.647 [0.234 1.205]	4.691	0.397
	eMBCT	0.157 [-0.216 0.535]	0.945 [0.380 1.969]	5.990	0.382
Negative affect	AAF	-0.108 [-0.420 0.207]	0.863 [0.280 1.628]	5.466	0.401
	eMBCT	0.087 [-0.339 0.510]	1.196 [0.452 2.463]	6.649	0.383
Positive affect	AAF	0.107 [-0.198 0.424]	0.875 [0.311 1.647]	5.719	0.399
	eMBCT	-0.249 [-0.681 0.186]	1.297 [0.517 2.658]	6.584	0.380

Abbreviations: AAF (ambulant activity feedback intervention), eMBCT (mindfulness based cognitive therapy), CI (credible interval). The growth estimates are expressed as change per month between T2 and T3. aAll credible intervals included zero. bAs time in the growth models was expressed in months, total second semester growth was calculated as follows: linear slope mean + 6·√(linear slope variance). Note. First semester growth parameter estimates and plots of these models are presented in the attachments.

Longitudinal relations

The longitudinal relations between fatigue and the other outcome measures were studied by means of correlations of the change scores. The analyses showed that reduced fatigue was weakly correlated with increased work ability in the first semester (r = -.226), but also the statistical support was very weak as the Bayes factor was barely higher than one (BF = 1.266). In the second semester, no relation between the change scores was supported (BF = 0.244).

Table 4. Bayesian correlations of change scores of fatigue with work ability and mental health.

Outcome measure	Group	Semester 1	Semester 2	Delayed effect (1 year)[a]
Work ability	All three	**-.188 (1.174)**		
	AAF & eMBCT	**-.226 (1.266)[b]**	-.120 (0.244)	-.211 (0.813)[d]
	AAF	-.120 (0.512)	-.191 (0.414)	-.192 (0.415)
	eMBCT	-.290 (0.913)	-.055 (0.229)	-.236 (0.502)
Distress	All three	**.209 (2.100)**		
	AAF & eMBCT	**.330 (19.076)[c]**	**.435 (375.7)**	.119 (0.242)[e]
	AAF	**.411 (15.019)**	**.423 (12.824)**	.240 (0.678)
	eMBCT	**.301 (1.026)**	**.446 (5.017)**	-.004 (0.217)
Negative affect	All three	**.183 (1.042)**		
	AAF & eMBCT	**.286 (5.223)[c]**	**.382 (51.901)**	**.235 (1.265)[e]**
	AAF	**.395 (10.278)**	**.393 (6.750)**	**.343 (2.994)**
	eMBCT	.205 (0.421)	**.369 (1.742)**	.113 (0.261)
Positive affect	All three	**-.252 (8.428)**		
	AAF & eMBCT	**-.407 (317.721)[c]**	**-.449 (664.014)**	**-.247 (1.600)[e]**
	AAF	**-.329 (2.720)**	**-.380 (5.221)**	**-.300 (1.500)**
	eMBCT	**-.540 (74.039)**	**-.515 (16.900)**	-.195 (0.382)

Note. Results are presented as Pearson's r's (Bayes factor). Bayes factors above one (**bold**) do not simply indicate *convincing* support of the estimated correlation, yet provide a direct measure of preference over the alternative model, which in this case represents 'no correlation'. Abbreviations: AAF (ambulant activity feedback intervention); eMBCT (mindfulness based cognitive therapy). [a]Correlation coefficients of first semester change of fatigue with full year change of work ability and mental health. [b]Hypothesis 5. [c]Hypothesis 6. [d]Hypothesis 7. [e]Hypothesis 8.

Our hypotheses on mental health were supported more firmly than those on work ability. Change in fatigue correlated weakly with change in distress (semester 1: r = .330, BF = 19; semester 2: r = .435, BF = 375.7), negative affect (semester 1: r = .286, BF = 5.2; semester 2: r = .382, BF = 52), and positive affect (semester 1: r = -.407, BF = 318; semester 2: r = -

.449, BF = 664) for both experimental groups combined. However, effects differed between groups: fatigue change correlated with change of distress and negative affect in the AAF group, but with change of positive affect in the eMBCT group.

No delayed effects of fatigue on work ability and distress were supported (all BFs below one). However, a relation between reduced fatigue in the first semester with improved affect in the second semester was found in the AAF group (r_{pos} = -.300 (BF = 1.500), r_{neg} = .343 (BF = 2.994)). Statistical support for both correlations was weak and not present in the eMCBT group. All correlation coefficients are presented in Table 4. Scatter plots are provided in Supplementary materials 4.

Discussion

The results of this study indicated that positive effects of an activity coaching intervention and a web-based mindfulness-based cognitive intervention aimed at reducing chronic cancer-related fatigue sustained up to one year after randomization: Fatigue, mental health, and work ability remained generally stable during the second semester of the trial. Also, decrease of fatigue was correlated with increased mental health.

Although the effects of both interventions were generally stable during the second semester, large variances were observed, thus individual trends were positive as well as negative during the second semester. Conceivably individuals would benefit from refreshment sessions or other tools to make their progression last, but it is unclear who these individuals are and why they relapsed.

This study also showed that work ability improved significantly in both experimental groups as well as in the PE group. One interpretation is that the PE intervention was sufficient for improving the perception of work ability, yet was inadequate to reduce fatigue. Changing the perception of work ability, or perhaps the interference of fatigue on working ability, is likely more feasible than reducing a persistent complaint such as fatigue. It should also be noted that participants in all three research groups had a lot to gain as their work ability was extremely low at baseline: 1.2 ± 1.7 (n = 166) compared to a work ability score of 6.7 ± 2.7 (n = 195) in another Dutch sample of cancer survivors at 18 months after the first day of sick leave who were not necessarily fatigued [12]. In that same study, recovery was on average 2.2 points over the course of one year [12], compared to an estimated average increase of 3.5 points over the course of six months in our study. Therefore, it is unlikely that only natural recovery occurred in our study, especially because time since diagnosis and duration of fatigue was so long. Also, a web-based personalized self-management psycho-educational intervention was effective in reducing fatigue and interference of fatigue [37]. This leaves to conclude that the PE could be an effective, low-priced tool during, parallel to, or as (basis for/part of a) follow-up program of cancer rehabilitation to improve work ability in severely fatigued cancer survivors.

In contrast to our hypothesis, support for a longitudinal relation between fatigue and work ability was scarce. Work ability and fatigue have often been associated cross-sectionally in various cancer survivor samples, but only few longitudinal studies on work ability have been performed [11]. Plausibly, other processes, such as setting different priorities or coping with fatigue caused work ability to improve, or the selected measure of fatigue was not specific enough to capture the relation between fatigue and work ability. For instance, lack of concentration ('cognitive tiredness') is a frequently reported work-related complaint in cancer survivors [38], that is explicitly associated with cancer-related fatigue [39], but is not addressed in the CIS-fatigue severity subscale[6].

In line with our hypotheses, the data supported the existence of longitudinal relations between mental health and fatigue, although correlations were generally weak. The fact that low mental health was not an inclusion criterion, and that psychiatric morbidity and HADS score $\geq$ 20 was even an exclusion criterion might explain the weak correlation. Other complaints than fatigue, such as burden from comorbid conditions that was reported by 39% of the participants, could have been responsible for elevated distress, limiting mental health gains associated with reduced fatigue in those participants.

The differences found in the relation of fatigue with the affect measures between both experimental groups (i.e. reduced fatigue relates to increased positive affect in eMCBT but with reduced negative affect in AAF) probably highlight the different approaches of both therapies. An explanation could be that participants in the eMBCT learned to disengage feelings of fatigue from distress and negative affect. Studying temporal precedence of these factors, or qualitative analysis of the interventions would elucidate on such hypotheses for cancer-related fatigue. In line with our findings, experience sampling among participants with depression showed that positive affect increased more in the mindfulness intervention than in the control group, and explained variance of more positive cognition of following days [40].

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A strength of this study is that it showed the societal value of Internet interventions for those who suffer from chronic cancer-related fatigue: This study shows that large and sustainable effects were established despite a clinical sample (eg. 39% reported limitations due to comorbid conditions), and that improvements of mental health likely form a welcome side effect of reducing severe fatigue. Another strength of this study is the statistical approach. Bayesian estimation allowed us to answer our questions by means of sophisticated structural equation modeling despite a limited sample size: the incorporation of prior, uninformative distributions prevented from estimating negative variances, and

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[6] In Supplementary materials 4, the results of a post-hoc analysis of the concentration subscale of the Checklist Individual Strength is provided.

missing data at T2 was dealt with elegantly by using the growth model of the first semester. Finally, by preregistration of outcome measures, hypotheses, and methods, and by openly reporting on changes from the original design, this study can be valued reliably on its quality.

It should be noted that measurement invariance, the ability of an instrument to measure latent concepts constantly over time and groups, has not been established for any of the outcome measures. Although beyond the scope of this work to do so, future longitudinal studies should definitely consider establishing measurement invariance, even when validity and retest-reliability has yet been established and scales are frequently used. Another limitation is that the current study, as do most long term follow-up studies, deals with a considerable amount of missing data on the follow-up assessment. Non-responders at T3 had reduced fatigue less between T0 and T2 compared to participants who did respond. Although this could underestimate the sample's mean fatigue at T3, bias of the second semester slope estimates is likely limited: covariance between the growth parameters of the first and second semester are small and credibly non-existent. Unfortunately, the follow-up measurement was uncontrolled for, as participants in the control group were offered to follow an experimental intervention after six months post randomization.

This study shows that reduced fatigue is differently associated with improved mental health in both interventions, probably reflecting the different working mechanisms of those interventions. Most importantly, this study supports that both Internet interventions reduce severe and prolonged fatigue sustainably.

Supplementary materials

https://progress.rrdweb.nl/39/

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Chapter seven
Working mechanisms of ambulant activity coaching

Abstract

Objective: Investigate the working mechanisms of an ambulant activity feedback therapy (AAF), an innovative intervention for reducing chronic cancer-related fatigue (CCRF).

Method: 167 adults suffering from severe CCRF were randomized to three arms: 62 in the AAF, 55 to online mindfulness-based cognitive therapy (eMBCT), and 50 in a minimal intervention control group. Development in time of sense of control over fatigue (SoC), physical activity level, moderate-to-vigorous physical activity (MVPA) time, and decline of physical activity from morning to afternoon was captured in latent growth models. Development in time of perceived activity and self-efficacy in time was captured in change scores. Correlates between the development of these constructs and the development of fatigue were established to study whether these constructs were specific, or generic working mechanisms for the AAF. Additionally, latent profile analysis of the AAF group explored whether participants had different patterns of change of the suggested working mechanisms.

Results: Increasing SoC and perceived activity as assessed with the Checklist Individual Strength were specific working mechanisms for AAF. Three other perceived activity measures and self-efficacy were supported as generic working mechanisms. Physical behavior generally improved, but was not correlated with development of fatigue, thus was not considered a working mechanism. The latent profiles revealed that changes in physical behavior happened via different patterns in different individuals, probably related to different goal settings.

Conclusions: Beneficial effects of activity coaching for CCRF were generally correlated with changed cognitions rather than increased physical activity or balance.

Introduction

Cancer-related fatigue can be effectively reduced by several treatments: various forms of exercise therapy [1,2], psychological treatments such as cognitive behavior therapy [3], mindfulness-based cognitive therapy [4], and combinations of those in multidisciplinary rehabilitation [5]. Introducing e-health interventions in this context seems promising for three reasons. First, an e-health intervention does not require a patient to travel, which likely reduces the threshold for patients to seek help and adhere to the intervention. Second, e-health interventions take place in the patient's own daily thus intended behavioral change environment. And finally, capacity of caregivers can be used more efficiently.

One promising e-health intervention is ambulant activity feedback therapy (AAF) [6]. It is a home-based intervention designed to reduce fatigue of cancer survivors, in which care and coaching can be given from a distance by a physiotherapist to patients using smart technology. Tailored persuasive technology supports the patient in their daily life decisions [6]. Changing physical behavior is a key component in this intervention, however, also psycho-educational components are incorporated. The AAF intervention was significantly more effective in reducing severe chronic cancer-related fatigue (CCRF) than a control intervention in which participants solely received weekly e-mails with psycho-educational information (Chapter 5) 66% clinically significantly reduced fatigue compared to 12% in the control intervention.

