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A randomized controlled intervention trial to study the effect of a personalized lifestyle program on cancer-related fatigue among colorectal cancer survivors: protocol for the SoFiT study

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Abbreviations:

SoFiT - **S**tudy **o**n **F**atigue: a lifestyle **in**t**e**rvention among colorectal cancer survivors

WCRF/AICR - World Cancer Research Fund/American Institute for Cancer Research

PLCRC - Prospective National Colorectal Cancer cohort

BMI – body mass index

SMART - Specific, Measurable, Achievable, Relevant, and Time-Bound

FACIT - Functional Assessment of Chronic Illness Therapy

FFQ – Food Frequency Questionnaire

SQUASH - Short QUestionnaire to ASsess Health-enhancing physical activity

PSQI - Pittsburgh Sleep Quality Index

FACT-C questionnaire - Functional Assessment of Cancer Therapy – Colorectal questionnaire

PHQ - Patient Healthcare Questionnaire

GAD questionnaire - Generalized Anxiety Disorder questionnaire

ANCOVA – Analysis of Covariance

CT – Computed Tomography

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Abstract

Observational studies suggest that a healthy diet in combination with ample physical activity is associated with a lower prevalence of cancer-related fatigue. The SoFiT trial (SoFiT: Study on Fatigue: a lifestyle intervention among colorectal cancer survivors) will assess the effect of a personalized lifestyle program on cancer-related fatigue in a randomised study.

We designed a program that aims to increase adherence to lifestyle recommendations on diet and physical activity. The program was person-centred with regards to the lifestyle and personal characteristics of participants, to the determinants of behaviour of that participant, and to the preference, opportunities, and barriers of the participant.

The effect of the program was tested in the SoFiT trial: a two-armed, parallel, randomized controlled trial among adult stage I-III colorectal cancer survivors, who experience cancer-related fatigue after treatment completion; intended sample size n=184. Participants randomized to the intervention group received the personalized lifestyle program. During six months, participants in the intervention group had individual sessions with a lifestyle coach of which four sessions were face-to-face and eight sessions were remote. After six months, participants randomized to the control group had access to two lifestyle coaching sessions and to the same materials that the intervention group also received.

The primary endpoint of the trial is cancer-related fatigue. Secondary endpoints are: sleep quality and duration, health-related quality of life, physical performance, depression and anxiety, skeletal muscle echo intensity and cross-sectional area, and gut microbiota composition.

This trial will show the effects of a personalized lifestyle program on cancer-related fatigue, and on an extensive set of secondary outcomes.

Keywords: behaviour change; multimodal intervention; nutrition; tailoring

BACKGROUND

Cancer-related fatigue has a major impact on psychological well-being, social relationships, work, and health-related quality of life[1; 2] of colorectal cancer survivors. The prevalence of cancer-related fatigue among colorectal cancer survivors varies across studies from 40-70% in the first five years after diagnosis [3; 4].

Observational data suggest that colorectal cancer patients with a healthy lifestyle experience less cancer-related fatigue after completion of treatment [1; 5; 6; 7], where a healthy lifestyle is defined as consuming a healthy diet and/or being physically active. Results of intervention studies conducted among colorectal cancer survivors who completed treatment are not consistent but suggest potential beneficial effects of exercise programs on cancer-related fatigue[8], only few intervention studies assessed whether healthy diet can affect cancer-related fatigue[9]. Interventions in which diet and physical activity or exercise are combined are even sparser: we identified one large and two smaller studies in specifically colorectal cancer survivors [10; 11; 12]. The larger study was a telephone-delivered multiple health behaviour change intervention ('CanChange') among 410 colorectal cancer survivors diagnosed within the previous 12 months [11]. CanChange showed that the six-month intervention was effective in improving physical activity and dietary habits. An effect on cancer-related fatigue was not observed, likely because participants of that study were not selected based on experiencing cancer-related fatigue and therefore did not or hardly experienced cancer-related fatigue.

The two smaller studies were both 12-week pilot/feasibility studies. The first study with 18 participants concluded that a lifestyle intervention was feasible in colorectal cancer survivors who had surgery 6 to 24 months ago[10]. Results of the other study, which included 50 participants, suggests that there is a potential effect of a web-based dietary intervention on cancer-related fatigue in colorectal cancer survivors who were disease-free or had stable disease and were not undergoing chemotherapy [12]. Importantly, the studies did not select participants based on level of cancer-related fatigue. Therefore, we argue that there is a clear need for a lifestyle intervention focused on both diet and physical activity in colorectal cancer survivors who are experiencing cancer-related fatigue.

