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Differences in total cognition and cerebrovascular function in female breast cancer survivors and cancer-free women

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ABSTRACT

Reduced cognition is often reported by breast cancer patients and survivors, but the mechanisms for this decline are yet to be determined. We compared the differences in cerebrovascular function and cognition in breast cancer survivors ($n = 15$) and cancer-free women ($n = 15$) matched by age and body mass index. Participants undertook anthropometric, mood, cardiovascular, exercise performance, strength, cerebrovascular, and cognitive measurements. Transcranial Doppler ultrasound was used to measure the cerebrovascular responsiveness (CVR) to physiological (hypercapnia; 5% carbon dioxide) and psychological stimuli. Breast cancer survivors had a lower CVR to hypercapnia (21.5 ± 12.8 vs 66.0 ± 20.9%, $P < 0.001$), CVR to cognitive stimuli (15.1 ± 1.5 vs 23.7 ± 9.0%, $P < 0.001$) and total composite cognitive score (100 ± 12 vs. 113 ± 7, $P = 0.003$) than cancer-free women. These parameters remained statistically different between the groups following adjustments for covariates using an analysis of co-variance. We observed significant correlations between multiple measures and exercise capacity the only variable positively correlated to all primary measures (CVR to hypercapnia, $r = 0.492$, $P = 0.007$; CVR to cognitive stimuli $r = 0.555$, $P = 0.003$; and total composite cognitive score, $r = 0.625$, $P < 0.001$). In this study, breast cancer survivors had lower cerebrovascular and cognitive function than age-matched cancer-free women, which may be attributable to the effects of cancer and cancer treatment on brain health.

1. Introduction

Breast cancer is the most diagnosed cancer globally, and the second leading cause of cancer death in women [1]. However, the rates of short- and long-term survivorship are increasing, particularly in developed countries such as Australia, where the current five year survival rate is 91.5% [2,3]. This is partly due to improved screening campaigns and advanced breast cancer therapies, which have significantly reduced mortality and recurrence [1]. Although the treatments for breast cancer are effective in prolonging life, they can be associated with both short and long-term side effects including reduced cognition, which is reported by some breast cancer patients and survivors [4]. This can reduce the ability of the brain to acquire, process, store and retrieve information, in order to guide thoughts, actions and behaviours [5], thus reducing their quality of life [6].

Up to 75% of breast cancer patients report cognitive decline during treatment and into survivorship [7]. This is typically self-reported [8], but several studies have objectively identified a decline in one or more cognitive domains including processing speed [9], language [10], attention [11], executive function [11], learning [12] and memory [13], all of which can reduce quality of life [14]. However, there are no studies that have objectively measured the total cognitive capacity of breast cancer survivors. Existing studies have focused upon measuring cognitive performance in only specific domains. This is a significant limitation as measurements of total cognitive capacity better reflect overall cognition [5] and demonstrate higher sensitivity and lower intra-individual variability than individual measures in other ageing, at-risk populations [15].

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Despite studies investigating the effect anti-cancer therapies have on cognition, the mechanisms underlying how reduced cognition occurs in breast cancer survivors have not been elucidated [16]. However, the development of reduced cognition may be associated with a reduction in cerebrovascular function, as it is well established that this precedes a decline in cognition in older adults with cognitive impairment [17]. The reduction in cerebrovascular function is associated with increased oxidative stress and inflammation, thus impairing the regulatory mechanisms associated with maintaining cerebral blood flow (CBF) [18]. These mechanisms include the cerebrovascular responsiveness (CVR) to increased neuronal metabolism (neurovascular coupling) and environmental changes [18]. These changes are readily measured by challenging an individual with either a physiological or psychological stimulus [19]. Further, the chronic increase in oxidative stress and inflammation, which is also observed in breast cancer, may exacerbate the decline in cerebrovascular function [20] and explain the resultant decline in cognitive function in breast cancer survivors.

Studies investigating the relationship between cerebrovascular function and cognition in breast cancer survivors are limited. A recent study demonstrated that breast cancer survivors treated with chemotherapy and radiotherapy (up to 20 years post-treatment) had lower total CBF than cancer-free, age-matched women [21]. However, this study was unable to demonstrate the impact of this decreased perfusion on cognition, as they did not measure the CVR to any stimuli. Measuring CBF alone does not reflect a physiological function, rather, it is the responsiveness to stimuli which reflects the impact of this decreased perfusion on overall brain health and cognitive function [17]. This limitation is important as both cerebrovascular function and cognition are interrelated and no studies to date have measured CVR to either physiological or psychological stimuli in breast cancer survivors.

The aim of this preliminary cross-sectional study was to compare cerebrovascular function and total cognition between breast cancer survivors and cancer-free, age-matched women. We hypothesised, that compared to non-cancer controls, breast cancer survivors would have lower cerebrovascular function and total cognition.

2. Methods

2.1. Participants

Fifteen female survivors of stage I to III breast cancer and fifteen females without a cancer diagnosis participated in the study. Participants were matched by age and body mass index (Table 2). Participants were recruited from South-East Queensland, Australia between February 2022 and September 2022 via an approved media campaign that incorporated physical advertisement via media releases and social media. For this study, a breast cancer survivor was defined as someone who had completed their primary treatment (surgery, chemotherapy and/or radiation therapy) and had no evidence of cancer. They were within five years of the end of their primary treatment. Inclusion criteria were: female breast cancer survivors and cancer-free women aged between 40 and 80 years. Exclusion criteria were: aged under 40 years or over 80 years; current smoker; blood pressure $\geq$160/100 mmHg (assessed during laboratory visitation); a significant history of cardiovascular, neurological or cerebrovascular disease. The Yale Physical Activity Survey [22] and a customised health and wellbeing screen were used to determine whether participants met the inclusion and/or exclusion criteria, as well as their self-reported physical activity behaviours. Participants also completed a nutritional questionnaire (Automated Self-Administered 24 h Dietary Assessment Tool; National Institute of Health, Bethesda, MA, USA) shortly after their visit to estimate energy intake over a typical 24 h period [23]. All study procedures were approved by the University of Southern Queensland Research Ethics Committee (H22REA103), which adheres to the Declaration of Helsinki. Participants provided written, informed consent prior to participation in the study.

2.2. Experimental design

The study utilised a cross-sectional design. Participants visited the laboratory on a single occasion and undertook anthropometric, cardiovascular, exercise performance, strength, cerebrovascular and cognitive measurements and completed the Profile of Moods State questionnaire (POMS). Scores for the POMS were calculated as previously described, where lower values in the negative mood states and total mood disturbance indicated better mood, while higher values in the positive mood states were associated with positive mood [24]. Participants were also instructed to abstain from food, coffee, tea and other stimulants for 2 h prior to testing. They were also requested to refrain from moderate-vigorous intensity exercise for 24 h before each visit and to take their daily supplements and medication, according to their normal schedule.