To further optimize and tailor the AAF, it is important to explore the working mechanisms, but also to distinct which working mechanisms are specific for this intervention with respect to other interventions. The authors hypothesized that increasing physical activity level (PAL) and reductions of daily physical activity decline (so improved balance) are specific working mechanisms for the AAF-intervention [7]. Additionally, sense of control over fatigue [8], changes in perceived activity [9], and self-efficacy on PAL [10] were studied as potential working mechanisms. The current research compared AAF with two other interventions that were studied in a three-armed randomized controlled trial: online mindfulness-based cognitive therapy (eMBCT) and a minimal intervention of receiving psycho-educational information by e-mail (PE) [7]. Three sub hypotheses were tested for each measure, to find out whether it was an intervention-specific working mechanism, a generic working mechanism, or none of both.

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Methods

Design

The current study was based on data from a three-armed randomized controlled trial (AAF, eMBCT or control), the FNK trial. Online questionnaires were assessed before inclusion to check eligibility (T0a), after inclusion yet before randomization (T0b), three times during the intervention period (M3, M6, and M9), and after the intervention period (T1). T1 took place two weeks or - if the intervention got delayed - at least one week after finishing the intervention. The design of the FNK trial is described extensively elsewhere [7] (Chapter 2).
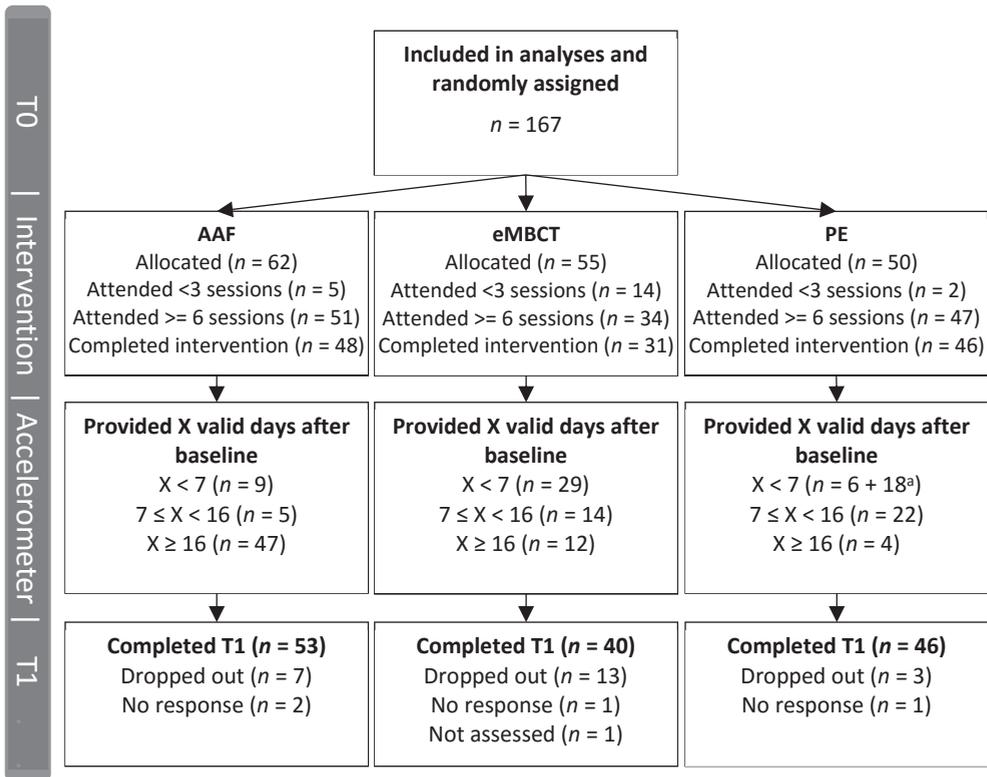
Figure 1. Flow chart of the FNK-trial. Analyses in this paper are performed on 167 participants that were included in the study and have not reported recurrence of cancer. [a]Eightteen participants were requested to return the accelerometer after randomization.

Participants were requested to wear an accelerometer five times: (1) for seven days at T0b; (2-4) for three days per week at M3, M6, and M9, and (5) seven days at T1. However, eighteen participants in the control condition (36%) were asked to return the accelerometer after randomization due to a shortage of accelerometers and as such we could only collect baseline activity data for these participants. Participants in the AAF used the accelerometer

as part of their intervention: they received feedback about their physical activity by means of a graph and text messages. Measurements at M3, M6, and M9 were therefore not blinded in this group.

Participants

Data of all participants that were included in the FNK trial and started the intervention were analyzed. A thorough description of the sample is presented elsewhere (Chapter 5). For an overview of the participant flow after randomization, see Figure 1.

Interventions

AAF

The activity coaching intervention is a nine week semi-structured protocol, in which a patient uses an activity coaching system and is guided and coached by a physiotherapist by e-mail. The system provides the patient with hourly feedback about his or her current activity level relative to a goal activity level that is set by the therapist. Both the therapist and the patient can monitor progression on a web portal. The intervention focusses on personal therapy goals, while making use of behavior change principles such as improving self-efficacy, and to handle activity and fatigue-related perceptions. The therapy is tailored to the patient's PAL at baseline and therapy goals.

Daily activity goals are monitored by the activity coach, which consists of an accelerometer and a smartphone with the activity coaching application installed. A feedback scenario is selected that matches the patient's goals: for example, when the participant is more active than the line of reference suggests, the feedback scenario that supports the goal 'increasing activity' will select endorsing feedback messages, when in the same situation, the feedback scenario that supports energy conservation-related goals could suggest to take a rest. The AAF-intervention was guided by six physiotherapists (male: n = 4) which were experienced with working with (former) cancer patients.

eMBCT and control condition

Both the eMBCT and the minimal intervention control condition served as a reference for the AAF condition. eMBCT is a web-based intervention that follows a nine week protocol and aims to reduce fatigue complaints through exposure, cognitive change, self-management, relaxation and acceptance [11]. On a personal web page participants can download mindfulness exercises (MP3 files), write down their experiences of doing the exercises in a log file, read information about a mindfulness, cancer and fatigue, and correspond with their personal therapist via e-mail. The psychologist can login on the webpage, and respond to the log of the patient, thereby guiding the patient through the intervention.

Participants in the control group received weekly psycho-educational information e-mails during nine weeks. All information was also provided in the AAF and eMBCT interventions, but participants in the control group were not supported by a health care professional.

Materials and Measures

Fatigue

Our outcome measure was fatigue, as assessed with the fatigue severity subscale (8 items) of the Checklist Individual Strength (CIS). Items are scored on a 7-point Likert scale. In chronic fatigue syndrome populations, the CIS has shown good discriminative validity [12], internal consistency [13], and sensitivity to changes [14], and has also been used with cancer survivors [8,15].

Physical behavior measures

Minutely data from the accelerometer (Promove 3D, outputs 10^{-3}m/s^2, which is referred to as counts per minute (cpm), described elsewhere [16]) was scanned for non-wear, which was removed in case of agreement between two researchers (HI and MW). A measurement day was considered valid when consisting of at least 600 minutes of data. Data of valid measurement days were used for calculating three physical behavior measures.

Three measures of physical behavior were selected based on a previous study [17] in which physical behavior profiles were explored among the baseline physical behavior data of this trial. The following three measures were most distinctive for the profiles and were therefore included as physical behavior measures in this study. The **physical activity level** (PAL) was expressed as the mean activity count per minute per day. **MVPA time** was the total time (minutes per day) at an intensity of 2588 cpm[1]. To calculate **activity balance**, two day parts were defined: morning (05h00-12h00) and afternoon (12h00-18h00). Each day part was considered valid if it consisted of ≥120 minutes of data). The change score was calculated of the average PAL of each day part, and divided by the daily PAL.

Cognitive measures

The Self-Efficacy Scale [18] was assessed to study **sense of control over fatigue** (SoC), at T0, M3, M6, M9, and T1. SoC was the only cognitive measure that was assessed multiple times during the intervention, and change of SoC was therefore analyzed by means of latent growth trajectories. The scale comprises 7 items on a 4-point Likert scale and has been previously used in cancer survivors. It was adjusted from a 5 item scale that was previously used in chronic fatigue syndrome [14].

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[1] 2588 cpm was selected being the right 95% confidence interval of treadmill walking at 6 kilometers per hour (2418 ± 275 cpm, *n* = 10) [16]. It corresponds with a z-score of 0.36 of walking at a comfortable speed, and a *z*-score of -0.32 of active office tasks [17].

Perceived activity was assessed with four measures: 1) reduced activity, assessed with the activity subscale of the CIS, the sum score of three questions on a 7 point Likert scale, 2) self-compared (internal) perceived activity assessed as "How physically active have you been the last week?" on a scale from 0 = *very inactive* to 100 = *very active*, 3) peer-compared (external) perceived activity, assessed with this question: "When compared to healthy contemporaries, how would you rate your level of physical activity over the last week?" peer-comparison (scale 0-100 with 0 = *much less active*, and 100 = *much more active*), and 4) satisfaction with physical activity, for which two questions were dichotomized: 1 = *unsatisfied* (score of 4 or higher on a 5 point scale) *and rather wants to be more active*.

Coping and planning self-efficacy were assessed with selected items from the self-efficacy scales of Bandura [19] and Rodgers [20,21]: 13 items on a numeric rating scale (0-100), all shown in Supplementary materials 1.

Missing data

Dropouts and missing questionnaire data are described extensively elsewhere [22], but missing data issues specific for this study (accelerometer data and data from the second semester of the control group) are discussed here.

The flow chart in Figure **1** shows that half (29 of 55) of all participants in the eMBCT provided less than 7 days of valid accelerometer data after the baseline measurement. Thirteen of these eMBCT participants also dropped out from the intervention. In the PE condition, most missing data was by design: 18 participants in the PE were asked to send back their system because too few systems were available to ensure swift inclusion of all participants. In the AAF 9 participants provided less than 7 days after baseline and all were dropouts from the intervention. A scatter plot of the number of wearing days versus intervention effect is shown in Supplementary materials 2.

As stated in the trial design, participants in the control group were offered to follow one of both experimental intervention after finishing the T2 assessment at six months. However, contrasting the trial design, data on following the experimental intervention of these participants were excluded from the analyses. These participants could not be analyzed in conjunction with the PE, in which they were already represented, a comparison that is crucial for this paper.

Analytic strategy

To test if a construct was a generic or intervention-specific working mechanism, a set of sub hypotheses were tested of which some are congruent to mediation analysis. Although comparable hypotheses were tested for all measures, the way in which the development of that measure was captured differed: For the measures that were assessed throughout the

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intervention, latent growth models were estimated, whereas for the other measures change scores were calculated.

This section will present the sub hypotheses, and how these hypotheses were tested from (i) the latent growth models and (ii) from the change scores. Subsequently, the specific ways in which development of the measures in time was operationalized will be described for the latent growth models and change scores. Lastly, post hoc analyses will be proposed to gain further insights in the different ways that individuals changed during the AAF intervention.

Hypotheses

Three sub hypotheses were studied for all measures that were addressed as working mechanism[2]:

a) The measure changes over time in the AAF (congruent with estimating the "action effect").
   i. The credible interval of the growth factor (GM) in the AAF does not include zero.
   ii. The post-assessment (T1) in the AAF is greater than the pre-assessment (T0) according to a Bayesian within-subjects t-test with Bayes factor > 1.
b) Change of that measure in the AAF is substantially greater than in both other groups (testing if the action effect is specific for the AAF intervention, 'specificity-of-action').
   i. The growth factor in the AAF differs from both other groups as its credible interval does not overlap with the credible intervals of the growth factors in both other groups.
   ii. The change score in the AAF differs from both other groups according to Bayesian between-subjects t-test with Bayes Factor >1.
c) Fatigue change and change of the measure are correlated in the AAF group (congruent with testing the "conceptual theory").
   i. The growth of fatigue ($G^{fatigue}$) correlates with growth of the measure (G^M).
   ii. The change score of fatigue correlates with the change score of the measure.

If hypotheses *a, b*, and *c* are supported, the construct will be considered a working mechanism specific for AAF. The acceptance of hypotheses *a* and *c* suggests that it is a working mechanism non-specific for AAF.

