

Physiological and psychosocial correlates of cancer-related fatigue

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Author contributions

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

1
2 **Purpose:** Cancer-related fatigue (CRF) is a common and distressing symptom of cancer that
3 may persist for years following treatment completion. However, little is known about the
4 pathophysiology of CRF. Using a comprehensive group of gold-standard physiological and
5 psychosocial assessments, this study aimed to identify correlates of CRF in a heterogenous
6 group of cancer survivors. **Methods:** Using a cross-sectional design to determine the
7 physiological and psychosocial correlates of CRF, ninety-three cancer survivors (51 fatigued,
8 42 non-fatigued) completed assessments of performance fatigability (i.e. the decline in muscle
9 strength during cycling), cardiopulmonary exercise testing, venous blood samples for whole
10 blood cell count and inflammatory markers and body composition. Participants also completed
11 questionnaires measuring demographic, treatment-related and psychosocial variables. **Results:**
12 Performance fatigability, time-to-task-failure, peak oxygen uptake ($\dot{V}O_{2peak}$), tumor necrosis
13 factor- α (TNF- α), body fat percentage and lean mass index were associated with CRF severity.
14 Performance fatigability, $\dot{V}O_{2peak}$, TNF- α and age explained 35% of the variance in CRF
15 severity. Those with clinically-relevant CRF reported more pain, more depressive symptoms,
16 less perceived social support, and were less physically active than non-fatigued cancer
17 survivors. **Conclusions:** The present study utilised a comprehensive group of gold-standard
18 physiological and psychosocial assessments and the results give potential insight into the
19 mechanisms underpinning the association between physical inactivity, physical deconditioning
20 and CRF. **Implications for cancer survivors:** Given the associations between CRF and both
21 physiological and psychosocial measures, this study identifies targets that can be measured by
22 rehabilitation professionals and used to guide tailored interventions to reduce fatigue.
23
24 **Keywords:** anthropometry, cancer-related fatigue, exercise, fatigability, inflammation

INTRODUCTION

25

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

42 Despite an increased awareness of the prevalence of CRF in cancer survivors, relatively little
43 is known regarding aetiology or risk factors. Although the aetiology remains elusive, it is
44 understood that CRF is a multi-factorial process that is influenced by a variety of physiological
45 and psychosocial factors [10]. Regarding psychosocial factors, depression, anxiety, sleep
46 disturbances and perceived social support are correlated with persistent CRF [11-14] and are
47 impaired in fatigued versus non-fatigued cancer survivors [15, 16]. Furthermore, it is advised
48 that interventions targeting psychosocial outcomes are tailored to meet individual needs [17,
49 18]. Understanding the psychosocial correlates of CRF could assist in assessing an individual's

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

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

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

83

84

METHODS

85 **Study population, recruitment and patient involvement**

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

99 instructions related to the study procedure. Interested participants contacted the study
100 coordinator via phone or email and were informed on the main aspects of the research.
101 Potentially eligible participants were provided with a participant information sheet and were
102 encouraged to ask questions about the risks and benefits of participation. Once participants had
103 time to review the information, the first visit to the laboratory was scheduled. Initially,
104 64 participants were recruited. The study was later extended to include the baseline data from
105 participants recruited for a randomized controlled trial investigating the effect of exercise
106 interventions on fatigue in cancer survivors [34]. An additional 33 participants from this study,
107 all with clinically relevant CRF, were included in the present study. Therefore, a total
108 of 97 participants provided written informed consent to participate and completed the
109 study procedures. The inclusion criteria for the two stages of recruitment was the same apart
110 from the requirement to have clinically relevant CRF during the second stage of recruitment.
111 All of the study procedures (described below) were identical for participants from both stages
112 of recruitment.

113

114 **Variable selection**

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

123

124 Procedures

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

140

141 *Screening, medical and demographic information*

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

147 and ≤ 94 mmHg, respectively, was cleared for physical activity by a CSEP-CEP, and no further
148 concerns were raised that would warrant physician approval, the participant continued to the
149 procedures described below. Otherwise, physician approval was sought. Medical information
150 was obtained via self-report, and included the cancer and treatment type (surgery only, single
151 modality, i.e. chemotherapy or radiotherapy, or multi-modality, i.e. chemotherapy and
152 radiotherapy). Demographic information included age, sex, marital status (single, married,
153 divorced, separated or widowed) and income ($< \$20,000$, $\$20,000-40,000$, $\$40,000-60,000$,
154 $\$60,000-80,000$, $> \$80,000$).

