Physiological and psychosocial correlates of cancer-related fatigue

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G.Y.M conceived and designed the study; R.T, J.T, T.M and M.M performed experiments; C.G.B, R.T, J.T and J.G.W analysed data; C.G.B, G.Y.M, R.T interpreted results of experiment; C.G.B drafted manuscript; R.T, J.T, J.G.W, T.M, M.M, N.C.R and G.Y.M edited and revised manuscript. C.G.B, R.T, J.T, J.G.W, T.M, M.M, N.C.R and G.Y.M approved final version of manuscript.

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ABSTRACT

Purpose: Cancer-related fatigue (CRF) is a common and distressing symptom of cancer that may persist for years following treatment completion. However, little is known about the pathophysiology of CRF. Using a comprehensive group of gold-standard physiological and psychosocial assessments, this study aimed to identify correlates of CRF in a heterogenous group of cancer survivors. **Methods:** Using a cross-sectional design to determine the physiological and psychosocial correlates of CRF, ninety-three cancer survivors (51 fatigued, 42 non-fatigued) completed assessments of performance fatigability (i.e. the decline in muscle strength during cycling), cardiopulmonary exercise testing, venous blood samples for whole blood cell count and inflammatory markers and body composition. Participants also completed questionnaires measuring demographic, treatment-related and psychosocial variables. **Results:** Performance fatigability, time-to-task-failure, peak oxygen uptake ($\dot{V}O_{2peak}$), tumor necrosis factor-α (TNF-α), body fat percentage and lean mass index were associated with CRF severity. Performance fatigability, $\dot{V}O_{2peak}$, TNF-α and age explained 35% of the variance in CRF severity. Those with clinically-relevant CRF reported more pain, more depressive symptoms, less perceived social support, and were less physically active than non-fatigued cancer survivors. **Conclusions:** The present study utilised a comprehensive group of gold-standard physiological and psychosocial assessments and the results give potential insight into the mechanisms underpinning the association between physical inactivity, physical deconditioning and CRF. **Implications for cancer survivors:** Given the associations between CRF and both physiological and psychosocial measures, this study identifies targets that can be measured by rehabilitation professionals and used to guide tailored interventions to reduce fatigue.

Keywords: anthropometry, cancer-related fatigue, exercise, fatigability, inflammation

INTRODUCTION

Cancer-related fatigue (CRF) is defined as a distressing, persistent sense of physical, emotional, and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning [1]. While CRF is most prevalent throughout cancer treatment [2, 3], around one-third of cancer survivors report persistent CRF for months and years after cancer treatment [4, 5], with CRF representing the most common and debilitating symptom among cancer survivors (defined here as people who that have completed cancer treatment) [6]. The persistent CRF in cancer survivors can have widespread adverse emotional, social, and physical consequences. Indeed, cancer survivors frequently report the negative impact of CRF on health-related quality of life (HRQL), and the interfering effect on their ability to perform activities of daily living and maintain functional independence [6]. In addition to the negative impact on HRQL, persistent CRF in cancer survivors can impact return to work, reduce the capacity to work [7], and result in increased utilization of health care resources [8], thereby having economic consequences. Given that the number of cancer survivors is increasing [9], the number of survivors with persistent CRF is likely to increase concomitantly. Consequently, understanding the correlates of CRF is a pertinent issue in order to develop interventions to attenuate this symptom.

Despite an increased awareness of the prevalence of CRF in cancer survivors, relatively little is known regarding aetiology or risk factors. Although the aetiology remains elusive, it is understood that CRF is a multi-factorial process that is influenced by a variety of physiological and psychosocial factors [10]. Regarding psychosocial factors, depression, anxiety, sleep disturbances and perceived social support are correlated with persistent CRF [11-14] and are impaired in fatigued versus non-fatigued cancer survivors [15, 16]. Furthermore, it is advised that interventions targeting psychosocial outcomes are tailored to meet individual needs [17, 18]. Understanding the psychosocial correlates of CRF could assist in assessing an individual's

distinctive profile with regard to psychosocial outcomes, and in turn facilitate the development of interventions aimed at alleviating these factors.

There is also evidence for the physiological underpinnings of CRF [19]. For example, various physiological measures relevant to physical function have been shown to be impaired in fatigued cancer survivors. In particular, a reduced aerobic capacity, as assessed through gas exchange measurements during incremental dynamic exercise, has previously been demonstrated in fatigued cancer survivors [20], as well as neuromuscular alterations [21], and cachexia [22]. Performance fatigability, defined as the change in an objective measure of physical performance measured following exercise [23], has also been shown to be impaired in fatigued cancer survivors [24]. Together, these physiological impairments could impede the ability to perform every-day tasks and increase fatigue during activities of daily living, thereby compounding CRF [25]. Moreover, negative anthropometric changes, such as increases in body fat and reduced lean mass index, could further contribute to CRF through impaired physical function, with previous studies on cancer survivors reporting links between CRF and anthropometric measures [26, 27]. Finally, chronic inflammation has also been linked with CRF in both cancer patients undergoing treatment [28, 29] and cancer survivors [30-32], with tumour necrosis factor alpha (TNF-α) [30-32] interleukin 1 beta (IL-1β) [28] and 6 (IL-6) [29] frequently implicated in neuro-immune interactions thought to exacerbate CRF. However, previous research examining the physiological correlates of CRF have often investigated variables in isolation [20, 21, 33], and a comprehensive assessment of the potential objective physiological correlates of CRF in cancer survivors is lacking. Given the multi-factorial nature of CRF, utilising a group of both physiological outcomes is warranted, and an examination of the correlates of CRF using such an approach can provide targets for future interventions to reduce CRF.

Accordingly, this is the first study to investigate CRF and include several physiological variables via the assessment of neuromuscular function, maximal exercise capacity, body composition, whole blood count and inflammation, alongside assessments of psychosocial and disease-related outcomes. The primary aim of this study was to identify physiological correlates of CRF in order to provide targets for future intervention studies, and to examine differences in these outcomes between a heterogenous group of fatigued compared with non-fatigued cancer survivors. A secondary aim was to assess psychosocial correlates of CRF severity and between-group differences in psychosocial outcomes as a replication of previous work.

METHODS

Study population, recruitment and patient involvement

The target population for the present study was cancer survivors, which, for the purposes of the present study, refers to people who have been diagnosed with cancer and completed active cancer treatment (e.g. surgery, chemotherapy and/or radiation) following any cancer diagnosis. Participants were recruited via the Alberta Cancer Registry (Alberta Health Services, Canada). Data extraction criteria included age (≥ 18 years), diagnosed with any invasive cancer, and postal codes within 20 km of the University of Calgary. From the resulting extraction, equal numbers of males and females were randomly sampled and sent a confidential invitation letter from the registry (such that the research team did not know who received the invitation, but participants could then contact the research team if interested). Participants meeting these criteria were also recruited via liaising with clinicians and/or advertising at cancer centres local to the University of Calgary. Additional Inclusion criteria included 1) approval to participate from a Canadian Society for Exercise Physiology Certified Physiologist (CSEP-CEP) and/or a physician and 2) having command of the English language and ability to understand

instructions related to the study procedure. Interested participants contacted the study coordinator via phone or email and were informed on the main aspects of the research. Potentially eligible participants were provided with a participant information sheet and were encouraged to ask questions about the risks and benefits of participation. Once participants had time to review the information, the first visit to the laboratory was scheduled. Initially, 64 participants were recruited. The study was later extended to include the baseline data from participants recruited for a randomized controlled trial investigating the effect of exercise interventions on fatigue in cancer survivors [34]. An additional 33 participants from this study, all with clinically relevant CRF, were included in the present study. Therefore, a total of 97 participants provided written informed consent to participate and completed the study procedures. The inclusion criteria for the two stages of recruitment was the same apart from the requirement to have clinically relevant CRF during the second stage of recruitment. All of the study procedures (described below) were identical for participants from both stages of recruitment.

