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Effect of Physical Exercise on MRI-Assessed Brain Perfusion in Chemotherapy-Treated Breast Cancer Patients: A Randomized Controlled Trial

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Background: Exercise is a promising intervention to alleviate cognitive problems in breast cancer patients, but studies on mechanisms underlying these effects are lacking.
Purpose: Investigating whether an exercise intervention can affect cerebral blood flow (CBF) in cognitively impaired breast cancer patients and to determine if CBF changes relate to memory function.
Study Type: Prospective.
Population: A total of 181 chemotherapy-treated stage I–III breast cancer patients with cognitive problems and relatively low physical activity levels (≤150 minutes moderate to vigorous physical activity per week), divided into an exercise (N = 91) or control group (N = 90).
Field Strength/Sequence: Two-dimensional echo planar pseudo-continuous arterial spin labeling CBF sequence at 3 T.
Assessment: The 6-month long intervention consisted of (supervised) aerobic and strength training, 4 × 1 hour/week. Measurements at baseline (2–4 years post-diagnosis) and after 6 months included gray matter CBF in the whole brain, hippocampus, anterior cingulate cortex, and posterior cingulate cortex. Physical fitness and memory function were also assessed. Subgroup analyses were performed in patients with high fatigue levels at baseline.
Statistical Tests: Multiple regression analyses with a two-sided alpha of 0.05 for all analyses.
Results: There was a significant improvement in physical fitness (VO_{2peak} in mL/minute/kg) in the intervention group (N = 53) compared to controls (N = 51, β = 1.47 mL/minute/kg, 95% CI: 0.44–2.50). However, no intervention effects on CBF were found (eg, whole brain: $P = 0.565$). Highly fatigued patients showed larger but insignificant treatment effects on CBF (eg, whole brain: $P = 0.098$). Additionally, irrespective of group, a change in physical fitness was positively associated

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with changes in CBF (eg, whole brain: $\beta = 0.75$, 95% CI: 0.07–1.43). There was no significant relation between CBF changes and changes in memory performance.
Data Conclusion: The exercise intervention did not affect CBF of cognitively affected breast cancer patients. A change in physical fitness was associated with changes in CBF, but changes in CBF were not associated with memory functioning.
Level of Evidence: 1
Technical Efficacy Stage: 5

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Many patients diagnosed and treated for cancer, especially with chemotherapy, must deal with long-lasting adverse effects, including cognitive problems. Approximately 25% of breast cancer patients have cancer-related cognitive impairment in domains such as learning and memory, attention, and executive functioning.[1,2] These cognitive problems are of mild to moderate severity but can profoundly affect quality of life and daily functioning.[2–4]

The exact mechanism of cancer-treatment damage leading to diminished cognitive performance is unclear and is likely to be multifactorial.[3] A known adverse effect of cancer treatment, especially chemotherapy, is an increased risk of cardiovascular diseases and damage to the vascular system.[5] Damage to the vascular system may result in changes in cerebral blood flow (CBF), a measure of brain function, which has been associated with cognitive functioning.[6] Absolute values of CBF can be measured noninvasively with arterial spin labeling (ASL),[7] which offers reasonable reproducibility over time, even in older subjects. In breast cancer patients, increased CBF, or hyperperfusion, has been observed from pre- to (within 1 month) post-treatment.[8,9] Results from functional MRI studies, using a different parameter to measure brain function, have agreed with these results, showing increased neuronal activity after cancer treatment.[10] Twenty years after diagnosis, however, hypoperfusion has also been reported in cancer survivors compared to age-matched noncancer controls.[11] Together, these results suggest that initially a compensatory mechanism may lead to hyperactivity and hyperperfusion to maintain cognitive performance, while over time, vascular damage may lead to hypoperfusion with diminished cognitive performance as a result.

Currently, no mechanistic-driven evidence-based therapies are available to diminish cognitive impairment, as assessed with formal testing.[12] Physical exercise, however, has the potential to affect brain structure and improve brain function.[13] Physical fitness and physical activity have been associated with increased CBF in studies involving healthy elderly,[14,15] and adults at risk for Alzheimer's disease.[16] Additionally, an increase in brain perfusion following an aerobic exercise intervention of 3 months or longer has been shown in healthy volunteers, patients with coronary artery disease, and patients with mild cognitive impairment.[17,18] This increased brain perfusion was related to improved memory functioning.[19–21] Furthermore, perfusion decrease after aerobic exercise has been reported in patients with mild cognitive impairment and Alzheimer's disease,[21,22] potentially as a result of perfusion normalization through exercise after a compensatory mechanism in (preclinical stages of) Alzheimer's disease.[23] Few studies have investigated the effects of an exercise intervention on CBF in patients treated for noncentral nervous system cancer. A pilot study in 17 female cancer survivors showed (nonsignificant) moderate to large effects of high-intensity interval training resulting in increased CBF.[24] Together, these results suggest that a countering effect of exercise on cancer therapy-related changes to CBF might explain the (potential) positive effects on cognition in breast cancer survivors. However, data from a large randomized controlled trial investigating exercise effects on CBF in cancer patients are still lacking.

The Physical Activity and Memory (PAM) study was designed to gain more insight into exercise effects on cognition and the brain in breast cancer patients.[25] Findings from the PAM study have indicated no significant intervention effects on tested cognitive functioning, but have shown significant improvements on tests for self-reported cognitive functioning.[26] Furthermore, learning and memory functioning and processing speed were improved in highly fatigued breast cancer patients who exercised, compared to highly fatigued patients from the control group.[26] The effects of physical exercise on CBF might be one of the mechanisms underlying this reduction of cognitive problems in cancer patients with noncentral nervous system disease.

