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A Preliminary Investigation on Patterns of Physical Activity in Cancer Patients Receiving Chemotherapy and Immunotherapy in Relation to Quality of Life and Depression Rates

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Abstract

Introduction: Patients undergoing chemotherapy or immunotherapy for cancer tend to remain sedentary following diagnosis. They also suffer from low quality of life (QoL) and increased rates of depression/depressive symptomology. Recent studies indicate that physical activity (PA) may improve QoL and reduce depression rates. The exact patterns of PA in this subject population are unknown. This study investigates patterns of PA in cancer patients receiving treatment to understand how level of PA and types of PA relate to QoL and depressive symptomology.

Methods: A cross-sectional survey study was conducted between June and July 2022 at the UConn Health Center's Comprehensive Cancer Center. Patients receiving chemotherapy and immunotherapy were invited to take a survey intending to collect information about physical activity patterns, depressive symptomology, and QoL. Significance testing, binomial regression, and multiple linear regression were all conducted to study differences in QoL and depressive symptomology between various subgroups of patients.

Results: 50 patients total responded to the survey. In sum, 36% of patients participated in aerobic and household activity; 13% participated in aerobic-only activity; 13% participated in a mixture of aerobic, resistance, and household activity. 34% of patients were either sedentary or lightly active. 66% were moderately to very active. A significant increase in QoL was observed in physically active patients compared to (near)-sedentary patients ($p=0.006$). Increased PA levels were associated with significantly superior physical, role, and social functioning. Fatigue and dyspnea were also significantly lower in physically active patients. Active patients had lower average CES-D scores, but moderate effect was observed ($p>0.05$, $g=0.454$).

Conclusions: Cancer patients undergoing treatment showed varied patterns of activity with a preference for aerobic activity over resistance training; most patients were moderately to very active. PA could be a possible non-pharmacologic intervention to improve QoL and reduce depressive symptomology. However, more research with controlled trials is needed to investigate the relationship between PA, QoL, and depression symptoms in patients with cancer undergoing chemotherapy and immunotherapy.

Appendix A: Key terms and abbreviations
Quality of life (QoL), Physical activity (PA), European Organization for Research and Treatment of Cancer (EORTC), Center for Epidemiologic Studies - Depression Scale (CES-D), Health-related quality of life (HRQoL), Resistance training (RT), Physical functioning (PF), Role functioning (RF), Emotional functioning (EF), Cognitive functioning (CF), Social functioning (SF), Fatigue (FA), Nausea and vomiting (NV), Pain (PN), Dyspnea (DY), Insomnia (SL), Appetite loss (AL), Constipation (CO), Diarrhea (DI), and Financial difficulties (FI), Visual analog scales (VAS), participation in both aerobic exercise and resistance training (A+RT)

1.0 Background and Introduction

Chemotherapy and immunotherapy patients remain sedentary following cancer diagnosis with overall physical activity (PA) drastically decreasing, especially in older patients above 60 years of age, men, and in patients who are professionally inactive following diagnosis.[1] Additionally, patients undergoing cancer therapy suffer from low quality of life (QoL) and depression at high rates.[2–5] QoL is a multi-faceted measure of understanding a patient's perception of their aims, expectations, interests and ideas, satisfaction, and values.[6] QoL is related to physical, social, psychological, and spiritual state, generally described as an overall sense of well-being.[7] Cancer, and treatment of cancer through standard medical practice including surgery and chemotherapy generally worsen aspects of QoL for some time immediately after treatment.[8] Obesity and related comorbid conditions may increase risk for treatment-related issues such as toxicity**,** lymphedema, fatigue, and poor functional health.[9] Additionally, cancer patients with diabetes are more likely to report worse health-related QoL (HRQoL), physical functioning (PF), and mental health than those without.[10,11]

Considering depressive symptomology, two thirds of cancer patients with diagnosed depression express clinically significant levels of anxiety as well.[12] Cancer patients are five times more likely to be depressed than the general population.[13] Even if patients are not clinically diagnosed with depression, 16.5% report subclinical symptoms.[14] Gender is a significant factor for depression diagnoses in the subpopulation, with females being more likely than males to develop depression; this is usually attributed to issues with self-perception and body image alterations as well as treatment procedures causing emotional distress.[15] Cancer metastasis and rising pain levels are also associated with higher levels of depression.[16]

Exercise is recommended by the American College of Sports Medicine (ACSM) and the Centers for Disease Control (CDC) during treatment; some evidence supports its potential inhibitory effect on risk and recurrence of certain cancers, likely mediated through mechanistic pathways that alter the tumor microenvironment.[17–20] The literature supports general trends in QoL improvement and depressive symptomology reduction when participating in regular exercise across a wide array of populations. The

ACSM also recommends resistance training (RT) for physiological benefits and QoL improvement, as RT may help manage and treat conditions related to cancer.[21] Prior research has shown that "dimensions of [health-related] QoL (HRQoL) showed the largest positive effects when the programs were delivered as part of cancer treatment and included RT"; RT may mitigate anxiety and depression while simultaneously improving QoL when completed in conjunction with treatment cycles.[22,23] Few studies have considered QoL and depression rates in relation to RT exercise in the *general* chemo- or immunotherapy recipient population.[24] Multiple studies have demonstrated the safety of RT in the cancer patient population given proper programming and progression, providing a feasible basis of expanding our current understanding of exercise during treatment past the sole involvement of aerobic movement, which is already generally well understood.[25–27]

Despite the demonstrated safety of RT-inclusive PA programs, however, physicians hesitate to prescribe RT, believing that their patients may be unable to handle the burden of this variation of PA.[28] More commonly, aerobic exercise is recommended and participated in (albeit still at low rates compared to how sedentary the average cancer patient is). It is well supported that aerobic training is sufficient to significantly improve QoL. Less is understood about RT involvement during treatment. Prior research suggests that aerobic exercise has significant effects on depression while resistance exercise alone has no effect.[29] While these findings are in accordance with the ACSM stand that RT alone is not enough to reduce depression, current established guidelines are amongst cancer *survivors* rather than patients currently receiving treatment. More research is needed to understand RT's associations with depressive symptomology in patients receiving *concurrent* treatment.[30]

The purpose of this study was twofold: 1.) understand patterns of PA in chemotherapy and immunotherapy patients currently receiving treatment and 2.) compare reports of PA from cancer patients receiving chemotherapy or immunotherapy to understand PA's associations with QoL and depressive symptomology. Further, this investigation hoped to understand relationships between inclusion of RT *specifically* in exercise behaviors and overall QoL and depressive symptomology, as there exists very little research on PA involving RT in this population. This was the first investigation of its nature that compared QoL in relation to PA among the chemotherapy- and immunotherapy-recipient population using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and CES-D questionnaires. This study additionally broadened the subject population as 83% of studies in this area specify or include breast cancer patients as the demographic of interest, necessitating additional data for a wider array of cancers.[31]

2.0 Hypotheses and specific aims

The major goal of this investigation was to collect preliminary data on exercise behaviors and PA trends among individuals who are receiving concurrent chemotherapy or immunotherapy following a cancer diagnosis.

We hypothesized that greater levels of PA would correlate with overall greater levels of QoL, lower levels of depressive symptomology, lower insomnia, lower pain (PN), and lower fatigue (FA). We also hypothesized, within the physically active subgroup of patients (also referred to as "active (sub)group throughout this paper), those combining RT with aerobic exercise will have better measures of QoL than those doing solely aerobic exercise. We were interested in patterns of activity in our patients and between-group differences between aerobic-only and aerobic-and-resistance-exercise subjects regarding QoL and depressive symptomology.

3.0 Methods

3.1 Study Design

This cross-sectional in-person survey study was conducted between June and July 2022 in the University of Connecticut Health Center's (UCHC) Carole and Ray Neag Comprehensive Cancer Center. Both male and female patients undergoing chemotherapy and immunotherapy were recruited for the study. The overall project sought to examine the impact of a variety of PA types on QoL, anxiety, and depression rates in the chemotherapy- and immunotherapy-recipient patient population in this Cancer Center. This proposal was funded by the Holster Foundation at the University of Connecticut as a research grant and received board approval from UCHC Board in May 2022. UConn's IRB deferred oversight to UCHC in June 2022 (IRB# 22X-297-2).

3.2 Sampling and Population

Surveys were distributed in the Oncology Infusion Center at the UCHC Comprehensive Cancer Center under oversight of Upendra Hegde, MD. The survey was primarily implemented in the infusion center, but some were also completed by patients currently receiving the previously described treatments that simply had check-ins with medical providers in the cancer center. Ultimately, a homogeneous study population of entirely chemotherapy/immunotherapy patients currently receiving treatment and during their treatment cycle was obtained. To this end, we excluded Cycle 1: Day 1 patients from our sampling. Our target sample size was n=50.