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[2] Note that in the trial design paper [7] also a fourth sub hypothesis was presented in relation to the working mechanisms of the interventions. This hypothesis was suggested to test the generalizability of the conceptual theory "Is such correlation [between the mediator change and fatigue change] independent of group?". However, this hypothesis is not specific enough, as only the PE and AAF can be compared for the intended cause, and is only relevant when the conceptual theory was supported. Therefore analysis of this hypothesis was left out in this study.

Latent growth models

Latent growth models (a specific type of structural equation modeling) were used to capture change of measures that were assessed multiple times throughout the intervention: the objective physical behavior measures and SoC [23]. The technique allows for examination of inter- and intrapersonal changes, and is insensitive for missing data as all available observations are used. To study how growth of the potential working mechanism was correlated with growth of fatigue, latent growth models were combined in one model as shown in Supplementary materials 3. The analyses were performed with Bayesian estimation so that the results of this study can be intuitively interpreted, and that the incorporation of prior specifications can aid in the model estimation, for example by forcing a variance parameter to be positive.

The Bayesian latent growth models were estimated in Mplus, version 7.4, and default Mplus prior specifications were used [24]. Two Markov chains were implemented, with the first half of the iterations as burn-in phase. For each model, the number of iterations was increased iteratively, until convergence was obtained, checked through visual inspection of the trace plots, i.e. both chains were stacked, with stable means and variances. Then, one model with double the iterations of the converged model was estimated to assure that the global solution was found.

Univariate and parallel growth models

Therapists were instructed to finish the 9-week protocol in maximally 11 weeks, but due to several reasons (illness, holidays, and malfunction of the activity coach) this was rarely accomplished. Therefore time between the moment of randomization (moment of opening T0c assessment) and the first post measurement T1 was standardized. A more thorough description of how exactly this standardization was performed is presented in Supplementary materials 2.

To test sub hypotheses a and b, multiple-group growth models were estimated for each measure. The three groups (AAF, eMBCT, PE) were allowed their own mean and variances of the intercept and one growth factor. Supplementary materials 3 shows that a linear model was the best latent growth model for all four measures when only one growth factor was allowed, but please note that a second order model (with a linear as well as a quadratic growth factor) described the data of MVPA, balance, and SoC better.

To test sub hypotheses c, parallel linear growth models were estimated as shown in Supplementary materials 3 by correlating the growth factors of both univariate models: one for all participants combined, and one for all groups separately.

Growth parameters of the models were reported with 95% credible intervals. For each model, posterior predictive p-values (PPPs) were provided, which are a measure of predictive value of the model, with an optimal value of .5.

Change scores

Measures of self-efficacy and perceived physical activity were assessed at baseline and at the post assessment T1. Change scores were calculated by detracting the baseline score from the T1 score. Correlations and *t*-tests were performed in JASP (JASP Team (2016) JASP version 0.7.5.6 [Computer software]), which is free software that includes Bayesian testing. Significance of the correlations and *t*-test results was provided in terms of Bayes factors (BFs), which can be interpret as the relative support for this specific parameter of interest compared to 'no correlation or 'no mean difference' exists.

Post hoc analyses

The personalized character of the AAF intervention allows to use the Activity Coach in different ways with different protocols, which expectedly correspond with different working mechanisms. Therefore, the expected working mechanisms were explored by means of latent profile analysis of their change scores and growth factors. All latent profile analyses were performed in Mplus with robust maximum likelihood estimation, syntaxes are provided in Supplementary materials 4.

The post hoc analyses were performed in three steps. First, a series of latent profile models with one to five classes was evaluated. This series included the standardized change scores or growth estimates of all continuous working mechanisms as indicator variables as shown in Figure 2 thus excluded the satisfaction variable, which was a dichotomous variable. From that series, the model with the lowest Bayesian information criterion (BIC) was selected. The growth factor of fatigue was added as predictor of class membership by means of the three-step approach of Vermunt [25] to check if the effectiveness of the intervention was predictive of the latent profiles.

In the second step, the former model was split, so that the cognitive measures and the physical behavior measures could be studied separately, and to study their independent change patterns in more detail. The same procedures were followed for both model series as in the first step.

In step three, the results of the separate latent profiles models of cognitions and physical behavior from the second step were combined in a cross table by using each participant's most likely class in both models. Chi-square testing was performed in JASP (JASP Team (2016). JASP (Version 0.7.5.6)[Computer software], to study how the cognition change profiles were related with the physical behavior change profiles.
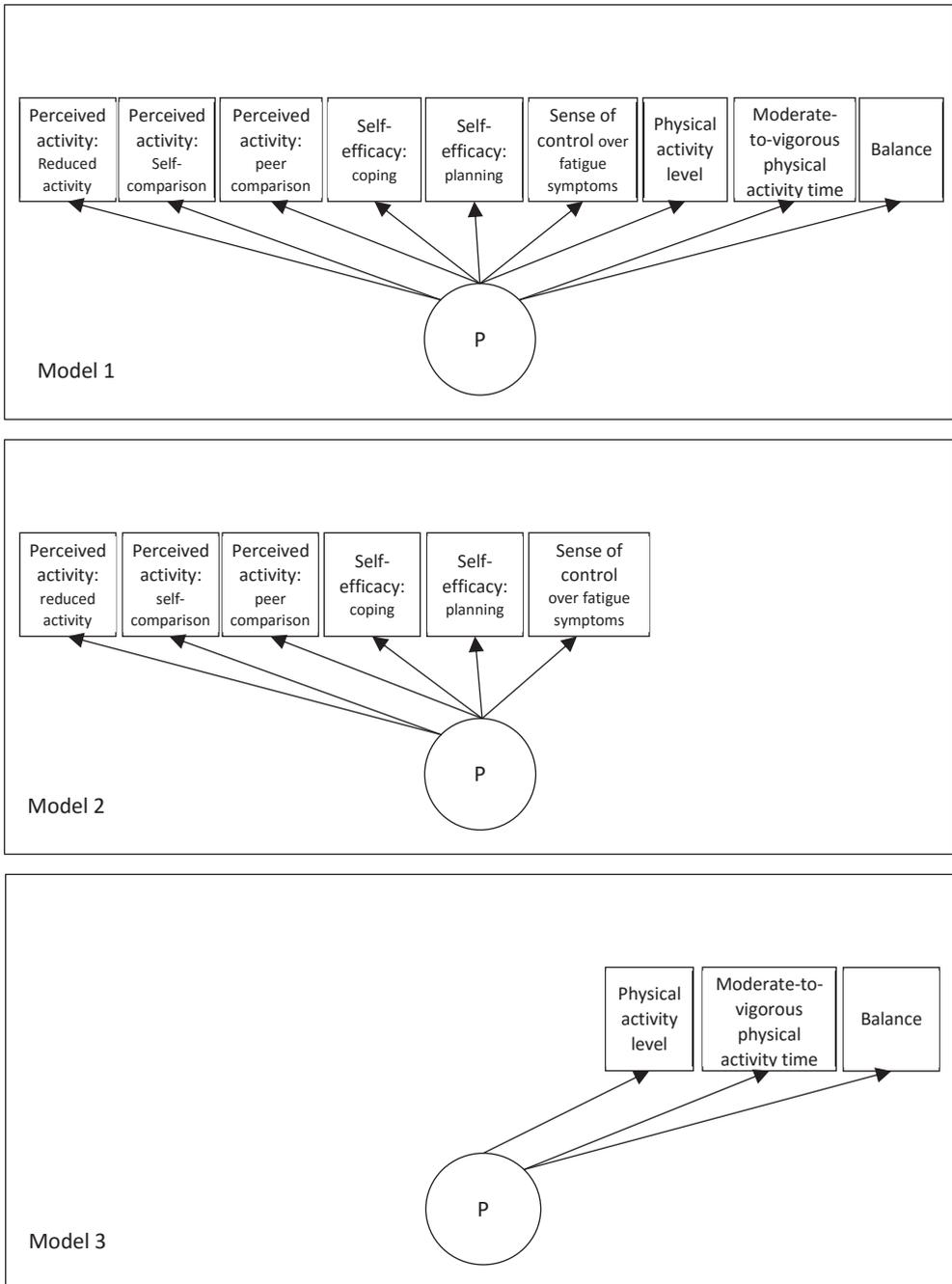
Figure 2. Three models of the post hoc analyses. The square indicators represent either modeled growth factors of that measure or change scores.

Results

Latent growth models

DICs and posterior PPPs of all estimated models are presented in Supplementary materials 3. Predictive value of the models in the AAF group was often poor (indicated by low PPPs with .5 being optimal, see Table 1) except for balance.

First, it was evaluated if the construct mean changed in the AAF, testing 'action' hypothesis *a.* The estimated slope of PAL [95% CI] was 65 [4, 128] for AAF, therefore the action hypothesis was accepted. However, the effect was not specific for the AAF intervention: CIs of the slope means overlapped between all three groups, thus sub hypothesis *b* was rejected. The conceptual theory (sub hypothesis *c*) was tested in the parallel growth model. No correlation between growth trajectories of fatigue and PAL was established in the AAF group (*r* [CI] = -.211 [-.623, .254]), therefore conceptual hypothesis *c* was rejected. Increasing PAL was not considered a working mechanism for AAF.

The estimated slope of time spent in MVPA [95% CI] in the AAF group was 7.557 [-1.917 17.032], so 'action' hypothesis *a* was rejected, although not very convincingly. Also, credible intervals of the growth factor overlapped between all three groups, meaning growth of MVPA did not differ between groups, thereby rejecting hypothesis *b*. Growth trajectories of fatigue and MVPA were not related within the AAF group (*r* [95% CI] = .067 [-.491, .368]), so also conceptual hypothesis *c* was rejected. Increasing MVPA was not considered a working mechanism for AAF.

The growth estimates of the balance measure did not increase considerably in the AAF group: estimated slope mean [95% CI] was 4.702 [-4.498, 13.996], thus hypothesis *a* was rejected. Also, growth trajectories were comparable between the three groups as credible intervals of the growth estimates overlapped, rejecting sub hypothesis *b*. Growth trajectories of fatigue and balance were not related within the AAF group (*r* [95% CI] = .398 [-.153, .875]), rejecting conceptual hypothesis *c*. Increasing balance was not considered a working mechanism for AAF.

SoC increased in both the AAF and in the eMBCT group (G_{AAF} [95% CI] = 2.234 [1.248, 3.202]; G_{eMBCT} [95% CI] = 1.500 [0.807, 2.191]), but not in the PE group, thus action hypothesis *a* was supported, but not *b*. Growth trajectories of SoC and fatigue were strongly correlated within the AAF (*r* [95% CI] = -.832 [-.968, -.544]), thus conceptual hypothesis *c* was supported. SoC was considered a working mechanism not-specific for the AAF.

Table 1. Growth parameters of the univariate and parallel latent growth models.

