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A pilot investigation of the impact of acute mental and physical fatigue exposure on inflammatory cytokines and state fatigue level in breast cancer survivors

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Abstract

Background This study aims to analyze the changes in inflammatory cytokines and state fatigue after exposure to a mental or physical fatiguing activity in breast cancer survivors (BCS).

Methods A total of 46 BCS women (age: 58.9 ± 9.1) were recruited for this study and randomly assigned to one of three groups: exposure to physical fatigue ($n = 16$), mental fatigue ($n = 15$), or control ($n = 15$). Participants exposed to physical fatigue performed a 6-minute walk/run test. Participants exposed to mental fatigue performed a version of a dual 2-back task on a computer. Participants in the control group watched a video for 6 min. Clinically significant fatigue was defined by the FACIT-F. Analytes in serum were profiled using the Bio-Plex 200 Suspension Array System, specifically IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, eotaxin, TNF-α, TGF-β1, and VEGF.

Results Changes in inflammatory factors in response to the assigned fatigue-inducing tasks were mainly not statistically significant. The presence of clinically significant fatigue reported at baseline was, however, related to reactions to fatigue-inducing stimuli. Levels of TGF-β and eotaxin were consistently altered in reactions to fatigue-inducing tasks, particularly in those with clinical fatigue.

Conclusions Clinically significant fatigue is related to increased inflammatory reactions to mentally or physically fatiguing tasks, highlighting the consistent impact that fatigue has across various challenges of daily activities. Acute fatigue challenges, the kind that BCS would be exposed to in everyday circumstances, does increase inflammatory responses, and those with clinically significant levels of fatigue at baseline are more likely to show these effects.

Keywords Cancer-related fatigue, Clinically significant fatigue, Reactivity, Inflammation, Breast cancer

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Background

According to the American Cancer Society, about 281,550 new cases of invasive breast cancer were diagnosed in women in 2021 and there are over 3.8 million women with a history of breast cancer in the US alone [1]. Breast cancer survivors (BCS) deal with various post-cancer issues, including: pain, fatigue, lymphedema, distress, and medication side effects, as well as longer-term concerns for cardiac and bone health [2]. Cancer-related fatigue (CRF) is one of the most common and troubling symptoms that breast cancer survivors face [3]. CRF is multi-dimensional and may have physical, mental, and emotional manifestations including generalized weakness, diminished concentration or attention, decreased motivation or interest to engage in usual activities, and emotional lability [4]. The fatigue is usually present during chemotherapy, but for about one in four of BCS, the fatigue will last years beyond their entry to remission and impact quality of life [5]. In particular, fatigue has a negative impact on everyday functioning and work capacity [6]. Cancer-related cognitive impairment (brain fog/chemo brain) has been documented in breast cancer survivors and is characterized by impairment of memory, executive functions, attention and processing speed [7]. There is significant overlap between cancer-related cognitive impairment and mental aspects of fatigue.

The role of inflammation in cancer development and progression is well-established and inflammatory cytokines have been identified as contributors to tumor progression at all stages [8]. Moreover, inflammatory signaling has also been found to contribute to fatigue [9–11]. However, more research is still needed to clarify the association between fatigue and inflammatory factors in BCS.

Fatigue has been closely linked to immune signaling, particularly through pro-inflammatory cytokines such as interleukin (IL)-6. IL-6 can cross the blood-brain barrier via active transport mechanisms and influence neural activity by interacting with brain regions involved in fatigue regulation, such as the hypothalamus and basal ganglia [12]. This process is also central to sickness behavior, a coordinated set of behavioral and physiological changes—including fatigue, reduced motivation, and cognitive slowing—driven by peripheral inflammation and its effects on the central nervous system [13, 14]. Given the role of IL-6 in neuroimmune communication, examining its changes in response to fatigue-inducing task may provide important insights into the mechanisms underlying fatigue.

Growing evidence has shown that there are different facets of fatigue. One way to distinguish types of fatigue is to divide it into physical and mental fatigue. For physical fatigue, which is more widely examined than mental fatigue, physical activity and exercise have been shown to be effective treatments. Specifically, physical activity and exercise decrease inflammatory measures related to cancer mortality and recurrence, decrease CRF, and improve cardiovascular health and sympathetic nervous system (SNS) stress responses in BCS [15–17]. However, the specific changes in inflammatory factors in response to individual bouts of physical activity and exercise have not been previously documented in BCS.

In relation to mental fatigue, upstream neural processes linking stress to higher risk of inflammation-related diseases have begun to be explored [18]. Inflammation seems to heighten the effect of negative emotional stimuli, a potential novel pathway to developing depression in BCS [19]. Peripheral inflammation has been shown to be strongly related to neural activity in threat-related brain regions like the amygdala in cancer survivors [20]. Thus, previous studies support an association of mental fatigue and inflammation in BCS. However, the specific connection between induced mental fatigue and inflammatory markers has not previously been studied.

So far, associations between inflammation and fatigue in BCS have not been examined in terms of the immediate responses to fatigue-inducing stimuli. In addition, the potential differences in physical and mental fatigue have not been well investigated. This study aims to uncover the changes in inflammatory cytokines after exposure to a mental or physical fatiguing activity in BCS.

Methods

Participants

Participants were female BCS. Participants were recruited via announcements on the campus of George Mason University, by word of mouth, in posting flyers around the Northern Virginia area, and by reaching out to BCS organizations. The inclusion criteria for the study were: females older than 21 years of age, with a diagnosis of breast cancer who had completed their primary cancer treatment at least 3 months prior to entry. The exclusion criteria were the following: ductal carcinoma in situ; any surgery within 3 months; arthritis; uncontrolled diabetes; congestive or ischemic cardiac disease interfering with running, walking, or a combination of the two exercises; inability to perform cognitive testing because of visual, cognitive or behavioral impairment; recent fracture; pregnancy; or failure to meet American College of Sports Medicine criteria for participation in a symptom limited exercise test (such as cardiac arrythmia, uncontrolled hypertension).

Procedures

Overview

George Mason University's Institutional Review Board approved all study procedures, and all participants provided written informed consent. After confirmation of

eligibility, participants completed baseline assessments. These baseline assessments included a blood draw and various questionnaires (explained in detail below). Then, participants were randomly assigned to one of three groups: physical fatigue, mental fatigue or control condition. A random number generator was used to assign group placements, generating 60 assignments (20 per group), each paired with a random number. These assignments were then sorted in ascending order based on their assigned random numbers, with the smallest number determining the first participant's group assignment. Only one investigator, responsible for the randomization process, had access to the spreadsheet containing the assignment list. The investigator conducting the study visit contacted this individual to obtain the participant's group assignment after completing informed consent and baseline assessments.

