

2025

Exercise and cardiorespiratory fitness in black men with prostate cancer receiving androgen deprivation therapy

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ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**EXERCISE AND CARDIORESPIRATORY FITNESS IN BLACK MEN WITH
PROSTATE CANCER RECEIVING ANDROGEN DEPRIVATION THERAPY**

by

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B.S., Boston University, 2023

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2025

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ACKNOWLEDGEMENTS

Completing this paper would not have been possible without help from many people. Thank you to my two mentors and readers, Dr. Christina Dieli-Conwright and Dr. Dustin Allen for their invaluable suggestions and feedback throughout this process. Thank you to everyone in the Dieli-Conwright Lab at Dana-Farber Cancer Institute for their constant feedback and professional advice that helped me create a thorough and complete paper - especially Rebekah Wilson, Hajime Uno, and Brett Ranieri. Lastly, thank you to all my family and friends who gave me endless encouragement and motivation to keep pushing through the long days and nights of crunching numbers and writing rough drafts.

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ABSTRACT

Background

Black men are more frequently diagnosed with prostate cancer (PCa), and often more aggressive forms, than their White counterparts. Androgen deprivation therapy (ADT) has become a first-line treatment despite some detriments including a higher risk of all-cause mortality and increased risk for cardiovascular disease (CVD).

Cardiorespiratory fitness is strongly associated with the risk of CVD and all-cause mortality and is a strong predictor of longevity.

Research Question

What is the impact of a 16-week virtually supervised combined resistance and aerobic exercise intervention on cardiorespiratory fitness among Black men with PCa on ADT?

Methods

This single-center randomized controlled trial included 25 Black men with PCa who were receiving ADT. Participants were randomized 1:1 to the exercise group (n=12) or the control group (n=13). The exercise intervention involved tri-weekly sessions virtually supervised by a certified exercise trainer. Each session lasted approximately one hour and consisted of high-intensity interval training (HIIT) and resistance exercises. The HIIT intervention consisted of (1) warm-up (five minutes at 50% VO_{2peak}), (2) alternating

a high-intensity exercise phase (one minute at 75-95% of VO_{2peak}) and a recovery phase (one minute at 40% of VO_{2peak}) repeating 10 times (20 minutes in total), and (3) cool-down (five minutes at 30% VO_{2peak}). Resistance exercises consisted of two groups completed on alternating days (i.e., odd sessions = group one exercises, even sessions = group two exercises). Each group of resistance exercises was comprised of five exercises targeting upper and lower body muscle groups. Each exercise was performed for 2-3 sets of 15-20 repetitions at 60-75% of 1-repetition max (1-RM) measured at a pre-intervention visit. Participants randomized to the control group were asked to maintain their normal exercise habits. Cardiorespiratory fitness was assessed by four different measures (i.e., relative VO_{2peak} , absolute VO_{2peak} , RER, and VE/ VCO_2 slope) through a graded maximal exercise stress test utilizing a ramp cycling protocol before and after the intervention. Normality was assessed with Q-Q plots and Shapiro-Wilks tests. Paired samples t-tests were used to compare pre-intervention and post-intervention measures within groups, while independent samples t-tests and Wilcoxon signed-rank tests were used to compare the effect between groups. ANCOVA analyses were used to compare the effect of different covariates (i.e., the pre-intervention value of variable, age, and cancer stage) on each measure of fitness.

Results

The mean age for participants was 67.5 ± 9.3 years. The average Gleason score for participants was 8.0 ± 1.4 . The mean body fat percentage was $35.2\% \pm 5.3\%$. Primary within-group analysis revealed no significant change in any of the variables for the exercise or control group. Secondary between-group analysis revealed no significant

difference between groups for any of the fitness measurements. ANCOVA analysis revealed that each pre-intervention variable was a strong predictor of its post-intervention measurement. Age and cancer stage were both strong predictors of post-intervention RER.

Conclusion

A 16-week virtually supervised exercise intervention did not have a significant effect on measures of cardiorespiratory fitness in Black men with PCa who received ADT.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS.....	iv
ABSTRACT	v
TABLE OF CONTENTS	viii
LIST OF TABLES.....	xi
LIST OF FIGURES	xii
LIST OF ABBREVIATIONS.....	xiv
INTRODUCTION	1
Overview	1
Androgen Deprivation Therapy	3
Inclusion of Black Men with PCa in Clinical Research.....	5
Measures of Cardiorespiratory Fitness.....	6
Previous Research	8
SPECIFIC AIMS	10
METHODS.....	11
Study Design.....	11
Recruitment.....	12
Exercise Intervention.....	14

Exercise Materials.....	17
Control Group.....	18
Data Collection.....	18
Safety and Adverse Events.....	19
Data Analysis.....	20
RESULTS.....	22
Study Recruitment.....	22
Group Compatibility.....	25
Normality.....	26
Analysis of Relative VO_{2max}	31
Analysis of Absolute VO_{2peak}	34
Analysis of RER.....	37
Analysis of VE/VCO_2 Slope.....	40
Secondary Analysis.....	43
Analyses of Covariates.....	47
DISCUSSION.....	51
Absolute VO_{2peak} and Relative VO_{2peak}	51
RER.....	54

VE/VCO ₂ Slope	55
Covariates	57
Limitations	58
Clinical and Scientific Implications	60
Future Work.....	60
CONCLUSION.....	62
BIBLIOGRAPHY	63
CURRICULUM VITAE	67

LIST OF TABLES

Table 1: Outline of Progressive Modifications to the Aerobic and Resistance Program..	17
Table 2: Participant Characteristics	25
Table 3: Independent Samples T-Test for Relative VO_{2peak}	43
Table 4: Independent Samples T-Test for Absolute VO_{2peak}	44
Table 5: Independent Samples T-Test for RER.....	45
Table 6: Independent Samples T-Test for VE/VCO_2 Slope.....	46
Table 7: Effect of Covariates on Post-Intervention Relative VO_{2peak}	47
Table 8: Effect of Covariates on Post-Intervention Absolute VO_{2peak}	48
Table 9: Effect of Covariates on Post-Intervention RER.....	49
Table 10: Effect of Covariates on Post-Intervention VE/VCO_2 Slope.....	50

LIST OF FIGURES

Figure 1: Estimated Age-Standardized Prostate Cancer Incidence	1
Figure 2: Mechanisms of ADT and Their Respective Side Effects.....	4
Figure 3: Flow Diagram	11
Figure 4: Summary of Aerobic Training (A) and Resistance Training (B)	16
Figure 5: Consort Diagram.....	23
Figure 6: Q-Q Plots for Relative VO_{2peak}	27
Figure 7: Q-Q Plots for Absolute VO_{2peak}	28
Figure 8: Q-Q Plots for RER.....	29
Figure 9: Q-Q Plots for VE/VCO_2 Slope	30
Figure 10: Pre-Intervention Relative VO_{2peak} by Group	31
Figure 11: Exercise Group Pre- and Post-Intervention Relative VO_{2peak}	32
Figure 12: Control Group Pre- and Post-Intervention Relative VO_{2peak}	33
Figure 13: Pre-Intervention Absolute VO_{2peak} by Group	34
Figure 14: Exercise Group Pre- and Post-Intervention Absolute VO_{2peak}	35
Figure 15: Control Group Pre- and Post-Intervention Absolute VO_{2peak}	36
Figure 16: Pre-Intervention RER by Group	37
Figure 17: Exercise Group Pre- and Post-Intervention RER.....	38
Figure 18: Control Group Pre- and Post-Intervention RER	39
Figure 19: Pre-Intervention VE/VCO_2 Slope by Group.....	40
Figure 20: Exercise Group Pre- and Post-Intervention VE/VCO_2 Slope.....	41
Figure 21: Control Group Pre- and Post-Intervention VE/VCO_2 Slope	42

Figure 22: Individual Changes in Relative VO_{2peak} - (A) Exercise Group and (B) Control Group, Individual Changes in Absolute VO_{2peak} - (C) Exercise Group and (D) Control Group 53

Figure 23: Individual Changes in RER by Group⁰ 55

Figure 24: Individual Changes in VE/VCO_2 Slope by Group⁰ 56

LIST OF ABBREVIATIONS

1-RM	1-Repetition Maximum
10-RM	10-Repetition Maximum
ADT.....	Androgen Deprivation Therapy
AE	Adverse Event
AR.....	Androgen Receptor
BIDMC	Beth Israel Deaconess Medical Center
CVD	Cardiovascular Disease
DFCI.....	Dana-Farber Cancer Institute
GLTEQ.....	Godin Leisure-Time Exercise Questionnaire
GnRH	Gonadotropin-Releasing Hormone
HIIT.....	High-Intensity Interval Training
PAR-Q.....	Physical Activity Readiness Questionnaire
PCa	Prostate Cancer
PSA	Prostate-Specific Antigen
RER.....	Respiratory Exchange Rate
RPE	Rate of Perceived Exertion
RS.....	Relative Survival Rate
SAE	Serious Adverse Event
VE	Minute Ventilation

INTRODUCTION

Overview

Prostate cancer (PCa) continues to be one of the most frequently diagnosed cancers across the world, with an estimated 1.4 million new cases in 2022. As a result of these diagnoses, there were an estimated 375,000 deaths.³

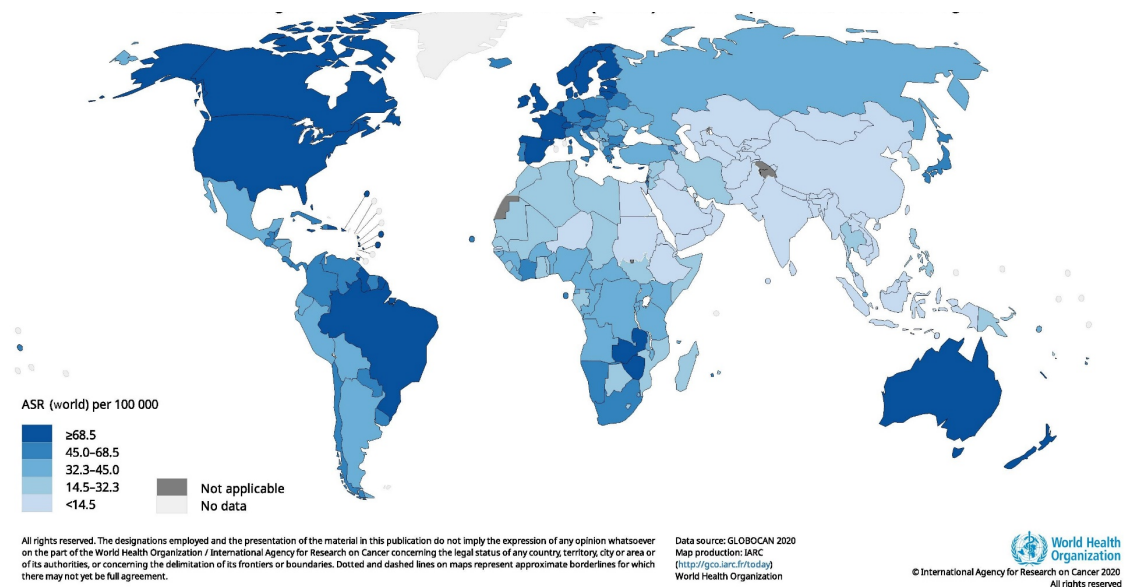


Figure 1: Estimated Age-Standardized Prostate Cancer Incidence^{(1),3}

PCa diagnoses make up more than half of male-diagnosed cancers in 112 out of 185 countries across the world (Figure 1). When rates are standardized by age, the areas with the highest prevalence are North America, Europe, South America, Africa, and Australia. This variance can be due to modifiable factors such as marital status, sexual activity, diet, or non-modifiable risk factors, which include age, genetic predisposition, and family history.³ Preventative screenings through superior methods such as prostate-

⁽¹⁾ Areas of more dark blue indicate a higher age-standardized rate of PCa.

specific antigen (PSA) monitoring have increased the detection of early-stage cancers and improved prognostic outcomes.

In the United States, the American Cancer Society estimates that in 2025, there will be 313,780 new cases of PCa and a resulting 35,770 deaths. Moreover, about one in eight men will be diagnosed with PCa in their lifetime.²⁵ However, in recent years, it has been found that PCa disproportionately affects men in minority and ethnic groups. In the United States, the incidence of PCa is almost 70% higher in Black or African American men, and rates of mortality are 2-3 times that of men of any other racial group.²⁵ Relative five-year survival rates (RS) were calculated using data collected by the Surveillance, Epidemiology, and End Results program through the National Cancer Institute and based on diagnosed individuals from 2014 through 2020. Results found no change in overall five-year RS across all races and ethnicities. For White men, five-year RS increased 1% to 98%, from 97% in 1995-1997. In contrast, five-year RS for Black men increased by 3% to 97%, from 94% in 1995-1997. While there is still an inequality in five-year RS, this is far improved from the 8% difference in 1975-1977, or 69% for White men and 61% for Black men.²⁵

In addition to the disparities in survival rates, disease characteristics are starkly different between White and Black men. Specifically, Black men present with higher PSA levels and Gleason scores that are more frequently greater than six at the time of diagnosis.¹⁶ While modifiable factors have been shown to have a strong influence on diagnosis and disease progression, new research is illuminating the great effects of genetic differences. For example, researchers have identified three germline variants

found on chromosome 8q24 that are consistently associated with more advanced-stage disease at diagnosis, higher risk for metastatic disease, and earlier development of disease.¹⁶

Androgen Deprivation Therapy

Hormone therapy, in the form of ADT, is a common treatment option for PCa. ADT treatments can act through four different mechanisms: (1) androgen receptor (AR) antagonists, (2) androgen biosynthesis inhibitors, (3) gonadotropin-releasing hormone (GnRH) antagonists, and (4) GnRH agonists (Figure 2). Each treatment decreases the amount of circulating testosterone by acting on androgen receptors, GnRH receptors, or enzymes necessary to synthesize androgen.¹⁰ While ADT can be used as a monotherapy, it is often combined with radiation therapy or used after surgical interventions for improved outcomes. In addition, ADT can be used in a cycle or continuously to maintain castrate levels of testosterone.