Variable selection

The selection of the comprehensive group of physiological variables included in the present study was based on previous literature identifying either differences between fatigued and non-fatigued cancer survivors, and/or correlates of CRF severity using a range of physiological variables related to cardiopulmonary function [20], neuromuscular function [21] and fatigability [35], body composition [26, 27] and inflammation [36, 31]. Similarly, for psychosocial variables, these were selected based on previous studies noting consistent associations between CRF severity and depressive symptoms [37, 38], pain [39], perceived social support [40, 41], physical activity and HRQL [39].

Procedures

Approval for all procedures was obtained by the Conjoint Health Research Ethics Board and the Health Research Ethics Board of Alberta Cancer Committee (REB14-0398 and HREBA.CC-16-10-10, respectively). The study was conducted in accordance with all aspects of the *Declaration of Helsinki*, apart from registration in a database. Participants completed all assessments over two separate visits to the laboratory, separated by ~2 weeks to prevent fatigue from the initial visit influencing performance during the second visit. During visit 1, patient reported outcomes, venous blood sampling, cardiopulmonary exercise testing and familiarisation with the performance fatigability assessment was performed, in the same order as written. During visit 2, the body composition and performance fatigability assessments were performed, in the same order as written. Laboratory visits commenced between 8 am – 9 am and lasted 2-3 hours. Visits were scheduled in the morning to ensure participants were as fresh as possible and to avoid fatigue accumulated throughout the day from influencing performance during the protocol. Participants were advised to consume breakfast 1.5 h prior to arrival at the laboratory, to arrive at the laboratory hydrated, and to refrain from alcohol, caffeine and strenuous activity for the preceding 24 h.

Screening, medical and demographic information

Prior to the study commencing, participants underwent a screening procedure. During the screening visit, participants completed a Physical Activity Readiness Questionnaire for Everyone (PAR-Q+), before being screened for arrhythmias and hypertension, determined during resting electrocardiography and blood pressure measurements, respectively. If the participant displayed a normal sinus rhythm and systolic and diastolic blood pressure of ≤ 144

and ≤ 94 mmHg, respectively, was cleared for physical activity by a CSEP-CEP, and no further concerns were raised that would warrant physician approval, the participant continued to the procedures described below. Otherwise, physician approval was sought. Medical information was obtained via self-report, and included the cancer and treatment type (surgery only, single modality, i.e. chemotherapy or radiotherapy, or multi-modality, i.e. chemotherapy and radiotherapy). Demographic information included age, sex, marital status (single, married, divorced, separated or widowed) and income (< $20,000, $20,000-40,000, $40,000-60,000, $60,000-80,000, > $80,000).

Patient reported outcomes

The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale was used to assess CRF. This scale comprises 13 items, and delineates the physical and functional consequences of CRF [42]. Using the FACIT-F scale, a higher score indicates less fatigue, and a score ≤ 34 is recommended for the diagnosis of CRF [43]. The FACIT-F cut-point (≤ 34) can be used to operationalize the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [44]. The cut point identifies over 90% of 'ICD-10 positive' cases and has been recommended for the 'diagnosis' of CRF [43]. In addition to CRF severity, a number of other patient-reported outcomes were assessed. These included HRQL, depressive symptomatology, pain, social provisions, leisure-time exercise and insomnia severity. Questionnaires to measure these patient-reported outcomes were chosen based on their established reliability and validity with specific emphasis on use in cancer populations. Participants' HRQL was assessed using the Functional Assessment of Cancer Therapy – General (FACT-G) [45], which includes subscales for physical, social/family, emotional and functional well-being, and additional concerns related to symptoms. An overall HRQL score

was derived from these subscales and used in the analysis. Depressive symptomatology was assessed using the Center for Epidemiological Studies on Depression Scale (CES-D) [46]. Pain severity and functional interference were assessed using the Brief Pain Inventory Short Form (BPI-sf) [47]. The Social Provisions Scale (SPS) [48] was used to assess social provisions, using the total score from six sub-group scores: guidance, reliable alliance, reassurance of worth, attachment, social integration, and opportunity for nurturance. The total physical activity score (leisure score index) and moderate and strenuous physical activity score ([moderate frequency per week × 5] + [strenuous frequency per week × 9]) derived from the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [49] was used to assess leisure-time exercise.

Physiological outcomes

Cardiopulmonary exercise test

Following the measurement of stature (cm) and mass (kg), a cardiopulmonary exercise test was performed to determine peak oxygen uptake ($\dot{V}O_{2peak}$), gas exchange threshold (GET) and respiratory compensation point (RCP). The tests were conducted using a custom-built recumbent ergometer, using an electromagnetically-braked Velotron system (RacerMate Inc., Seattle, WA). Heart rate (HR) and breath-by-breath pulmonary gas exchange and ventilation was measured throughout the cardiopulmonary exercise test (Quark CPET, COSMED, Rome, Italy). The starting power output (25-50 W) and increment (8-20 W) were estimated and adjusted on an individual basis for a desired test duration of 8-12 min. The power output was increased at 1-min intervals until volitional exhaustion. Verbal encouragement was provided by the same experimenters every 20-60 s. The highest 30 s mean oxygen uptake was considered $\dot{V}O_{2peak}$. The GET and RCP were determined through visual inspection of relevant gas

exchange variables. The GET was defined as the $\dot{V}O_2$ at which the rate of $\dot{V}CO_2$ began to increase disproportionally in relation to $\dot{V}O_2$, while the ventilatory equivalent of $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$) and end-tidal PCO_2 was stable [50]. The RCP was defined as the $\dot{V}O_2$ at which end-tidal PCO_2 began to decrease after a period of isocapnic buffering, as well as a second breakpoint in $\dot{V}E/\dot{V}CO_2$, with further confirmation provided through examining the $\dot{V}O_2$ at which $\dot{V}E/\dot{V}CO_2$ began to systemically increase [51]. The GET and RCP were subsequently expressed as a percentage of $\dot{V}O_{2peak}$.

Venous blood sample

A venous blood sample was collected from the antecubital fossa by a certified phlebotomist, with blood collected ≥ 2 h post-prandial. The sample was analysed for whole blood count (haemoglobin, white blood cell and platelet concentration), TNF-α, IL-1β and IL-6. Whole blood count was analysed within 2 h of collection at the laboratory of Foothills Medical Centre (Calgary, Canada). Blood collected in an EDTA tube was centrifuged at 4°C and 3000×g for 15 min, divided into aliquots and stored at −80°C. Samples were stored until laboratory evaluation, performed at Eve Technologies Corp (Calgary, Alberta, Canada) using the Bio-Plex™ 200 system (Bio-Rad Laboratories, Inc., Hercules, CA).

