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DOI
10.1136/bmjopen-2018-028117

Publication date
2019

Document Version
Final published version

Published in
BMJ Open

License
CC BY-NC

Link to publication

Citation for published version (APA):
Witlox, L., Schagen, S. B., de Ruiter, M. B., Geerlings, M. I., Peeters, P. H. M., Koevoets, E. W., van der Wall, E., Stuiver, M., Sonke, G., Velthuis, M. J., van der Palen, J. A. M., Jobsen, J. J., May, A. M., & Monninkhof, E. M. (2019). Effect of physical exercise on cognitive function and brain measures after chemotherapy in patients with breast cancer (PAM study): protocol of a randomised controlled trial. *BMJ Open*, *9*(6), Article e028117. https://doi.org/10.1136/bmjopen-2018-028117

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BMJ Open

Effect of physical exercise on cognitive function and brain measures after chemotherapy in patients with breast cancer (PAM study): protocol of a randomised controlled trial

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To cite: Witlox L, Schagen SB, de Ruiter MB, *et al*. Effect of physical exercise on cognitive function and brain measures after chemotherapy in patients with breast cancer (PAM study): protocol of a randomised controlled trial. *BMJ Open* 2019;**9**:e028117. doi:10.1136/bmjopen-2018-028117

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-028117).

Received 22 November 2018
Revised 1 March 2019
Accepted 11 April 2019

Check for updates

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ABSTRACT

Introduction After treatment with chemotherapy, many patients with breast cancer experience cognitive problems. While limited interventions are available to improve cognitive functioning, physical exercise showed positive effects in healthy older adults and people with mild cognitive impairment. The Physical Activity and Memory study aims to investigate the effect of physical exercise on cognitive functioning and brain measures in chemotherapy-exposed patients with breast cancer with cognitive problems.

Methods and analytics One hundred and eighty patients with breast cancer with cognitive problems 2–4 years after diagnosis are randomised (1:1) into an exercise intervention or a control group. The 6-month exercise intervention consists of twice a week 1-hour aerobic and strength exercises supervised by a physiotherapist and twice a week 1-hour Nordic or power walking. The control group is asked to maintain their habitual activity pattern during 6 months. The primary outcome (verbal learning) is measured at baseline and 6 months. Further measurements include online neuropsychological tests, self-reported cognitive complaints, a 3-tesla brain MRI, patient-reported outcomes (quality of life, fatigue, depression, anxiety, work performance), blood sampling and physical fitness. The MRI scans and blood sampling will be used to gain insight into underlying mechanisms. At 18 months online neuropsychological tests, self-reported cognitive complaints and patient-reported outcomes will be repeated.

Ethics and dissemination Study results may impact usual care if physical exercise improves cognitive functioning for breast cancer survivors.

Trial registration number NTR6104

Strengths and limitations of this study

- Since only small pilot studies have been conducted, the Physical Activity and Memory study is the first large and sufficiently powered randomised controlled trial examining the effect of physical exercise on cognitive functioning and brain measures in breast cancer survivors.
- The study is designed to investigate the effect of exercise and aims to provide insight into the underlying mechanisms.
- Patients with self-reported cognitive problems confirmed by neuropsychological tests are included in the study.
- The present study might hamper generalisability to a broader patient population who experience cognitive problems after cancer.

INTRODUCTION

Increased survival of patients with breast cancer has led to more emphasis on studying long-term consequences of treatment. Research has shown that a portion of patients with breast cancer experience cognitive decline after cancer treatment. The observed cognitive changes frequently concern learning and memory functioning, speed of information processing and executive functioning.[1 2] The number of affected patients varies between studies from 18% to 60% following cancer diagnoses and treatment with chemotherapy.[2–4] This wide range is largely explained by differences in timing of assessment, criteria held for cognitive decline and treatment characteristics.[4 5] Cognitive problems can persist after completion of treatment.[6] Even after 20 years, cognitive differences between chemotherapy-treated patients and non-cancer controls have been established.[6 7] The cognitive problems are generally mild to moderate and can adversely affect work ability, interpersonal relationships and leisure activities.[8]

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Chemotherapy is an important pillar in the treatment of primary breast cancer, which impairs cognition by several mechanisms.[2] Preclinical studies showed that chemotherapy agents can disrupt various neurobiological processes, which can lead to cognitive impairment. Effects of cellular toxicity on cognitive impairment are described (neurons, glial cells, progenitor and stem cells), but also reduced white matter integrity and inflammatory reactions as vascular toxicity and oxidative stress.[9–11] These mechanisms are not mutually exclusive and one can also influence the other.