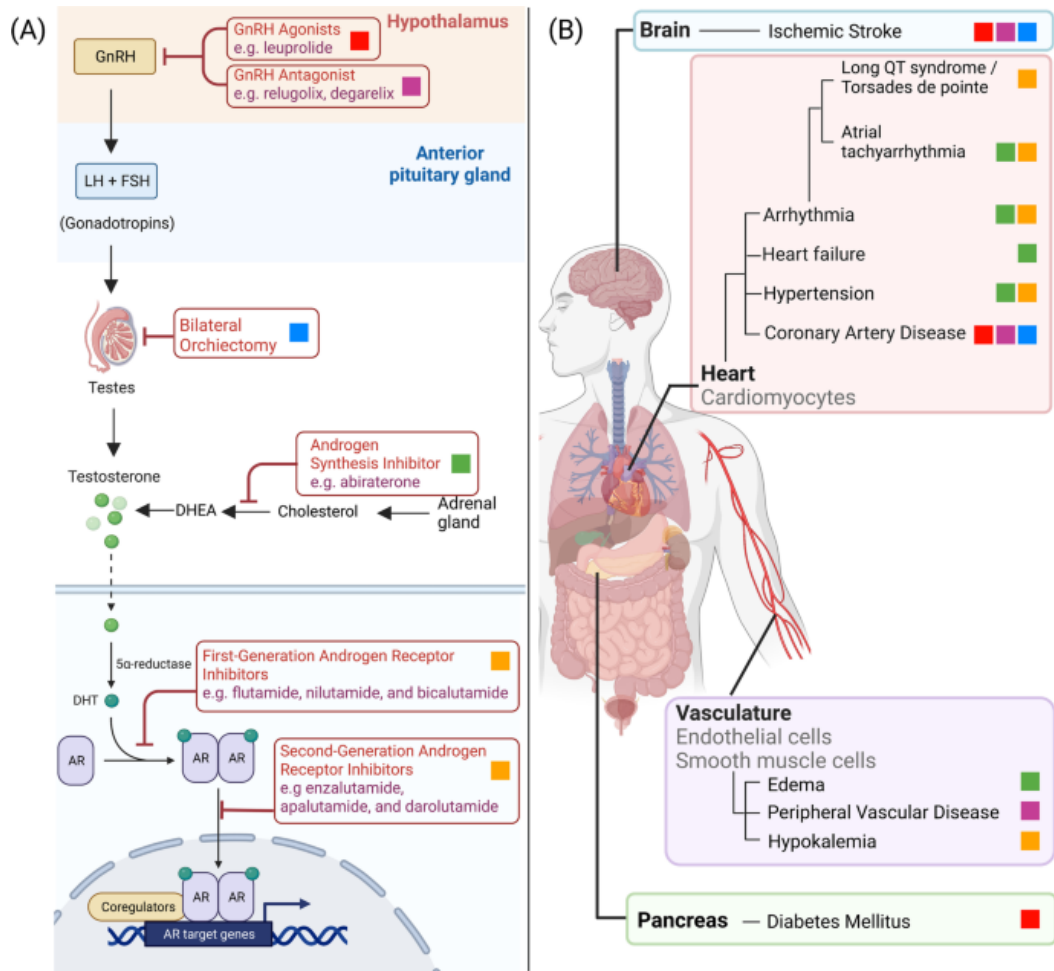


Figure 2: Mechanisms of ADT and Their Respective Side Effects¹⁴

Unfortunately, novel research has discovered that there may be detriments to ADT that were not previously known, with the most consequential being an increased risk for cardiovascular disease (Figure 2). The earliest research found that treatment with GnRH agonists for more than one year resulted in a 20% greater risk for serious cardiovascular morbidity.¹⁴ These findings sparked alarm among the scientific and medical community and led to an increase in the number of studies analyzing the risk of cardiovascular disease (CVD) associated with the various types of ADT. In a separate study, it was found that GnRH agonists increased the risk for myocardial infarction,

incident diabetes, and coronary artery disease when compared to men not receiving hormone treatment. In addition, GnRH antagonists showed significantly fewer cardiovascular events than GnRH agonists, 20% and 3% respectively.¹⁴ Moreover, medications that target enzymes in the biosynthesis of androgen were associated with fatigue, back pain, hypertension, hypokalemia, and edema. Enzalutamide, an androgen receptor inhibitor, has been proven to have an association with acquired long QT syndrome, Torsades de Pointe, and sudden death.¹⁴

Inclusion of Black Men with PCa in Clinical Research

Despite the disproportionate effects of PCa on Black men, there is far less clinical research focusing on specifically Black men. A recent survey found that out of 72 phase three trials completed between 1987 and 2016, Black men only made up 6.7% of the total participants.¹⁶ A primary reason cited for the lack of participation is mistrust of the healthcare system. This has a profound effect on the rate of preventative screenings and care for asymptomatic PCa patients. As an example, Black men with PCa reported concerns surrounding negligent use of PCa screening information and fear of positive test results. Consequently, they are less likely to seek treatment or evaluation when their disease first presents with distinguishing symptoms. This problem is further exacerbated since Black men are more frequently diagnosed with late-stage disease. Even when patients seek treatment, Black men report worse physician-patient communication than their White counterparts.¹⁶

While some of the causes of decreased participation may take time to correct, more immediate changes such as targeted trials for prospective minority patients could

immediately increase involvement. In a recent survey conducted by the Prostate Health Education Network, researchers found that the overwhelming reason Black men with PCa did not participate in a clinical trial was because they were never asked. The most influential characteristic for future participation in a research trial was whether the treatment or diagnosis would directly benefit the patient. Furthermore, the group asked prospective patients what traits research coordinators exhibit that would make them the most comfortable participating, and the overwhelming answer was a team that thoroughly explains study procedures, benefits, and possible risks.⁷

Measures of Cardiorespiratory Fitness

VO_{2max} is the maximum amount of oxygen the body can utilize during intense exercise and is a direct measure of cardiorespiratory fitness.²³ VO_{2max} can be represented in two variations: absolute maximum measured in liters per minute (L/min) or relative maximum with units of milliliters per minute per kilogram of body weight (mL/kg/min). The key distinguishing factor between the two is that relative maximum considers body weight in its calculation. Due to the extreme physical requirements of maximal exercise testing, VO_{2peak} , or peak oxygen consumption, has been established and validated as an alternative for VO_{2max} in vulnerable patients who cannot handle the rigors of maximal testing.⁹ Peak oxygen consumption has been proven to be clinically relevant in a variety of populations. For example, an increase in VO_{2peak} over three months was associated with more favorable outcomes in patients who experienced chronic heart failure. Additionally, when adjusted for other factors, a 6% increase in VO_{2peak} was

associated with an 8% lower risk of cardiovascular mortality or heart failure requiring hospitalization and a 7% decrease in all-cause mortality.²⁶

RER, or respiratory exchange rate, is a ratio of the body's CO₂ production to its O₂ uptake. Also, RER indirectly estimates the contribution to energy expenditure from carbohydrate and lipid sources. A high RER indicates primarily carbohydrates being used for energy, while a low RER indicates lipids as the primary source of energy. Although measures such as VO_{2max} have been viewed as the gold standard for evaluating cardiorespiratory fitness, more research is being done on alternative variables such as RER. Current research has shown that a sedentary lifestyle increases RER, but decreases insulin sensitivity and muscle oxidative capacity. RER also makes a substantial contribution to whole-body fat oxidation. Additionally, individuals who are more physically active exhibit lower RERs than untrained subjects at similar workloads. Lastly, the research shows that RER can be considered a good measurement for exercise interventions due to its validity when maximum conditions are not met.²¹

VE/VCO₂ slope, or ventilatory efficiency, numerically depicts how the minute ventilation (VE) changes in response to increased CO₂ production from the body. The calculated values of VE and VCO₂ are displayed on a graph, and the slope is equal to the ventilatory efficiency.²⁰ Furthermore, unlike other cardiopulmonary exercise testing measurements, the VE/VCO₂ slope does not require the participant to reach maximal effort. In a clinical setting, ventilatory efficiency has been established as a good predictor of cardiorespiratory health, possibly better than VO_{2max} as it works well in the VO_{2peak} grey area.⁵ Interestingly, the time and level of exertion at which the ventilatory efficiency

is collected changes how the value is interpreted. Increases in ventilatory efficiency collected at the beginning of an exercise bout are associated with worse hemodynamic profiles and future cardiovascular hospitalization and death. In contrast, late exercise increases in ventilatory efficiency are correlated with better fitness and lower cardiometabolic burden.²⁰ Additional research has attempted to create risk classifications similar to the Weber Classification System of Heart Failure, which utilizes VO_{2peak} . The studied system sorted patients into four ranges of ventilatory efficiency and prognostically outperformed the Weber system in predicting risk for cardiac-related hospitalizations.²

Together, these three measures of cardiorespiratory fitness can provide insight into the overall health status of individuals. This can be more specifically applied to Black men with PCa, as they are usually treated with ADT, which is known to decrease cardiorespiratory health and increase all-cause mortality and risk for CVD.

Previous Research

Despite the known detriments of ADT and the increased disease burden Black men face, research focusing on using exercise as a means to improve health is minimal. More research groups have recently begun similar studies, but more is required. The issue at hand is apparent, as one study found that men with PCa on ADT and over 75 years of age had a greater variance in measures of physical fitness, metabolic health, and obesity. Furthermore, across all ages, obesity and low levels of physical activity are associated with low cardiopulmonary fitness levels.¹¹ Another trial analyzed the effects and moderators of exercise medicine on various outcomes related to cardiovascular health.

Results indicated a significant decrease in body fat percentage, no significant change in systolic or diastolic blood pressure, and no change in lipid profile.¹⁷ While this information is pertinent to altering treatment protocols and revising guidelines, more research can be done to identify methods to improve these outcomes.

Research that focuses on improving outcomes has mainly investigated the feasibility of exercise interventions in men with PCa, maintenance of bone mass, improvements in quality of life, and other measures of physical or cognitive health. As of now, there is no current work that analyzes how exercise will impact fitness through measures related to cardiovascular health (i.e., VO_{2peak} , RER, and VE/ VCO_2 slope). Furthermore, research targeted to investigate outcomes for Black men with PCa, who are frequently excluded from clinical research, continues to be limited.

SPECIFIC AIMS

Black men with PCa receiving ADT face an increased risk for CVD and all-cause mortality compared to their White counterparts. While previous epidemiologic research has shown that physical activity decreases the risk for CVD and mortality, little research has investigated the impact of exercise specifically among Black men with PCa on ADT in a clinical trial setting. Therefore, this 16-week virtually supervised exercise intervention sought to analyze the effect of exercise on cardiorespiratory fitness.

To achieve this goal, cardiorespiratory fitness testing was conducted with the following measures assessed.

- 1a. Peak oxygen consumption (relative VO_{2peak} and absolute VO_{2peak} ; co-primary endpoints)
- 1b. Respiratory exchange rate (RER)
- 1c. Ventilatory efficiency (VE/VCO_2 slope)

METHODS

Study Design

This study was designed as a 16-week virtually supervised combined aerobic and resistance training intervention (Figure 3). The population consisted of Black men with PCa who were receiving hormone therapy in the form of ADT. The study was executed as a randomized control trial with two parallel groups: an exercise group and a control group. The consented participants were randomized at a 1:1 ratio.

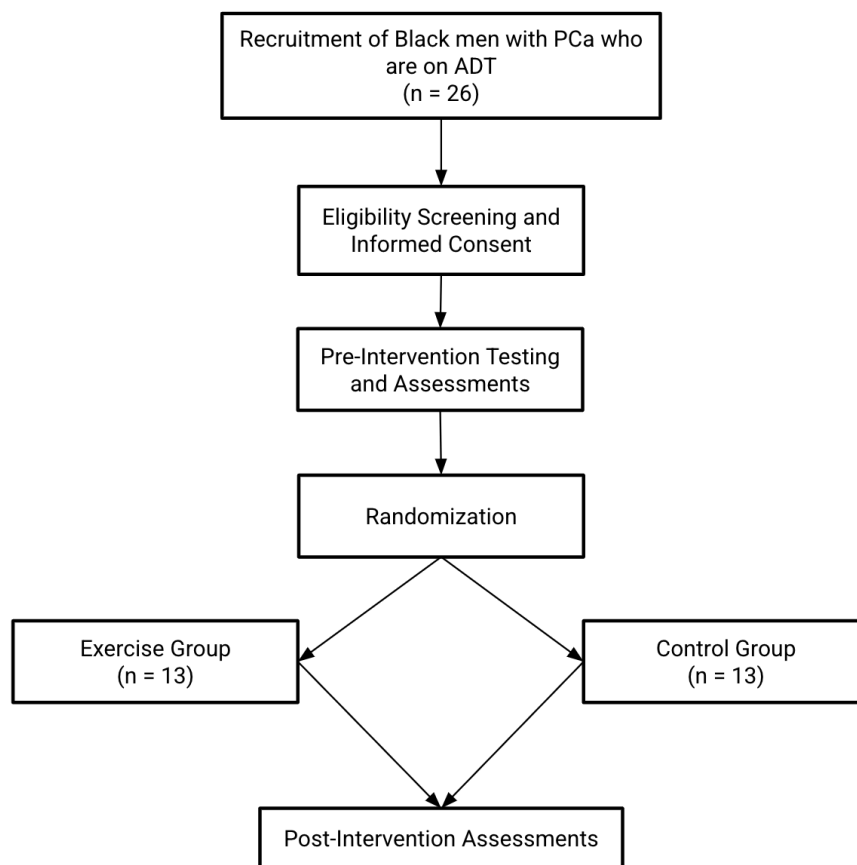


Figure 3: Flow Diagram⁽²⁾

⁽²⁾ (n = x), where x is equal to the expected number of participants randomized to each group.

The trial biostatistician generated the randomization scheme before any recruitment efforts. The final scheme used allocation sequences produced by computer-generated random numbers using variable block sizes of four to eight. The randomization list was entered into REDCap, and participants were randomized by the study-specific clinical research coordinator after completing pre-intervention testing. Due to the nature of the study, it was impossible to blind participants, as they were either directly receiving the exercise intervention or not receiving it.

Recruitment

All participants were recruited, screened, and consented by research staff in the Dieli-Conwright lab, part of the Division of Population Sciences at Dana-Farber Cancer Institute (DFCI). Prospective participants were identified using multiple strategies at DFCI and Beth Israel Deaconess Medical Center (BIDMC). Mainly, research staff routinely screened genitourinary oncology clinic lists and posted advertisements for the trial in patient waiting rooms. Potential participants were initially screened by study staff through medical record extraction and compared against the inclusion criteria for the study:

1. Histologically diagnosed with localized or metastatic PCa
2. Have been receiving ADT (i.e., luteinizing-hormone releasing hormone agonist/antagonist and/or AR agonist/antagonist and/or GnRH agonist/antagonist) for at least one month with a plan to continue ADT for at least 4 months at the time of recruitment
3. Self-identify as Black

4. Medically cleared to participate in exercise by their referred physician or a certified clinical exercise physiologist
5. Are without medical conditions that could exacerbate with exercise, such as bone disease (excluding bone metastases) at imminent risk of fracture or uncontrolled cardiopulmonary or metabolic diseases
6. Speak English and/or Spanish
7. Currently participate in less than or equal to 60 minutes of moderate or vigorous structured exercise per week
8. Willing to travel to DFCI for necessary data collection
9. Ability to communicate and complete written forms in English and/or Spanish

In the event a prospective participant met all inclusion criteria, staff would first contact the participant's medical oncologist to inquire if they thought their patient would be a good fit for the study. If the provider had not responded within 72 hours, the study team would approach the patient but could not consent the patient onto the study until their medical oncologist approved. If a BIDMC patient was identified, their information would be sent through secure messaging to the team at DFCI for initial communications with the prospective participant. After receiving approval to contact, potential participants were screened over the phone using two questionnaires: the Godin Leisure-Time Exercise Questionnaire (GLTEQ) and the Physical Activity Readiness Questionnaire (PAR-Q). The GLTEQ assesses current exercise habits, and the PAR-Q assesses the patient's ability to exercise, given their current medical status. If a patient was confirmed as eligible and expressed interest, a consent call would be scheduled, and

an email containing a study brochure and blank informed consent would be sent for review. Consent was obtained remotely through an e-consent process that allowed for easier processing and minimized the number of participant trips to the DFCI campus. After consent was obtained, a pre-intervention testing visit would be scheduled to collect pre-intervention data and complete randomization.