Thus, the aim of this study was to evaluate the effects of exercise on CBF (whole brain, and in areas known to be involved in memory function (hippocampus) and other important cognitive functions (anterior cingulate cortex [ACC] and posterior cingulate cortex [PCC]) in chemotherapy-treated breast cancer patients with self-reported cognitive complaints and cognitive problems as assessed with neuropsychological tests. Also, we aimed to determine whether these effects were related to changes in memory function.

Materials and Methods

Design and Patients

An extensive description of the PAM study can be found in Witlox et al.[25] In short, the PAM study is a randomized controlled trial with an intervention and control group. Measurements, at baseline and 6-month follow-up, were collected between December 2016 and September 2020 at the University Medical Center (UMC), Utrecht, The Netherlands. The study was approved by the Medical Ethics

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Committee of the UMC Utrecht and written informed consent was collected from all patients before baseline measurements. This trial was registered in the Netherlands Trial Registry: Trial NL5924 (NTR6104), https://www.trialregister.nl/trial/5924.

Female patients with affected cognition (see below) were included in the PAM study. Inclusion criteria were 2–4 years after stage I–III breast cancer diagnosis, (neo)adjuvant chemotherapy treatment, age 30–75 years, no evidence of disease recurrence, relatively inactive lifestyle (≤150 minutes of moderate to vigorous physical activity per week), sufficient proficiency in the Dutch language, and agreed to be randomized to one of the study arms. Women were excluded if they were diagnosed with neurological disorders that may affect cognitive functioning (eg, dementia, multiple sclerosis), had contraindications for MRI scanning or were unable to (safely) perform the exercise program, and/or planned to switch or stop using endocrine therapy 4 months prior to study enrolment or during the study period.

Recruitment and Randomization

Patients were invited to participate in the study through letters sent from 21 Dutch hospitals (N = 3258), or self-registered (N = 165) (Fig. 1). Eligibility screening was performed by phone (N = 841) and included questions about the severity and onset of the cognitive complaints, activity level, and ability to safely undergo an MRI examination and execute the exercise intervention. To confirm affected cognition, eligible patients were requested to complete an online neuropsychological test battery: the Amsterdam Cognition Scan (ACS) (N = 409).[27] Cognitive functioning was considered affected if performance was ≥1 normative standard deviation below the average performance of healthy females aged 30–75 years, on at least 2 of the 11 test scores in different cognitive domains (Table 1).[25–27]

Randomization to the intervention or control group (1:1) was performed after baseline measurements by a study team member using an in-house computer algorithm ensuring blinded intervention allocation. Randomization was stratified by age category (30–44, 45–59, 60–75 years) and endocrine therapy (yes, no).

Exercise Intervention and Control Group

The intervention consisted of 6 months of physical exercise. Twice per week 1 hour of supervised exercise was delivered by a physiotherapist and comprised of aerobic training and strength exercises (Table 2). Additionally, patients were requested to perform Nordic walking or power walking for 1 hour, twice per week. Training sessions were logged by the physiotherapist and the patient. The intensity of the supervised aerobic training was based on individual fitness levels measured with a cardiopulmonary exercise test (CPET) at baseline. Repeatedly performed 20-repetition maximum (20-RM) and 15-RM muscle strength tests, supervised by the physiotherapist, were used to determine the intensity of the strength training. As the supervised program progressed, the intensity increased. The intensity of the Nordic/power walking was also based on the CPET performed during baseline measurements. Patients were requested to walk at an intensity that achieved between 55% and 65% of their calculated heart rate reserve. Heart rate monitors were provided by the study team. A monitoring visit at the physiotherapy practice was performed 1 month after the start of the intervention, to verify protocol adherence.

Patients randomized to the control group were requested to maintain their habitual physical activity level during the study period. After study completion, they were offered a shortened supervised exercise intervention program of 12 weeks.

MRI ACQUISITION AND ASL IMAGE PROCESSING. MRI was performed with a 3.0 T Philips Achieva full-body scanner using an 8-channel head coil (Best, The Netherlands). Patients were requested to abstain from alcohol consumption and moderate-to-high intensity physical exercise 24 hours before measurements and refrain from caffeine consumption prior to the MRI scan on the day of measurements. Additionally, a CPET was conducted after MRI scan acquisition, to prevent acute exercise effects on CBF. Perfusion-weighted images measuring CBF were obtained with a 2D EPI pseudo-continuous arterial spin labeling sequence (repetition time [TR]/echo time [TE] = 4400 msec/15 msec; 19 slices; 3.0 × 3.0 × 7.0 mm^3 voxels; 30 repetitions; 2 background suppression pulses at 1830 and 3155 msec after the start of labeling; post-labeling delay = 1800–2560 msec (accounting for the 40 msec slice readout time); labeling duration = 1800 msec). An M0 image with identical readout was acquired without labeling and background suppression, and TR = 2000 msec. A sagittal 3D T1-weighted turbo field echo sequence (TR/TE = 7.9/4.5 msec; 192 slices; 1.0 mm isotropic voxels) was included for registration and segmentation purposes and a fluid-attenuated inversion recovery sequence (TR/TE/inversion time [TI] = 11,000/125/2800 msec; 48 contiguous slices; 0.96 × 0.95 × 3.0 mm^3 voxels) for filling white matter (WM) hypointensities on the T1-weighted image. More details are described in Witlox et al.[25]

