THESIS

EXAMINING CANCER-RELATED FATIGUE THROUGH FITT PRINCIPLES OF EXERCISE: A CROSS-SECTIONAL ANALYSIS OF CANCER WELLNESS PROGRAM BASELINE DATA

Submitted by

Jacob Dawson

Department of Health and Exercise Science

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Master's Committee:

Advisor: Heather Leach

Ryan Marker
Kirsten Eilertson

ABSTRACT

EXAMINING CANCER-RELATED FATIGUE THROUGH FITT PRINCIPLES OF EXERCISE: A CROSS-SECTIONAL ANALYSIS OF CANCER WELLNESS PROGRAM BASELINE DATA

Background: Cancer-related fatigue (CRF) is a distressing and prevalent symptom with limited treatment options. While exercise is the most effective treatment for CRF, more evidence is needed to recommend individualized prescription to meet the complex needs of those experiencing fatigue. Moreover, literature on CRF's subdomains is sparse, and no framework exists to target physical or cognitive dimensions. Therefore, the purpose of this study was to examine how exercise frequency, intensity, time, and type (FITT) are related to general, physical, and cognitive CRF. Methods: Retrospective, secondary analysis of baseline data from individuals with a cancer diagnosis enrolled in a clinical exercise program. Exercise was self-reported using the Godin-Lesiure-Time Exercise Questionnaire. CRF was self-reported using the FACIT-F for general fatigue, and QLQ-FA12 for fatigue subdomains. Univariate associations between exercise volume, frequency, and time were assessed using Pearson correlations. Group mean differences were compared using two sample t-tests and supplemented with effect sizes. Post-hoc regression analyses were performed to control for exercise volume. Results: Higher reported exercise volume, time, and frequency were all significantly associated with lower general fatigue ($p < 0.05$). Only exercise volume had a significant association with physical fatigue ($p < .05$); no significant associations were observed for cognitive fatigue. Those who reported moderate-to-vigorous intensity exercise reported lower fatigue across all measures when compared to those who reported light intensity only, but differences were not statistically significant. Those who reported combined aerobic and resistance training on average reported lower fatigue across all measures, but only differences in physical fatigue were significant. After controlling for volume, no significant differences in general fatigue or subdomains were found by exercise intensity or type. Conclusion: Individuals looking to reduce general and physical cancer-related fatigue may benefit from exercising according to preference, prioritizing a combination of FITT principles that promote greater volumes of exercise, as fatigue-specific benefits do not appear to differ across intensity and type. Prospective studies are needed to investigate the impact of specific FITT prescriptions on cognitive fatigue before exercise can be recommended as a viable treatment.

TABLE OF CONTENTS

1. INTRODUCTION

Cancer is the second leading cause of death globally, surpassed only by heart disease [1]. Fortunately advances in therapeutic interventions and treatment have improved relative survival rates and overall incidence in recent decades, with the American Cancer Society observing a greater number of individuals living longer after a cancer diagnosis [2]. Treatment for cancer often includes surgery, chemotherapy, radiotherapy, immune and hormone therapies [3]. These treatment regimens often result in unintended side effects, fatigue being among the most common and distressing [4]. Approximately half of all individuals living with and beyond a cancer diagnosis report some level of fatigue [5].

Cancer-related fatigue (CRF) is characterized by persistent tiredness that is not relieved by rest and is not proportional to the amount of activity one may engage in [6]. Unlike fatigue experienced by healthy individuals after exercise or a long day at work, cancer-related fatigue is often persistent and debilitating. This distinction is vividly illustrated in Wu and colleagues' qualitative analysis, as one individual with cancer recounts: "Sometimes I can function and sometimes I can't function. Sometimes I have no energy at all. Some days it's so bad I can't get out of my chair to go to the bathroom..." [7]. This sentiment is echoed by the majority of individuals undergoing treatment(s), and can also persist for years into survivorship [8]. Beyond its persistence, research has also shown CRF is often all-encompassing, impacting individuals not just physically, but cognitively and emotionally as well [9].

Currently, there are few effective treatments for CRF. The European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) have not included any pharmacological agents in their recommendations/guidelines to treat CRF, other than corticosteroids, which are not recommended for long-term use [6,10]. The only two treatments recommended by NCCN and ESMO to help manage CRF are exercise and psychosocial interventions, such as cognitive behavioral therapy [6,10]. Of these two therapies, exercise has been shown to have a consistent positive effect on reducing CRF, with standardized means differences ranging from 0.23–0.43 [11].

Currently, NCCN exercise guidelines for the management of CRF recommend both aerobic and resistance exercise, tailored to an individual's age, cancer type, etc. that begins at low intensity and time, that progresses gradually [6]. These guidelines also acknowledge that more evidence is needed to advise a specific amount of exercise. The American College of Sports Medicine (ACSM) exercise guidelines recommend exercise prescription (ExRx) based on frequency, intensity, time, and type (FITT). Specifically, moderate intensity (65% HRmax, 45% VO_2max) aerobic exercise, for at least three days per week, for at $\geq$ 30 minutes, and resistance training twice per week to improve CRF [12].

Despite these general exercise guidelines to manage CRF from NCCN and ACSM, more information about the frequency, intensity, time, and type of exercise is needed. While the guidelines listed above provide a framework for ExRx, it's been evidenced that a one-size-fits-all approach is not optimal for meeting the complex needs of individuals within the cancer continuum [13,14]. Given the cyclical nature of treatment and corresponding fluctuations in fatigue, individuals may struggle to meet the guideline's recommendations. Additionally, the impact of exercise appears to vary throughout the treatment timeline, underscoring the need for more individualized ExRx [14].

Recent research has attempted to address this, manipulating FITT principles with mixed results. Frequency is rarely investigated alone, often accompanied by changes in intensity and/or time as well. Conversely, intensity has been investigated thoroughly. One randomized control trial compared low-to-moderate and high-intensity programs in individuals undergoing treatment. No clinically meaningful differences in fatigue measures were found, and it was concluded individuals can exercise according to preference [15]. Another trial compared low-intensity and moderate-to-high intensity programs and again found no difference in general fatigue [16]. Few studies have looked at light, moderate, and vigorous intensity groups separately. Research on exercise time is limited, but when paired with higher intensity, may be just as effective as traditional aerobic training, as in the case of high-intensity interval training [17,18]. The impact of exercise type (i.e. aerobic vs resistance training) has been examined, with evidence suggesting that aerobic and resistance training offer comparable benefits [19]. Moreover, both combined training and resistance alone have been shown to result in similar effect sizes [20].

Despite the sizeable amount of literature regarding FITT principles and CRF, gaps remain present. There is still a lack of consensus regarding optimal ExRx, with recent systematic reviews finding current evidence was not sufficient to recommend individualized prescriptions for CRF [21,22]. Informing precision ExRx may require investigating FITT principles individually. Additionally, the most recent guidelines also differ little from those present for apparently healthy individuals, potentially signaling a need for greater research [23]. This could stem from specific exercise variables being understudied. For example, few interventions stray from typical frequency (3 ± 1 days/week) and time (40 ± 20 minutes) [24,25]. Exploring combinations of FITT prescription, including those outside existing literature, could provide insight on how to potentially further tailor exercise, benefitting individuals unable to adhere to current recommendations.

Building on limitations in the current evidence base, it is important to recognize CRF is multifaceted, impacting individuals in multiple ways, often physically and cognitively [26]. The physical subdomain of fatigue is characterized by a lack of energy, exhaustion, and "feeling slow", whereas the cognitive manifests as impaired concentration and confusion [27,28]. While no "gold standard" measure exists for fatigue, scales have been developed to reflect its multidimensional nature, with almost all accounting for physical and cognitive domains separately [27,29]. However, most interventions implemented to reduce CRF evaluate it through a unidimensional lens, failing to account for these subdomains independently [22].

For those attempting to assess and treat CRF thoroughly, overlooking subdomains could be problematic. Different methods of exercise programming have been shown to impact fatigue subdomains disproportionately [30]. Literature has evidenced subdomains vary throughout one's treatment course, and across cancer types [31,32]. Unlike general CRF, no ExRx framework has been devised to specifically ameliorate specific subdomains, due to the sparsity of literature, prompting researchers to call for greater study in this area [30].

In summary, while there is strong evidence demonstrating that exercise can reduce CRF, there is a need for studies to further explore the impacts of FITT variables (i.e., frequency, intensity, time and type) on CRF to contribute evidence in favor of individualized ExRx, which could improve patient-reported outcomes and provide flexibility for individuals unable to meet current recommendations. Further, to inform a potential exercise framework that addresses fatigue subdomains, more studies are needed to explore the differential effects of exercise on cognitive and physical fatigue. Therefore, the purpose of this study was to examine the association between exercise frequency, intensity, time (duration), and type (aerobic & resistance) on general CRF, and separately for the subdomains of physical and cognitive fatigue.