Exercise Intervention

Participants randomized to the exercise intervention group were asked to complete a combined aerobic and resistance exercise session three times a week for sixteen weeks, for a total of forty-eight exercise sessions. Sessions were completed in a home-based setting over Zoom and led by a certified clinical exercise trainer. Before the first exercise session, each participant completed an orientation session where they were guided through training movements to ensure proper technique and safety for exercising. Each session lasted around sixty minutes and began with the aerobic exercise portion followed by the resistance exercise portion. Intensity for both portions was personalized using each participant's pre-intervention testing and scaled to increase over the sixteen-week intervention period with the expected physiological adaptations to exercise in mind. Before each session, the certified exercise trainer assessed the participant's ability to exercise that day. This was accomplished by taking blood pressure, heart rate, and recording any other ailments participants mentioned. A blood pressure greater than 200/120mmHg, a body temperature greater than 100 degrees Fahrenheit, or the presence of a cardiac arrhythmia led to the session's termination. Examples of arrhythmias included bradycardia (a heart rate less than 60 beats per minute) and tachycardia (a heart

rate greater than 100 beats per minute). Both cases resulted in the immediate termination of that exercise session.

Aerobic exercise was performed as high-intensity interval training (HIIT) on a stationary bike provided to each participant. HIIT training alternated between bouts of high-intensity exercise and low-intensity exercise (Figure 4A). Adjustments to intensity were made by changing the resistance (watts), or the speed (revolutions per minute) of pedaling. The HIIT protocol began with a 5-minute warm-up at 50% of VO_{2peak} . Next, alternating minutes of high-intensity work and recovery were repeated ten times for a total of twenty minutes. High-intensity work started at 75% of VO_{2peak} , while recovery intensity was at 40% of VO_{2peak} . At the end, a 5-minute cooldown was completed at 30% of VO_{2peak} . At each minute, a heart rate and participant-reported exertion level were recorded by the session's exercise trainer to monitor intensity and patient safety.

Resistance training was prescribed as ten different exercises organized into two groups of five exercises. Group one exercises were performed on odd days and consisted of chest presses, shoulder presses, triceps extensions, deadlifts, and alternating lunges. Group two exercises were performed on even days and consisted of chest flies, rows, bicep curls, chair squats, and hip thrusts. Each movement was performed for 2-3 sets of 15-20 repetitions (Figure 4B). All exercises were completed with PowerBlock™ adjustable dumbbells, and the weight used was determined by the results of pre-intervention maximal testing. The preliminary weight started at 60% of each participant's calculated 1-repetition maximum (1-RM).

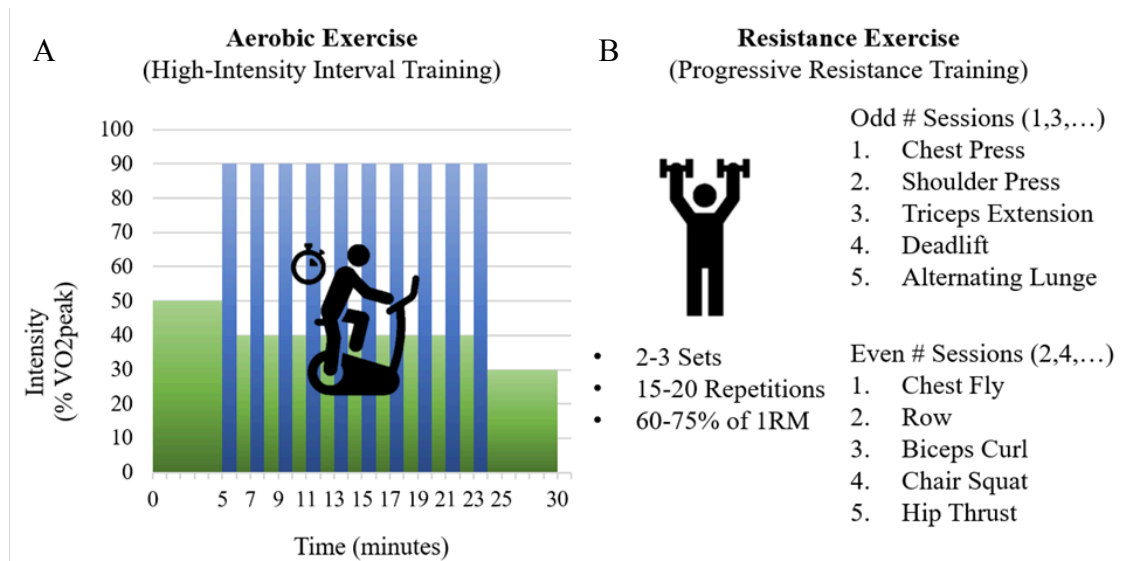


Figure 4: Summary of Aerobic Training (A) and Resistance Training (B)⁽³⁾

Throughout the study, the intensity of aerobic and resistance exercise was increased according to expected muscular and cardiovascular adaptations (Table 1). Intensities were increased in four phases, with each phase lasting four weeks. The aerobic intensity was increased by 5% of VO_{2peak} each phase with no change in the duration of the exercise. Resistance exercise intensity increased by 5% of the 1-RM with no change in the 15-20 repetitions per set. The only exception was an increase in aerobic intensity between weeks two and three by 5% of VO_{2peak} and an increase from two to three sets of resistance exercises at the same point. This allowed for the first two weeks on study to be a gradual increase to the expected exercise volume. By the end of the intervention, aerobic intensity was 95% of VO_{2peak}, and resistance intensity was 75% of the 1-RM. The

⁽³⁾ Adapted from the POWER Trial protocol, courtesy of the Dieli-Conwright Lab at Dana Farber Cancer Institute.

duration and intensity of the 5-minute warmup, recovery intervals in the HIIT protocol, and 5-minute cooldown were unchanged throughout the intervention.

Table 1: Outline of Progressive Modifications to the Aerobic and Resistance Program⁽⁴⁾

Phase	Aerobic Intensity		Resistance Exercise		
	Intensity (%VO _{2peak})	Volume (minutes)	Intensity (%1-RM)	Sets	Repetitions
Phase 1					
Week 1	75%	30	60%	2	15-20
Week 2	75%	30	60%	2	15-20
Week 3	80%	30	60%	3	15-20
Week 4	80%	30	60%	3	15-20
Phase 2					
Week 5	85%	30	65%	3	15-20
Week 6	85%	30	65%	3	15-20
Week 7	85%	30	65%	3	15-20
Week 8	85%	30	65%	3	15-20
Phase 3					
Week 9	90%	30	70%	3	15-20
Week 10	90%	30	70%	3	15-20
Week 11	90%	30	70%	3	15-20
Week 12	90%	30	70%	3	15-20
Phase 4					
Week 13	95%	30	75%	3	15-20
Week 14	95%	30	75%	3	15-20
Week 15	95%	30	75%	3	15-20
Week 16	95%	30	75%	3	15-20

Exercise Materials

All exercise materials were provided at no cost to the participant. Furthermore, due to the remote nature of the study, all study materials were ordered by the study staff and delivered to each participant's residence. Materials included one stationary exercise bike, two adjustable dumbbells, one Polar™ heart rate watch, one Polar heart rate chest

⁽⁴⁾ Adapted from the POWER Trial protocol, courtesy of the Dieli-Conwright Lab at Dana Farber Cancer Institute.

strap monitor, one automatic blood pressure monitor, and one yoga mat. Upon request, participants were also provided with a Wi-Fi-enabled tablet with Zoom installed, but this and the Polar items had to be returned at the end of the intervention. Some participants were provided additional materials such as a platform for step-ups to complete modifications in resistance exercises.

Control Group

Participants randomized to the control group did not receive any of the exercise intervention equipment. Additionally, they were asked to not begin any structured exercise program or change their current habits throughout the 16-week intervention. At study completion, they were offered the same intervention as the exercise group with the materials included.

Data Collection

Testing visits included collecting anthropometric measures, 10-repetition maximum testing (10-RM), and assessing cardiorespiratory fitness. Study-specific clinical research coordinators completed all testing at DFCI. Furthermore, the methodology was identical for pre-intervention and post-intervention visits. Body composition was measured with a whole-body dual-energy X-ray absorptiometry scan (DEXA). Collected measures included body fat percentage, total fat mass in grams, and total lean mass in grams.

Cardiorespiratory fitness was assessed through relative $\text{VO}_{2\text{peak}}$ (mL/kg/min), absolute $\text{VO}_{2\text{peak}}$ (L/min), RER, and VE/ VCO_2 slope using a graded maximal cycle exercise stress test. A Parvo Medics™ metabolic cart was used for all testing and was

calibrated before each maximal testing session. Additionally, study staff explained the various instruments and procedures before each pre-intervention and post-intervention testing session. Research coordinators measured heart rate, blood pressure, and the rate of perceived exertion (RPE) before and during testing to ensure patient safety.

Muscular strength was assessed through the completion of a 10-RM for two exercises, machine-loaded chest presses and machine-loaded leg presses. Both exercises were performed for 3-5 warm-up sets with 1-2 minutes of rest between each set. After each set, the study coordinator asked the participants for an RPE and about any discomfort they may have felt. Once a 10-RM was collected, it was used to calculate 1-RM for both exercises. Participants who were randomized to the exercise group could also complete the 10-RM for the ten exercises included in the intervention design. These ten movements were all completed with adjustable dumbbells and included chest presses, seated shoulder presses, triceps extensions, deadlifts, alternating lunges, chest flies, seated bent-over rows, biceps curls, chair squats, and floor hip thrusts. These 10-RM were used to calculate a 1-RM for exercise prescription.

Safety and Adverse Events

Before each session, participants were evaluated about symptoms they may have experienced since their last session. If a patient was experiencing a minor symptom such as musculoskeletal pain (i.e., joint pain, muscle soreness, etc.), the session was still completed per protocol with decreased duration, intensity, or volume to minimize participant discomfort.

Participants or exercise trainers could report an adverse event (AE), defined as any undesirable symptom, medical condition, or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol. All AEs were reported and graded using the NCI Common Terminology for Adverse Events version 5.0. Events were analyzed by their relatedness to the intervention - possible answers included definitely, probable, possible, unlikely, or unrelated. All AEs whether reported by the participant, discovered through trainer questioning, directly observed, or found during testing were reported and graded on the aforementioned scale. If a patient experienced adverse events during the session (i.e., chest pain, fainting, nausea), the session was immediately terminated, and the event was reported to the principal investigator and the participant's medical oncologist.

Serious adverse events (SAEs) were defined as any adverse event that occurred at any dose regardless of the causality that resulted in death, a life-threatening condition that required hospitalization, or any event that required medical or surgical intervention. This did not include routine treatments or monitoring, pre-planned treatments for a pre-existing condition, or emergency outpatient treatments that did not meet the criteria above. Reporting for SAEs followed the same protocol as AEs.

Data Analysis

Relative VO_{2peak} , absolute VO_{2peak} , RER, and VE/VCO_2 slope were analyzed as dependent variables to represent cardiorespiratory fitness. Each variable was collected at the end of maximal testing. Analysis for each dependent variable used a similar methodology. First, normality was visually assessed through Q-Q plots and numerically

assessed through Shapiro-Wilkes tests. If normality was assumed ($p > 0.05$), a paired sample's t-test was used to compare the within-groups effects for the exercise and control group. If the data was non-parametric, a Wilcoxon signed-ranked test was used. Regardless of the test used, a p-value less than 0.05 would indicate that the difference in pre-intervention and post-intervention values was statistically significant.

A second analysis using independent samples t-tests was performed to test the between-groups effect. Similar to the within-groups analysis, this analysis and methodology were repeated for each dependent variable: relative VO_{2peak} , absolute VO_{2peak} , RER, and VE/ VCO_2 slope. A p-value less than 0.05 indicated a significant difference in the means of the variable between the two groups and, therefore, a significant effect from the intervention.

ANCOVA analyses were used to compare the significance of other factors such as the pre-intervention value, participant age, and cancer stage. These tests were used to determine if the covariates significantly affected post-intervention measures and possibly masked the effect of the exercise intervention.

RESULTS

Study Recruitment

A total of 442 Black men with PCa were assessed for eligibility. Eligibility screening through medical record extraction resulted in 351 possible participants being ineligible. The top three reasons for ineligibility were (1) not identifying as Black/African American, (2) participating in equal to or more than 60 minutes of structured exercise per week, or (3) a language barrier (Figure 6). Of the remaining 91 prospective participants, 64 were contacted by a member of the DFCI recruitment team and declined to participate. The top three reasons for declining to participate were (1) lack of interest, (2) not answering screening calls or returning voicemails, and (3) lack of time or a scheduling issue (Figure 5).

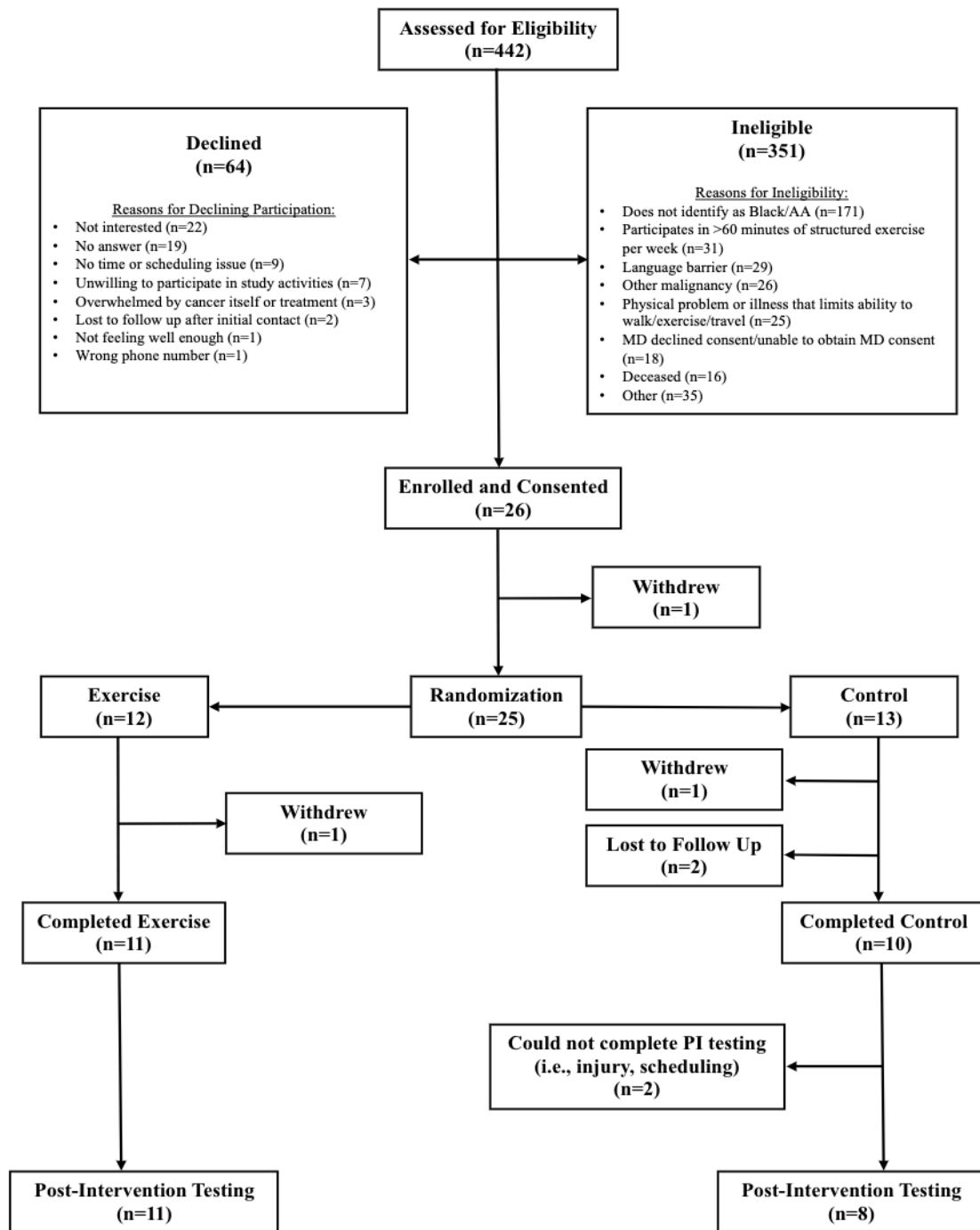


Figure 5: Consort Diagram⁽⁵⁾

⁽⁵⁾ (n = x), where x is equal to the number of participants that completed that stage of the study. Patients were screened from August 2022 through March 2024.