Neuroimaging studies in patients with non-central nervous system cancer have been performed to shed light on the neural substrate of the cognitive changes in patients after diagnosis and treatment with chemotherapy. Various MRI studies have shown brain volume reductions after chemotherapy, particularly in neocortex, which is sometimes directly associated with cognitive decline.[6 12–16] Although these reductions seem to be transient to some extent, they can persist for many years.[16] MRI diffusion imaging studies found reductions in white matter microstructure,[6 12 13 17 18] with some studies observing that patients who showed more severe cognitive decline also showed more intense reductions in white matter microstructure.[19] Additionally, alterations in cerebral blood flow as measured with arterial spin labelling have been associated with cognitive performance in women receiving chemotherapy.[20 21] Using functional MRI a study of Deprez *et al*[22] reported decreased brain activation during multitasking of chemotherapy-treated patients, which was associated with an increase in subjective cognitive complaints.

A promising non-pharmacological intervention for cognitive problems is physical exercise. In healthy older adults and people with mild cognitive impairment, evidence of positive effects of exercise on cognition is accumulating.[23 24] A meta-analysis and also three more recent randomised controlled trials (RCTs) showed that physical activity in healthy older adults improved cognitive function in several domains including memory,[24–26] executive function,[24 27] attention[24] and processing speed.[24]

Until now, little is known about the mechanisms underlying this effect. Results from animal and human studies have elucidated several mechanisms by which exercise might affect the brain during ageing. These mechanisms include neurogenesis,[28] vascular changes (ie, increased oxygen saturation, the promotion of angiogenesis and increased cerebral blood flow[29]), changes in neurotransmitters (specifically catecholamine synthesis[30]) and inflammatory factors. Systematic reviews reported potential effects of exercise after completion of chemotherapy on tumour necrosis factor-alpha,[31] C reactive protein ,[32] interleukin(IL)-2, IL-6 and IL8, although no consistent effects have been found. The hypothesised mechanism that is currently best supported by evidence is that exercise leads to increased levels of neurotrophic factors, which in turn have a positive influence on neurogenesis.[33] Brain-derived neurotrophic factor (BDNF) has been implicated in the differentiation, extension and survival of neurons in the hippocampus, cortex, striatum and cerebellum.[34 35] Results from a meta-analysis indicated that aerobic exercise increased resting BDNF levels.[36] In animal studies, BDNF has already been shown a mediating factor of exercise effects on cognitive function.[37]

In addition, neuroimaging data provide insights into the neurobiological mechanisms underlying cognitive recovery by exercise. In healthy elderly and patients with mild cognitive impairment, exercise training led to a significantly increased hippocampal volume,[38 39] which was associated with improvements in spatial memory.[38] In another study, increased brain volume in both grey and white matter regions were reported after a 6-month aerobic fitness programme.[40] Furthermore, cerebral blood flow was increased in the anterior cingulate region, which was related to a better memory performance.[41]