155

156 *Patient reported outcomes*

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

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

181

182 *Physiological outcomes*

183 *Cardiopulmonary exercise test*

184 Following the measurement of stature (cm) and mass (kg), a cardiopulmonary exercise test was
185 performed to determine peak oxygen uptake ($\dot{V}O_{2\text{peak}}$), gas exchange threshold (GET) and
186 respiratory compensation point (RCP). The tests were conducted using a custom-built
187 recumbent ergometer, using an electromagnetically-braked Velotron system (RacerMate Inc.,
188 Seattle, WA). Heart rate (HR) and breath-by-breath pulmonary gas exchange and ventilation
189 was measured throughout the cardiopulmonary exercise test (Quark CPET, COSMED, Rome,
190 Italy). The starting power output (25-50 W) and increment (8-20 W) were estimated and
191 adjusted on an individual basis for a desired test duration of 8-12 min. The power output was
192 increased at 1-min intervals until volitional exhaustion. Verbal encouragement was provided
193 by the same experimenters every 20-60 s. The highest 30 s mean oxygen uptake was considered
194 $\dot{V}O_{2\text{peak}}$. The GET and RCP were determined through visual inspection of relevant gas

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

202

203 *Venous blood sample*

204 A venous blood sample was collected from the antecubital fossa by a certified phlebotomist,
205 with blood collected ≥ 2 h post-prandial. The sample was analysed for whole blood count
206 (haemoglobin, white blood cell and platelet concentration), $TNF-\alpha$, $IL-1\beta$ and $IL-6$. Whole
207 blood count was analysed within 2 h of collection at the laboratory of Foothills Medical Centre
208 (Calgary, Canada). Blood collected in an EDTA tube was centrifuged at $4^\circ C$ and $3000\times g$ for
209 15 min, divided into aliquots and stored at $-80^\circ C$. Samples were stored until laboratory
210 evaluation, performed at Eve Technologies Corp (Calgary, Alberta, Canada) using the Bio-
211 Plex™ 200 system (Bio-Rad Laboratories, Inc., Hercules, CA).

212

213 *Performance fatigability test*

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

219 participants performed an incremental cycling test to task-failure on a validated custom-built
220 cycle ergometer, which permits the immediate assessment of neuromuscular function after
221 cycling [52, 34]. Each stage of the cycling test lasted 3 min, beginning with a power output of
222 $0.3 \text{ W}\cdot\text{kg}^{-1}$, with an increment of $0.3 \text{ W}\cdot\text{kg}^{-1}$ for the next four stages and $0.4 \text{ W}\cdot\text{kg}^{-1}$ for the
223 following five stages. Pre-exercise, between each stage, and following task-failure, a
224 neuromuscular assessment was performed. The neuromuscular assessment consisted of
225 participants performing a maximal isometric voluntary contraction (MVC) of the knee
226 extensors of the right leg, delivering a supramaximal electrical stimulation of the femoral nerve
227 during the plateau in MVC force, and delivering the same electrical stimulation 3 s following
228 the MVC while the participants relaxed. The stimuli delivered during the plateau in MVC
229 evoked a superimposed force response (superimposed twitch, SIT) while the subsequent
230 stimulation delivered while participants relaxed evoked a resting twitch response (resting peak
231 twitch force, P_{tw} , respectively) of the knee extensors. During cycling, participants received real-
232 time feedback for cadence, which was self-selected by the participants (≥ 60 rpm). Participants
233 were instructed to maintain their self-selected cadence, and verbal instructions were provided
234 when the cadence drifted ≥ 4 rpm. The exercise was terminated when rpm fell below 60 rpm,
235 or if participants verbally indicated that they were unable to continue the task.