Of the total 442 possible participants screened, 26 were enrolled and consented to the study. One participant withdrew before randomization due to no longer wanting to participate. 25 participants were randomized with 12 participants assigned to the exercise group and 13 assigned to the control group. One participant assigned to the exercise group withdrew during the intervention after no longer wanting to participate. One participant assigned to the control group was lost to follow-up during the control period, and another withdrew during the control period. Two participants assigned to the control group completed the 16-week control but did not complete post-intervention testing. In the end, 11 exercise group participants completed the study, and 8 control group participants completed the study.

Attendance for exercise sessions was measured as a percentage of the number of sessions completed. Participants were expected to complete three sessions per week for 16 weeks, for a total of 48 sessions. There was a two-week grace period at the end of the preliminary 16-week period where participants could make up any sessions they missed. Across the 11 participants who completed the exercise intervention, the total participation was 89.3% or approximately 43/48 sessions.

Adverse events were tracked and graded as soon as they occurred during exercise sessions or via participant-reported symptoms outside of sessions. There were two adverse events unrelated to the intervention (i.e., side effects from outside medication and episode of syncope). There were three occurrences of exercise-related adverse events (i.e., nausea and back pain).

Group Compatibility

Table 2: Participant Characteristics⁽⁶⁾

	Exercise Group	Control Group
Age, years	68.9 ± 8.4	66.0 ± 10.3
Cancer Staging	3.0 ± 1.2	3.4 ± 0.9
Gleason Score	7.5 ± 1.1	8.0 ± 1.1
Body Fat, %	35.6 ± 4.9	34.8 ± 5.8
Total Lean Mass, grams	53010.4 ± 6248.3	58557.0 ± 12617.3
Total Fat Mass, grams	31772.4 ± 8938.0	34449.8 ± 12860.5
Prior Surgery		
Yes:	6 (50.0%)	2 (15.4%)
No:	6 (50.0%)	11 (84.6%)
Prior Chemotherapy		
Yes:	4 (33.0%)	2 (15.4%)
No:	8 (67.0%)	11 (84.6%)
Prior Radiation Therapy		
Yes:	11 (91.7%)	9 (69.2%)
No:	1 (8.3%)	4 (30.8%)
ADT Type		
GnRH Agonist	6 (50.0%)	3 (23.1%)
GnRH Agonist + ARI	5 (41.7)	8 (61.5%)
GnRH Antagonist +	1 (8.3%)	1 (7.7%)
ARI	0 (0.0%)	1 (7.7%)
Highest Level of School		
19 years	1 (8.3%)	0 (0.0%)
18 years	0 (0.0%)	1 (9.1%)

⁽⁶⁾ Units are specified with each variable. Values are presented as the mean ± standard deviation, and as the number of participants and % of each group.

17 years	0 (0.0%)	3 (27.3%)
16 years	7 (58.3%)	3 (27.3%)
15 years	1 (8.3%)	0 (0.0%)
14 years	0 (0.0%)	1 (9.1%)
13 years	1 (8.3%)	1 (9.1%)
12 years	2 (16.7%)	2 (18.2%)
Household Income		
>\$25,000	2 (16.7%)	1 (9.1%)
\$25,000-\$50,000	1 (8.3%)	2 (18.2%)
\$50,000-\$75,000	1 (8.3%)	2 (18.2%)
\$75,000-\$100,000	3 (25.0%)	1 (9.1%)
\$100,000-\$150,000	0 (0.0%)	1 (9.1%)
>\$150,000	2 (16.7%)	2 (18.2%)
Declined to Answer	3 (25.0%)	1 (9.1%)
Unsure/Do Not Know	0 (0.0%)	1 (9.1%)
Marital Status		
Single	4 (33.3%)	5 (45.5%)
Married	3 (25.0%)	5 (45.5%)
Divorced	3 (25.0%)	1 (9.0%)
Other	2 (16.7%)	0 (0.0%)
Smoking Status		
Never Smoked	8 (66.7%)	7 (70.0%)
Ex-Occasional Smoker	1 (8.3%)	1 (10.0%)
Ex-Smoker	3 (25.0%)	2 (20.0%)
Alcohol Status		
Never Drank	1 (8.3%)	3 (27.3%)
Ex-Occasional Drinker	6 (50.0%)	6 (54.5%)
Ex-Heavy Drinker	2 (16.7%)	1 (9.1%)
Occasional Drinker	2 (16.7%)	1 (9.1%)
Prefer Not To Answer	1 (8.3%)	0 (0.0%)

Normality

Normality was assessed for each variable (i.e., relative VO_{2peak} , absolute VO_{2peak} , RER, and VE/VCO_2 slope) at pre-intervention and post-intervention through visual and statistical tests to aid the decision for parametric or non-parametric statistical analysis (Figures 6-9). The control group's measured relative VO_{2peak} was the only variable that did not meet the requirements for normality (Figure 6D).

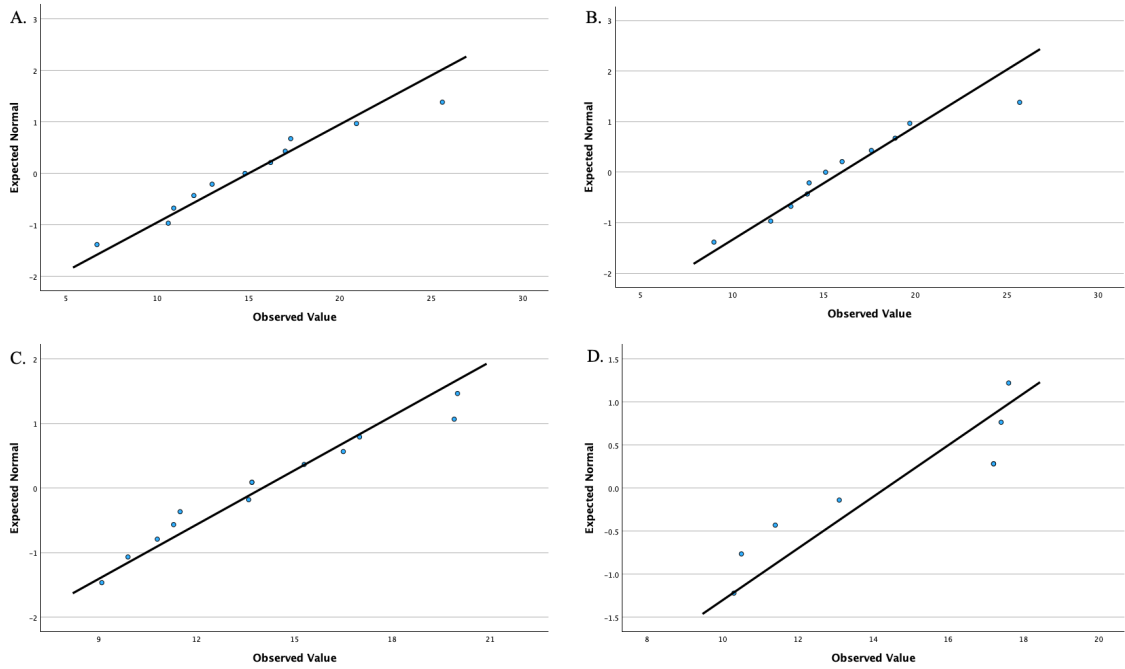


Figure 6: Q-Q Plots for Relative VO_{2peak} ; (A) Exercise Group at Pre-Intervention: $W = 0.97$, $p = 0.91$, (B) Exercise Group at Post-Intervention: $W = 0.96$, $p = 0.75$, (C) Control Group at Pre-Intervention: $W = 0.94$, $p = 0.44$, (D) Control Group at Post-Intervention: $W = 0.79$, $p = 0.02^{(7)}$

⁽⁷⁾ Data collected from study participants. Data analyzed and graphs created using SPSS Statistics.



Figure 7: Q-Q Plots for Absolute VO_{2peak} ; (A) Exercise Group at Pre-Intervention: $W = 0.93$, $p = 0.41$, (B) Exercise Group at Post-Intervention: $W = 0.95$, $p = 0.59$, (C) Control Group at Pre-Intervention: $W = 0.90$, $p = 0.14$, (D) Control Group at Post-Intervention: $W = 0.97$, $p = 0.87^{(8)}$

⁽⁸⁾ Data collected from study participants. Data analyzed and graphs created using SPSS Statistics.

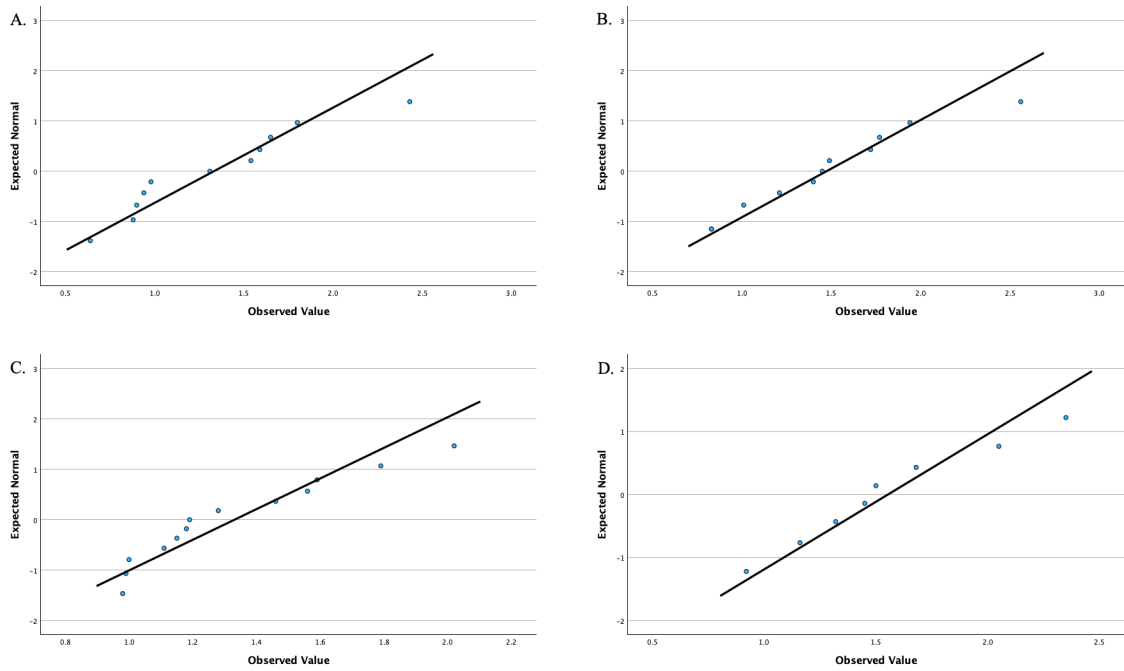


Figure 8: Q-Q Plots for RER; (A) Exercise Group at Pre-Intervention: $W = 0.97$, $p = 0.86$, (B) Exercise Group at Post-Intervention: $W = 0.97$, $p = 0.83$, (C) Control Group at Pre-Intervention: $W = 0.93$, $p = 0.35$, (D) Control Group at Post-Intervention: $W = 0.84$, $p = 0.07^{(9)}$

⁽⁹⁾ Data collected from study participants. Data analyzed and graphs created using SPSS Statistics.

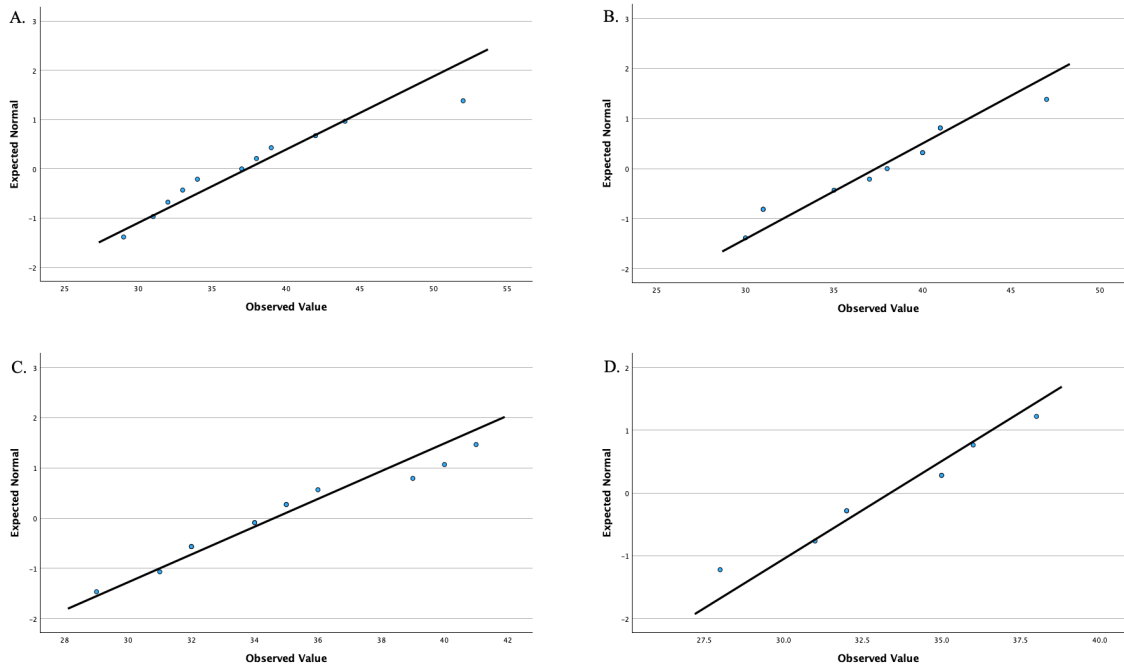


Figure 9: Q-Q Plots for VE/VCO₂ Slope; (A) Exercise Group at Pre-Intervention: $W = 0.94$, $p = 0.48$ (B) Exercise Group at Post-Intervention: $W = 0.94$, $p = 0.46$, (C) Control Group at Pre-Intervention: $W = 0.94$, $p = 0.51$ (D) Control Group at Post-Intervention: $W = 0.97$, $p = 0.85^{(10)}$

⁽¹⁰⁾ Data collected from study participants. Data analyzed and graphs created using SPSS Statistics.