		Univariate latent growth model					Parallel model
	PPP	Intercept mean [95% CI]	Intercept variance [95% CI]	Growth[b] mean [95% CI]	Growth variance [95% CI]	PPP	Correlation $G^{mediator}$ with $G^{fatigue}$
Fatigue							
AAF	.081	41.952 [40.109, 43.737]	35.289 [16.898, 58.678]	-11.259 [-14.307, -8.180]*	81.784 [40.472 146.604]		
eMBCT	.388	41.344 [39.291, 43.362]	21.860 [6.508, 51.397]	-8.641 [-12.290, -5.119]*	63.339 [21.809, 144.631]		
PE	.410	39.529 [36.989, 42.087]	52.310 [25.185, 97.690]	-1.601 [-4.569, 1.336]	44.764 [10.067, 107.948]		
Physical activity level							
All						.014	.026 [-.946, .943]
AAF	.045	774.980 [711.99, 837.77]	47446 [31409, 75737]	65.516 [3.935, 128.342]*	32794 [16115, 60735]	.045	-.211 [-.623, .254][c]
eMBCT	.194	787.538 [719.12, 856.24]	25046 [12508, 53141]	5.006 [-59.222, 68.166]	9713 [1418, 31189]	.194	-.319 [-.875, .509]
PE	.219	840.578 [733.92, 946.24]	60984 [31094, 128027]	-30.365 [-102.782, 38.658]	8624 [860, 33290]	.219	.084 [-.773, .807]
Moderate-to-vigorous intensity physical activity							
All						.025	-.323 [-.948, .817]
AAF	.038	48.516 [39.712, 57.291]	951.110 [631, 1504]	7.557 [-1.917, 17.032]	864.828 [480, 1502]	.028	.067 [-.491, .368][c]
eMBCT	.290	52.871 [42.480, 63.459]	563.248 [280, 1279]	-2.163 [-11.249, 6.840]	220.359 [26, 684]	.137	-.565 [-.926, .194]
PE	.349	57.123 [45.073, 69.147]	784.427 [400, 1657]	-4.774 [-13.771, 4.087]	161.810 [17, 581]	.397	.362 [-.593, .912]
Balance[a]							
All						.071	.516 [-.390, .950]
AAF	.518	-14.354 [-23.071, -5.524]	781.397 [451, 1328]	4.702 [-4.498, 13.996]	423.026 [104, 1058]	.265	.398 [-.153, .875][c]
eMBCT	.299	-14.559 [-31.273, 2.080]	1502.675 [581, 3211]	3.662 [-11.742, 18.606]	578.840 [75, 1742]	.201	-.399 [-.875, .439]
PE	.157	-22.053 [-41.823, -2.017]	2280.883 [1072, 4727]	1.504 [-20.031, 23.053]	1413.828 [335, 3821]	.357	.360 [-.478, .892]
Sense of control over fatigue symptoms							
All						.062	-.954 [-.987, -.855]*
AAF	.017	18.861 [18.207, 19.513]	4.591 [2.353, 7.968]	2.234 [1.248, 3.202]*	8.204 [4.156, 14.657]	.005	-.832 [-.968, -.544]*[c]
eMBCT	.601	18.121 [17.301, 18.932]	7.891 [4.750, 12.923]	1.500 [0.807, 2.191]*	2.311 [0.378, 5.729]	.339	-.668 [-.929, -.174]*
PE	.545	18.440 [17.392, 19.487]	10.052 [5.538, 17.724]	0.592 [-0.346, 1.542]*	3.481 [0.427, 9.622]	.346	-.776 [-.968, -.301]*

Note that the growth estimates are interpretable as modeled change scores between T0c and T1 as time between T0c and T1 was set at one. Abbreviations: CI (credible interval), PPP (posterior predictive p-value, closer to .5 indicates better predictive value, a PPP below .025 indicates that >95% of all model-generated chi-squares were below the observed chi-square, meaning that the predictive value of the model was very bad), $G^{fatigue}$, G^{m} (estimated growth of the mediator), $G^{fatigue}$ (estimated growth of fatigue), r (Pearson's r correlation). [a] balance (relative decline of physical activity level from morning to afternoon). [b] These parameters are used to test if the action theory is valid (sub hypothesis a) and intervention-specific (sub hypothesis b). [c] This correlation tests the conceptual theory, sub hypotheses c. *Credible interval does not include zero.

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Change scores

For all measures that were assessed pre and post intervention only, the change scores were calculated. Sample and group descriptions as well as the results from the Bayesian *t*-tests and correlations are provided in Table 2. When evaluating the action hypothesis *a*, convincing support (Bayes factors higher than 50) was provided from the within-subjects *t*-tests that all suggested cognitive measures had changed in the AAF group, except for satisfaction (BF = 1.201) in which the support for increased satisfaction was very weak. This means that all action hypotheses were confirmed.

Recalling hypothesis *b*, effects were considered specific for the AAF intervention when change scores differed between AAF and the other groups. Reduced activity was the only measure that had decreased more in the AAF compared to both other groups, but the Bayes factor was small (BF = 2.204) meaning that the data only provided weak support for this difference. Hypothesis b was rejected for all other measures.

The conceptual hypothesis *c* was confirmed for most cognitive measures: change of perceived physical activity (reduced activity and peer-comparison), and both self-efficacy measures correlated weakly or moderately with fatigue change. Support for the conceptual hypothesis on planning self-efficacy was poor within the AAF (*r* (BF) = -.337 (3.345)), but on the sample level very strong (-.353 (691.10)). Similar contrasts were seen for satisfaction and self-compared perceived activity: correlations were not supported within AAF, but on a sample level, weak (satisfaction) or convincing support (self-compared perceived activity) was presented.

This leads to conclude that – for the measures that were analyzed by change scores – specific working mechanisms include perceived physical activity (reduced activity), and non-specific working mechanisms include perceived physical activity (peer comparison) and both self-efficacy scales.

Table 2. Descriptions of observed pre and post assessments, and correlations with fatigue change

Potential working mechanism	Group	N	Baseline score M (SD)	Change score M (SD)	Within-subjects t-tests (T0b vs T1) Bayes factor	Between-subjects t-tests of change scores (AAF vs eMBCT and PE)[b] Bayes factor	Correlation of change score mediator with fatigue change score r (Bayes factor)
Perceived activity							
reduced activity[a]	All	139	12.95 (4.846)	-1.892 (4.676)		2.204*	.561 (1.34e+10)*
	AAF	53	13.66 (4.246)	-3.057 (4.672)	1245.112*		.525 (469.68)*c
	eMBCT	40	12.24 (5.000)	-1.825 (4.361)	3.576*		.499 (34.878)*
	PE	46	12.84 (5.324)	-0.061 (4.697)	0.230		.581 (1071.9)*
self-comp.	All	135	54.10 (20.72)	8.963 (24.18)		0.324	-.354 (697.72)*
	AAF	52	54.39 (20.77)	11.83 (22.54)	63.253*		-.220 (0.572)*c
	eMBCT	38	51.51 (18.90)	13.82 (21.96)	67.678*		-.213 (0.449)*
	PE	45	56.60 (22.58)	1.556 (26.45)	0.174		-.465 (28.348)*
peer-comp.	All	134	38.86 (21.86)	14.49 (25.64)		0.222	-.444 (174195)*
	AAF	51	42.69 (22.59)	12.84 (24.36)	59.458*		-.502 (164.64)*c
	eMBCT	38	36.05 (17.41)	17.68 (24.76)	278.050*		-.393 (3.569)*
	PE	45	37.20 (24.89)	13.67 (28.01)	15.392*		-.529 (159.22)*
unsatisfied[b]	All	137	.4850	-.1752		0.188	.225 (3.418)*
	AAF	53	.4194	-.1698	1.201*		.150 (0.300)c
	eMBCT	38	.5455	-.2632	2.746*		.267 (0.718)
	PE	46	.5000	-.1087	0.280		.246 (0.686)
Self-efficacy							
coping	All	136	47.33 (17.89)	9.150 (19.18)		0.408	-.378 (2775.6)*
	AAF	52	46.58 (17.96)	11.87 (18.03)	1154.919*		-.457 (49.143)*c
	eMBCT	38	46.57 (16.35)	13.95 (18.11)	730.151*		-.248 (0.596)
	PE	46	49.09 (19.57)	2.102 (19.66)	0.205		-.214 (0.494)
planning	All	136	56.47 (18.46)	8.763 (19.74)		0.398	-.353 (691.10)*
	AAF	53	55.16 (17.87)	11.48 (19.70)	246.636*		-.337 (3.345)*c
	eMBCT	38	56.08 (16.78)	9.346 (16.84)	21.230*		-.186 (0.369)
	PE	45	58.51 (20.98)	5.070 (21.81)	0.496		-.431 (12.816)*

Abbreviations: CIS (checklist individual strength), comp (comparison), M (mean), SD (standard deviation), r (Pearson's r). [a]Subscale of Checklist Individual Strength. [b]Dichotomized variable, ratios are presented. * Bayes factor greater than one. [c]Testing conceptual hypothesis c.

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Post hoc analyses

In the post hoc analyses, a more general concept of change within the AAF was studied by estimating latent profile models from the previously studied change scores/estimates. In the first step, five models were estimated that included change measures of all continuous measures (thus excluding satisfaction) that were studied as potential working mechanisms. Descriptions and model characteristics of the entire series are provided in Supplementary materials 4. The two-class solution performed best, with 23 and 39 participants per class (BIC = 1422.279, entropy = .746). A diagram with the standardized class means is shown in Figure 3**Figure** , class means and variances are provided in Supplementary materials 4. The two-class model was not predictive for reduced fatigue (log odds = .244, p = .126).
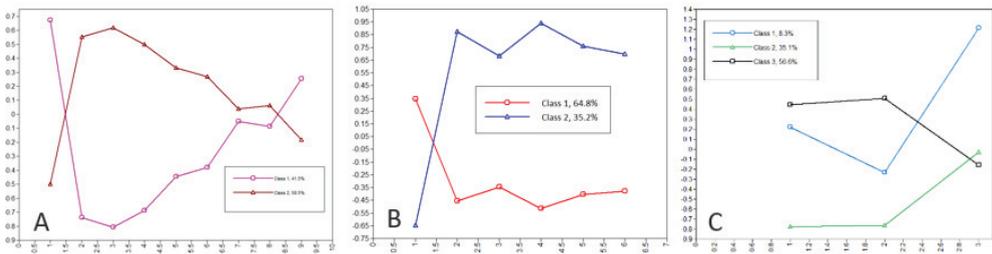

Figure 3. Standardized class means of the post hoc latent profiles models. Panel A: Final model in step 1 (all continuous measures), Panel B: models of cognitive measures, Panel C: model of physical behavior measures.

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In the second step, two other series of five models were estimated, separating cognitions and physical behavior measures. Descriptions of both model series are provided in Supplementary materials 3. The model for cognitions was best for two classes (BIC = 942.620, entropy = .755). Class counts were 22 for the group with changed cognitions, and 40 for the group with more stable cognitions. The two-class model was predictive for change of fatigue (log odds = 0.322, p = .006) such that the group with greater improved cognitions was related with more reduced fatigue. In Table 3, the class means are provided for all indicators, and Figure 3 shows the standardized profile means of the two-class cognitions model.

Table 3. Descriptives of two-class model for cognitive change.

Latent profile	n (%)	Δ pPAL$_{redact}$ M (SD)	Δ pPAL$_{peer}$ M (SD)	Δ pPAL$_{self}$ M (SD)	Δ SE$_{coping}$ M (SD)	Δ SE$_{planning}$ M (SD)	G^{SOC} M (SD)
High cognitive change (blue)	22 (35.2%)	-6.06 (4.31)	33.90 (18.47)	27.04 (16.77)	28.65 (12.65)	26.33 (9.72)	3.74 (1.71)
Low cognitive change (red)	40 (64.8%)	-1.46 (3.95)	1.857 (18.84)	4.12 (20.77)	2.66 (12.91)	3.56 (18.79)	1.46 (1.88)

Abbreviations. Δ (change score), M (mean), SD (standard deviation), pPAL (perceived physical activity level), SE (self-efficacy), redact (reduced activity, checklist individual strength), SoC (sense of control over fatigue symptoms).

The model for physical behavior change was best for three classes (BIC = 453.553, entropy = 0.831). In Table 4, the class means and variances are provided, and Figure 3 shows the standardized profile means for the three-class physical behavior model. Class counts were 4 for the group with the most extreme change of balance (cyan), 19 for the group with slightly reduced PAL and MVPA (green), and 29 participants for the group with increased PAL and MVPA (black). This three-class latent profile model for physical behavior change was not predictive for change of fatigue (smallest *p*-value = .319), meaning that reductions of fatigue could be established independently of the profiles of physical behavioral change.

Table 4. Descriptives of three-class model for physical behavior change

Latent profile (color in Figure 3)	n (%)	G^{PAL} M (SD)	G^{MVPA} M (SD)	G^{balance} M (SD)
Increased PAL and balance (cyan)	4 (8.3%)	129.969 (65.096)	19.644 (9.862)	1.953 (12.132)
Reduced PAL and MVPA (green)	19 (35.1%)	-30.545 (73.61)	-9.171 (10.20)	3.717 (9.580)
Increased PAL and MVPA (black)	29 (56.6%)	100.246 (297.02)	2.836 (53.62)	20.904 (24.258)

Abbreviations. G^{PAL} (estimated growth of physical activity level), G^{mvpa} (estimated growth of moderate-to-vigorous intensity physical activity), G^{balance} (estimated growth of relative activity decline from morning to afternoon), M (mean), SD (standard deviation).