Physical exercise might also be beneficial for patients with cancer experiencing cancer-related cognitive problems.[42] Two pilot studies studied the effect of exercise on cognitive functioning of patients with breast cancer after primary treatment.[43 44] Both studies included women with self-reported cognitive problems after chemotherapy. The 19 women in the study of Campbell *et al*[43] and 87 women in the study of Hartman *et al*[44] were randomly allocated to an aerobic exercise intervention of 150 min per week, moderate to vigorous exercise or control group. The intervention of Campbell *et al* consisted of 24-week supervised and home-based aerobic exercise programme, while Hartman *et al* assessed a 12-week home-based aerobic exercise intervention.[43 44] Even though the studies were small and included patients with breast cancer with cognitive problems based on self-report only which might also be influenced by other factors, processing speed in the exercise group was improved compared with the control group.[43 44] However, Hartman *et al* found this improvement only in a subgroup of patients within 2 years from breast cancer diagnosis.[44] Furthermore, this study also suggested an improvement in self-reported cognition, although not statistically significant.[44] In another pilot study conducted during chemotherapy(n=17), the strength exercise group performed better on concentration and verbal memory than the control group.[45] In addition, two larger RCTs found an indication that physical exercise during cancer treatment improved objective cognitive functioning like processing speed.[46 47] Limitations of these studies are that cognition was not the primary outcome and was only measured by one neuropsychological test. Larger clinical trials are warranted to prove potential benefits of physical exercise in patients with cancer with cognitive problems.

Therefore, we designed an RCT to examine the effects of physical exercise on cognitive functioning in chemotherapy-exposed patients with breast cancer with self-reported cognitive problems confirmed by standardised and validated neuropsychological tests. We anticipate that exercise improves cognitive functioning. Neurogenesis in the hippocampus is one of the most important proposed mechanisms by which exercise might affect the brain.

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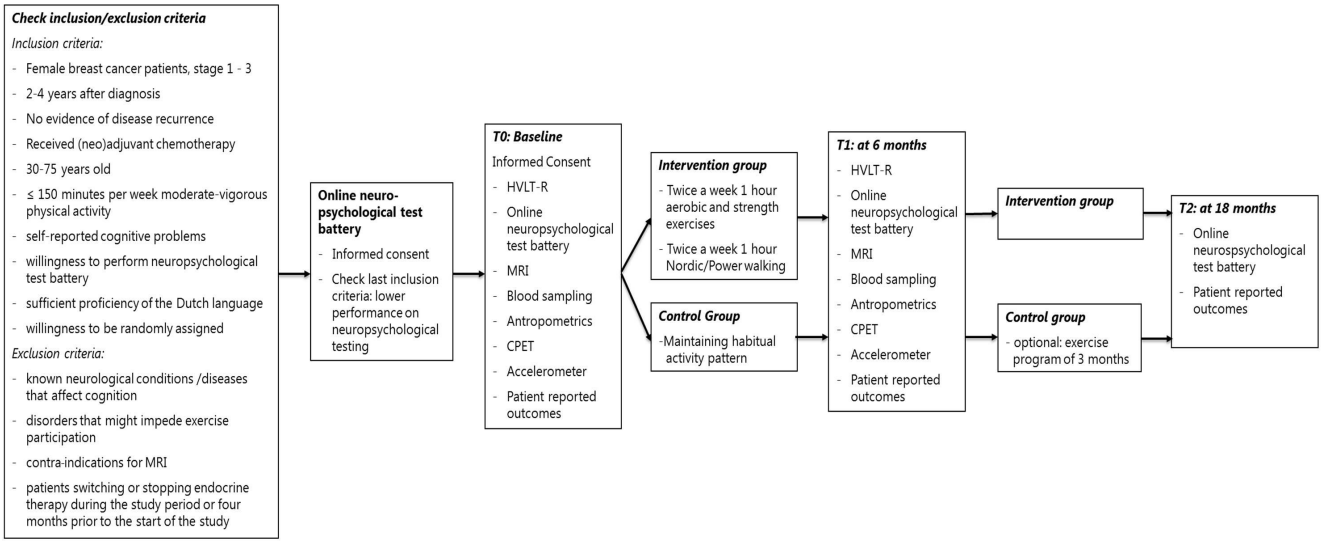

Figure 1 Overview of the PAM study. CPET, cardiopulmonary exercise test; HVLT-R, Hopkins Verbal Learning Test-Revised; PAM, Physical Activity and Memory.

Since the hippocampus is also associated with memory functioning, our primary outcome is verbal learning and memory. Furthermore, we hypothesise that exercise training will result in changes, visible on brain MRI, such as increased brain volume (including the hippocampus), increased connectivity of white matter (especially connections with the hippocampus) and increased perfusion. To study this hypothesis, we designed an RCT to examine the effects of physical exercise on cognitive functioning in chemotherapy-exposed patients with breast cancer with self-reported cognitive problems confirmed by standardised and validated neuropsychological tests.