2.3. Basal cerebral haemodynamics

Transcranial Doppler ultrasonography (TCD; DopplerBox X; Compumedics DWL, Singen, Germany) was used to measure basal cerebrovascular haemodynamics, including minimum, maximum and mean values for both middle cerebral artery velocity (MCA_V) and cerebral pulsatility, as well as CVR in response to hypercapnia and cognitive stimuli following at least 10 min of quiet rest in a seated position [25–27]. Participants were seated and fitted with a headpiece which housed two 2-MHz TCD ultrasound probes that were fixed and aligned bilaterally to the left and right cranial temporal bone windows to insonate the MCA bilaterally at a depth of approximately 40–65 mm through the transtemporal window using standardised techniques as previously described [27,28]. Once a suitable blood flow signal was obtained, participants were asked to sit quietly while basal measurements were recorded for 30 s.

2.4. Cerebrovascular responsiveness to hypercapnia

Participants were subsequently challenged with a hypercapnic stimulus for 3 min and monitored for another 1 min following removal. This process was performed in duplicate following a 5 min rest period (whilst participants breathed in room air) to ensure mean MCA_V returned to baseline values [25,26]. Participants breathed through a two-way non-rebreathing valve (model 2730, Hans Rudolph, Kansas City, MO, USA) whilst wearing a nose-clip. The inspiratory port of the two-way valve was connected to 1 m of wide bore tubing distal to a 100 L Douglas bag which contained carbogen gas (5% carbon dioxide and 95% oxygen; Carbogen 5; BOC, Toowoomba, Australia). Flow was measured from the expiratory port of the two-way valve using a pneumotachograph (MLT 1000 L; AD Instruments, Bella Vista, Australia) which was calibrated with a 3 L syringe prior to the commencement of each test. Volume was obtained by numerical integration of the flow signal. End-tidal partial pressures of carbon dioxide ($P_{ET}CO_2$) were sampled from the expiratory port of the two-way valve connected to a gas analyser (ADI ML206; AD Instruments, Bella Vista, Australia) that was calibrated across the physiological range with known gas concentrations (BOC, Toowoomba, Australia). Flow and $P_{ET}CO_2$ measurements were sampled at 200 Hz using an 8-channel Powerlab analog-to-digital converter (AD Instruments, Bella Vista, Australia) interfaced with a computer and displayed in real time during testing. Data were stored for subsequent offline analysis using LabChart software (version 7.2, AD Instruments, Bella Vista, Australia).

2.5. Cognitive function and cerebrovascular responsiveness to cognitive stimuli

Cognitive tests included the Trail Making Task Parts A and B and a National Institute of Health (NIH) Toolbox, which is a battery of cognitive examinations [26,29]. Table 1 describes the domains assessed

Table 1
Summary of cognitive tests and the cognitive domains assessed in each task.

Test	Domain	Reference
Trail Making Task (TMT)		
Parts A and B	Central executive function	[33,34]
National Institute of Health Toolbox		
Dimensional Change Card Sort Test (DCCST)	Cognitive flexibility and attention	[15,35,36]
Picture Vocabulary Test (PVT)	Language and crystallised cognition	[15,35,36]
List Sorting Working Memory Test (LSWMT)	Working memory	[15,35,36]
Oral Reading Recognition Test (ORRT)	Language and crystallised cognition	[15,35,36]
Flanker Inhibitory Control and Attention Test (FICAT)	Attention and inhibitory control	[15,35,36]
Picture Sequence Memory Test (PSMT)	Episodic memory	[15,35,36]
Pattern Comparison Processing Speed Test (PCT)	Processing speed	[15,35,36]

by the individual cognitive tests used in this study. An age adjusted total composite cognitive function score was also derived from the NIH Toolbox [30]. All NIH Toolbox test scores were automatically computed within the program to control for examiner bias. The outputs for all tests were normalised based on the participant demographics entered into the program (age, education level, familial education history, sex, ethnicity and occupation). The number of years participants spent in education was also recorded using the NIH Toolbox. A full description of how these tests are administered, how these scores are calculated and the validation of these tests and scores have been previously described in detail [30–32]. All tests excluding the Trail Making Task were delivered using an iPad (6th generation, Apple Inc, Cupertino, CA, USA). The CVR to cognitive stimuli was assessed during each cognitive task and 30 s of baseline data was recorded before the start of each cognitive task. Participants were also asked to indicate their perceived level of stress and mental fatigue using a digitised visual analog scale (Visual Scale; Bit Genoma Digital Solutions SL, Badalona, Spain) pre and post cognitive testing.

2.6. Data capture and processing for cerebrovascular responsiveness

Beat-to-beat measurements of MCA_V were recorded onto software (QL Reader; Compumedics DWL, Singen, Germany) sampling at 100 Hz and were stored for subsequent offline analysis. If a bilateral signal was not obtained, analysis took place with only the obtainable side. These data were then normalised and analysed using Curve Expert Professional software (Hyams Development, Chattanooga, TE, USA) to determine peak MCA_V, resting MCA_V and resting cerebral pulsatility index (CPI). CVR and CPI were calculated based on the equations [1,2] from previous work [37–39].

$$\mathrm{CPI} = \frac{\text{peak systolic MCAv} - \text{end diastolic MCAv}}{\text{mean MCAv during a cardiac cycle}} \quad [1]$$

$$\mathrm{CVR}\ (\%) = \frac{(\text{peak MCAv} - \text{resting MCAv})}{\text{resting MCAv}} \times 100 \div \text{resting CPI} \quad [2]$$

2.7. Anthropometrics

Participants were instructed to wear light clothing prior to testing and subsequently asked to remove their shoes for measurements. Body mass was measured to the nearest 100 g using an electronic scale (Tanita Ultimate Scale 2000; Tokyo, Japan) and waist and hip circumferences were recorded to the nearest 1 cm using a standard tape measure as previously described [40]. Height was recorded to the nearest 1 cm using a wall-mounted telescopic stadiometer (Seca220; Vogel & Halke, Hamburg, Germany). Height, body mass and waist and hip circumference measurements were measured in duplicate and the mean of the two measurements were analysed.

2.8. Cardiovascular function

Systolic and diastolic blood pressure, mean arterial pressure, heart rate and arterial elasticity were measured non-invasively using a HDI/Pulsewave™ CR-2000 Research Cardiovascular Profiling System (Hypertension Diagnostics, Eagan, MN, USA) [41]. Prior to measurement, participants rested in a seated position for 10 min. Four consecutive readings were recorded approximately 5 min apart by an automated oscillometer, using an appropriately sized blood pressure cuff over the left brachial artery, to assess blood pressure. A tonometer was also placed over the right radial artery, to assess heart rate and estimate arterial elasticity, cardiac output and cardiac index by pulse wave analysis [25,41]. The first reading was used to familiarise participants with the procedure, and then discarded, and the mean of the three subsequent readings was used for analysis.