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

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

247

248 *Body composition*

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

252

253

254 **Statistical analysis**

255 The variables included in the statistical analyses are displayed in Figure 1. Statistical analyses
256 were performed with the R statistical software package [54]. Missing data was evident across
257 multiple variables, with a maximum of nine (~10%) participants missing data for TNF- α , IL-
258 1 β and IL-6. Missing data were inputted using the k- nearest neighbour (k=5) method, from the
259 ‘VIM’ package wherein 5 ‘(k)’ samples were used to estimate the value of the missing data
260 points [55]. Patient demographics were compared between fatigue groups using Chi-squared
261 and Mann-Whitney U-tests. Relevant predictors of FACIT-F score were selected using Least
262 Absolute Shrinkage and Selection Operator (LASSO) regression. LASSO regression is a sparse
263 regularized regression which uses a penalty term to shrink regression coefficients and selects
264 for only the most significant predictors [56]. Ten-fold cross-validated linear LASSO regression
265 was performed using the ‘glmnet’ package [57]. Selected predictors from the linear LASSO

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

268

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

RESULTS

279

280 Of the 97 participants recruited, four were excluded due to having incomplete data sets.
281 Specifically, participants who had ≥ 6 missing variables (with 6 variables equating to 37.5% of
282 all included variables) were excluded, as it was deemed that too high a proportion of the data
283 for those participants would be estimated. The data for 93 cancer survivors were thus analysed.
284 Of the included participants, the percentage of missing data points was $6 \pm 12\%$. The fatigued
285 group comprised 51 participants (55%) with clinically-relevant fatigue: FACIT-F ≤ 34 , $n = 21$
286 from initial recruitment and $n = 30$ from subsequent RCT [34] (baseline measures). The
287 remaining 42 participants from the initial recruitment formed the non-fatigued group (FACIT-
288 F > 34). The median age of the sample was 57 years (range 24-82 years), and 56 participants
289 (60%) were female. Sex ($\chi^2 = 1.0$, $p = 0.33$) and age ($U = 819$, $p = 0.05$) were not different
290 between fatigue groups. Participant socio-demographic and clinical characteristics are
291 displayed in Table 1.

292

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

294 *Univariate analyses*

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

301

302 *Multivariate model predicting fatigue severity*

303 In a secondary analysis, the significant predictors of fatigue identified from the LASSO
304 regressions were entered into a robust multivariate linear regression model. The results showed
305 that the identified predictors explained 35% of the variance in FACIT-F score (multiple $R^2 =$
306 0.35). Within the multivariate model, relative decrease in MVC post-stage 3 ($\beta = 23.9$, Std.
307 Error = 9.9, $P = 0.02$), $\dot{V}O_{2\text{peak}}$ ($\beta = 0.4$, Std. Error = 0.2, $P = 0.04$), TNF- α concentration ($\beta =$
308 -0.49 , Std. Error = 0.17, $P < 0.01$) and age ($\beta = 0.29$, Std. Error = 0.10, $P < 0.01$) were retained
309 as independent factors that were associated with more severe fatigue.

310

311 *Between-group comparison*

312 For fatigue vs non-fatigued between-group comparison, the binomial LASSO regression
313 identified four predictors of fatigue-group, including relative decrease in MVC post-stage 3,
314 time-to-task failure, $\dot{V}O_{2\text{peak}}$, and TNF- α (Table 2 Figure 3A-D, respectively). Independent
315 samples t-tests revealed that $\dot{V}O_{2\text{peak}}$ ($t_{91} = 4.2$, $P < 0.01$, $d = 0.86$) and time to task failure (t_{91}
316 $= 4.0$, $P < 0.01$, $d = 0.84$) were lower in the fatigued group compared with the non-fatigued
317 group, while the relative decrease in MVC post-stage 3 ($t_{91} = 3.7$, $P < 0.01$, $d = 0.77$) and TNF-
318 α (Mann Whitney U test $U = 739$, $P = 0.01$, $d = 0.55$) were higher in the fatigued group
319 compared with the non-fatigued group.