Analysis of Relative VO_{2max}

The pre-intervention relative VO_{2peak} for participants assigned to the exercise group was 15.0 mL/kg/min \pm 5.3 mL/kg/min (n=11), while the relative VO_{2peak} for the control group was 14.0 mL/kg/min \pm 3.6 mL/kg/min (n=13). Pre-intervention relative VO_{2peak} for the exercise group ranged from 6.7 mL/kg/min to 25.6 mL/kg/min, while the control group ranged from 9.1 mL/kg/min to 20.0 mL/kg/min (Figure 10).

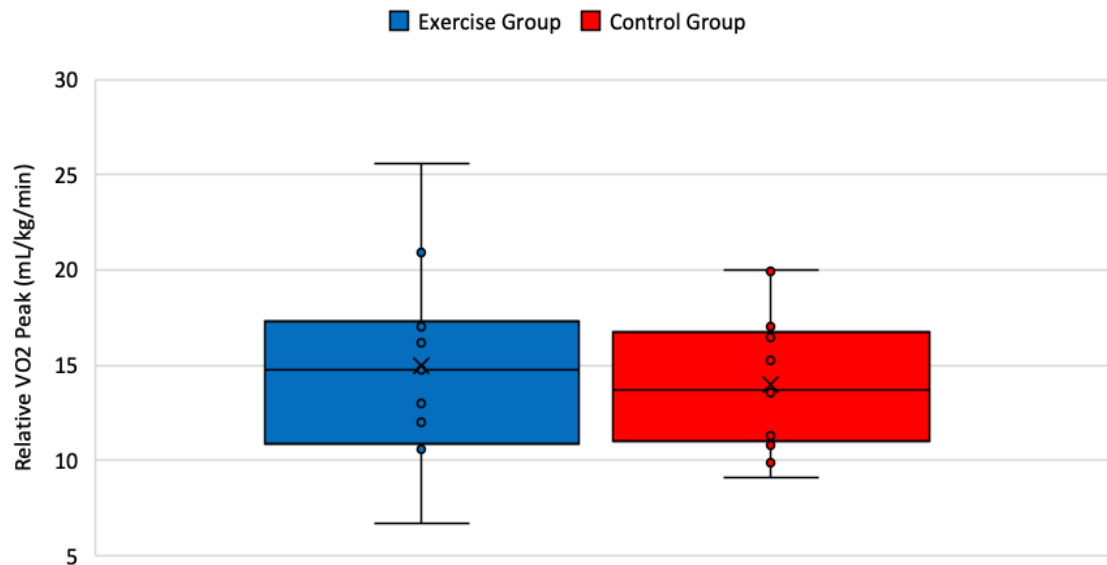


Figure 10: Pre-Intervention Relative VO_{2peak} by Group⁽¹¹⁾

⁽¹¹⁾ Exercise group (n=11) and is represented in blue. Control group (n=13) and is represented in red. Data collected by DFCI study staff.

Post-intervention relative VO_{2peak} ($M = 16.0$ mL/kg/min, $SD = 4.5$ mL/kg/min) was not significantly different when compared to pre-intervention values ($M = 15.0$ mL/kg/min, $SD = 5.25$ mL/kg/min), $t(10) = 1.35$, $p = 0.21$ in the exercise group (Figure 11.)

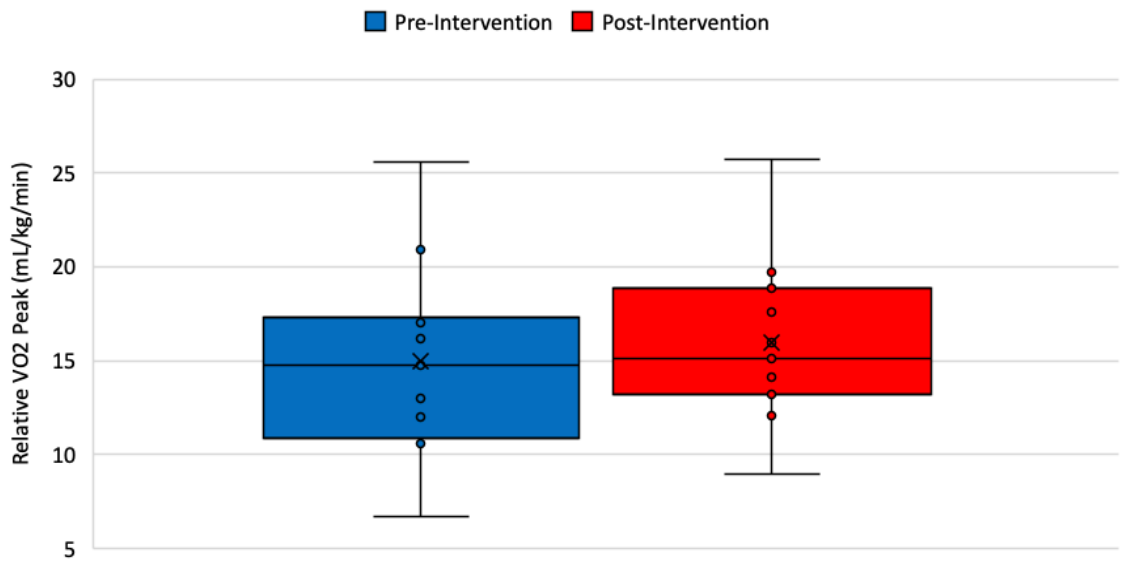


Figure 11: Exercise Group Pre- and Post-Intervention Relative VO_{2peak} ⁽¹²⁾

⁽¹²⁾ Pre-intervention and post-intervention (n=11). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff.

Post-intervention relative VO_{2peak} ($M = 14.3$ mL/kg/min, $SD = 3.3$ mL/kg/min) was not significantly different when compared to pre-intervention values ($M = 13.6$ mL/kg/min, $SD = 3.9$ mL/kg/min), $Z = 25.00$, $p = 0.33$ among the control group (Figure 12).

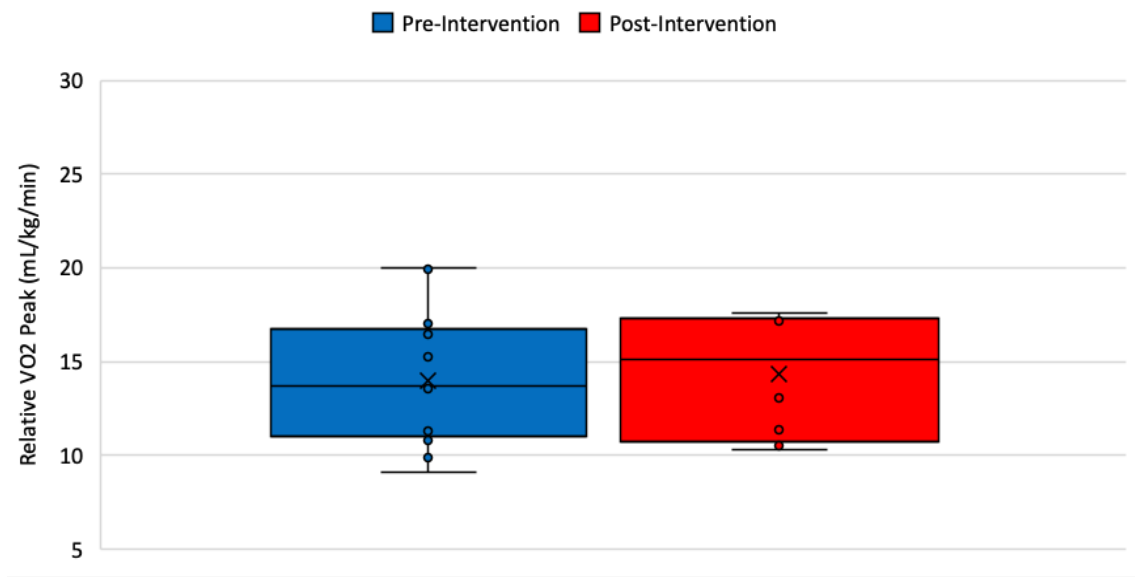


Figure 12: Control Group Pre- and Post-Intervention Relative VO_{2peak} ⁽¹³⁾

⁽¹³⁾ Pre-intervention (n=13) and post-intervention (n=8). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff.

Analysis of Absolute $\text{VO}_{2\text{peak}}$

The pre-intervention absolute $\text{VO}_{2\text{peak}}$ for participants assigned to the exercise group was $1.3 \text{ L/min} \pm 0.5 \text{ L/min}$ ($n=11$), while the absolute pre-intervention $\text{VO}_{2\text{peak}}$ for the control group was $1.3 \text{ L/min} \pm 0.3 \text{ L/min}$ ($n=13$). Absolute $\text{VO}_{2\text{peak}}$ for the exercise group ranged from 0.6 L/min to 2.4 L/min , while absolute $\text{VO}_{2\text{peak}}$ for the control group ranged from 1.0 L/min to 2.0 L/min (Figure 13).

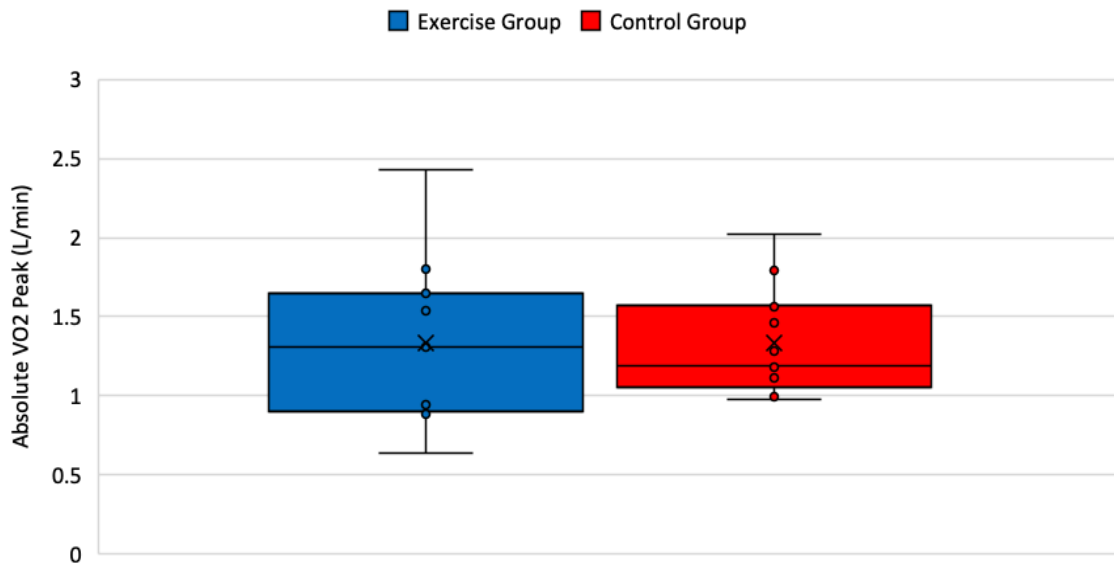


Figure 13: Pre-Intervention Absolute $\text{VO}_{2\text{peak}}$ by Group⁽¹⁴⁾

⁽¹⁴⁾ Exercise group ($n=11$) and is represented in blue. Control group ($n=13$) and is represented in red. Data collected by DFCI study staff.

Post-intervention absolute VO_{2peak} ($M = 1.5$ L/min, $SD = 0.5$ L/min) was not significantly different when compared to pre-intervention values ($M = 1.3$ L/min, $SD = 0.5$ L/min), $t(10) = 1.86$, $p = 0.09$ (Figure 14).

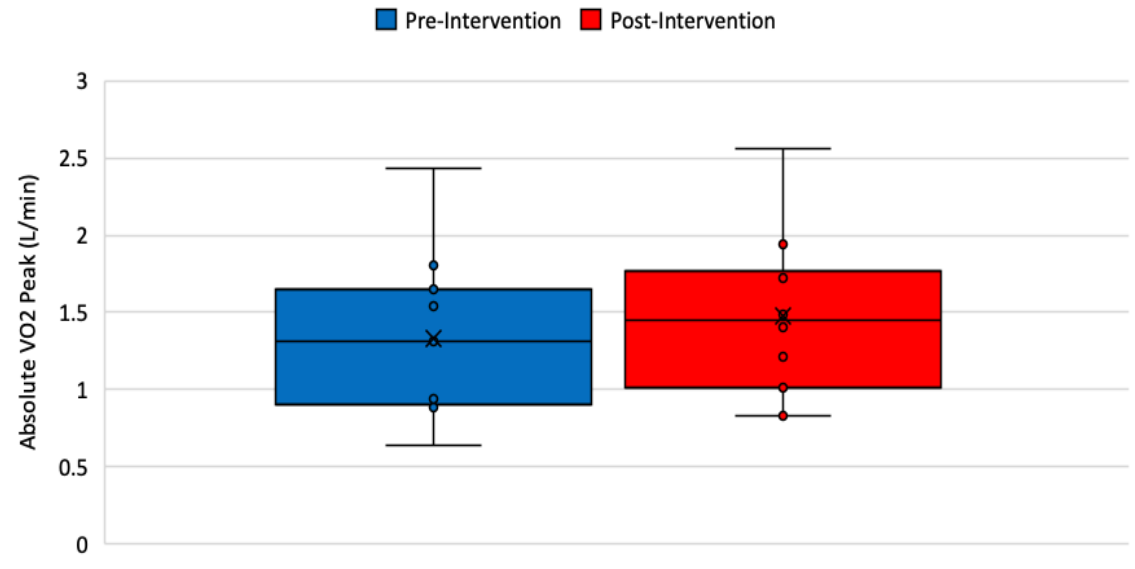


Figure 14: Exercise Group Pre- and Post-Intervention Absolute VO_{2peak} ⁽¹⁵⁾

⁽¹⁵⁾ Pre-intervention and post-intervention (n=11). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff.

Post-intervention absolute VO_{2peak} for the control group ($M = 1.6$ L/min, $SD = 0.5$ L/min) was not significantly different when compared to pre-intervention values ($M = 1.4$ L/min, $SD = 0.4$ L/min), $t(7) = 1.78$, $p = 0.12$ (Figure 15).