ExploreASL version 1.9.0 with default settings was used to process the images.[28] In brief, ASL raw data were motion corrected and aligned to the T1-weighted scans. T1-weighted scans were automatically spatially normalized to the Montreal Neurological Institute template and segmented into gray matter (GM) and WM using CAT12. ASL data were quantified according to the consensus recommendations.[7] The mean GM CBF was calculated for the whole brain, hippocampus, ACC, and PCC. The hippocampus was mainly chosen for its involvement in learning and memory functioning, which was the primary endpoint of the PAM study.[25] Furthermore, the hippocampus, ACC, and PCC were chosen based on previous findings, their interconnectivity, and relation with cognitive functioning.[18–21,29] GM and WM segmentations were visually checked. Quantified CBF maps were checked for motion artifacts, labeling asymmetry, and the presence of arterial transit artifacts. This was done through consensus reading by EWK (1 year of experience in ASL processing) and JP (10+ years of experience in ASL processing).

Average values in the ASL control and M0 images varied between subjects and sessions up to an order of magnitude, which is beyond the commonly seen variability. This variation was also present between control and M0 images within a session and thus effectively prevented reliably using M0 images for CBF quantification. The issue persisted despite the fact that the correct Philips scaling factors were applied. Possible sources of the error were a change in scanner gain or issues with data saving in the research Picture Archiving and Communication System. As an alternative way to obtain the correct equilibrium magnetization, we have compensated for the background suppression in the control images. The correction was done in GM voxels only assuming

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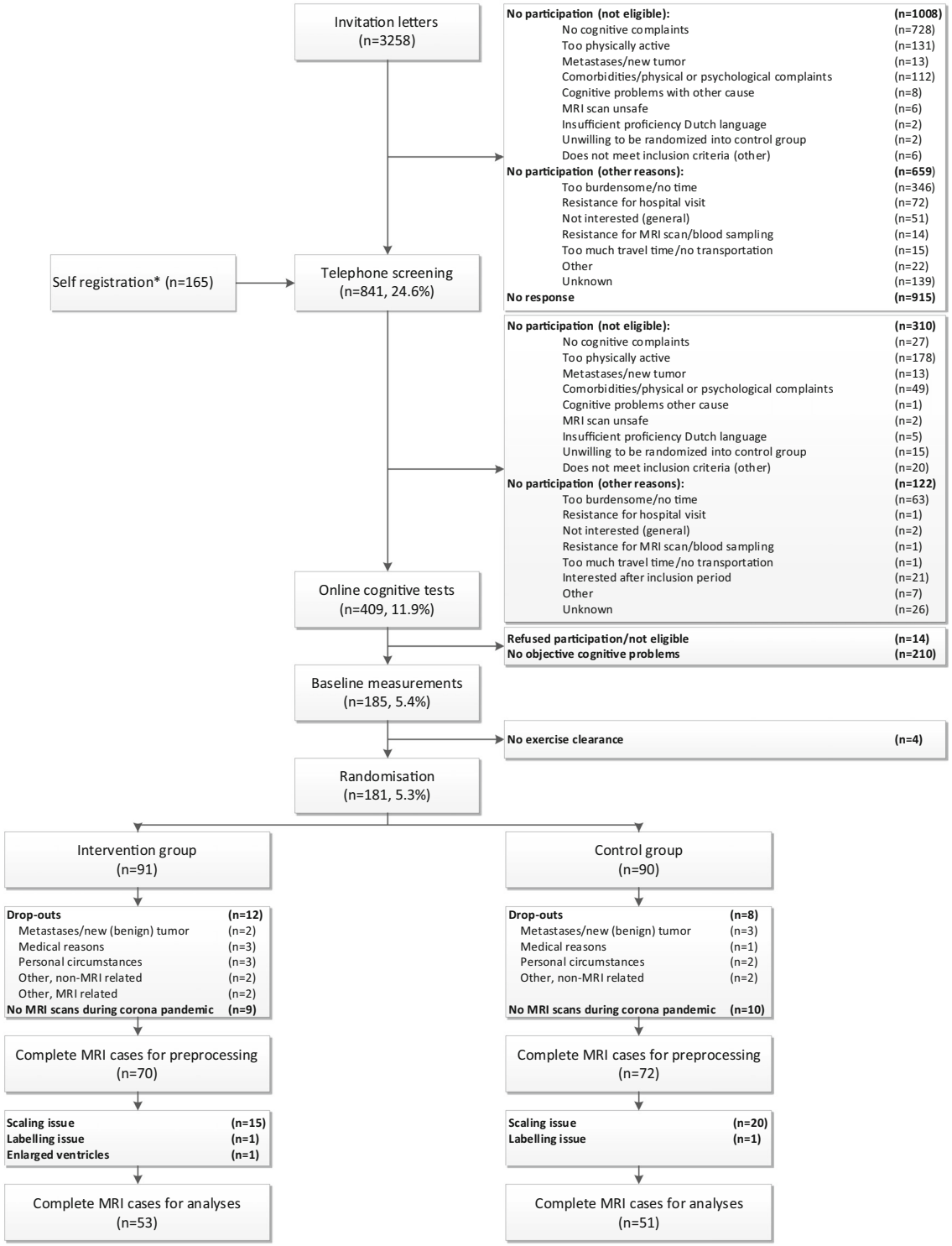

FIGURE 1: Flowchart of inclusion and randomization procedures of the Physical Activity and Memory (PAM) study patients. *Information through social media, pamphlets, and by word of mouth.

tissue T1 time of 1240 msec.[7] The evolution of tissue magnetization in time was estimated after an initial 90° saturation and two 180° inversions at the known background-suppression timings. The relative reduction of the signal at the time of readout was calculated in comparison to the equilibrium signal. This correction factor was applied in all GM voxels and used to approximate a control image without background correction. This corrected control image was then used as an M0 image for the calibration of CBF quantification.

