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ORIGINAL ARTICLE

Aerobic exercise and CogniTIVe functioning in women with breAsT cancEr (ACTIVATE): A randomized controlled trial

Jennifer Brunet PhD[1,2,3] | Sitara Sharma MA[1] | Kendra Zadravec PT, MSc[4] | Monica Taljaard PhD[5,6] | Nathalie LeVasseur MD[7] | Amirrtha Srikanthan MD[8] | Kelcey A. Bland MSc[9] | Elham Sabri PhD[5] | Barbara Collins PhD[10] | Sherri Hayden PhD[11] | Christine Simmons MD[7] | Andra M. Smith PhD[10] | Kristin L. Campbell PT, PhD[4,9]

[1]School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada

[2]Cancer Therapeutic Program, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada

[3]Institut du Savoir Montfort, Hôpital Montfort, Ottawa, Ontario, Canada

[4]Rehabilitation Sciences, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[5]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[6]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

[7]British Columbia Cancer–Vancouver, Vancouver, British Columbia, Canada

[8]Department of Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada

[9]Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[10]School of Psychology, Faculty of Social Sciences, University of Ottawa, Ottawa, Ontario, Canada

[11]Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence

Jennifer Brunet, School of Human Kinetics, Faculty of Health Sciences, University of

Abstract

Background: As the prevalence of chemotherapy-related cognitive impairment rises, investigation into treatment options is critical. The objectives of this study were to test the effects of an aerobic exercise intervention initiated during chemotherapy compared to usual care (wait list control condition) on (1) objectively measured cognitive function and self-reported cognitive function, as well as on (2) the impact of cognitive impairment on quality of life (QOL) postintervention (commensurate with chemotherapy completion).

Methods: The Aerobic exercise and CogniTIVe functioning in women with breAsT cancEr (ACTIVATE) trial was a two-arm, two-center randomized controlled trial conducted in Ottawa and Vancouver (Canada). Fifty-seven women (M_{age}, 48.8 ± 10 years) diagnosed with stage I–III breast cancer and awaiting chemotherapy were randomized to aerobic exercise initiated with chemotherapy ($n_{EX} = 28$) or usual care during chemotherapy with aerobic exercise after chemotherapy completion ($n_{UC} = 29$). The intervention lasted 12–24 weeks and consisted of supervised aerobic training and at-home exercise. The primary outcome was objective cognitive function measured via 13 neuropsychological tests (standardized to M ± SD, 0 ± 1); secondary outcomes of self-reported cognitive function and its impact on QOL were assessed via questionnaires. Data collected pre- and postintervention (the primary end point) were analyzed.

Results: Although no significant differences between groups were found for objective cognitive function outcomes postintervention after accounting for multiple testing, four of six self-reported cognitive function outcomes showed significant differences favoring the aerobic exercise group.

This trial was registered at ClinicalTrials.gov (NCT03277898).

Ottawa, 125 University Private, Montpetit Hall 339, Ottawa, ON K1N 6N5, Canada.
Email: jennifer.brunet@uottawa.ca

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Conclusions: Among women initiating chemotherapy for breast cancer, aerobic exercise did not result in significant differences in objective cognitive function postintervention after chemotherapy completion; however, the results do support the use of this intervention for improving self-reported cognitive function and its impact on QOL.

KEYWORDS
breast neoplasm, cognition, exercise, oncology, randomized controlled trial

INTRODUCTION

Chemotherapy-related cognitive impairment (CRCI) is one of the greatest challenges reported by women diagnosed with breast cancer.[1] Nearly 75% of women who receive chemotherapy report a decreased ability to remember, concentrate, and/or think, both in the short and long term.[2–5] Additionally, women who receive chemotherapy tend to perform worse on neuropsychological tests assessing executive functioning, working memory, processing speed, spatial ability, and language/verbal ability as compared to women diagnosed with breast cancer who have *not* received chemotherapy or to controls without a history of cancer.[6–9] Declines in cognitive function adversely affect women's quality of life (QOL),[10–13] yet no established standard of care exists to prevent or manage CRCI among women diagnosed with breast cancer. Identifying empirically validated interventions to maintain/ameliorate cognitive function and thereby maintain/ameliorate QOL is necessary to reduce the individual and societal burden of cancer.

Aerobic exercise is shown to improve cognitive function and attenuate cognitive decline in older adults and those with mild cognitive impairment.[14,15] Drawing on such research, exercise interventions have been implemented among people living with and beyond cancer under the premise that they will lead to positive cognitive changes.[16,17] However, there are remaining uncertainties about the efficacy (and effectiveness) of exercise interventions for improving cognitive function among women diagnosed with breast cancer because of discordant results.[16,17] Indeed, despite 53 randomized controlled trials conducted in this area,[16] conclusions regarding the effects of exercise on cognitive function are based on studies with limited generalizability and small sample sizes.[16–20] Moreover, although randomized controlled trials remain the gold standard to detect differences between intervention and control arms, there are additional issues to consider when evaluating the available evidence (even in cases of high-quality trials) on the effects of exercise on cognitive function. First, several studies have not had clearly defined self-report measures of cognitive function. For example, many have used general self-report measures of QOL (e.g., European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire[21]), which do not account for the complex, multidimensional nature (e.g., learning, memory, attention, and executive function) of cognitive function.[16,18] Second, most studies have not used objective measures of cognitive function as recommended by the International Cognition and Cancer Task Force.[22] It is important to recognize that self-reported data from measures developed *specifically* to assess cognitive function (e.g., Functional Assessment of Cancer Therapy–Cognitive Function [FACT–Cog][23] and Patient-Reported Outcomes Measurement Information System Applied Cognition [PROMIS–Cog][24]) seldom agree with data from objective measures of cognitive function.[25–27] Thus, without objective measures of cognitive function, the applicability of exercise for improving cognitive performance among women diagnosed with breast cancer remains uncertain. Last, few studies have targeted women undergoing treatment such as chemotherapy,[16] which highlights the need for further evidence to support the use of exercise to mitigate CRCI for those initiating chemotherapy as part of treatment for breast cancer so as to improve their daily functioning and QOL.