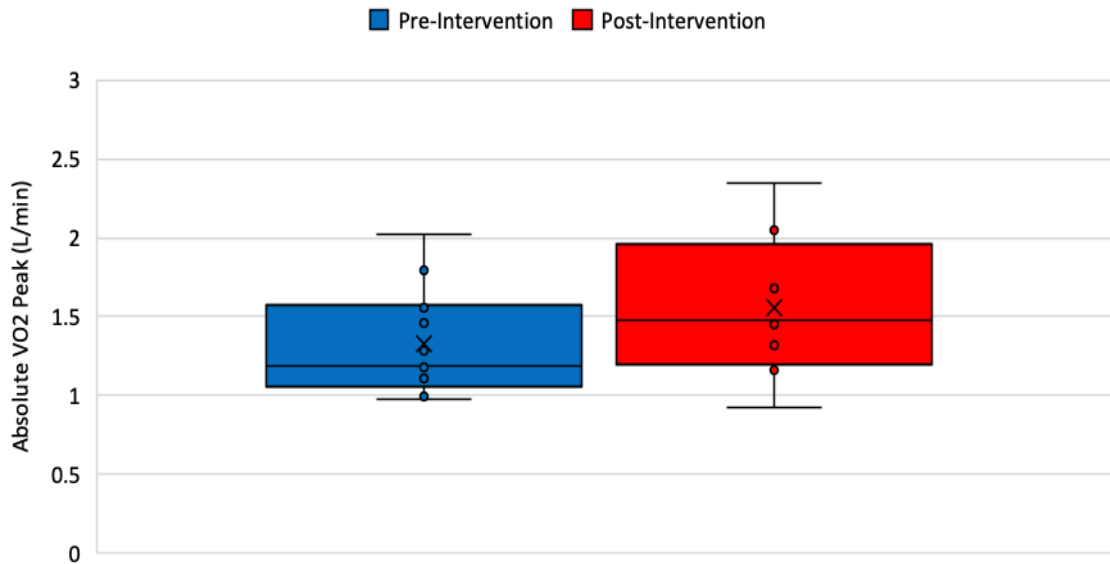


Figure 15: Control Group Pre- and Post-Intervention Absolute VO_{2peak} ⁽¹⁶⁾

⁽¹⁶⁾ Pre-intervention (n=13) and post-intervention (n=8). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff.

Analysis of RER

The pre-intervention RER for participants assigned to the exercise group 1.07 ± 0.11 ($n = 11$), while the pre-intervention RER for participants assigned to the control group was 1.13 ± 0.12 ($n = 13$). Pre-intervention RER ranged from 0.86 to 1.25 and 0.89 to 1.28, for exercise and control groups respectively (Figure 16).

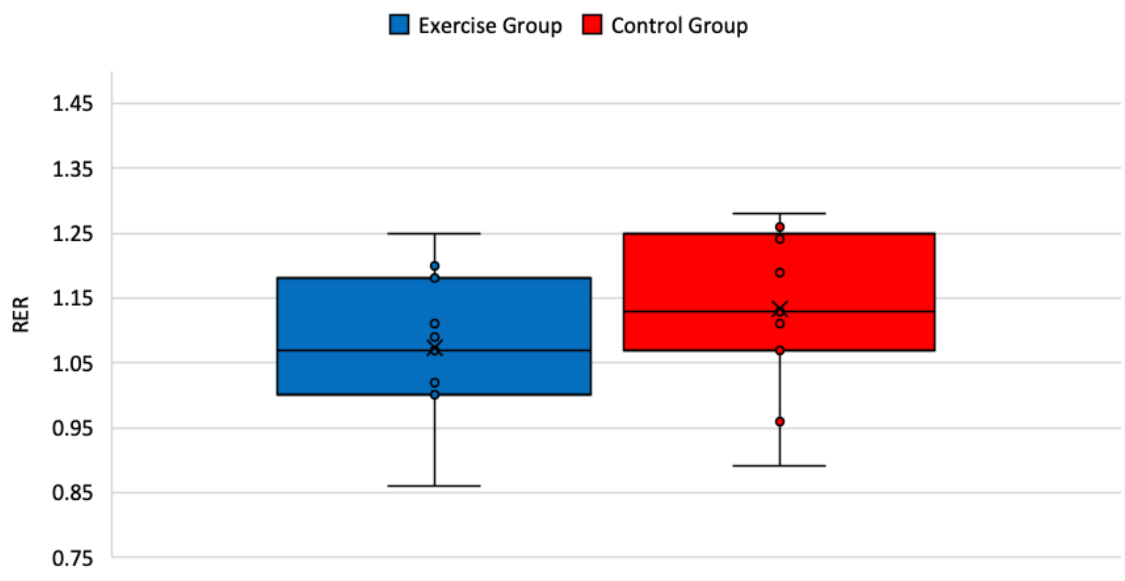


Figure 16: Pre-Intervention RER by Group⁽¹⁷⁾

⁽¹⁷⁾ Exercise group ($n=11$) and is represented in blue. Control group ($n=13$) and is represented in red. Data collected by DFCI study staff.

Post-intervention RER for the exercise group ($M = 1.06$, $SD = 0.10$) was not statistically significant when compared to pre-intervention values ($M = 1.07$, $SD = 0.11$), $t(10) = -1.12$, $p = 0.29$ (Figure 17).

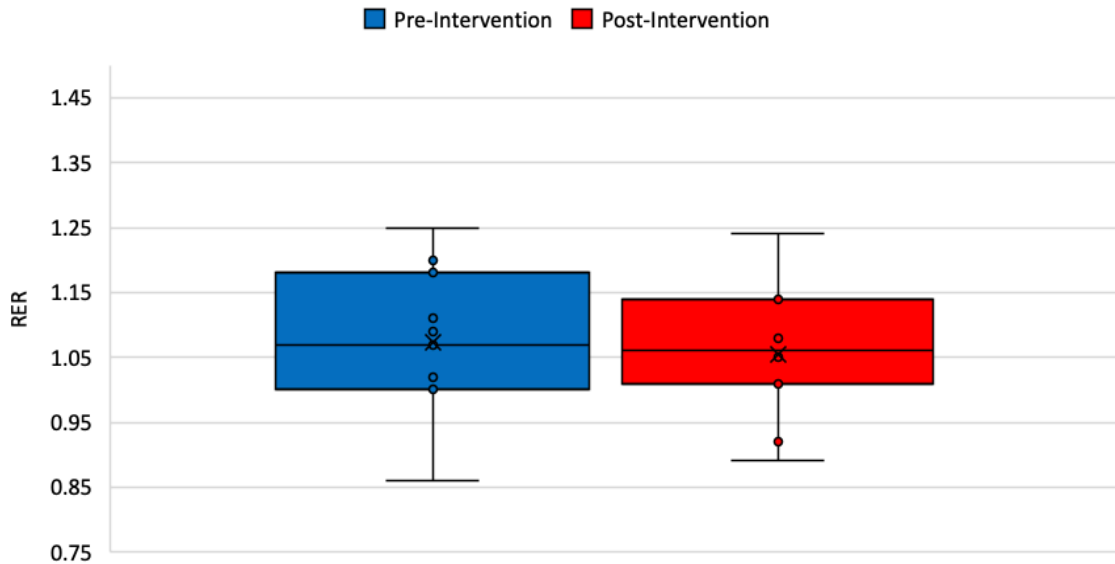


Figure 17: Exercise Group Pre- and Post-Intervention RER⁽¹⁸⁾

⁽¹⁸⁾Pre-intervention and post-intervention ($n = 11$). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff.

Post-intervention RER of control participants ($M = 1.12$, $SD = 0.11$) was not statistically different when compared to control pre-intervention values ($M = 1.12$, $SD = 0.13$), $t(7) = 0.129$, $p = 0.90$ (Figure 18).

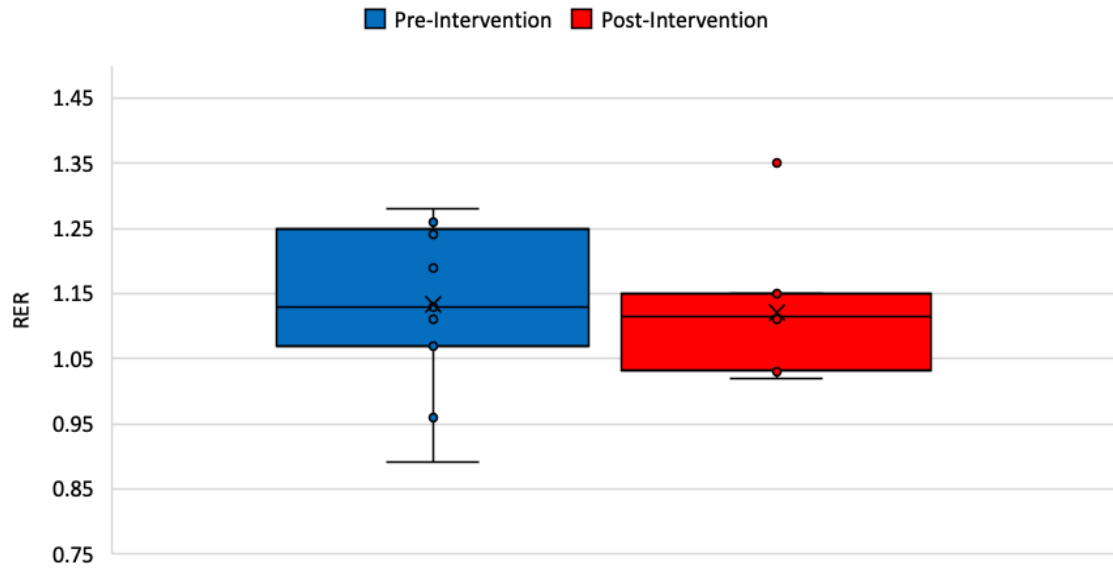


Figure 18: Control Group Pre- and Post-Intervention RER⁽¹⁹⁾

⁽¹⁹⁾ Pre-intervention (n=13) and post-intervention (n=8). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff.

Analysis of VE/VCO₂ Slope

The pre-intervention VE/VCO₂ slope for the exercise group was 37.4 ± 6.7 (n=11), while the pre-intervention VE/VCO₂ slope for the control group was 34.6 ± 3.6 (n=13). Pre-intervention VE/VCO₂ slope for the exercise group ranged from 29 to 52, whereas the pre-intervention range for the control group was 29 to 41 (Figure 19).

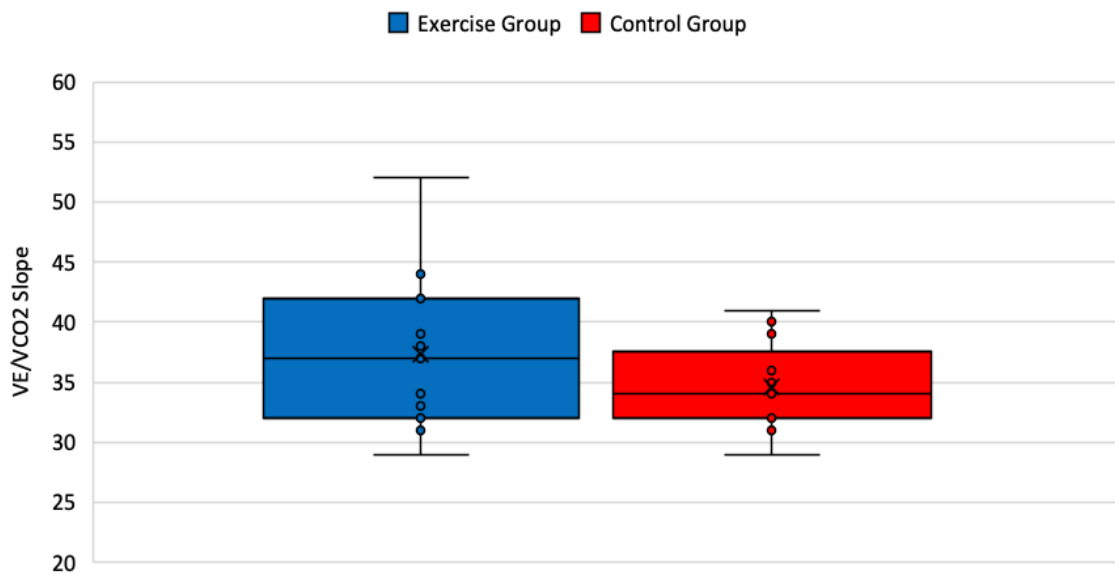


Figure 19: Pre-Intervention VE/VCO₂ Slope by Group⁽²⁰⁾

⁽²⁰⁾ Exercise group (n=11) and is represented in blue. Control group (n=13) and is represented in red. Data collected by DFCI study staff.

Post-intervention VE/VCO₂ slope of exercise participants (M = 37.4, SD = 5.2) was not statistically different when compared to pre-intervention values (M = 37.4, SD = 6.7), $t(10) = 0.00$, $p = 1.00$ (Figure 20).

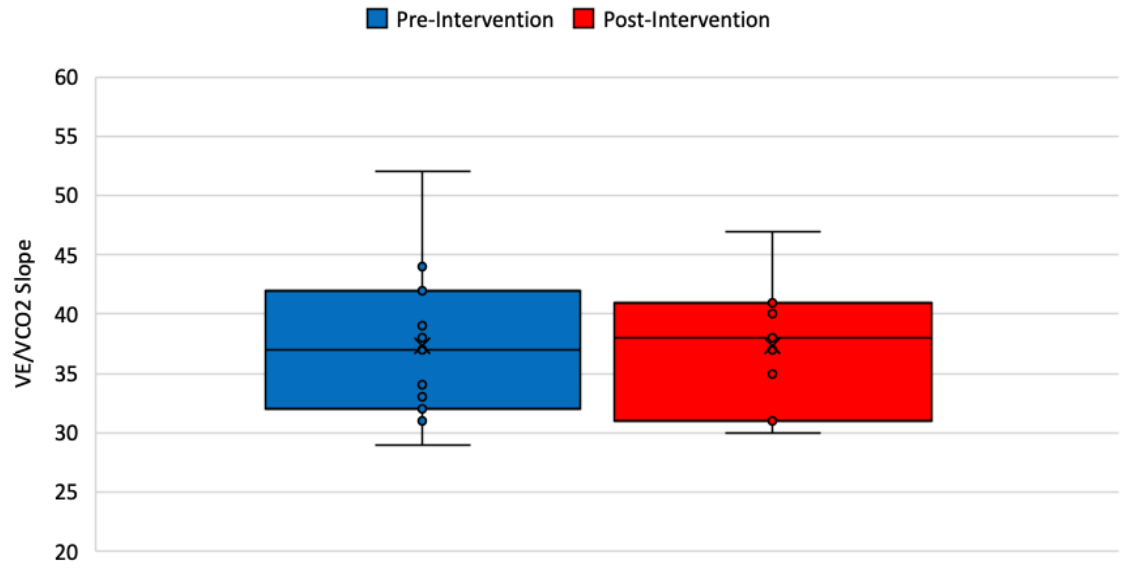


Figure 20: Exercise Group Pre- and Post-Intervention VE/VCO₂ Slope⁽²¹⁾

⁽²¹⁾ Pre-intervention and post-intervention (n=11). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff

Post-intervention VE/VCO₂ slope of control participants (M = 33.4, SD = 3.2) was not statistically different when compared to pre-intervention values (M = 33.6, SD = 3.0), $t(7) = -0.33$, $p = 0.75$ (Figure 21).