Lifestyle interventions among colorectal cancer survivors may require a specific approach for several reasons. Colorectal cancer survivors may have disease-related barriers, such as having a

stoma and/or experiencing bowel dysfunction; this may make it challenging to adhere to general advice on healthy eating and to engage in exercise [13]. In addition, cancer-related fatigue may limit the ability to conduct activities of daily living, such as food preparation, or participating in exercise activities [14], which may ask for further adaptations to a lifestyle program.

As lifestyle interventions often contain several interacting components, and involve a range of behaviours, expertise, and skills, these interventions ask for a systematic design[15; 16]. In the current report, we describe our approach on developing a person-centred lifestyle program for colorectal cancer survivors based on the World Cancer Research Fund/American Institute for Cancer Research cancer prevention guidelines[17]. Moreover, we describe the design of the SoFiT trial. The primary aim of the SoFiT trial is to test the effect of the personalized lifestyle intervention on cancer-related fatigue among colorectal cancer survivors experiencing cancer-related fatigue.

Development of the lifestyle program

The goal of the lifestyle program was to increase the participants' adherence to the World Cancer Research Fund/American Institute for Cancer Research cancer prevention guidelines[17]. These guidelines are a set of recommendations on diet, physical activity, and body weight, see **table 1**.

We aimed to design a program that would foster lasting changes in the adherence to these guidelines and that would sustain behaviour change beyond the duration of the program[18].
The program was developed based on the acknowledgement that in behaviour change interventions, relevant personal and environmental determinants of that specific behaviour need to be targeted with behaviour change techniques[19; 20]. To select effective behaviour change techniques, it is crucial to understand the factors that influence the target behaviour. This involves the identification of key personal and environmental determinants linked to the behaviour, based on theories of behaviour and behaviour change. Therefore, we conducted a systematic review to identify the most important determinants of healthy lifestyle behaviours among colorectal cancer survivors[21]. Complementary, we conducted interviews with eight colorectal cancer survivors, of whom six experienced cancer-related fatigue. The focus of these interviews, which lasted 30-90 minutes, was to assess which factors influenced

compliance or non-compliance with the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cancer prevention recommendations. Thematic content analysis [22] was used to identify determinants of health behaviours. The determinants that emerged from the interviews, and that resulted from the systematic literature review are described in the chapter Data Collection. In addition, we published a systematic review to show which behaviour change techniques are frequently used and which behaviour change techniques appear most promising to effectively change behaviour in lifestyle interventions in cancer survivors[23].

Within our systematic review, we observed that the behaviour change technique 'generalisation of the target behaviour' is a promising technique that was often used in lifestyle interventions that were effective in reducing cancer-related fatigue among cancer survivors[23]. Generalisation of the target behaviour means that it is important to incorporate change in the own environment and in daily life. Indeed, both theory and evidence suggest that creating habits and learning behaviour in the most relevant contexts is important for long-term behaviour change[24; 25; 26; 27]. Moreover, behaviour change is more likely to be maintained if people are motivated by their own needs and desires [28], and if newly adopted behaviour reflects the values of the person and is seen as personally relevant[24]. For the lifestyle program, we decided that the focus should be on supporting participants in integrating lifestyle changes into their daily lives, by considering the relevance of that behaviour for the participant, the specific barriers for that behaviour, its easiness to continue on the long-term, and the motivation of the participant. This led to a program that is person-centred and autonomy supportive, which are both important predictive factors of maintenance of behaviour change[29].

Our reviews [21; 23] and interviews, in combination with the 'Theory and Technique Tool[20], set the stage for the selection of behaviour change techniques for our program. The Theory and Technique Tool[20] serves as a guide, offering insights into the most likely links between behaviour change techniques and specific determinants. We chose behaviour change techniques that are most likely linked to the identified determinants of lifestyle behaviour, thereby enhancing the likelihood of successful and sustained behaviour change among participants. Once we established the links between the determinants and suitable behaviour change techniques, we decided on practical applications of this combination. See

supplementary table S2 for an overview of the behaviour change techniques per determinant and examples of how they were applied.

This development phase led to a program that had a general core and a person-centred approach, which is described below, details can be found **in supplementary figure S1**.

General core of the lifestyle program

During six months, participants of the lifestyle program were coached to increase their adherence to the WCRF recommendations on diet and physical activity: weight loss was not a specific goal of the program but may have happened as a result of adopting a healthier lifestyle.

A six-month period with a contact moment every two weeks was chosen for the program, as a previously conducted RCT showed that a six-month period with a contact moment every two weeks was sufficient to improve lifestyle behaviour among colorectal cancer survivors[11].