Aims

Aim 1: Exercise & General Fatigue

The goal of Aim 1 is to examine the associations between total exercise volume, frequency, intensity, time and type and general CRF. Adult cancer survivors on or within <6 months of completing chemo or radiation therapy completed the modified Godin Leisure Time Exercise Questionnaire to collect self-reported exercise over the last 7 days, and the FACIT Fatigue Scale to measure general fatigue. This aim was assessed by evaluating the following hypotheses:

- H1: Higher reported exercise volume, frequency, and time will be associated with lower general fatigue.
- H2: Compared to those who reported only light-intensity exercise, individuals who reported moderate and vigorous-intensity exercise will report lower general fatigue
- H3: Compared to those who reported aerobic alone, individuals who reported both aerobic and resistance exercise will report lower general fatigue.

Aim 2: Exercise & Fatigue Subdomains

The goal of aim 2 was to examine associations between exercise volume, frequency, intensity, time and type between physical and cognitive fatigue. Exercise was self-reported using the modified Godin Leisure Time Exercise Questionnaire, and the EORTC QLQ-FA12 measured fatigue subdomains. This aim was assessed by evaluating the following hypotheses:

- H1: Higher reported exercise frequency, time, and volume (min/week) will be associated with lower reported physical fatigue & cognitive fatigue.
- H2: Compared to those who reported only light-intensity exercise, individuals who reported moderate and vigorous-intensity exercise will report lower physical and cognitive fatigue.
- H3: Compared to those who reported aerobic alone, individuals who reported combined aerobic and resistance exercise will report lower physical and cognitive fatigue.

2. METHODS

Retrospective cross-sectional analysis of baseline data from cancer patients and survivors who participated in a clinical exercise program.

Participant Data

Participant data was extracted from the University of Colorado Cancer Center's BfitBwell program research database. Specifically, participation dates between July 2016 and March 2024. BfitBwell is a 3-month supervised exercise program tailored specifically for cancer patients and survivors [33]. BfitBwell is open to individuals who (1) are ≥ 18 years of age, (2) have a current cancer diagnosis, (3) obtain medical clearance from their physician, (4) are on treatment (chemo or radiotherapy) OR 6 months within completing treatment at the time of enrolling in the program, (5) and are willing to drive to the study site twice per week for the duration of the program. Individuals were not excluded by baseline activity status or cancer type [34]. For participants to be included in the current study they had to have the following data: age, sex, BMI, cancer diagnosis, treatment status (i.e., currently undergoing or completed treatment), pre-program measures of self-reported fatigue and exercise.

All participants who enrolled in the BfitBwell program completed an informed consent allowing their data to be stored in a Colorado Multiple Institutional Review Board (COMIRB) approved Redcap database for future analysis [34]. For the current secondary analysis, study procedures were pre-approved by COMIRB.

Measures

Self-Reported Exercise

Exercise was measured using a modified version of the *Godin Leisure-Time Exercise Questionnaire (GLTEQ)*, which has been validated for use in various clinical populations, including cancer patients and survivors [35,36]. The modified GLTEQ consists of four items to estimate weekly aerobic and resistance exercise. Participants are asked to recall frequency (days/week) and time (minutes) for exercise bouts that lasted ≥ 15 minutes separately for light, moderate, and vigorous-intensity aerobic exercise over the last seven days, and one item that asks about frequency and time of resistance exercise. Examples of exercise across intensity groups and types are included for participants to reference. Independent variables were:

- Total Exercise Volume (min/week) = [Light Frequency * Light Time] + [Moderate Frequency * Moderate Time] + [Vigorous Frequency * Vigorous Time] + [Resistance Frequency * Resistance Time]
- Total Exercise Frequency (bouts/week) = [Light Frequency + Moderate Frequency + Vigorous Frequency + Strength Frequency]
- Exercise Time (minutes) = [(Light Time + Moderate Time + Vigorous Time + Strength Time) ÷ # of Categories Reported]
- Exercise Intensity
    - Light Intensity Only
    - Light and Moderate and/or Vigorous Intensity
- Exercise Type
    - Aerobic Exercise Only
    - Combined Aerobic + Resistance Exercise

Cancer-Related Fatigue

For Aim 1, general fatigue was measured using the *Functional Assessment of Chronic Illness- Fatigue (FACIT-F)* scale. The FACIT-F is unidimensional and seeks information on self-reported fatigue and its impact on physical function. The measure consists of 13 items on a 5-point Likert scale with scores ranging from 0 to 52, with higher scores indicative of lower fatigue [37].

For Aim 2, fatigue subdomains were measured using the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Fatigue (QLQ-FA12)* scale. The QLQ-FA12 is designed to capture the physical, emotional, and cognitive dimensions of CRF. It consists of 12 items on a 4-point Likert scale, with certain items assigned to specific subdomains [27]. Items 1-5 account for physical fatigue, 6-8 for emotional, and 9-10 for cognitive. Items 11 and 12 measure the effect of fatigue on daily life and social sequelae, respectively [27]. The impact of each subdomain is calculated using the following formulas:

$$Raw\ Score\ (RS) = \left\{\frac{I_1 + I_2 + \dots I_n}{n}\right\}$$

$$Symptom\ Scale\ Score\ (S) = \left\{\frac{RS - 1}{item\ range}\right\} \times 100$$

Symptom scale scores range from 0 – 100, with higher scores indicative of greater fatigue [27]. Once calculated the impact of individual subdomains can be compared.

Data Analysis

De-identified data were provided in Excel and transferred to R version 4.4.1 statistical software for analyses [38]. Once imported into R, all datasets were checked for observations with missing values in relevant variables, which were removed (n = 1). Outliers were detected by calculating a modified z-score for volume and time variables across each observation. Any observation with a score above 3 MAD (Median Absolute Deviations) from the median of the dataset, which amounted to >890 minutes/week of exercise, was excluded (n = 4). All individuals removed reported descriptive statistics (i.e., means, standard deviations, frequencies) were calculated for participant characteristics (age, sex, cancer type, and baseline treatment status), independent and dependent variables.

Associations between FITT principles, general fatigue, and fatigue subdomains were assessed using Pearson correlations. Between group differences for exercise intensity and type were assessed using two sample t-tests, supplemented with effect sizes. Post-hoc regression analyses were run to control for exercise volume.

3. RESULTS

Participant Characteristics

The sample (*N* = 161) was majority female (n = 103) and consisted of participants ranging from 19 – 84 years of age, with a mean of 56 ± 14 years. The most common cancer diagnoses were breast (n = 50), followed by prostate (n = 25), and hematologic (n = 14). Approximately a third of the sample (n = 50) were on treatment at program baseline. Baseline FACIT-F scores, representing general fatigue, ranged from 7 – 52, with a mean of 33 ± 11.

For aim 2, a subset of N = 59 had QLQ-FA12 scores, and were therefore available for analysis. This subsample was similar to the overall sample, having been majority female (%) with a mean age of 54 ± 14 years. The most common cancer diagnoses were breast (n = 23), followed by hematologic (n = 8), and prostate (n = 7). Baseline physical fatigue scores ranged from 0 – 100, with a mean of 46 ± 26. Baseline cognitive fatigue scores ranged from 0 – 100, with a mean of 20 ± 22.

Table 1. Participant Characteristics Across Aims

Characteristic	Aim 1 (N = 161)	Aim 2 (N = 59)
Age, mean (SD), y	56 (14)	54 (14)
Sex		
Female, n (%)	103 (64%)	38 (64%)
Male, n (%)	58 (36%)	21 (36%)
Cancer diagnosis, n (%)		
Breast	50 (31%)	23 (39%)
Prostate	25 (16%)	7 (12%)
Hematologic	14 (8.7%)	8 (14%)
Colorectal	13 (8.1%)	4 (6.8%)
Other (≤ 5%)	59 (37%)	17 (29%)
Current Medical Treatment, n (%)	49 (31%)	10 (17%)
FACIT Score, mean (SD)	33 (11)	---
Physical Fatigue Score, mean (SD)	---	46 (26)
Cognitive Fatigue Score, mean (SD)	---	20 (22)
Self-Reported Weekly Exercise		
Frequency (bouts/week), median (IQR)	7 (5)	6 (5)
Intensity		
Light Intensity Only, n (%)	49 (30%)	21 (36%)
Moderate to Vigorous Intensity, n (%)	112 (70%)	38 (64%)
Time (min), median (IQR)	30 (23)	34 (25)
Type		
Aerobic Exercise Only, n (%)	91 (57%)	35 (59%)
Combined Exercise, n (%)	70 (43%)	24 (41%)
Volume (min/week), median (IQR)	201 (205)	210 (210)

Aim 1: Exercise and General Fatigue

Hypothesis 1: Associations Between Volume, Frequency, Time & General Fatigue

Median self-reported volume was 201 minutes per week, with individual responses ranging from 6 to 679. Displayed below in Figure 1, Pearson's correlation revealed a moderate, positive, and statistically significant correlation between self-reported exercise volume and FACIT-Fatigue scores (r = .28, p <.01).