METHODS AND ANALYSIS

Design

The Physical Activity and Memory (PAM) study is an RCT with two study groups, that is, a 6-month exercise intervention group and a control group (see figure 1 for an overview). Recruitment for the study started in December 2016 and still is ongoing.

Participants

In total, 180 patients will participate in the PAM study. Inclusion criteria the PAM study are: female patients with breast cancer with stages 1–3, 2–4 years after their cancer diagnosis, who received treatment with (neo)adjuvant chemotherapy, 30–75 years of age at inclusion, no evidence of disease recurrence, ≤150 min per week moderate-vigorous physical activity, self-reported cognitive problems, moderate to lower performance on neuropsychological testing, sufficient proficiency of the Dutch language and willing to be randomly assigned to one of the two study arms. Exclusion criteria are: known neurological conditions and/or diseases that affect cognition (eg, dementia, multiple sclerosis, traumatic brain injury), disorders that might impede exercise participation, contraindications for MRI and patients switching or stopping endocrine therapy during the study period or 4 months prior to the start of the study. The latter is chosen since we do not know if different endocrine therapies may differ in their potential impact on cognitive performance.[48] In this explanatory study, we chose to include patients with breast cancer with self-reported cognitive problems confirmed by neuropsychological tests only, since self-reported cognitive problems might also be influenced by other factors such as distress.[3]

Recruitment and randomisation

Patients are recruited by their treating physician or the study team. First, the treating physician sends potential eligible candidates an invitation letter with study information. With the invitation letter, also the information brochure and study leaflet are provided. In addition, study information is shared via social media such as the Facebook page of patient organisations and funding bodies. Interested women who experience cognitive problems interfering with daily life are asked to contact the study team. Subsequently, the study team calls these women to explain further details of the study, to answer questions and to screen for inclusion and exclusion criteria. After the telephone screening, eligible women sign written informed consent specifically for performing a full online neuropsychological test battery: the Amsterdam Cognition Scan[49] and sent the original written informed consent to the study team by post. The patients receive an email with instructions to conduct the test battery.[50] Patients performing lower than expected, that is, a worse z-score of at least 1 compared with a control group, on at least two tests of the different domains (learning and memory, attention and working memory, processing speed, executive functioning, motor functioning) compared with the normative data of a healthy female population by

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Table 1 Content of the online test battery

Test domain	Online test
Learning and memory	Wordlist learning Wordlist delayed recall Wordlist recognition
Attention and working memory	Digit sequences I Digit sequences II Box tapping
Processing speed	Connecting the dots I Reaction time
Executive functioning	Connecting the dots II Place the beads
Motor functioning	Fill the grid

age, are eligible for inclusion. The domains and the corresponding tests are described in table 1. The cut-off z-scores are similar to cut-offs used in a previous intervention study.[51]

Finally, patients visit the University Medical Center (UMC) Utrecht to sign informed consent for study participation and randomisation. After baseline measurements, patients are randomly allocated via a blinding procedure of a computer-generated sequence to the intervention or control group, stratified by age (30–44, 45–59, 60–75 years) and endocrine therapy (yes or no). The randomisation programme is provided by department of data management of the Julius Center (UMC Utrecht). Enrolment and randomisation is performed by a member of the study team.

EXERCISE INTERVENTION

The 6-month exercise intervention consists of twice weekly, 1-hour sessions of aerobic and strength exercises supervised by a physiotherapist, nearby the patients' home and Nordic or power walking for 2 hours per week. The programme is tailored to the women's physical fitness level and potential constraints. The level of intensity is increased during the exercise programme. During the aerobic exercises, participants wear heart rate monitors to train on the level of intensity, as proposed in their personalised exercise protocol.