In our program, the participant received four face-to-face appointments with one of the two lifestyle coaches, who visit them at their home. Additionally, there were eight contact moments with the coach by telephone or video call. Both coaches graduated from a post graduate program for lifestyle coaching. At the beginning of the program, the participant received a paper handbook with an introduction to the program; information on the WCRF recommendations and on its possible health benefits and suggestions for implementation; information on the home visits and measurements; weekly fill-in schemes for goal setting and action planning involving stating, planning, monitoring, evaluating, and revising goals, and several brochures (See for a list of brochures and information **supplementary table S1**).

Throughout the program, several behaviour change techniques were applied for all participants as these are crucial for guiding behaviour change. Coaches provided information on the importance of a healthy lifestyle and its health consequences. Furthermore, behaviour change techniques around setting, reviewing, and adjusting goals on behaviour and anticipated outcome (e.g. feeling more fit) were applied, since goal setting is found to be an important predictor for maintaining behaviour change in the long-term[29]. Goal setting was always coupled with the behaviour change technique 'Action planning' to help individuals plan the specific actions they took to achieve their overarching goals[30]. Barriers for changing behaviour were also identified and formed part of action plans. Furthermore,

participants monitored their own behaviour by filling in the weekly fill-in schemes in the participant handbook, and coaches gave feedback on behaviour and outcomes.

During the first appointment, the focus of the coach was on building trust with the participant, and on obtaining a clear impression of the participant. Moreover, the goal of that first appointment was to discuss mutual expectations, and to get commitment of the participant for the program. During this first meeting, the coach also discussed a baseline report that contained the results on the diet quality of the participant (see later for details about dietary assessment), physical activity level of the participant (see later for details on assessment), determinants of behaviour, and other information (body weight and BMI, stoma, allergies/intolerances, cancer-related side effects, co-morbidities). Based on this, participant and coach together set 2 or 3 goals towards reaching the WCRF recommendations (see Table 1), and 2 or 3 goals on an anticipated outcome of behaviour (e.g., experiencing less fatigue or feeling more active). The coach and participant made an action plan for the next two weeks.

The next appointments focussed on evaluating and monitoring goals, on providing feedback, and on changing and/or adding goals when possible. Barriers were identified and action or coping plans were made together with the participant. Additional goals towards reaching the WCRF recommendations could be added throughout the program. After three months, the coach presented a mid-term report to the participant, compiled from the data that the participant provided at the three-month assessment. Similar to the baseline report, this report contained information on diet quality, physical activity, determinants of behaviour, and body weight and BMI. The coach used this information to discuss progress and to plan the content of the individual program for the next three months. During the following appointments, participants worked on the goals again. Now, the focus was also on relapse prevention. At the final appointment, the progress and program were evaluated and a long-term planning was made to prevent relapse and maintain a healthy lifestyle after the program.

Person-centred approach of the program

The program was person-centred as it was 1) tailored towards the current lifestyle and personal characteristics of the participant, 2) targeting personal behavioural determinants, and 3) taking into account the preferences, opportunities and disease-related barriers of the participant.

1) Personalization to current lifestyle & personal characteristics

To tailor the program to the current lifestyle and personal characteristics of the participant, the following information of the participant was used at baseline and at three months: diet quality, physical activity level, weight/BMI, any co-morbidities, allergies and intolerances, cancer-related side effects, and having a stoma.

2) Personalization to the determinants of behaviour

To tailor the program to individual behavioural determinants of the participant, we created a questionnaire to assess these behavioural determinants (see more details on this questionnaire later). In this questionnaire, we concentrated on a specific set of determinants that we deemed crucial to achieve sustained long-term changes in dietary intake and physical activity. The participant completed this questionnaire at baseline and after three months. The coaches received an overview of determinants of behaviour of the participant and used practical applications of matched behaviour change techniques to target those determinants, see **Supplementary table S1**.

3) Preference, opportunities, and disease-related barriers

The preferences and opportunities of the participant were taken into account in shaping the coaching. The coach and participant together decided on which WCRF recommendations were targeted and how these were targeted considering the challenges participants had (e.g., lack of financial resources) by setting SMART goals (Specific, Measurable, Achievable, Relevant, and Time-Bound) and by creating action plans. Moreover, it is often crucial to address other issues that affected the participant, to enable the participant to change their lifestyle behaviour[31]. This could be: attention for mental health (e.g. anxiety for recurrence), sleep problems, weight management, acknowledgement for the cancer-related fatigue and acceptance of self, the disease and their place in society (e.g. not being able to work anymore). This mostly involved giving the participant room to express such problems.

METHODS OF THE RANDOMIZED CONTROLLED TRIAL

To represent the patient voice throughout all aspect of the study, a patient representative of a national patient organisation ‘Stichting Darmkanker’ was involved in the writing of the project proposal to acquire funding, in the writing of the protocol for medical-ethical

approval, in testing questionnaires, with recruitment efforts, and other study procedures. The study was approved by the Medical Research Ethics Committee (Committee on Research Involving Human Subjects region Arnhem-Nijmegen, NL75999.091.21, nr 2021-8182). All participants provide written informed consent.