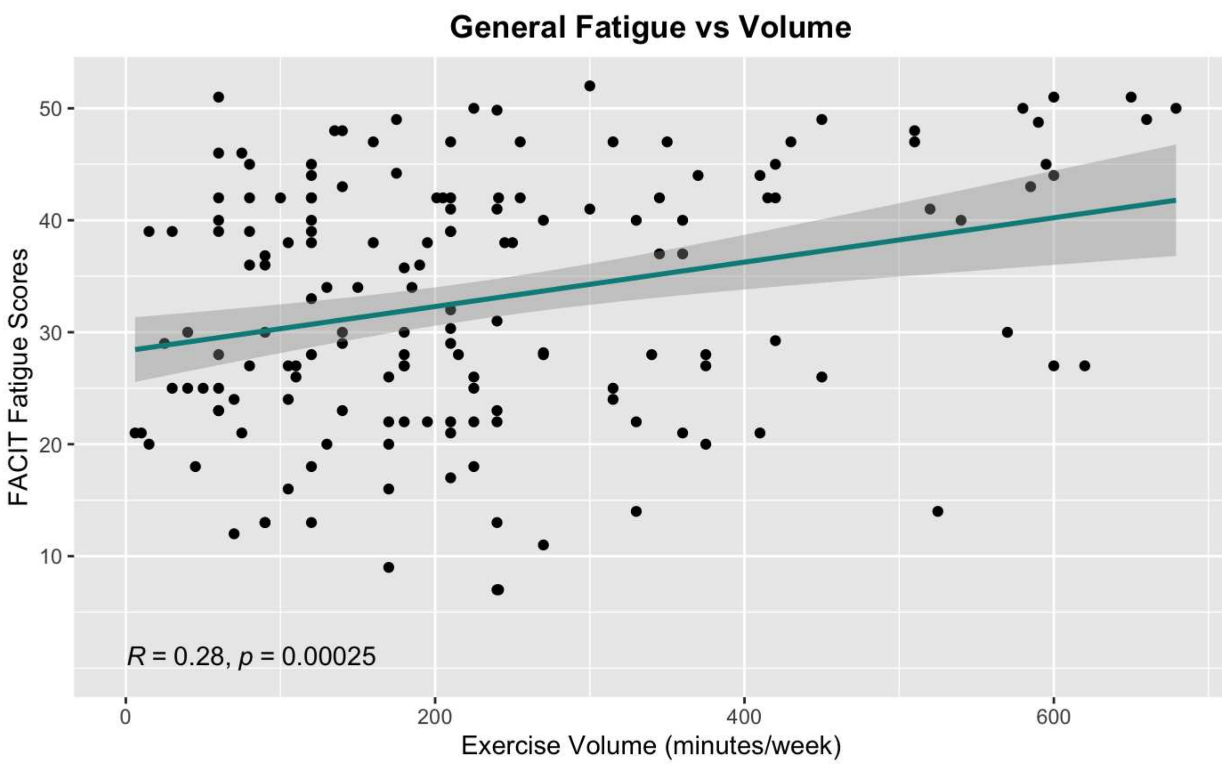

Figure 1: Correlation plot displays FACIT-Fatigue scores across self-reported exercise volume, measured in minutes per week. The line of best fit shows a moderate, positive correlation (r = .28, p < .01) between these two variables, indicating that higher self-reported exercise frequency is associated with lower general fatigue

Median self-reported frequency was 7 exercise bouts per week, with individual responses ranging from 1 to 23. Displayed below in Figure 2, Pearson's correlation revealed a weak, positive, and statistically significant association between self-reported total exercise frequency and FACIT-Fatigue scores (r = .20, p = .012). With the FACIT-F scale, higher scores indicate lower fatigue, and positive associations are indicative of lower fatigue being observed in individuals who reported higher amounts of a given exercise variable.

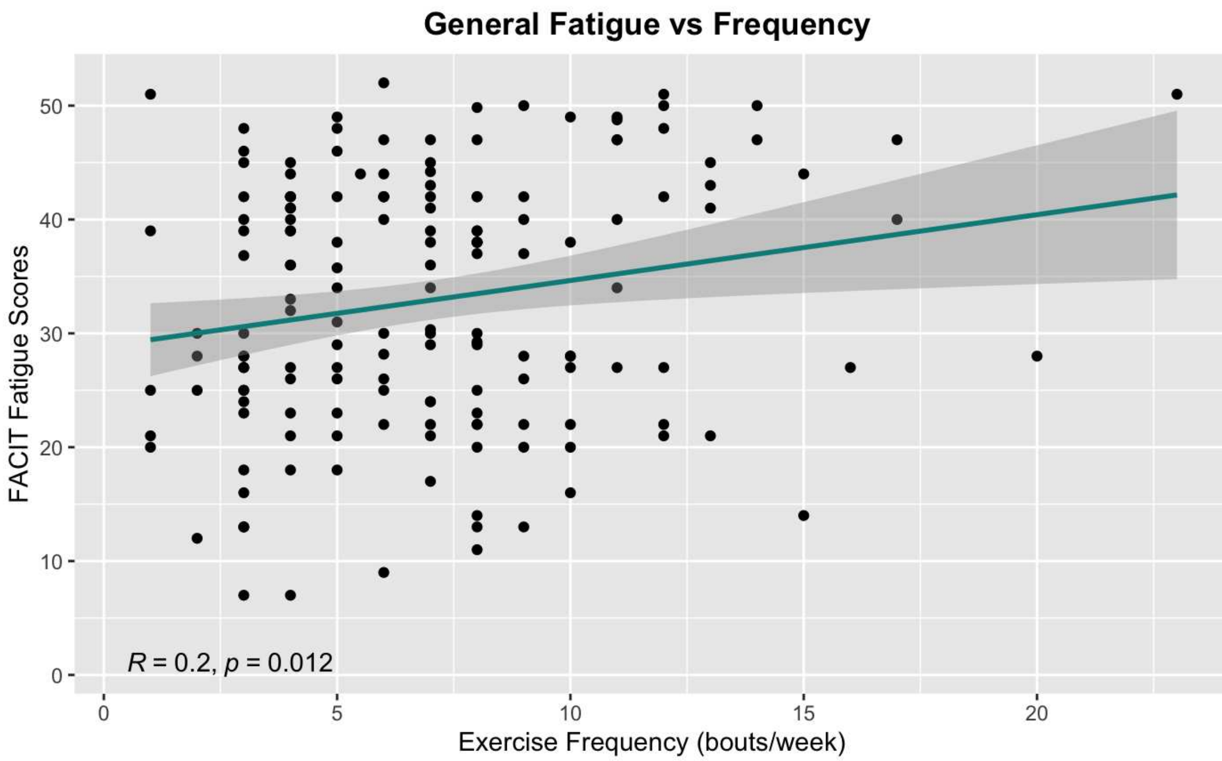

Figure 2: Correlation plot displays FACIT-Fatigue scores across self-reported exercise frequency, measured in bouts per week. The line of best fit shows a weak, positive correlation (r = .20, p = .012) between these two variables, indicating that higher self-reported exercise frequency is associated with lower general fatigue.

Median self-reported time was 30 minutes, with individual responses ranging from 1.5 to 80. Displayed below in Figure 3, Pearson's correlation revealed a weak, positive, and statistically significant association between self-reported exercise time and FACIT-Fatigue scores (r = .18, p = .021).

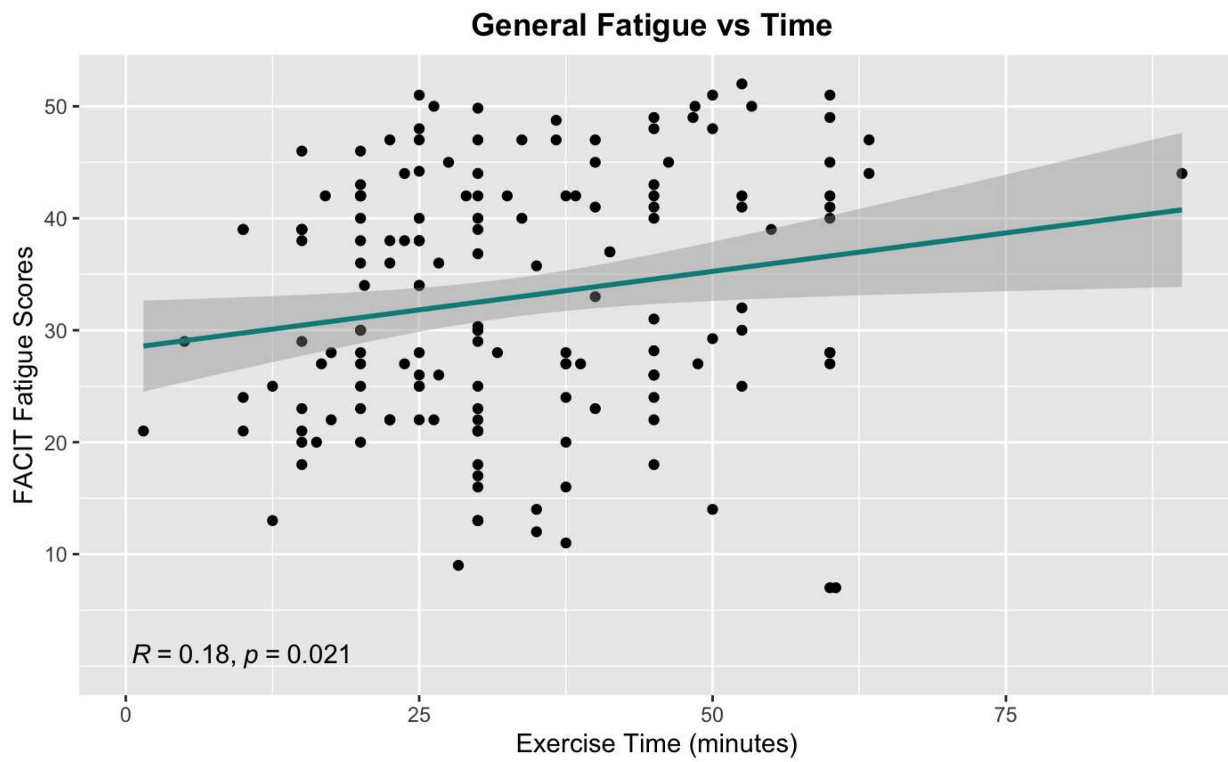

Figure 3: Correlation plot displays FACIT-Fatigue scores across self-reported exercise time, measured in minutes. The line of best fit shows a weak, positive correlation (r = .18, p = .021) between these two variables, indicating that higher self-reported exercise time is associated with lower general fatigue.