Given mixed results within and across existing studies and issues with trial methods (e.g., measures and samples), the right kind of data needed to draw inferences about the effects of exercise on women undergoing chemotherapy for breast cancer is lacking. This article presents results from the Aerobic exercise and CogniTIVe functioning in women with breAsT cancEr (ACTIVATE) trial—a trial designed to prospectively assess the effects of aerobic exercise on cognitive function and the impact of cognitive impairment on QOL (henceforth labeled "its impact on QOL") among women initiating chemotherapy as part of treatment for breast cancer. The primary objective of this study was to test the effects of an aerobic exercise intervention (EX) compared to usual care (UC; wait list control condition) on objectively measured cognitive function postintervention after chemotherapy completion (henceforth labeled "post-intervention"; the primary end point). A secondary objective was to test the effects of EX compared to UC on self-reported cognitive function and its impact on QOL. It was hypothesized that the EX group would outperform the UC group on objective neuropsychological tests and self-report better cognitive function and reduced impact of cognitive impairments on QOL postintervention.

MATERIALS AND METHODS

Study design

The ACTIVATE trial was a two-arm, two-center, investigator-blinded parallel randomized controlled trial conducted in Canada. Full details

of the ACTIVATE protocol, including the trial design, randomization process, intervention, outcomes, and statistical plan, were published previously.[28] For this study, only the pre- and postintervention methods are relevant and described in the following sections.

Ethics approval and consent to participate

Ethics approval was granted by the research ethics boards at the University of Ottawa and the University of British Columbia/BC Cancer as well as by the relevant hospital research ethics committees (i.e., Ottawa Health Science Network and Royal Ottawa Mental Health Centre). All patients received written and oral information before participation and provided informed consent for the results to be published.

Reporting and registration

The results of this study are reported according to guidelines for reporting parallel-group randomized trials (CONSORT 2010 statement[29]) and for reporting completed trials modified as a result of the 2019 coronavirus disease (COVID-19) pandemic (CONSERVE 2021 statement[30]); see Files S1 and S2 for completed checklists. The ACTIVATE trial was registered at ClinicalTrials.gov (NCT03277898; September 11, 2017). Amendments to the protocol, as well as a description of patient and public involvement in the research, are provided in File S3.

Patients and setting

Patients were recruited from two large Canadian health care centers —BC Cancer Vancouver and The Ottawa Hospital. Inclusion criteria for women (female sex) were (1) aged 19–70 years, (2) diagnosed with stage I–III breast cancer, (3) scheduled to receive adjuvant or neoadjuvant chemotherapy, (4) able to speak/understand English, and (5) received approval from a medical oncologist to participate in the trial. Additionally, patients were only eligible if they could complete a cardiopulmonary exercise test (CPET) before randomization and be cleared by a cardiologist. Exclusion criteria were (1) previous exposure to chemotherapy or radiation therapy, (2) score ≤23 on the Montreal Cognitive Assessment (MoCA[31]) during screening, (3) diagnosis of a severe anxiety or mood disorder by a physician within the past year, (4) traumatic brain injury or concussion with residual symptoms at the time of screening, (5) diagnosis of a substance use disorder, (6) self-report engaging in ≥150 min of moderate- to vigorous-intensity aerobic exercise per week in the past 3 months, (7) body mass index ≥45 kg/m^2, and (8) mobility issues that require a mobility aid or an injury/illness that would prohibit exercising on a bike, treadmill, or elliptical.

The primary recruitment strategy for the ACTIVATE trial was health care provider referral; self-referral strategies included the use of printed posters placed in waiting and examination rooms at both sites, online advertisements (e.g., websites), and word of mouth. Trial staff offered information about the trial and screened prospective patients by phone. If all inclusion criteria were fulfilled and no exclusion criteria were met, an in-person assessment was scheduled for patients to complete the MoCA to determine final eligibility. Those who scored ≥24 on the MoCA were declared eligible to participate, invited to provide written informed consent, and asked to complete a CPET. Patients cleared by a cardiologist after the CPET then completed baseline assessments before randomization.

Randomization

Patients were randomized to EX or UC in a 1:1 ratio. The allocation sequence was computer generated by an independent statistician from the Ottawa Methods Centre via randomly permuted blocks of variable lengths stratified by site (i.e., Vancouver vs. Ottawa) and menopausal status at breast cancer diagnosis (i.e., pre/perimenopausal vs. menopausal). The allocation sequence was concealed from all (i.e., patients, trial staff [i.e., research coordinators, trainees, and exercise trainers], data collectors, outcome adjudicators, and investigators) until baseline assessments were completed via a password-protected website maintained by the Ottawa Methods Centre. Each time a patient completed baseline assessments, a research coordinator logged onto the website to receive the next group allocation. Patients learned of their group allocation from a research coordinator within 1 week of baseline assessments.

Blinding

Randomization occurred after patients completed all baseline assessments. Afterward, patients and specific trial staff (i.e., research coordinators and exercise trainers) were unblinded to group allocation. Clinicians involved in the trial became unblinded to group allocation while providing follow-up care to patients, and the statistician and two research assistants were unblinded to group allocation for data analysis. All other trial staff who participated in data collection and management (i.e., data collectors and outcome adjudicators) remained blinded. Last, the researchers/investigators remained blinded until the analyses were completed for the outcomes of this study.

Sample size

As stated in the published trial protocol,[28] a sample size of 74 women was necessary to achieve 80% power via an analysis of covariance (ANCOVA) at a two-sided 5% level of significance. This determination was based on detecting a difference of 0.4 standard deviation (SD) units in the primary outcome between the EX and UC groups postintervention, and assumed a correlation of 0.8 with the baseline measure of the outcome. Considering a possible dropout rate of 10%,

the target was 84 patients, although extenuating circumstances led to a premature closure of the trial (see the protocol amendments in File S3).

Intervention: EX group

The exercise intervention involved progressive aerobic training, and it was delivered in person during chemotherapy; however, in-person supervised exercise sessions were replaced with unsupervised sessions while COVID-19 restrictions were in place, and coupled with remote communication (i.e., email communication, text messages to cell phones, and voice telephone calls) to assist patients in exercising once they received their weekly exercise prescription from the exercise trainer. The intervention length corresponded to the duration of patients' chemotherapy regimen, which ranged from 12 to 24 weeks. Patients received three sessions weekly that were individually tailored (on the basis of baseline CPET data), and thus focused on reaching personalized exercise intensity zones on the basis of heart rate and power output in watts. Sessions varied in length from 20–25 to 40 min and were supervised by trained exercise professionals who had valid cardiopulmonary resuscitation (Level C) certification and experience supervising exercise in populations with chronic disease. Patients interacted with the same exercise professional throughout the intervention, who encouraged them to complete an unsupervised session when a supervised session was missed. Both sites had treadmills, stationary bikes, and elliptical machines for supervised sessions, and participants were encouraged to use at least two different modes of exercise each week as a strategy to reduce overuse injuries. During supervised sessions and while institutional and public health restrictions to in-person research at both sites were in place, patients wore a heart rate monitor (Polar Electro Inc, Lake Success, New York) to monitor the exercise intensity for their individually tailored weekly sessions. Notably, if the side effects of chemotherapy limited patients' ability to reach their target heart rate zone, they were encouraged to work at the rating of perceived exertion associated with the heart rate zone via the 6–20 Borg scale.[32]