320

321

322 **Patient reported outcomes and fatigue score – associations and between-group** 323 **differences**

324 *Univariate analyses*

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

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

330

331 *Between-group differences*

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

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DISCUSSION

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

362

363 *Performance fatigability*

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

372 dynamic exercise). Furthermore, the ergometer permits the measurement of neuromuscular
373 function without a delay between exercise cessation and the neuromuscular assessment, a delay
374 that is normally associated with measuring fatigability in response to whole-body exercise [60].
375 We found that fatigability at the final common stage of exercise (i.e. the final stage completed
376 by all participants) was more pronounced in fatigued (-16%) compared with non-fatigued (-
377 9%) participants, and was associated with fatigue severity. Likely due at least in part to the
378 more rapid decline in neuromuscular capacity, the time-to-task-failure during the cycling task
379 was 18% shorter in fatigued compared with non-fatigued participants, and this effect was large.
380 Using isometric exercise tasks, previous studies have similarly demonstrated that those with
381 CRF reach task failure during sustained contractions more quickly than controls [24, 33, 21]
382 and that fatigability during isometric tasks is associated with CRF severity [35]. However, the
383 present study improves on previous designs by utilising a more ecologically valid exercise-
384 mode to assess performance fatigability, which might be more closely related to fatigue than
385 isometric protocols [61], as well as gold-standard assessments of neuromuscular function.
386 These methods have previously been shown to be sensitive in detecting cancer treatment-
387 induced changes in muscle function [62].

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

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

411

412 *Anthropometrics and physical activity variables*

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

422 in the fatigued group were lower than those derived from age-matched healthy participants
423 [66]. Similar to the present findings, previous studies have shown that cardiorespiratory fitness
424 [20] and anthropometric measures [26, 27] are predictors of fatigue in cancer patients. While a
425 causal role of these measures in CRF cannot be deduced from the present findings, the
426 associations between physical activity levels, physical activity related measures, and CRF
427 highlight the importance of performing regular physical activity in order to prevent
428 cardiorespiratory deconditioning and deleterious changes which might contribute to CRF.
429 Indeed, the Oncology Nursing Society ‘Putting Evidence into Practice’ tool on CRF proposes
430 exercise and physical activity as a first-line intervention for CRF [67], and the American
431 College of Sports Medicine guidelines similarly recommend regular structured and progressive
432 physical activity to reduce CRF severity [68]. This notwithstanding, it is estimated that only
433 one-third of cancer survivors achieve physical activity guidelines outlined by the American
434 Cancer Society [69-72]. Thus, there is a requirement for health professionals to understand the
435 psychological, social and environmental barriers to exercise in cancer survivors, and to develop
436 strategies to mitigate these barriers to enable cancer survivors to be more physically active.
437 Furthermore, a tailored approach to exercise interventions is warranted to meet individual
438 needs regarding physical activity interests, preferences, tolerance, and physiological
439 requirements [34] in order to improve adherence to exercise guidelines and potentially mitigate
440 persistent CRF in cancer survivors.

441

442 *Inflammation*

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

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

461

462 *Psychosocial outcomes*

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

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

484

485 ***Implications***

486 The present study found multiple physiological and psychosocial correlates of CRF in cancer
487 survivors. While the directions of these relationships are unclear, this study highlights the wide
488 range of potential contributing factors to CRF. The multi-factorial nature of CRF poses a
489 challenge when developing effective treatments to alleviate this symptom, and indicate that a
490 comprehensive, multi-modal and individualized approach could be advantageous. The
491 implementation of a valid, time efficient battery of tests is required to help provide insight into
492 potential underlying causes of fatigue in order to help guide treatment. In addition, the
493 relationship between fatigue severity and physical activity levels, cardiorespiratory fitness and
494 fatigability identifies pathways for the improvement of CRF. At present, evidence-based
495 guidelines for exercise interventions to alleviate CRF recommend a standardized approach in
496 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 (<i>N</i> = 51)	Non-fatigued (<i>N</i> = 42)
Age (years)		
Mean (SD)	54 (9)	58 (12)
Median	56	62
Range	29-71	24-82
Sex, <i>N</i> (%)		
Male	18 (35)	19 (45)
Female	33 (65)	23 (55)
Marital status, <i>N</i> (%)		
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, <i>N</i> (%)		
< \$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, <i>N</i> (%)		
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, <i>N</i> (%)		
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