Hypothesis 3: Exercise Intensity & General Fatigue

Approximately 30% of the sample (N=49) reported participating in light-intensity exercise only, while the remainder (N=112) reported some amount of moderate to vigorous activity. Figure 4 below displays general fatigue score distributions between groups. A two-sample t-test was performed to compare scores among these two groups. There was a borderline statistically significant difference between those who reported light intensity only (M = 30.7, SD = 10.3) and moderate to vigorous intensity (M = 33.9, SD = 11.6); t (159) = 1.64, p = .051. A small effect was also found (*d* = .28). Given that exercise volume was found to be significantly associated with general fatigue, a post-hoc regression analysis was conducted. In this model, volume remained a significant predictor of fatigue scores ($p < .01$), whereas exercise intensity group did not (p = .64). This suggests that any observed differences were likely driven by volume rather than intensity alone.

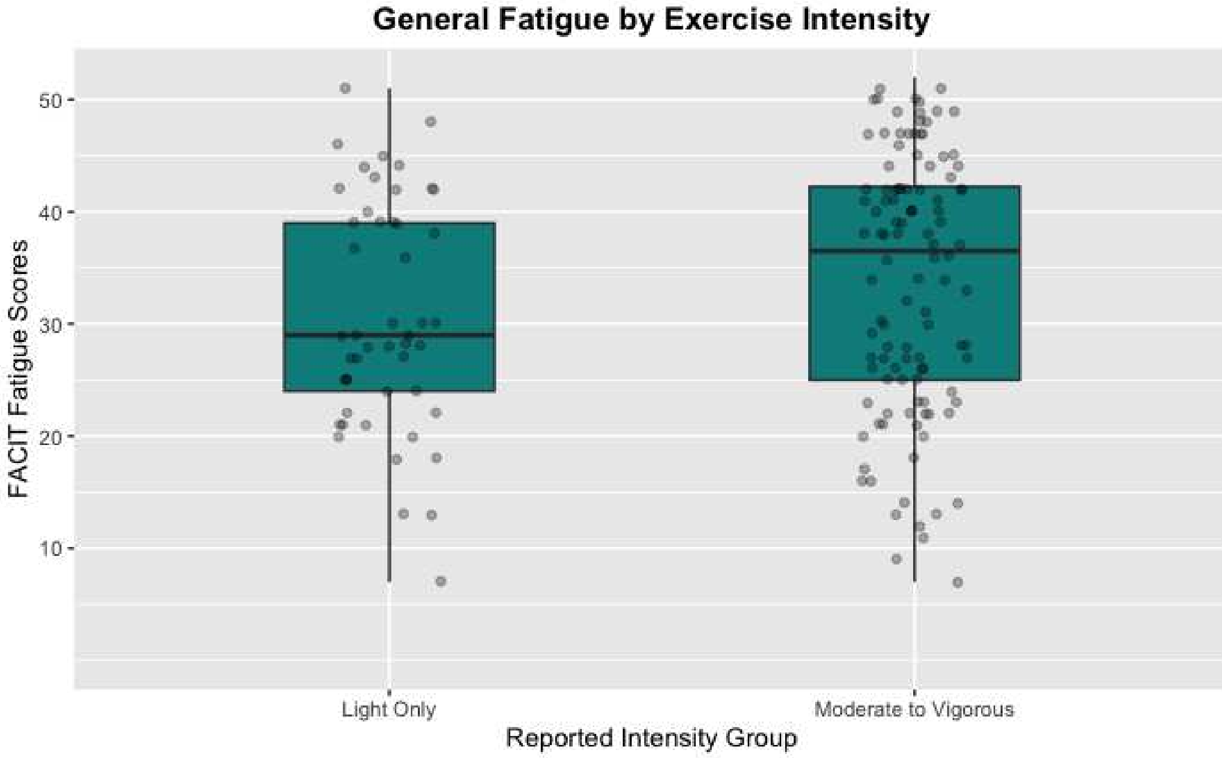

Figure 4: Boxplots display the distribution FACIT-Fatigue scores across exercise intensity groups, with median and IQR shaded. Median general fatigue scores were higher in the moderate to vigorous group, indicating the majority of those who reported higher intensity also reported lower general fatigue compared to light intensity only reporters..

Hypothesis 3: Exercise Type & General Fatigue

The majority of the sample (N=91) reported participating in aerobic exercise only, while the remainder (N=69) reported participating in both aerobic and resistance exercise. Fatigue score distributions between groups are displayed below in Figure 5. A two-sample t-test was performed to compare scores among these two groups. There was not a statistically significant difference between those who reported aerobic exercise only (M = 32.1, SD = 11.5) and combined aerobic resistance exercise (M = 34.0, SD = 10.9); t (158) = 1.05, p = .15. The effect observed was negligible (*d* = .17). A post-hoc regression analysis was conducted to control for exercise volume. In this model, volume remained a significant predictor of fatigue scores ($p < .01$), whereas exercise type group did not ($p = .47$). This suggests that any observed differences were likely driven by volume rather than type alone.

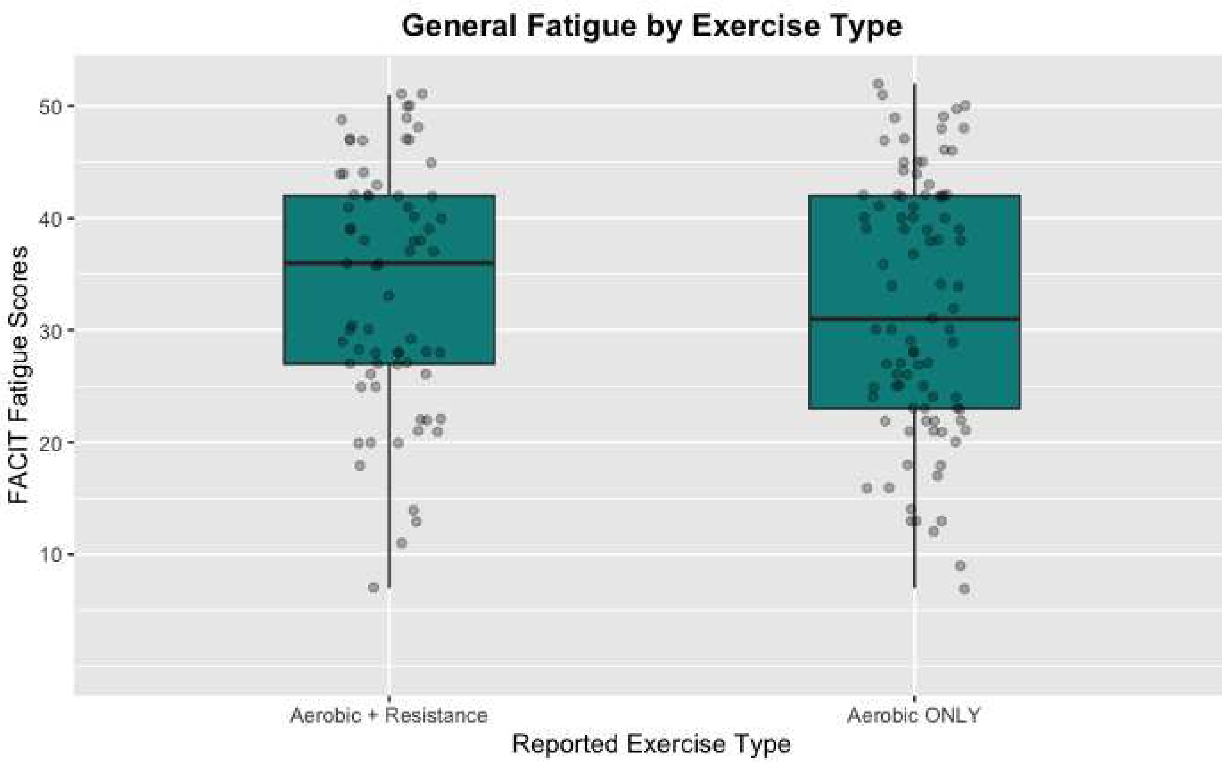

Figure 5: Boxplots display FACIT-Fatigue score distributions across exercise type groups, with median and IQR shaded. Median general fatigue scores were higher in the aerobic & resistance group, indicating the majority of those who reported combined training also reported lower general fatigue.