Further assessments were taken immediately after and 30 min after completing the randomly assigned task. Assessments taken at these time points were blood samples and assessment of fatigue responsiveness. In addition, during the mental and physical fatigue tasks, performance of the participants was evaluated.

Tasks

Physical Fatigue. The women randomly assigned to the physical fatigue group performed a 6-minute walk/run test. Participants were encouraged to cover as much distance as possible in 6 min. The distance travelled by the participant was recorded (in feet). In addition, ratings of perceived exertion were also assessed. Specifically, the Borg Rating of Perceived Exertion (RPE) (6–20 version) [21] was used. Participants were asked to rate their exertion at 2 min into the task, 4 min into the task, and at the completion of the task. This scale is widely used in monitoring progress and mode of exercise in cardiac patients as well as in other patient populations undergoing rehabilitation and endurance training.

Mental Fatigue. The participants who were randomly assigned to the mental fatigue group performed a Dual N-Back computer task that requires constant attention and concentration. This type of task has been used previously to induce mental fatigue [22]. The version used in the current investigation is downloadable and freely available (http://www.brainworkshop.net). With the downloadable version, you are able to change parameters and we set the time length for the participants for 6 min, set it to 2-Back, and used the position-version of this task. For 6 min, participants were asked to look at a 3×3 grid on the computer screen. A blue square would appear in one of the 9 boxes within the grid and then disappear. It would then reappear in one of the 9 boxes and so on. Participants were asked to press the letter "A" when the position of the blue square was in the same position as it was two trials back. Participants were given feedback during the task. Words were written on the bottom left of the screen (A: position match). When the words become green, it indicated correctness, when the words become red, it indicated incorrectness. This task requires a high level of visual, cognitive, and behavioral persistence. The number of correct trials, the number of errors, and the correct percentage were recorded.

Control. The participants assigned to the control group watched a National Geographic video for 6 min. The participants were asked to sit relatively sit and pay close attention to the video.

Measurements and instruments

Feasibility

Feasibility was assessed based on participant recruitment and retention, task adherence, and data quality. Recruitment feasibility was determined by tracking the number of eligible participants successfully enrolled and retained throughout the study. Task adherence was evaluated based on participant completion rates for both the physical and mental fatigue tasks. Data quality was assessed by monitoring the successful collection and processing of blood samples, as well as the completion rates of fatigue assessments. Any challenges encountered during these processes were documented and addressed to optimize study procedures.

Fatigue

To measure the participants' level of fatigue, two assessments were utilized – the Functional Assessment of Cancer Therapy: Fatigue (FACIT-F) [23] and the Multidimensional Fatigue Inventory (MFI) [24].

The FACIT-F instrument has a total of 41 items with five categories: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and fatigue (13 items). Each item uses a 5-point Likert rating scale. The internal consistency Cronbach's alpha coefficient range is 0.95–0.96 [23]. The FACIT-F is used to determine an overall level of fatigue and has been used to categorize individuals into severely fatigued (score of less than 34 indicates presence of severe fatigue) [25]. For the current investigation, both the pre-defined cut-off score and the total score on the scale were used.

The MFI was given multiple times while the participants were at the testing site, at baseline, immediately after the task, and 30 min after the task to assess the state (changing) level of fatigue across the study visit. This instrument is a 20-item self-report to measure state levels of fatigue. It has good internal consistency with a Cronbach's alpha coefficient of 0.84 [24]. It has multiple sub-scales, but for this investigation only the physical and mental fatigue subscales were utilized. The subscales

covered for the physical/mental fatigue are: general, physical, and mental fatigue, and reduced motivation and reduced activity [24]. The subscale total scores (physical and mental) were used in the current investigation.

Depressive symptoms

The Beck Depression Scale II (BDI-II) is a 21-item self-administered assessment for measuring depressive symptom severity [26]. Each item is rated on a 0–3 scale with higher numbers indicative of greater depressive symptoms, the total score on this scale is reported. This instrument is widely used and has an internal consistency Cronbach's alpha coefficient range of 0.92–0.93 [27].

Blood collection and assays

Blood samples were collected at three time points: at baseline, immediately after the completion of the task, and 30 min after the completion of the task (recovery). Blood samples were collected by a certified phlebotomist in vacuum tubes, mixed gently for 30 s and plasma was separated by centrifuge. Aliquots of plasma were stored at -80 degrees C until analysis.

The analytes in serum were profiled using the Bio-Plex 200 Suspension Array System according to manufacturer protocols including the use of all standards and calibration procedures (BioRad laboratories, Hercules, California). All Bio-Plex assays were run in duplicates to assure consistency. The Bio-Plex Pro Human Cytokine 27-plex Assay was used for IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, eotaxin, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF) (BioRad laboratories, Hercules, California). The Bio-Plex Pro™ Human Chemokine Gro-α / CXCL1 Set was added to the 27-plex assay to measure chemokine ligand 1 (CXCL1) (BioRad laboratories, Hercules, California). Bio-Plex Pro TGF-β1 set was used to measure the TGF- β1 analyte (BioRad laboratories, Hercules, California). Cortisol was measured using the Cortisol Parameter Assay Kit ELISA assay according to the manufacturer protocols and repeated in triplicate (R&D Systems, Minneapolis, MN).

All the assays were used according to the manufacturers' protocols for serum samples with no deviations. All the bioplex (including the duplex and single-plex) analyte measurements were measured in pg/mL and cortisol was measured in ng/mL.

Statistical analyses

To investigate potential baseline differences between the participants that were randomly assigned to the physical fatigue, mental fatigue, or control groups, one-way analyses of variance (ANOVA) were conducted. If statistically significant results were found, then post-hoc tests were conducted to determine which groups were significantly different from each other.

To determine the impact of fatigue-inducing tasks on inflammatory cytokines and self-reported state fatigue measurements, repeated measures ANOVAs were conducted, that were separate for each type of task (physical, mental, control). The baseline measurement, post-task measurement, and recovery measurements were added as a three-level within-subject factor. If statistically significant results were found, post-hoc analyses were conducted.

To investigate the potential differences in reactions to the fatigue-inducing tasks based on those with clinically significant fatigue compared to individuals with non-clinical fatigue, mixed ANOVAs were conducted with the clinically fatigued group compared to the non-clinically fatigued group (two-level between subject factor) with a three-level within-subject factor (baseline measurement, post-task measurement, recovery measurement). These were performed separately for each type of task (mental fatigue, physical fatigue, or control groups). The outcomes investigated were inflammatory cytokines and self-reported state fatigue measurements. If statistically significant results were found, post-hoc analyses were conducted.