Performance fatigability test

The incremental cycling test was performed during the second visit to the laboratory, 2 weeks following the first visit in which the cardiopulmonary exercise test was performed. During the initial visit, participants were familiarised with all procedures involved in the incremental cycling test. A detailed description of the procedures for the incremental cycling test and measurements of neuromuscular function are provided by Twomey *et al*. [34]. Briefly,

participants performed an incremental cycling test to task-failure on a validated custom-built cycle ergometer, which permits the immediate assessment of neuromuscular function after cycling [52, 34]. Each stage of the cycling test lasted 3 min, beginning with a power output of 0.3 $W \cdot kg^{-1}$, with an increment of 0.3 $W \cdot kg^{-1}$ for the next four stages and 0.4 $W \cdot kg^{-1}$ for the following five stages. Pre-exercise, between each stage, and following task-failure, a neuromuscular assessment was performed. The neuromuscular assessment consisted of participants performing a maximal isometric voluntary contraction (MVC) of the knee extensors of the right leg, delivering a supramaximal electrical stimulation of the femoral nerve during the plateau in MVC force, and delivering the same electrical stimulation 3 s following the MVC while the participants relaxed. The stimuli delivered during the plateau in MVC evoked a superimposed force response (superimposed twitch, SIT) while the subsequent stimulation delivered while participants relaxed evoked a resting twitch response (resting peak twitch force, P_{tw}, respectively) of the knee extensors. During cycling, participants received real-time feedback for cadence, which was self-selected by the participants (≥ 60 rpm). Participants were instructed to maintain their self-selected cadence, and verbal instructions were provided when the cadence drifted ≥ 4 rpm. The exercise was terminated when rpm fell below 60 rpm, or if participants verbally indicated that they were unable to continue the task.

For the neuromuscular assessments throughout the incremental cycling test, the peak force during MVCs was calculated at each time-point. The amplitude of the potentiated mechanical response following a single electrical stimulus delivered on relaxed muscles was analysed to determine the P_{tw}. Voluntary activation was calculated using the interpolated twitch technique, where the amplitude of the superimposed twitch was normalised to the corresponding P_{tw} using the equation $VA\ (\%) = (1 - SIT/P_{tw}) \times 100$ [53]. The P_{tw} provides a measure of contractile function, while VA measures the capacity of the central nervous system to activate the muscle, and together these variables can determine the locus of reductions in

MVC. The relative decline in MVC force, VA and P_{tw} compared to pre-exercise values at the final common stage (i.e. the minimum number of stages that all participants completed, which was three stages) and at task failure was analysed, as well as the total exercise duration.

Body composition

Participants underwent a whole-body scan using dual energy X-ray absorptiometry (DXA; Discovery W, Hologic, Bedford, MA), for the assessment of percentage body fat, body-mass index (BMI; kg/m^2) and lean mass index (LMI; kg/m^2).

Statistical analysis

The variables included in the statistical analyses are displayed in Figure 1. Statistical analyses were performed with the R statistical software package [54]. Missing data was evident across multiple variables, with a maximum of nine (~10%) participants missing data for TNF-α, IL-1β and IL-6. Missing data were inputted using the k- nearest neighbour (k=5) method, from the 'VIM' package wherein 5 '(k') samples were used to estimate the value of the missing data points [55]. Patient demographics were compared between fatigue groups using Chi-squared and Mann-Whitney U-tests. Relevant predictors of FACIT-F score were selected using Least Absolute Shrinkage and Selection Operator (LASSO) regression. LASSO regression is a sparse regularized regression which uses a penalty term to shrink regression coefficients and selects for only the most significant predictors [56]. Ten-fold cross-validated linear LASSO regression was performed using the 'glmnet' package [57]. Selected predictors from the linear LASSO

regression were then subsequently entered into a robust regression model with FACIT-F score as the dependent variable.

Using the FACIT-F cut-point, relevant predictors of fatigue group were selected using binomial LASSO regression. Selected predictors were compared between groups using independent Student's *T*-tests or Mann-Whitney *U*-tests where data violated assumptions of normality or homogeneity of variance, assessed using the Shapiro Wilk's and Levene's tests. For both analyses, control for multiple testing was performed by adjusting the false discovery rate [58]. Six cancer types (breast, prostate, head and neck, colon, haematological and other cancer types) and the three treatment type categories (surgery only, single modality and multiple modality) were assigned a number and entered into the model. The threshold for rejecting the null hypothesis was set at $p<0.05$. Cohen's d was calculated to provide a standardized measure of the magnitude of the effects, small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$) [59].

RESULTS

Of the 97 participants recruited, four were excluded due to having incomplete data sets. Specifically, participants who had ≥ 6 missing variables (with 6 variables equating to 37.5% of all included variables) were excluded, as it was deemed that too high a proportion of the data for those participants would be estimated. The data for 93 cancer survivors were thus analysed. Of the included participants, the percentage of missing data points was 6 ± 12%. The fatigued group comprised 51 participants (55%) with clinically-relevant fatigue: FACIT-F ≤ 34, n = 21 from initial recruitment and n = 30 from subsequent RCT [34] (baseline measures). The remaining 42 participants from the initial recruitment formed the non-fatigued group (FACIT-F > 34). The median age of the sample was 57 years (range 24-82 years), and 56 participants (60%) were female. Sex ($\chi 2 = 1.0$, $p = 0.33$) and age ($U = 819$, $p = 0.05$) were not different between fatigue groups. Participant socio-demographic and clinical characteristics are displayed in Table 1.

Physiological outcomes and fatigue score – associations and between-group comparison

Univariate analyses

In the initial analysis, LASSO regressions identified seven variables as significant predictors of fatigue severity (FACIT-F score): three related to exercise (relative reduction in MVC post-stage 3, time to task failure during the fatigability test and $\dot{V}O_{2peak}$,), two related to body composition (body fat percentage and lean mass index) and TNF-α concentration. The Spearman's Correlation Coefficients for the associations between FACIT-F score and the identified predictors are displayed in Figure 2, as well as Supplementary Table 1.

Multivariate model predicting fatigue severity

In a secondary analysis, the significant predictors of fatigue identified from the LASSO regressions were entered into a robust multivariate linear regression model. The results showed that the identified predictors explained 35% of the variance in FACIT-F score (multiple R^2 = 0.35). Within the multivariate model, relative decrease in MVC post-stage 3 (β = 23.9, Std. Error = 9.9, P = 0.02), $\dot{V}O_{2peak}$ (β = 0.4, Std. Error = 0.2, P = 0.04), TNF-α concentration (β = –0.49, Std. Error = 0.17, P < 0.01) and age (β = 0.29, Std. Error = 0.10, P < 0.01) were retained as independent factors that were associated with more severe fatigue.

Between-group comparison

For fatigue vs non-fatigued between-group comparison, the binomial LASSO regression identified four predictors of fatigue-group, including relative decrease in MVC post-stage 3, time-to-task failure, $\dot{V}O_{2peak}$, and TNF-α (Table 2 Figure 3A-D, respectively). Independent samples t-tests revealed that $\dot{V}O_{2peak}$ (t_{91} = 4.2, P < 0.01, d = 0.86) and time to task failure (t_{91} = 4.0, P < 0.01, d = 0.84) were lower in the fatigued group compared with the non-fatigued group, while the relative decrease in MVC post-stage 3 (t_{91} = 3.7, P < 0.01, d = 0.77) and TNF-α (Mann Whitney U test U = 739, P = 0.01, d = 0.55) were higher in the fatigued group compared with the non-fatigued group.

Patient reported outcomes and fatigue score – associations and between-group differences

Univariate analyses

Of the patient reported outcomes, depression (CES-D; P < 0.01), pain intensity and severity (both P < 0.01), self-reported physical activity levels (P = 0.02), HRQL (P < 0.01), and

perceived social support (SPS; $P < 0.01$) were significantly associated with FACIT-F score. The correlation matrix displaying the Spearman's Correlation Coefficients is displayed in Figure 4, as well as Supplementary Table 2.