Aim 2: Exercise and Fatigue Subdomains

Hypothesis 1: Associations Between Volume, Frequency, Time & Fatigue Subdomains

For the subsample with subdomain scores available, median self-reported volume of 210 minutes per week of exercise, with individual responses ranging from 6 to 600. Displayed below in Figure 6, Pearson's correlations revealed a moderate, negative, statistically significant association between self-reported exercise volume and physical subdomain scores (r = -.30, p = .02) and a weak, negative, association for cognitive subdomain scores (r = -.19, p = .16). With the QLQ-FA12, lower scores indicate lower fatigue, and negative associations are indicative of lower fatigue being observed in individuals who reported higher amounts of a given exercise variable.

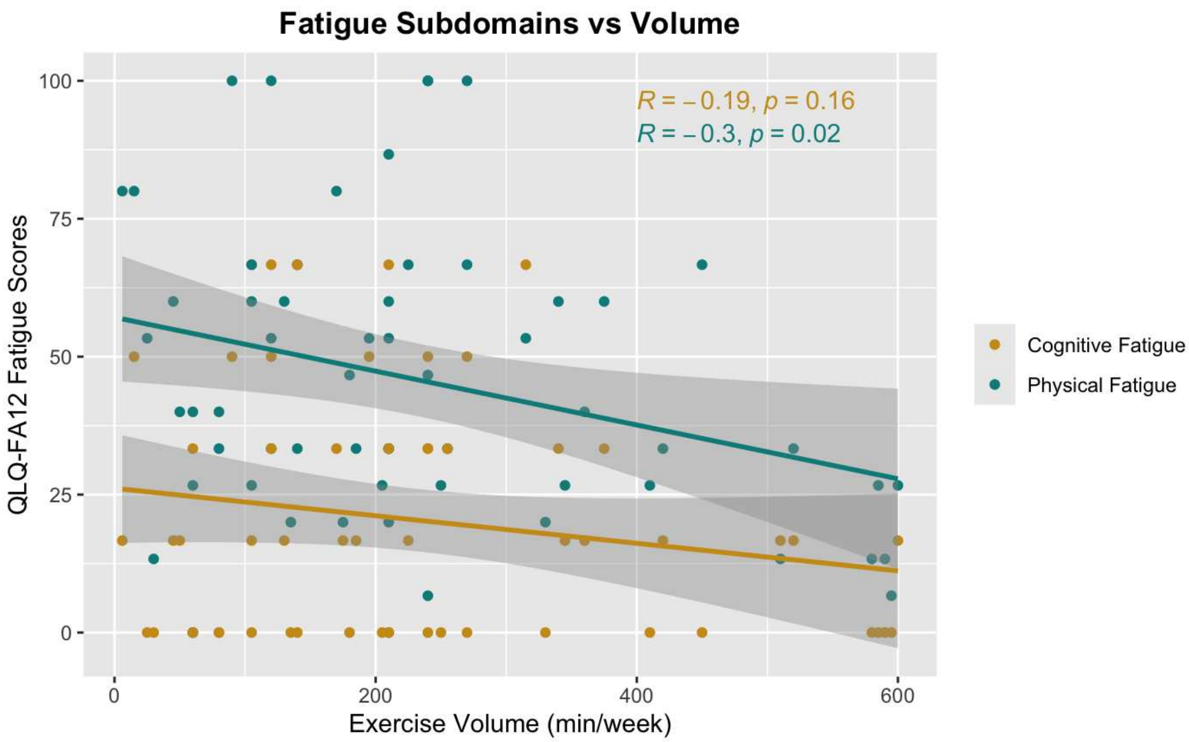

Figure 6: Correlation plot displays QLQ-FA12 subdomain scores across self-reported exercise volume, measured in minutes per week. The lines of best fit show weak to moderate, negative correlations in both physical (r = -.30, p = .02) and cognitive (r = -.19, p = .16) subdomains. This indicates that higher self-reported exercise volume may be moderately associated with lower physical fatigue.

For the subsample with subdomain scores available, median self-reported frequency was 6 bouts per week, with individual responses ranging from 1 to 20. Displayed below in Figure 7, Pearson's correlations revealed a weak, negative, association between self-reported total exercise frequency, physical subdomain scores (r = -.17, p = .19) and cognitive subdomain scores (r = -.08, p = .56).

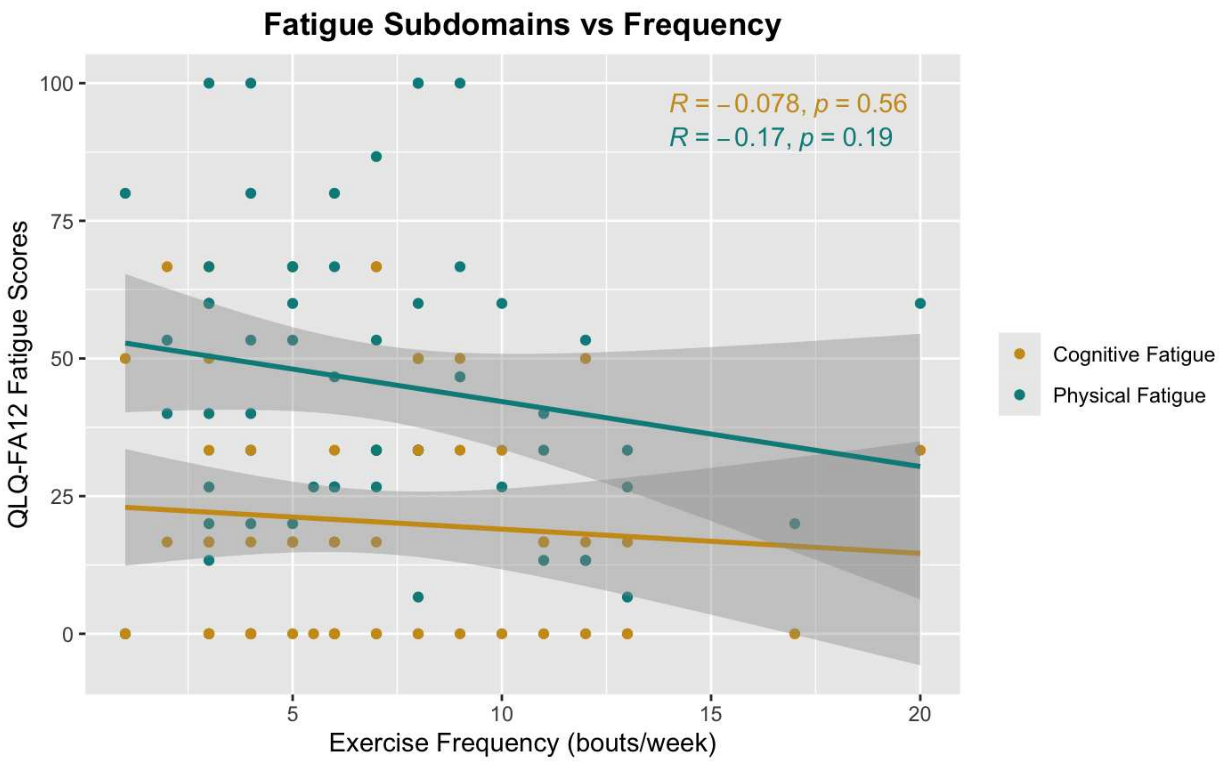

Figure 7: Correlation plot displays QLQ-FA12 subdomain scores across self-reported exercise frequency, measured in bouts per week. The lines of best fit show weak, negative correlations in both physical (r = -.17, p = .19) and cognitive (r = -.08, p = .56) subdomains. This indicates that higher self-reported exercise frequency is associated with lower physical fatigue.

For the subsample with subdomain scores available, median self-reported time was 30 minutes, with individual responses ranging from 1.5 to 90. Displayed below in Figure 8, Pearson's correlations revealed a weak, negative, association between self-reported exercise time, physical subdomain scores (r = -.21, p = .10), and cognitive subdomain scores (r = -.06, p = .65).