The exercise intervention was designed to help patients progress toward meeting exercise guidelines for adults diagnosed with cancer[33] and encourage integration with lifestyle. Accordingly, after an introductory phase of 3 weeks, patients were asked to add ≥1 unsupervised aerobic training session per week to their protocol and record the number of weekly sessions and duration in a logbook. The prescribed duration of the unsupervised session was increased from 15 to 20 min for the first 3 weeks to 20–30 min thereafter. The exercise intensity was guided by patients' rating of perceived exertion during the unsupervised sessions (i.e., patients were instructed to perform their aerobic training at an intensity corresponding to 12–13 on the 6–20 Borg scale,[32] if they were able; if not, they were to perform the exercise session at the highest intensity they deemed possible). Full details of the intervention and an overview of the "chemotherapy-periodized" nonlinear aerobic exercise training protocol[34] are provided in the published trial protocol.[28]

During the intervention period, data derived from the heart rate monitors and logbooks were analyzed to monitor exercise adherence and enable reporting of adherence (defined as the proportion of sessions where the target exercise duration and intensity were achieved). Additionally, exercise trainers logged (1) number of supervised sessions completed, (2) reasons for missed supervised sessions, (3) type(s) and duration of exercise performed, (4) average heart rate obtained from the monitors, (5) ratings of perceived exertion via the 6–20 Borg scale,[32] (6) exercise-related adverse events, and (7) patients' comments regarding sessions, including reasons for nonadherence to the prescribed exercise targets. While institutional and public health restrictions to in-person research at both sites were in place, patients were asked to record these data on their own. To monitor fidelity, the exercise trainers' logs were discussed during biweekly team meetings.

Comparison: UC group

UC was a no-treatment, wait list control condition (i.e., delayed exercise intervention) that consisted of standard care at the participating site. Patients in the UC group were asked to maintain their usual level of exercise, without exercise restrictions. After chemotherapy completion, the UC group received the same exercise intervention as the EX group, except the length was standardized to 12 weeks. Patients' exercise prescriptions were based on their postchemotherapy CPET results.

Data collection

Full details regarding outcome measures relevant to this study are provided in the published protocol.[28] Briefly, the data analyzed for this study were collected at two time points: preintervention (i.e., baseline) and postintervention (i.e., after chemotherapy completion). For objective cognitive function, patients completed a battery of paper-and-pencil neuropsychological tests that were administered in person by trained research assistants; however, virtual administration was necessary for 15 postintervention assessments while COVID-19 restrictions were in place (see the protocol amendments in File S3). Covering a range of cognitive domains (e.g., verbal/visual memory, attention, working memory, processing speed, executive function, and psychomotor performance), the testing battery included the following tests administered in the order listed: Hopkins Verbal Learning Test–Revised (HVLT-R[35]), Brief Visuospatial Memory Test–Revised (BVMT-R[36]), Digit Symbol Coding (DSC) and Letter–Number Sequencing (LNS) subtests of the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV[37]), Auditory Consonant Trigrams Test (ACTT[38]), Controlled Oral Word Association Test (COWAT[39]), Trail Making Test parts A and B (TMT[40]), and delayed recall versions of the HVLT-R[35] and BVMT-R.[36] Alternate forms, where available, were used at each time point to minimize practice effects from serial testing, and raw neuropsychological test scores were standardized to have a mean (SD) of 0 (1)

via the pooled sample of all patients at baseline (to reflect the same scale and thus allow for easier comparison across measures). For self-reported cognitive function and its impact on QOL, patients completed the FACT–Cog (version 3)[23] and PROMIS–Cog (four-item short-form version)[24] online via a secure web application (i.e., REDCap platform) at both time points. Additionally, ventilatory threshold and aerobic capacity (relative VO_2 peak) were measured via a metabolic cart (Vancouver: Parvo Medics; Ottawa: VMAX CPET Systems). CPETs were performed by trained technicians and staff in a medically supervised setting. Last, patients self-reported sociodemographic information via an online questionnaire and gave permission to have medical information (e.g., disease stage, treatment protocol, and current medication use) extracted from their medical records; these data were collected to describe the sample and enable potential future exploratory subgroup analyses examining differences in the results on the basis of these characteristics.

Statistical analysis

For descriptive purposes, outcomes have been summarized as means with SD pre- and postintervention. The primary analyses for the primary and secondary outcomes examined differences between the EX and UC groups postintervention, which were adjusted for baseline values via ANCOVA. Of note, a separate, forthcoming publication will present analyses and results involving the secondary end point (i.e., follow-up). Additional covariates included age, education, and self-reported exercise at baseline. Intervention effects are reported as the adjusted least squares mean difference with 95% confidence intervals (CIs) and p values. t-tests were used to examine between-group differences in ventilatory threshold, relative VO_2 peak, and time to VO_2 peak from baseline to postintervention; comparisons were for exploratory purposes only. Statistical analyses were performed via SAS (SAS Institute Inc, Cary, North Carolina).

All randomized patients were included in the analyses according to the intention-to-treat principle (i.e., patients were analyzed according to their allocated group). The analysis relied on complete case analysis for one secondary outcome (i.e., FACT–Cog Perceived Cognitive Impairment subscale); however, multiple imputation was used to impute missing data for all other outcomes under the assumption that the data were missing at random. Specifically, multiple imputation with 20 imputations was used to create complete data sets for analysis. The imputation model included all outcomes, the group indicator, covariates (i.e., age, education, and self-reported exercise), and general QOL (as assessed by the RAND 36-item health survey, version 1[41]) as a result of the links to outcomes noted in the literature. The fully conditional specification method in SAS via PROC MI was used. Predictive mean matching was used for continuous variables with 20 burn-in iterations and eight nearest neighbors. Trace plots of the imputed values and standard errors were examined to check for patterns in the imputation chains. The analyses for the primary and secondary outcomes were conducted for each imputation-completed data set, and the results were pooled via Rubin's rules.[42] Notably, prespecified methods of analysis reported in the published protocol were altered *before* examination of the data, with deviations documented in the protocol amendments (see File S3).