Between-group differences

For between group differences in patient reported outcomes, Mann-Whitney U-Test showed that depression ($U = 540$, $P < 0.01$, $d = 0.89$), pain intensity ($U = 658$, $P < 0.01$, $d = 0.63$) and severity ($U = 640$, $P < 0.01$, $d = 0.66$) were higher in the fatigued compared with the non-fatigued group, while self-reported physical activity levels ($U = 698$, $P < 0.001$, $d = 0.62$), perceived social support ($U = 655$, $P < 0.01$, $d = 0.69$), and HRQL ($U = 261$, $P < 0.01$, $d = 1.6$) were lower in the fatigued vs. non-fatigued group.

DISCUSSION

The primary aim of the present study was to (i) identify correlates of CRF severity in a cohort of cancer survivors using a comprehensive group of physiological variables, and (ii) examine differences in fatigued vs. non-fatigued cancer survivors. We identified that several variables measured during exercise testing, including cardiorespiratory fitness, alterations in neuromuscular function during exercise, and cycling exercise time were significantly associated with CRF severity. For the first time, we show that a decrease in the maximal force generating capacity caused by exercise is a significant independent predictor of CRF severity, alongside $\dot{V}O_{2peak}$, age and TNF-α concentration. Together, these four variables explained 35% of the variance in CRF severity. Furthermore, using the most widely-recommended measure of CRF severity and a cut-point based on diagnostic interview [43], we confirm earlier reports that people with clinically-relevant CRF experience more pain, more depressive symptoms, have less perceived social support, and are less physically active than cancer survivors with no or mild fatigue.

Performance fatigability

In the present study, participants performed incremental cycling exercise at intensities relative to their body mass, with cycling stages interspersed with assessments of neuromuscular function (MVC, P_{tw} and VA) in order to determine performance fatigability following the final common stage of cycling exercise and at task failure. A custom-built cycle ergometer which permits the immediate assessment of neuromuscular function between stages of cycling and following exercise was used to assess fatigability [52]. This original methodology provides a means of measuring neuromuscular function in response to an ecologically valid mode of exercise which resembles the type of activity performed in every-day life (i.e. whole-body,

dynamic exercise). Furthermore, the ergometer permits the measurement of neuromuscular function without a delay between exercise cessation and the neuromuscular assessment, a delay that is normally associated with measuring fatigability in response to whole-body exercise [60]. We found that fatigability at the final common stage of exercise (i.e. the final stage completed by all participants) was more pronounced in fatigued (–16%) compared with non-fatigued (–9%) participants, and was associated with fatigue severity. Likely due at least in part to the more rapid decline in neuromuscular capacity, the time-to-task-failure during the cycling task was 18% shorter in fatigued compared with non-fatigued participants, and this effect was large. Using isometric exercise tasks, previous studies have similarly demonstrated that those with CRF reach task failure during sustained contractions more quickly than controls [24, 33, 21] and that fatigability during isometric tasks is associated with CRF severity [35]. However, the present study improves on previous designs by utilising a more ecologically valid exercise-mode to assess performance fatigability, which might be more closely related to fatigue than isometric protocols [61], as well as gold-standard assessments of neuromuscular function. These methods have previously been shown to be sensitive in detecting cancer treatment-induced changes in muscle function [62].

While we have demonstrated that a relationship exists between fatigue severity and performance fatigability, the nature of this relationship, and whether impaired performance fatigability is a contributor or consequence of CRF, is unclear. For example, the impaired fatigability in those with CRF likely occurs secondary to reduced physical activity levels and subsequent physical deconditioning, with physical activity levels and $\dot{V}O_{2peak}$ lower in fatigued versus non-fatigued participants and associated with fatigue severity in the present study, similar to previous findings [63, 64, 20]. Although speculative, it has been suggested that exacerbated impairments in neuromuscular function in response to physical activity (considering the reduced exercise tolerance) could lead to increases in the perception of fatigue

when performing daily activities [25]. Indeed, the greater impairment in MVC in the fatigued versus non-fatigued group occurred following 3 stages of incremental cycling exercise, and the intensity at this stage could correspond with low-intensity activities of daily living, such as walking or climbing stairs. In turn, the physiological disturbances (such as greater cardiorespiratory demand and metabolic perturbations) at relatively low intensities (relative to sex and age) would lead to an increased sense of effort [65] and fatigue when performing tasks in the presence of impaired neuromuscular function [25]. Accordingly, disease and treatment-related factors may initially lead to acute fatigue, and limit daily activities (especially if a patient is recommended to rest during treatment). This decreased physical activity may lead to deconditioning and impairments in fatigability, which in turn may contribute to the continuation of CRF into long-term survivorship. Further longitudinal research is warranted to assess the temporal associations between fatigue, physical inactivity, and fatigability in cancer survivors in order to determine the potential causal role of increased fatigability in persistent CRF [34].

Anthropometrics and physical activity variables

In addition to the increased fatigability in those with CRF, numerous other variables relevant to physical activity levels and anthropometrics, including $\dot{V}O_{2peak}$, body fat percentage, and LMI, were associated with fatigue severity. Regarding the anthropometric measures, the associations between body fat percentage and LMI with CRF suggest that these could provide useful measures to monitor potential risk factors for those with CRF, and that efforts to improve patient anthropometry could help to mitigate CRF in cancer survivors. Anthropometric measures could be integrated into the analysis from computerized tomography scans routinely used in people with cancer. Regarding cardiorespiratory function, $\dot{V}O_{2peak}$ in the fatigued group was lower than the non-fatigued group, and this effect was large. Furthermore, $\dot{V}O_{2peak}$ values

in the fatigued group were lower than those derived from age-matched healthy participants [66]. Similar to the present findings, previous studies have shown that cardiorespiratory fitness [20] and anthropometric measures [26, 27] are predictors of fatigue in cancer patients. While a causal role of these measures in CRF cannot be deduced from the present findings, the associations between physical activity levels, physical activity related measures, and CRF highlight the importance of performing regular physical activity in order to prevent cardiorespiratory deconditioning and deleterious changes which might contribute to CRF. Indeed, the Oncology Nursing Society 'Putting Evidence into Practice' tool on CRF proposes exercise and physical activity as a first-line intervention for CRF [67], and the American College of Sports Medicine guidelines similarly recommend regular structured and progressive physical activity to reduce CRF severity [68]. This notwithstanding, it is estimated that only one-third of cancer survivors achieve physical activity guidelines outlined by the American Cancer Society [69-72]. Thus, there is a requirement for health professionals to understand the psychological, social and environmental barriers to exercise in cancer survivors, and to develop strategies to mitigate these barriers to enable to cancer survivors to be more physically active. Furthermore, a tailored approach to exercise interventions is warranted to meet individual needs regarding physical activity interests, preferences, tolerance, and physiological requirements [34] in order to improve adherence to exercise guidelines and potentially mitigate persistent CRF in cancer survivors.

Inflammation

The present results further demonstrated that TNF-α was higher in fatigued compared with non-fatigued participants and was associated with fatigue severity. Several studies have similarly shown a link between TNF-α and CRF in cancer survivors [30, 32, 31], indicative of heightened systemic inflammation in those with CRF. In turn, inflammation has emerged as a

key biological pathway contributing towards CRF [73], with a strong mechanistic link between pro-inflammatory cytokines and fatigue. For example, neuro-immune interactions are known to occur through various pathways, including the transport of cytokines across the blood-brain barrier, activation via afferent vagal nerves, and through cytokine receptors located on brain vascular endothelial cells, which initiate cytokine production in the brain [74]. Cytokine receptors are contained in diverse areas of the brain, with an abundance of receptors located on the hypothalamus. In turn, the hypothalamus has rich connections with the brain stem, frontal cortex, and limbic system, areas involved in emotion, behavior, motivation, memory, and motor dexterity. These neuro-immune interactions mediated through pro-inflammatory cytokines are implicated in 'sickness behavior', the coordinated set of adaptive behavioral changes that occur in infected individuals to promote survival, a major component of which is an increase in fatigue [75]. Thus, the link between TNF-α and fatigue found in the present study corroborates numerous previous findings, and strong evidence points towards a cause-and-effect association between inflammation and fatigue in individuals with cancer.