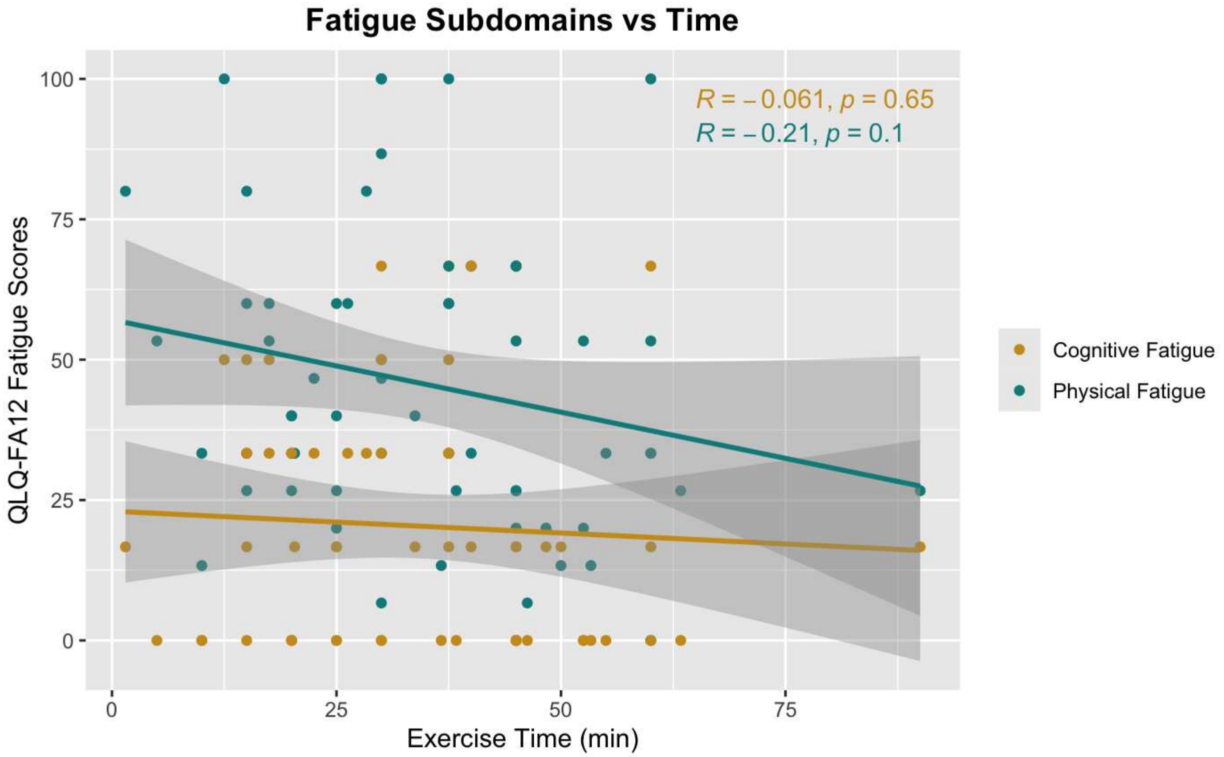

Figure 8: Correlation plot displays QLQ-FA12 subdomain scores across self-reported exercise time, measured in minutes. The lines of best fit show weak, negative correlations in both physical (r = -.21, p = .10) and cognitive (r = -.06, p = .65) subdomains. This indicates that higher self-reported exercise time may be weakly associated with lower physical fatigue.

Hypothesis 3: Exercise Intensity & Fatigue Subdomains

Approximately 36% of the subset sample (N=21) reported participating in light-intensity exercise only, while the remainder (N=38) reported some amount of moderate to vigorous activity. Subdomain score distributions across domains are displayed below in Figure 9. A two-sample t-test was performed to compare subdomain scores among these two groups. For physical fatigue scores, there was not a statistically significant difference between those who reported light intensity only (M = 45.3, SD = 24.9) and moderate to vigorous intensity (M = 46.7, SD = 27.3); t (57) = -0.19, p = .42. Analyses for cognitive subdomain scores showed similar results; light intensity only (M = 23.0, SD = 25.0), moderate to vigorous (M = 18.9, SD = 20.2); t (57) = -0.69, p = .25. Effects observed on both subdomains were negligible (*d* = -.05, -.19). Given exercise volume's borderline significant association with physical fatigue, a post-hoc regression analysis was conducted. In this model, volume remained a significant predictor of fatigue scores ($p = .02$), whereas exercise intensity group did not ($p = .43$). This suggests that any observed differences in physical fatigue were likely driven by volume rather than intensity alone.

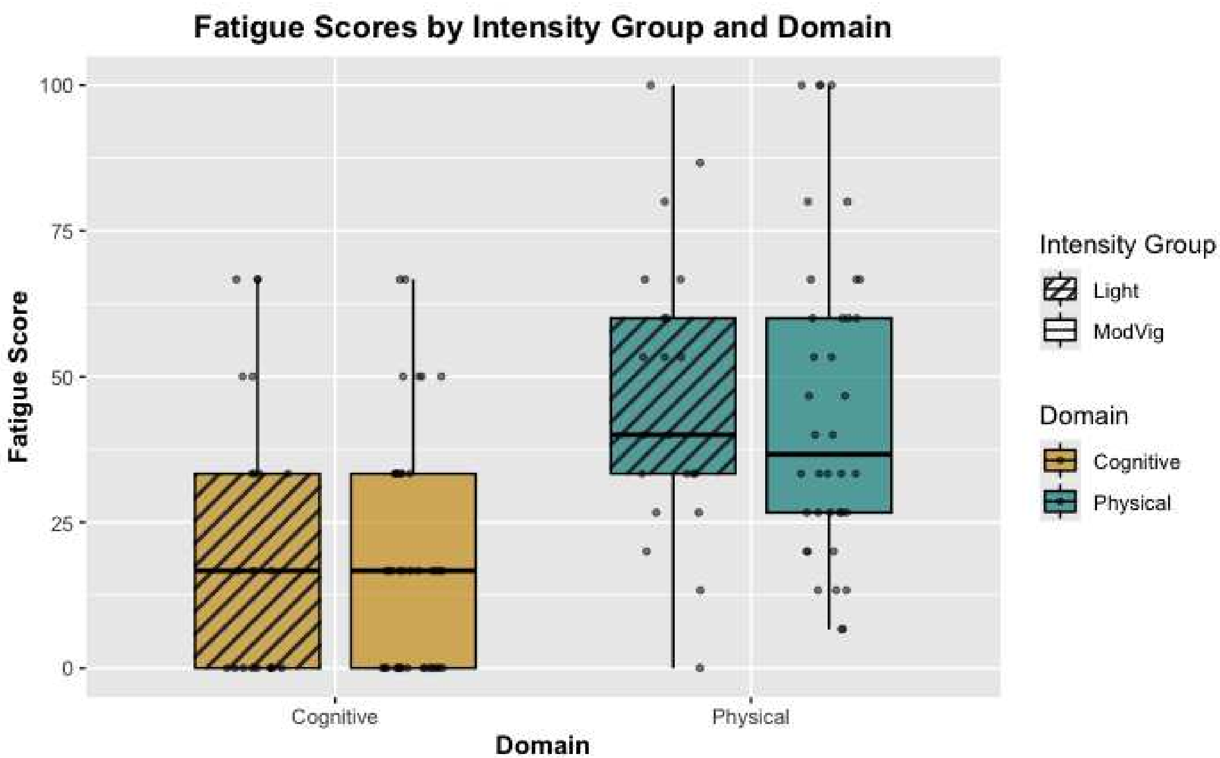

Figure 9: Boxplots display subdomain score distributions across exercise intensity groups, with median and IQR shaded. Physical fatigue scores were slightly lower in the majority of the moderate to vigorous intensity reporters. Distributions in cognitive fatigue scores between groups were similar.

Hypothesis 4: Exercise Type & Fatigue Subdomains

Most of the subset sample (N=35) reported participating in aerobic exercise only, while the remainder (N=24) reported participating in both aerobic and resistance exercise. Subdomain score distributions across reported exercise types are displayed in Figure 10. A two-sample t-test was performed to compare subdomain scores among these two groups. For physical fatigue scores, there was a statistically significant difference between those who reported aerobic exercise only (M = 51.2, SD = 26.0) and combined aerobic resistance exercise (M = 37.8, SD = 25.1); t (57) = -1.98, p = .03. A moderate sized effect was observed (*d* = -.52). Analyses for cognitive subdomain scores displayed a non-significant difference; aerobic exercise only (M = 23.8, SD = 24.3), combined aerobic resistance exercise (M = 15.3, SD = 17.0); t (57) = -1.48, p = .93). A small sized effect was observed (*d* = -.39). Given exercise volume's borderline significant association with physical fatigue, a post-hoc regression analysis was conducted. In this model, the effect of exercise type was no longer statistically significant (p = .49). Exercise volume was also not a significant predictor in this model (p =.146). This suggests that any observed differences were likely confounded by differences in exercise volume rather than type alone.