Supervised aerobic and strength exercise

The supervised exercise sessions consist of 20–25 min aerobic and 20–25 min strength training. Sessions start and end with 5–10 min warming up and cooling down. The intensity of the aerobic exercises determined by the heart rate reserve (HRR) is based on the resting heart rate and peak heart rate and resting heart rate, which are measured during the cardiopulmonary exercise test (CPET) performed at baseline.

The muscle strength exercises are performed for all major muscle groups: arms, legs, shoulders and trunk. The intensity of the strength exercises is determined by pragmatic 15 and 20 repetition maximum (RM, the maximum weight at which a muscle group can perform repetitions) tests and repeated every 4 weeks (table 2). A 15 and 20 RM is assessed instead of a 1 RM test, since this is less sensitive for injuries and easier for the physical therapist to use (without making use of calculations). A member of study team visits a training session for monitoring 1 month after the first training.

Nordic or power walking

Participants in the intervention group additionally perform twice weekly, 1 hour of Nordic or power walking at 55%–65% of the HRR. Patients receive Nordic walking poles and an instruction leaflet. Patients choose whether they prefer Nordic or power walking. By using poles for Nordic walking, the technique will focus more on the trunk and arms to reduce the load on the legs.[52] Power walking consists of a fast walking pace including an active upper body movement. We choose these types of walking since these are more effective to increase cardiovascular fitness compared with standard walking.[52–55] Besides, patients are encouraged to join supervised walking sessions to increase motivation and adherence. If walking is not possible, due to medical constraints, other exercises are allowed such as cycling (also at 55%–65% HRR). The

Table 2 Supervised exercise programme of the PAM study

Week	Aerobic	Strength
1–4	40%–60% HRR	One circuit of 20–25 repetitions. Weights based on 20 RM tests (repeated every 4 weeks) Exercises: legs (squat, lunges, calve raises), arms (biceps curl, triceps extension), shoulder (shoulder press), thorax (barbell bench press), back (rowing). Abdomen: crunch 30–40 repetitions.
5–9	60%–70% HRR 15–20 min, Plus 70%–89% HRR 5–10 min.	
10–17	Interval training: 10×30 s vigorous to maximal exercise, alternated with 1 min active rest Plus 10 min 60%–75% endurance.	Two circuits of 15–20 repetitions. Weights based on 15 RM tests (repeated every 4 weeks) Exercises: legs (squat), arms (biceps curl, triceps extension), shoulder (shoulder press), thorax (barbell bench press), back (rowing). Abdomen: crunch 30–40 repetitions; hoover/planking 2×45 s.
18–26	Interval training: 2 circuits of 8×30 s vigorous to maximal, alternated with 1 min active rest Plus 5 min 60%–75% endurance.	

HRR, heart rate reserve; PAM, Physical Activity and Memory; RM, repetition maximum.

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patient registers the exercise sessions and average heart rate per session in an exercise log, which is monitored by the physiotherapist.

CONTROL GROUP

Patients in the control group are requested to maintain their habitual physical activity pattern next to the usual care. A supervised exercise programme of 3 months is offered after the study period.

STUDY ENDPOINTS

At baseline and 6-month follow-up, participants visit the UMC Utrecht for outcome assessments following the same standard operating procedures. At 18-month follow-up, a selection of study endpoint will be assessed.

Baseline and 6-month follow-up measurements

Primary outcome

Primary outcome is the total recall score on the Hopkins Verbal Learning Test-Revised (HVLT-R), a test to assess verbal learning and memory. With this outcome, we also adhere to the guidelines of the International Cognition and Cancer Task Force.[56] The HVLT-R consists of a 12-word list from three semantic categories, which is read aloud by the researcher. The patient has to recall as many words as possible for three consecutive learning trials (total recall). After 20 min, the patient is asked again to recall as many words as possible (delayed recall). Lastly, a list of 24 words is read by the researcher and the patient is asked to declare if the concerned word was mentioned in the previous list with target words or not (recognition discrimination index). At 6-month follow-up, a parallel version of the 12-word list with different words is used.