To examine whether reactions to fatigue-inducing tasks were related to the level of fatigue (total FACIT-F scores), two difference scores were calculated for inflammatory cytokines and self-reported state fatigue measurements by subtracting baseline measurements from post-task measurements and then subtracting baseline measurements again, but from recovery measurements. Pearson product-moment correlation coefficients were then calculated to determine an association between these difference scores and the level of fatigue (total FACIT-F score).

Values of $p < 0.05$ were considered statistically significant.

Results

Participant characteristics

A total of 46 BCS women were recruited for the present study and randomly assigned to one of three groups: physical fatigue ($n = 16$), mental fatigue ($n = 15$), and control ($n = 15$). The physical fatigue, mental fatigue, and control groups were all comparable with respect to: age, BMI, FACIT-F score, systolic and diastolic blood pressure, BDI-II score, heart rate, and time since last treatment (Table 1). Additionally, baseline measurements for inflammatory cytokines and self-reported state fatigue level measurements were comparable for each group, except eotaxin measurements (Table 2).

Feasibility

Overall, the study demonstrated that it was feasible to recruit and assess participants, implement the fatigue-inducing tasks, and collect relevant inflammatory

Table 1 Participant characteristics

	Total ($n=46$)	Physical Fatigue ($n=16$)	Mental Fatigue ($n=15$)	Control ($n=15$)	*p*-value
Age	58.9 (9.1)	63.6 (8.1)	56.1 (6.7)	56.7 (10.5)	0.32
BMI (kg/m^2)	25.6 (5.0)	26.1 (4.1)	25.4 (6.4)	25.3 (6.4)	0.90
FACIT-F Score	36.8 (11.0)	37 (11.5)	37.8 (11.4)	35.5 (13.2)	0.87
SBP (mmHg)	114.7 (13.4)	117.0 (13.4)	112.7 (14.4)	114.3 (14.0)	0.68
DBP (mmHg)	71.2 (7.3)	70.1 (7.0)	72.3 (7.6)	71.2 (7.8)	0.69
Heart Rate (BPM)	68.3 (8.3)	68.8 (9.1)	69.6 (8.8)	66.5 (6.8)	0.60
BDI-II Score	10.1 (7.5)	9.1 (7.9)	11.4 (7.8)	9.8 (6.9)	0.70
Time Since Last Treatment (years)	5.6 (4.9)	6.0 (5.5)	5.2 (4.5)	5.6 (4.9)	0.92

Data are presented as mean (SD). BMI: body-mass index; FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue; SBP: systolic blood pressure; DBP: diastolic blood pressure; BPM: beats per minute; BDI-II: Beck Depression Inventory-II; *p*-value is for the ANOVA of differences between physical, mental, and control groups

cytokine and fatigue data. The recruitment process was successful, with participants meeting the eligibility criteria and completing all required baseline assessments. A total of 47 participants were enrolled, and all participants completed all parts of the study protocol. Participants in both the physical and mental fatigue groups were able to complete the respective tasks as intended. The physical fatigue group effectively performed the 6-minute walk/run test, with the Borg Rating of Perceived Exertion used to assess effort. The mental fatigue group was able to engage in the 6-minute Dual 2-Back task, a complex cognitive task requiring sustained attention and concentration. However, while these tasks were feasible, it was noted that participants in both fatigue groups reported varying levels of exertion and cognitive challenge, which may have contributed to the observed variability in cytokine responses. Blood samples were successfully collected at baseline, immediately post-task, and 30 min after task completion for all groups. Similarly, assessments of fatigue responses were conducted at the appropriate time points, with participants demonstrating good compliance. Despite a few minor challenges in processing the samples and managing scheduling, the data quality was generally high, and there were no significant issues that compromised the study's ability to capture the necessary outcome measures.

Impact of task on inflammatory cytokine measurements and self-reported state fatigue level measurements

The majority of inflammatory cytokine levels and self-reported state fatigue level measurements did not display a significant interaction with time factors, including baseline, post-task, and recovery from task measurements.

In the physical fatigue group, time points had a significant impact on cortisol ($F[2, 26] = 4.482$; $p = 0.021$) and on eotaxin measurements ($F[2, 28] = 4.519$; $p = 0.020$). Cortisol decreased from baseline to post to recovery, while eotaxin increased from baseline to post and then went to below baseline levels at recovery (Table 2). On the other hand, time had no significant impact on any of the self-reported state fatigue level measurements for the physical fatigue group. For the mental fatigue group, time had a significant impact on the levels for many more inflammatory cytokine measurements than the physical fatigue group. Time had a significant impact on the levels of VEGF ($F[2, 18] = 4.127$; $p = 0.033$), TGF-β measurements ($F[2, 22] = 3.630$; $p = 0.043$), and a significant impact on the levels of eotaxin ($F[2, 26] = 3.365$; $p = 0.050$).

For the mental fatigue groups, no significant impact of time points on fatigue score measurements was detected. In the control group, there was a significant effect of time point on the levels of cortisol ($F[2, 26] = 3.623$; $p = 0.041$), and the fatigue score measurements for the physical fatigue score ($F[2, 26] = 3.562$; $p = 0.043$).

Comparison of inflammatory cytokine levels and self-reported state fatigue levels in reaction to the tasks for clinically fatigued and non-clinically fatigued groups

To investigate differences in inflammatory cytokine changes between clinically fatigued (CF) and non-clinically fatigued (NCF) participants, the following subgroups were profiled: physical fatigue (CF, $n = 7$; NCF, $n = 9$), mental fatigue (CF, $n = 6$; NCF, $n = 9$), and control group (CF, $n = 5$; NCF, $n = 10$). Participant characteristics were comparable between CF and NCF subgroups; however, CF subgroups showed significant higher BDI-II Total Score when compared to NCF subgroups in the physical fatigue ($t[14] = -4.882$; $p = 0.0002$) and control group ($t[13] = -4.207$; $p = 0.001$) (Table 3).

Examination of inflammatory cytokine levels and state fatigue scores indicated a significant difference between CF and NCF subgroups for TGF- β and self-reported physical and mental fatigue scores within the physical fatigue task and on physical fatigue score within the mental fatigue task with the CF participants having consistently higher levels of all significant factors (Table 4; Fig. 1).