552 Note: Single modality refers to chemotherapy or radiotherapy only, multi-modality refers to chemotherapy and
553 radiotherapy. Multiple cancer types refers to ≥ 2 cancer types. * Due to missing data, data for time since diagnosis
554 and time since treatment is derived from 76 (38 fatigued, 38 non-fatigued) and 60 (30 fatigued, 30 non-fatigued)
555 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 (25th-75th percentile). All other variables are mean \pm 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 \pm 12.0	143.6 \pm 9.2
White blood cells ($10^9/L$)	5.6 \pm 1.6	5.2 \pm 1.4
Platelets ($10^{19}/L$)	238.6 \pm 71.1	232.2 \pm 58.9
TNF- α (pg/ml)	13.4 (10.8-16.9)	11.3 (7.8-14.1) *
IL-1 β (pg/ml)	1.9 \pm 3.6	1.2 \pm 2.7
IL-6	1.8 \pm 3.6	1.2 \pm 2.7
Body composition		
Body fat (%)	32.6 \pm 9.0	27.7 \pm 6.2
Lean mass index (kg/m^2)	18.8 \pm 8.5	18.8 \pm 2.8
Body mass index (kg/m^2)	27.6 \pm 5.5	26.0 \pm 4.0
Maximal exercise test		
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	25.0 \pm 5.4	30.1 \pm 6.7 *
RCP (% $\dot{V}O_{2peak}$)	81.7 \pm 7.0	82.1 \pm 8.0
GET (% $\dot{V}O_{2peak}$)	58.2 \pm 7.0	59.0 \pm 8.0
Performance fatigability test		
MVC post-stage 3 (% pre-exercise)	-16.0 \pm 9.4	-9.1 \pm 9.6 *
P_{tw} post-stage 3 (% pre-exercise)	-28.0 \pm 16.0	-20.2 \pm 13.3
VA post-stage 3 (% pre-exercise)	-5.8 \pm 0.7	-2.3 \pm 6.2
Time-to-task failure (s)	936 \pm 263	1147 \pm 240 *

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

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585 **Figure captions**

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

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

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

603 circles and error bars represent the mean \pm 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 ($P < 0.01$). $\dot{V}O_{2\text{peak}}$, 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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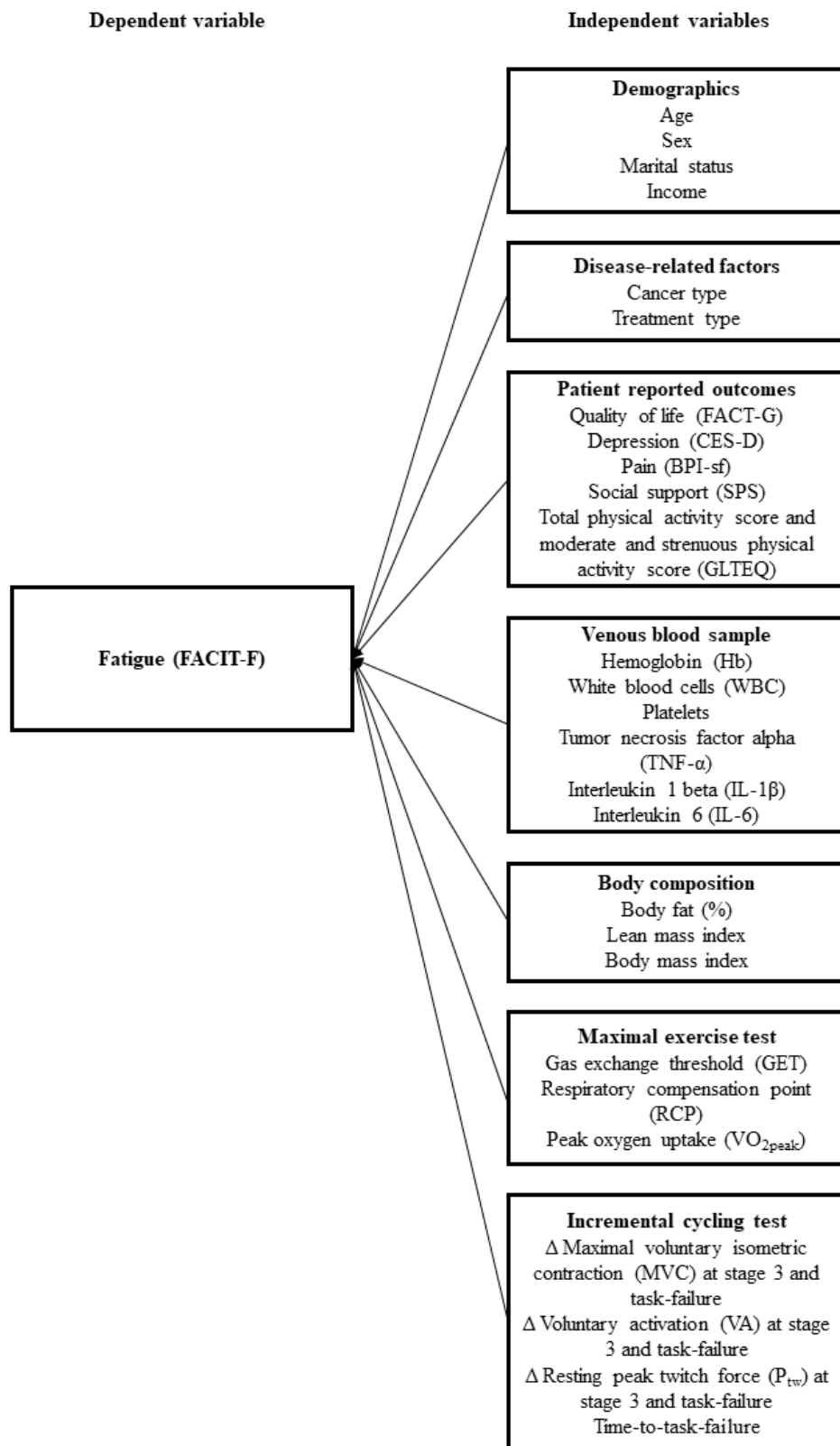