Secondary outcomes

Cognitive functioning

Self-reported complaints measured by two symptom severity questions on memory and attention and six symptom interference items of the MD Anderson Symptom Inventory for multiple myeloma (MDASI-MM) questionnaire. The MDASI has been proven to be valid, reliable and concise to assess symptoms in patients with cancer.[57]

Overall cognitive functioning is measured by the Amsterdam Cognition Scan, an online neuropsychological test battery which is also performed to select eligible patients.[49] The neuropsychological test battery includes seven tests including eleven outcome measures and two questionnaires. It contains the following domains: learning and memory, attention and working memory, processing speed, executive functioning and motor functioning. Most tests start with an instruction video and a practice session with feedback. The outcome measures including the corresponding test domains are described in table 1. This online test battery has shown a high usability and reliability for measuring cognitive functioning.[49]

Neuroradiological assessment

Changes in brain structure and perfusion are measured by a Philips 3-tesla (T) MRI scanner at the UMC Utrecht. All scans are acquired with a standardised protocol that consists of an axial T2*- (repetition time in ms (TR)/echo time in ms (TE)=shortest/20),T2-/proton density-weighted (PD) sequence (TR/TE1/TE2=3198/19/140) inversion recovery (IR) (TR/TE/inversion time in ms (TI)=4416/15/400), fluid-attenuated inversion recovery (FLAIR) (TR/TE/TI=11 000/125/2800), all with 48 contiguous slices and 0.96×0.95×3.00 mm^3 voxels, 3D T1-weighted sequence (sagittal acquisition, TR/TE=shortest/4.5; 192 slices; 1.00 mm isotropic voxels). This allows for multispectra tissue segmentation. Additionally, a Pseudocontinuous Arterial Spin Labelling (pCASL, axial acquisition, TR/TE 4400 ms/shortest, 19 slices, 3.0×3.0×7.0 mm voxels, 30 volumes, M0 images following the pCASL scan with identical readout) is acquired, and a diffusion tensor imaging (DTI) sequence (TR/TE=shortest/90, 40 directions, b value 1500, 56 slices, 2.50 mm isotropic voxels). The MRI scan protocol duration is 24 min.

Fully automated brain tissue segmentation is used including segmentation of hippocampus. T1 scans are corrected for intensity inhomogeneity and segmented into different tissue types and subregions including hippocampus. FLAIR is used to determine white matter hyperintensities and for lesion masking. The DTI sequence is used for assessing changes in white matter connectivity/microstructure by calculating the fractional anisotropy). pCASL is added to evaluate changes in brain perfusion.

Patient-reported outcomes

Sociodemographic data (age, education, marital status), menopausal status, age at menopause, alcohol intake and smoking status are assessed by a self-developed questionnaire.

Fatigue is assessed by the Multidimensional Fatigue Inventory-20. It consists of 20 items including five subscales (general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation) to measure multiple fatigue characteristics.[58]

Self-rated anxiety and depression are measured by the Hospital Anxiety and Depression Scale which incorporates 14 items organised in seven questions about anxiety and seven questions about depression.[59] In addition, depressive symptoms will also be assessed by the Patient Health Questionnaire-9, which has been validated in patients with cancer.[60]

Health-related quality of life (HRQoL) is assessed by the European Organisation Research and Treatment of Cancer-Quality of Life-C30 scale. This validated questionnaire consists of five functional scales (physical, emotional, role, cognitive and social functioning), one quality of life scale and one symptom scale.[61] Additionally, an overall sum score can be calculated that represents overall HRQoL.[62]

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Health status is measured using the EuroQol five dimensions and three levels questionnaire consisting of five items with aspect to health status.[63]

Physical activity levels are measured by the short questionnaire to assess health-enhancing physical activity (SQUASH) and an accelerometer. The SQUASH is used to assess habitual physical activity, which includes commuting, leisure time and household activities, and activities at work and/or school.[64] In addition, all participants wear an accelerometer (Actigraph) for 7 days at the beginning of the intervention period (before the start of the exercise programme) and during the final 7 days of the intervention period.