Psychosocial outcomes

In addition to the numerous physiological correlates of CRF in the present study, psychosocial measures of depression, pain, and perceived social support were also associated with fatigue severity. Both depression and pain have been consistently associated with CRF [13, 37, 38], and have been shown to be greater in fatigued versus non-fatigued cancer survivors [16]. However, the nature and directionality of the depression-fatigue relationship is incompletely understood [37], although previous research has shown CRF to be an important predictor of subsequent depression in cancer patients [76, 77]. However, the consistent associations found between CRF and depressive symptoms could also arise due to measurement issues, particularly due to the overlap across dimensions of measurement tools used to assess both

constructs. Moreover, there have been suggestions there could be common mechanisms between depression and fatigue [78], although differences in the temporal pattern of CRF and depressive symptomology have been noted in patients undergoing radiotherapy [79], and pharmacological interventions shown to reduce depressive symptoms in cancer patients had no effect on CRF [80]. Future longitudinal studies should aim to determine the directionality of the relationship between fatigue and depression in order to assist in developing interventions to reduce these symptoms. Furthermore, a perceived lack of social support has been associated with more severe fatigue in patients undergoing cancer treatment [40, 41]. While discrepancies exist in perceived social support in cancer survivors [81, 16], the association between lack of perceived social support and CRF severity found in the present study corroborates the findings of Tibubos et al. [81]. Thus, the present study replicates numerous previous studies identifying psychosocial correlates of CRF [82, 16, 77].

Implications

The present study found multiple physiological and psychosocial correlates of CRF in cancer survivors. While the directions of these relationships are unclear, this study highlights the wide range of potential contributing factors to CRF. The multi-factorial nature of CRF poses a challenge when developing effective treatments to alleviate this symptom, and indicate that a comprehensive, multi-modal and individualized approach could be advantageous. The implementation of a valid, time efficient battery of tests is required to help provide insight into potential underlying causes of fatigue in order to help guide treatment. In addition, the relationship between fatigue severity and physical activity levels, cardiorespiratory fitness and fatigability identifies pathways for the improvement of CRF. At present, evidence-based guidelines for exercise interventions to alleviate CRF recommend a standardized approach in regards to the type, intensity and volume of exercise [68]. However, given the multitude of

497 physiological variables found to be associated CRF in the present study, utilizing an
498 individualized, tailored approach to exercise interventions may be beneficial in targeting
499 specific physiological outcomes, and we are currently testing this hypothesis in a randomized
500 controlled trial [34]. Moreover, the relationships between depression, social support and fatigue
501 highlight the requirement for health professionals to assess psychosocial outcomes, and to refer
502 patients to social work and psychological support when required to ensure a multimodal
503 approach to CRF. Overall, by employing the physiological measures related to CRF severity
504 in the present study, future studies might be able to better identify the potential contributors to
505 fatigue on an individual basis, and tailor their intervention accordingly.
506

507 ***Limitations***

508 While the present study provides important and novel results on the associates of CRF, the
509 limitations should be acknowledged. The cross-sectional design of this study cannot determine
510 cause and effect relationships of the observed correlates, nor the temporal relationship between
511 CRF and correlated variables. However, this design permitted the inclusion of numerous
512 physiological and psychosocial variables, and the results provide targets for future intervention
513 studies aimed at mitigating CRF. Using the FACIT-F questionnaire, a score of ≤ 34 is
514 recommended for diagnosis the of CRF [43], and this score was thus used to separate
515 participants into the fatigued and non-fatigued group for the secondary between-group analysis
516 in the present study. However, it is possible that this dichotomization of FACIT-F scores could
517 have resulted in some participants being misclassified, though this is unlikely to influence our
518 conclusions given that numerous measures which were different between groups were
519 concurrently correlated with CRF severity. Furthermore, while the study uses what we believe
520 to be the most comprehensive group of physiological outcomes to predict CRF severity to date,
521 there are a number of other physiological variables which have been previously associated with

522 fatigue which were not included in the present study, such as hormone concentrations [83],
523 measures of autonomic nervous system function [84] and sleep characteristics [85, 86].
524 Nevertheless, our physiological measures were able to predict a substantial proportion of the
525 variance in FACIT-F score.

526

527 ***Conclusions***

528 The present study is the first attempt to comprehensively assess physiological variables
529 potentially correlated with CRF severity in a cohort of cancer survivors. The key and novel
530 findings from the present study are that several exercise-related variables, including
531 performance fatigability, $\dot{V}O_{2peak}$, LMI, body fat percentage, and self-reported physical activity
532 levels, were different between fatigued and non-fatigued groups and were significantly
533 associated with CRF severity. These results highlight the importance of performing regular
534 physical activity in order to prevent physical deconditioning which might contribute to CRF.
535 Taking this into account, exercise testing provides an important target for exercise interventions
536 aimed at alleviating CRF, and exercise physiologists should be integrated in the management
537 of CRF. In addition to physiological variables, a number of psychosocial measures, including
538 depressive symptoms, pain, and social support, were associated with CRF severity,
539 corroborating previous findings. The numerous associates of CRF found in the present study
540 highlight the multi-factorial nature of this symptom, and the requirement to use an
541 individualised approach in the treatment and prevention of CRF. The results from this study
542 can be used to guide future research when devising strategies to attenuate CRF in cancer
543 survivors.

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551 **Table 1.** Participant socio-demographic and clinical characteristics and fatigue scores.

Variable	Fatigued (*N* = 51)	Non-fatigued (*N* = 42)
Age (years)		
Mean (SD)	54 (9)	58 (12)
Median	56	62
Range	29-71	24-82
Sex, *N* (%)		
Male	18 (35)	19 (45)
Female	33 (65)	23 (55)
Marital status, *N* (%)		
Single	6 (12)	0 (0)
Married	35 (67)	33 (78)
Separated	3 (6)	3 (7)
Divorced	3 (6)	6 (14)
Widowed	2 (4)	0 (0)
Missing data	2 (4)	0 (0)
House Income, *N* (%)		
< $20,000	1 (2)	1 (2)
$20,000-40,000	7 (14)	4 (10)
$40,000-60,000	2 (4)	5 (12)
$60,000-80,000	3 (6)	5 (12)
> $80,000	36 (71)	26 (62)
Missing data	2 (4)	1 (2)
Cancer type, *N* (%)		
Breast	23 (44)	19 (37)
Prostate	4 (8)	12 (23)
Head and neck	7 (13)	2 (4)
Colon	5 (13)	3 (6)
Testicular	0 (0)	2 (5)
Lymphoma	1 (2)	1 (2)
Thyroid	2 (4)	0 (0)
Endometrial	1 (2)	1 (2)
Other	9 (18)	4 (12)
Multiple cancer types	1 (2)	1 (2)
Treatment received, *N* (%)		
Chemotherapy	23 (45)	15 (29)
Radiotherapy	21 (41)	14 (27)
Surgery	39 (76)	32 (63)
Single modality	14 (27)	8 (19)
Multi-modality	15 (29)	11 (26)

Time since diagnosis (months)*		
Mean (SD)	59 (54)	63 (40)
Median	41	52
Range	5-221	12-185
Time since treatment (months)*		
Mean (SD)	33 (33)	46 (29)
Median	23	40
Range	1-173	4-150
Fatigue (FACIT-F score)		
Mean (SD)	26 (6)	44 (5)
Median	27	45
Range	10-34	35-51

Note: Single modality refers to chemotherapy or radiotherapy only, multi-modality refers to chemotherapy and radiotherapy. Multiple cancer types refers to ≥ 2 cancer types. * Due to missing data, data for time since diagnosis and time since treatment is derived from 76 (38 fatigued, 38 non-fatigued) and 60 (30 fatigued, 30 non-fatigued) participants, respectively.