In the third step, Bayesian contingency tables investigated the interrelatedness of the profiles of cognitive and the physical behavior change measures. Results are provided in Supplementary materials 4. Bayes factor for the dependence of cells was 0.206, meaning that *independence* of the cells was five times more likely compared to dependence of the cells. In other words, cognitions could improve regardless of the type of physical behavior change that was established during the intervention.

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Discussion

Principle findings

This study focused on the working mechanisms of an ambulant activity feedback therapy (AAF) in which an activity coaching system was used to reduce chronic cancer-related fatigue. Unique for this intervention is that it does not only focus on increasing physical activity level (PAL), but also opts to focus on improving daily balance of physical activities. Through the incorporation of behavioral change principles, such as acknowledging stages of change, proper goal setting, and social comparison [6], AAF also intervened on cognitive concepts. This study provided strong support that SoC, perceived physical activity (reduced activity and peer-comparison), and coping self-efficacy, but none of the physical behavior measures were found to be working mechanisms for the AAF.

Surprisingly, on average, all objective physical behavior measures changed in the AAF group and not in both other groups, but changes of none of the measures were related to fatigue change. The personalized nature of the intervention, and accompanying differences in goal settings, resulted in a large variability of objective physical behavior change. In other words, differences between goals distorted the linear dose-response effect that was tested with that correlation. The relative change in physical behavior, opposed to absolute change, for example, or merely being able to achieve certain goals might be better – still objective – predictors of fatigue change. Also, it is still unclear if a dose-response relation existed within the latent groups for which a certain objective physical behavior change was established.

Other interventions have studied the relation between changing physical behavior and reducing cancer-related fatigue. PAL was studied as mediator for fatigue in the context of cognitive behavior therapy [26], but in that study PAL did not increase at all, whereas average PAL in our intervention did increase. PAL was found to mediate the intervention effect on fatigue in exercise therapy [10]. However, participants were not necessarily fatigued, and PAL was assessed with questionnaires in that study, making it appealing to compare their findings with our results on perceived physical activity that *was* found to be a working mechanism.

In another exercise intervention among cancer survivors, MVPA mediated fatigue [27], which contrasts with the current results. Differences in established MVPA change might explain that contrast: In their study, MVPA increased more than in our study (63% compared with 12%), even when considering only the latent group which increased MVPA most (40%). A meta-analysis of exercise interventions for cancer-related fatigue found no effect of exercise type on the effectiveness of those interventions [2], which supports the idea that different objective physical behavior goals can be equally effective in reducing fatigue. However, actual behavioral change was not addressed in that meta-analysis. The effects of

improving balance between morning and afternoon has to the best of our knowledge not yet been studied.

Most cognitive measures were found to be working mechanisms for the AAF, although the strength of the statistical support varied. Similar findings were found previously: reduced fatigue correlated with increase of personal control beliefs (chronic fatigue syndrome) [28], self-efficacy (cancer survivors) [10] during exercise interventions, and with sense of control over symptoms and perceived physical activity (chronic fatigue syndrome) [29] during cognitive behavior therapy.

Interestingly, change in self-compared perceived activity and self-efficacy was also observed in the eMBCT, and change of peer-compared perceived activity was observed in all three interventions although neither eMBCT nor PE explicitly focused on these constructs.

In the post hoc analyses, we tried to 'tame' the variability of change within the AAF by means of capturing coherent growth patterns in latent profiles. The physical behavior change profile model (see Supplementary materials 3) indicates that generally three classes (two substantial classes and one 'waste class') can be distinguished. When focusing on the two larger classes, their profiles seem to reflect the personalized approach. The profiles were not predictive of fatigue change, meaning that equal fatigue change could be established with any of the change profiles. Combining the latent profiles of physical behavior and cognitions showed that cognitive change was established regardless of the physical behavior change that was established. These findings could reflect that setting realistic goals on itself is a key component for successful behavior interventions, of which it is relatively irrelevant what it is as long as they are accomplishable and improve participants SoC or perceived physical activity. Or, when regarding physical behavior change as a catalyst for changing cognitions, different physical behavior change profiles were equally sufficient for establishing cognitive change. It should be noted that the classes in the physical behavior change profiles model were small, and should be interpreted with caution.

Strengths and limitations

Some limitations of the current study should be mentioned. As can be seen in the flow chart, the availability of objective PA data was limited in the eMBCT and PE. Instructions differed between AAF and the two other groups during the intervention: Participants in the AAF wore the system as part of the intervention whereas participants in the eMBCT and PE were asked to wear the system three days per week, in three different weeks without feedback on their physical activity, so did not experience profit from wearing the system. These different instructions could have led to bias: Participants replied that they preferred not to wear the system when they would 'go out' because of esthetic objections, potentially causing an underestimation of physical activity during the intervention but not in the pre

and post assessments. However, the observed means in the appendix provide no support for that assumption. A second limitation is that some adjustments to the prepublicated analysis plan had to be made to answer the research questions at hand. For example, testing sub hypothesis *b*, on the independence of the growth correlations between all three interventions, was – on reconsideration –unsupportive of our research question. Changes to the original analysis plan were explicitly named, so that conclusions can nevertheless be interpreted rightly. Thirdly, the quality of some measurements had not yet been studied, as they were self-conceptualized. The self-compared perceived activity question was not specific and future use of that specific question is not recommended. Assessing perceptions of physical activity explicitly instead of attempting to objectify the PAL with questionnaires has shown to be useful, but further validation of the perceived activity measures is recommended.

Strong points of this study include the use, and appreciation of multiple assessments throughout the intervention, and the use of Bayesian estimation to deal with our small sample size and to produce intuitively interpretable statistic results. The latent profile modeling provided a valuable supportive evaluation of the working mechanisms.

Conclusion

In conclusion, this work presents a thorough study of the working mechanisms of activity coaching for cancer-related fatigue, presents a strong argument for personalized goal setting, and emphasizes the importance of cognitive change for the success of behavioral interventions.

Supplementary materials

https://progress.rrdweb.nl/39/

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Chapter eight
General discussion

Principle findings

In the previous chapters, insights were gained into effectiveness, and working mechanisms of an ambulant activity coaching intervention in reducing chronic cancer-related fatigue (CCRF). This research was performed as part of the FNK ('Fitter na kanker') trial, a three-armed randomized controlled trial that studied two online interventions for CCRF.

To summarize: the baseline data showed different phenotypes of patients among cancer patients with severe fatigue which can be distinguished based on physical activity level, moderate-to-vigorous intensity physical activity (MVPA), and balance. This highlights the need for personalized physical behavior targets (Chapter 4). The intervention, described in Chapter 3, was able to support different types of physical behavior targets, and was found more effective than the active control intervention in which participants received psycho-educational information (relative effect size of 1.18) (Chapter 5). Effects sustained up to a year after inclusion in the trial (Chapter 6). The intervention effects on fatigue were correlated with changed cognitions (perceived physical activity and self-efficacy), but not with change of the objective measures of physical behavior (Chapter 7).

This chapter further elaborates on these results, gives recommendations for improvement of the intervention as well as future research, but also describes some methodological considerations of the performed studies and recommendations for future research.

Ambulant activity feedback therapy

Although consensus exists about the fact that being physically active has benefits for cancer survivors [1], much is currently unknown about the physical activity in relation to CCRF, and current findings are not always in line. One main goal of this thesis was to learn more about the relationship between physical activity and cancer related fatigue by investigating whether cancer survivors who are severely fatigued benefit from an online intervention that uses an innovative activity coach thereby incorporating different physical behavior measures, acknowledge interindividual differences among patients, and studying the cognitive concepts and behavioral change models. This paragraph will reflect on what we learned about these different aspects, and the practical recommendations for improvements of the AAF that can be defined based on this.

Chapter 4 provided insights in the physical behaviors of patients with chronic cancer-related fatigue (CCRF). We showed that three profiles can be distilled: an 'average', 'sedentary', and 'active' profile with respectively 42%, 41%, and 16% of the participants fitting these three profiles. The profiles, distinct strongest on PAL, MVPA, and balance, revealed that the active group was almost twice as active compared with the sedentary group, that even participants in the 'active' group (on average) did not meet physical activity guidelines, and that decline of activity during the day was least in the average group. As the differences between the groups are considerable, it seems that generic goals in terms of increasing physical activity are not appropriate for all patients, or at least benefits are expected to vary.

From this result that different behavioral profiles can be discerned among our patients it becomes clear that during the intervention also different targets would be optimal. From literature different physical behavior targets were found that could be of use for reducing CCRF, and could enable better tailoring of behavioral interventions. These targets concern increasing moderate-to-vigorous intensity physical activity (MVPA), increasing the overall physical activity level (through graded activity or increasing the amount of opportunistic activities, such as taking the stairs instead of the elevator), and better energy conservation. So far the activity sensing tool studied in this thesis was only used to increase the overall level of physical activity. [2]. Starting from the targets defined in the literature the Activity Coach in the FNK project was implemented in such a way that it was able to support multiple target behaviors, e.g. to better divide energy or to temper the activity.

Results of Chapter 7 show that on average the level of MVPA increased with 16% in the AAF group (Chapter 7) but also that it was successful in targeting multiple types of physical behaviors. Some participants showed increased physical activity level whereas others did not. Similarly, some participants improved balance from morning to afternoon, whereas others did not. However as the change of the physical behaviors did not correlate with fatigue or

predicted fatigue change, one should question if it actually matters which of these behaviors is targeted. Another explanation could be that it reflects that not absolute change, which was studied in Chapter 7, but relative change, or other measures that reflect the challenge for the individual, are important for reducing fatigue in this context. Be that as it may, on the group level, AAF was able to reduce fatigue notwithstanding absolute increased physical activity level or time spent in MVPA.

Another important element of the AAF as implemented in this thesis compared to previous use of the Activity Coach in patients suffering from chronic fatigue syndrome [2], is the stronger incorporation of behavioral change models, for instance by implementing its use in a nine-week intervention protocol that was guided by a physiotherapist. Until then, it had only been used parallel to the rehabilitation program, and therapists were not involved. Chapter 7 showed that physical activity related cognitions have a direct relation with fatigue. Sense of control over fatigue symptoms, perceived activity and self-efficacy all improved in the AAF intervention and were related with fatigue reduction, which shows how important these factors were. This results is expected to be attributed to two different main elements of the AAF

1) Feedback

The feedback was assumed to be very effective in targeting cognitions regarding physical activity for a number of reasons: it provides the participant with objective feedback about the physical activity level throughout the day, it endorses previously established behavior change, and reinforces current behavior directly. As assumed, interviews among AAF participants (Bruggeman-Everts et al, *in preparation*) suggest that 'it was comfortable to be guided' and that 'use of the system is reassuring as it provides clear input on what to do to be less fatigued, which helped'.

2) Involvement of therapists

It was suggested that involvement of therapists would encourage participants to comply with the system and that the involvement of psychologists would increase effectiveness as it would take cognitions about physical activity in account [3]. Although physiotherapists, and not psychologists were involved in the AAF, the suggested cognition change took place and showed to have the expected relevance for reducing fatigue (Chapter 7).

Although in the current trial participants were guided by physiotherapists, the flexibility of the system is up to the point that its use might not only fit in the daily practice of physiotherapists, but also in the work of occupational therapists and psychologists, although the following example shows that also energy conservation targets match the comfort zone of physiotherapists. One of the physiotherapists stated: some participants really appreciated

the analogy of over trained athletes; they are not helped with another training program, but need to learn to rest before they can start building things up again.

A logic follow-up question in this context, and a recurring issue in online therapy, is whether a functional therapeutic alliance can be built with online interventions, and if it is necessary to build up a therapeutic alliance [4]. Both questions were addressed in the design of the FNK trial, therefore, therapeutic alliance was assessed multiple times during the intervention. While in the initial weeks of the intervention some participants indicated that it was difficult to answer the questions (Bruggeman-Everts et al, *in preparation*), working alliance in week 4 of the intervention showed to be acceptable in the AAF. Mean working alliance sub scales were above a 'neutral' score of 8/16 for task (mean score of 9.8/16), goal (mean score of 10.35/16), and bond (mean score 11.9/16) sub scales, and weak correlations were found for the task (r = -.325) and goal subscales (r = -.321) with fatigue change. On average, an acceptable therapeutic bond was established, and thus the involvement of the therapist succeeded through online contact, but it did not correlate with fatigue change. The lack of a cross-sectional correlation could indeed indicate such a relationship 'did not matter', or that other factors were more important for fatigue reduction than therapeutic bond, but also that 'dose-response' effects could not be tested within the AAF group as all therapeutic bonds were sufficient for guiding and coaching the participant. The current study is not able to distinct between both explanations.