Significant interactions between CF/NCF subgroup status and time points were observed in all three groups: the physical fatigue, the mental fatigue, and the control group (Table 4). The physical fatigue group showed a

Table 2 Baseline inflammatory cytokine levels and Self-Reported state fatigue measurements

	Time	Total (*n* = 46)	Physical Fatigue (*n* = 16)	Mental Fatigue (*n* = 15)	Control (*n* = 15)
	Baseline	1.5 (0.5)	1.4 (0.6)	1.5 (0.5)	1.4 (0.5)
IL-1β (pg/ML)	Post	1.5 (0.6)	1.6 (0.5)	1.5 (0.6)	1.4 (0.6)
	Recovery	1.4 (0.6)	1.4 (0.6)	1.4 (0.5)	1.4 (0.8)
	Baseline	4.8 (2.6)	4.3 (2.6)	5.4 (2.9)	4.7 (2.3)
IL-4 (pg/ML)	Post	4.7 (2.3)	5.0 (2.1)	4.6 (2.1)	4.6 (2.8)
	Recovery	4.6 (2.5)	4.8 (2.5)	4.7 (2.3)	4.3 (2.9)
	Baseline	4.7 (2.6)	4.7 (2.7)	5.2 (2.9)	4.4 (2.2)
IL-5 (pg/ML)	Post	4.5 (2.6)	4.9 (2.6)	4.4 (2.8)	4.2 (2.7)
	Recovery	4.3 (2.4)	4.6 (2.3)	4.4 (2.4)	4.0 (2.6)
	Baseline	7.0 (14.3)	4.7 (4.2)	12.8 (24.0)	3.7 (3.2)
IL-6 (pg/ML)	Post	6.7 (12.3)	5.2 (4.7)	11.0 (20.3)	4.0 (4.4)
	Recovery	7.0 (14.7)	4.7 (3.6)	12.7 (24.7)	3.8 (4.1)
	Baseline	18.8 (7.4)	18.0 (7.7)	19.8 (7.8)	18.6 (7.0)
IL-8 (pg/ML)	Post	18.9 (9.2)	20.4 (10.3)	18.3 (8.4)	17.7 (9.2)
	Recovery	18.1 (8.4)	20.2 (10.5)	16.9 (5.5)	17.0 (8.6)
	Baseline	25.6 (32.0)	23.9 (15.2)	20.9 (12.4)	32.2 (53.0)
IL-10 (pg/ML)	Post	25.4 (31.8)	27.1 (20.2)	18.9 (12.6)	30.2 (50.7)
	Recovery	24.7 (33.4)	24.1 (15.6)	19.7 (10.6)	30.5 (56.0)
	Baseline	27.5 (42.8)	21.1 (9.3)	40.6 (73.5)	21.0 (10.7)
TNF-α (pg/ML)	Post	27.8 (52.5)	22.3 (10.)	42.0 (91.1)	19.6 (11.4)
	Recovery	27.9 (51.6)	22.4 (8.7)	43.1 (89.5)	18.5 (9.7)
	Baseline	45644.4 (25305.5)	45588.3 (22507.3)	48743.8 (27874.5)	42811.5 (27020.8)
TGF-β (pg/ML)	Post	42510.9 (26551.8)	48098.5 (25724.5)	40382.2 (29239.9)	38537.7 (25606.)
	Recovery	46054.8 (22880.5)	49561.9 (21475.5)	45851.5 (23651.7)	42503.7 (24579.5)
	Baseline	54.5 (23.5)	58.3 (28.4)	55.1 (21.2)	49.7 (20.4)
Cortisol (ng/ML)	Post	48.4 (25.9)	47.9 (25.7)	45.4 (16.1)	51.8 (34.1)
	Recovery	42.8 (24.4)	44.5 (33.2)	41.3 (13.7)	42.6 (23.1)
	Baseline	2277.5 (3875.9)	2088.0 (2437.0)	3184.5 (6319.3)	1572.7 (732.0)

Table 2 (continued)

	Time	Total (*n* = 46)	Physical Fatigue (*n* = 16)	Mental Fatigue (*n* = 15)	Control (*n* = 15)
CXCL1 (pg/ML)	Post	2096.7 (2559.3)	2123.4 (2356.1)	2639.8 (3738.0)	1525.0 (682.4)
	Recovery	1783.9 (1913.2)	1700.3 (1661.6)	2192.2 (2812.1)	1464.7 (776.6)
	Baseline	58.5 (26.6)	68.0 (31.4)	56.6 (27.4)	50.2 (17.0)
Eotaxin (pg/ML)	Post	59.6 (29.7)	78.6*! (34.8)	50.2 (22.9)	48.7 (19.5)
	Recovery	54.2 (22.8)	61.7! (25.3)	54.9 (24.6)	45.4 (15.3)
	Baseline	54.6 (49.1)	47.4 (41.2)	66.8 (61.9)	51.9 (46.5)
VEGF (pg/ML)	Post	52.5 (47.5)	56.1 (41.9)	50.0 (58.4)	50.7 (45.6)
	Recovery	45.8 (37.4)	47.1 (26.8)	47.5 (55.3)	42.8 (25.8)
	Baseline	7.1 (2.7)	6.9 (2.5)	7.5 (3.4)	6.9 (2.0)
Physical Fatigue Score	Post	6.9 (2.8)	6.8 (2.9)	6.5 (3.4)	7.3 (2.2)
	Recovery	7.4 (3.3)	7.3 (3.3)	7.0 (3.7)	7.9 (2.9)
	Baseline	9.3 (3.9)	9.0 (4.0)	9.5 (3.7)	9.5 (4.2)
Mental Fatigue Score	Post	9.5 (3.9)	8.9 (4.1)	10.1 (4.1)	9.5 (3.7)
	Recovery	9.7 (3.6)	9.3 (4.1)	10.3 (3.5)	9.5 (3.3)