2.9. Exercise performance and handgrip strength

Exercise performance was assessed using a 6 min walk test (6 MW T) in accordance with published guidelines [42]. Handgrip strength was determined using hand dynamometry as previously described [43]. Participants were permitted three attempts with their dominant and non-dominant hands. The first reading for each hand was used to familiarise participants with the procedure, and then discarded. The second and third readings for each hand were each averaged and used for analysis. Both the 6 MW T and handgrip strength measurements were used to estimate endurance exercise capacity and whole-body strength [42,43].

2.10. Statistical analysis

Statistical analyses were performed using SPSS for Windows (IBM, Chicago, IL, USA). An initial power calculation was performed on the basis of previous research that investigated the differences in CVR between aerobic exercise trained and untrained participants [44]. The power analysis demonstrated that a sample size of 12 per group would be required to detect a 5% difference in CVR between breast cancer survivors and cancer-free participants (alpha = 0.05 and power = 0.8). Normality of data was assessed using a Shapiro-Wilk test. Comparisons between groups for anthropometric, cardiovascular, cognitive, exercise performance, baseline cerebrovascular, baseline respiratory, both CVR to hypercapnia and CVR to cognitive stimuli and strength measures were determined using independent t-tests or Mann-Whitney U-tests for parametric and non-parametric data, respectively. Between-group differences for raw cerebrovascular (excluding CVR) and respiratory measures were analysed using a two-way analysis of variance to determine the effects of 'group' (cancer vs. cancer-free) and 'time' (baseline vs. peak during a challenge). Significant group × time interaction effects were followed by planned pairwise comparisons between groups using the Bonferroni method. Effect sizes were determined using Cohen's d using the following thresholds: $\leq$0.19 = trivial, $\geq$0.2 $\leq$ 0.49 = small, $\geq$0.5 $\leq$ 0.79 = medium, and $\geq$0.8 = large [45]. Pearson's product moment correlation coefficient (parametric data) or Spearman's (non-parametric data) correlation analysis was used to examine the relationship between variables and reported cut-off points to examine these relationships were applied as previously described [46]. An analysis of co-variance (ANCOVA) was performed using objective (non-self-reported) measures that demonstrated a significant relationship with the primary outcomes (covariates) as independent variables and the primary outcomes (CVR to hypercapnia; CVR to cognitive stimuli; total composite cognitive score) as dependent variables. These objectives included average handgrip strength, 6 MW T distance, systolic and diastolic blood pressures, mean arterial pressure, large arterial

compliance, heart rate, resting $P_{ET}CO_2$, resting minute ventilation and years of education. Statistical significance was set at $P < 0.05$. Data are presented as means ± SD.

3. Results

3.1. Participant characteristics

Participant characteristics are shown in Table 2. There were no differences between the groups for age, height, weight and hip and waist circumferences, and years spent in education. Cancer-free women had higher handgrip strength ($d = 0.86$) and walked a longer distance during the 6 MW T ($d = 1.58$) than breast cancer survivors. There were no differences in self-reported physical activity levels between the groups, except for participation in vigorous activity ($d = 0.63$) and standing time ($d = 1.21$), which was higher in the cancer-free women. Breast cancer survivors had a lower nutritional intake compared with cancer-free women ($d = 0.80$). Fatigue was higher in breast cancer survivors than cancer-free women ($d = 0.85$). There were five women currently taking adjuvant treatment for their breast cancer.

3.2. Cardiovascular function

Cardiovascular function is shown in Table 3. Heart rate ($d = 1.16$), systolic ($d = 0.85$) and diastolic ($d = 1.12$) blood pressures, mean arterial pressure ($d = 1.04$) and systemic vascular resistance ($d = 0.86$) were higher in breast cancer survivors compared to cancer-free women. Both large ($d = 1.24$) and small ($d = 1.08$) arterial compliance were lower in breast cancer survivors than cancer-free women. There were no other differences in cardiovascular function between the groups.

Table 2
Participant demographics, anthropometrics, grip strength, exercise performance, nutritional intake and mood for breast cancer survivors and cancer-free women. Values are means ± SD.

Variable	Breast cancer survivors (n = 15)	Cancer-free women (n = 15)	*P* value
Demographics			
Age (years)	63 ± 10	63 ± 7	1.000
Education (years)	17 ± 5	19 ± 5	0.436
Currently prescribed adjuvant treatment (%)	33%	–	–
Anthropometrics			
Body mass (kg)	72.8 ± 16.3	73.1 ± 15.6	0.963
Height (m)	1.63 ± 0.05	1.63 ± 0.05	0.967
Body mass index (kg/m^2)	27.5 ± 5.8	26.5 ± 5.7	0.920
Hip circumference (cm)	108 ± 13	109 ± 13	0.833
Waist circumference (cm)	91 ± 12	94 ± 14	0.367
Hip-to-waist ratio	0.9 ± 0.1	0.8 ± 0.1	0.412
Grip strength			
Dominant hand (kg)	22.2 ± 6.3	27.6 ± 7.6	**0.041**
Non-dominant hand (kg)	20.6 ± 4.6	25.8 ± 5.9	**0.011**
Mean (kg)	21.6 ± 5.0	26.7 ± 6.7	**0.026**
Exercise performance			
6-min walk test distance (m)	449 ± 54	560 ± 83	**<0.001**
Nutritional intake			
Total energy intake (kcal)	1966 ± 797	2675 ± 952	**0.049**
Physical activity levels			
Energy expenditure (kcal/min)	6235 ± 3207	8174 ± 7320	0.650
Vigorous activity index	6 ± 12	17 ± 22	**0.043**
Leisurely walking index	12 ± 9	18 ± 13	0.185
Moving index	10 ± 4	8 ± 4	0.325
Standing index	3 ± 2	6 ± 2	**0.004**
Sitting index	2 ± 1	3 ± 1	0.105
Flights of stairs climber per day	8 ± 13	2 ± 3	0.685
Seasonal adjustment score	1 ± 0.1	1 ± 0.1	0.185
Mood			
Tension	9 ± 5	6 ± 5	0.151
Depression	11 ± 10	8 ± 10	0.174
Anger	9 ± 7	7 ± 7	0.653
Fatigue	12 ± 6	7 ± 6	**0.027**
Confusion	9 ± 5	6 ± 5	0.198
Vigour	16 ± 6	17 ± 6	0.552
Total mood disturbance	34 ± 30	18 ± 34	0.196

Table 3
Cardiovascular function for the breast cancer and cancer-free groups. Values are means ± SD.