Sedentary time is assessed by two questions of the International Physical Activity Questionnaires for an estimated sitting time weekly.[65]

Work performance is assessed by the Work Ability Index containing seven items on demand of work, worker's health status and recourses which results in a summary score.[66 67]

Anthropometrics (height, weight, waist and hip circumference) are measured in light clothing and without shoes. Body weight is measured on an analogue weighting scale and height by a measuring rod. The body mass index is calculated as the weight in kilograms divided by the height in metre squared (kg/m^2). Waist circumference (to the nearest 0.5 cm) is measured standing at the smallest circumference between abdomen and chest. Hip circumference (to the nearest 0.5 cm) is measured standing as the largest circumference between waist and thigh. Waist and hip circumferences are measured twice and averaged.

Physical fitness is assessed by a sports medicine physician using a CPET with continuous breathing gas analysis at a cycle ergometer. After a 1 min warm-up under no load, the workload increases by 10, 15, or 20 watt, dependent on the patient's condition. The workload increases gradually and the peak workload is reached around 10 min after the start. The test stops at patients' symptoms or at the physicians' discretions. After the test is terminated, a 3 min cooling-down is performed. Borg scores are taken for fatigue, pain and dyspnoea before and directly after the exercise test. Expired gases and minute ventilation, heart rate and ECG are monitored continuously. Peak workload, peak oxygen uptake and peak heart rate are used for analyses. The peak heart rate achieved on the CPET is also used for determining the HRR to estimate the individual training intensity for patients participating in the exercise programme.

Medical data (date of diagnosis, tumour type, disease stage, type of treatment, comorbidity, endocrine therapy, menopausal status) are retrieved from medical records and The Netherlands Cancer Registry. Medication use is asked at every visit.

Blood sampling is performed to determine biomarkers, such as inflammatory factors and BDNF. Blood samples are stored in the Utrecht Medical Center Utrecht biobank and will be determined in the future.

Adherence to the exercise intervention incorporating both attendance and compliance for the exercise protocol is registered in the exercise logs of the intervention group by the physiotherapist (supervised exercise programme) or the participant (Nordic/power walking).

All adverse events potentially related to the study reported by the patient or observed by the investigator or the physiotherapists are recorded. Serious adverse events are reported to the ethical committee who approved the protocol (Medische Ethical Committee (METC), UMC Utrecht).

Eighteen months follow-up measurements

Eighteen months after baseline, the online outcome assessments are repeated. These consist of the online neuropsychological test battery and the same patient-reported outcomes used during baseline and 6 months follow-up.

Sample size

Our primary outcome is the total recall score on the HVLT-R. We consider a change in score from baseline of 5 or more points as a clinical relevant improvement defined by the Reliable Change Index.[68 69] This test is recommended for assessment of patients with cancer experiencing late cognitive problems and has good sensitivity.[4] Each patient's total recall score recorded at 6 months is assigned a binary outcome as improvement or failure (stable or declined). A sample size of 73 patients per group is needed to detect an absolute difference of 20% between groups, considering a Fisher's exact test with a nominal 0.05 two-sided significance level and power of 82%. Taking into account 20% drop-out, 90 patients per group are needed (total 180). This sample size also achieves >90% power to detect a meaningful important difference of 1.0 and 0.9 for 'remembering' and 'paying attention' for self-reported cognitive complaints measured with the MDASI-MM.

Data analysis

Demographics and other characteristics will be reported descriptively, by treatment group. Means and SD will be calculated for continuous (near-)normally distributed variables and medians and ranges for non-normally distributed variables. Categorical variables will be presented by frequencies per group (absolute numbers and percentages).

For the primary intention-to-treat (ITT) analysis, we will compare the number of patients showing postintervention improvement in the HVLT-R between the intervention group and control group using Fisher's exact tests. The treatment effect will be expressed as an effect estimate with 95% CIs, adjusted for key prognostic factors (eg, age) and baseline HVLT-R, estimated from log-binomial regression models.

Analysis of covariance (ANCOVA) will be used to analyse the ITT effect on other neuropsychological outcome measures (continuous outcomes of the online

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test battery) and imaging outcomes. The ANCOVA will include the baseline measure and stratification factors as covariates. Complete cases for both baseline and follow-up measurements will be analysed for the different outcomes.[70] If missing values exceed 10%, we additionally will repeat the analysis by using multiple imputation.