Recommendation for improvement of the AAF

The AAF has shown to be effective in reducing fatigue: 66% of the participants clinically improved, which means that there might be more to gain. Improvements can be established for different aspects and from different angles. For example, how could the involvement of the therapist's time be further optimized, how could the therapy be better fitted and tailored to individual patients, their starting points, their experience, and what problems need to be covered to aid implementation and adoption? Answers to these questions are clustered into recommendations for the technology (e.g., sensing, reasoning, feedback, and the platform in general) as well as for the intervention protocol.

Technology

Sensing

Participants in the AAF used a hip-worn accelerometer, the size of a cigarette package, to sense the physical activity. Hip-worn accelerometers are known to underestimate bicycling, a common way of transportation and exercise in The Netherlands. Underestimation of this behavior hampers the credibility and usefulness of the system. Different adjustments are prone to fix that issue: on the reasoning perspective by allowing user input on the sensor

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placement or type of activity, which would require validation studies, and clear instructions of the user. From a hardware perspective, the addition of a goniometer, which would require sensor placement on the upper leg such as used in the ActivPal, such as in Chastin *et al.* (2015) [5], would also provide the input that is needed to estimate physical activity more validly for different types of behavior.

Furthermore, when considering the hardware, limitations include different aspects of the sensor (unaesthetic, uncomfortable to wear, falls from the holder, short battery life) that should undoubtedly be fixed in any serious attempt to implement the use of the Activity Coach in daily practice.

Reasoning and feedback

The most visible component of the Activity Coach for patients is the feedback, consisting of a graph and text messages. Three feedback scenario's made sure that the content of the feedback messages would add to the patients physical activity target (Chapter 3). Feedback messages were provided hourly, showing a message that was selected from one of five categories, depending on the current accumulated activity of the patient. When considering the feedback, four major components encompass timing, intention, content, and representation [6], which will be used for discussing the recommendations for the feedback. For each component, the reasoning that is used for improving the component is shortly addressed.

Timing of the feedback messages could be improved by using context information for message selection, such as weather, place, or opportunities provided by the environment, connecting it with a patients digital calendar, and being able to set up feedback-free periods: ad hoc and in advance.

At this point, intent of the feedback messages (e.g. to reward, motivate to become more active, or pull the break) can be adapted with the different feedback scenarios (Chapter 3). The scenarios provide flexibility in delivering appropriate intent of the messages regarding the physical behavior targets. Still, interviews showed us that mismatching content of the feedback messages was a prone limitation of the Activity Coach (Bruggeman-Everts *et al.*, *in preparation*). For example, the system would suggest to a participant to walk stairs, while the participant was physically not able to do so, or the system would suggest to plan a bike ride, when a participant hated cycling. Such mismatch could be easily prevented by incorporating a decision system that can translate preferred and not-preferred physical activities and relaxation activities into messages. One could even think of incorporating an exercise in the intervention protocol that consists of selecting proper and appealing feedback messages during the initial phase of the treatment. Other mismatching, for example, suggesting rest when a participant was not tired at all, should - to my opinion - be overcome by proper education about the theoretical background and intended goals of using the Activity Coach, and providing participants with coping skills to deal with the 'stupidity' of the system.

Furthermore, content of the feedback messages as well as the graphs should be adjusted to make interpretation of physical activity level (in the Activity Coach quantified with counts per minute, CPM) easier, to make a more direct and practical link between CPM values and actual activity suggestions.

Representation could play a role in translating the use of the system to every-day life. Participants stated that the social environment had internalized the feedback, so would help or remind the patient to perform the new behavior. Such a social aspect could be further utilized by adjusting the representation of the feedback messages so that certain feedback messages are provided by the participant's social environment. This would require as little as a photo of that person and linking it to a message that would likely come from that person: Imagine a message from your spouse or roommate asking to do the groceries at a moment at which the system would normally motivate you to be more active, or the therapist suggesting to take a rest at certain moments.

Platform

The AAF as is, provides the history of the physical activity level and balance of patients at a Web-portal, however it was seldom used by patients. Therapists used it to set the reference line and to review the physical activity of patients. Integrating the Web-portal to a Mobile web app, or using responsive web design, thereby integrating the information that is provided on the mobile application and the Web-portal, would be a great opportunity for this intervention.

Firstly, the information of and communication with the participant and uses of the technology should be incorporated on such a platform to ensure a structured but comprehensive overview of the patient, the patient's profile, and current status. Such an overview, and especially the patient profile, would reduce many of the issues that are associated with having to rely on online contact: such an overview should provide at least photos of both the therapist and the patient, as effective learning requires not only words, but preferably the use of different modalities: faces will and a short profile will contribute to that learning process.

Also the implementation of psycho-educational information throughout the intervention could be enhanced on such a platform, as up to now that was performed by manually adding a *pdf* file as attachment to an e-mail. The availability of standard texts should be expanded and compiling standard or previously used texts should be easy and could be optimized by incorporating a certain degree of automatization. One could also consider the possibility for therapists to mark and code text from the patients, a functionality that quickly provides overviews on certain themes, so that the therapist can easily look up, and target these themes effectively in their communication with the patient. These adaptations would reduce the time a therapist needs for each consult. Similarly, the use of automatized physical

activity recommendations, yet without the intermediation of a therapist, is currently being tested in cancer patients (OncoActive+ project, registered at The Netherlands Trial registry: NTR4296). To improve automatization processes, it should at least be examined what were key tasks, what were repetitive and time consuming tasks, and what tasks were experienced as personal or bonding.

Intervention protocol

A frequently heard comment was that therapists sometimes would preferred to have one face-to-face session in the initial phase of the intervention. Although this comment partially weakened by habituation, it reflects some serious issues that can be easily addressed. Incorporating a face-to-face contact would enhance getting to know each other, make it easier for therapists to remember the patient and to switch between patients, to enhance and speed up goal setting, and to allow physiological testing in patients. In many cases, a phone call (as is) or the incorporation of video contact would be sufficient. One face-to-face session could be a valuable *option* in case physiological testing is crucial. This is not necessarily done by the online therapist, and could be a colleague in a more convenience practice for the patient. However, in many cases adjustments to the platform could dissolve the issues at hand.

Methodological considerations

Within the following paragraph, the different methodological considerations of this thesis will be discussed. First, we focus on the sample, its selection and size, and potential bias that might occur from it. Second, we focus on quality of measures that were used. Third, we focus on trial design, and how methodological choices might have influenced the course and results from this trial.

Sample selection

The FNK trial studied two Internet interventions for cancer-related fatigue: the ambulant activity feedback intervention as well as a mindfulness-based cognitive intervention. As we wanted participants to start the intervention relatively open-minded, we did not provide them with specific information about the intervention, and limited it to: 'web-based, directed at cancer-related fatigue, guided by a psychotherapist or physiotherapist'. The name of this trial (in Dutch "Fitter na kanker"), translated 'More vigorous after cancer' or 'Fitter after cancer', was – among others – picked to prevent from attracting participants that are generally participating in mindfulness studies: highly educated female baby boomers [7–9]. Unfortunately, our sample was not younger than the mentioned samples (on average 55.1 years old) and still primarily female (72%) (Chapter 5). With breast cancer being the most prevalent cancer type among females in the Netherlands, having a relatively good and still

improving prognosis [10], breast cancer survivors inevitably yields a prominent group among cancer survivors. However, the fact that, again, this is the group that participate for intervention could reflect an external validation that they actually represent a prominent part of the clinical sample that needs and applies for help.

Our recruitment did not result in the expected 254 participants that were anticipated for this trial despite great effort with online and offline advertising and the use of social media (Chapter 5). Most effective was a paid advertisement in a national newspaper. Fortunately, the use of Bayesian estimation allowed us to answer most questions anyhow, as was explained in Chapter 6. In that chapter, the use of Bayesian statistics allowed us to model mental health with a more complex model that suited the data better compared to the less complex model.

A noteworthy sample characteristic is the inclusion of participants with comorbid conditions. Although the participant's physician confirmed that a participant likely suffered from cancer-related fatigue, participants with all types of conditions were allowed to participate in the trial. Including participants who suffer from comorbidities brings 'noise' to the data that is difficult to separate and might have biased or covered effects in Chapter 7. For example, a study in lymphoma survivors showed that having more comorbid conditions was associated with long lasting fatigue [11]. At the same time, such selection is a strength of this study as it assures clinically relevant results of our trial. The psycho-educational control group provided a strong control mechanism for spontaneous recovery of any kind that is non-specific for the experimental interventions at hand.

Quality of measurements

Questionnaires

The measure that we used most during the FNK trial was the Checklist Individual Strength. Its first use during the trial was for selecting participants; only those with CIS-fatigue severity scores of 35 and higher were included. Implementing this criterion resulted in 48 rejections (Chapter 5), of whom we occasionally received reactions – in the range from disappointed to angry – that participants were *still* extremely fatigued, but that the scale failed to address the erratic character of the fatigue. Assumedly, some patients tended to average out the severity of fatigue throughout the week, where others would focus more on the sharp edges or extreme periods of fatigue. The Brief Fatigue Inventory has the advantage of giving more attention to the erratic nature of cancer-related fatigue, it assesses the current, usual, and worst fatigue in the past 24 hours [12]. Multidimensional fatigue measures provide a detailed assessment of fatigue, and help in identifying underlying mechanisms [13], but its erratic character should not be ignored.

Physical behavior measures

Other measures that have a prominent role in this thesis are the objective physical behavior measures. Although thorough discussion of the data reduction (e.g. data screening, the selection and use of cut-off values for intensity and time, the definition of minimally valid wear time), parameter selection, and analysis really deserves an entire thesis, two of the matters will addressed here: cut-off values for different intensities.

In the processing of the accelerometer data, a continuous measurement of acceleration was reduced to different physical behavior measures. We specified cut-off values for sedentary behavior and moderate relative to light intensive physical activity. Such a distinction in intensities is very useful as opposed to evaluating a general daily level of acceleration: different health aspects are related with the behaviors that are tried to be captured with the distinction [14]. Although it is very common practice to make such a distinction on accelerometer data only [15], it brings about a number of difficulties that are easily overlooked.

Providing a short background, we collected physical behavior data with an accelerometer, which produces a measure of acceleration in three directions that, by integration, can be processed to an average acceleration (mm/s^2) during a certain amount of time, in our case and many others [15], minutes.

The first difficulty is to categorize full minutes of constant behavior correctly among different settings and participants. We wanted to distinct MVPA from light physical activity by using the normal distribution of walking at a speed of 6 kilometers per hour (kmph), brisk walking, generally referred to as MVPA (Supplementary materials from (Ainsworth et al., 2011, [16], http://links.lww.com/MSS/A82). However, when using the mean (2418 ± 275 counts per minute (CPM), n = 10) [17] or negative z-scores of that distribution as the cut-off score, still large proportions of the distributions of walking at a comfortable speed and active office tasks [18] would mistakenly be considered as MVPA too.

Secondly, real-life behavior does not take place in the homogenous one-minute intervals that are typically used for validation of the cut-off values. Although sedentary behavior can be distinct with 96.43% specificity and sensitivity from non-sedentary tasks [18], this only holds for full minutes of equal behaviors: lab minutes. In real life, different types of behaviors occur within one minute. As active seconds have a relative heavier burden on the activity count of a certain minute compared to sedentary seconds, a proper definition of a sedentary minute requires specific attention. For giving a general overview of ones day with such a limitation is not problematic, but focusing on bout durations is much more sensitive for this issue.

Trial design

The FNK trial has some notable features that I would like to reiterate here. The three-armed design provided a neat control for taking action on fatigue, receiving psycho-educational information on fatigue, being involved in a randomized controlled trial (RCT) and self-evaluation during the assessments of the RCT. Also, it allowed us to study the specificity of working mechanisms.

Another significant feature of this trial was the repeated assessment of working mechanisms and outcomes during the course of the intervention. It showed us that the initial phase had the most prominent fatigue reduction (Chapter 5), and allowed us to estimate trajectories in which missing data – a recurring problem in longitudinal research – was elegantly handled.