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574 **Table 2.** Physiological outcomes for fatigued and non-fatigued cancer survivors. Values for TNF-α,
575 which violated homogeneity of variance and was analysed using Mann Whitney U test, are median
576 (25^{th}-75^{th} percentile). All other variables are mean ± SD. *, $P \leq 0.01$ Significant between-group
577 difference.

Variable	Fatigued (N = 51)	Non-fatigued (N = 42)
Venous blood sample		
Hemoglobin (g/L)	144.2 ± 12.0	143.6 ± 9.2
White blood cells (10^9/L)	5.6 ± 1.6	5.2 ± 1.4
Platelets (10^{19}/L)	238.6 ± 71.1	232.2 ± 58.9
TNF-α (pg/ml)	13.4 (10.8-16.9)	11.3 (7.8-14.1) *
IL-1β (pg/ml)	1.9 ± 3.6	1.2 ± 2.7
IL-6	1.8 ± 3.6	1.2 ± 2.7
Body composition		
Body fat (%)	32.6 ± 9.0	27.7 ± 6.2
Lean mass index (kg/m^2)	18.8 ± 8.5	18.8 ± 2.8
Body mass index (kg/m^2)	27.6 ± 5.5	26.0 ± 4.0
Maximal exercise test		
$\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1})	25.0 ± 5.4	30.1 ± 6.7 *
RCP (% $\dot{V}O_{2peak}$)	81.7 ± 7.0	82.1 ± 8.0
GET (% $\dot{V}O_{2peak}$)	58.2 ± 7.0	59.0 ± 8.0
Performance fatigability test		
MVC post-stage 3 (% pre-exercise)	–16.0 ± 9.4	–9.1 ± 9.6 *
P_{tw} post-stage 3 (% pre-exercise)	–28.0 ± 16.0	–20.2 ± 13.3
VA post-stage 3 (% pre-exercise)	–5.8 ± 0.7	–2.3 ± 6.2
Time-to-task failure (s)	936 ± 263	1147 ± 240 *

TNF-α, tumour-necrosis factor alpha; IL-1β, interleukin 1-beta; IL-6, interleukin 6; $\dot{V}O_{2peak}$, peak oxygen consumption; RCP, respiratory compensation point; GET, gas exchange threshold, MVC, maximal voluntary contraction force; P_{tw}, resting peak twitch force; VA, voluntary activation; TTF, time to task failure; TNF-α.

Figure captions

Figure 1. Outcome measures used to assess the physiological, psychosocial and disease-related correlates of cancer-related fatigue (CRF). For the incremental cycling test, the change in MVC, VA and P_{tw} at the final common stage of exercise (stage 3) and at task failure were included in the analysis. FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Scale; FACT-G, Functional Assessment of Cancer Therapy – General; CES-D, Center for Epidemiological Studies on Depression Scale; BPI-sf, Brief Pain Inventory – Short Form; SPS, Social Provisions Scale; GLTEQ, Godin Leisure-Time Exercise Questionnaire.

Figure 2. Correlation matrix containing Spearman's correlation coefficients for physiological variables identified as significant predictors of fatigue scores (FACIT-F) using linear regressions. Note that a lower score using the FACIT-F scale reflects higher fatigue, and a higher score represents lower fatigue. LMI, lean mass index; TNF-α, tumour-necrosis factor alpha concentration; TTF, time to task failure; ΔMVC, change in maximal voluntary contraction force at final common stage (stage 3); $\dot{V}O_{2peak}$, peak oxygen consumption. FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue.

Figure 3. Fatigued and non-fatigued group differences for $\dot{V}O_{2peak}$ (Panel A), relative change in MVC post-stage 3 (Panel B), time to task failure (Panel C) and TNF-α (Panel D). A Mann-Whitney U test was used for TNF-α since homogeneity of variance was violated. The black

603 circles and error bars represent the mean ± 95% confident interval, black triangles represent
604 median data for TNF-α analysed using Mann Whitney U test, while red circles and blue
605 triangles represent individual data points. All variables were significantly different between
606 groups ($P < 0.01$). $\dot{V}O_{2peak}$, peak oxygen consumption; MVC, change in maximal voluntary
607 contraction force after stage 3 of cycling test; TTF, time to task failure; TNF-α, tumour-necrosis
608 factor alpha concentration.

609

610 **Figure 4.** Correlation matrix containing Spearman's correlation coefficients for patient
611 reported outcomes identified as significant predictors of fatigue scores (FACIT-F) using linear
612 regressions. Note that a lower score using the FACIT-F scale reflects higher fatigue, and a
613 higher score represents lower fatigue. CES-D, Center for Epidemiologic Studies Depression
614 Scale; Pain-Int, pain intensity scale; Pain-Sev, pain severity scale; Total PA, total physical
615 activity derived from the Godin Leisure-Time Exercise Questionnaire; SPS, Social Provisions
616 Ccale, FACT-G, Functional Assessment of Cancer Therapy – General; FACIT-F, Functional
617 Assessment of Chronic Illness Therapy – Fatigue.