As per protocol analyses, we will repeat the cognitive and imaging analyses for the patients with a minimal adherence of 80% only. Adherence to the physical therapy training and the Nordic/power walking will be defined as a percentage (the number of attended sessions divided by the number of sessions offered).

Linear regression analysis adjusted for baseline will be used to assess the association between changes in brain structure/function and changes in cognitive functioning. The same analyses will be performed for the association between changes in cognitive functioning and changes in quality of life and work performance.

For the long-term effects, mixed-effect models will be used to analyse the effects of the baseline measurements and two follow-up measurements at 6 and 18 months simultaneously.

Patient and public involvement

During the development and recruitment phase of the PAM study, two patient advocates advised the study team. A comparable exercise intervention was used in earlier studies in patients with cancer (Physical Activity during Cancer Treatment (PACT) study[71 72]) and a study in postmenopausal women (Sex Hormones And Physical Exercise (SHAPE) II study[73]). The burden of the intervention is also assessed by the patient advocates. We will communicate the results of the study to the participating women by a newsletter and a seminar.

Ethics and dissemination

Ethics

Exercise programmes are recommended in breast cancer survivors as part of care according to multiple guidelines.[74–77] Physical exercise has beneficial effects on fatigue, HRQoL, anxiety, cardiorespiratory fitness, emotional or perceived physical and social function in patients with breast cancer.[78] Exercise interventions for cancer survivors are feasible, although achieving high adherence rates appears to be challenging.[79]

Patients who are randomised into the control group have the opportunity to follow a 3-month exercise programme after the study period. Earlier research has shown that patients participating in exercise-oncology studies are motivated to become more physically active and subsequently the risk of contamination between study groups is increased. A systematic review on control group design, contamination and drop-out in exercise-oncology trials showed that control groups receiving an intervention after the study period had lower contamination and drop-out rates.[80] For this reason and for ethical reasons, we offer patients randomised to the control group an exercise programme after the study period.

This study includes MRI assessments of the brain and a CPET with ECG monitoring, which might involve incidental findings. The majority of the incidental findings will presumably not have clinical consequences and include a wait-and-see policy.[81] In healthy people, the prevalence of incidental findings with clinical consequences on brain MRI scans is 2.7% and increases with age.[82] More incidental findings are expected in this study since metastases will happen more frequently in the study population. Furthermore, a previous study showed a higher prevalence of pituitary macroadenomas in patients with breast cancer compared with a reference group.[83] If an incidental finding is found which is clinically relevant, the participant and her physician will be informed as stated in the informed consent form. Since incidental findings might include metastases, informing patients might result in increased stress. Therefore, particular attention will be given to the quality of communication to the patient.

Dissemination

To date, no pharmacological intervention exists that can prevent or diminish cognitive problems in patients with non-central nervous system cancer. Physical exercise is a promising non-pharmacological intervention for cognitive decline. If physical exercise appears to be effective, patients with breast cancer with cognitive problems can be offered an evidence-based intervention to reduce these problems and hence improve their quality of life. Furthermore, if effective, this might provide further evidence to support the implementation of routine exercise programmes during cancer treatment with the aim to minimise cognitive problems that might arise.

Since preclinical and human studies have shown that a much wider spectrum of chemotherapy than applied in treatment of breast cancer is associated with cognitive change, we expect that the results of this study will also be applicable for chemotherapy-exposed patients with other solid cancer types with cognitive problems.[2] Consequently, this study might have a large positive impact on the quality of life of the growing community of (breast) cancer survivors.

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neuropsychological, neuroimaging and physiological expertise. LW wrote the first draft of this manuscript. All authors contributed and approved the final version of the manuscript for publication. We would like to thank the patient advocates, Yve Brouwers and Cornelie Bierens de Haan, who contributed to the design and conduction of the PAM study.

Funding This work is supported by KWF kankerbestrijding, grant number UU 2015-7954.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Medical Ethics Committee of the University Medical Center (UMC) Utrecht approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

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