Other Measures

SOCIODEMOGRAPHIC. Sociodemographic measures including age at baseline, highest education attained, menopausal status, and

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TABLE 1. Content of the Amsterdam Cognition Scan

Test Domain	Online Test	Main Outcome Measures	Traditional Equivalent
Learning and memory	Wordlist Learning	Total number of correct responses (Learning: trials 1–5)	Dutch version of Rey Auditory Verbal Learning Test (immediate recall, delayed recall and recognition)
	Wordlist Delayed Recall		
	Wordlist Recognition		
Attention and working memory	Box Tapping	Total number of correctly repeated sequences	Corsi Block-Tapping Test
	Digit Sequences I		WAIS-III Digit Span forward
	Digit Sequences II		WAIS-III Digit Span backward
Processing speed	Reaction Time	Mean reaction time (msec)	Visual Reaction Time (subtest FePsy)
	Connecting the Dots I	Completion time (seconds)	Trail Making Test A
Executive functioning	Connecting the Dots II	Completion time (seconds)	Trail Making Test B
	Place the Beads	Total number of extra moves	Tower of London, Drexel University (ToL-dx)
Motor functioning	Fill the Grid	Completion time (seconds)	Grooved Pegboard

TABLE 2. Supervised Exercise Program 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 minutes, plus 70%–89% HRR 5–10 minutes	
10–17	Interval training: 10 × 30 seconds vigorous to maximal exercise, alternated with 1 minute active rest, plus 10 minutes 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 seconds.
18–26	Interval training: 2 circuits of 8 × 30 seconds vigorous to maximal exercise, alternated with 1 minute active rest, plus 5 minutes 60%–75% endurance	

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

age at menopause were gathered by a questionnaire. Clinical data were obtained from medical records. Information on medication use was collected in a structured interview at the baseline measurement.

PHYSICAL FITNESS. To measure physical fitness, a CPET with a ramp protocol, which included analysis of continuous gas exchange and electrocardiogram monitoring was used. Fitness was expressed as

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TABLE 3. Baseline Demographic and Clinical Characteristics

	Exercise Intervention (N = 53)	Control (N = 51)	*P*
Age (years)	51.7 (9.2)	53.1 (8.9)	0.453
Age category, N (%)			
30–44 years	9 (17.0)	9 (17.6)	
45–59 years	33 (62.3)	29 (56.9)	
60–75 years	11 (20.7)	13 (25.5)	0.824
Education level, N (%)			
High	25 (47.2)	17 (33.3)	
Middle	28 (52.8)	34 (66.7)	
Low	0 (0)	0 (0)	0.151
Physical fitness (VO_{2peak} in mL/minute/kg)	23.5 (4.7)	24.2 (5.9)	0.502
Menopausal status, N (%)			
Pre/peri	6 (11.3)	4 (7.8)	
Post	47 (88.7)	47 (92.2)	0.548
Age of menopause (years)	47.5 (6.7)	47.2 (5.2)	0.812
Time since diagnosis (years)[a]	3.0 (0.7)	3.1 (0.6)	0.326
Tumor grade, N (%)			
I	7 (13.2)	3 (5.9)	
II	21 (39.6)	22 (43.1)	
III	18 (34.0)	20 (39.2)	
Unknown	7 (13.2)	6 (11.8)	0.658
Surgery, N (%)	53 (100)	51 (100)	1.000
Chemotherapy timing, N (%)			
Neoadjuvant	28 (52.8)	24 (47.0)	
Adjuvant	25 (47.2)	26 (51.0)	
Both	0 (0)	1 (2.0)	0.525
Time since completion chemotherapy (years)[a]	2.5 (0.7)	2.7 (0.6)	0.196
Radiotherapy, N (%)			
Yes	40 (75.5)	36 (70.6)	
No	13 (24.5)	15 (29.4)	0.575
Targeted therapy, N (%)			
Yes	13 (24.5)	12 (23.5)	
No	40 (75.5)	39 (76.5)	0.905
Endocrine therapy, N (%)			
Yes	33 (62.3)	30 (58.8)	
No	20 (37.7)	21 (41.2)	0.720
Medication use, N (%)			

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TABLE 3. Continued

	Exercise Intervention (N = 53)	Control (N = 51)	*P*
Cardiovascular	10 (18.9)	10 (19.6)	0.924
Anti-diabetic	1 (1.9)	1 (2.0)	0.978
Psychotropic	17 (32.1)	10 (19.6)	0.147
Pain medication	10 (18.9)	9 (17.6)	0.872

Values indicate mean (SD), unless indicated otherwise. *P*-values indicate overall group differences.
[a]For time since diagnosis, average years were based on 51 intervention patients and 49 control patients. For time since completion chemotherapy, average years were based on 50 intervention patients and 45 control patients.

relative maximum oxygen uptake (VO_{2peak} in mL/minute/kg), which was calculated as an average over the final 30 seconds of exercise on the CPET.

MEMORY FUNCTIONING. The Hopkins Verbal Learning Test-Revised total recall score (HVLT-R total recall), a recommended test to measure memory functioning in cancer patients, was the primary outcome measure of the PAM study. Also, Wordlist Learning of the ACS (ACS Wordlist Learning) was used as an additional measure of memory functioning, since significant intervention effects were observed on this measure in highly fatigued patients.[26]

FATIGUE. Clinically relevant fatigue symptoms were defined by a score of ≥39 on the "fatigue" symptom scale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[30]

STUDY ADHERENCE. Adherence to the exercise program was defined as a combined (average) score for attendance to the supervised sessions and the Nordic or power walking sessions.