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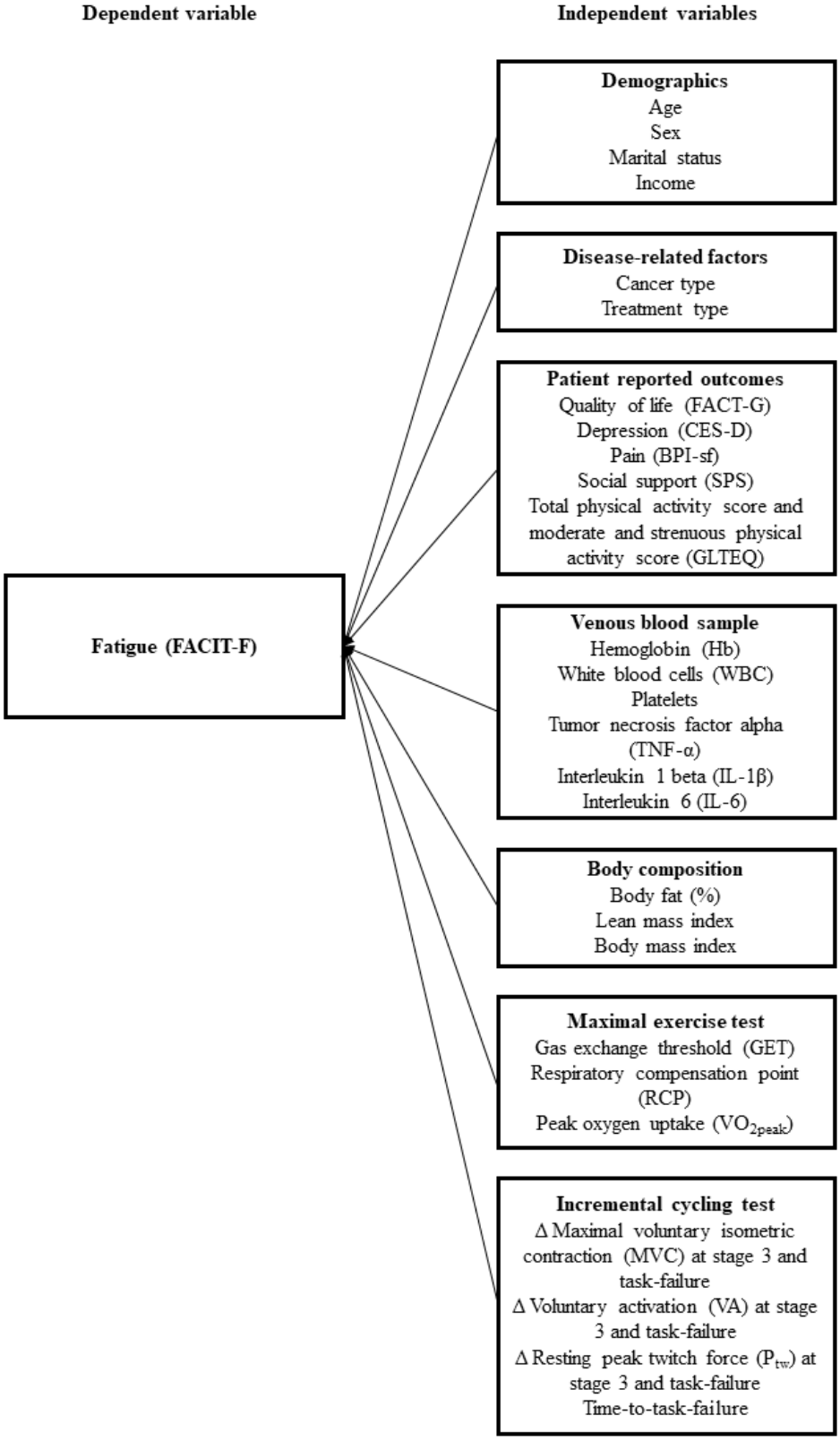
Dependent variable
Independent variables
Fatigue (FACIT-F)
Demographics
Age
Sex
Marital status
Income
Disease-related factors
Cancer type
Treatment type
Patient reported outcomes
Quality of life (FACT-G)
Depression (CES-D)
Pain (BPI-sf)
Social support (SPS)
Total physical activity score and moderate and strenuous physical activity score (GLTEQ)
Venous blood sample
Hemoglobin (Hb)
White blood cells (WBC)
Platelets
Tumor necrosis factor alpha (TNF-α)
Interleukin 1 beta (IL-1β)
Interleukin 6 (IL-6)
Body composition
Body fat (%)
Lean mass index
Body mass index
Maximal exercise test
Gas exchange threshold (GET)
Respiratory compensation point (RCP)
Peak oxygen uptake (VO_{2peak})
Incremental cycling test
Δ Maximal voluntary isometric contraction (MVC) at stage 3 and task-failure
Δ Voluntary activation (VA) at stage 3 and task-failure
Δ Resting peak twitch force (P_{tw}) at stage 3 and task-failure
Time-to-task-failure

Figure 1

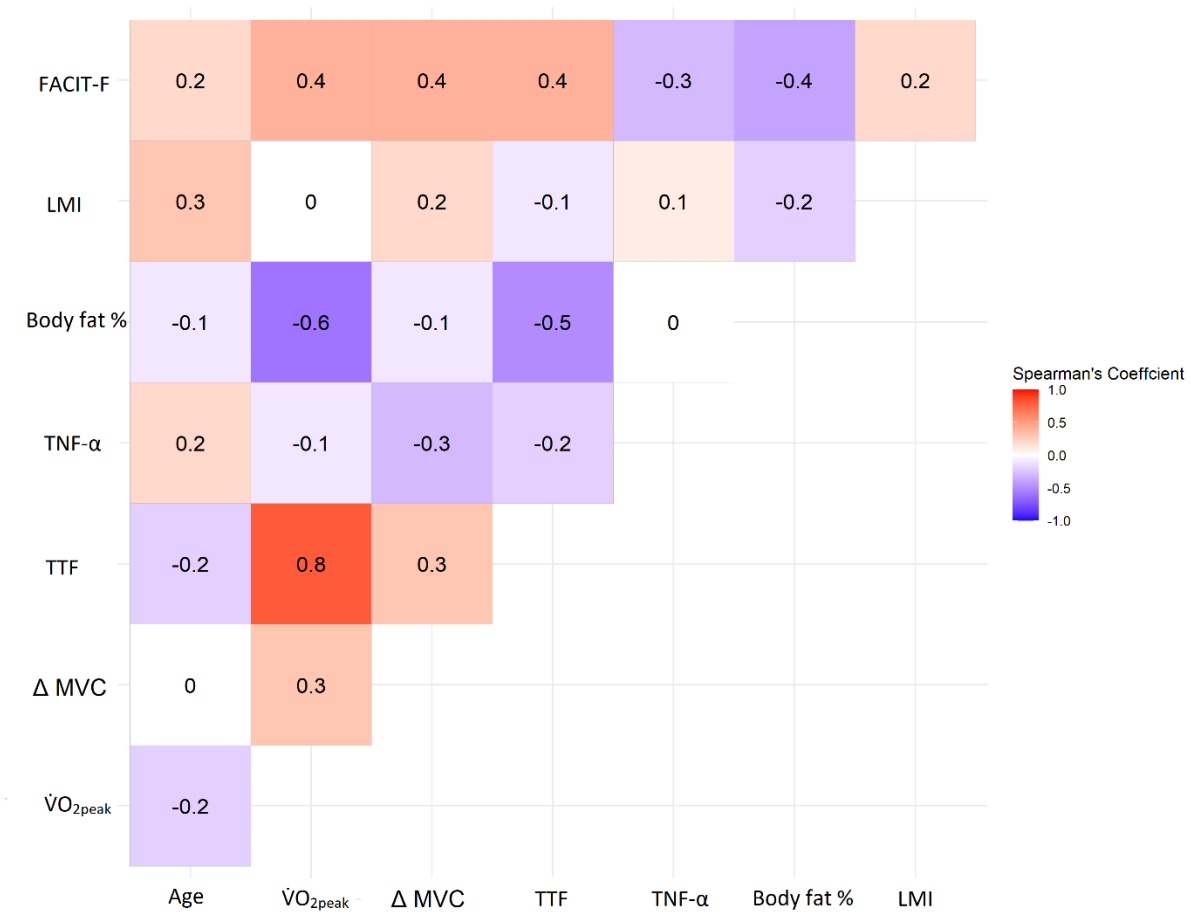
FACIT-F
LMI
Body fat %
TNF-α
TTF
Δ MVC
V̇O2peak
0.2
0.4
0.4
0.4
-0.3
-0.4
0.2
0.3
0
0.2
-0.1
0.1
-0.2
-0.1
-0.6
-0.1
-0.5
0
0.2
-0.1
-0.3
-0.2
-0.2
0.8
0.3
0
0.3
-0.2
Age
V̇O2peak
Δ MVC
TTF
TNF-α
Body fat %
LMI
Spearman's Coeffcient
1.0
0.5
0.0
-0.5
-1.0