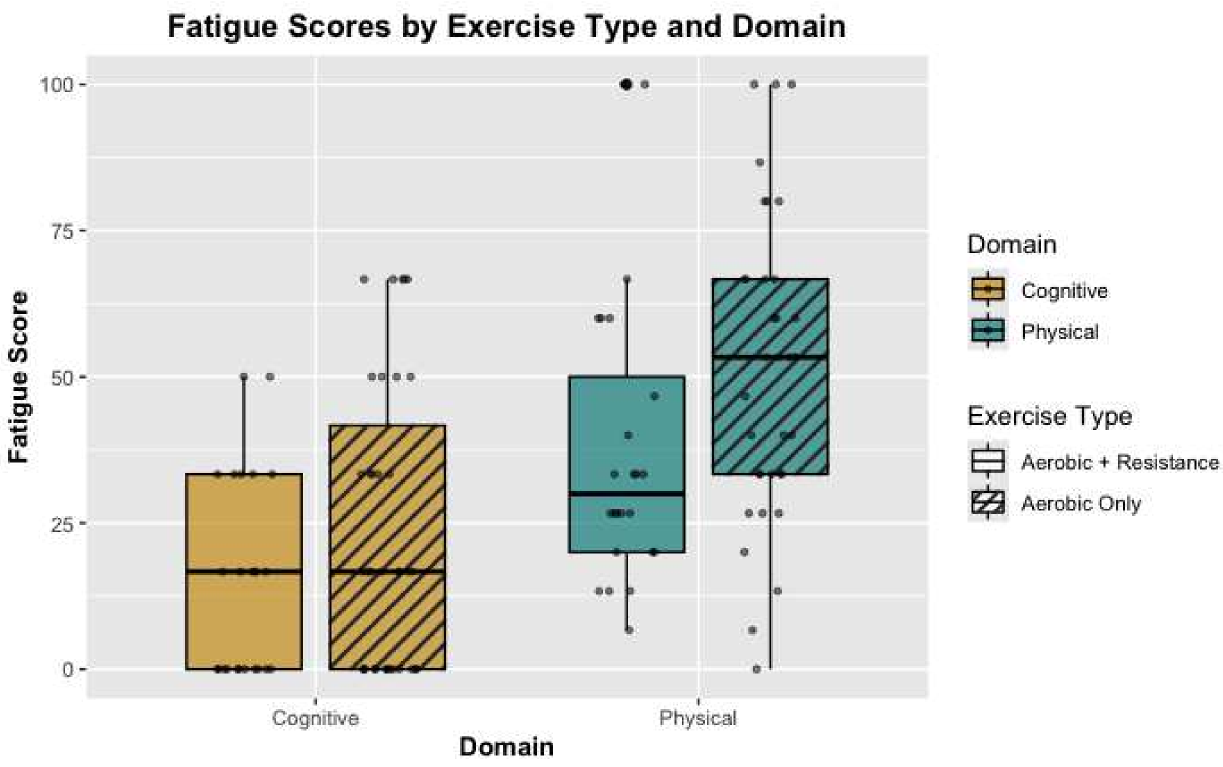

Figure 10: Boxplots display subdomain score distributions across exercise type groups, with median and IQR shaded. Physical fatigue scores appear lower in the majority of the combined training reporters. Distributions in cognitive fatigue scores between groups were similar, with a slightly lower score in the 75th percentile in combined training reporters.

4. DISCUSSION

CRF is a prevalent and distressing symptom among those living with and beyond cancer. Exercise has been shown to be an effective intervention for supportive care, reducing fatigue in appropriate doses. While evidence points towards the benefits of exercise, how exercise should be prescribed to confer the greatest benefit remains underexamined, especially as it applies to fatigue subdomains. The purpose of this retrospective, cross-sectional analysis was to examine the associations between self-reported exercise frequency, intensity, time, and type and cancer-related fatigue. Exercise volume appears to play a central role in both general and physical fatigue regardless of intensity or type.

Exercise and General Fatigue

Aim 1 sought to examine associations between exercise volume (min/week) frequency (bouts/week), time (min), intensity, and type and general fatigue. Results were confirmatory for hypothesis 1, indicating that a greater exercise volume, frequency and time were significantly associated with lower general fatigue. This finding is similar to findings published in existing literature, which have found that greater volume and frequency had significant associations with lower general fatigue, but not time [39]. Of the three variables included in this analysis, self-reported volume displayed the greatest correlation with general fatigue scores. Given that volume is comprised of both time and frequency, offering a more comprehensive view of one's exercise behavior, this was not unexpected. Displayed below in Figure 11, comparing frequency and time correlation coefficients with confidence intervals showed there was not a significant difference between the two variables' associations with general fatigue. This makes it difficult to recommend prioritizing one of these principles over the other, as opposed to recommending greater amounts of exercise volume, which had the greatest association.

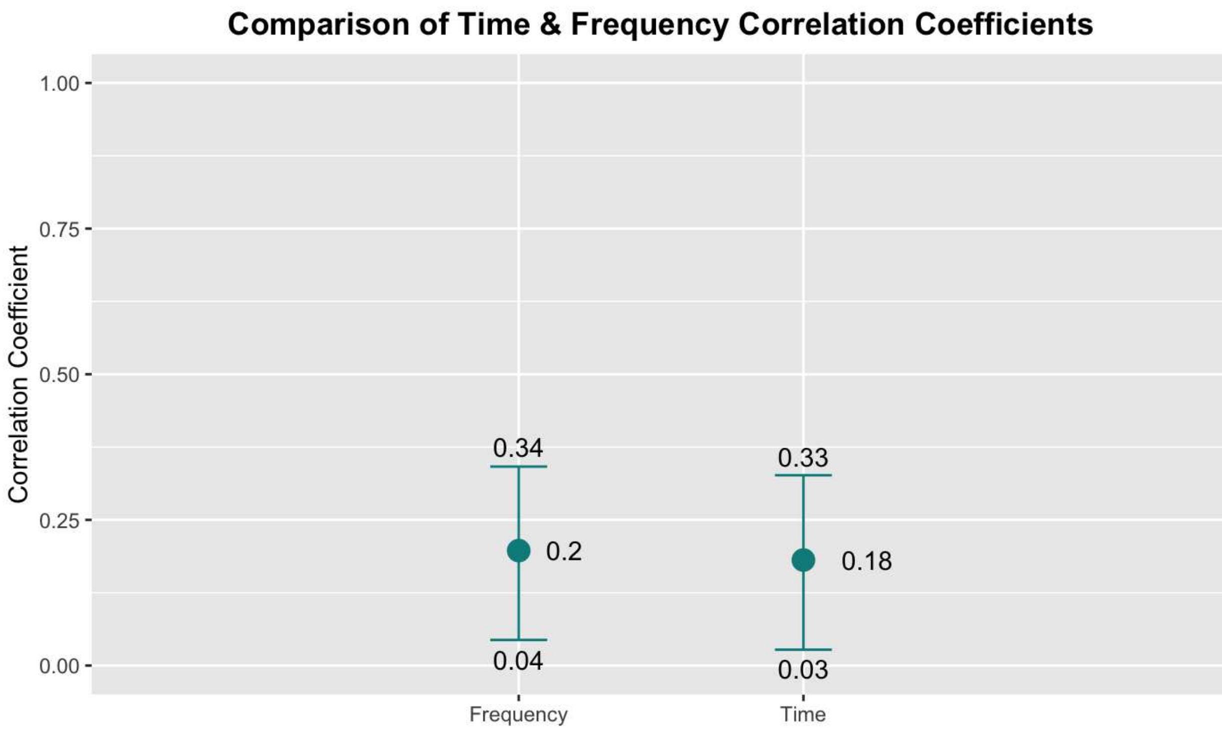

Figure 11: This plot displays the estimated correlation coefficients and confidence intervals for general fatigue and exercise, specifically reported frequency and time. Overlap in error bars between plots suggests there is not a significant difference between variables and their associations with general fatigue.

Hypothesis 2 results were not confirmatory, with no significant difference in general fatigue scores between those who reported doing only light-intensity exercise and those who reported doing light and moderate to vigorous-intensity exercise; especially when controlling for exercise volume. This aligns with what we see in existing literature, as recent trials have shown no significant differences in 1) light to moderate vs vigorous interventions and 2) light vs moderate to vigorous interventions [15,16]. This may suggest those looking to reduce general CRF may benefit from a wide range of intensities, assuming exercise volume is adequate. Under this assumption, exercise could be a more accessible form of treatment for those suffering from higher levels of CRF, as lighter-intensity bouts may still be of benefit.

Hypothesis 3 results were not confirmatory, with no difference in general fatigue scores between those who reported doing only aerobic exercise and those who reported doing both aerobic and resistance exercise, especially when controlling for volume. This finding differs from previous literature. A recent meta-analysis found that combined training had the largest effect on general fatigue when compared to aerobic or resistance training alone [40]. However, other studies have shown resistance training can lower CRF, with or without the presence of aerobic exercise, though these were specific to individuals with prostate cancer [41]. Given the mixed results of previous literature and these findings, those looking to reduce general fatigue may be able to leave exercise type up to preference.

In summary, exercise volume may play a central role in the reduction of fatigue, regardless of intensity or type. Those experiencing general fatigue may see benefits from exercising according to preference, rather than adhering to specific frequency, time, intensity or type, assuming they're adequately active.

Exercise and Fatigue Subdomains

Aim 2 sought to examine associations between exercise volume (min/week) frequency (bouts/week), time (min), intensity, type and fatigue subdomains. Hypothesis 1 results were mixed. For physical fatigue, only exercise volume's association was significant ($p = .02$). Displayed below in Figure 12, comparing frequency and time correlation coefficients with confidence intervals showed there was not a significant difference between the two variables' associations with physical fatigue.