RESULTS

Enrollment and patient characteristics

Figure 1 provides the Consolidated Standards of Reporting Trials (CONSORT) flow diagram for this study; a complete CONSORT flow diagram outlining the progress of patients throughout the ACTIVATE trial is provided in File S4. In total, 175 women were screened for eligibility from February 2018 to February 2022, 113 of whom were excluded. The most common reasons for ineligibility were having already started chemotherapy (36 of 113; 31.9%) and engaging in moderate- to vigorous-intensity aerobic exercise for ≥150 min/week in the 3 months before enrollment (22 of 113; 19.5%; see Figure 1 or File S4 for a complete list of reasons). Of the 175 women screened, 62 (35.4%) enrolled, provided consent to participate, and completed baseline assessments for the primary and secondary outcomes. However, three did not receive exercise clearance on the basis of their CPET, and two withdrew from the trial before randomization (see Figure 1 or File S4 for reasons). Accordingly, 57 patients were randomized to EX (n = 28; 49.1%) or UC (n = 29; 50.9%). Fewer patients (two of 28; 7.1%) randomized to EX dropped out of the trial before completing postintervention assessments than patients randomized to UC (nine of 29; 31.0%) (see Figure 1 or File S4 for reasons). The analysis in this study was based on 57 patients; the relative efficiency of the imputation for these patients was >99.0%.

Patients' baseline characteristics are presented in Table 1; these were well balanced across both groups, except for self-reported exercise. In brief, the sample ranged in age from 29 to 70 years, and most patients self-identified as White, were working full/part time, had an annual household income <$100,000 (Canadian dollars), held postsecondary degrees, were married/in a common-law relationship, and were diagnosed with stage II breast cancer.

Exercise adherence

The EX group had a mean attendance of 33.8 supervised sessions out of an average of 43.3 prescribed sessions (median [interquartile range] attendance, 87.9% [78.2%–96.1%]). The EX group met the prescribed exercise duration and intensity (i.e., heart rate zones or power output [watts]) for an average of 28.0 sessions (64.6%). Because of COVID-19 (see the protocol amendments in File S3), 31 patients (n_{EX} = 19; n_{UC} = 12) had VO_2 peak and ventilatory threshold measured at baseline and postintervention as well as time to VO_2 peak, whereas for 32 patients (n_{EX} = 20; n_{UC} = 12) only time to VO_2 peak could be assessed because of missing metabolic data at postintervention. Compared to the EX group, the UC group had a significantly greater decrease in time to VO_2 peak from baseline to postintervention (EX:

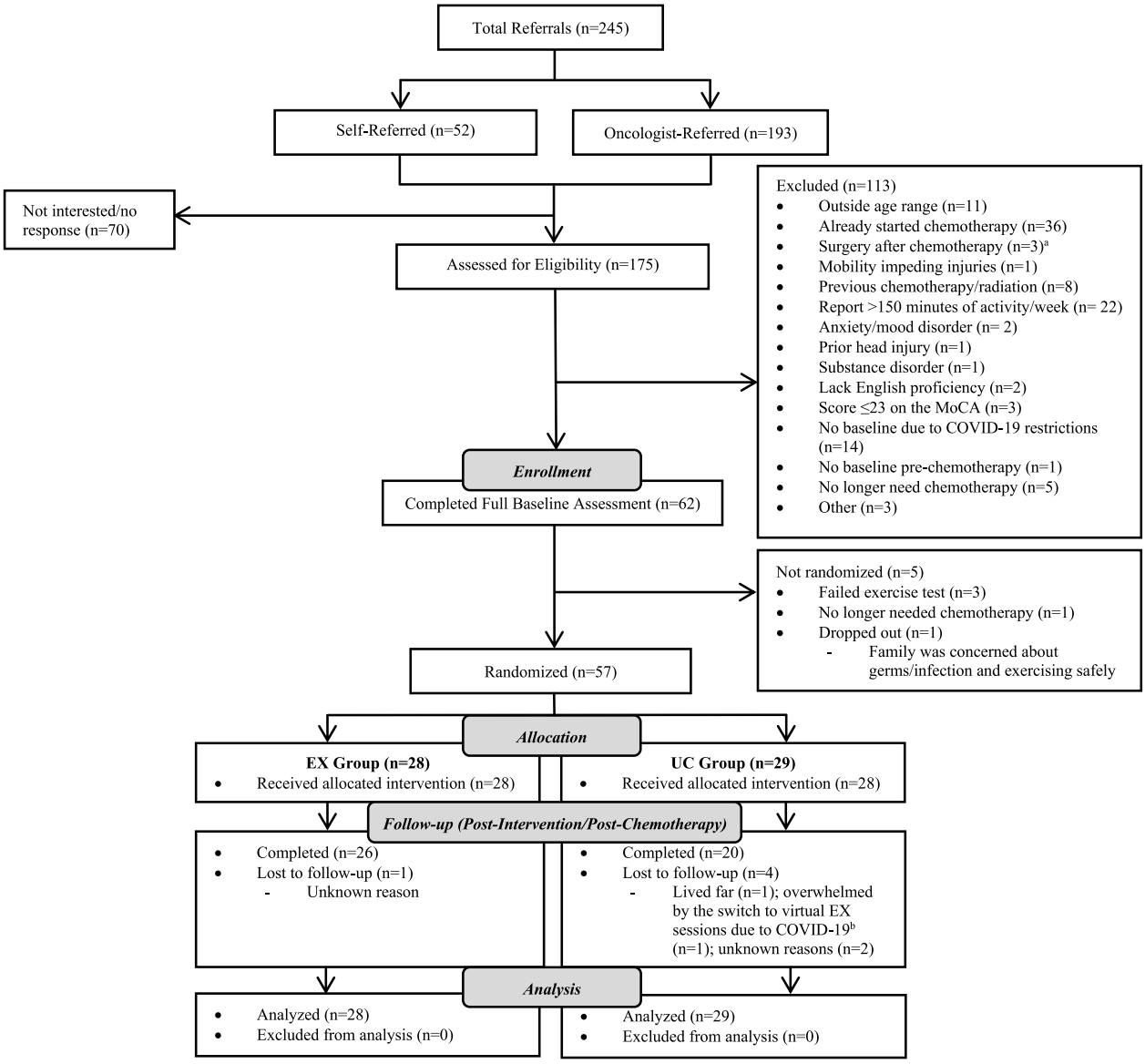

FIGURE 1 Consolidated Standards of Reporting Trials flow diagram of progress throughout specific phases of this study. COVID-19 indicates coronavirus disease in 2019; EX, exercise; MoCA, Montreal Cognitive Assessment; UC, usual care. [a]Neoadjuvant chemotherapy was initially an exclusion criterion (see the protocol amendments in File S3). [b]Exercise sessions were switched to virtual (i.e., online delivery via a computer or device) while COVID-19 restrictions were in place (see the protocol amendments in File S3).