Figure 2

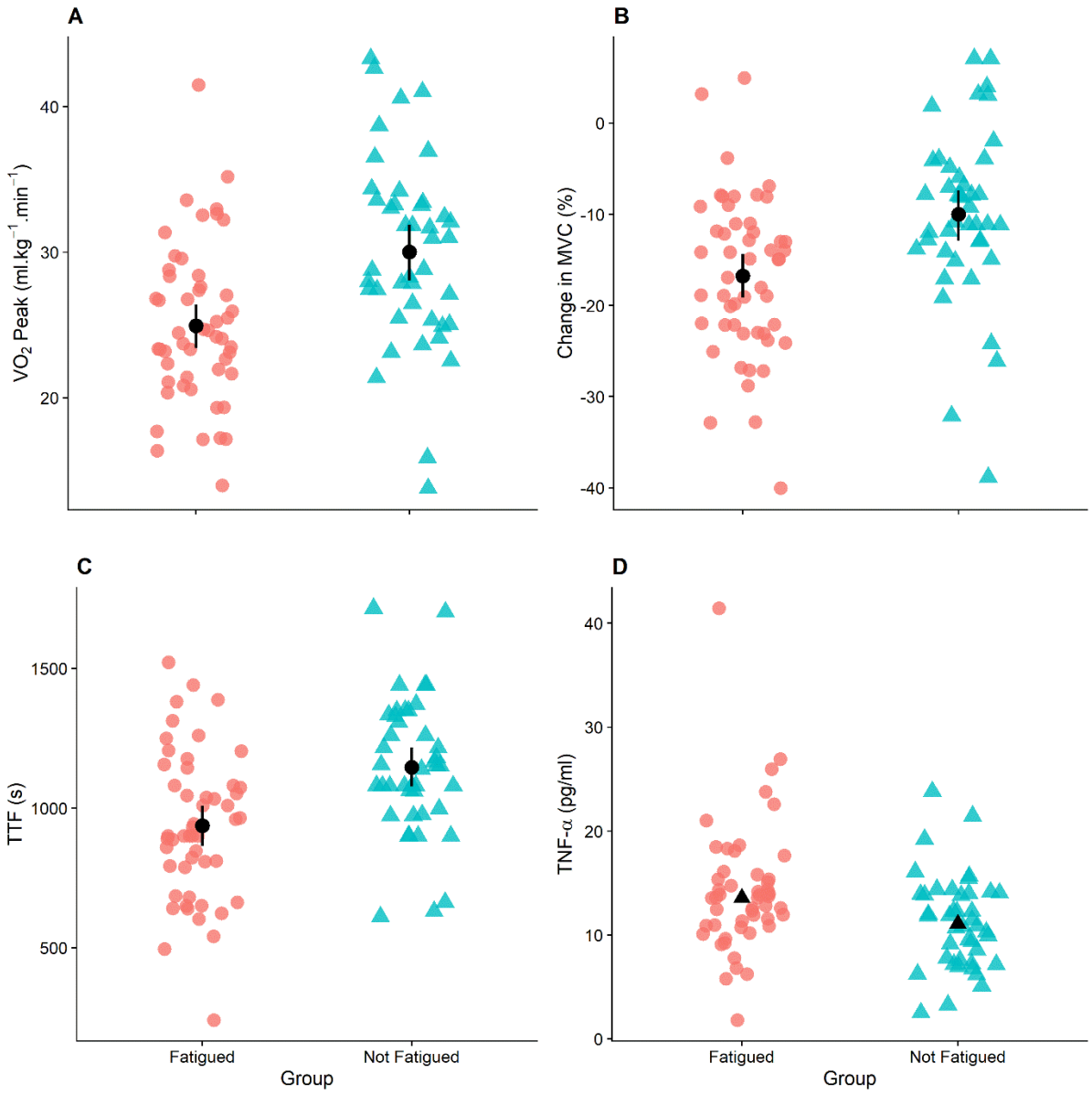
A
B
C
D
VO_2 Peak (ml.kg^{-1}.min^{-1})
Change in MVC (%)
TTF (s)
TNF-α (pg/ml)
Fatigued
Not Fatigued
Group

Figure 3

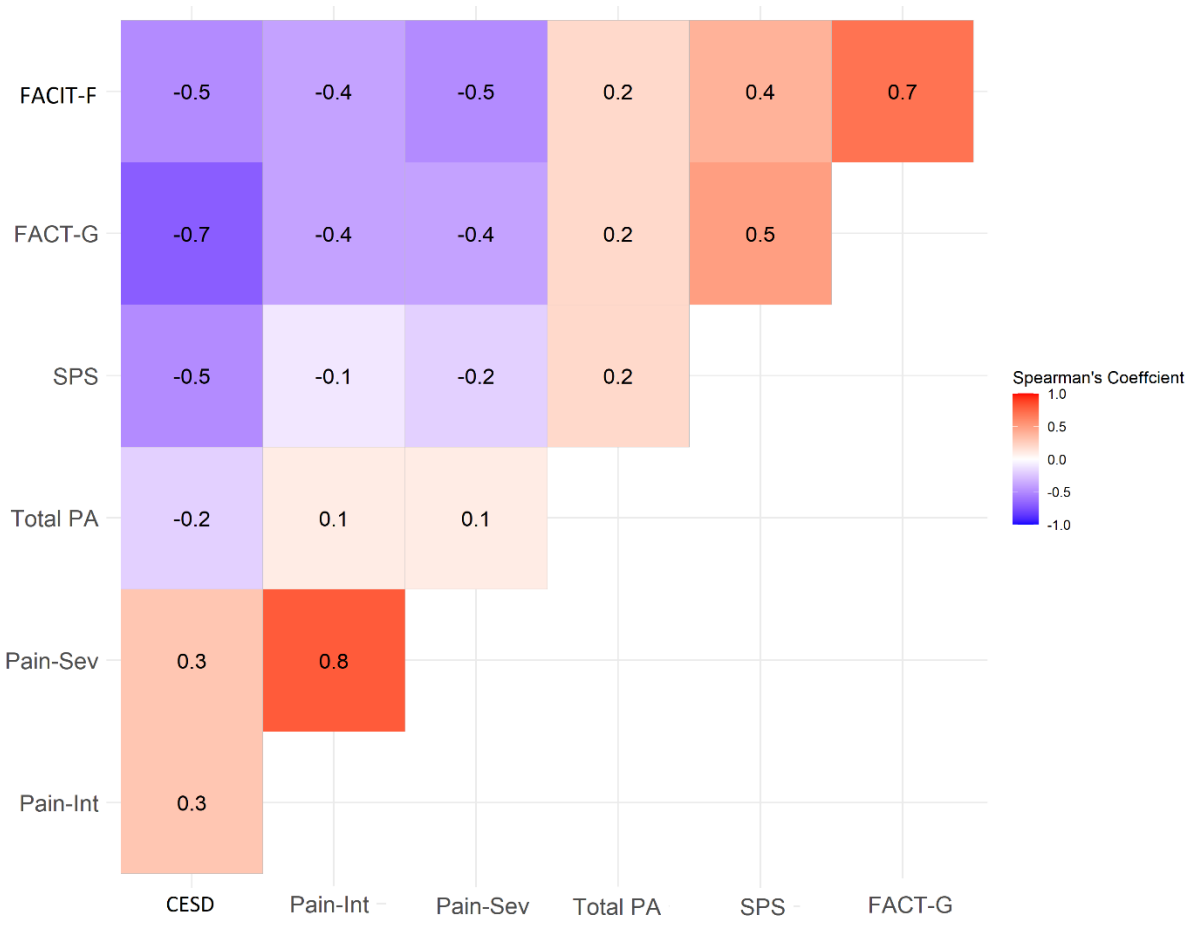
FACIT-F
FACT-G
SPS
Total PA
Pain-Sev
Pain-Int
-0.5
-0.4
-0.5
0.2
0.4
0.7
-0.7
-0.4
-0.4
0.2
0.5
-0.5
-0.1
-0.2
0.2
-0.2
0.1
0.1
0.3
0.8
0.3
CESD
Pain-Int
Pain-Sev
Total PA
SPS
FACT-G
Spearman's Coeffcient
1.0
0.5
0.0
-0.5
-1.0

Figure 4