Statistical Analysis

All analyses were performed with SPSS version 26.0.0.1. Critical two-sided alpha value was set at 0.05 for all analyses.

Differences in demographic variables between the intervention and control group and between the included subjects and dropouts were analyzed with independent samples *t* tests for continuous variables and chi-square tests for categorical variables.

First, the association between age and whole brain CBF at baseline was assessed using simple regression analysis, to verify the presence of this expected relation. Next, baseline association analysis between VO_{2peak} and whole brain CBF was executed with age as a covariate, using multiple regression analyses.

The effect of the intervention on VO_{2peak} was investigated with multiple regression analysis, including age, endocrine therapy use, and baseline VO_{2peak} as covariates. Moreover, intervention effects on CBF were investigated with multiple regression analyses for the whole brain, hippocampus, ACC, and PCC, respectively. Age, endocrine therapy use (stratification factors), and baseline measurements (whole brain, hippocampus, ACC, or PCC) were included as covariates. After the intention-to-treat analysis, multiple regression analyses were repeated twice: once according to the per protocol principle, including only intervention patients who reached at least 80% adherence to the intervention program ([number of attended sessions/number of offered sessions] × 100), and once including only patients who reported clinically relevant levels of fatigue (EORTC QLQ-C30 "fatigue" ≥ 39) at baseline, because of previous findings in these highly fatigued patients.[26]

To investigate the association between change in VO_{2peak} and CBF change in the whole brain, hippocampus, ACC, and PCC, multiple regression analyses were performed in the entire cohort, with baseline CBF (whole brain, hippocampus, ACC, or PCC) as a covariate.

Association analyses between change in CBF measures and change in cognitive functioning (HVLT-R total recall and ACS Wordlist Learning) were performed using multiple regression analyses with the CBF difference scores and baseline cognitive performance (HVLT-R total recall or ACS Wordlist Learning) included as covariates.

Results

Patient Characteristics

Of the 181 patients included in the PAM study, 142 patients had ASL scans available both at baseline and 6-month follow-up (Fig. 1). Reasons for dropout included: corona pandemic (N = 19), metastases/new (benign) tumor (N = 5), other medical reasons (N = 4), personal circumstances (N = 5), MRI related (N = 2), and other non-MRI related reasons (N = 4) (Fig. 1). Further exclusion during ASL processing included: the scaling issue (only the control/label difference was saved instead of the full control label pairs, background-suppression-corrected control images could not be used for M0 calibration) (N = 35), failed GM and WM segmentation because of an enlarged ventricle system (N = 1), and labeling issues resulting in lack of ASL signal on two follow-up scans (N = 2). Patients not included in these analyses (both patients who dropped out and patients with the scaling issue) more often received a combination of neoadjuvant and adjuvant treatment than included patients. No significant differences between the included patients and the dropouts were found for all other demographic and clinical characteristics (*P*-values lay between 0.072 [menopausal status] and 0.858 [targeted therapy use]).

The final dataset included 53 patients in the intervention group (mean age = 51.7 ± 9.2 years) and 51 patients in

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TABLE 4. Exercise Intervention Effects on Cerebral Blood Flow in Breast Cancer Patients

Outcome Measures		Exercise Intervention, N = 53	Control, N = 51	Between-Group Difference[a] (95% CI)	Effect Size[b]	% Change Intervention[c]	% Change Control[c]	*P*
Whole brain	Baseline	64.4 (11.3)	66.5 (13.5)	0.98 (−2.38 to 4.34)	0.08	+1.49%	−2.02%	0.565
	Follow-up	65.3 (11.3)	65.1 (11.1)					
Hippocampus[d]	Baseline	51.4 (10.2)	53.7 (12.0)	0.50 (−2.70 to 3.69)	0.04	+2.55%	−0.71%	0.758
	Follow-up	52.7 (10.7)	53.3 (9.8)					
ACC	Baseline	73.7 (13.4)	77.0 (16.4)	0.73 (−3.27 to 4.73)	0.05	+1.60%	−1.53%	0.718
	Follow-up	74.9 (13.3)	75.8 (14.4)					
PCC	Baseline	86.0 (15.5)	89.6 (19.8)	0.77 (−3.93 to 5.47)	0.04	+1.05%	−2.09%	0.746
	Follow-up	86.9 (15.4)	87.7 (16.5)					

Values indicate mean (SD) and are presented in mL/100 g/minute, unless denoted otherwise.
ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.
[a]The intervention effect is the regression coefficient of a linear regression analysis adjusted for baseline, age, and endocrine therapy.
[b]Effect sizes (ES) were calculated by dividing beta by the pooled SD at baseline, with positive ES meaning a beneficial effect of the exercise intervention on a specific outcome. ES <0.2 indicate "no effect," ES between 0.2 and 0.5 indicate "small effects," ES between 0.5 and 0.8 indicate "medium effects," and ES ≥0.8 indicate "large effects."
[c]Calculation for average % change between baseline and follow-up: (follow-up − baseline)/baseline × 100.
[d]Data of one additional patient from the control group was missing, because hippocampus size was below threshold settings.