Data are presented as mean (SD). IL: interleukin; TNF-α: tumor necrosis factor alpha; TGF-β: tumor growth factor beta; CXCL1: chemokine ligand 1; VEGF: vascular endothelial growth factor; * indicative of a statistically significant difference between the physical fatigue and the mental fatigue groups ($p < 0.05$); ! indicative of a statistically significant difference between the physical fatigue and the control groups ($p < 0.05$)

significant interaction of CF/NCF subgroup status and time points for TGF-β ($F_{interaction}[2, 28] = 3.400$; $p = 0.048$), with the CF group having a greater increase from baseline to post and then a return to below baseline level and the NCF having a consistent but smaller increase over time. Significant interactions between CF/NCF subgroups and time were also observed within the mental fatigue group for IL-8 ($F_{interaction}[2, 26] = 3.636$; $p = 0.041$) with the CF groups having a relative decrease in IL-8 over time and the NCF having a slight increase and then a decrease, TGF-β ($F_{interaction}[2, 22] = 4.706$; $p = 0.020$) with the CF having a large decrease at post while the NCF had a large increase at post, and eotaxin ($F_{interaction}[2, 26] = 6.714$; $p = 0.004$) with the CF having a large decrease at post while the NCF had a small increase at post. The control group displayed significant CF/NCF subgroup by time interactions for IL-8 ($F_{interaction}[2, 26] = 3.549$; $p = 0.043$) with the CF having a consistent small decrease over time and the NCF having little change, VEGF ($F_{interaction}[2, 24] = 4.090$; $p = 0.030$) with the CF having a significant decrease over time while the NCF had a slight increase and then a slight decrease, and IL-6 ($F_{interaction}[2, 26] = 6.050$; $p = 0.007$) with the CF having a decrease over time while the NCF had an increase.

Association between level of fatigue and reactions to fatigue-inducing tasks

Significant associations between total FACIT-F scores (fatigue) and inflammatory cytokine levels were observed in the physical fatigue, mental fatigue, and control group (Fig. 2). Nevertheless, the majority of associations between the total FACIT-F score and inflammatory cytokine changes have not reached statistical significance (Table 5). Negative correlations indicate decreases in inflammatory cytokine levels or self-reported state fatigue level measurements, in response to fatigue-inducing tasks as level of fatigue increases, while positive correlations indicate increases in inflammatory cytokine measurements or self-reported state fatigue level measurements as level of fatigue increases.

Within the physical fatigue group, there was a significant negative association between the difference of post-task and baseline measurements for mental fatigue score and the total FACIT-F score (r[14] = -0.512;

Table 3 Clinical fatigue and Non-Clinical fatigue subgroup participant characteristics

	Physical Fatigue (*n* = 16)		**Mental Fatigue (*n* = 15)**		**Control (*n* = 15)**	
	Clinical Fatigue (*n* = 7)	**Non-Clinical Fatigue (*n* = 9)**	**Clinical Fatigue (*n* = 6)**	**Non-Clinical Fatigue (*n* = 9)**	**Clinical Fatigue (*n* = 5)**	**Non-Clinical Fatigue (*n* = 10)**
Age	65.1 (6.5)	64.8 (9.3)	55.5 (9.0)	56.4 (5.3)	49.6 (9.8)	60.3 (9.3)
BMI (kg/m^2)	27.8 (4.5)	24.8 (3.5)	26.8 (7.5)	24.4 (5.8)	24.7 (4.8)	25.7 (4.6)
FACIT-F Score	25.7 (5.2)	45.8 (5.5)	25.2 (4.5)	46.2 (3.9)	20.6 (11.3)	42.9 (5.4)
SBP (mmHg)	118.4 (10.4)	115.9 (14.4)	113.5 (11.1)	112.2 (16.9)	111.6 (7.9)	115.6 (16.4)
DBP (mmHg)	69.1 (5.9)	70.8 (7.9)	68.3 (7.6)	75.0 (6.7)	69.6 (9.2)	72.0 (7.3)
Heart Rate (BPM)	72.1 (11.1)	66.2 (6.7)	71.0 (9.6)	68.6 (8.7)	68.6 (8.4)	65.3 (6)
BDI-II Score	16.0* (6.5)	3.8 (3.5)	15.7 (7.3)	8.6 (7.1)	17.0* (6.2)	6.2 (3.8)
Time Since Last Treatment (Years)	6.5 (5.7)	5.6 (5.7)	3.5 (2.07)	6.3 (5.4)	4.0 (3.7)	6.4 (5.4)

Data are presented as mean (SD). BMI: body-mass index; FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue; SBP: systolic blood pressure; DBP: diastolic blood pressure; BPM: beats per minute; BDI-II: Beck Depression Inventory-II; * indicative of a statistically significant difference between CF and NCF subgroups ($p < 0.05$)

$p = 0.043$). The mental fatigue group showed significant positive associations with the difference of post-task and baseline measurements for IL-8 and total FACIT-F score (r[13] = 0.557; $p = 0.031$), and with the difference of post-task and baseline measurements for eotaxin (r[13] = 0.633; $p = 0.011$).

Significant positive associations between recovery and baseline measurements and total FACIT-F score were observed within the control group for eotaxin (r[13] = 0.613; $p = 0.015$), and IL-6 (r[13] = 0.528; $p = 0.043$).

Discussion

The primary purpose of the current study was to investigate potential changes in inflammatory cytokine levels after exposure to fatigue-inducing tasks in two domains of fatigue (physical and mental) in BCS. The study further examined the association between inflammation and fatigue-inducing tasks specifically by determining if clinically significant fatigue was a factor related to the short-term responses to fatigue-inducing stimuli. Changes in inflammatory factors in response to the assigned fatigue-inducing tasks mainly did not reach significance, but the when clinically significant fatigue was reported at baseline, its association with fatigue-inducing stimuli was detected.

When the TGF-β levels in the group with physical fatigue were compared to those without, the differences were significant. Notably, TGF-β levels were consistently associated with responses to fatigue-inducing tasks, particularly in individuals with clinical fatigue. Given that participants with clinically significant fatigue also exhibited higher depressive symptomatology, it is important to consider the well-documented role of TGF-β in depression [28]. Prior research has identified TGF-β as a key immunoregulatory cytokine involved in neuroinflammatory processes linked to depressive disorders, with studies suggesting both neuroprotective and neurotoxic effects depending on the context [29]. Elevated TGF-β levels have been associated with mood disturbances and maladaptive stress responses, which may contribute to fatigue-related depressive symptoms. These findings suggest the existence of a distinct fatigue-depression profile in which TGF-β may serve as a biological link between fatigue and depressive symptomatology. Further exploration of this connection could clarify the mechanisms underlying fatigue in populations at risk for depression.

In the physical fatigue group, there was a significant association between overall levels of fatigue with the changes in TGF-β and the state mental fatigue score. In the mental fatigue group, there were significant associations observed with IL-8 and eotaxin.