Design of the trial

The SoFiT study was a parallel randomized controlled trial with two groups: an intervention and a control group. For a timeline of the research activities of the study see supplementary figure S2. The intervention group received the six-month program described above. Participants in the control group did not receive that program but were contacted every 1.5 months to promote retention. At 1.5 months, participants in the control group received a newsletter in which general tips were given about books to read (tips are about novels, not related to lifestyle) or podcasts to listen to (podcasts are entertaining stories, not related to lifestyle). At three months, participants in the control group received a phone call to collect study-related data (see table 2). At 4.5 months, participants in the control group received a newsletter with general information on the importance of a control group. After completion of data collection at six months, the control group received the information booklets that the intervention group also received, and two lifestyle coaching sessions with a coach.

Population & recruitment

Inclusion criteria were: adult colorectal cancer survivors with stage I-III disease who completed colorectal cancer treatment at least six months and no more than five years ago, and who were experiencing cancer-related fatigue as assessed during screening. We assessed cancer-related fatigue with the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale [(32)], and defined cancer-related fatigue as a score lower than 34 [(32)]. Additional inclusion criteria: persons had to live on a reasonable distance from the research centre (within approximately 1.5 hours driving by car from Wageningen University & Research), had to be willing to be randomized into either the intervention or control group; and had to be able to speak, write and read Dutch.

Exclusion criteria are: participation in another study that could interfere with the current study; excessive alcohol consumption (more than 4 glasses/day on average); chronic recreational drug use; unwilling or unable to comply with the intervention (e.g. through dementia or mental illness).

Recruitment took place via 3 routes: through the Prospective National Colorectal Cancer cohort (PLCRC)[33; 34], through regional hospitals, and through newsletters, websites, and social media channels of patient organizations.

Recruitment through PLCRC was as follows. PLCRC is an open cohort of colorectal cancer patients diagnosed across >60 hospitals in the Netherlands [33; 34] and consists of >10,000 participants. Upon recruitment into that PLCRC cohort, all participants are asked whether they would like to be informed about future studies of other research institutes.
The PLCRC research team selected which cohort members signed informed consent to be invited for future research studies. Out of those cohort members, the PLCRC research team assessed who completed treatment six months to five years ago, and who lives on a reasonable distance from the SoFiT research centre. Those cohort members received an information package about the SoFiT study from the PLCRC research team. This contained an invitation letter, flyer, and postcard to send back to the study team to express their interest.

Recruitment through regional hospitals was as follows. A member of the hospital research team regularly checked whether there were colorectal cancer survivors who completed cancer treatment at least six months ago. Those colorectal cancer survivors received the information package about the study.

Persons interested to hear more about the study were requested to contact the SoFiT research team at Wageningen University & Research. The research team provided written and oral information about the study, screened the person for eligibility and answered any questions that the person had. Eligibility screening involved completing an online (or paper) questionnaire through Castor Electronic Data Capture (Castor EDC, Amsterdam, the Netherlands). This questionnaire consisted of the 13-item FACIT-Fatigue scale[32] to assess whether the person was experiencing cancer-related fatigue, and of questions to assess the other in- and exclusion criteria. Eligible persons who signed written informed consent were included in the study.

Sample size calculation

The intended sample size is based on an estimated differential change in cancer-related fatigue from baseline to six months between intervention and control group of 3 points on the FACIT Fatigue scale[35; 36]. A change of 3 points is considered a clinically important difference[35; 36]. In the calculations, we used an SD of 6.7 which was inferred from a 12-week physical activity intervention aimed to decrease cancer-related fatigue in colorectal cancer survivors[37]. Assuming an α of 0.05 and a power of 80%, the required sample size was estimated as 78 per group. Comparable lifestyle interventions show drop-out rates of ~15%. We increased the estimated sample size with 15% to account for possible drop-out, resulting in a total sample size of 184 participants, 92 per group. If persons were diagnosed with cancer, cancer recurrence or metastasis during the six months of the study, participants were taken out of the study and not replaced.

Data collection

Measurements and assessments were done at baseline, at three months, six months and twelve months, see **Table 2** for an overview of which measurement and assessments were done. At baseline and six months, a member of the research team collected data from participants during a home visit; shortly before or after those visits, participants completed questionnaires via paper or online. At three and twelve months, data participants completed questionnaires via paper or online and via telephone. All data were entered and/or collected through Castor EDC.

Data are only accessible to members of the research team. Depending on the role of the team member access can be restricted to specific subgroups or items. Data on adverse events were reported to the Medical Ethical Committee once a year, and data on serious adverse events were reported to the Medical Ethical Committee as soon as the research team was notified about those.