The study team advised clinicians, APRNs, and Medical Assistants (MAs) to mention the survey to patients and, if patients were interested, to provide copies of the survey packet to complete. Patients had the option of completing the survey in an empty room following their appointment, during an

infusion session, or taking the survey packet home to complete on their own time and return later in the data collection period to return the completed survey.

We implemented multiple inclusion/exclusion criteria to yield a final data set for analysis. Those who did not meet the inclusion criteria (current cancer diagnosis, currently receiving chemotherapy or immunotherapy treatment; English-speaking; 18-years or older) or fell under the exclusion criteria (decisionally impaired, at the discretion of the treating care provider; UCONN students, faculty, or staff) were excluded from the study. Patients could be of any race, ethnicity, age (above 18 years old), and gender-identity. Participants were given an information sheet detailing all aspects of the study and were told that completion of the implemented survey packet was implied consent.

A total of 56 surveys were handed out during the data collection period. A total of 50 respondents agreed to and completed the survey sufficiently, resulting in a response rate of 89.29%. Some patients handed back blank packets or only completed the first page and nothing else, rendering those packets entirely unusable. We did not include incomplete data collection forms (DCFs) from packets that were not otherwise mostly filled out in the data analysis. We did not calculate scores for incomplete EORTC subscales or CES-D surveys.

3.3 Survey Implementation and Measures

The implemented survey instrument was designed to take ~15 minutes to complete and asked participants to provide general demographic and clinical details such as age, gender, cancer diagnosis, cancer stage (if known), life expectancy (if known), comorbidities, and a list of medications being taken. No identifying information was collected – this survey was completely anonymous. The survey then had patients describe their PA level across 5 options ranging from sedentary to highly active. Next, the survey asked patients to describe their activity type across 4 options: aerobic, resistance training, both aerobic and resistance training, or household chores/leisure activities. A fifth option was provided titled “Other” for patients to write in a different description. The survey asked patients how many minutes they spent exercise each week, and to describe their social support system (i.e., any family, friends, pets, etc. that the patient could spend time with and rely on).

Participants were asked to fill out the 20-item Center for Epidemiological Studies-Depression (CES-D) scale to assess how they felt in the past week. CES-D was developed with the primary aim of assessing epidemiology of depressive symptoms in the general populous, and captures four main factors: depressed affect, anhedonia, somatic complaints, and interpersonal complaints.[32] The scale’s summed depression score allows assessment of patterns of PA in relation to depressive symptomology in the patient population. This scale has been validated numerous times in this patient population in prior, similar studies with only minor internal validity problems like selective reporting, further justifying use.[33]

The EORTC QLQ-C30 scale, designed and developed by the European Organization for Research and Treatment of Cancer, assesses overall QoL in the patient population, calculated through the official scoring guide. The tool contains a Global Health Status/QoL subscale; 5 Functional Subscales: Physical Functioning (PF), Role Functioning (RF), Emotional Functioning (EF), Cognitive Functioning (CF), Social Functioning (SF); and 9 Symptom Subscales: Fatigue (FA), Nausea and Vomiting (NV), Pain (PN), Dyspnea (DY), Insomnia (SL), Appetite Loss (AL), Constipation (CO), Diarrhea (DI), and Financial Difficulties (FI). The EORTC QLQ-C30 was critical to understanding the relationships between patterns of PA and subgroups' overall QoL.

Visual analog scales (VAS) were employed as continuous measurements (scored 0-100% on the scale) to measure PN, sleep quality, and energy levels. VAS are validated in patients with cancer, considered to be easy to understand and accurately assess symptoms.[34]

The questions on the CES-D scale were Likert Rating Scales; EORTC QLQ-C30 also employed Likert Rating Scales; the initial DCF was a combination of open-ended and multiple-choice questions. VAS were marked off as tick marks.

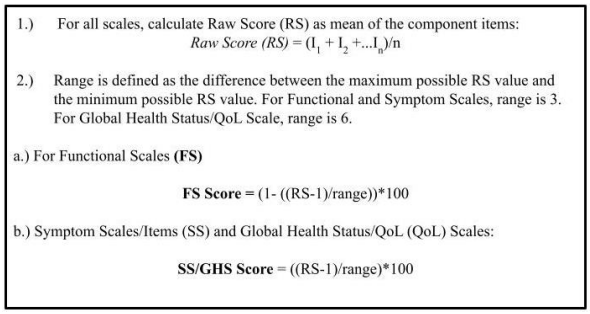
3.4 Missing Values

Given the nature of the survey, and how some questions may be difficult to answer or reflect on for patients in trying conditions, we expected for some questions to be left blank. The consent form provided with the packet made note of the option for patients to leave questions that they were uncomfortable answering or didn't know how to answer blank. After collecting all completed surveys, we, as expected, had some patients who skipped questions. Though the EORTC QLQ-C30 survey does have computational measures to fill in missing values, the 20-item CES-D scale does not have a validated way of dealing with missing values, nor does the DCF have a meaningful way of dealing with missing answers to certain questions. To ensure that we could make the most of the data we had, we entirely omitted incomplete CES-D surveys and omitted incomplete EORTC subscales from analysis. We also omitted incomplete portions of the DCF but did include information from what patients filled out besides the missing portions if we deemed the survey packet to be sufficiently completed.

3.5 Data Analysis

We used descriptive statistics to measure the major features of the sampled population. We summarized the sample size, population demographics, and clinical characteristics. From there, we split the data into subgroups (sedentary v. (near)-sedentary; activity not including RT vs. activity not including RT; male vs. female, etc.) and studied the overall average scores of depressive symptomologies and QoL. We employed inferential statistics–2-sample t-tests, binomial logistic regressions, and multiple linear regression (MiniTab, SPSS). Regression testing was used to account for potential skewed data in population demographics and minutes of exercise/week.

Standard scoring procedures were used for EORTC QLQ-C30 and 20-item CES-D scales. For EORTC, raw scores were calculated for each category and then linearly transformed to be out of a 100-point scale (see Figure 1). Following the official EORTC Scoring Guide, a *higher* score on functional scales and global health status scale are indicative of higher/healthier level of functioning and higher QoL, while a higher score on symptom scales represents a *worse* level of symptomology (or *more* presentation of a particular symptom). For example, a functional scale score of 100 would be equivalent to the highest level of functioning for a given sub-scale, but a symptom scale score of 100 would be equivalent to the *highest* level of symptomology, or highest presentation of that symptom.


1.) For all scales, calculate Raw Score (RS) as mean of the component items:
Raw Score (RS) = $(I_1 + I_2 + ...I_n)/n$

2.) Range is defined as the difference between the maximum possible RS value and the minimum possible RS value. For Functional and Symptom Scales, range is 3. For Global Health Status/QoL Scale, range is 6.

a.) For Functional Scales **(FS)**

FS Score = (1- ((RS-1)/range))*100

b.) Symptom Scales/Items (SS) and Global Health Status/QoL (QoL) Scales:

SS/GHS Score = ((RS-1)/range)*100

Figure 1. Standard linear transformation scoring procedures for EORTC QLQ-C30, where Raw Score is manipulated as directed by EORTC scoring manual to calculate scores for functional scales and symptom scales.

For 20-item CES-D scale, response options ranged from 0 to 3 for each item: 0 = Rarely; 1 = Sometimes; 2 = Moderately; 3 = Most or Almost Always. Scores could reach a maximum of 60 points, with higher scores indicating greater depressive symptoms. Following Lewinsohn et al.'s findings, scores ≥16 were indicative of risk of clinical depression.[35] We interpreted "risk" as level of depressive symptomology for our analyses

For self-reported PA levels, we considered responses of "Sedentary" and "Lightly Active" as (Near)-Sedentary, and "Moderately Active", "Very Active", and "Highly Active" as Active. This allowed us to divide the subject population into two categories of general PA levels/trends for direct comparisons. We also considered household chores to be non-exercise activity; while we did not discount the effects of household chores on activity levels, they are not necessarily equivalent to the intensity/rigor of aerobic or resistance activity that would fall under the "exercise" umbrella.

We compared the QoL and CES-D differences between the subgroups with significance testing (MiniTab). We reported 95% CI in addition to Hedge's g (corrected) for effect size. Hedge's *g* was selected over Cohen's d to account for different population numbers in subgroups. We reported the corrected value due to the upward bias observed in Hedge's g. We followed standard practice of reporting effect size: small effect size = <0.2; medium effect size = $0.2 \leq x \leq 0.5$; large effect size≥0.5.