Figure 1

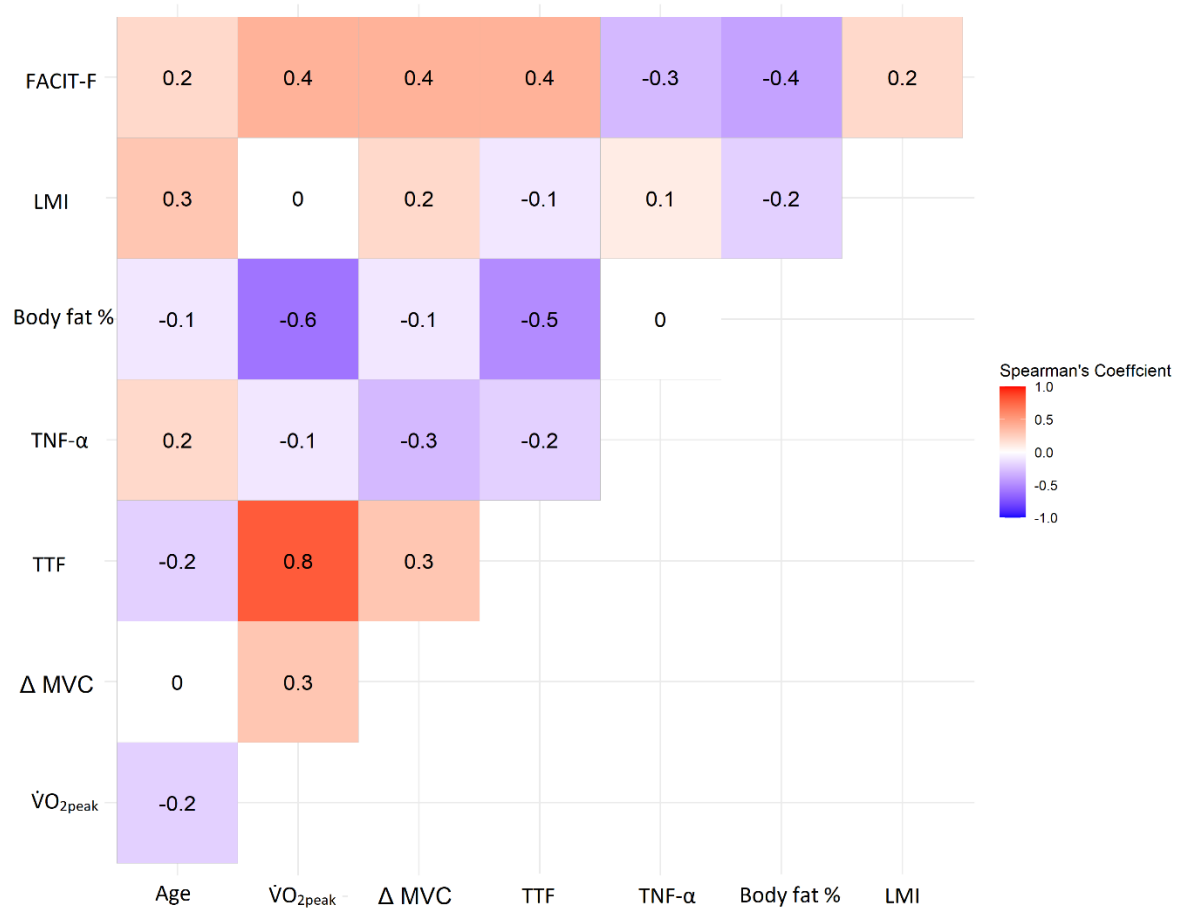