Randomization and blinding

After collecting baseline data during the home visit, the participant was randomized to intervention or control group (1:1 allocation ratio) through the randomization module of Castor EDC using a stratified block-randomisation procedure. Stratification was done for level of cancer-related fatigue (≤20, or >20 on the FACIT-Fatigue Scale) and for whether or

not chemotherapy was received as part of treatment (chemotherapy yes/no). Permuted blocks of 4, 6 of 8 were used.

The nature of the intervention did not allow us to blind participants to treatment allocation. However, the baseline measurements were carried out blinded and participants were immediately afterwards randomized, so that they were aware of their group allocation at the end of the first home visit. The primary outcome of the trial could not be collected blinded, as this is self-reported cancer-related fatigue: participants completed the FACIT-Fatigue questionnaire online or via paper at home, before or shortly after the measurement visit. After completion of data collection, the database will be locked and pseudo-anonymized by an independent researcher to ensure that data analysis is conducted blinded. Full details of the statistical analysis plan of any primary or secondary outcome or mediation analyses will be finalized prior to database lock and unblinding, as previously recommended [38].

Primary and secondary outcomes

Primary outcome: Cancer-related fatigue

Cancer-related fatigue was assessed with the FACIT-Fatigue Scale. This scale comprises of 13 items that assess cancer-related fatigue and its impact. Each item is scored on a 5-point Likert scale ranging from: 'Not at all' to 'Very much'[39]. Lower scores mean higher cancer-related fatigue levels. We chose the FACIT-Fatigue scale based on two reviews [35; 40] that concluded that this questionnaire is valid and user-friendly, relatively brief, and can easily be combined with other quality of life instruments.

Secondary outcome: Changes in lifestyle behaviour

To assess how lifestyle behaviour changed during the six months of the study, we assessed dietary intake, physical activity level and anthropometrics at baseline and six months.

Diet

To assess changes in dietary intake, participants completed a semi-quantitative Food Frequency Questionnaire (FFQ) [41; 42]. Participants reported the intake of foods and drinks consumed during the previous month.

In addition, participants completed a brief dietary screener 'Eetscore', which was developed to assess diet quality by comparing intake with the Dutch food-based dietary guidelines 2015

[43]. This Eetscore estimates adherence to each of the 15 components of the Dutch dietary guidelines and includes an additional 16th component on unhealthy choices of foods and drinks. For each of these 16 components, 10 points can be awarded, resulting in a total score of 0 (no adherence) to 160 (complete adherence to all guidelines). The coach used the Eetscore to tailor the intervention to the current dietary intake of the participant. As timing of dietary intake may be relevant in the context of cancer-related fatigue[44], data on timing of dietary intake was assessed with a 26-item questionnaire on meal regularity, meal frequency, and meal clock time[45].

Physical activity

Physical activity level was assessed in two ways: subjectively via the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) [46] questionnaire and objectively via an accelerometer (ActivPal™ Micro3). The questions in SQUASH focus on commuting, work/school activities, household activities, leisure time, and sports in a representative week. Scores are assigned to the reported activities based on intensities in MET and translated to minutes of physical activity. The coach used the information from the SQUASH questionnaire to tailor the intervention. Participants wore the accelerometer for nine consecutive days on the midline of the thigh. This is in line with previous research[47] which showed that 5 days with at least 1 weekend day is needed for reliable estimation of activities and considered that the days of placement and removal are not used for analyses.

Anthropometrics

A researcher measured body weight of the participant with a calibrated scale, waist circumference with a tape measure, and height with a stadiometer. At three months and twelve months, participants were asked to weigh themselves using their own weighing scales and self-report their weight.

<u>Secondary outcome: echo intensity of skeletal muscle & skeletal muscle cross-sectional circumference and thickness</u>

We previously showed that prevalence of cancer-related fatigue was higher among colorectal cancer patients who had more fat infiltration in skeletal muscle [48], [49]. Lifestyle may affect fat infiltration in skeletal muscle [49]. In the current study, we aim to assess whether a

potential change in cancer-related fatigue is mediated by changes in fat infiltration in skeletal muscle.

Ultrasound of skeletal muscle

Information on echo intensity of skeletal muscle, skeletal muscle thickness and circumference, and thickness of subcutaneous fat[50; 51; 52] was obtained through ultrasound assessment in brightness mode (B-mode). We used ultrasound as this is a portable, non-invasive technique that does not involve radiation. Echo intensity of skeletal muscle is considered indicative of fat infiltration in skeletal muscle[50; 53]. Ultrasound assessments of the rectus femoris, lateral gastrocnemius and biceps brachialis were done during the home visits using a portable ultrasound, the Terason® uSmart 3300 with Terason® linear transducer 15WL4 (Terason, Burlington, US). The settings were sat at: gain level to 58 dB, Dynamic Range (DR) at 72 and transducer frequency to 8 MHz giving a frequency of 23 Hz with OmniBeam switched on.