Notable is also the limited standardization of the AAF intervention. Benefits of this approach are that it allowed therapists flexibility and comfort in performing their profession (even though they were explicitly *not* providing participants with evidence-based therapy), allowed for personalization and creative use of the Activity Coach, assured a realistic treatment that would agree with clinical practice. However, a severe side-effect of the degrees of freedom that were provided to therapists during the AAF intervention is that it harms the replicability of this work. This underlines the need to find out for who, and in which circumstances the intervention did and did *not* match or was helping for participants. Such evaluation could include a detailed comparison of the group of 33% in which fatigue was unchanged after six months (Chapter 5) compared to those who did, or the latent group of 63% of the participants who had not changed cognitions during the intervention (Chapter 7) with those who had.

Non-quantified aspects

The current research would not been as it is without contact with the participants. 'Short lines' through e-mail and telephone, and open end questions at the end of each questionnaire actually showed us how much we did *not* know of the participants despite extensive questionnaires. Luckily, the qualitative study (Bruggeman-Everts, no date b) elucidated on the experience of the participants. Therefore it is recommended that – not only in pilot studies but also in larger evaluations – participants should be able to speak their mind, and that it is clear where to leave general comments. And for experiments in an earlier stage, experience sampling techniques directed at the experience of the intervention, instead of emotions or cognitions, would help to better understand what components of the intervention work and do not work, and provide more – time and place specific – insights on what patients need.

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Implications for clinical practice

AAF has shown to be sustainably effective in the FNK trial. Although the practical relevance was generally acceptable due to a realistic sample selection, the current implementation is quite different from anticipated clinical practice: participants were randomly assigned to the intervention, technical support was provided by researchers (who were very eager to establish good research compliance), planning and intake were partially prescribed by the trial, and patients were requested to fill in multiple assessments during the trial. What are - notwithstanding the differences - the implications of this study and the other findings for clinical practice?

The finding that physical behavior profiles at baseline differed so much (Chapter 4) should attend health care professionals (e.g. behavior therapists, physiotherapists and rehabilitation physicians) that one size does not fit all: even highly active patients can be severely fatigued, and exercising will likely not benefit.

The finding that physical behavior change profiles were unrelated with fatigue change during the intervention (Chapter 7) shows that there are different ways to establish reduced fatigue by means of behavior change interventions; different physical behavioral goals can provide equal benefits for reducing fatigue. That means that goals could be selected by focusing on the patient preferences, and opportunities. For example, for patients with aversion for exercise, the intervention can (initially) focus on increasing opportunistic activity and improving balance.

The differences in focus and working mechanisms of both interventions studied in the FNK trial make that both interventions could supplement each other in the care for patients suffering from CCRF. For example, Chapter 6 indicated that in AAF reduced fatigue was accompanied with reduced negative affect, whereas in eMBCT with increased positive affect. Referral could take into account the individual state of affect, which might increase a broader sense of effectiveness and provide better match for the patient. Interviews with participants indicated that, although a participant was generally helped with the AAF, the participant was left with an explicit desire for psychological help of which he was unaware before starting the AAF intervention (Bruggeman-Everts *et al., in preparation*).

Compared to currently available treatments, particularly intramural treatments, it is a great advantage that the intervention is offered as part of primary care, implying accessible care that corresponds with current trends toward self-management. Already now, individuals can get a grip on their physical activity level, and how that is divided throughout the day by using the accelerometer of their smartphone, or consumer accelerometer with standard protocols.

Recommendations for further research

Typically, the thesis at hand presented more questions than it answered. The following paragraph is aimed at recapitulating key questions and recommendations for further research.

One recommendation considers the question 'what works for whom'. A first step has been made in one paper that considered working mechanism of online mindfulness-based cognitive therapy in the FNK trial (Bruggeman-Everts *et al.*, *in preparation*). Creating multivariate profiles of baseline characteristics that are predictive of relative outcome between the interventions would likely contribute to better understanding of the interventions, and improve referral of patients to matching interventions.

Additionally, further research into behavioral interventions for CCRF should acknowledge the heterogeneity of the patient population. Patient profiling is currently already used for prognostic research, but likewise, establishing evidence base for interventions in a heterogeneous group would benefit from patient profiling. It makes sense to find or define subpopulations that are more homogenous and are therefore more likely to benefit similarly from comparable treatment strategies when studying such strategies. Currently, patient profiling is mostly done by means of regression models. Although regression models provide structured means for predictive modeling, it is often used for direct testing of predictive value of one or more hypothesized factors. More complex processes such as interaction effects among the variables are generally ignored due to a lack of statistical power. Mixture modeling, 'the art of unscrambling eggs' [19], - such as latent profile analysis that was used in Chapters 4 and 7 - provide a different, more wide-angle tool to study latent categories among patients. The availability of tools (not only those in our shed) influence the way in which we can formulate questions and think about problems. As such, mixture modelling could provide a promising supplement to statistical toolboxes in research fields that have to deal with heterogeneous patient populations, such as persons suffering from CCRF.

Vice versa, our questions on the development of physical behavior in relation to that of fatigue, enhanced by the availability of intensive longitudinal data such as the physical behavior data in the FNK trial, urges for suitable statistical tools. In the FNK trial, we tried to reduce the physical behavior data to point estimates with negligible duration, fixed at a certain time point (within and between participants) so that we could estimate its dynamics. This reduction relied on assumptions that did not hold in our study, for example when interventions delayed). Curbing or taming such data fails the complexity and richness of the data at hand. By using a standardization of time, we 'fixed' this, acting in moderation, but actually, entirely different techniques suit the data at hand and our questions better: continuous-time or dynamic models that facilitate the analysis of intensive longitudinal data [20]. Such analysis is not yet possible, yet will provide tools to answer our questions on the

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dynamics of constructs by actually capturing the dynamics directly. The availability of these types of analyses would bring the research of physical behavior to a whole new level as data reduction procedures would become simpler, capturing the dynamics of physical activity in latent constructs, thereby acknowledging measurement error, variance between days (week vs weekend days), and during the day.

Finally, with the knowledge that was gained in the FNK project and more specifically in this thesis, I would gladly recommend to implement a version of this intervention with – at least – less obstructive hardware, improved visualizations of the feedback on one's personal smartphone, more flexible message selection, and reduced burden from the assessments that came with participating in the current comprehensive RCT. Less intrusive assessment of effectiveness would be recommended, for example by implementing it in the smartphone application. Explicitly no RCT is recommended for such research, as it is too ponderous of a method for studying technologies that change so quickly. However, when using Bayesian analysis, the results from the FNK trial could be included as prior information so that knowledge can be updated and accumulated, instead of gathered.

Concluding remarks

This thesis presented an effective intervention for reducing fatigue sustainably (Chapters 3, 5, and 6), that acknowledges different physical behavior patient profiles (Chapters 3 and 4) on which we were able to highlight working mechanisms (Chapter 7) and made suggestions for improvements for implementation and future studies (current chapter).

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Appendices

Summary

Fatigue is a common and distressing long-term consequence of cancer. Cancer-related fatigue affects work ability, hampers in maintaining social relations, and impacts patients' well-being. If fatigue continues three months after treatment, it is unlikely to decrease of its own accord; in this thesis we will mention that as 'chronic cancer-related fatigue' (CCRF). Given the growing incidence of cancer and improving associated life expectancy, there is a strong need for effective and accessible treatments.

Most treatments for CCRF focus to some extend on changing physical behavior, but there is a large variability in the way they do this. We see a focus on fitness related activities and exercise interventions, graded activity, or energy conservation; that is, different dimensions of physical behavior are targeted in order to reduce fatigue (**Chapter 1**). This thesis focuses on an online intervention that targets physical behavior by using an ambulant activity coach.

The chapters of this thesis gradually provide insight in physical behaviors of this patient group as well as in, the effectiveness and working mechanisms of the ambulant activity feedback intervention (AAF) for reducing CCRF. Chapters 2 and 3 introduce the trial in which all studies of this thesis are performed and development and rationale of the AAF intervention. Subsequently, four chapters describe studies into differences among patients that suffer from CCRF (Chapter 4), the effectiveness (Chapters 5 and 6), and working mechanisms of the AAF intervention (Chapter 7). Chapter 8 completes this thesis with a general discussion.

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All studies are performed within the FNK ('Fitter na kanker') trial, for which **Chapter 2** provides a detailed research design and analysis plan. The FNK trial was set up to study two Internet interventions aimed at reducing CCRF: an ambulant activity feedback therapy (AAF) supervised by physiotherapist using e-mail and a mindfulness-based cognitive therapy supervised online by a psychologist (eMBCT). In the control condition, participants received psycho-educational information. This three-armed randomized controlled trial was proposed to (1) investigate the effectiveness, (2) investigate potential mediators of the interventions, and (3) study what intervention works best for whom. The analysis plan entails the use of longitudinal structural equation models that focus specifically on change throughout time and in which missing data is handled elegantly.

Chapter 3 describes the AAF, both its rationale and the technology. As part of the AAF, participants use an ambulant activity coach. That is a system that consists of a sensor that measures physical behavior and a smartphone that processes, shows, and provides feedback on the level of physical activity and how it is accumulated throughout the day. Previous research had shown that patients who suffer from chronic fatigue syndrome were able to behave towards visually presented physical activity goals when using such an ambulant activity coach as a standalone tool parallel to cognitive behavior therapy. In this thesis the AAF was further developed by integrating the ambulant activity coach in a 9 weeks physiotherapist-guided intervention for CCRF patients so that behavioral change processes could be supported by a health professional.

To gain insight in the starting point of the patients, in **Chapter 4** a study of the baseline accelerometer data is presented. This study focused on nine accelerometer-derived measures of physical behavior, and was performed to gain more insight in the heterogeneous character of this patient group. Results show that by means of latent class analysis, three physical behavior profiles could be distilled that were best distinguished by overall level of physical activity (PAL), and time spent in moderate-to-vigorous intensity physical activity (MVPA). The most active group was the smallest group (16% of the sample), of which on average 28% of the waking day was spent on MVPA. The 'average' group consisted of 42% of the sample, spent 13% of the waking time on MVPA and spent 276 minutes per day in sedentary behavior of bouts of 30 minutes and longer. This group had the lowest decline of physical activity from the morning to the afternoon. The least active group spent less than 1% of the waking day in MVPA, and spent 391 minutes per day sedentary in bouts of 30 minutes and longer. The results indicate that individual differences in physical behavior among CCRF patients are so large that it might be expected that different patients need substantially different treatment goals

Chapters five and six report on the effectiveness of the interventions that were tested in the FNK trial. The results show that – on average – fatigue in both experimental groups

reduced during the first six months and remained reduced up to a year after randomization. Respectively, 66% of all participants in the AAF and 49% of all participants in eMBCT reported a clinically significant improvement of fatigue, compared to – on average – no change of fatigue in the minimal intervention control group, in which still 12% of the participants improved clinically significant in terms of fatigue. It should be noted that individual differences were large, meaning that the interventions were not (equally) effective for all participants.

The second outcome was mental health, for which we used the 'Hospital Anxiety and Depression Scale' and the 'Positive and Negative Affect Schedules'. The average trajectories of the experimental groups were not statistically different from those of the control group, meaning that the experimental interventions were not better in improving mental health than the psycho-educational intervention. However, the correlates of fatigue change differed between both experimental interventions: decreased fatigue was associated with decreased negative affect in the AAF, whereas in the eMBCT decreased fatigue was associated with positive affect. This suggests that both experimental interventions could offer supplementary benefits for patients suffering from CCRF.

The third outcome of this trial was perceived work ability, measured with the Work Ability Index. Average perceived work ability was very low at baseline (3.2. out of 10), increased similarly in all three groups during the first semester, and was stable in both experimental groups during the second semester. This suggests that both experimental interventions were not superior in improving perceived work ability compared to the psycho-educational intervention.

A study on the working mechanisms of the AAF is presented in **Chapter 7**. This chapter focuses on factors that were expected to be specific working mechanisms for the AAF intervention. We studied three of the physical behavior measures that were also studied in Chapter 4 (PAL, MVPA, and decline of PAL from morning to afternoon), and cognitive measures (sense of control over fatigue (SoC), self-efficacy, and perceived physical activity).