Unexpectedly, the control group exhibited changes in inflammation over the course of the study visit, particularly among those with clinically significant fatigue. While this was not initially hypothesized, several factors may explain this finding. For participants with higher baseline fatigue, the mere act of attending the study visit may have contributed to increased inflammatory responses. Additionally, the non-verbal National Geographic nature

Table 4 CF and NCF inflammatory cytokine levels and Self-Reported state fatigue measurements

		Physical Fatigue (*n* = 16)		Mental Fatigue (*n* = 15)		Control (*n* = 15)	
	Time	Clinical Fatigue (*n* = 7)	Non-Clinical Fatigue (*n* = 9)	Clinical Fatigue (*n* = 6)	Non-Clinical Fatigue (*n* = 9)	Clinical Fatigue (*n* = 5)	Non-Clinical Fatigue (*n* = 10)
IL-1β (pg/ML)	Baseline	1.4 (0.7)	1.5 (0.5)	1.4 (0.6)	1.6 (0.4)	1.4 (0.4)	1.4 (0.6)
	Post	1.9 (0.5)	1.5 (0.4)	1.1 (0.5)	1.7 (0.6)	1.3 (0.5)	1.5 (0.7)
	Recovery	1.6 (0.7)	1.3 (0.4)	1.2 (0.7)	1.6 (0.4)	1.2 (0.4)	1.6 (0.9)
IL-4 (pg/ML)	Baseline	5.0 (3.1)	3.8 (2.2)	5.5 (3.1)	5.2 (2.9)	4.6 (1.8)	4.7 (2.6)
	Post	6.1 (2.0)	4.2 (1.7)	3.2 (2.0)	5.5 (1.7)	3.7 (2.3)	5.0 (2.9)
	Recovery	5.0 (2.6)	4.7 (2.5)	3.8 (2.5)	5.3 (2.0)	3.0 (1.6)	5.0 (3.2)
IL-5 (pg/ML)	Baseline	5.2 (3.3)	4.3 (2.3)	4.5 (3.1)	5.6 (2.9)	4.3 (2.6)	4.4 (2.1)
	Post	6.1 (2.4)	4.0 (2.4)	2.8 (2.7)	5.4 (2.5)	3.2 (3.0)	4.6 (2.5)
	Recovery	4.9 (2.4)	4.3 (2.4)	3.3 (2.1)	5.2 (2.3)	3.0 (2.3)	4.5 (2.8)
IL-6 (pg/ML)	Baseline	6.3 (4.6)	3.6 (3.7)	13.6 (24.3)	12.3 (25.3)	3.1 (2.8)	4.0 (3.5)
	Post	7.1 (4.5)	3.8 (4.5)	13.0 (26.2)	9.6 (17.0)	1.8 (2.8)	5.1 (4.8)
	Recovery	5.6 (3.7)	4.1 (3.6)	13.7 (25.7)	12.0 (25.6)	1.2 (1.6)	5.1 (4.3)
IL-8 (pg/ML)	Baseline	21.5 (8.1)	15.3 (6.4)	19.5 (7.0)	19.9 (8.7)	18.0 (5.4)	18.9 (7.9)
	Post	25.4 (10.8)	16.5 (8.5)	13.1 (7.8)	21.8 (7.2)	14.3 (7.6)	19.4 (9.9)
	Recovery	22.3 (11.8)	18.5 (9.7)	14.5 (6.9)	18.6 (4.0)	13.1 (6.0)	19.0 (9.2)
IL-10 (pg/ML)	Baseline	25.5 (12.3)	22.7 (17.8)	20.6 (10.5)	21.1 (14.1)	22.7 (13.3)	37.0 (64.9)
	Post	27.4 (12.6)	26.8 (25.4)	16.1 (13.1)	20.7 (12.7)	16.8 (13.3)	36.9 (61.4)
	Recovery	23.6 (11.6)	24.4 (18.8)	18.4 (10.0)	20.5 (11.6)	15.9 (9.2)	37.8 (68.3)
TNF-α (pg/ML)	Baseline	21.9 (12.4)	20.5 (7.0)	66.9 (116.3)	23.2 (11.5)	19.4 (11.7)	21.9 (10.7)
	Post	26.0 (9.9)	19.4 (9.7)	70.2 (146.4)	23.2 (11.1)	15.8 (12.9)	21.5 (10.8)
	Recovery	23.6 (10.3)	21.4 (7.7)	75.2 (142.2)	21.7 (9.6)	15.5 (7.7)	20.0 (10.7)
TGF-β (pg/ML)	Baseline	59200.4* (6573.6)	35001.1 (25083.8)	54587.2 (33531.1)	44361.2 (24262.5)	50389.7 (36760.6)	39022.3 (22074.7)
	Post	64813.6* (21605.4)	35098.0 (21355.9)	25364.6 (24920.6)	51645.4 (28388.6)	29430.3 (26720.8)	43091.3 (25168.9)
	Recovery	50623.5 (20566.7)	48736.2 (23361.3)	51104.4 (23048.5)	41911.8 (24860.7)	29460.3 (15413.7)	49025.4 (26313.9)
Cortisol (ng/ML)	Baseline	44.8 (17.0)	68.8 (31.8)	50.8 (22.1)	58.0 (21.4)	47.6 (4.1)	50.8 (25.3)
	Post	34.0 (12.5)	58.6 (28.8)	43.9 (15.8)	46.5 (17.2)	39.9 (7.7)	57.8 (40.7)

Table 4 (continued)