VAS were studied in the context of multiple linear regression analysis to understand whether PN, sleep quality, and energy levels could be predictors for QoL or depressive symptomology.

4.0 Major Results

4.1 Subject demographic information

Patient Characteristics (n=50)		
Age	Mean±SD	63.4±14.37
	Range	56
Sex	M	36%
	F	64%
Social Support System	Spouse/Lifemate	16%
	Family	26%
	Friends	26%
	Parent/Step-parent	2%
	Pets	11%
	Children	14%
	Community Group	4%
	Siblings	1%
Cancer Stage	2	n=1
	3	n=8
	4	n=20
	Not Reported	n=21
Comorbidities	Arthritis	4%
	Diabetes	14%
	Eczema	1%
	Emphysema	1%
	Gorlin's Syndrome	1%
	Hernia	1%
	High Cholesterol	3%
	Hypertension	29%
	Hyperthyroidism	1%
	Kidney Dysfunction	3%
	Low Thyroxine	1%
	Lupus	1%
	Neuropathy	1%
	Overactive Bladder	1%
	Overweight	1%
	Sleep Apnea	3%
	None Reported	30%
Cancer Type	Amyloidosis	4%
	Anaplastic Thyroid	2%
	Blood	2%
	Brain	4%
	Breast	22%
	Cervical	4%
	Colon	4%
	Fallopian Tube	2%
	Gastric	2%
	Lung	8%
	Lymphoma	6%
	Melanoma	10%
	Squamous Cell	4%
	Multiple Myeloma	2%
	Neck/Throat	4%
	NH Lymphoma	4%
	Ovarian	6%
	Pancreatic	4%
	Prostate	2%
	Not Reported	6%

Table 2. Demographic information of all participants (n=50)

Demographic information of participants is shown in Table 2 above. Average age of respondents was 63.4±14.37 years old, with 36% male and 64% female respondents. Additionally, subject population

makeup of cancer stage, comorbidities, and cancer type are provided alongside described social support systems.

4.2 Self-reported QoL and Depression Scores of Subject Population

EORTC Score Summary for Entire Subject Population		
Scale	Mean±SD	Median
QoL	60.99±21.36	58.33
	0.00±0.00	
PF	73.93±21.73	80.00
RF	67.75±30.10	66.67
EF	77.84±21.30	83.33
CF	77.66±26.07	83.33
SF	61.70±29.47	66.67
	0.00±0.00	
FA	45.62±28.29	33.33
NV	9.93±15.80	0.00
PN	20.57±23.11	16.67
DY	20.57±27.41	0.00
SL	37.59±35.86	33.33
AP	21.28±29.83	0.00
CO	12.77±23.62	0.00
DI	12.06±18.94	0.00
FI	26.24±34.01	0.00

Table 3. EORTC QLQ-C30 data for entire patient sample, presented with mean±SD and median values for all subscales.

Table 3 displays the patient sample's QoL data. When compared to the reference values provided by the EORTC, this patient sample overall matches what would be expected in a larger-scale sample.[36] These data are also normally distributed based on Anderson-Darling test for normality, allowing for 2-sample t-testing.

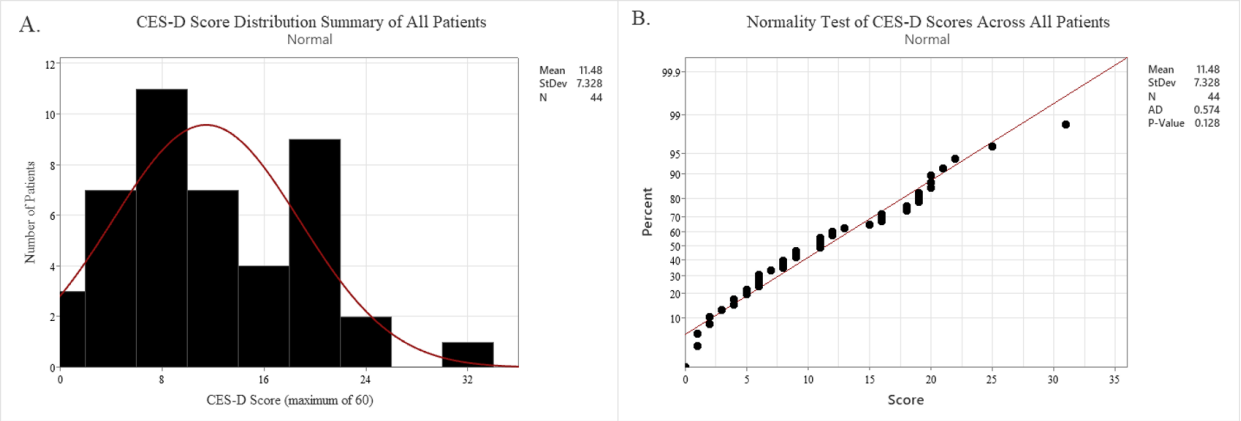


Figure 2. A: 20-item CES-D data for entire patient sample, with distribution fit displayed. **B:** Anderson-Darling normality test for CES-D score data for entire patient sample

Figure 2 displays the patient sample's self-reported CES-D scores. The average score of subjects was 11.48±7.328. The cutoff score for "clinically significant depression" as defined by the creators of CES-D is 16 points. A total of 70.5% of patient scores were not in the range for clinical depression, though all but one subject presented some level of depressive symptomology. A total of 29.5% patients' CES-D scores were in the range for clinically significant depression. Out of the 44 patients that responded

completely to the CES-D survey, a total of 13 had scores suggesting clinically significant depression. This data passes Anderson-Darling normality test (p=0.128), allowing for 2-sample t-testing (**Figure 3B)**.

4.3 PA trends for entire subject population

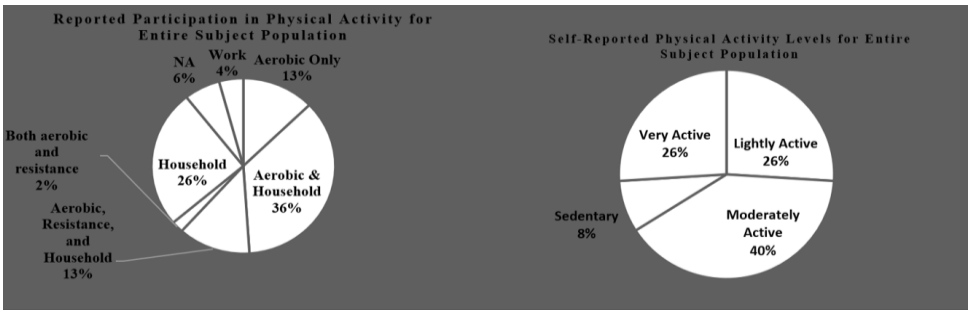


Figure 3. Physical activity intensity levels and types of all subjects, recorded through self-report/assessment.

A total of 34% of respondents fell under our definition of (Near)-Sedentary, while 66% fell under our definition of Active. A mixture of aerobic and household activity was most reported, with 36% of subjects participating. A total of 26% of subjects participated solely in Household Activity. 13% participated in aerobic, RT, and household activity, while another 13% only participated in aerobic activity. Some subjects, 4%, reported work as the entirety of their PA. As we had no way of classifying the work under aerobic or resistance activity specifically, we disregarded this factor from our analyses since it was a very minute portion of the entire subject sample anyways (**Figure 3)**.

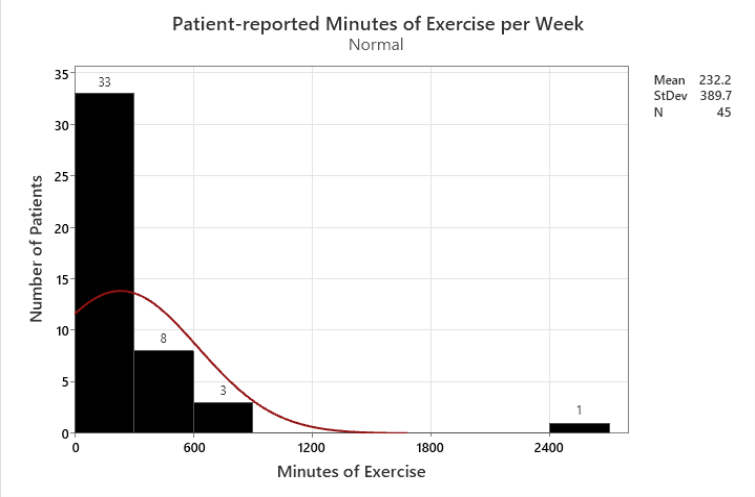


Figure 4. Minutes of exercise per week performed by all subjects across the data sample. Note that the bucket at 2400mins/week is an outlier and is removed from later analysis.