Variable	Breast cancer survivors (n = 12)	Cancer-free women (n = 15)	*P* value
Heart rate (beats/min)	78 ± 10	68 ± 8	**0.008**
Cardiac output (L/min)	4.1 ± 1.0	4.6 ± 0.8	0.183
Cardiac index (L/min/m^2)	2.3 ± 0.4	2.6 ± 0.4	0.277
Systolic blood pressure (mmHg)	137 ± 13	126 ± 12	**0.043**
Diastolic blood pressure (mmHg)	78 ± 7	69 ± 8	**0.007**
Mean arterial pressure (mmHg)	103 ± 11	93 ± 8	**0.018**
Large arterial compliance (ml/mmHg x 10)	7.8 ± 3.2	11.8 ± 3.2	**0.004**
Small arterial compliance (ml/mmHg x 10)	2.8 ± 1.0	4.3 ± 1.7	**0.009**
Systemic vascular resistance (dyne/sec/cm^{-5})	2170 ± 805	1673 ± 288	**0.037**
Total vascular impedance (dyne/sec/cm^{-5})	236 ± 93	170 ± 35	0.083

3.3. Cerebrovascular responsiveness to hypercapnia

The CVR to hypercapnia is shown in Fig. 1 and Table 4. All variables measured increased during hypercapnia, except for CPI, which decreased in both groups (main effect of time $P < 0.001$). The CVR to hypercapnia was higher in cancer-free women than the breast cancer survivors (time × group interaction, $P < 0.001$, $d = 2.59$). $MCA_V/P_{ET}CO_2$ increased from baseline to peak in the cancer-free women, however decreased in breast cancer survivors (main effect of time $P < 0.001$, $d = 0.59$). $P_{ET}CO_2$ increased in both groups, however, was different between groups (main effects of time $P < 0.001$ and group $P < 0.001$). Maximum tidal volume (main effect of time, $P = 0.004$), breathing frequency and minute ventilation (time × group interaction $P = 0.048$) all increased during hypercapnia, for both groups.

3.4. Cognitive function and cerebrovascular responsiveness to cognitive stimuli

Cognitive function and cerebrovascular responses to cognitive stimuli are shown in Fig. 1 and Table 5. Cancer-free women had higher overall cognitive function than breast cancer survivors, which was demonstrated by a 13% higher total compositive cognitive score ($d = 1.25$). Cancer-free women had higher language and crystallised cognition, demonstrated by the ORRT ($d = 1.36$) and PVT ($d = 0.96$), as well as working memory, demonstrated by the LSWMT ($d = 1.005$). Cancer-free women also performed Parts A and B of the TMT with less errors than breast cancer survivors TMT-A, $d = 0.84$; TMT-B, $d = 1.09$). Breast cancer survivors were more stressed following cognitive testing than cancer-free women ($d = 0.84$) and had an increase in stress compared with cancer-free women following cognitive testing. Cancer-free women had higher CVR to all individual cognitive stimuli than breast cancer survivors except to the ORRT and a higher total composite CVR to cognitive stimuli ($d = 1.35$).

3.5. Correlations between measured variables and cerebrovascular responsiveness to hypercapnia and cognitive stimuli, and cognitive function

Correlations between measured variables and CVR to hypercapnia

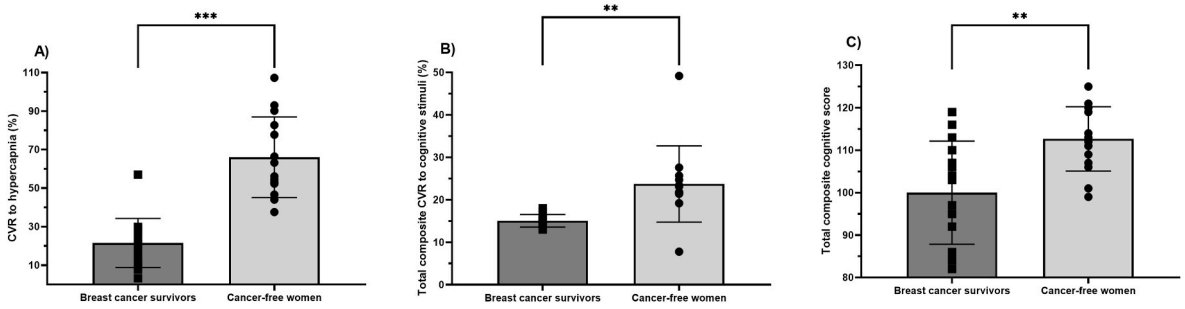

Fig. 1. Cerebrovascular responsiveness (CVR) to hypercapnia (A), CVR to total composite of cognitive stimuli (B) and total composite cognitive score (C) for breast cancer survivors and cancer-free women. Significantly different between groups ** ($P < 0.005$), *** ($P < 0.001$).

Table 4
Cerebrovascular responsiveness to hypercapnia for the breast cancer and cancer-free groups. Values are means ± SD.

Variable	Breast cancer survivors (n = 15)		Cancer-free women (n = 14)		*P* value		
	Baseline	Peak	Baseline	Peak	Time	Group	Time x Group
MCA_V (cm/s)	42.2 ± 11.6	50.7 ± 13.3	39.8 ± 6.4	61.4 ± 11.9*	**<0.001**	0.312	**<0.001**
$MCA_V/P_{ET}CO_2$ (cm/s/mmHg)	1.6 ± 0.5	1.4 ± 0.4	1.3 ± 0.2*	1.6 ± 0.2	**<0.001**	0.624	**<0.001**
Cerebral pulsatility index	1.0 ± 0.2	0.8 ± 0.2	0.9 ± 0.1	0.8 ± 0.1	**<0.001**	0.315	0.121
$P_{ET}CO_2$ (mmHg)	28.2 ± 4.6	36.1 ± 5.0	31.8 ± 2.4*	37.6 ± 2.8	**<0.001**	**<0.001**	0.092
Tidal volume (L)	1.0 ± 0.5	1.1 ± 0.5	0.8 ± 0.4	1.1 ± 0.3	**0.004**	0.543	**0.027**
Breathing frequency (breaths/min)	12 ± 4	14 ± 4	11 ± 4	12 ± 4	0.178	**<0.001**	0.468
Minute ventilation (L/min)	12.8 ± 7.6	13.4 ± 7.7	8.4 ± 3.5	10.9 ± 3.4	**0.002**	0.131	**0.048**

Abbreviations = MCA_V, middle cerebral artery blood velocity; $P_{ET}CO_2$, partial pressure of end tidal carbon dioxide; *Significantly different between groups ($P < 0.05$).

and cognitive stimuli, and cognitive function are shown in Table 6. There were significant moderate positive correlations between the distance walked during the 6 MW T and cognitive function, CVR to cognitive stimuli and CVR to hypercapnia. Significant moderate correlations between education, average grip strength, tension, peak MCA_V, fatigue, baseline $P_{ET}CO_2$ and total mood disturbance and cognitive function were observed. Significant moderate correlations between standing index, stress, heart rate, total energy intake, large arterial compliance and peak MCA_V and CVR to hypercapnia were also observed. Significant moderate correlations were also observed between CVR to cognitive stimuli and diastolic blood pressure, vigorous activity, standing index, fatigue, heart rate, mean arterial pressure and baseline minute ventilation.