−57.4 ± 100.1 s; UC: −120.3 ± 50.8 s; $p = .03$). For patients with metabolic cart data, compared to the EX group, the UC group exhibited a greater decrease in VO_2 peak (EX: −2.4 ± 5.5 mL/kg/min; UC: −3.6 ± 3.6 mL/kg/min; $p = .50$) and ventilatory threshold (EX: −0.07 ± 0.34 L/min; UC: −0.24 ± 0.47 L/min; $p = .25$) from baseline to postintervention, although these differences were not statistically significant. No adverse events attributable to the exercise intervention were reported by patients during the trial.

Objective cognitive function

Table 2 presents raw scores (for ease of interpretation and comparison across studies) for cognitive outcomes as well as ANCOVA results (i.e., adjusted mean differences with 95% CIs and p values). To maintain the familywise error rate associated with testing multiple primary outcomes, the Bonferroni adjustment was used,[43] such that the significance level was set to .0038 (α of .05 divided by the number of tests [i.e., 13]). Postintervention, there were no significant mean differences in neuropsychological standardized test scores between the EX and UC groups for HVLT-R total recall, BVMT-R total, DSC, LNS, ACTT total, COWAT, TMT part A, TMT difference (B – A), HVLT-R delayed recall, HVLT-R recognition discrimination index, HVLT-R retention, and BVMT-R delayed recall. One exception was that there was greater improvement for the EX group compared to the UC group on TMT part B (mean difference, −0.45 [95% CI, −0.86 to −0.04]), although the difference barely crossed the significance threshold after multiplicity correction.

TABLE 1 Baseline sample characteristics.

	Total (N = 57)	EX (n = 28)	UC (n = 29)
Sociodemographic characteristics			
Age, M ± SD (range), years	48.83 ± 9.95 (29–70)[a]	48.69 ± 10.62 (30–66)[b]	48.96 ± 9.47 (29–70)[c]
Ethnicity, White, No. (%)	39 (72.22)[d]	19 (70.37)[e]	20 (74.07)[c]
Menopausal status, pre/perimenopausal, No. (%)	35 (61.40)	17 (60.71)	18 (62.07)
Marital status, married/common law, No. (%)	34 (62.96)[d]	15 (55.56)[e]	19 (70.37)[c]
Education, completed postsecondary degree/certificate, No. (%)	44 (81.48)[d]	23 (85.19)[e]	21 (77.78)[c]
Employment status, working part/full time, No. (%)	41 (75.93)[d]	20 (74.07)[e]	21 (77.78)[c]
Annual household income, >$100,000 CAD, No. (%)	24 (44.44)[d]	11 (40.74)[e]	13 (48.15)[c]
Medical characteristics			
Cancer stage, No. (%)			
I	15 (27.78)[d]	8 (29.63)[e]	7 (25.93)[c]
II	24 (44.44)[d]	13 (48.15)[e]	11 (40.74)[c]
III	10 (18.52)[d]	4 (14.81)[e]	6 (22.22)[c]
Do not know	5 (9.26)[d]	2 (7.41)[e]	3 (11.11)[c]
Body mass index, M ± SD (range), kg/m^2	26.82 ± 5.43 (19.47–39.20)[f]	25.57 ± 4.19 (20.40–35.89)[g]	28.22 ± 6.40 (19.47–39.20)[h]
Relative maximal aerobic capacity, M ± SD (range), mL/kg/min	22.84 ± 6.53 (8.71–38.93)[i]	22.68 ± 6.08 (8.71–38.93)[j]	23.00 ± 7.07 (12.29–37.23)[k]
Perceived general health status, M ± SD (range), no units[l]	61.65 ± 17.65 (20.00–91.67)[d]	61.48 ± 17.20 (20.00–90.00)[e]	61.82 ± 18.41 (20.00–91.67)[c]
Self-reported MVPA/week, M ± SD (range), min	77.53 ± 92.25 (0.00–360.00)[a]	90.19 ± 98.61 (0.00–360.00)[e]	64.38 ± 85.06 (0.00–300.00)[m]

Abbreviations: CAD, Canadian dollars; EX, exercise; M, mean; MVPA, moderate- to vigorous-intensity physical activity; SD, standard deviation; UC, usual care.

[a]Based on 53 total patients.
[b]Based on 26 EX group patients.
[c]Based on 27 UC group patients.
[d]Based on 54 total patients.
[e]Based on 27 EX group patients.
[f]Based on 34 total patients.
[g]Based on 18 EX group patients.
[h]Based on 16 UC group patients.
[i]Based on 45 total patients.
[j]Based on 22 EX group patients.
[k]Based on 23 UC group patients.
[l]Based on responses to the single-item measure of health perceptions on the RAND 36-item health survey (range, 0–100).
[m]Based on 26 UC group patients.

Self-reported cognitive function and its impact on QOL

Analyses involving self-reported outcomes are presented in Table 2. These secondary outcomes were not adjusted for multiplicity,[44] such that the significance level was set at .05 and results should be considered exploratory. Postintervention, there were significant mean differences between the groups for four outcomes. As assessed via the FACT–Cog, the EX group reported significant improvements in Perceived Cognitive Impairments (mean difference, 11.4 [95% CI, 5.0–17.8]), Perceived Cognitive Abilities (mean difference, 4.7 [95% CI, 2.0–7.4]), and Total FACT–Cog scores (mean difference, 18.4 [95% CI, 7.8–29.0]) compared to the UC group. No significant differences were identified for the following FACT–Cog subscales: Comments from Others and Impact of Perceived Cognitive Impairments on QOL. As assessed via the PROMIS–Cog, the EX group reported significantly improved perceived cognitive function (mean difference, 3.3 [95% CI, 0.9–5.8]).

TABLE 2 Primary and secondary outcome results.