Average level of exercise (mins/week) was around 232.2±389.7 (95%CI: 115.09, 349.27). Most patients fell between 0 and 450 minutes of exercise/wk with one outlier falling at 2400mins of exercise/wk. This outlier was removed from further analysis. When this outlier was removed, average minutes of exercise/wk fell to 182.9±208.9 mins/wk (**Figure 4)**. This data is non-parametric, so we avoided including it in significance testing.

4.4 Comparison between (Near)-Sedentary and Active patients in regard to QoL and Depression Scores

A. Comparison of EORTC QLQ-C30 Scores between (Near)-Sedentary and Active Patients

	(Near)-Sedentary (n=17)		Active (n=30)		Significance		Effect Size
Scale	Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
QoL	47.06±22.43	50.00	68.89±16.37	66.67	<<**0.05**	(9.05, 34.61)	-1.145
PF	61.18±22.39	66.67	81.67±17.56	86.67	<<**0.05**	(7.43, 33.55)	-1.038
RF	54.90±32.15	50.00	75.29±26.59	83.33	<<**0.05**	(1.48, 39.29)	-0.699
EF	69.61±25.67	83.33	82.50±17.14	87.50	0.077	(-1.49, 27.28)	-0.616
CF	66.67±32.27	83.33	83.89±19.81	83.33	0.058	(-0.66, 35.11)	-0.678
SF	45.10±31.05	50.00	71.11±24.34	66.67	<<**0.05**	(8.07, 43.95)	-0.950
FA	61.44±29.69	55.56	36.65±23.53	33.33	<<**0.05**	(7.58, 41.99)	0.941
NV	12.75±18.19	0.00	8.33±14.35	0.00	0.397	(-14.94, 6.12)	0.274
PN	26.47±27.67	16.67	17.22±19.81	16.67	0.236		0.397
DY	37.25±35.12	33.33	11.11±15.98	0.00	<<**0.05**	(7.30, 44.99)	1.047
SL	43.14±40.42	33.33	34.44±33.31	33.33	0.457	(-24.95, 6.45)	0.237
AP	25.49±32.34	0.00	18.89±28.61	0.00	0.489	(-25.85, 12.64)	0.216
CO	17.65±29.15	0.00	10.00±19.87	0.00	0.345	(-24.05, 8.75)	0.319
DI	9.80±15.65	0.00	13.33±20.71	0.00	0.514	(-7.29, 14.35)	-0.182
FI	37.25±40.62	33.33	20.00±28.50	0.00	0.134	(-40.2, 5.7)	0.509

B. Comparison of Depression Scores Between Sedentary and Active Patients

Near-sedentary (n=16)		Active (n=28)		Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
13.475±7.30	11	10.357±6.70	8.5	0.212	(-8.03, 1.87)	0.454

Table 4. A: Comparison of EORTC QLQ-C30 scores (all subscales) between (near)-sedentary and active subjects, with associated significant values bolded, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores between (near)-sedentary and active subjects, with associated significance values, 95% CI, and effect size.

(Near)-sedentary subjects had significantly lower QoL compared to active subjects ($p<<0.05$) with a strong effect observed ($g=-1.145$). PF and RF were significantly elevated in active patients ($p<<0.05$), with strong effect in PF ($g=-1.038$) and moderate effect in RF ($g=-0.699$). SF was significantly elevated in active patients ($p<<0.05$) with a strong effect observed ($g=-0.950$). Regarding symptom sub-scales, FA and DY were significantly lower in active patients ($p<<0.05$) with strong effect observed in both **(Table 4A)**.

While active patients had lower average depression score as rated by CES-D, 10.357±6.7, neither group was in the clinically significant range for depression. There was a small-approaching-moderate effect size observed, with g=0.454 (**Table 4B**).

4.5 Trends among subjects with stages 3 and 4 cancer diagnoses

Summary of Stage 3 and Stage 4 Patient Subpopulation			
Stage 3 (n=9)		Stage 4 (n=20)	
Activity Level Split	Percentage	Activity Level Split	Percentage
Sedentary	11%	Sedentary	10%
Lightly Active	11%	Lightly Active	30%
Moderately Active	44%	Moderately Active	35%
Very Active	33%	Very Active	25%
PA Type	Participation	PA Type	Participation
Aerobic	78%	Aerobic	65%
Household	67%	Household	80%
Resistance	22%	Resistance	25%

Table 5. Summary of all PA trends between subjects that self-reported having Stage 3 and 4 cancer diagnoses.

In general, stage 3 and 4 cancer patients reported that they were moderately to very active, falling under the active subgroup. A higher percentage of patients with stage 4 cancer reported that they were lightly active in comparison to those with stage 3 cancer and were thus under the umbrella of (near)-sedentary. Aerobic activity and household chores were the most common types of PA for both stages, while RT only made up around a quarter of both stages **(Table 5)**.

A. Comparing (Near)-Sedentary vs. Active Stage 3 and 4 Cancer Patients' QoL							
	(Near)-Sedentary (n=9)		Active (n=18)		Significance		Effect Size
Scale	Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
QoL	50.93±23.36	50.00	68.98±13.65	66.67	0.058	(-36.83, 0.72)	-1.01
PF	57.04±25.63	53.33	84.44±17.41	86.67	<<**0.05**	(-48.27, -6.55)	-1.30
RF	51.85±33.79	50.00	74.07±25.06	66.67	0.106	(-49.9, 5.5)	-0.77
EF	78.70±17.73	83.33	83.33±16.42	87.50	0.522	(-19.69, 10.43)	-0.27
CF	72.22±31.18	83.33	82.41±19.36	83.33	0.389	(-35.2, 14.8)	-0.42
SF	51.85±28.19	50.00	70.37±24.63	66.67	0.116	(-42.2, 5.2)	-0.70
FA	61.74±29.44	55.56	35.19±19.88	33.33	**0.033**	(2.6, 50.5)	1.10
NV	12.96±18.21	0.00	9.26±13.06	0.00	0.596	(-11.13, 18.54)	0.24
PN	20.37±27.36	16.67	16.67±21.39	8.34	0.728	(-18.8, 26.2)	0.15
DY	25.93±36.43	0.00	12.96±16.72	0.00	0.336	(-15.9, 41.8)	0.51
SL	33.33±40.82	33.33	29.63±25.28	33.33	0.808	(-29.0, 36.4)	0.12
AP	29.63±38.89	0.00	20.37±28.33	0.00	0.537	(-22.5, 41.0)	0.28
CO	22.22±33.33	0.00	12.96±23.26	0.00	0.469	(-17.7, 36.3)	0.33
DI	3.70±11.11	0.00	20.37±23.26	16.67	**0.019**	(-30.32, -3.01)	-0.80
FI	25.92±32.39	33.33	22.22±30.25	0.00	0.779	(-23.9, 31.3)	0.12

B. Comparing Depression Scores of (Near)-Sedentary vs. Active Patients with Stages 3 and 4 Cancer						
(Near)-Sedentary (n=8)		Active (n=19)		Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
10.5±6.35	12.00	10.26±7.07	8.00	0.93	(-5.70, 6.18)	0.03

Table 6. A: Comparison of EORTC QLQ-C30 scores (all subscales) between (near)-sedentary and active subjects with Stage 3 or 4 cancer diagnoses, with associated significant values bolded, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores between (near)-sedentary and active patients with Stage 3 or 4 cancer diagnoses, with associated significance values, 95% CI, and effect size.

Active patients with Stage 3 or 4 cancer had higher QoL compared to (near)-sedentary patients, with a mean score of 68.98±13.65 compared to 50.93±23.36, though this finding was not significant (p=0.058); it should be noted, however, that there was a large effect size observed (g=-1.01). Active patients had significantly higher PF (p<<0.05) with a large observed effect size. There was a moderate effect size observed for RF (g=-0.77). FA was significantly lower in active patients (p=0.033) with a large effect (g=1.10). DI was significantly higher in active patients (p=0.019, g=-0.80) **(Table 6A)**.

There was no significant difference observed between the risk of clinical depression between (near)-sedentary and active patients with stage 3 or 4 cancer (p=0.93, g=0.03) **(Table 6B)**.