3.6. Analysis of covariance between the primary outcomes and covariates

Objective (non-self-reported) measures that demonstrated a significant relationship with the primary outcomes (CVR to hypercapnia; CVR to cognitive stimuli; total composite cognitive score) and were considered clinically significant were used in the ANCOVA (described above; shown in Table 6). Those that demonstrated significant relationships with the primary outcomes and were clinically significant included average handgrip strength, 6 MW T distance, systolic and diastolic blood pressures, mean arterial pressure, large arterial compliance, heart rate, resting $P_{ET}CO_2$, resting minute ventilation and years of education. Following adjustment for covariates (6 MW T distance, large arterial compliance, heart rate, resting minute ventilation and resting $P_{ET}CO_2$) the ANCOVA revealed that the CVR to hypercapnia remained statistically different between the groups ($P = 0.001$). The ANCOVA performed for the composite CVR to cognitive stimuli (covariates: 6 MW T distance, systolic and diastolic blood pressures, mean arterial pressure, heart rate, and resting minute ventilation; $P = 0.048$) was also not statistically different between the groups. This was the same for the ANCOVA performed for the total composite cognitive score (covariates: total years educated, 6 MW T distance, average handgrip strength, maximum MCA_V during hypercapnia, resting $P_{ET}CO_2$; $P = 0.001$).

4. Discussion

4.1. Main findings

The main findings of this study were that breast cancer survivors showed lower CVR to both physiological and psychological stimuli and demonstrated lower total cognitive function than age and BMI matched, cancer-free women. These findings supported our hypothesis that cerebrovascular function and total cognition would be lower in breast cancer survivors than cancer-free women.

4.2. Primary measures: cognitive function

Breast cancer survivors had a 13% lower total composite cognitive score than cancer-free women, thus indicating reduced cognitive function in breast cancer survivors. Cognition is one of the most highly ordered and complex functions of the brain, and reflects the ability of the brain to acquire, process, store and retrieve information, in order to guide thoughts, actions and behaviours [5]. We used a total composite cognitive score, as this is a collective measurement of overall cognitive function across multiple cognitive domains and better reflects the cognitive requirements of daily life. Typically, each cognitive domain does not operate independently of one another, and single cognitive domains are rarely used in isolation [47]. Notwithstanding, we did find that breast cancer survivors had lower crystallised cognition, working memory and executive function, than cancer-free women. These results are supported by the literature, which shows that breast cancer and its treatments are associated with reduced cognition. Reduced cognition has been observed in patients prior to treatment commencement [18], during and after chemotherapy [48], radiotherapy [49] and hormonal therapy [50] and also into survivorship [9].

4.3. Primary measures: cerebrovascular function

The decline in total cognitive function may be associated with reduced cerebrovascular function, which was observed in this study by measuring the CVR to both physiological (44% lower) and psychological

Table 5
Cognition and cerebrovascular responsiveness to cognitive stimuli for the breast cancer and cancer-free groups. Values are means ± SD.

Variable	Breast cancer survivors (n = 15)	Cancer-free women (n = 15)	*P* value
Cognition			
Dimensional change card sort[a]	8.0 ± 0.9	8.2 ± 0.6	0.967
Pattern comparison processing speed[a]	46 ± 11	47 ± 8	0.924
Picture vocabulary test[a]	5.4 ± 1.9	7.2 ± 2.0	**0.014**
Flanker inhibitory control and attention[a]	7.7 ± 0.8	8.0 ± 0.5	0.285
Picture sequence memory[a]	−0.8 ± 0.9	−0.6 ± 0.7	0.442
List sorting working memory[a]	16 ± 2	18 ± 2	**0.010**
Oral reading recognition[a]	4.6 ± 2.2	7.2 ± 1.6	**0.001**
Trail making task (Part A)			
Time (s)	35.8 ± 18.7	32.1 ± 9.3	0.595
Errors made	2.0 ± 2.8	0.3 ± 0.6	**0.023**
Trail making task (Part B)			
Time (s)	74.2 ± 36.8	58.9 ± 19.7	0.061
Errors made	3.4 ± 3.4	0.6 ± 1.2	**0.003**
Part B – Part A time difference	38.4 ± 20.1	26.7 ± 13.2	0.081
Stress			
Prior to cognitive testing	2.2 ± 2.1	1.9 ± 1.8	1.000
Post cognitive testing	3.8 ± 2.4	2.1 ± 1.6	**0.033**
Difference	1.5 ± 1.7	0.1 ± 1.4	**0.016**
Mental Fatigue			
Prior to cognitive testing	3.8 ± 2.4	3.0 ± 1.9	0.332
Post cognitive testing	5.4 ± 3.1	3.9 ± 2.2	0.125
Difference	1.7 ± 2.3	0.9 ± 2.5	0.395
Cerebrovascular responses to cognitive stimuli (%)			
Dimensional change card sort test	13.0 ± 3.9	21.8 ± 10.6	**0.016**
Pattern comparison processing speed test	14.1 ± 5.1	23.6 ± 10.0	**0.001**
Picture vocabulary test	17.0 ± 2.9	27.9 ± 9.6	**<0.001**
Flanker inhibitory control and attention test	12.6 ± 5.2	21.0 ± 9.8	**0.008**
Picture sequence memory test	17.5 ± 3.6	27.6 ± 10.3	**0.001**
List sorting working memory test	16.7 ± 3.5	23.8 ± 11.7	**0.011**
Oral reading recognition test	15.6 ± 3.1	19.7 ± 10.7	0.219
Trail making task (Part A)	13.6 ± 4.0	27.8 ± 10.1	**<0.001**
Trail making task (Part B)	15.2 ± 3.2	26.7 ± 10.8	**0.001**

[a] Normalised, computed and standardised automatically by NIH Toolbox, based on validated measures [31].

Table 6
Correlations between measured variables and cerebrovascular responsiveness (CVR) to hypercapnia and cognitive stimuli, and cognitive function **(total composite cognitive score)**.