Secondary outcome: Symptom clusters

Cancer-related fatigue is rarely an isolated symptom and occurs often in symptom clusters with symptoms such as disturbed sleep quality [54], emotional distress and other concerns [55]. We will assess the effect of the lifestyle intervention on this cluster of symptoms, including sleep outcomes, health-related quality of life, colorectal cancer-related concerns, depression, and anxiety.

Sleep quality and duration

Sleep quality was assessed with the self-reported Pittsburgh Sleep Quality Index PSQI[56]. This validated questionnaire contains 19 questions on 7 domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The scores range from 0-21, with higher scores indicating worse sleep quality. Participants also completed the 15-item Consensus Sleep Diary (CSD)[57] to obtain information about sleep characteristics. Participants completed this diary during the period that they wore the accelerometer.

Health-related quality of life & colorectal cancer-related concerns

The FACIT-Fatigue Scale was used in combination with the Functional Assessment of Cancer Therapy – Colorectal (FACT-C) questionnaire [39]. The FACT-C contains 36 items and was used to assess physical well-being, social/family well-being, emotional well-being, and functional well-being and to assess concerns about colorectal cancer specific issues; the recall period is 7 days. Higher scores mean better quality of life.

Depression and Anxiety

Participants completed the Patient Healthcare Questionnaire (PHQ)-8 [58; 59] to assess signs of possible depressive disorders and the Generalized Anxiety Disorder (GAD)-7 questionnaire to identify probable cases of generalized anxiety disorder[60]. Both questionnaires have a recall period of 2 weeks, and higher scores mean higher indication of possible depressive disorder and generalized anxiety disorder.

Additional outcomes and measurements

Behavioural determinants

Behavioural determinants were assessed for two reasons: to tailor the program to the determinants of the participant and to estimate the influence of those determinants on behaviour change. Participants completed a questionnaire with questions on selected determinants: knowledge, motivation, attitude, task and barrier self-efficacy, skills, perceived outcomes/benefits, physical environment, social influence, habits for dietary behaviour and physical activity and identity/values/norms (see **supplementary material** for the questionnaire). The questions are based on an adapted version of the Determinants of Physical Activity Questionnaire[61] and the 'Self-Report Behavioural Automaticity Index' for the determinant 'habit'[62]. We based our questions for our specific determinants on these existing questionnaires to reflect the aim of the intervention to increase adherence to the WCRF guidelines. Examples of included questions are: 'I find it important to live healthily' (determinant: attitude), and 'The people in my surroundings who are important to me support me or encourage me to live healthily' (determinant: social influence). Each determinant is scored on a scale from 1 to 7. Higher scores indicate a more positive evaluation of that underlying determinant of behaviour (e.g. better knowledge about guidelines, sufficient skills to prepare healthy foods etc), and a score below 5.5 on any of the determinants was considered a point of attention in the lifestyle program.

The behavioural determinants that we examined were chosen as follows. In our systematic review[21], we identified knowledge, motivation, social support, norms and influence, beliefs (included under attitude), skills, environmental factors (i.e. weather and lack of access to facilities and equipment), dealing with symptoms related to the disease and/or treatment (included under barrier self-efficacy), and perceived outcomes/benefits as important population-specific determinants of behaviour. We also included attitude (i.e. including general beliefs about healthy living), self-efficacy (i.e. task self-efficacy), , habits and identity/values/norms as those factors were deemed important according to the colorectal cancer survivors whom we interviewed. Specifically, changing habits is important because substituting unhealthy habitual behaviour with healthy habits significantly predicts long-term behaviour change[63; 64]. In addition, the determinant 'identity, values & norms' is important, since behaviour that reflects ones identity, values, and adheres to social norms are more meaningful, create a sense of belonging and become integrated into a person's sense of self[24].

Biospecimens

Participants were asked to collect faecal samples into collection tubes (Sarstedt faeces tubes with sterile screw cap). The participant collected the samples within three days prior to the home visit and stored the sample in an air-tight plastic bag in a freezer. A member of the study team transported the samples on dry ice to the research facility where it is stored at -80°C until further analysis. We plan to use 16S rRNA sequencing data for the taxonomic characterization of gut microbiota, possibly with shotgun metagenome sequencing for further characterization.

Blood pressure

Blood pressure was measured during the home visits by a member of the research team using a sphygmomanometer (OMRON M2, Omron, Kyoto, Japan) on the non-dominant arm. The participant was asked to sit in rest for 5 minutes before blood pressure was measured.