Outcomes	Preintervention (baseline), M (SD)[a]		Postintervention (after chemotherapy completion), M (SD)[a]		Mean difference[b]	SE	95% CI	*p*
	EX (n = 28)	UC (n = 29)	EX (n = 28)	UC (n = 29)				
Primary outcome: objective cognitive function								
HVLT-R (total recall)	26.50 (4.04)	27.17 (3.19)	28.96 (3.57)[c]	28.36 (4.61)[d]	0.14	0.31	−0.47 to 0.76	.65
BVMT-R (total)	24.82 (5.65)	25.17 (5.69)	27.39 (6.13)[c]	28.43 (4.39)[e]	−0.09	0.28	−0.65 to 0.47	.75
DSC	73.32 (13.54)	75.07 (14.63)	74.85 (15.52)[c]	74.38 (17.61)[e]	0.18	0.24	−0.29 to 0.64	.46
LNS	20.04 (2.25)	20.07 (2.89)	21.31 (2.28)[c]	20.77 (2.69)[d]	0.17	0.28	−0.39 to 0.73	.55
ACTT (total)	48.93 (5.60)	48.07 (6.24)	52.19 (5.15)[c]	50.32 (6.48)[d]	0.22	0.27	−0.33 to 0.76	.42
COWAT	43.54 (10.94)	43.72 (12.86)	44.68 (11.89)[c]	44.18 (13.73)[d]	−0.07	0.20	−0.46 to 0.32	.72
TMT part A	28.99 (11.55)	31.03 (15.62)	28.81 (11.82)[f]	29.20 (11.21)[e]	−0.03	0.17	−0.35 to 0.30	.88
TMT part B	69.52 (19.41)	65.29 (27.43)	59.54 (24.30)[f]	65.80 (25.28)[e]	−0.45	0.21	−0.86 to −0.04	.03
TMT difference (B − A)[g]	40.53 (14.01)	34.26 (27.12)	30.73 (19.12)[f]	36.60 (19.27)[e]	−0.37	0.23	−0.81 to 0.08	.11
HVLT-R (delayed recall)	9.11 (2.89)	10.14 (1.43)	10.19 (1.65)[c]	10.05 (1.79)[d]	0.28	0.19	−0.10 to 0.66	.14
HVLT-R (RDI)	10.86 (1.38)	11.35 (0.72)	10.50 (2.60)[c]	11.00 (1.38)[d]	−0.32	0.63	−1.55 to 0.91	.61
HVLT-R (retention)	86.01 (24.33)	91.95 (10.91)	90.11 (8.90)[c]	92.83 (11.23)[d]	0.00	0.16	−0.33 to 0.32	.98
BVMT-R (delayed recall)	9.67 (1.86)[h]	10.45 (1.76)	10.23 (1.84)[c]	10.52 (1.54)[e]	−0.11	0.23	−0.57 to 0.34	.63
Secondary outcomes: self-reported cognitive function and its impact on QOL								
FACT–Cog PCI	59.23 (10.88)[h]	57.59 (13.89)[i]	57.62 (11.09)[c]	46.18 (16.95)[j]	11.42	3.16	5.01 to 17.84	<.001
FACT–Cog Oth	15.41 (1.15)[h]	15.37 (1.67)[i]	15.21 (1.32)[k]	14.60 (2.54)[j]	0.13	0.44	−0.72 to 0.98	.76
FACT–Cog PCA	21.85 (4.50)[h]	22.00 (5.97)[i]	20.85 (5.27)[c]	16.65 (5.31)[j]	4.66	1.37	1.97 to 7.35	<.001
FACT–Cog QOL	12.59 (4.02)[h]	13.44 (2.60)[l]	12.05 (3.34)[f]	11.75 (4.50)[j]	0.20	1.31	−2.36 to 2.77	.88
FACT–Cog Total	109.08 (17.53)[h]	107.41 (20.53)[i]	104.09 (19.39)[c]	89.18 (27.36)[j]	18.37	5.41	7.77 to 28.98	<.001
PROMIS–Cog	15.67 (3.71)[h]	15.33 (4.92)[i]	14.08 (4.44)[c]	11.05 (4.05)[j]	3.33	1.22	0.86 to 5.79	<.001

Note: Intention-to-treat analyses included 57 patients. The objective cognitive function data were standardized to a mean (SD) of 0 (1) for analysis. The level of significance used for the primary outcome was .0038, or α of .05/13, to deal with issues of multiplicity; secondary outcomes were not adjusted for multiplicity ($p < .05$ was considered statistically significant). Higher scores reflect better performance for all neuropsychological tests *except* the TMT (for which higher scores reflect worse performance). Higher scores reflect better perceived cognitive function for both the FACT–Cog and PROMIS–Cog.

Abbreviations: ACTT, Auditory Consonant Trigrams Test; BVMT-R, Brief Visuospatial Memory Test–Revised; CI, confidence interval; COWAT, Controlled Word Association Test; DSC, Digit Symbol Coding; EX, exercise group; FACT–Cog, Functional Assessment of Cancer Therapy–Cognitive Function; FACT-Cog Oth, Functional Assessment of Cancer Therapy-Cognitive Function: Comments from Others subscale; FACT-Cog PCA, Functional Assessment of Cancer Therapy-Cognitive Function: Perceived Cognitive Abilities subscale; FACT-Cog PCI, Functional Assessment of Cancer Therapy-Cognitive Function: Perceived Cognitive Impairments subscale; FACT-Cog QOL, Functional Assessment of Cancer Therapy-Cognitive Function: Impact of Perceived Cognitive Impairments on Quality of Life subscale; HVLT-R, Hopkins Verbal Learning Test–Revised; LNS, Letter–Number Sequencing; M, mean; PROMIS–Cog, Patient-Reported Outcomes Measurement Information System Applied Cognition; RDI, recognition discrimination index; SD, standard deviation; SE, standard error; TMT, Trail Making Test; UC, usual care wait list group.

[a]Represents raw scores.

[b]Represents the least squares mean difference adjusted for baseline value, age, education, and self-reported exercise at baseline.

[c]Based on 26 EX group patients.

[d]Based on 22 UC group patients.

[e]Based on 21 UC group patients.

[f]Based on 25 EX group patients.

[g]Indicates the difference in time in seconds taken to complete TMT parts A and B (i.e., TMT B – A).

[h]Based on 27 EX group patients.

[i]Based on 27 UC group patients.

[j]Based on 20 UC group patients.

[k]Based on 24 EX group patients.