A. Comparing QoL of Subjects with Stages 3 and 4 Cancer Doing Aerobic-Only Exercise vs. Resistance Training

	Aerobic-Only (n=12)		Aerobic and Resistance (n=6)		Significance		Effect Size
Scale	Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
QoL	67.36±18.96	70.84	65.28±12.27	62.50	0.783	(-13.83, 17.99)	0.12
PF	84.45±16.41	86.67	84.44±15.01	83.33	1	(-17.25, 17.26)	0.00
RF	75.00±29.73	83.34	69.45±22.15	66.67	0.663	(-21.4, 32.5)	0.19
EF	86.11±11.96	87.50	69.45±17.21	70.84	0.071	(-1.85, 35.18)	1.15
CF	87.50±12.56	83.33	77.78±25.09	83.33	0.405	(-16.9, 36.3)	0.53
SF	73.61±27.02	75.00	61.11±25.09	66.67	0.355	(-16.2, 41.2)	0.45
FA	37.98±22.44	33.33	35.16±23.73	27.78	0.815	(-23.5, 29.2)	0.12
NV	11.11±12.97	8.34	11.11±13.61	8.34	1	(-15.6, 15.6)	0.00
PN	12.50±17.59	0.00	22.22±17.21	16.67	0.288	(-29.04, 9.59)	-0.53
DY	5.56±12.97	0.00	22.22±17.21	33.33	0.075	(-35.49, 2.16)	-1.10
SL	22.22±16.41	33.33	44.44±34.43	33.33	0.185	(-58.5, 14.1)	-0.90
AP	25.00±32.18	16.67	33.33±36.51	33.33	0.647	(-48.1, 31.4)	-0.24
CO	22.22±32.82	0.00	16.67±27.89	0.00	0.715	(-27.0, 38.2)	0.17
DI	19.44±22.28	16.67	16.67±27.89	0.00	0.837	(-27.4, 32.9)	0.11
FI	22.22±32.82	0.00	11.11±17.21	0.00	0.361	(-14.0, 36.3)	0.37

B. Comparing Depression Scores of Patient with Stages 3 and 4 Cancer Doing in Aerobic-Only Exercise vs. Resistance Training

Aerobic-Only (n=12)		Aerobic and Resistance (n=7)		Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
9.17±6.97	7.50	13.43±6.90	16.00	0.22	(-11.44, 2.91)	-0.586

Table 7. A: Comparison of EORTC QLQ-C30 scores (all subscales) of subjects with Stage 3 or 4 cancer diagnoses who participated in only aerobic exercise or aerobic & resistance exercise, with associated significance values, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores of subjects with Stage 3 or 4 cancer diagnoses who participated in only aerobic exercise or aerobic & resistance exercise, with associated significance values, 95% CI, and effect size.

Regarding aerobic-only participation vs participation in both aerobic exercise and RT (A+RT), there were no significant differences between the two populations across any subscale. Large effect was observed for the difference in EF (g=1.15), DY (g=-1.10) and SL (g=-0.90) (**Table 7A)**.

There were no significant differences on CES-D scores observed between aerobic-only and A+RT PA participation in this subpopulation. A moderate effect was observed for the differences between the two groups (g=-0.586). A+RT patients had slightly elevated average scores on CES-D (13.43±6.90 for A+RT compared to 9.17±6.97) **(Table 7B)**.

A binomial regression was conducted to investigate if cancer stage could be a predictor of activity levels in this population. Cancer stage is *not* a predictor of activity level between stages 3 and 4 (p=0.282).

4.6 Comparing Aerobic-only vs combined Aerobic & RT participation in all patients

A. Comparing QoL Scores of All Patients Doing Aerobic-Only Exercise vs. Resistance Training

	Aerobic and Resistance (n=7)		Aerobic-Only (n=23)		Significance		Effect Size
Scale	Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
QoL	65.48±11.21	66.67	61.96±23.55	58.33	0.593	(-9.93, 16.97)	0.159
PF	81.90±15.26	73.33	77.58±18.81	80.00	0.549	(-10.97, 19.63)	0.233
RF	73.81±23.29	66.67	69.57±29.15	66.67	0.698	(-19.1, 27.6)	0.148
EF	73.81±19.50	75.00	77.17±22.78	83.33	0.709	(-22.66, 15.94)	-0.148
CF	80.95±24.40	83.33	79.71±24.08	83.33	0.908	(-22.5, 25.0)	0.050
SF	59.52±23.29	66.67	66.67±31.78	66.67	0.528	(-30.9, 16.7)	-0.230
FA	36.47±21.94	0.00	47.34±29.42	33.33	0.311	(-33.2, 11.4)	-0.378
NV	9.52±13.11	0.00	13.04±17.38	0.00	0.576	(-16.78, 9.74)	-0.207
PN	23.81±16.26	16.67	21.01±23.69	16.67	0.728	(-14.12, 19.71)	0.122
DY	19.05±17.82	33.33	18.84±28.12	0.00	0.982	(-18.72, 19.13)	0.008
SL	47.62±32.53	33.33	39.13±32.80	33.33	0.56	(-22.9, 39.8)	0.252
AP	28.57±35.63	33.33	26.09±31.71	33.33	0.872	(-31.5, 36.4)	0.074
CO	14.29±26.23	0.00	18.84±28.12	0.00	0.701	(-30.2, 21.1)	-0.160
DI	14.29±26.23	0.00	15.94±19.77	0.00	0.881	(-26.4, 23.1)	-0.076
FI	9.52±16.26	0.00	30.43±38.81	0.00	0.051	(-41.9, 0.1)	-0.578

B. Comparison of Depression Scores of Patients Doing Aerobic-Only Exercise vs. Resistance Training

Aerobic-Only (n=22)		Aerobic and Resistance (n=8)		Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
12.09±7.82	11.00	12.25±7.21	13.50	0.959	(-6.74, 6.42)	-0.020

Table 8. A: Comparison of EORTC QLQ-C30 scores (all subscales) between all subjects who participated in only aerobic exercise or aerobic & resistance exercise, with associated significance values, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores of subjects who participated in only aerobic exercise or aerobic & resistance exercise, with associated significance values, 95% CI, and effect size.

There were no significant differences or notable effect sizes between subjects participating in only aerobic exercise and subjects including both aerobic and resistance exercise. A moderate effect size

was observed for FI differences (g=-0.578) **(Table 8A).** There was no significant difference between aerobic-only and A+RT PA participation regarding CES-D scoring. No effect was observed between the group differences (g=-0.020) **(Table 8B).**

4.7 Comparisons of males vs. females across the subject population

A. Comparing QoL Scores of Active Males vs. (Near)-Sedentary Males

	Active Males (n=10)		(Near)-Sedentary Males (n=6)		Significance		Effect Size
Scale	Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
QoL	63.33±12.55	62.50	61.11±22.15	50.00	0.829	(-21.94, 26.39)	0.126
PF	81.33±24.91	90.00	71.11±27.22	80.00	0.472	(-20.6, 41.0)	0.375
RF	65.00±31.87	58.34	63.89±35.62	75.00	0.951	(-38.9, 41.1)	0.032
EF	82.50±19.82	87.50	90.28±9.74	91.67	0.314	(-23.81, 8.26)	-0.435
CF	86.67±17.21	91.67	66.67±33.33	83.33	0.221	(-15.9, 55.9)	0.780
SF	63.33±20.49	66.67	50.00±39.44	66.67	0.471	(-29.1, 55.8)	0.439
FA	41.10±28.22	33.33	40.74±24.00	33.33	0.979	(-28.5, 29.2)	0.013
NV	10.00±14.05	0.00	2.78±6.81	0.00	0.191	(-4.10, 18.54)	0.570
PN	11.67±22.29	0.00	8.34±9.13	8.34	0.683	(-14.04, 20.71)	0.169
DY	13.33±17.21	0.00	22.22±27.22	16.67	0.496	(-38.1, 20.4)	-0.394
SL	26.67±34.43	16.67	22.22±27.22	16.67	0.780	(-29.4, 38.3)	0.131
AP	20.00±32.20	0.00	5.56±13.61	0.00	0.235	(-10.6, 39.5)	0.504
CO	16.67±28.33	0.00	5.56±13.61	0.00	0.311	(-11.7, 33.9)	0.435
DI	20.00±23.31	16.67	5.56±13.61	0.00	0.142	(-5.49, 34.38)	0.670
FI	33.33±35.14	33.33	22.22±27.22	16.67	0.493	(-23.1, 45.3)	0.323

B. Comparison of Depression Scores of Active Males vs. (Near)-Sedentary Males

Active Males (n=10)		(Near)-Sedentary Males (n=7)		Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
8.20±5.65	7.50	10.57±7.04	7.04	0.475	(-9.43, 4.69)	-0.360

Table 9. A: Comparison of EORTC QLQ-C30 scores (all subscales) between active and (near)-sedentary males with associated significance values, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores between active and (near)-sedentary males, with associated significance values, 95% CI, and effect size.