Hemoglobin

Hemoglobin was assessed as we previously identified this as a potential contributing factor for cancer-related fatigue in this population[65]. A finger prick blood sample was taken during the home visits by a member of the research team and analysed immediately to assess haemoglobin as indicator of anaemia using a HemoCue Hb 201+ (HemoCue AB, Ängelholm, Sweden).

Physical performance

The following tests were conducted during the home visits. We chose tests that were feasible in an area with limited space and that required minimal materials.

1: Three minute step test: indicates cardiopulmonary fitness by heart rate measurement for one minute after the completion of the three minutes of stepping [66].

2: Five times sit-to-stand test: assesses the time necessary to achieve the standing position after the 5th repetition [67], which is considered a measure of strength of the lower extremities.

3: Tandem test: measures balance while standing in three different positions for at least 10 seconds [68].

4: Chair sit-and-reach test: measures flexibility of lower extremity and lower back[69].

Participants sat on a chair with one leg bent at a 90° angle and the other leg extended. They reached towards their toes with the hand on the same side as the extended leg. The distance between the hand and toes was measured. This was repeated on the other side. The side with the greatest stretching was measured twice, and the mean value will be used.

5: Hand grip strength using Jamar dynamometer [70]. Participants sat in a chair with the dominant arm unsupported next to their body positioned at a 90° angle. Measurements were taken twice, and the mean value will be used.

Other study parameters

Sociodemographic information (age, sex, marital status, education, employment, and smoking) is collected via standardized questionnaires online, and other personal parameters (medicine use, use of dietary supplements) are collected via standardized questionnaires during the baseline visit; during following assessments/visits, the research team asks whether there are changes in those personal factors. Clinical data are collected through questionnaires and through linkage with the Netherlands Cancer Registry.

Process evaluation

During and after the trial, we will investigate the experiences of 20 participants and of the lifestyle coaches with the program by means of interviews. With these interviews, we gather information on the barriers and facilitators experienced during the intervention, about the reach, dose delivered and received, about the fidelity and about the acceptability of the intervention[71].

Costs and cost-effectiveness

We collected the following data on costs through an online self-reported questionnaire: medical costs and costs for lifestyle behaviours, productivity at work [72], unpaid/volunteer work, and data on how much participants would want to pay for participation in the lifestyle program. These data will allow us to evaluate cost-effectiveness of the six-month lifestyle program using a similar approach as previously used by researchers of our group[73; 74].

Data analysis of primary outcome

The primary study outcome is cancer-related fatigue at six months. To test the effect on the primary outcome, we will perform an Analysis of Covariance (ANCOVA), assuming that the assumptions of normality of residuals and homogeneity of variance are met. In the ANCOVA analysis that will be conducted on an intention-to-treat basis, we will compare cancer-related fatigue at six months between intervention and control group and adjust for cancer-related fatigue at baseline, results will be reported as effect sizes and 95% confidence intervals. We will include the stratification factors used during randomization in the ANCOVA model[75], assuming similar variance in cancer-related fatigue across stratification factors. We will apply multiple imputation to impute missing data of cancer-related fatigue at baseline or six months.

Several sensitivity analyses are planned for the primary outcome. As sensitivity analysis, we will conduct a 'complete case' analysis in which we will only include participants of whom we have complete data on cancer-related fatigue at baseline and six months. Moreover, we will conduct a per protocol analysis in which we will only include those participants who were adherent to the protocol. Full adherence is defined as having at least 11 sessions with the coach.

Data analysis of secondary outcomes & mediation analyses

Secondary outcomes

We will explore the effect of the intervention on skeletal muscle fat infiltration (echo intensity data), sleep quality and behaviour, quality of life, depression and anxiety using a series of ANCOVA models using the same approach as described for the primary outcome. In addition, we will explore the prolonged effects of the intervention at twelve months.

Mediation analyses

We will examine whether changes in dietary behaviour, physical activity and/or skeletal muscle fat infiltration act as mediators in the relation between the lifestyle intervention and cancer-related fatigue calculating percentile bootstrap confidence intervals for indirect effects[76]. We also plan to evaluate whether changes in behavioural outcomes are mediated by changes in behavioural determinants.

Discussion

Cancer-related fatigue can affect many aspects of health-related quality of life. The SoFiT trial aims to assess whether a personalized lifestyle intervention focussed on a healthier dietary intake, and more physical activity can help to reduce cancer-related fatigue among colorectal cancer survivors. The SoFiT lifestyle program has several unique features. The first is that it is rooted in behaviour change principles. The systematic design of the program is based on behavioural determinants of a healthy lifestyle in colorectal cancer survivors and on evidence- and theory-based behaviour change techniques. Furthermore, the program has a person-centred approach as it is tailored to the lifestyle of the individual, to behavioural determinants, and to the preference, opportunities, and disease-related barriers of the individual. Tailored approaches are needed to take into account the complexity of lifestyle behaviours: the precision health approach[77].