Figure 2

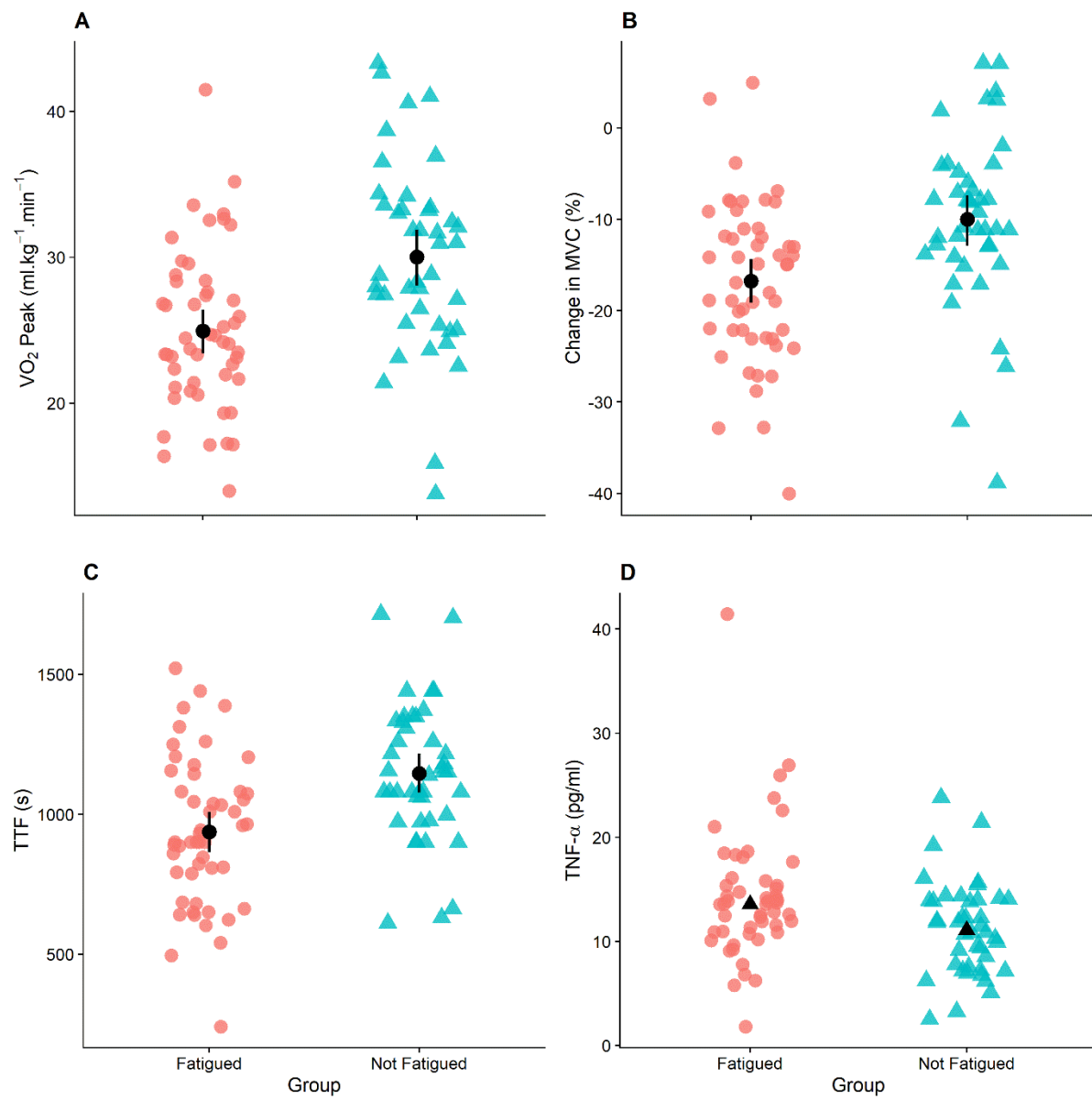


Figure 3