A moderate-approaching-strong effect was observed for the differences in CF between active males and (near)-sedentary males (g=0.780). Active males had lower DY than sedentary, but (near)-sedentary males had lower scores in every other subscale. None of these findings were significant. Moderate effects were observed for differences in NV (g=0.570), AP (g=0.504), and DI (g=0.670) **(Table 9A).**While active males had a lower average CES-D score of 8.20±5.65 compared to the (near)-sedentary male population average of 10.57±7.04, these findings were not significant (p=0.475) **(Table 9B).**

A. Comparing QoL Scores of Active Females vs (Near)-Sedentary Females							
	Active Females (n=17)		(Near)-Sedentary Females (n=11)		Significance		Effect Size
Scale	Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
QoL	72.55±15.80	75.00	41.67±19.40	41.67	**<<0.05**	(15.88, 46.07)	1.736
PF	66.67±13.02	80.00	53.33±18.44	53.33	**<<0.05**	(12.25, 39.37)	0.844
RF	81.37±23.48	100.00	50.00±30.73	50.00	**<<0.05**	(8.4, 54.3)	1.149
EF	84.31±15.83	91.67	66.67±24.72	66.67	**<<0.05**	(8.11, 43.85)	0.868
CF	86.27±18.85	100.00	83.33±33.33	83.33	0.097	(-4.1, 43.3)	0.112
SF	74.51±26.43	83.33	50.00±27.25	50.00	**<<0.05**	(10.4, 53.8)	0.890
FA	32.02±21.44	33.33	66.67±26.92	66.67	**<<0.05**	(-60.96, -20.46)	-1.420
NV	5.88±11.70	0.00	16.67±20.35	16.67	0.090	(-26.80, 2.20)	-0.671
PN	17.65±18.13	16.67	33.33±29.64	33.33	0.081	(-40.08, 2.65)	-0.655
DY	11.76±16.42	0.00	33.33±37.34	33.33	**<<0.05**	(-59.7, -7.7)	-0.790
SL	37.25±30.92	33.33	66.67±42.88	66.67	0.264	(-49.0, 14.4)	-0.794
AP	17.65±29.15	0.00	33.33±34.82	33.33	0.156	(-45.3, 7.9)	-0.484
CO	5.88±13.10	0.00	0.00±33.64	0.00	0.112	(-41.8, 5.0)	0.246
DI	11.76±20.21	0.00	0.00±16.82	0.00	0.960	(-14.91, 14.20)	0.602
FI	13.73±23.74	0.00	33.33±45.39	33.33	0.052	(-63.8, 0.4)	-0.564

B. Comparison of Depression Scores of Active Females vs. (Near)-Sedentary Females						
Active Females (n=17)		(Near)-Sedentary Females (n=10)		Test for Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
11.06±6.93	11.00	15.70±8.22	16.50	0.153	(-11.20, 1.92)	-0.606

Table 10. A. Comparison of EORTC QLQ-C30 scores (all subscales) between active and (near)-sedentary females with associated significance values, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores between active and (near)-sedentary females, with associated significance values, 95% CI, and effect size.

Active females had significantly higher QoL, PF, RF, EF, and SF than (near)-sedentary females (for all metrics, $p<<0.05$). Strong effect sizes were observed for QoL ($g=1.736$), PF ($g=0.844$), RF ($g=1.149$), EF ($g=0.868$), and SF ($g=0.890$). While active females had higher CF as well, this was not significant ($p=0.097$), and there was no effect observed ($g=0.112$).

Regarding symptom subscales, active females had significantly lower FA and DY (for both, $p<<0.05$), with strong effect size observed for FA ($g=-1.420$) and moderate effect size for DY ($g=-0.790$). Active females had non-significant, but lower, NV ($g=-0.671$), PN ($g=-0.655$), SL ($g=-0.790$), AP ($g=-0.484$), and FI ($g=-0.564$). (Near)-sedentary females had lower DI with moderate effect size ($g=0.602$) (**Table 9A).**

Active females had lower CES-D scores than (near)-sedentary females, though this was not significant ($p=0.153$). However, a moderate effect was observed ($g=-0.606$) **(Table 9B)**.

A. Comparing QoL Scores of Active Males vs. Active Females							
	Active Males (n=10)		Active Females (n=17)		Significance		Effect Size
Scale	Mean±SD	Median	Mean	Median	p-value	95% CI	Hedge's g (corrected)
QoL	63.33±12.55	62.50	72.55±15.80	75.00	0.109	(-20.66, 2.22)	-0.607
PF	81.33±24.91	90.00	66.67±13.02	80.00	0.978	(-18.91, 18.44)	0.781
RF	65.00±31.87	58.34	81.37±23.48	100.00	0.179	(-41.2, 8.5)	-0.592
EF	82.50±19.82	87.50	84.31±15.83	91.67	0.808	(-17.48, 13.85)	-0.101
CF	86.67±17.21	91.67	86.27±18.85	100.00	0.957	(-14.44, 15.22)	0.021
SF	63.33±20.49	66.67	74.51±26.43	83.33	0.233	(-30.08, 7.73)	-0.443
FA	41.10±28.22	33.33	32.02±21.44	33.33	0.393	(-12.9, 31.1)	0.365
NV	10.00±14.05	0.00	5.88±11.70	0.00	0.446	(-7.06, 15.29)	0.317
PN	11.67±22.29	0.00	17.65±18.13	16.67	0.482	(-23.59, 11.63)	-0.294
DY	13.33±17.21	0.00	11.76±16.42	0.00	0.819	(-12.60, 15.74)	0.091
SL	26.67±34.43	16.67	37.25±30.92	33.33	0.434	(-38.5, 17.3)	-0.319
AP	20.00±32.20	0.00	17.65±29.15	0.00	0.852	(-23.8, 28.5)	0.075
CO	16.67±28.33	0.00	5.88±13.10	0.00	0.281	(-10.13, 31.71)	0.524
DI	20.00±23.31	16.67	11.76±20.21	0.00	0.366	(-10.53, 27.00)	0.374
FI	33.33±35.14	33.33	13.73±23.74	0.00	0.141	(-7.4, 46.6)	0.670

B. Comparison of Depression Scores of Active Males vs. Active Females						
Active Males (n=10)		Active Females (n=17)		Test for Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
8.20±5.65	7.50	11.06±6.93	11.00	0.257	(-7.95, 2.23)	-0.426

Table 11. A: Comparison of EORTC QLQ-C30 scores (all subscales) between active males and females with associated significance values, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores between active males and females, with associated significance values, 95% CI, and effect size.

Active females had higher, though insignificant, QoL overall than active males (g=-0.607). There were no significant differences between active males and active females on any subscale, nor were there any large effect sizes of note **(Table 11A)**.

Active males had slightly lower CES-D scores than active females, but this was not significant (p=0.257, g=-0.426) **(Table 11B)**.

A. Comparing QoL Scores of (Near)-Sedentary Males vs. (Near)-Sedentary Females							
	(Near)-Sedentary Males (n=6)		(Near)-Sedentary Females (n=11)		Significance		Effect Size
	Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
QoL	61.11±22.15	50.00	41.67±19.40	41.67	0.075	(-26., 46.1)	0.906
PF	71.11±27.22	80.00	53.33±18.44	53.33	0.256	(-14.0, 44.7)	0.775
RF	63.89±35.62	75.00	50.00±30.73	50.00	0.441	(-25.1, 52.9)	0.406
EF	90.28±9.74	91.67	66.67±24.72	66.67	**<<0.05**	(13.83, 50.06)	1.069
CF	66.67±33.33	83.33	83.33±33.33	83.33	1.000	(-37.7, 37.7)	-0.475
SF	50.00±39.44	66.67	50.00±27.25	50.00	0.688	(-35.2, 50.3)	0.000
FA	40.74±24.00	33.33	66.67±26.92	66.67	0.029	(-60.0, -4.0)	-0.947
NV	2.78±6.81	0.00	16.67±20.35	16.67	0.040	(-29.95, -0.85)	-0.772
PN	8.34±9.13	8.34	33.33±29.64	33.33	0.013	(-49.13, -6.93)	-0.958
DY	22.22±27.22	16.67	33.33±37.34	33.33	0.166	(-57.4, 10.9)	-0.307
SL	22.22±27.22	16.67	66.67±42.88	66.67	0.079	(-68.9, 4.2)	-1.099
AP	5.56±13.61	0.00	33.33±34.82	33.33	0.021	(-56.3-5.3)	-0.894
CO	5.56±13.61	0.00	0.00±33.64	0.00	0.128	(-43.5, 6.1)	0.185
DI	5.56±13.61	0.00	0.00±16.82	0.00	0.400	(-22.95, 9.82)	0.333
FI	22.22±27.22	16.67	33.33±45.39	33.33	0.209	(-61.0, 14.6)	-0.262

B. Comparison of Depression Scores of (Near)-Sedentary Males vs. (Near)-Sedentary Females						
(Near)-Sedentary Males (n=7)		(Near)-Sedentary Females (n=10)		Significance		Effect Size
Mean±SD	Median	Mean±SD	Median	p-value	95% CI	Hedge's g (corrected)
10.57±7.04	7.04	15.70±8.22	16.50	0.19	(-13.11, 2.85)	-0.626

Table 12. A: Comparison of EORTC QLQ-C30 scores (all subscales) between (near)-sedentary males and females with associated significance values, 95% CI, and effect size. **B:** Comparison of 20-item CES-D scores between (near)-sedentary males and females, with associated significance values, 95% CI, and effect size.