Variable	CVR to hypercapnia		CVR to cognitive stimuli		Cognitive function	
	r value	*P* value	*r* value	*P* value	*r* value	*P* value
Education (years)	0.075	0.699	0.132	0.520	**0.579**	**0.001**
6-min walk test distance (m)	**0.492**	**0.007**	**0.555**	**0.003**	**0.625**	**<0.001**
Average grip strength (kg)	0.218	0.255	0.236	0.246	**0.520**	**0.003**
Total energy intake (kcal)	**0.531**	**0.006**	0.071	0.755	−0.088	0.669
Vigorous activity index	**0.443**	**0.024**	**0.520**	**0.011**	0.321	0.103
Standing index	**0.563**	**0.003**	**0.473**	**0.023**	0.200	0.318
Tension	−0.021	0.914	−0.180	0.378	**−0.412**	**0.024**
Fatigue	−0.311	0.101	**−0.420**	**0.033**	**−0.390**	**0.033**
Total mood disturbance	−0.092	0.634	−0.195	0.339	**−0.371**	**0.043**
Heart rate (beats/min)	**−0.544**	**0.004**	**0.417**	**0.047**	−0.246	0.216
Diastolic blood pressure (mmHg)	−0.300	0.136	**−0.539**	**0.008**	−0.313	0.112
Mean arterial pressure (mmHg)	−0.349	0.081	**−0.415**	**0.049**	−0.380	0.050
Large arterial compliance (ml/mmHg x 10)	**0.502**	**0.009**	0.053	0.811	0.220	0.271
Peak MCA_V (cm/s)	**0.474**	**0.009**	0.093	0.652	**0.413**	**0.026**
Baseline $P_{ET}CO_2$ (mmHg)	**0.389**	**0.041**	0.363	0.074	**0.395**	**0.038**
Baseline Minute ventilation (L/min)	**−0.408**	**0.031**	**−0.390**	**0.049**	0.011	0.957
Stress Post – Pre cognitive testing score	**−0.533**	**0.003**	−0.206	0.313	−0.047	0.808

stimuli (9% lower). CVR reflects the sensitivity of the vasculature to respond to physiological and psychological challenges, in order to maintain CBF. CBF is regulated by autoregulation and neurovascular coupling (NVC) [51]. Cerebrovascular autoregulation ensures CBF is maintained during changes in systemic blood pressure by modulating the vascular resistance applied to the vasculature [52]. NVC is the complex interaction, or 'coupling' between neuronal activity and local haemodynamic changes, which ensures the metabolic demands of active neural tissues are met by the microvasculature [53]. Derangements to these mechanisms lead to reduced CBF, which can reduce and eventually impair cerebral functions, such as cognition. Our results suggest that there may be a quantifiable impairment in CVR to hypercapnia and to cognitive stimuli, which is present in some breast cancer survivors, thus leading to reduced cognitive function, which was also present in the breast cancer survivors in this study.

Studies investigating cerebrovascular function in breast cancer survivors, are limited. Koppelmans et al. (2021) [21] demonstrated that decreased CBF persisted in breast cancer survivors for up to 20 years post-treatment. Silverman et al. (2007) [54] reported a decrease in fluorodeoxyglucose PET scans during a short-term memory, thus suggesting reduced cerebral activation and altered neuronal metabolism stemming from a reduced CBF in chemotherapy-treated patients, which was not apparent in apparently healthy controls. However, to our knowledge, we are the first to evaluate the differences in CVR to both physical and psychological stimuli in breast cancer survivors, compared to cancer-free women.

Reduced cerebrovascular function leading to cognitive impairment has been associated with increased oxidative stress and chronic inflammation caused by both cancer and anti-cancer treatments [18,44]. These have significant repercussions on endothelial function, by reducing its ability to synthesise and release nitric oxide (NO) [18,44]. NO is vital in maintaining cerebrovascular structure and function, as endothelial-derived NO prevents reductions in CBF, CBF velocity and cerebral hypoperfusion [18]. It ensures that the ability of the microvasculature to respond to local changes and to modify regional CBF in response to these changes is maintained [55]. When a physical or psychological stimuli is introduced, any observable change in CBF velocity reflects a change in flow rate in the microvasculature downstream [56]. This is due to the rapid release of NO, which induces a sudden and sustained change in dilatation in response to such stimuli and is therefore a surrogate measure of endothelial function. These changes were evident in our study, as breast cancer survivors showed significantly lower CVR to both physical and psychological stimuli, thus providing a potential mechanism involving impaired endothelial function and

resulting hypoperfusion that could lead to reduced cognition.

4.4. Secondary findings

Our secondary findings indicated that this cohort of breast cancer survivors had lower levels of physical activity, exercise capacity, musculoskeletal strength and nutritional intake, as well as higher levels of fatigue, compared to cancer-free women. Cancer patients generally have lower levels of physical activity following diagnosis, and typically fail to regain their pre-diagnosis physical activity levels post-treatment and into survivorship [21]. Additionally, breast cancer survivors report more intense and more frequent fatigue than women without a history of cancer [57]. Taken together, these findings suggest that there may be an inverse relationship between these variables. Our results suggest that survivors are more fatigued, and as a result, may be disinclined to participate in regular or vigorous physical activity, which could further increase this fatigue. Here, cancer-free women do not experience this cancer-related fatigue and may therefore be more inclined to participate in physical activity and exhibit higher nutritional intake in order to account for this.

Lower levels of physical activity are associated with reduced cardiovascular health and increased risk of cardiovascular disease (CVD) [58]. Results of this study suggest that breast cancer survivors, also demonstrated reduced cardiovascular function compared to the cancer-free women. This was associated with reduced vascular compliance (i.e., increased arterial stiffness), which is reflective of reduced endothelial function. These findings are significant because breast cancer survivors are at increased risk of CVD [59]. CVD is one of the leading causes of death in women and among breast cancer survivors in particular [58]. In breast cancer survivors aged over 50 years, deaths due to CVD account for 35% of non-cancer related deaths and cardiovascular mortality is the greatest single non–cancer-related cause of death in this population [59]. A recent, large population-based study reported that breast cancer survivors between 10 and 15 years post-diagnosis had a 29–42% higher risk of developing CVD compared with cancer-free women (matched by age and geographical location) [60]. Collectively, our results may suggest that cancer-related fatigue may initiate a series of events that result in reduced nutritional intake and physical activity levels, which in turn reduces cardiovascular health, resulting in reduced cerebrovascular and cognitive function.

4.5. Limitations and future directions

The primary limitation of this study is the low participant number. As a result, participants were not able to be stratified according to cancer stage and treatment modality. However, the significance, effect sizes and results of the ANCOVA indicate that after accounting for all other significant variables, brain health is still significantly reduced in breast cancer survivors compared to cancer-free women. Further, there are a lack of similar studies which are able to provide support to the findings herein, indicating the need for further exploration surrounding the cerebrovascular and cognitive changes which occur during the different stages of breast cancer. Hence, future larger longitudinal studies that investigate cerebrovascular and cognition changes associated with breast cancer that are corrected for age, stage, treatment and time for treatment are warranted.