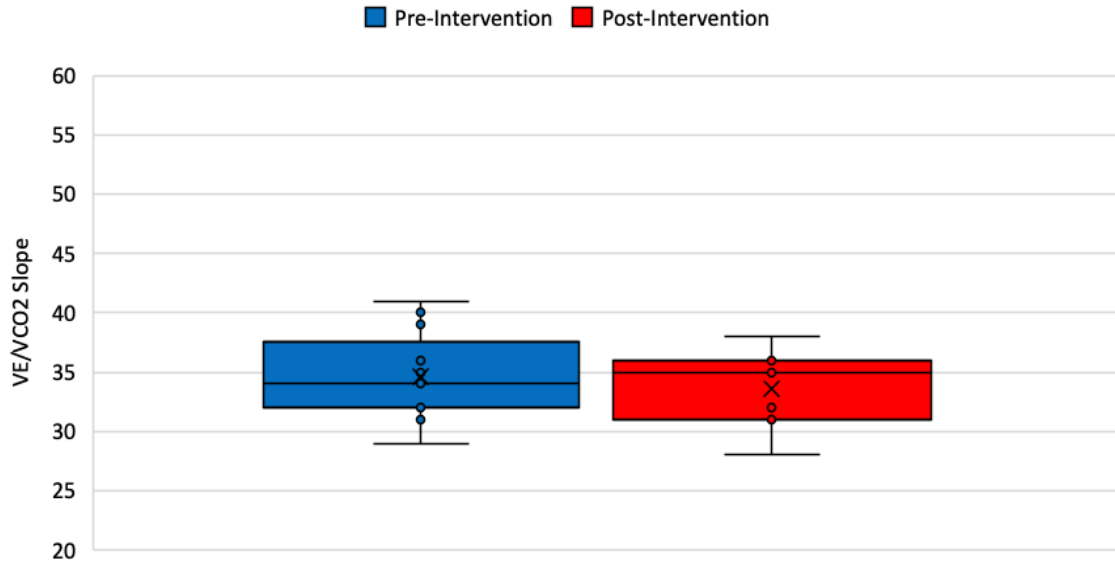


Figure 21: Control Group Pre- and Post-Intervention VE/VCO₂ Slope⁽²²⁾

⁽²²⁾ Pre-intervention (n=13) and post-intervention (n=8). Pre-intervention is represented by blue, and post-intervention by red. Data collected by DFCI study staff.

Secondary Analysis

Levene's test analysis for equal variances of relative VO_{2peak} was not significant ($p = 0.21$), indicating that equal variances were assumed. The results of the independent samples t-test implied that there is not a significant difference in relative VO_{2peak} between the exercise and control group, $t(17) = -0.15$, $p = 0.88$ (Table 3).

Table 3: Independent Samples T-Test for Relative VO_{2peak} ⁽²³⁾

	Levene's Test for Equality of Variances		T	df	T-Test for Equality of Means		95% Confidence Interval of the Difference	
	F	Sig			Two-Sided Significance	Mean Difference	Lower	Upper
Equal variances assumed	1.687	.211	-.152	17	0.881	-.250	-3.72	3.22
Equal variances not assumed			-.168	15.41	0.869	-.250	-3.42	2.92

⁽²³⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

Levene's test analysis for equal variances of absolute VO_{2peak} was not significant ($p = 0.74$), indicating that equal variances were assumed. The results of the independent samples t-test implied that there is not a significant difference in absolute VO_{2peak} between the exercise and control group, $t(17) = 0.04$, $p = 0.97$ (Table 4).

Table 4: Independent Samples T-Test for Absolute VO_{2peak} ⁽²⁴⁾

	Levene's Test for Equality of Variances		T	df	T-Test for Equality of Means		95% Confidence Interval of the Difference	
	F	Sig			Two-Sided Significance	Mean Difference	Lower	Upper
Equal variances assumed	.117	.736	.036	17	0.972	.004	-.234	.242
Equal variances not assumed			.037	15.95	0.971	.004	-.232	.240

⁽²⁴⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

Similar to relative and absolute VO_{2peak} , Levene's test for equal variances of RER was not significant ($p = 0.14$), and equal variances were assumed. The results of the independent samples t-test did not find a significant difference between the change in RER among the exercise and control group, $t(17) = 0.61$, $p = 0.55$ (Table 5).

Table 5: Independent Samples T-Test for RER⁽²⁵⁾

	Levene's Test for Equality of Variances		T	df	T-Test for Equality of Means		95% Confidence Interval of the Difference	
	F	Sig			Two-Sided Significance	Mean Difference	Lower	Upper
Equal variances assumed	2.45	.136	.613	17	0.548	.023	-.057	.103
Equal variances not assumed			.533	9.46	0.593	.023	-.071	.117

⁽²⁵⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

Levene's test for VE/VCO₂ slope was not significant (p = 0.21), and equal variances were assumed. The independent samples t-test did not find a statistically significant difference between the VE/VCO₂ slope for the exercise and control group, t (17) = -0.15, p = 0.88 (Figure 26).

Table 6: Independent Samples T-Test for VE/VCO₂ Slope⁽²⁶⁾

	Levene's Test for Equality of Variances		T	df	T-Test for Equality of Means		95% Confidence Interval of the Difference	
	F	Sig			Two-Sided Significance	Mean Difference	Lower	Upper
Equal variances assumed	1.69	.211	-.152	17	0.881	-.250	-3.72	3.22
Equal variances not assumed			-.168	15.41	0.869	-.250	-3.42	2.92

⁽²⁶⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

Analyses of Covariates

ANCOVA analyses were used to examine the effect of the exercise intervention on each dependent variable's post-intervention value while controlling for differences in pre-intervention variable measurements, age, and cancer stage.

The ANCOVA analysis of relative VO_{2peak} found the main effect of the group to be insignificant ($F(1,11) = 0.38, p = 0.55$). For the covariates, pre-intervention relative VO_{2peak} ($F(1,11) = 56.91, p < 0.01$) was a strong predictor of post-intervention relative VO_{2peak} . The other two covariates, age ($F(1,11) = 0.83, p = 0.38$) and cancer stage ($F(1,11) = 0.91, p = 0.36$), were not significant predictors of post-intervention relative VO_{2peak} (Table 7).

Table 7: Effect of Covariates on Post-Intervention Relative VO_{2peak} ⁽²⁷⁾

Source	Type III Sum of Squares	df	Mean Square	F	Significance
Group	1.331	1	1.331	.384	.034
Pre-Intervention Relative VO_{2peak}	197.334	1	197.334	56.906	.838
Age	2.867	1	2.867	.827	.070
Cancer Stage	3.139	1	3.139	.905	.076
Error	38.145	11	3.468	-	-
Total	257.230	16	-	-	-

⁽²⁷⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

ANCOVA for absolute VO_{2peak} found the main effect of the group was insignificant ($F(1,11) = 0.20, p = 0.66$). For the covariates, pre-intervention absolute VO_{2peak} ($F(1,11) = 48.15, p < 0.01$) was a strong predictor of post-intervention absolute VO_{2peak} . The other two covariates, age ($F(1,11) = 1.84, p = 0.20$) and cancer stage ($F(1,11) = 2.32, p = 0.16$), were not significant predictors of post-intervention absolute VO_{2peak} (Table 8).

Table 8: Effect of Covariates on Post-Intervention Absolute VO_{2peak} ⁽²⁸⁾

Source	Type III Sum of Squares	df	Mean Square	F	Significance
Group	.009	1	.009	.203	.661
Pre-Intervention Absolute VO_{2peak}	2.101	1	2.101	48.149	<.001
Age	.080	1	.080	1.843	.202
Cancer Stage	.101	1	.101	2.315	.156
Error	.480	11	.044	-	-
Total	39.276	16	-	-	-

⁽²⁸⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

ANCOVA analysis found for post-intervention RER that the main effect of the group was insignificant ($F(1,11) = 0.19, p = 0.67$). For the covariates, pre-intervention RER ($F(1,11) = 51.60, p < 0.01$), age ($F(1,11) = 7.75, p = 0.02$), and cancer stage ($F(1,11) = 7.78, p = 0.02$) were strong predictors of post-intervention RER (Table 9).

Table 9: Effect of Covariates on Post-Intervention RER⁽²⁹⁾

Source	Type III Sum of Squares	df	Mean Square	F	Significance
Group	.000	1	.000	.189	.017
Pre-Intervention RER	.135	1	.135	51.598	.824
Age	.020	1	.020	7.745	.413
Cancer Stage	.020	1	.020	7.778	.414
Error	.029	11	.003	-	-
Total	18.830	16	-	-	-

⁽²⁹⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

The ANCOVA analysis for the post-intervention VE/VCO₂ slope found the main effect of the group to be insignificant ($F(1,11) = 0.20$, $p = 0.67$). For the covariates, pre-intervention VE/VCO₂ slope ($F(1,11) = 14.53$, $p < 0.01$) and cancer stage ($F(1,11) = 5.15$, $p = 0.04$) were strong predictors of post-intervention VE/VCO₂ slope. Age ($F(1,11) = 0.50$, $p = 0.50$) was not a predictor of post-intervention VE/VCO₂ slope (Figure 10).

Table 10: Effect of Covariates on Post-Intervention VE/VCO₂ Slope⁽³⁰⁾

Source	Type III Sum of Squares	df	Mean Square	F	Significance
Group	1.649	1	1.649	.199	.018
Pre-Intervention VE/VCO ₂ Slope	120.704	1	120.704	14.533	.569
Age	4.121	1	4.121	.496	.043
Cancer Stage	42.740	1	42.740	5.146	.319
Error	91.363	11	8.306	-	-
Total	210069.00	16	-	-	-

⁽³⁰⁾ Data collected by DFCI study staff. Analysis completed on SPSS.

DISCUSSION

This study examined the effects of exercise on cardiorespiratory fitness in Black men with PCa who are being treated with ADT. The variables analyzed included relative VO_{2peak} , absolute VO_{2peak} , RER, and VE/ VCO_2 slope. No within-group effect was found for any of the variables in the exercise or control group. Similarly, no between-group effect was found for any of the cardiorespiratory measures tested. Analyses of the three covariates found differing results between pre-intervention variables. All post-intervention values were strongly predicted by their pre-intervention values, with age and cancer stage having different strengths in predicting post-intervention measures depending on the variable.

Absolute VO_{2peak} and Relative VO_{2peak}

VO_{2peak} , or peak oxygen consumption, is a strong predictor of cardiorespiratory health and mortality risk. Furthermore, in a study on colorectal cancer diagnoses, it was found that cancer patients had a VO_{2peak} 23% below age-matched control participants and only 17% higher than patients who experienced a previous heart failure.¹⁵ In our population of untrained PCa survivors, the expectation of similar pre-intervention VO_{2peak} was met between the exercise and control groups. While the increase in VO_{2peak} was not statistically significant, there was still a sizeable increase between the exercise groups' pre- and post-intervention measures that was nearly statistically significant (Figure 22). In another randomized control trial with progressive resistance and aerobic intervention, similar results were found. Their 12-week, twice-weekly intervention included eight resistance movements and 15-20 minutes of cycling or jogging and found a borderline

significant increase in aerobic walking capacity.¹² While both this study and the aforementioned study did not provide statistically significant results, both did see a mean increase in aerobic capacity. In contrast, many other studies have proved that an exercise intervention will improve VO_{2peak} . For example, a 6-month, twice-weekly study of combined progressive aerobic and resistance exercise found a significant increase in VO_{2max} . Their intervention included six resistance exercises targeting different parts of the body and 20-30 minutes of aerobic training at in-person group training sessions.²⁷ One of the more interesting contrasts between the two mentioned studies and this trial was the duration of the intervention. The two shorter interventions, 12-week, and 16-week, did not yield significant results, while the longer 6-month intervention did.

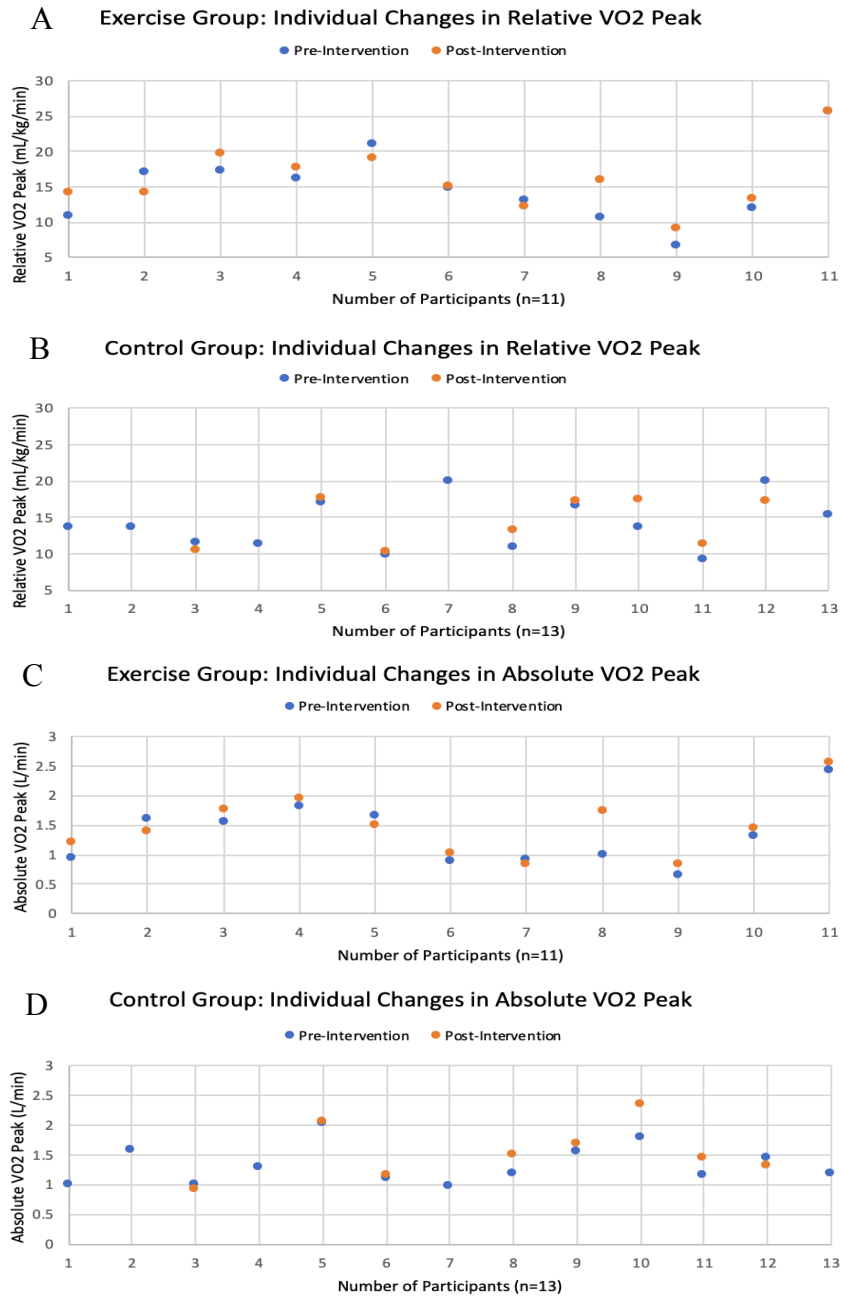


Figure 22: Individual Changes in Relative VO_{2peak} - (A) Exercise Group and (B) Control Group, Individual Changes in Absolute VO_{2peak} - (C) Exercise Group and (D) Control Group⁽³¹⁾

⁽³¹⁾ (n = x) indicates number of participants, with each line in x-axis one participant. Blue dots indicate pre-intervention values, while orange dots indicate post-intervention values. Data collected by DFCI study staff.