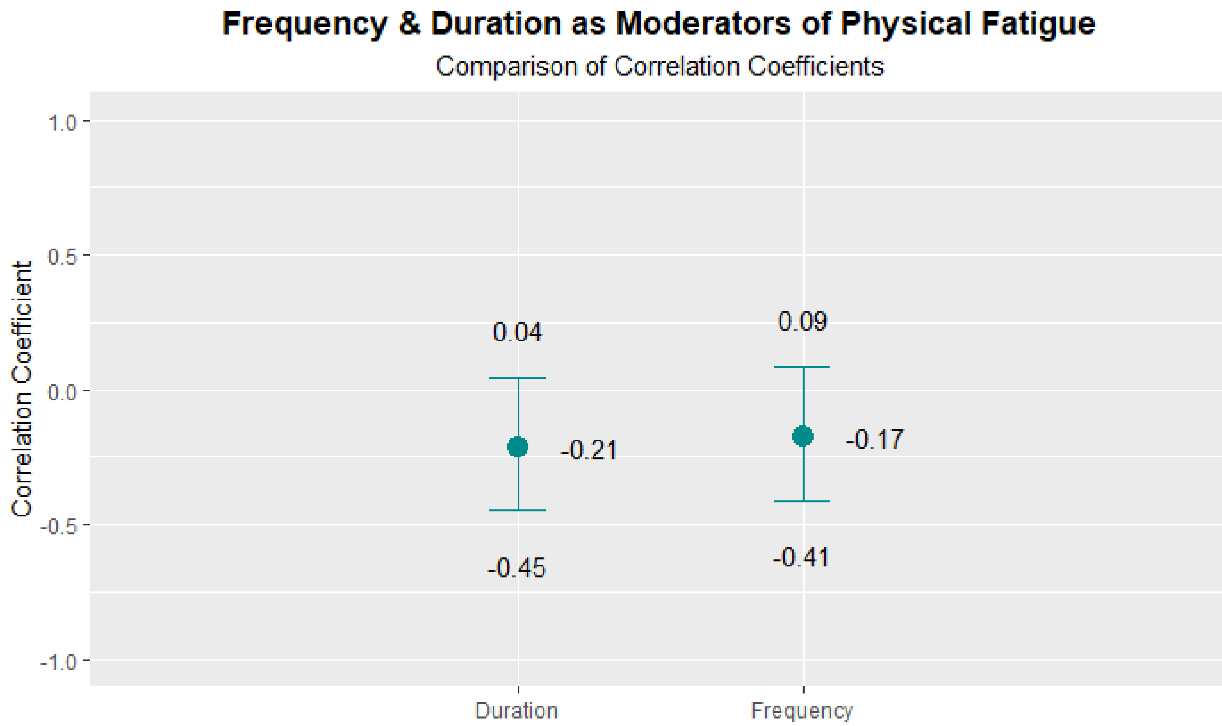

Figure 12: This plot displays the estimated correlation coefficients and confidence intervals for physical fatigue and exercise, specifically reported frequency and time. Overlap in error bars between plots suggests there is not a significant difference between variables and their associations with physical fatigue.

For cognitive fatigue, results were also not confirmatory. Across all three variables no significant associations were observed. Due to the association between volume and cognitive fatigue lacking remote significance, no sub-analysis to compare frequency and time was performed.

Given the lack of publications on self-reported exercise and fatigue subdomain scores using the QLQ-FA12, it was difficult to assess how these results compare to existing literature. In similar studies that utilized a multidimensional measure, only a correlation coefficient for a sum score was reported [39]. However, previous literature that can be found indicates exercise interventions may have less of an effect on cognitive fatigue opposed to physical [42]. This current study's findings in the context of previous literature may suggest exercise volume plays a larger role in physical fatigue compared to frequency and time. and may simply not have a significant impact on cognitive fatigue.

Hypothesis 2 results were not confirmatory, with no significant difference in physical or cognitive scores between those who reported doing only light-intensity exercise and those who reported doing light and moderate to vigorous-intensity exercise; especially when controlling for exercise volume. These results both align and differ with the few findings available in existing literature. Moderate to vigorous-intensity exercise has been seen result in a significantly greater reduction in physical fatigue compared to light-intensity, though this was not seen for cognitive fatigue[16]. It appears exercise intensity has little impact on cognitive fatigue, while more work needs to be done to elicit the effects of intensity on physical fatigue.

Hypothesis 3 results were mixed. For physical fatigue, results appeared confirmatory with a significant difference in scores between groups and moderate effect size. However, after adjusting for volume, the effect of exercise type was no longer observed to be significant. For cognitive fatigue, no significant differences were observed. These findings align with previous literature which has not shown significant differences between exercise types across subdomains [20].

In summary, more work should be done to prospectively investigate combinations of FITT principles that may be effective in reducing cognitive fatigue, and future guidelines should guide individuals toward alternative therapies. For physical fatigue, exercise volume may attenuate any observed improvements, regardless of intensity or type. Future guidelines should consider recommending individuals stay active according to preference, as opposed to adhering to specific exercise frequency, intensity, time, or type for the treatment of physical fatigue.

Strengths and Limitations

This study has several key strengths and was not without limitations. Multiple notable strengths of this study lie in the sample. First, it consisted specifically of those living with or beyond cancer who were either actively undergoing treatment (chemotherapy and/or radiotherapy) or within 6 months of completing treatment. While CRF can commonly persist through survivorship, it disproportionately impacts those undergoing active treatment [10]. This inclusion criteria ensures that findings from this analysis are relevant to those most likely to be impacted by the primary outcome measure. Second, participant characteristics also mirrored what has been observed in other studies on fatigue and cancer and reported scores markedly different from those found in the general population, for both general fatigue and subdomains [39,43,44]. This confirmed the sample was sufficiently more fatigued than apparently healthy individuals and appropriate for analysis.

Another strength lay within the measures used, specifically those used to capture fatigue. Both the FACIT-F and QLQ-FA12 have established validity and reliability. Moreover, given their widespread adoption in a variety of fields, population norms for the FACIT-F and QLQ-FA12 have been established [44,45]. This allowed for comparisons against both healthy and oncologic populations. In light of the numerous scales available, those discussed here have demonstrated to be the best choices when considering NCCN definitions and guidelines for CRF [46]. Despite the QLQ-FA12 being considered one the best tools to evaluate fatigue subdomains, literature on its use concerning exercise remains sparse and its use in this study should be considered novel.

Study results should be interpreted with consideration of the following limitations. First, the cross-sectional design of this study does not allow for causal inference. While we posit that exercise may have a positive impact on CRF due to the existing body of evidence, those who reported higher amounts of exercise may have been enabled to do so by experiencing lower amounts of fatigue.

Second, the use of self-report measures to capture exercise has the potential for recall bias and the GLTEQ also does not capture physiologic markers of exercise intensity (e.g. heart rate, rate of perceived exertion, etc.). Future cross-sectional studies should consider utilizing wearable physical activity monitors. Such devices provide an abundance of accelerometer and heart rate data, which could eliminate recall bias and provide a much more objective look into one's exercise behavior. Beyond this, it's also possible the retrospective, self-reported exercise from this analysis did not contain a combination of exercise that could be optimal for reducing CRF both generally and across the measured subdomains, especially cognitive.

Third, measuring exercise using the FITT principles came with inherent caveats. While they can aid in streamlining exercise prescription, they may also oversimplify certain aspects. For example, the GLTEQ cannot account for aerobic intervals that vary in intensity over a given session. Rather it is a assumed an entire session is light, moderate or vigorous intensity.

Fourth, given the constraints of using an existing data set, other potentially important factors for CRF were not captured. CRF is not only multifaceted in its subdomains, but also its influences. When exercise volume was regressed on general fatigue scores, the $r^2 = .08$. This can be interpreted as exercise volume only explaining 8% of the variability in general fatigue for this sample. Future studies should account for potential covariates such as mental health, pain index, and socioeconomic status all of which have been shown to impact CRF [47,48]. This, along with the various other limitations mentioned above, should lead to a conservative interpretation of results.

Future Directions

To ameliorate general or physical CRF, individuals should focus on preference, prioritizing frequencies, intensities, times, and types, of exercise in free living that encourage one to achieve greater amounts of volume. Future studies looking to analyze cancer-related fatigue, its subdomains, and exercise to make concrete recommendations for ExRx should consider the following.

Accelerometers or widely available physical activity trackers could provide a more objective look into participants' exercise. Specifically, heart rate data could provide insight into intensity, and allowing participants to record specific, labeled activities in real time could provide information on frequency, duration, and volume of exercise. If an objective measure is not available, one should employ a measure that allows for exercise intensity to be quantified with a standard, recognized, value, such as MET's or rate of perceived exertion.

Fatigue influences and risk factors should be accounted for, including but not limited to socioeconomic status, pain index, and stress. Building a model with these factors included could help identify potential responders and nonresponders, ultimately informing individuals who are likely to benefit from exercise. Other sources of variability, such as gender differences, cancer type, and treatment status should also be accounted for to enhance the generalizability of findings.

In conclusion, results indicate general and physical CRF can be reduced through a greater volume of exercise, regardless of how that exercise is structured. Higher quality evidence is needed to elicit the impact of specific FITT principles on these outcomes. Randomized control trials should address why greater amounts of volume contribute to reductions in fatigue. Specifically, the impact of individual intensity ranges, exercise types outside of aerobic &

resistance training, and any investigation of dose-response in regard to CRF could help further existing prescription.

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