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TABLE 5. Exercise Intervention Effects on Cerebral Blood Flow in Breast Cancer Patients, Per Protocol Analyses

Outcome Measures		Exercise Intervention, N = 37	Control, N = 51	Between-Group Difference[a] (95% CI)	Effect Size[b]	% Change Intervention[c]	% Change Control[c]	*P*
Whole brain	Baseline	64.1 (12.7)	66.5 (13.5)	0.30 (−3.48 to 4.07)	0.02	+0.29%	−2.02%	0.876
	Follow-up	64.3 (12.5)	65.1 (11.1)					
Hippocampus[d]	Baseline	51.7 (11.5)	53.7 (12.0)	0.41 (−3.26 to 4.08)	0.04	+1.89%	−0.71%	0.824
	Follow-up	52.6 (12.0)	53.3 (9.8)					
ACC	Baseline	73.6 (15.0)	77.0 (16.4)	−0.75 (−5.26 to 3.75)	−0.05	−0.67%	−1.53%	0.740
	Follow-up	73.2 (14.5)	75.8 (14.4)					
PCC	Baseline	85.3 (17.4)	89.6 (19.8)	−0.02 (−5.35 to 5.30)	0.00	+0.10%	−2.09%	0.993
	Follow-up	85.4 (16.8)	87.7 (16.5)					

Values indicate mean (SD) and are presented in mL/100 g/minute, unless denoted otherwise.
ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.
[a]The intervention effect is the regression coefficient of a linear regression analysis adjusted for baseline, age, and endocrine therapy.
[b]Effect sizes (ES) were calculated by dividing beta by the pooled SD at baseline, with positive ES meaning a beneficial effect of the exercise intervention on a specific outcome. ES <0.2 indicate "no effect," ES between 0.2 and 0.5 indicate "small effects," ES between 0.5 and 0.8 indicate "medium effects," and ES ≥0.8 indicate "large effects."
[c]Calculation for average % change between baseline and follow-up: (follow-up − baseline)/baseline × 100.
[d]Data of one additional patient from the control group was missing, because hippocampus size was below threshold settings.

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TABLE 6. Exercise Intervention Effects on Cerebral Blood Flow in Highly Fatigued Breast Cancer Patients

Outcome Measures		Exercise Intervention, N = 27	Control, N = 19	Between-Group Difference[a] (95% CI)	Effect Size[b]	% Change Intervention[c]	% Change Control[c]	*P*
Whole brain	Baseline	65.1 (9.1)	65.2 (14.1)	3.72 (−0.72 to 8.16)	0.33	+1.75%	−3.42%	0.098
	Follow-up	66.3 (10.3)	62.9 (10.0)					
Hippocampus	Baseline	51.5 (8.9)	52.1 (12.2)	2.25 (−2.16 to 6.66)	0.22	+2.50%	−1.86%	0.309
	Follow-up	52.8 (9.9)	51.1 (9.5)					
ACC	Baseline	73.7 (10.7)	75.5 (16.7)	3.33 (−2.52 to 9.18)	0.32	+1.73%	−3.19%	0.257
	Follow-up	74.9 (12.1)	73.1 (13.5)					
PCC	Baseline	86.1 (13.3)	87.8 (20.0)	4.48 (−1.74 to 10.70)	0.28	+2.29%	−2.93%	0.153
	Follow-up	88.1 (13.7)	85.2 (16.0)					

Values indicate mean (SD) and are presented in mL/100 g/minute, unless denoted otherwise.
ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.
[a]The intervention effect is the regression coefficient of a linear regression analysis adjusted for baseline, age, and endocrine therapy.
[b]Effect sizes (ES) were calculated by dividing beta by the pooled SD at baseline, with positive ES meaning a beneficial effect of the exercise intervention on a specific outcome. ES <0.2 indicate "no effect," ES between 0.2 and 0.5 indicate "small effects," ES between 0.5 and 0.8 indicate "medium effects," and ES ≥0.8 indicate "large effects."
[c]Calculation for average % change between baseline and follow-up: (follow-up − baseline)/baseline × 100.

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the control group (mean age = 53.1 ± 8.9 years). There were no between-group differences in demographic and clinical characteristics (Table 3).

Baseline Associations With Age and Physical Fitness

At baseline, an inverse association between whole brain CBF and age was observed ($\beta = 0.52$ mL/100 g/minute, 95% CI: −0.77 to −0.27), that is, older patients had lower whole brain CBF. No association between physical fitness (VO_{2peak}) and whole brain CBF, controlled for age, was found at baseline ($P = 0.970$).

Intervention Effects

There was a significant effect of the exercise intervention on physical fitness (VO_{2peak}) compared to the control group ($\beta = 1.47$ mL/minute/kg, 95% CI: 0.44–2.50). In the intervention group, 66% showed an increase in physical fitness, compared to 31% in the control group. A relevant increase in physical fitness (>10%) was seen in 32% of the patients in the intervention group, compared to 6% in the control group.

Although between-group differences were not significant (whole brain: $P = 0.565$; hippocampus: $P = 0.758$; ACC: $P = 0.718$; PCC: $P = 0.746$), we observed an increase in CBF both globally and regionally in the intervention group and a decrease in the control group (Table 4).

Per protocol analyses (intervention: N = 37 [70% reached ≥80% attendance], control: N = 51) yielded similar results (Table 5).

Analyses in highly fatigued patients (intervention: N = 27; control: N = 19) showed nonsignificant exercise effects on CBF (whole brain: $P = 0.098$; hippocampus: $P = 0.309$; ACC: $P = 0.257$; PCC: $P = 0.153$), with larger effect sizes (0.22–0.33) (Table 6).