How brain health in breast cancer patients can be improved is poorly investigated. However, increasing attention is being paid to the effect of exercise training. The mechanisms underlying reduced cognition related to cancer and its treatments are unclear but may involve similar processes to age-related effects on the brain. Exercise has been shown to be an effective treatment for age-related cerebrovascular and cognitive decline, by helping to maintain cerebral perfusion and cognitive capacity [44]. However, limited studies have investigated this effect in breast cancer survivors. Given our results, which highlight an association between exercise capacity demonstrated by the 6 MW T and the three primary objectives of this study, it may be plausible to investigate whether exercise training can improve both cerebrovascular function and cognition in breast cancer survivors.

5. Conclusion

The main findings of this study were that breast cancer survivors showed lower CVR to both physiological and psychological stimuli and demonstrated lower total cognitive function than age and BMI matched, cancer-free women. These findings supported our hypothesis. To our knowledge, this is the first study to investigate differences in cerebrovascular function and cognition in breast cancer survivors compared to cancer-free women. Although the mechanisms underlying these differences are yet to be elucidated, we provide preliminary evidence that the reduced cerebrovascular function and cognition, which may be observed in breast cancer survivors, could be due to reduced endothelial function and therefore reduced cardiovascular function.

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Author contributions

ESB and GF conceptualised and designed the study protocol. ESB and DEM designed the experiments. ESB and TLD collected the data. ESB and TLD analysed the data. ESB and TLD performed statistical analysis, with all authors contributing to data interpretation. All authors contributed to revisions of intellectual content. All authors approved the final manuscript.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2021;71:209–49.
[2] Who. Breast cancer. Geneva, Switzerland: World Health Organization; 2021.
[3] AIHW. Cancer data in Australia: cancer mortality (age-standardised rates and 5-year age groups). Canberra: Australian Institute of Health and Welfare; 2020.
[4] Mijwel S, Backman M, Bolam KA, Olofsson E, Norrbom J, Bergh J, et al. Highly favorable physiological responses to concurrent resistance and high-intensity interval training during chemotherapy: the OptiTrain breast cancer trial. Breast Cancer Res Treat 2018;169:93–103.
[5] Harvey PD. Domains of cognition and their assessment. Dialogues Clin Neurosci 2019;21:227–37.
[6] Herold F, Hamacher D, Schega L, Muller NG. Thinking while moving or moving while thinking - concepts of motor-cognitive training for cognitive performance enhancement. Front Aging Neurosci 2018;10:1–11.
[7] Northey JM, Pumpa KL, Quinlan C, Ikin A, Toohey K, Smee DJ, et al. Cognition in breast cancer survivors: a pilot study of interval and continuous exercise. J Sci Med Sport 2019;22:580–5.