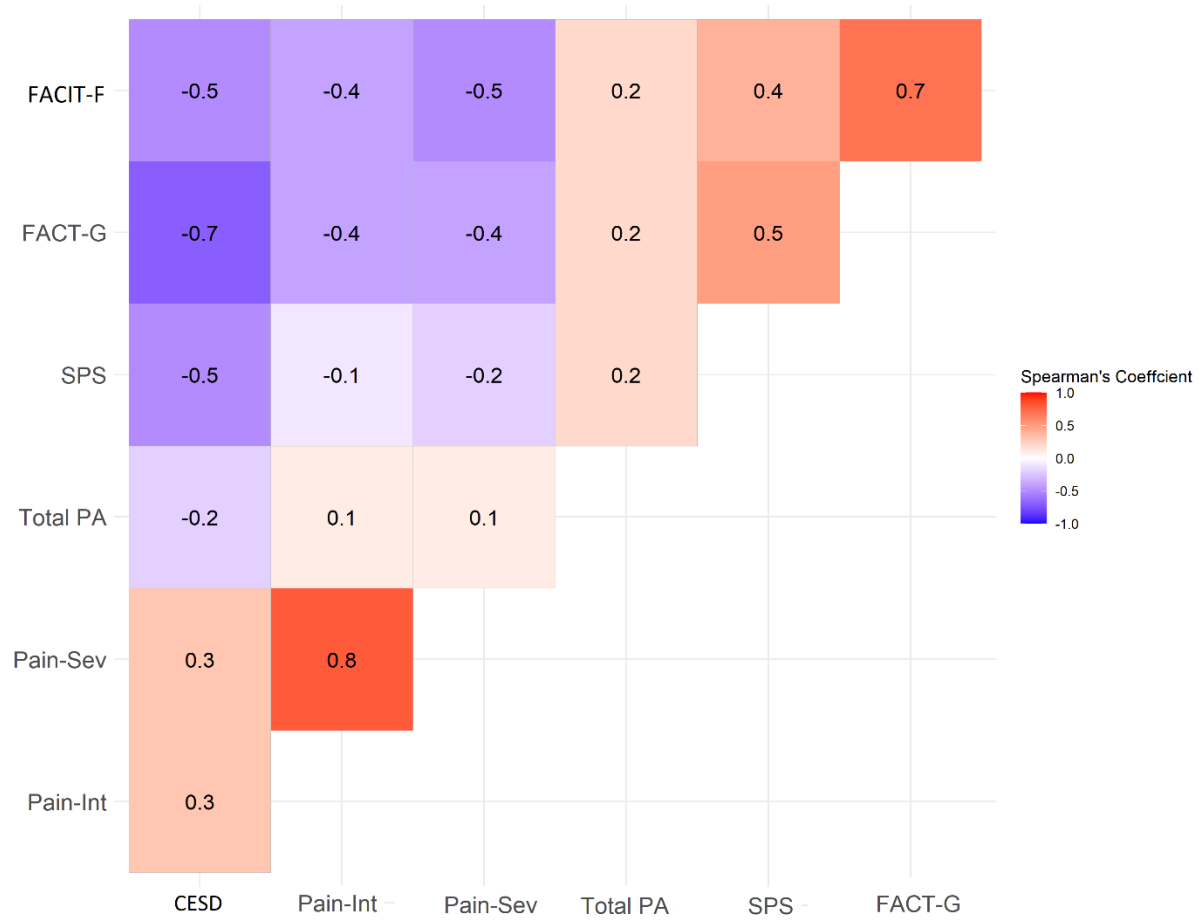


Figure 4