		Physical Fatigue (*n* = 16)		Mental Fatigue (*n* = 15)		Control (*n* = 15)	
	Time	**Clinical Fatigue (*n* = 7)**	**Non-Clinical Fatigue (*n* = 9)**	**Clinical Fatigue (*n* = 6)**	**Non-Clinical Fatigue (*n* = 9)**	**Clinical Fatigue (*n* = 5)**	**Non-Clinical Fatigue (*n* = 10)**
	Recovery	33.3 (19.5)	53.2 (39.9)	41.1 (14.9)	41.4 (13.8)	35.9 (8.6)	45.9 (27.5)
	Baseline	1489.4 (581.9)	2553.6 (3213.2)	1813.9 (440.4)	4098.2 (8210.6)	1992.6 (958.)	1362.8 (527.9)
CXCL1 (pg/ML)	Post	1490.2 (413.8)	2615.8 (3107.5)	1416.6 (438.2)	3455.3 (4739.3)	1830.3 (865.)	1372.3 (560.6)
	Recovery	1462.8 (1054.3)	1885.1 (2062.9)	1475.0 (780.2)	2670.3 (3579.9)	1776.9 (1019.2)	1308.6 (628.8)
	Baseline	76.7 (24.4)	61.2 (35.8)	75.7 (29.4)	43.9 (17.8)	54.9 (16.8)	47.9 (17.5)
Eotaxin (pg/ML)	Post	92.5 (29.4)	67.8 (36.4)	53.7 (32.0)	47.8 (16.3)	46.5 (25.2)	49.9 (17.4)
	Recovery	73.7 (33.4)	52.4 (11.9)	65.7 (28.6)	47.7 (20.0)	40.6 (14.8)	47.7 (15.8)
	Baseline	56.8 (53.9)	39.2 (27.2)	57.8 (48.0)	75.8 (76.9)	78.5 (66.7)	38.7 (28.2)
VEGF (pg/ML)	Post	75.4 (51.2)	41.0 (27.4)	45.0 (42.6)	53.1 (69.2)	65.5 (76.2)	44.8 (30.6)
	Recovery	63.2 (33.5)	36.3 (15.4)	46.4 (42.6)	48.3 (66.1)	48.2 (31.)	40.7 (24.9)
	Baseline	8.9* (2.0)	5.4 (1.9)	9.3 (4.1)	6.3 (2.4)	7.6 (1.5)	6.6 (2.2)
Physical Fatigue Score	Post	9.1* (2.5)	5.0 (1.6)	8.5 (4.8)	5.1 (1.1)	7.6 (1.8)	7.1 (2.4)
	Recovery	10.3* (2.4)	4.9 (1.5)	9.7* (4.8)	5.2 (1.1)	10.0 (2.9)	6.9 (2.4)
	Baseline	11.3* (3.3)	7.2 (3.7)	9.8 (3.8)	9.2 (3.9)	11.6 (4.0)	8.4 (4.0)
Mental Fatigue Score	Post	12.4* (2.9)	6.1 (2.4)	10.8 (3.7)	9.7 (4.5)	11.6 (3.1)	8.5 (3.7)
	Recovery	12.1* (2.7)	7.0 (3.6)	10.3 (2.9)	10.3 (4.1)	11.0 (3.1)	8.8 (3.3)

Data are presented as mean (SD). IL: interleukin; TNF-α: tumor necrosis factor alpha; TGF-β: tumor growth factor beta; CXCL1: chemokine ligand 1; VEGF: vascular endothelial growth factor; * indicative of a statistically significant difference between CF and NCF subgroups ($p < 0.05$)

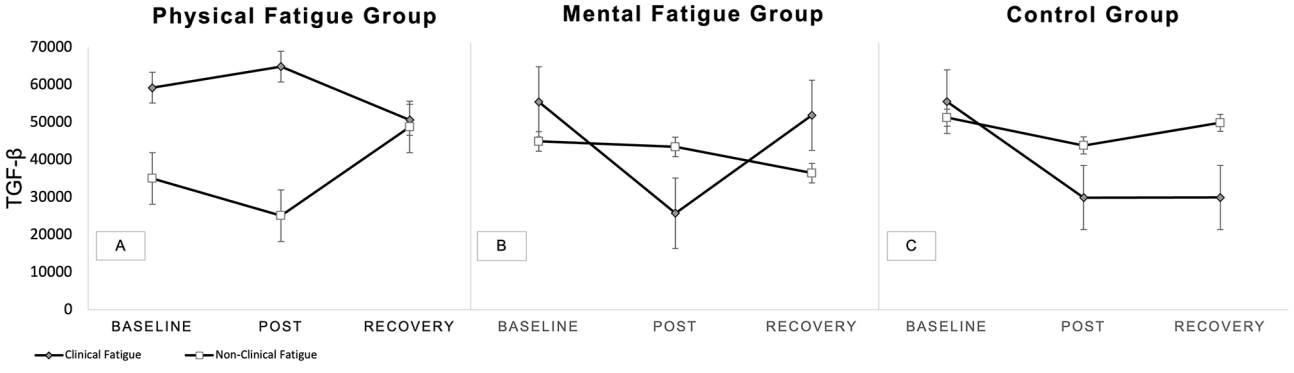

Fig. 1 Interaction between clinical/non-clinical fatigue and fatigue-inducing tasks for the physical fatigue group (Panel A), mental fatigue group (Panel B), and control group (Panel C). Error bars represent standard error of mean. TGF-β: tumor growth factor beta

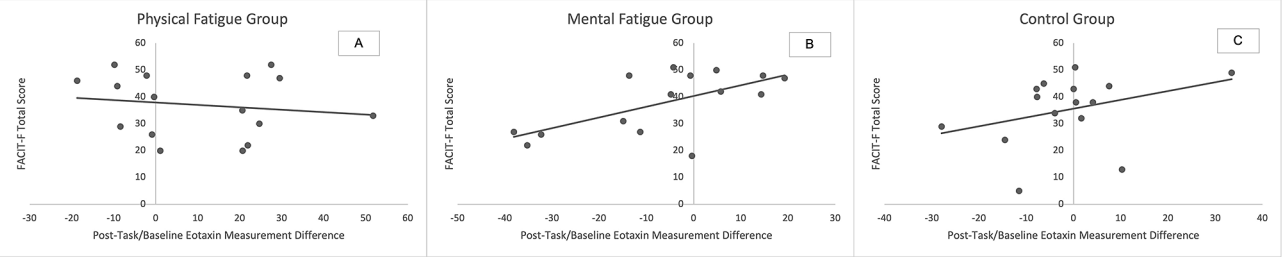

Fig. 2 Scatterplot depicting association between total FACIT-F (Functional Assessment of Chronic Illness Therapy – Fatigue) score and post-task/baseline eotaxin difference for the physical fatigue group (r = -0.151) (Panel A), post-task/baseline for the mental fatigue group (r = 0.633) (Panel B), and post-task/baseline for the control group (r = 0.343) (Panel C)

Table 5 Association between baseline level of fatigue and reactions to fatigue-Inducing tasks (Pearson correlation coefficients)

	Physical Fatigue (n = 16)		**Mental Fatigue (n = 15)**		**Control (n = 15)**	
	Post-Task/ Baseline Difference	**Recovery/ Baseline Difference**	**Post-Task/ Baseline Difference**	**Recovery/ Baseline Difference**	**Post-Task/ Baseline Difference**	**Recovery/ Baseline Difference**
IL-1β	-0.216	-0.244	0.344	0.11	0.146	0.495
IL-4	-0.046	0.058	0.411	0.279	0.295	0.485
IL-5	-0.076	0.064	0.37	0.158	0.25	0.35
IL-6	0.027	0.227	-0.025	-0.15	0.258	0.528*
IL-8	0.004	0.153	0.557*	0.285	0.367	0.453
IL-10	0.212	0.272	0.492	0.121	0.114	0.293
TNF-α	-0.14	-0.096	0.053	-0.137	-0.055	-0.03
TGF-β	0.097	0.474	0.441	-0.355	0.447	0.478
Cortisol	-0.129	-0.293	-0.309	-0.3	0.447	0.23
CXCL1	0.189	-0.231	-0.074	-0.18	0.44	0.457
Eotaxin	-0.151	0.009	0.633*	0.311	0.34	0.613*
VEGF	-0.058	0.095	0.211	-0.196	0.222	0.531
Physical Fatigue Score	-0.398	-0.408	0.111	-0.111	0.235	-0.106
Mental Fatigue Score	-0.512*	-0.162	0.091	0.273	0.065	0.23