(Near)-sedentary males significantly higher EF than (near)-sedentary females ($p<<0.05$, $g=1.069$). (Near)-sedentary males had significantly lower FA ($p=0.029$, $g=-0.947$) than (near)-sedentary females. They also had significantly lower NV ($p=0.040$, $g=-0.772$), PN (0.013, $g=-0.958$), and AP ($p=0.021$, $g=-0.894$). While SL differences were not significant, (near)-sedentary males had lower SL than (near)-sedentary females, with effect size $g=-1.099$ indicating a strong effect **(Table 12A)**. Though differences in CES-D scores between (near)-sedentary males and (near)-sedentary females were not significant, on average it seemed that (near)-sedentary males had lower CES-D scores, with a moderate effect size observed of $g=-0.626$ **(Table 12B)**.

4.8 Univariate and multiple linear regression analysis and regression results

Self-reported Activity Level (Classified As (Near)-Sedentary and Active)		
	Univariate Model	Multivariate Model
	p-value	p-value
QoL	**0.0006**	0.3592
CES-D	0.2218	0.6825

Table 13. Self-reported Activity Levels (subgroups: (near)-sedentary and active) and associated p-values in univariate and multiple linear models, with significant values highlighted. Multiple linear regression independent variables: level of PA, type of PA (aerobic, RT, non-exercise activity, or combinations), gender, minutes of exercise per week, hypertension (HTN), diabetes, pet ownership, cancer stage, energy levels, sleep quality, and PN levels.

We conducted a multiple linear regression to understand how QoL can be predicted by level of PA, type of PA (be it aerobic, RT, non-exercise household chores, or a combination of these 3 variables), gender (M or F), minutes of exercise per week, two major comorbidities: hypertension (HTN) and diabetes, pet ownership, cancer stage, energy levels, sleep quality, and PN levels. Analysis showed that when controlling for all other variables in the regression, none were significant predictors ($p>0.5$). This model was also not a good predictor of QoL ($p=0.455$). In univariate analysis (Wilcoxon two-sample test) solely looking at QoL scores of (near)-sedentary and active patients, self-reported activity level was a significant predictor of QoL ($p=0.0006$). In multiple linear regression analysis, self-reported activity level was not a significant predictor of QoL ($p=0.3592$) **(Table 13)**.

We employed the same analytical model with the same independent variables, instead looking at depressive symptomology as the dependent variable of interest. Again, none of the independent variables were significant predictors of depressive symptomology. This model was not a good predictor of depressive symptomology (p=0.6926). In univariate analysis (Wilcoxon two-sample test) solely looking at CES-D scores of (near)-sedentary and active patients, self-reported activity level was not a significant predictor of depressive symptomology (p=0.2218). In multiple linear regression analysis, self-reported activity level was not a significant predictor of depressive symptomology (p=0.6825) **(Table 13)**.

4.9 Effects of minutes of exercise/wk on QoL and depressive symptomology

We categorized minutes of exercise weekly into two distinct categories, to account for the skew in the variable: <150mins/weekly and ≥150mins/weekly. Linear regression results displayed minutes of exercise per week to not be a good predictor for neither QoL nor depressive symptomology.

5.0 Discussion

The primary aim of the study was to understand patterns of PA in chemotherapy and immunotherapy patients, specifically to investigate associations between certain training variables and overall QoL and CES-D depressive symptomology.

5.1 QoL Findings

PA participation in the chemotherapy & immunotherapy-recipient population generally correlated with increased QoL, with some marked increases in functional scales such as PF, RF, and SF that were both significant and moderate to large in effect size. EF and CF in the active subpopulation were also higher than in the (near)-sedentary population, with moderate effect size suggesting that increased participation in PA during treatment potentially contributes to overall increase in QoL and functional scales. Additionally, FA and DY were significantly lower in the active population compared to the (near)-sedentary population. While other symptom subscales were not significantly higher in the active population, every metric besides DI (which had no observable effect size) was on average lower in the active population, with each metric having small to moderate effect sizes. These findings, in general, correspond with prior literature surrounding PA during cancer treatment which found that increased PA corresponded with increased QoL, increases in every EORTC QLQ-C30 functional scale, and decreases in every symptom subscale besides DI.[37] It should be noted that literature has not found significant causal effect between FI and PA trends in the general population; there is no real basis to consider differences in FI as associated with, or contributed to by PA behaviors. Thus, this symptom subscale specifically can be mostly disregarded in the context of this investigation.

Active patients with stage 3 or 4 cancer diagnoses had non-significant but very large effect in improvement of overall QoL compared to (near)-sedentary patients. Additionally, active patients had significantly higher PF with large effect, and non-significant improvements in RF, EF, CF, and SF (with moderate effect sizes for all scales). Further, active patients had significantly lower FA, with large effect. Interestingly, DI was significantly higher in active patients ($p=0.019$, $g=-0.80$); this, however, might be contributed to by the presence of a higher number of stage 4 patients in the active subgroup. More intense treatment cycles in stage 4 patients may contribute to increased incidence of GI distress regardless of PA levels. DY was lower in active patients than (near)-sedentary patients and while this was not significant, there was moderate effect observed. The finding of lower DY in active patients on average compared to (near)-sedentary patients is consistent with prior research that suggests exercise therapy as a possibility in managing and limiting dyspnea in patients with lung cancer.[38] One key issue in this area of investigation is high dropout rates and large levels of reluctance in participants to enroll in PA-based studies, so further research is warranted before making concrete claims that increased levels of PA can help with managing DY.

Subjects participating in A+RT had higher QoL, PF, RF, and CF compared to aerobic-only subjects. Aerobic-only subjects had higher EF and SF. This follows some prior work that suggested that participation in exercise during cancer treatment has the best associations with increased HRQoL when exercise programs include both aerobic and resistance exercise. However, none of our findings in this subpopulation were significant, and small effects were only observed in PF and SF differences. These findings warrant more research to be done in larger populations to see if increases in QoL and functional scales are significantly associated with involvement in both aerobic and resistance exercise as opposed to solely aerobic movement. Subjects participating in A+RT had lower, but non-significant, FA, NV, CO, DI, and FI, whereas aerobic-only subjects had non-significant but lower PN, DY, SL, and AP. While some small to moderate effect sizes were observed, more research is needed to come to a specific conclusion on associations between aerobic-only training and A+RT in this subject population.

When considering gender differences, active males had overall lower QoL than active females, though it was not a significant difference. Moderate effects were observed, though. Activity in males was associated with higher, but non-significant, PF ($g=0.781$). Active females had higher, but non-significant, RF, EF, and SF. There were no significant differences in symptom subscales. The literature generally supports that males with cancer undergoing treatment have higher HRQoL than females undergoing treatment, so it is possible that the observations in this regard simply mirror prior findings.[39]

5.2 CES-D Findings

Though no significance was found for associations between CES-D scores and activity levels, a moderate effect size of g=0.454 was observed, potentially indicating that increased activity levels may have some association with decreased CES-D scores. Prior literature has found that increased exercise activity levels, especially aerobic exercise, can have moderate-to-large significant effect on reduction of depressive symptomology.[29] However, the literature concludes that resistance exercise alone is not sufficient in reducing depressive symptomology, generally with lone RT having small significant effects. In fact, prior work suggests that aerobic exercise alone is more effective at reducing depressive symptomology than A+RT. Interestingly, our data runs contrary to this conclusion; rather, we found there to be *no* significant effect between aerobic-only exercise and A+RT in the general subject population (p=0.959, g=-0.020) in relation to association with lower CES-D scores. However, we *did* observe there to be a moderate, yet not statistically significant (p=0.22, g=-0.614), effect between aerobic-only and A+RT subjects with Stages 3 and 4 cancer diagnoses. In this subpopulation, aerobic-only exercise was associated with CES-D scores of 9.17±6.97 while A+RT was associated with scores of 13.43±6.90.