Considering the cognitive measures, this study provided strong support that SoC, perceived physical activity (reduced activity and peer-comparison), and coping self-efficacy were working mechanisms for the AAF. Post-hoc 'latent profiles' of all participants in the AAF intervention revealed that participants either improved, or barely improved on any of the cognitive measures. The group that improved more showed greater reductions of fatigue than the group that had barely improved on these measures.

The physical behavior measures – on average – all changed significantly in the AAF group and not in both other groups, but changes of none of the measures were related to fatigue change. Probably, differences between goals due to the personalized approach distorted

the linear dose-response effect that was tested with the correlational analysis. Post-hoc 'latent profiles' analyses of participants in the AAF intervention revealed that generally three types of behavioral change took place. These profiles were not predictive of fatigue change, meaning that equal fatigue change was established with any of the change profiles.

Typically, this thesis presented more new questions than it answered. Luckily, we can now conclude that indeed AAF is a promising intervention for reducing CCRF. Also, our hypotheses on the cognitive factors as working mechanisms are largely confirmed, and are in line with current literature on that subject. However, new questions about the role of physical behavior have emerged as change in the individual physical behavior measures were not related with fatigue change. **Chapter 8** further elaborates on the results that are presented in the previous chapters and gives recommendations for improvement of the intervention as well as future research.

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Samenvatting

Vermoeidheid is een veelvoorkomende klacht bij mensen die kanker hebben. Ook als alle behandelingen zijn afgerond kan vermoeidheid nog jaren een hardnekkige klacht blijven. Vermoeidheid na kanker is heel beperkend voor het dagelijkse leven op gebieden zoals werk en relaties met anderen. Als de vermoeidheid langer dan drie maanden voortduurt, neemt deze zelden vanzelf weer af. In dit proefschrift wordt het in dat geval chronische vermoeidheid na kanker genoemd. Gezien de groeiende incidentie voor kanker en een toegenomen levensverwachting is er een sterke behoefte aan effectieve en toegankelijke behandelingen van chronische vermoeidheid na kanker.

In veel van de behandelingen van vermoeidheid wordt op een of andere manier op fysieke activiteit of fitheid geïntervenieerd, maar opvallend is dat de manier waarop men dit doet sterk varieert. Zo zijn er behandelingen die leren om energie anders te verdelen, die helpen gedoseerd fysieke activiteit op te bouwen, of die zich richten op kracht- of conditietraining.

Dit proefschrift richt zich op een online behandeling voor chronische vermoeidheid na kanker die inspeelt op fysieke activiteit door gebruik te maken van een bewegingsmeter. De hoofdstukken van dit proefschrift geven geleidelijk inzicht in het potentieel, de effectiviteit en werkingsmechanismen van deze activiteiteninterventie. In Hoofdstuk 2 en 3 worden het Fitter na kanker onderzoek en de interventie beschreven, waarna in vier deelstudies de verschillen tussen patiënten op het gebied van fysieke activiteit worden onderzocht (Hoofdstuk 4) en de effecten (Hoofdstuk 5 en 6) en werkingsmechanismen (Hoofdstuk 7) van de activiteiteninterventie. In Hoofdstuk 8 wordt dit proefschrift met een algemene discussie afgerond.

Alle studies zijn uitgevoerd als onderdeel van het Fitter na kanker onderzoek. In **Hoofdstuk 2** wordt een gedetailleerd ontwerp en analyseplan voor het onderzoek 'Fitter na kanker' gepresenteerd. Twee experimentele interventies worden vergeleken met een controlegroep: een interventie die gebruik maakt van een bewegingsmeter (ambulante activiteitenfeedback-therapie, AAF) waarin deelnemers online worden begeleid door een fysiotherapeut en een online 'mindfulness-based' cognitieve gedragstherapie waarin deelnemers online worden begeleid door een psycholoog (eMBCT). In de controlegroep krijgen deelnemers enkel psycho-educatieve informatie over chronische vermoeidheid na kanker. In **Hoofdstuk 2** wordt beschreven hoe de effectiviteit kan worden onderzocht en hoe we meer te weten kunnen komen over de werkingsmechanismen ervan. Daarbij wordt gebruik gemaakt van longitudinale '*structural equation*' modellen die specifiek focussen op verandering in de tijd en waarbij de impact van missende data minimaal is.

In **Hoofdstuk 3** wordt de activiteitenfeedback-therapie, AAF, omschreven. Centraal in de interventie staat de bewegingsmeter, een systeem dat bestaat uit een versnellingsmeter

die op de heup wordt gedragen en een smartphone waarmee feedback wordt gegeven over hoeveel iemand heeft bewogen en hoe dat is opgebouwd gedurende de dag. In dit onderzoek is deze toepassing verder ontwikkeld tot een interventie waarbij de fysiotherapeut via e-mail de patiënt volgens een negen weken-durend protocol begeleidt door het ondersteunen van duurzame gedragsverandering, het formuleren van doelstellingen en het therapeutisch proces in het algemeen.

Om beter inzicht te krijgen in het fysieke activiteitengedrag van de onderzoekspopulatie voor aanvang van de behandeling wordt in **Hoofdstuk 4** een studie beschreven van de baseline-data die voornamelijk gericht was op de verschillen tussen deelnemers. Door middel van een 'latent class' analyse zijn op basis van negen potentieel relevante beweegmaten subtypen van patiënten onderscheiden. Het resultaat van deze analyse is een onderverdeling in drie groepen: (1) een kleine groep (16% van de deelnemers) die het meest actief is, 28% van de dag besteedt aan matig intensieve activiteit, (2) een 'gemiddelde' groep (42% van de deelnemers), die gemiddeld 13% van de tijd matig intensief actief is en die gemiddeld 276 minuten per dag zittend doorbrengt in 'blokken' van een half uur of langer, en het laagste verval van activiteit hebben van de ochtend naar de middag, en (3), de minst actieve groep (41% van de deelnemers), is gemiddeld minder dan 1% van de tijd matig intensief actief en zit gemiddeld 391 minuten per dag in 'blokken' van een half uur of langer. Deze onderverdeling laat zien dat de verschillen tussen patiënten zodanig groot zijn dat optimale beweegdoelen waarschijnlijk substantieel verschillen binnen deze groep.

Hoofdstuk 5 en 6 rapporteren over de effectiviteit van de interventies. De resultaten laten zien dat – gemiddeld genomen – de vermoeidheid in beide experimentele groepen afnam gedurende de eerste zes maanden en daarna gelijk bleef: 66% van de deelnemers in de AAF en 49% in eMBCT liet een klinisch significante afname zien van vermoeidheid. Daarentegen was er – gemiddeld genomen – geen vermindering van vermoeidheid te zien in de controlegroep, bij 12% was de vermoeidheid klinisch significant afgenomen. Het is belangrijk om op te merken dat individuele verschillen groot waren: niet iedereen had evenveel baat bij de interventies en niet iedereen bleef gedurende het tweede semester 'constant'.

De tweede effectiviteitsmaat betrof mentale gezondheid, daarvoor werden de 'Hospital Anxiety and Depression Scale' en de 'Postive and Negative Affect Schedules' gebruikt. De experimentele interventies bleken niet beter in het verbeteren van mentale gezondheid dan de controle-interventie. Opvallend was wel dat afnemende vermoeidheid bij de AAF gepaard ging met afnemend *negatief* affect (dus vermindering van negatieve emoties en gevoelens), en dat afgenomen vermoeidheid bij de eMBCT gepaard ging met toenemend *positief* affect. Dit duidt erop dat de interventies van aanvullende waarde zouden kunnen zijn, dit is echter niet onderzocht.

De derde effectiviteitsmaat betrof het 'ervaren werkvermogen' van de deelnemers. Deelnemers werden gevraagd op een schaal van 0 tot 10 hun werkvermogen in te schatten ten opzichte van hun beste werkvermogen in hun leven (score 10). Een score van 0 stond voor 'niet in staat om te werken'. Het ervaren werkvermogen was erg laag tijdens de baseline-meting (deelnemers gaven gemiddeld een rapportcijfer van 1.2) en nam gedurende de interventie bij alle drie de groepen vergelijkbaar toe, dus hier waren de experimentele interventies niet beter dan de psycho-educatie die werd gegeven in de controlegroep.

In de laatste studie (**Hoofdstuk 7**) werd onderzocht welke factoren gerelateerd waren aan verandering van vermoeidheid binnen de AAF interventie. Zowel beweegmaten als cognitieve maten zijn onderzocht. Uit deze studie bleek dat van de cognitieve maten een toegenomen 'sense of control', activiteitsperceptie en 'coping self-efficacy' werkingsmechanismen waren voor de AAF. Een post-hoc 'latent class' analyse liet zien dat er grofweg twee groepen konden worden onderscheiden: deelnemers die wel of geen veranderde cognities hadden. Dit onderscheid hing samen met meer of minder verandering van vermoeidheid.

Zoals verwacht verbeterden alle drie de beweegmaten in de AAF meer dan in beide andere interventies. Geen van die beweegmaten kon echter worden aangemerkt als werkingsmechanisme omdat meer verbetering op de afzonderlijke beweegmaten niet gecorreleerd was met sterker verminderde vermoeidheid. Post-hoc 'latent class' analyse van de beweegmaten liet zien dat deelnemers op verschillende manieren veranderd waren gedurende de AAF interventie. De resultaten duidden erop dat afname van vermoeidheid met verschillende soorten gedragsveranderingen werd bereikt.

Al met al heeft dit proefschrift ten minste evenveel nieuwe vragen opgeroepen als dat het heeft beantwoord. We kunnen concluderen dat de AAF daadwerkelijk een beloftevolle interventie is voor het verminderen van chronische vermoeidheid na kanker. Ook onze verwachtingen wat betreft de cognitieve werkingsmechanismen bleken grotendeels te kloppen en aan te sluiten bij de bestaande literatuur. De rol van fysieke gedragsverandering in het verminderen van vermoeidheid na kanker is nog onduidelijk, mede doordat er grote verschillen tussen deelnemers waren en doordat er werd ingezet op verschillende pijlers van fysieke activiteit. Ten slotte geeft **Hoofdstuk 8** aanbevelingen voor verbetering van de interventie en toekomstig onderzoek.

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[1] Dit was tijdens een congrespresentatie van hoofdstuk 4 uit dit boekje, imitaties op aanvraag.

About the author

Marije Wolvers was born in 1987 in Leiderdorp, The Netherlands. She was raised in Hoogmade and received her high school diploma in 2005 at the Bonaventuracollege in Leiden. That summer she started the bachelor Human Movement Sciences at VU University in Amsterdam. Her Bachelor's research project titled "Reliability and validity of the extended wheelchair circuit" was performed at Rehabilitation centre Reade, Amsterdam. Immediately after, she continued the Master's programme, rehabilitation track. Her research intership titled "The influence of seat position on efficiency, effectiveness and push characteristics of level and uphill wheelchair propulsion" was performed at the spinal cord injury research centre ICORD of the University of British Columbia.

In 2012, Miriam Vollenbroek appointed her as PhD student at Roessingh Research and Development (Enschede) on the project 'Fitter na kanker' funded by Alpe d'HuZes/KWF. She worked in close collaboration with Fieke Bruggeman-Everts and Marije van der Lee at the Helen Dowling Institute (Bilthoven), and was welcomed by the group of Rens van de Schoot (Utrecht University) to improve her statistical and methodological skills.

Starting February 2017, she holds a post-doctoral position at the Coronel Institute of Occupational Health at the Academic Medical Center (AMC) in Amsterdam at another Alpe d'HuZes/KWF-funded project on return to work. Additionally, she contributes to the development of a physical activity module of a mobile app (Tired of Cancer).

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Wolvers MDJ, Bruggeman-Everts FZ, Van der Lee ML, Van de Schoot R, Vollenbroek-Hutten MMR. Effectiveness, mediators, and effect predictors of Internet interventions for chronic cancer-related fatigue: The design and an analysis plan of a 3-armed randomized controlled trial. JMIR Res Protoc, 2015;4(2):e77.

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Progress range

De following publications have been published in the 'Progress in rehabilitation science' range by Roessingh Research and Development, Enschede, the Netherlands. Copies can be ordered, when available, via info@rrd.nl.

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