Relation Between Physical Fitness Change and CBF Change

Regardless of randomization, an increase in VO_{2peak} from baseline to 6-month follow-up was associated with a

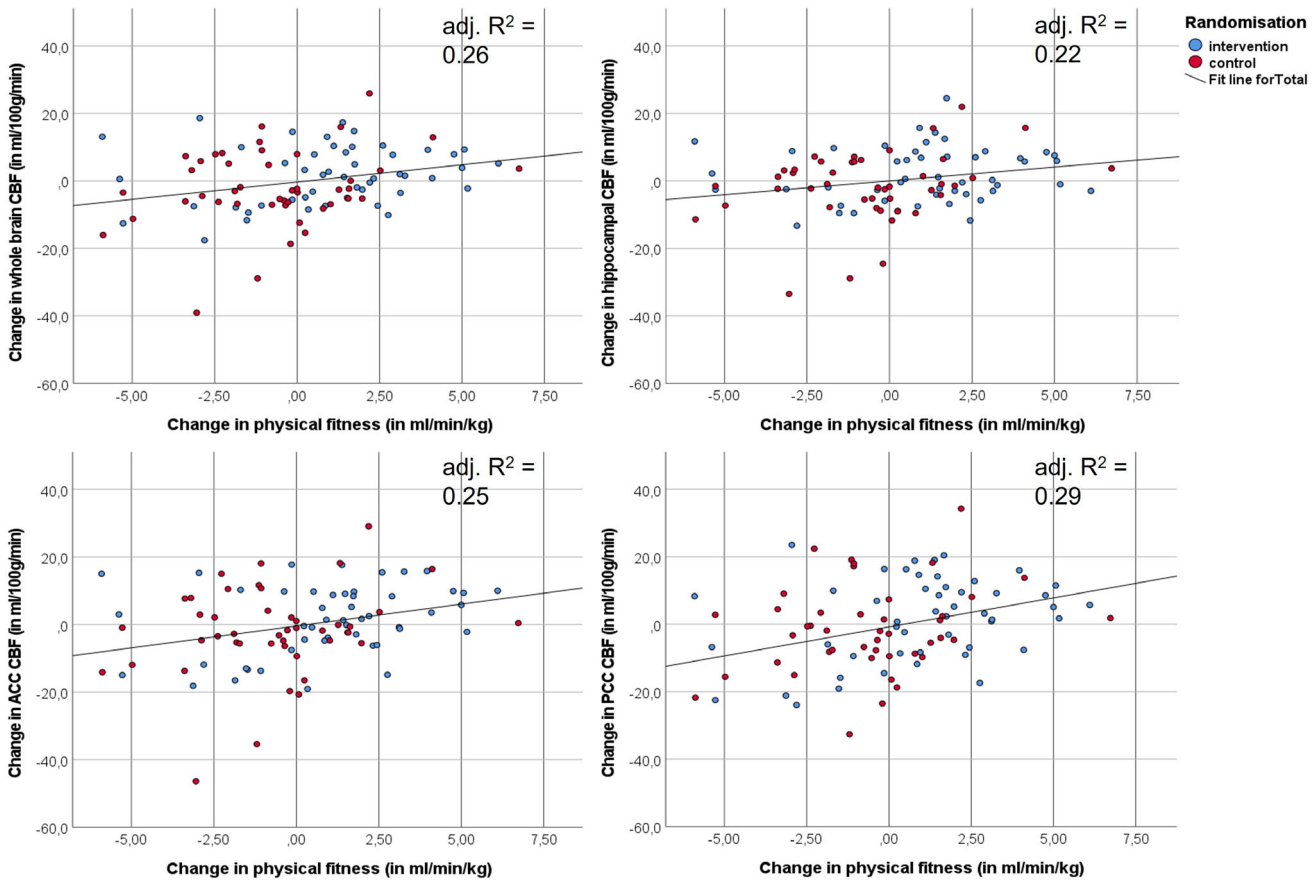

FIGURE 2: Positive associations in a mixed group of all patients between change in physical fitness and changes in gray matter cerebral blood flow, in the whole brain, hippocampus, anterior cingulate cortex, and posterior cingulate cortex. Regression equations: 1) change in whole brain CBF = 25.9 + 0.75 × change in physical fitness − 0.40 × whole brain CBF at baseline; 2) change in hippocampal CBF = 20.3 + 0.54 × change in physical fitness − 0.38 × hippocampal CBF at baseline; 3) change in ACC CBF = 26.8 + 1.03 × change in physical fitness − 0.36 × ACC CBF at baseline; 4) change in PCC CBF = 32.7 + 1.33 × change in physical fitness − 0.38 × PCC CBF at baseline. CBF, cerebral blood flow; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

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significant increase in CBF in the whole brain ($\beta = 0.75$, 95% CI: 0.07–1.43, $R^2 = 0.28$), ACC ($\beta = 1.03$, 95% CI: 0.23–1.82, $R^2 = 0.27$), and PCC ($\beta = 1.33$, 95% CI: 0.40–2.26, $R^2 = 0.31$) (Fig. 2). Change in VO_{2peak} was not significantly related to the change in hippocampal CBF ($P = 0.098$).

Relation Between CBF and Memory Function

CBF changes in the whole brain, hippocampus, ACC, and PCC were not significantly related to changes in memory functioning, both on the HVLT-R total recall score (whole brain: $\beta = -0.038$ [95% CI: −0.115 to 0.040], $P = 0.337$; hippocampus: $\beta = -0.027$ [95% CI: −0.108 to 0.055], $P = 0.518$; ACC: $\beta = -0.061$ [95% CI: −0.127 to 0.004], $P = 0.067$; PCC: $\beta = -0.030$ [95% CI: −0.085 to 0.024], $P = 0.269$) and ACS Wordlist Learning (whole brain: $\beta = -0.004$ [95% CI: −0.142 to 0.134], $P = 0.954$; hippocampus: $\beta = -0.008$ [95% CI: −0.157 to 0.140], $P = 0.910$; ACC: $\beta = -0.019$ [95% CI: −0.139 to 0.101], $P = 0.750$; PCC: $\beta = 0.011$ [95% CI: −0.088 to 0.111], $P = 0.821$).