Active males had lower, but non-significant, CES-D scores than active females, with moderate effect observed. Additionally, (near)-sedentary males had lower, but insignificant, CES-D scores than (near)-sedentary females, with moderate effect observed. This might be accounted for by prior work that found higher prevalence of depression and depressive symptomology in women than men; in women with breast cancer, depressive symptomology is commonly observed in women with breast cancer especially due to factors like treatment-related distress, altered body image, sexuality, and attractiveness.[15,40–42] Ultimately, however, it seems that activity levels did not have significant associations with differences in CES-D scores between active and (near)-sedentary males and active and (near)-sedentary females. Other factors may be more important in explaining these CES-D differences.

5.3 PA trends in subject population

PA trends in the subject population leaned towards more participation in aerobic activity compared to RT. This is to be expected given the traditional view of RT being “dangerous” by clinicians, a view that could potentially carry over to patients receiving treatment as well. Household non-exercise activity was very common, as is to be expected, but it is still encouraging to note that many patients reported at least some type of daily PA even if it was not exercise-based. Research has shown that even non-exercise activities such as household chores that involve some type of movement rather than a day consisting of solely horizontal-sedentary positioning can have significant health benefits, as is already understood in the literature.

Average time spent exercising (mins/wk) across the subject population was 182.9±208.9, which falls under CDC guidelines of 150 minutes of moderate intensity aerobic PA or 75 minutes of vigorous PA per week; however, there are a few limitations to this finding. Primarily, we do not know what the exact breakdown of exercise minutes per week is, so there could be any combination of intensities, types of PA, etc. Additionally, this data has large variation between values and large skew, so more research should be done on adherence to CDC guidelines during treatment cycles for patients receiving chemotherapy and immunotherapy for cancer.

The literature supports inclusion of both types of activity in the daily lifestyle of a cancer patient receiving treatment. Pain and insomnia are reported to be improved by aerobic, but not resistance, activity while other studies support that inclusion of RT (especially in association with high-intensity training styles) is associated with the greatest increases in HRQoL.[22,43] Some researchers suggest that inclusion of resistance-based strength training is critical in improvement of muscle function, reduced sarcopenia risk, reduced mortality risk, reduction in dynapenia, and reduced treatment toxicity, providing some reasoning for potentially working towards increasing participation in RT and aerobic activity in the patient population.[44–46]

5.4 Minutes of exercise/week

The CDC recommends that individuals with chronic conditions should receive at least 150 minutes a week of moderate-intensity aerobic PA, and at least two days should involve muscle-strengthening RT to improve general QoL as it relates to sleep quality, mental health, risk of other disease development, and pain.[47] We found that participants receiving more than 150 mins of exercise per week did not have significantly higher scores in QoL and depressive symptomology compared to those receiving less than 150 minutes a week, when controlling for all other variables. One potential explanation of this result is that our study did not account for session durations of exercise daily. One prior study found that depressive symptoms were only reduced when session durations were greater than 30 minutes each in cancer survivors.[48] Patsou et al. interestingly found that more than 135 mins exercise/week yielded no effect on depressive symptomology, while less than 135 mins/week yielded moderate to large effect in breast cancer survivors.[49] While both of these studies only account for survivors rather than current cancer patients, and only address depressive symptomology, it is possible that there may be carryover to this investigation's subject population. Another meta-analysis on high-intensity exercise training in cancer survivors found that the greatest PF improvements came about as a result of greater than 120mins/week, while fatigue improved in both less than and greater than 120mins/week.[22] It seems that research is lacking in addressing current cancer patients' depressive

symptomology and QoL as it relates to minutes of exercise weekly, and there is a lot of conflicting data. Future works should account for session duration as a variable to address this gap in the literature.

5.5 Regressions and univariate analyses

Our regression analysis found that self-reported level of PA was only a significant variable in predicting QoL but not depressive symptomology in univariate analysis. It is possible that this factor is only significant in the context of QoL (but not depressive symptomology) *because of* its association with other factors in the analysis; this is one potential explanation for our findings. Other confounding variables may be critical in working in conjunction with PA level in affecting QoL and depressive symptomology. It should be noted that while not significant, lower self-reported PA did correspond with increased depressive symptomology. In general, it seems that increased PA corresponds with increased QoL and decreased depressive symptomology.

Prior work found that following a 6-week exercise program, older patients (>50 years old) had better mental health, lower anxiety, and better mood; exercise also notably improves general health, physical functioning and fitness, QoL, and increases life expectancy.[50,51] While we ourselves did not find all of these significant associations in our investigation, there are a few potential reasons for this that we will delve into.

5.6 Strengths and limitations of the study

One strength of this study is that it is a novel look at the use of EORTC, an already well-validated and accepted tool, in understanding PA trends and associations in the chemotherapy- and immunotherapy-recipient population. Additionally, the large variety of cancer diagnoses allows for a greater breadth of data that is not specifically limited to breast and prostate cancer patients (which is a common hurdle in this type of research that must be overcome). While not enough patients responded to study associations between cancer types, it opens the possibility for further research to look at variations in the investigated associations between different cancer diagnoses.

However, there are some limitations to this study. One significant limitation is lack of power associated with the small study size in this investigation. Chiefly, the small sample size of n=50, and even smaller subgroups that sometimes fell to just n=6, is not enough to adequately understand associations between PA behaviors and QoL and depressive symptomology. One potential reason that many insignificant associations were found despite small or moderate effect sizes being observed could be simply because there were not enough data points to find significance. This investigation should be used by other researchers as a starting point for a larger-scale study that is more adequately powered.

Additionally, QoL is obviously highly multifactorial. For example, the large variety of medications that patients were likely taking from anti-nausea to blood thinners could also impact QoL in ways that we couldn't analyze in the given timeframe. Furthermore, we were unable to separate chemotherapy vs immunotherapy patients to understand if there is variation in QoL and CES-D that is associated with different behaviors in PA, limiting some extra complexity in the investigation. Future research should clarify different intervention modalities such as frequency, intensity, dose-response, at-home v. at-fitness-center, supervised v. unsupervised, and time spent exercising in a given session. Future work should also be directed towards identifying relationships between chemotherapy vs. immunotherapy QoL and CES-D outcomes in relation to PA. These variables may be crucial in understanding how exercise behaviors can variably be associated with improvement or worsening of QoL and depressive symptomology. Further work should look to identify causal physiological mechanisms on which various exercise behaviors act in this patient population to understand why or why not exercise and physical activity affects QoL and depressive symptomology.

UConn Health, the institution at which this study was conducted, predominantly caters to individuals with insurance. Uninsured populations may face significantly lower QoL, and increased rates of depression compared to insured populations, especially when considering chronic conditions.[52] This confounding variable was not accounted for in the original study design, and should be considered as an important variable in future work. Additionally, the study design did not consider ethnicity, which is a well-established confounding variable in this area of research, with marginalized populations have largely different and traditionally poorer, outcomes in healthcare and cancer research. Future work should look to quantify disparities in cancer patients' PA levels and how they correspond with HRQoL and general health status.

6.0 Conclusions

This preliminary investigation on patterns of PA in chemotherapy and immunotherapy recipients identified increased QoL and decreased CES-D scores in patients who were more physically active than their less-active counterparts. This supports our hypothesis that greater levels of PA correlate with overall greater levels of QoL and lower depressive symptomatology. In general, active subjects had lower levels of FA, PN, and SL. While some of these findings were significant and/or had moderate to large effect sizes, the findings in general line up with previous research.

Additionally, we found that patients participating in both aerobic and resistance exercise had overall higher QoL compared to patients only participating in aerobic exercise, suggesting that there might be associations between A+RT training and improved QoL and CES-D outcomes. More work

should be done to further study these findings, and to better understand how functional and symptom subscales are associated with A+RT vs aerobic exercise in larger populations. Future research should be directed in identifying associations between other training modalities such as dose-response and intensity and QoL and CES-D. Future studies should also focus on separating chemotherapy and immunotherapy patient populations to investigate differences between the two treatment-types and PA trends.

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