[8] Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA A Cancer J Clin 2015;65:123–38.
[9] Koppelmans V, Breteler Mm Fau - Boogerd W, Boogerd W Fau - Seynaeve C, Seynaeve C Fau - Gundy C, Gundy C Fau - Schagen SB, Schagen SB. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. J Clin Oncol 2012;30:1080–6.
[10] Chen X, Li J, Chen J, Li D, Ye R, Zhang J, et al. Decision-making impairments in breast cancer patients treated with tamoxifen. Horm Behav 2014;66:449–56.
[11] Yao C, Rich JB, Tirona K, Bernstein LJ. Intraindividual variability in reaction time before and after neoadjuvant chemotherapy in women diagnosed with breast cancer. Psycho Oncol 2017;26:2261–8.
[12] Lejbak L, Vrbancic M, Fau - Crossley M, Crossley M. Endocrine therapy is associated with low performance on some estrogen-sensitive cognitive tasks in postmenopausal women with breast cancer. J Clin Exp Neuropsychol 2010;32:836–46.
[13] Kesler S, Janelsins M, Koovakkattu D, Palesh O, Mustian K, Morrow G, et al. Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. Brain Behav Immun 2013;30:S109–16.
[14] Lv L, Mao S, Dong H, Hu P, Dong R. Pathogenesis, assessments, and management of chemotherapy-related cognitive impairment (CRCI): an updated literature review. Journal of Oncology 2020;2020:1–11.
[15] Heaton RK, Akshoomoff N, Tulsky D, Mungas D, Weintraub S, Dikmen S, et al. Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. J Int Neuropsychol Soc 2014;20:588–98.
[16] Menning S, de Ruiter MB, Veltman DJ, Boogerd W, Oldenburg HSA, Reneman L, et al. Changes in brain activation in breast cancer patients depend on cognitive domain and treatment type. PLoS One 2017;12:e0171724–.
[17] Bliss ES, Wong RH, Howe PR, Mills DE. Benefits of exercise training on cerebrovascular and cognitive function in ageing. J Cerebr Blood Flow Metabol 2021;41:447–70.
[18] Bogorad MI, DeStefano JG, Linville RM, Wong AD, Searson PC. Cerebrovascular plasticity: processes that lead to changes in the architecture of brain microvessels. J Cerebr Blood Flow Metabol 2019;39:1413–32.
[19] Kim D, Hughes TM, Lipford ME, Craft S, Baker LD, Lockhart SN, et al. Relationship between cerebrovascular reactivity and cognition among people with risk of cognitive decline. Front Physiol 2021;12:1–10.
[20] Hajjar I, Hayek SS, Goldstein FC, Martin G, Jones DP, Quyyumi A. Oxidative stress predicts cognitive decline with aging in healthy adults: an observational study. J Neuroinflammation 2018;15:1–7.
[21] Koppelmans V, van der Willik KD, Aleman BMP, van Leeuwen FE, Kavousi M, Arshi B, et al. Long-term effects of adjuvant treatment for breast cancer on carotid plaques and brain perfusion. Breast Cancer Res Treat 2021;186:167–76.
[22] Dipietro L, Caspersen CJ, Ostfeld AM, Nadel ER. A survey for assessing physical activity among older adults. Medicine & Science in Sports & Exercise; 1993.
[23] Pannucci TE, Thompson FE, Bailey RL, Dodd KW, Potischman N, Kirkpatrick SI, et al. Comparing reported dietary supplement intakes between two 24-hour recall methods: the automated self-administered 24-hour dietary assessment Tool and the interview-administered automated multiple pass method. J Acad Nutr Diet 2018;118:1080–6.
[24] Heuchert JP, McNair DM. Profile of mood states 2nd Edition™: POMS 2. North Tonawanda, NY: Multi-Health Systems Inc.; 2012.
[25] Barbour JA, Howe PRC, Buckley JD, Bryan J, Coates AM. Cerebrovascular and cognitive benefits of high-oleic peanut consumption in healthy overweight middle-aged adults. Nutr Neurosci 2017;20:555–62.
[26] Evans H, Howe P, Wong R. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; A 14-week randomised placebo-controlled intervention trial. Nutrients 2017;9:27.
[27] Edmonds Jr HL, Isley MR, Sloan TB, Alexandrov AV, Razumovsky AY. American society of neurophysiologic monitoring and American society of neuroimaging joint guidelines for transcranial Doppler ultrasonic monitoring. J Neuroimaging 2011;21:177–83.
[28] Willie CK, Colino FL, Bailey DM, Tzeng YC, Binsted G, Jones LW, et al. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. J Neurosci Methods 2011;196:221–37.
[29] Strauss E, Sherman E, Spreen O. A compendium of neuropsychological tests. third ed. New York: Oxford University Press; 2006.
[30] Heaton RK, Akshoomoff N, Tulsky D, Mungas D, Weintraub S, Dikmen S, et al. Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. J Int Neuropsychol Soc 2014;20:588–98.
[31] Slotkin J, Nowinski C, Hays R, Beaumont J, Griffith J, Magasi S, et al. NIH Toolbox scoring and interpretation guide. Washington (DC): National Institutes of Health; 2012. p. 6–7.
[32] Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Slotkin J, et al. The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample. J Int Neuropsychol Soc 2014;20:567–78.
[33] Senior G, Piovesana A, Beaumont P. Discrepancy analysis and Australian norms for the Trail making test. Clin Neuropsychol 2018;32:510–23.
[34] Thaung Zaw JJ, Howe PR, Wong RH. Long-term effects of resveratrol on cognition, cerebrovascular function and cardio-metabolic markers in postmenopausal women: a 24-month randomised, double-blind, placebo-controlled, crossover study. Clin Nutr 2021;40(3):820–9.
[35] Slotkin J, Nowinski C, Hays R, Beaumont J, Griffith J, Magasi S, et al. NIH Toolbox scoring and interpretation guide. Washington, DC: National Institutes of Health; 2012.
[36] Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Slotkin J, et al. The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample. J Int Neuropsychol Soc 2014;20:567–78.
[37] Wong RA-O, Thaung Zaw JJ, Xian CA-O, Howe PA-O. Regular supplementation with Resveratrol improves bone mineral density in postmenopausal women: a randomized, placebo-controlled trial. J Bone Miner Res 2020;35:2121–31.
[38] Harris S, Reyhan T, Ramli Y, Prihartono J, Kurniawan M. Middle cerebral artery pulsatility index as predictor of cognitive impairment in hypertensive patients. Front Neurol 2018;9:1–6.
[39] Bakker SL, de Leeuw FE, den Heijer T, Koudstaal PJ, Hofman A, Breteler MM. Cerebral haemodynamics in the elderly: the Rotterdam study. Neuroepidemiology 2004;23:178–84.
[40] Welborn TA, Dhaliwal SS, Bennett SA. Waist-hip ratio is the dominant risk factor predicting cardiovascular death in Australia. Med J Aust 2003;179:580–5.
[41] Prisant LM, Pasi M, Jupin D, Prisant ME. Assessment of repeatability and correlates of arterial compliance. Blood Pres Monit 2002;7:231–5.
[42] ATS. ATS statement: guidelines for the six-minute walk test. ATS committee on proficiency standards for clinical pulmonary function laboratories. Am J Respir Crit Care Med 2002;166:111–7.
[43] Hillman TE, Nunes QM, Hornby ST, Stanga Z, Neal KR, Rowlands BJ, et al. A practical posture for hand grip dynamometry in the clinical setting. Clin Nutr 2005;24:224–8.
[44] Bliss E, Biki S, Wong R, Howe P, Mills D. The benefits of regular aerobic exercise training on cerebrovascular function and cognition in older adults. Eur J Appl Physiol 2023 Feb;19:1–20. https://doi.org/10.1007/s00421-023-05154-y.
[45] Cohen J. Statistical power analysis for the behavioural sciences. second ed. Hillsdale, NJ: Lawrence Erlbaum Associates Inc; 1988.
[46] Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. Anesth Analg 2018;126:1763–8.
[47] Jonaitis EM, Koscik RL, Clark LR, Ma Y, Betthauser TJ, Berman SE, et al. Measuring longitudinal cognition: individual tests versus composites. Alzheimer's Dementia 2019;11:74–84.
[48] Pendergrass J, Targum S, Harrison J. Cognitive impairment associated with cancer: a brief review. Innovations in Clinical Neuroscience 2018;15:36–44.
[49] Van Dyk K, Bower JE, Crespi CM, Petersen L, Ganz PA. Cognitive function following breast cancer treatment and associations with concurrent symptoms. Breast Cancer 2018;4:1–4.
[50] Lambert M, Ouimet LA, Wan C, Stewart A, Collins B, Vitoroulis I, et al. Cancer-related cognitive impairment in breast cancer survivors: an examination of conceptual and statistical cognitive domains using principal component analysis. Onco Rev 2018;12:90–7.
[51] Bliss E, Wong R, Howe P, Mills D. The effects of aerobic exercise training on cerebrovascular and cognitive function in sedentary, obese, older adults. Front Aging Neurosci 2022;14:1–15.
[52] Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. Am J Physiol Heart Circ Physiol 2017;312:H1–20.
[53] Phillips AA, Chan FH, Zheng MM, Krassioukov AV, Ainslie PN. Neurovascular coupling in humans: physiology, methodological advances and clinical implications. J Cerebr Blood Flow Metabol 2016;36:647–64.
[54] Silverman DH, Dy CJ, Castellon SA, Lai J, Pio BS, Abraham L, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. Breast Cancer Res Treat 2007;103:303–11.
[55] Zhu J, Song W, Li L, Fan X. Endothelial nitric oxide synthase: a potential therapeutic target for cerebrovascular diseases. Mol Brain 2016;9:1–8.
[56] Joris PJ, Mensink RP, Adam TC, Liu TT. Cerebral blood flow measurements in adults: a review on the effects of dietary factors and exercise. Nutrients 2018;10:530–45.
[57] Ruiz-Casado A, Álvarez-Bustos A, de Pedro CG, Méndez-Otero M, Romero-Elías M. Cancer-related fatigue in breast cancer survivors: a review. Clin Breast Cancer 2021;21:10–25.
[58] Coughlin SS, Ayyala D, Majeed B, Cortes L, Kapuku G. Cardiovascular disease among breast cancer survivors. Cardiovascular Disordors and Medicine 2020;2:1–10.
[59] Gulati M, Mulvagh SL. The connection between the breast and heart in a woman: breast cancer and cardiovascular disease. Clin Cardiol 2018;41:253–7.
[60] Koric A, Chang C-P, Mark B, Rowe K, Snyder J, Dodson M, et al. Cardiovascular disease risk in long-term breast cancer survivors: a population-based cohort study. Cancer 2022;128:2826–35.