[l]Based on 25 UC group patients.

DISCUSSION

In this multisite trial involving women initiating chemotherapy for breast cancer, an aerobic exercise intervention did not result in significant differences in objective cognitive performance post-intervention as compared to UC. These results do not support the hypothesis that exercise improves cognitive performance in key domains affected by chemotherapy (e.g., verbal/visual memory, attention, working memory, processing speed, executive function, and psychomotor performance). However, the intervention resulted in greater improvements in self-reported cognitive function and its impact on QOL for the EX group compared to the UC group.

Objective cognitive function outcomes

Despite observational and quasiexperimental evidence supporting an association between exercise and objective cognitive function in persons diagnosed with cancer,[16] few studies to date have tested the effects of exercise on objective cognitive function outcomes in women receiving chemotherapy for breast cancer. In the ACTIVATE trial, there were no significant effects of aerobic exercise on objective cognitive function, and these null results are consistent with some randomized controlled trialse[45–48] and a pragmatic follow-up trial.[49] There are several possible reasons for the lack of effects on cognitive function. First, the extent to which patients were performing within normal ranges at baseline and the extent to which this remained unchanged *during* chemotherapy may have left little room for improvement in performance postintervention. Because the onset of cognitive impairments varies between patients, with some patients having late-onset impairments (i.e., posttreatment[5]), it is reasonable to expect the effects of exercise when either baseline cognitive impairment is high or cognitive function decline has occurred during chemotherapy as there is greater room for improvement. Also, nonsignificant results could be attributed to using cognitive performance tests not sensitive enough to detect small changes in cognitively high-functioning women. Second, improvements in cognitive performance on neuropsychological tests may have dissipated shortly after exercise, especially if exercise levels were not maintained during the time that elapsed between the last exercise session and testing; consequently, improvements in cognitive performance in this trial may have been missed. Third, it is possible that the EX group experienced domain-specific improvements in cognitive function that are not evident during controlled neuropsychological testing or on the tests used but may be more noticeable in the context of cognitively demanding lifestyles or on other neuropsychological tests. Indeed, using the selected valid neuropsychological tests improves internal validity though the *ecological* validity of these tests (i.e., how they relate to overall cognitive function in everyday life within varying environments with possible co-occurring problems such as mood disturbances, sleep impairments, and fatigue) is unclear. Relatedly, it is also possible that the effects of exercise on cognitive function only emerge when cognitive tasks are extremely difficult. Fourth, any changes in the EX group could be paralleled by the UC group because of practice effects from prior exposure to the tests at baseline[50] or cognitive reserve (i.e., capacity to cope with normal and disease-related changes in the brain[51]); indeed, the latter may have allowed patients in the UC group to maintain their cognitive function during the early course of cognitive decline. Fifth, to elicit changes in cognitive performance, the exercise intervention may have needed to include cognitively stimulating activities; these have become a focus of early intervention cognitive rehabilitation programs in cancer groups,[52,53] and are shown to further enhance cognitive performance when performed in conjunction with exercise across populations.[54,55] Last, although the EX dosage and type were similar to those in prior trials,[16,17] the prescribed length (i.e., 12–24 weeks, which depended on each patient's chemotherapy regimen), intensity, volume, or type (i.e., aerobic) may have been insufficient to produce changes in the putative mechanisms underlying cognitive function, and thus did not lead to significant cognitive benefits. Mechanistically, the neural and vascular adaptations induced by exercise are hypothesized to promote cognitive improvements via stimulation of neurogenesis, angiogenesis, and synaptic plasticity, and by reducing proinflammatory processes and cellular damage brought about by oxidative stress.[56–58] Longer (>6 months), multicomponent (e.g., aerobic, strength, and balance) exercise interventions or higher intensity aerobic exercise may be necessary for neural and vascular adaptations to occur and to influence cognitive function. These are all issues ripe for empirical investigation.

Self-reported cognitive function and its impact on QOL outcomes

Analysis of self-reported outcomes as assessed via the FACT–Cog and PROMIS–Cog indicated that this aerobic exercise intervention had positive effects on perceived cognitive impairment, perceived cognitive ability, overall (i.e., total) perceived cognitive function, and associated QOL among women undergoing chemotherapy for breast cancer as compared to UC. This finding is important given the association between these constructs and global QOL.[59,60] The main implication of this result is that regular aerobic exercise is influential in preserving or improving these self-reported cognitive function and QOL outcomes. When considered alongside existing evidence,[61–64] improved self-reported cognitive function adds further weight to the call to action on making exercise assessment, prescription, and referral a medical standard of care.

Discrepant results

Self-report and objective measures are both options for assessing the effects of exercise on cognitive function, and can be used to complement each other. Combining both types of measures is common, as evident in a recent review of studies exploring exercise and cognition among persons with cancer.[16] However, the correlations between

subjective (self-report) and *objective* (performance-based neuropsychological) measures of cognitive function have been weak-to-moderate across samples,[65,66] and evidence for an association between exercise and cognitive function has been more robust for self-report than for objective measures of cognitive function in persons diagnosed with cancer.[16,17] Conceptual and methodological differences between self-report and objective measures might contribute to the discrepant results in this study and the literature. Conceptually, *performance* on neuropsychological tests is an indicator of a person's ability to *perform* in a structured optimal-performance setting, whereas self-report considers patients' reports of success in everyday performance or real-world functioning,[67] and their reports may be influenced by other factors affecting their functioning and QOL (e.g., mood disturbances, personal characteristics, sleep impairments, and fatigue). Moreover, subjective measures of cognitive impairment may precede changes in neuropsychological test performance because patients may be more sensitive to subtle changes in cognitive function that are not yet detectable via current neuropsychological tests.[68] Furthermore, rather than being an issue of the accuracy of assessments or reporting errors, subjective and objective measures of cognitive function reflect meaningful but distinct features of cognitive function that affect self-reported outcomes (e.g., vocational readiness, personal health, and wellbeing), which makes research on both relevant. An important practical implication could be that different interventions may be appropriate for objective and subjective cognitive difficulties.