IL: interleukin; TNF-α: tumor necrosis factor alpha; TGF-β: tumor growth factor beta; CXCL1: chemokine ligand 1; VEGF: vascular endothelial growth factor; *indicative of a statistically significant correlation ($p < 0.05$)

video shown during the session may have influenced participants' arousal levels. Prior research on breast cancer survivors suggests that arousal, even in positive contexts, can affect inflammation [30]. Thus, the nature video may have inadvertently activated participants. Future studies should ensure that control group stimuli are entirely neutral to avoid unintended effects.

This was a pilot investigation; therefore, it is imperative that the current findings be replicated in a larger sample size. However, this pilot study did demonstrate three important things. First, it is clear that fatigue is associated with inflammatory cytokines and growth factors in the design we used to physically or mentally perturb BCS. The role of inflammation in breast cancer has been well documented in previous studies that indicate a correlation between cancer progression and inflammatory cytokines [8]. However, these long-term associations are most likely representative of the accumulation of acute changes. This pilot investigation highlights the importance of investigating both the acute and long-term associations.

In the physical fatigue group, it is important to account for the known effects of exercise on serological measures, as it was used to induce the physical fatigue. Exercise itself can influence cortisol and inflammatory markers, with effects depending on the type and intensity of exercise [31]. Therefore, the observed changes in blood parameters in this group may not be due solely to the pre-exercise level of physical fatigue. In fact, changes in the serological profiles reported are likely to be influenced by the exercise introduced as part of the study. However, the differences identified between individuals with clinically significant fatigue and those without provide insight into the serological response to exercise in the two groups.

The group that had clinically significant fatigue reacted differently to the potential fatigue producers. Because of this, we suggest that both short-lived reactions and the longer-term persistence of symptoms are important considerations when assessing the impact of fatigue. While

persistent fatigue may result from repeated exposure to short-term fatigue-inducing events, it is also important to acknowledge that cancer survivors often experience persistent mild inflammation throughout the survivorship trajectory. In this context, additional stressors may compound existing inflammation rather than solely reflect an acute response. This perspective underscores the importance of using longitudinal study designs to capture the cumulative effects of inflammation and fatigue over time.

Lastly, we should acknowledge that the effort demand of even participating in a study was higher for those with clinically significant fatigue. In the group with clinically significant fatigue at baseline, self-report evaluations of fatigue across all three groups (physical, mental, and control), showed increased recovery scores compared to baseline scores. The same pattern of results was not found in the non-clinically significant fatigue group. The CF group had higher perception of fatigue in response to simply participating in the study (as evidenced by those in the control group). Further, the report of fatigue is associated with pro-inflammatory markers. While we do not know how persistent the elevation of these markers is, it is plausible that this change may interfere with complete return to a more normal physiological state.

This pilot study was unique because it examined temporally changes in microanalytic responses to a physical or mental fatigue-inducing stimulus. There have been many investigations linking long-term fatigue and inflammatory pathways [9, 10]. The current pilot investigation did reveal that acute fatigue challenges, the kind that BCS would be exposed to in everyday circumstances, does increase inflammatory responses, and those with clinically significant levels of fatigue at baseline are more likely to show these effects.

However, the results of this study need to be examined with its inherent limitations in mind. First, this is pilot investigation with a small sample size, which demands replication. Participants in the study did not experience particularly challenging tasks, therefore, more difficult tasks of longer duration might be needed to better understand the importance of difficulty or duration to the perception of fatigue and its association with microanalyte changes. In prior research, racial and ethnic differences in chronic inflammation have been documented. However, data were not collected on participants' racial or ethnic backgrounds in this study, which limits the generalizability of the findings and the ability to examine potential differences in inflammatory responses.

A key limitation of this study is the challenge of standardizing the 'dose' of physical fatigue induced by exercise. While the 6-minute run/walk was chosen to account for differences in physical condition, and it offers the individual the opportunity of self-selecting a walking/running speed, individual variations in effort and fitness levels may have influenced that choice and hence, the degree of perceived exertion and fatigue. Although perceived exertion ratings did not differ significantly between those with and without clinically significant fatigue, there was a small difference observed, suggesting that individuals with greater fatigue had higher levels of perceived exertion. Future studies should consider alternative methods for tailoring fatigue-inducing tasks to account for individual variability more precisely. In spite of these limitations, our study suggests the associations between various types of fatigue, mental and physical, and particular inflammatory biomarkers.

Conclusions

In BCS, introduction of a physically or mentally fatigue-inducing task is associated with the rise in the levels of pro-inflammatory cytokines in general and TGF-B, eotaxin and interleukins in particular. This association is particularly notable in the BCS with pre-existing clinically significant fatigue. Both physical and mental fatigue-producing stimuli are associated with higher levels of cytokines, thus, suggesting a common pathway for the response to fatigue-inducing stimuli.

Abbreviations

ANOVA	Analyses of variance
BCS	Breast cancer survivors
BDI-II	Beck Depression Inventory-II
bpm	Beats per minute
BMI	Body-mass index
CF	Clinically fatigued
CRF	Cancer-related fatigue
CXCL1	Chemokine ligand 1
DBP	Diastolic blood pressure
FACIT-F	Functional Assessment of Cancer Therapy: Fatigue
IL	Interleukin
MFI	Multidimensional Fatigue Inventory
NCF	Non-clinically fatigued
SD	Standard deviation
SBP	Systolic blood pressure
TGF	Tumor growth factor
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

Author contributions

AW and LG conceived of and designed the study. Data acquisition, analysis, and interpretation of the data were conducted by AW, KS, SG, KJ, NN, AB, AB, PW, LG. The manuscript was drafted by AW, KS, SG, KJ, NN. Critical revision of the paper for intellectual content was given by: AW, KS, SG, KJ, NN, AB, AB, PW, LG. All authors approved the final version of the paper.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of George Mason University (#7994). Informed written consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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