The second unique feature is that only persons who experience cancer-related fatigue were eligible for the study. This is an important strength as very few previous trials were conducted among populations experiencing cancer-related fatigue. As a consequence, participants in previous trials were mostly high functioning and were not or hardly experiencing fatigue, which limited the possibility whether lifestyle can affect cancer-related fatigue.

The third unique feature is that we assessed a wide range of outcomes. Cancer-related fatigue often occurs in symptom clusters with symptoms such as disturbed sleep quality [54], emotional distress and other concerns [55; 78], and we therefore took a wide variety of outcomes into account in this trial.

The fourth unique aspect is that we included outcomes that focus on physiological changes while we also assess changes in behaviour and behavioural determinants to gain more insight in the mechanisms of action. As physiological outcome, we assess skeletal muscle echo intensity as an indicator of skeletal muscle fat infiltration. Previous studies on body composition among colorectal cancer patients/survivors used clinical Computed Tomography (CT) images to gather information on fat infiltration in skeletal muscle[48; 79; 80]. In the context of intervention studies, use of CT images to track changes in fat infiltration is problematic: CT includes exposure to radiation, and a CT machine is not portable. We therefore chose to use ultrasound to obtain information on skeletal muscle echo intensity as an indicator of fat infiltration in skeletal muscle.

Recruitment for the SoFiT trial started in January 2022 and was completed by June 2023. We expect to complete data collection of the 12-months timepoint by June 2024.

Author contributions: Formulation of research questions and design of the study ALL; carrying out the study JdV-tH, KM, AV, LW, RW; writing of the manuscript JdV-tH, RW, all authors provided input on and approved the final version of the manuscript.

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Table 1: Description of the WCRF recommendations. These recommendations are the core of the lifestyle program that is tested in the SoFiT trial

Recommendation	**How assessed?**	**Instrument**
Eat a diet rich in whole grains, vegetables, fruit, and beans	Consumption of fruit (g/day)	Food Frequency Questionnaire (FFQ)
	Consumption of vegetables (g/day)	FFQ
	Consumption of beans/legumes (g/day)	FFQ
	Total fibre intake (g/day)	FFQ
Limit consumption of "fast foods" and other processed foods high in fat, starches, or sugars	Consumption of foods high in fat, starch and/or sugar (g/day)	FFQ
Limit consumption of red and processed meat	Unprocessed red meat (g/day)	FFQ
	Processed meat (g/day)	FFQ
Limit consumption of sugar-sweetened drinks	Consumption of sugar-sweetened beverages (g/day)	FFQ
Limit alcohol consumption	Consumption of alcoholic beverages (glasses/day)	FFQ
Be physically active	Moderate-vigorous physical activity (min/week)	Questionnaire & Accelerometer
Be a healthy weight	Body Weight (kg)	Scale
	Waist Circumference (cm)	Tape measure

Table 2: Timing of the measurements and assessments in the SoFiT trial, a randomized controlled study among colorectal cancer survivors

Outcome	**Instrument***	**Baseline** Home visit & online survey	**3 months** Online/paper or via phone	**6 months** Home visit & online survey	**12 months** Online/paper or via phone
Cancer-related fatigue	FACIT-Fatigue questionnaire	X		X	X
Dietary intake	FFQ	X		X	
	Dietary screener	X	X	X	X
	(Eetscore)	X		X	
	Chrono-nutrition				
Physical activity	SQUASH	X	X	X	X
	Questionnaire	X		X	
	Accelerometer				
Body weight, waist circumference, height	Scale, tape, stadiometer	X		X	
			X		X
	Self-reported body weight				
Skeletal muscle and subcutaneous fat thickness, and cross-sectional area and echo intensity of skeletal muscle	Ultrasound	X		X	
Sleep quality and duration	PSQI	X		X	X
	CSD	X		X	
Health-related quality of life & colorectal cancer related health concerns	FACT-C	X		X	X
Depression and Anxiety	PHQ-8, GAD-7	X		X	
Behavioural determinants	Survey	X	X	X	X
Biospecimens	Faecal sample	X		X	
Blood pressure	Sphygmomanometer	X		X	
Hemoglobin	HemoCue Hb 201+	X		X	

Physical performance	Battery of tests	X		X
Cost effectiveness	Survey	X	X	X
Sociodemographic, clinical, and personal parameters	Survey	X		X

*Participants completed surveys online or via paper, except for the SQUASH questionnaire and the survey on medicine and vitamin use, which were assessed by the research team during the home visits and via telephone. All measurements were done by the research team during the home visits.