Methodologically, although objective and self-report measures were administered pre- and postintervention, the exact time frame differed, with the neuropsychological tests having been conducted over a short period of time. Thus, the neuropsychological tests reflect patients' abilities to perform during the testing session, and could be influenced by any number of personal or environmental factors occurring at that time. In contrast, patients responded retrospectively (i.e., in the past 7 days) on the self-report measures (i.e., FACT–Cog and PROMIS–Cog). Plausibly, this longer time frame may have led patients to consider several different scenarios/situations and summarize their responses over a longer period. Nevertheless, the discrepant results raise an important question for those who are interested in developing interventions (exercise or otherwise) to ameliorate cognitive function: is it conceptual aspects, methodological aspects, or differences in the responses themselves that are driving the discrepant results? Addressing this question, while further probing discrepant findings in future trials, perhaps via focused exit interviews to elicit patients' views of the possible reasons for the observed discrepancy, may help to build a more nuanced understanding of the effects of exercise on cognitive function in women diagnosed with breast cancer.

Strengths and limitations

The ACTIVATE trial has several strengths, including its multisite randomized controlled design. Furthermore, patients demonstrated high adherence to the aerobic exercise intervention and retention to the trial, exercise trainers were qualified and supervised for fidelity, the intervention was individually tailored with a similar dosage to that in prior trials, and the trial used a comprehensive approach to assessing cognitive function via objective and self-report measures with evidence of score reliability and validity. Moreover, this trial focused on a particularly vulnerable period (i.e., during chemotherapy) wherein cognitive complaints often arise.[69,70] Finally, study staff who participated in data collection and management and researchers/investigators remained blinded until the analysis of the outcomes in this study to minimize potential bias.

Important limitations with the ACTIVATE trial and this study include recruitment challenges to achieve the sample size proposed in the study protocol.[28] A shift in the traditional sequence of treatment from adjuvant chemotherapy to neoadjuvant chemotherapy[71] left a severely limited window of recruitment opportunity for some prospective patients. Furthermore, the COVID-19 pandemic compounded the difficulty of recruiting women for a number of reasons (e.g., lockdown, anxieties relating to the pandemic, redeployment of staff, social distancing, and avoidance of public transport). Relatedly, the trial protocol was amended to accommodate COVID-19 safety arrangements for in-person visits such that virtual methods of intervention delivery and testing were used (i.e., patients completed the exercise sessions and neuropsychological tests online with study staff); although great care was taken on the part of the trial staff to maintain consistency in procedures across patients, this protocol change could have resulted in unknown differences in intervention and testing conditions. Additionally, although a rigorous randomization procedure was performed, women initiating chemotherapy for breast cancer are a heterogeneous group that could include those experiencing varying side effects of medications; these and other potential confounders were not examined in this study, and the specific characteristics of the sample limit the generalizability of the results to other cohorts. Moreover, the need for a multiplicity adjustment was not anticipated in the design of the trial, such that the sample size calculation was based on a single composite score assessed at the 5% significance level. Other key trial limitations include the smaller than planned sample size of patients, the questionnaires used to assess subjective cognitive function and its impact on QOL being subject to recall and social desirability bias, and the number of dropouts within the UC group exceeding that of the EX group, which could have influenced the results. Last, the included patients were potentially somewhat active and were not sampled for cognitive dysfunction, which thereby limited the potential to identify effects either because there may have been little room for improvement (especially if patients showed no/little evidence of cognitive impairment) or because the neuropsychological tests may have lacked the sensitivity to detect variations within the normal range.[72]

Future directions

The current findings highlight several future directions for research. First, the effectiveness of the face-to-face ACTIVATE intervention

may be examined in future randomized controlled trials with a longer intervention period. Second, in addition to aerobic exercise, further research could test the effectiveness of multicomponent (i.e., aerobic, strength, and balance exercises) and multidomain (e.g., exercise, mind–body practices, and cognitive stimulation) interventions for improving cognitive function. Third, because the internet and the proliferation of internet-enabled devices allows for the inclusion of people from many walks of life worldwide, researchers should leverage virtual delivery methods and compare these to more traditional in-person interventions. If virtual interventions are found to have similar effects, they may be a relevant alternative for patients who rarely receive interventions because of barriers often encountered with face-to-face interventions (e.g., geographic distance to intervention centers and poor public transportation options[73,74]). Fourth, because the impact of the COVID-19 pandemic on research in this area (and others) is likely to persist (and future pandemics are possible), research quantifying the likely impact on outcomes is necessary. Finally, because concerns regarding generalizability are recurrent across studies (including this study), more diverse sampling from sociodemographic and medical standpoints is required in future research.

In conclusion, among women initiating chemotherapy for breast cancer, an aerobic exercise intervention offered during chemotherapy did not result in significant differences in objective cognitive function after chemotherapy completion in comparison to UC. However, the results do support the use of this intervention for improving self-reported cognitive function and its impact on QOL in this cohort.

AUTHOR CONTRIBUTIONS

Jennifer Brunet: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, and writing–original draft. **Sitara Sharma**: Data curation, formal analysis, and writing–review and editing. **Kendra Zadravec**: Data curation and writing–review and editing. **Monica Taljaard**: Conceptualization, formal analysis, methodology, supervision, and writing–review and editing. **Nathalie LeVasseur**: Conceptualization, methodology, and writing–review and editing. **Amirrtha Srikanthan**: Conceptualization, methodology, and writing–review and editing. **Kelcey A. Bland**: Conceptualization and writing–review and editing. **Elham Sabri**: Formal analysis and writing–review and editing. **Barbara Collins**: Conceptualization, methodology, resources, validation, and writing–review and editing. **Sherri Hayden**: Writing–review and editing. **Christine Simmons**: Conceptualization, methodology, and writing–review and editing. **Andra M. Smith**: Conceptualization and writing–review and editing. **Kristin L. Campbell**: Conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Nathalie LeVasseur reports consulting for Eli Lilly, F. Hoffmann-La Roche, Novartis, AstraZeneca Canada, Pfizer Canada, Merck, Gilead Sciences, TerSera Therapeutics, and Seagen and receiving grants from Gilead Sciences, Pfizer Canada, AbbVie, Eli Lilly, and Exact Sciences. Christine Simmons reports consulting for AstraZeneca Canada, Gilead Sciences, Pfizer Canada, Merck, and Novartis. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article cannot be made available by the authors because patients were assured that their data would be kept private and confidential to the extent permitted by law and that only the research team would have access to the data.

ORCID

Jennifer Brunet https://orcid.org/0000-0003-3242-5444
Sitara Sharma https://orcid.org/0000-0001-6716-7401
Nathalie LeVasseur https://orcid.org/0000-0002-2581-4903
Amirrtha Srikanthan https://orcid.org/0000-0002-8903-0040
Kristin L. Campbell https://orcid.org/0000-0002-2266-1382

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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