RER

RER, or respiratory exchange rate, quantifies the amount of carbon dioxide produced by the body compared to the oxygen that is consumed. Unlike the VO_{2peak} , RER changed in different directions for the exercise and control groups. Average RER decreased in the exercise group across the intervention period, while average RER increased in the control group (Figure 23). Neither of these differences was significant and could be due to normal standard error. In comparison, one study of trained versus untrained individuals highlighted that trained subjects exercising at higher intensities had significantly lower RER values and a higher VO_{2max} . Additionally, it was found that RER in both groups was associated with body fat percentage, heart rate, VO_{2max} , and lactate threshold.²¹ This complements the decrease seen in the exercise (trained) group, and the increase in the control (untrained) group.

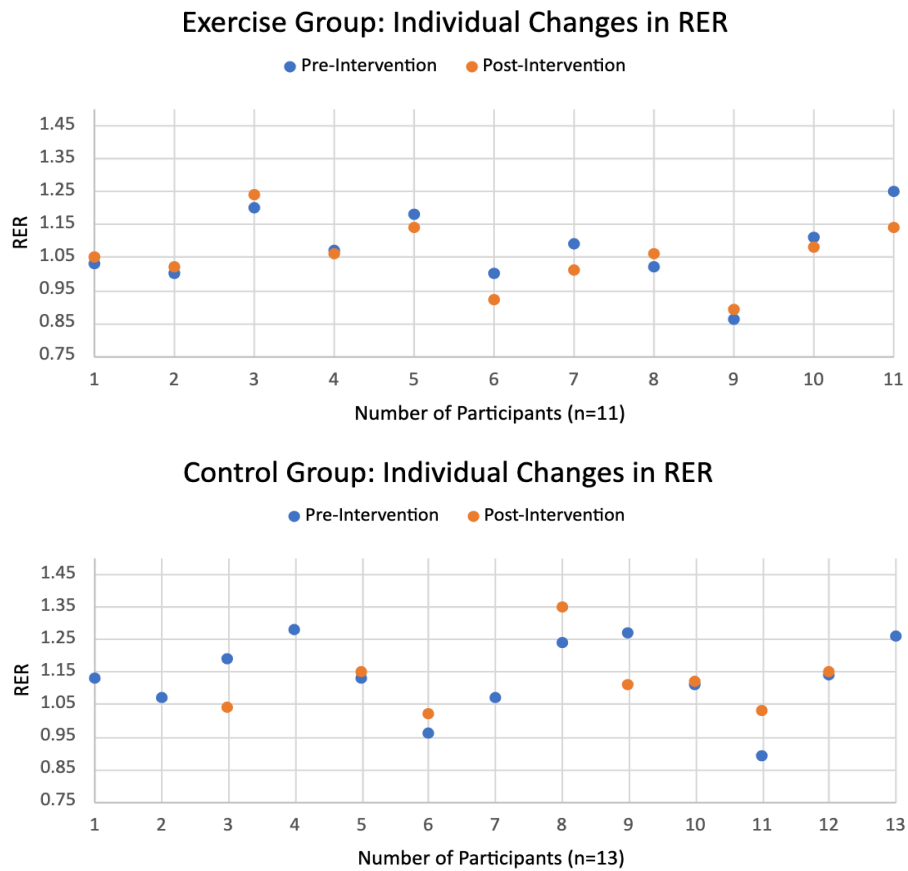


Figure 23: Individual Changes in RER by Group⁽³²⁾

VE/VCO₂ Slope

VE/VCO₂ slope, or ventilatory efficiency, is a measure of how much ventilation is required to remove carbon dioxide from the body. VE/VCO₂ slope has been found to reflect the right ventricular-pulmonary vascular function during exercise, and a value greater than 34 is associated with a poor prognosis in patients with heart failure.¹⁹ In this study, the exercise group displayed no change in the VE/VCO₂ slope, and the control

⁽³²⁾ (n = x) indicates number of participants, with each line in x-axis one participant. Blue dots indicate pre-intervention values, while orange dots indicate post-intervention values. Data collected by DFCI study staff.

group showed a small decrease (Figure 24). This is in direct contrast to what would be expected as the ventilatory efficiency should decrease with improved fitness. For example, in a study of older adults, it was found that strength training increased exercise tolerance and peak ventilatory efficiency.⁶

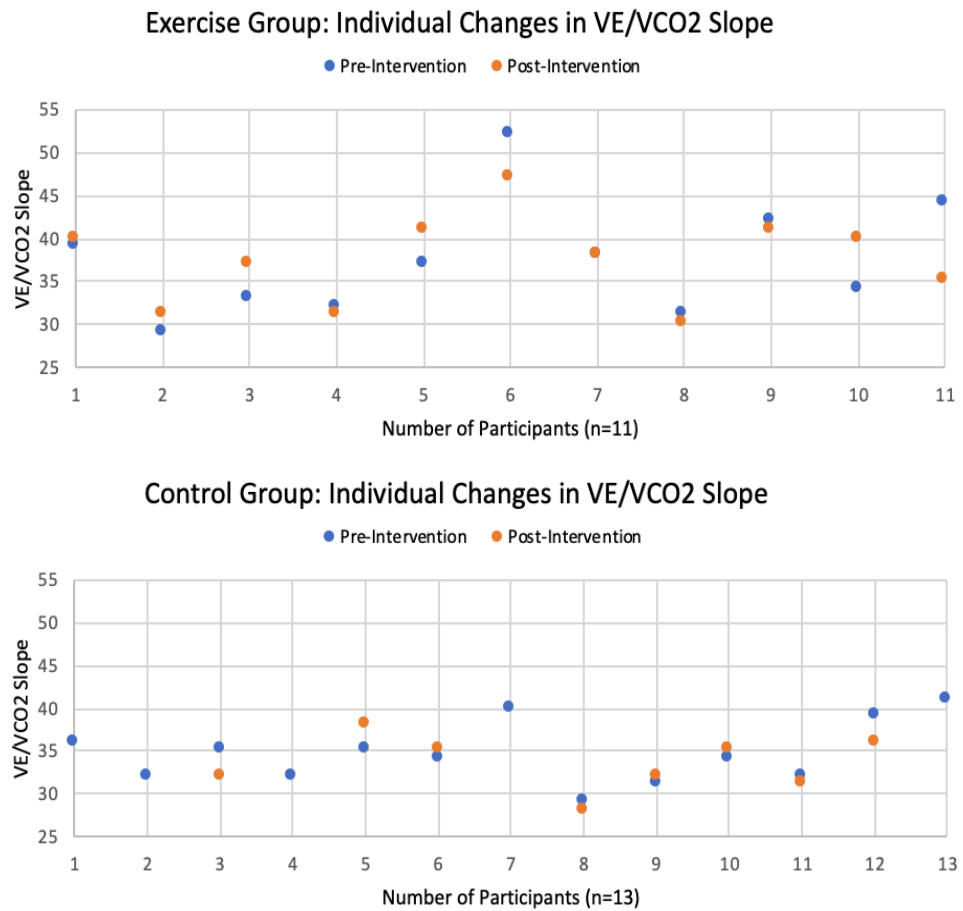


Figure 24: Individual Changes in VE/VCO₂ Slope by Group⁽³³⁾

⁽³³⁾ (n = x) indicates number of participants, with each line in x-axis one participant. Blue dots indicate pre-intervention values, while orange dots indicate post-intervention values. Data collected by DFCI study staff.

Covariates

As expected, the pre-intervention relative VO_{2peak} , absolute VO_{2peak} , RER, and VE/ VCO_2 slope were significant predictors of their post-intervention values. This means that the effect of the intervention could have been masked by the effects of the covariates. In contrast, neither of the groups were significant predictors of post-intervention relative VO_{2peak} , absolute VO_{2peak} , RER, or VE/ VCO_2 slope. However, the significance of the group in the ANCOVA improved from the significance in the between-groups analysis through the independent samples t-tests. The increased significance implies that the pre-intervention measurements and covariates played an important role in the post-intervention values and that the intervention had a stronger effect than what was initially detected.

Through ANCOVA analyses, age was deemed a significant predictor of post-intervention RER and was not a significant predictor of post-intervention relative VO_{2peak} , absolute VO_{2peak} , or VE/ VCO_2 slope. The correlation of the two would be expected as aerobic capacity decreases with age. In a study determining the factors contributing to RER, it was found that RER will decrease with age and a variety of other factors²⁴. In contrast to this study, one would also expect age to be a strong predictor of relative VO_{2peak} . This is confirmed in other trials investigating VO_{2max} in different age groups. Results found that when compared to the 21-30-year-old group, the 41-50-year-old and 50-year-old or older cohorts had significantly decreased VO_{2max} .²⁹

Cancer stage was found as a significant predictor of post-intervention RER but was not a significant predictor of post-intervention relative VO_{2peak} , absolute VO_{2peak} , or

VE/VCO₂ slope. Since a higher RER is associated with decreased physical activity, a patient with later-stage disease is most likely more sedentary. In addition, later-stage cancer may have a more aggressive treatment plan that can be more debilitating for the patient. For example, in patients with advanced-stage cancer, fatigue is the most commonly reported symptom, with other symptoms of generalized weakness and decreased functional status.¹ In contrast, other trials have shown the opposite. In a study of women with advanced-stage breast cancer, participants randomized to the seat exercise intervention reported significantly decreased fatigue scores.¹

Limitations

One of the main limiting factors in this study was the number of participants at the time of analysis; however, the trial is currently ongoing, and thus, future analyses will integrate additional participant data.

A large challenge was the dropout of participants at all time points of the study. This can be partly attributed to the fear of not receiving the intervention, concern with the randomization process, or side effects from the intervention. In one study, it was found that the acceptance of randomization was the largest predictor of participation for women with breast cancer in a hypothetical trial.²² Additionally, once in the study, participants assigned to control groups were less likely to return for follow-up testing. As a result of the small sample size, the effect size and power of the many analyses are small or may not be representative of the population as a whole.

Interestingly, the analysis of the absolute VO_{2peak} revealed an increase in the control and exercise groups. This could be attributed to the practice effect, which is the

change in testing outcomes due to practice or prior exposure to testing equipment.¹⁸ Control participants may have felt more comfortable with VO_{2max} testing equipment and procedure in the post-intervention testing, resulting in an improvement in the tested absolute VO_{2peak} . Another possibility is that the participants in the control group increased their exercise despite being told to maintain their current levels. In a recent systemic review of trials with physical activity as an intervention, 28% of the trials reported control group activity levels reaching magnitudes similar to the intervention group. Possible factors for increased physical activity were methods of physical activity assessment, screening to exclude active participants and preexisting health status.²⁸

Lastly, participants could have experienced a placebo effect, leading to an increase in physical performance during the graded maximal exercise testing that was not correlated to any intervention. This has been shown to affect control participants and intervention participants. An example of this is a study of hotel attendants who were sorted into an informed group and a control group. The informed group was told that they currently met national exercise recommendations, while the control group was not notified of the recommendations. While the level of activity did not increase in either group, the informed group saw a significant decrease in body fat percentage, body mass index, and systolic blood pressure.⁸ This proves that the thought of improved exercise and perception of increased levels could have a physiological benefit. This could similarly be applied to control participants who feel that participating in an exercise study and completing exercise during testing increased their activity levels.

Clinical and Scientific Implications

Prostate cancer is one of the most frequently diagnosed cancers across the world and disproportionately affects Black men. ADT, a common treatment for prostate cancer, has been proven to increase the risk for CVD and all-cause mortality through a variety of mechanisms. In addition, patients on prolonged ADT (> six months) were found to have worse cardiorespiratory fitness.¹³ While the exercise intervention did not achieve a statistically significant change in the three measures of fitness, the trend towards significance with ANCOVA tests suggests there may be a benefit to structured exercise. The mean relative and absolute VO_{2peak} and RER for the exercise group both improved between pre-intervention and post-intervention testing, indicating a more fit population and decreased risk for CVD. Since exercise has already been proven to be feasible and safe in PCa patients, more work is needed to define its specific effect. As an example, one study of a home-based exercise intervention was found to be safe, while preventing or improving the decline of functional fitness and quality of life measures associated with treatment.⁴ Despite these insignificant results, the trend of cardiorespiratory markers could be illuminating a positive effect of exercise. Considering the lack of studies that include Black men and their worse clinical outcomes, further work is needed.

Future Work

One of the most apparent ways to improve this research would be through increasing the sample size of the population. Increasing each group would establish more similar pre-intervention characteristics while increasing statistical power for detecting significant effects. This could produce better results as the pre-intervention value of each

variable was significant in predicting the post-intervention value. This was similar across all variables and could potentially explain how the effect of the intervention could have been masked. On a similar note, increasing the duration of the intervention may allow more time for physiological adaptations to occur.

As mentioned earlier, Black men with PCa face worse clinical outcomes and differing disease characteristics. Further studies are needed to continue advancing research and finding ways to combat the side effects of common treatments such as ADT.

CONCLUSION

This study examined the impact of exercise on four measures of fitness: relative VO_{2peak} , absolute VO_{2peak} , RER, and VE/VCO_2 slope in Black PCa survivors who are undergoing ADT. The necessity for this study is outlined by the fact that Black men are often excluded from clinical research, despite facing worse PCa disease characteristics and prognoses. Furthermore, ADT, a first-line treatment for PCa, has been shown to have a negative impact on cardiovascular health and overall mortality. Analyses within the group did not show significant changes between any pre-intervention and post-intervention measures. Similarly, between-group analysis also did not show any significant changes in any of the four measures. Analyses of the covariates improved the significance for each measure of cardiorespiratory fitness but still failed to reach the appropriate significance level. This suggests that the intervention may have had more of an effect than what was first noticed but is still insignificant in its findings. Regardless, there was an improvement in relative VO_{2peak} , absolute VO_{2peak} , and RER that depicts increased fitness in exercise participants. It is worth noting that all three could have also been a result of a practice or placebo effect. While the results were not significant, the potential increase lays the groundwork for further analysis with a larger sample. More alterations to the intervention such as longer duration, different modalities, and using other fitness measures could shed more light on the possibility of significant results. With the high rate of PCa diagnosis in Black men, the known side effects of ADT, and the disproportionate effect the disease has on Black men there is a reason to continue research on improving cardiovascular fitness and overall health.

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CURRICULUM VITAE