Discussion

This study has three main findings. First, the exercise intervention had no significant effects on CBF. Also in highly fatigued patients, exercise effects on CBF were not significant, although the effects were numerically stronger in this specific group. Second, independent of randomization, there was a significant association between improvement of physical fitness and an increase in global and regional CBF, despite the lack of a relationship at baseline between fitness levels and CBF. Finally, changes in CBF were not related to changes in memory functioning.

Improved physical fitness is an established result of exercise participation.[31] The PAM study confirmed this as the intervention successfully resulted in higher levels of physical fitness. In the current study, we observed a relation between physical fitness gains and increased CBF, indicating a dose–response relation between physical fitness and CBF. A comparable result of a (marginally significant) positive association between physical fitness and CBF has recently been reported in patients with mild cognitive impairment[32] and healthy young adults.[33] Kaiser et al argued that physical fitness has a more global, rather than a regional effect on CBF,[33] and our results are in agreement with this statement. We reported associations between improved physical fitness and increased CBF in the whole brain, and regionally in the ACC and PCC. The association for hippocampal CBF was not significant, but the direction and magnitude of the association were comparable to the analyses for whole brain and regional CBF. This is consistent with previous findings of significant CBF changes after exercise in the ACC,[17–19,21] but not in the hippocampus.[19] The most probable reason is that the effect is more difficult to measure in the hippocampus, due to its smaller size and vascularization.[34] Furthermore, although we observed an association between improved physical fitness and increased CBF, we did not find an intervention effect on CBF. This is not an uncommon finding[33] as the effect of the exercise intervention on physical fitness might have been too small to observe.

In previous studies with PAM data, we additionally focused on the subgroup of patients who had cognitive complaints combined with high fatigue levels. We observed significant improvements in learning and memory functioning and processing speed[26]; a decrease in hippocampal (subfield) volume, which was related to improved memory functioning[35]; and a decrease in regional fractional anisotropy in the intervention group compared to the controls. In the current study, we found small positive, but not significant, effects of the exercise intervention on CBF in highly fatigued patients. The decrease, instead of an increase, in hippocampal (subfield) volume and regional fractional anisotropy seemed counterintuitive. Nevertheless, in the current study, we also reported (stronger) intervention effects on the brain in this subgroup than in the total group of breast cancer patients. In these highly fatigued patients, the intervention had a similar effect on physical fitness (data not shown[35]), which suggests that participating in the exercise intervention had a more pronounced effect on the brain and cognitive functioning in these patients than in other cognitively affected breast cancer patients. Research into the underlying mechanisms in this group is needed. We speculated that inflammation might initially have been higher in these patients and that this might have contributed to developing cognitive problems and fatigue symptoms.[26,35] Both fatigue and cognitive problems have been associated with (neuro)inflammation,[2,36] and even 20 years after breast cancer treatment, higher inflammatory markers have been observed in patients compared to controls.[37] Physical exercise might attenuate these inflammatory effects.

Strengths of this PAM study are the design of the study and the intervention. We included relatively inactive breast cancer patients with affected cognitive functioning to ensure we targeted a relevant patient population. Also, many possible confounding factors in measuring CBF, such as caffeine use, alcohol intake, acute exercise effects, and diurnal rhythm, were anticipated in the study design. Additionally, we carefully considered the design of the intervention in terms of duration (6 months) and intensity (moderate-to-high, 4 hours/week of aerobic and resistance training). We also (partly) supervised the patients to target the mechanisms expected to influence cognitive functioning and they showed good adherence to the training program. At the baseline measurement, we found CBF decreases with older age, which is in accordance with other literature reports.[38] This instills confidence in the correct execution of (pre)processing procedures.[38]

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Limitations

First, we encountered an ASL image scaling issue. No effect of the scaling correction is to be expected on within-subject longitudinal changes in CBF. However, the scaling correction might have led to additional between-subject variance in CBF values and thus lowered the statistical power for baseline associations (eg, physical fitness and CBF). Second, by selecting relatively inactive breast cancer patients, the variance in physical fitness level was lower than it would have been in a random selection of breast cancer patients, which could have additionally impacted the baseline association of physical fitness and CBF. Also, note that, for all analyses, approximately 25% of data were lost, thereby reducing statistical power. Potential interesting subgroup analyses in, for example, different age categories would be underpowered. Third, we could not correct for hematocrit changes. The exercise intervention might have resulted in an increased hematocrit level.[39] Increased hematocrit decreases the T1-time of blood, which translates to lower ASL signal.[40] This might have resulted in an underestimated CBF at follow-up, and may contribute to the lack of finding positive intervention effects.

Conclusion

A moderate-to-high intensity exercise intervention of 6 months did not result in significant effects on CBF in relatively inactive breast cancer patients with affected cognitive functioning. However, across exercise and control groups, an increase in physical fitness over 6 months was associated with an increase in CBF, both whole brain and regionally, suggesting that physical fitness has a widespread effect on CBF. In highly fatigued breast cancer patients, the intervention showed a larger, yet not significant, effect on CBF. More research on intervention effects in highly fatigued breast cancer patients with affected cognition is necessary to replicate this finding.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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