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The influence of exercise intensity on insulin sensitivity and the insulin-like growth factor axis in colorectal cancer survivors.

Andrew Thomas Sax

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ABSTRACT

Of all cancers, colorectal cancer has the fourth highest incidence rate worldwide and it is estimated that colorectal cancer is responsible for the deaths of approximately 608,000 people each year. Due to improved detection and treatment protocols, mortality from this disease has decreased in recent years, with 5-year survival rates for localised tumours approximately 90%. However, the risk of developing second primary colorectal cancers is higher in survivors, with an estimated 1.4 fold increased risk compared to healthy controls.

Physical activity is significantly related to colorectal cancer risk; individuals who engage in higher levels of physical activity are at a 26% reduced risk of developing colorectal cancer compared to those who engage in lower levels of physical activity. Moreover, there is convincing epidemiological evidence to suggest that vigorous activity elicits a greater risk reduction for the development of colorectal cancer than activity performed at a moderate intensity. Previous research has implicated insulin sensitivity and the insulin-like growth factor (IGF) axis as factors related to the risk of colorectal cancer. The aim of this study was to investigate the influence of exercise intensity on insulin sensitivity and the IGF axis in colorectal cancer survivors. Twenty-nine men and women aged 33 – 82 years completed a 4-week randomised controlled exercise intervention incorporating three sessions per week of moderate intensity exercise (MIE) or high intensity interval training (HIE). For this trial, the MIE protocol was considered a 'usual care' control group in the context of physical activity recommendations, given that the exercise demands for those in the MIE group align with the current exercise oncology guidelines. Before and after the intervention, insulin sensitivity using an oral glucose tolerance test (OGTT), insulin-like growth factor-I (IGF-I), and insulin-like growth factor binding protein-III (IGFBP-III) were measured. Peak cardiorespiratory (VO2peak) test, fat mass, lean mass, and body fat percentage were also measured pre- and post-intervention. HIE significantly improved 120 min glucose readings from the

OGTT following the 4-week intervention (-7.1%, $p = 0.037$). No significant ($p > 0.05$) between- or within-group changes were found for other measures of insulin sensitivity, IGF-I, or IGFBP-III. VO2peak significantly increased in both the HIE (+23.0%, $p = 0.013$) and MIE group (+1.7%, $p = 0.025$) with training, with no significant between-group differences ($p = 0.124$). In the HIE group only, significant changes were found for fat mass (-3.3%, $p \leq 0.001$), lean mass (+1.8%, $p \leq 0.001$), and body fat percentage (-3.3%, $p \leq 0.001$) following the intervention. There were no significant ($p > 0.05$) changes in body composition for the MIE group.

The absence of change in insulin sensitivity and the IGF axis following the exercise interventions are likely due to baseline values in these measures falling within ranges described in healthy persons. The significant training-induced changes in VO_2peak, fat mass, lean mass, and body fat percentage observed in the HIE group are potentially clinically meaningful, as improvements in these markers have previously been associated with reduced cancer specific- and all cause-mortality. The present study has shown that HIE is a safe and effective mode of exercise for rapidly improving cardiorespiratory fitness and body composition, but not insulin sensitivity or the IGF axis, in colorectal cancer survivors.

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PUBLICATIONS DURING CANDIDATURE

Sax AT, Jenkins DG, Devin JL, Hughes GI, Bolam KA, Skinner TL. The insulin-like growth factor axis: A biological mechanism linking physical activity to colorectal cancer survival. Cancer Epidemiology. 2014;38:455–9.

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Contributor	Statement of contribution
Andrew Sax (Candidate)	Conception and design (70%) Literature search (100%) Writing (100%)
Tina Skinner	Conception and design (10%) Editing (30%)
David Jenkins	Conception and design (10%) Editing (30%)
Kate Bolam	Conception and design (10%) Editing (30%)
James Devin	Editing (5%)
Gareth Hughes	Editing (5%)

CONTRIBUTIONS BY OTHERS TO THE THESIS

Dr Tina Skinner, Associate Professor David Jenkins and Dr Kate Bolam contributed to drafting significant components of the thesis and revising it so as to contribute to the interpretation; Mr James Devin and Mr Gareth Hughes significantly contributed to the collection and interpretation of research data.

STATEMENT OF PARTS OF THE THESIS SUBMITTED TO QUALIFY FOR THE AWARD OF ANOTHER DEGREE

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Alone we can do so little, together we can do so much. --Helen Keller

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Any intelligent fool can make things bigger, more complex, and more violent. It takes a touch of genius—and a lot of courage to move in the opposite direction. --Albert Einstein

KEYWORDS

cancer, neoplasm, colorectal, insulin, growth factor, binding protein, exercise, physical activity.

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LIST OF ABBREVIATIONS

ALS	Acid Labile Subunit
BMI	Body Mass Index
BP	Blood Pressure
CV	Coefficient of Variation
DXA	Dual-energy X-Ray Absorptiometry
GH	Growth Hormone
HIE	High Intensity Exercise
HOMA-IR	Homeostatic Model Assessment – Insulin Resistance
HR	Heart Rate
IGF	Insulin-like Growth Factor
IGFBP	Insulin-like Growth Factor Binding Protein
IQR	Interquartile Range
ISI	Insulin Sensitivity Index
LID	Liver IGF Deficient
MET	Metabolic Equivalent of Task
MIE	Moderate Intensity Exercise
NS	Not Significant
OGTT	Oral Glucose Tolerance Test
PA	Physical Activity
VO_2	Volume of Oxygen Consumed

CHAPTER 1 GENERAL INTRODUCTION

Colorectal cancer is the second most prevalent cancer in both men and women in Australia and has the second highest burden of disease of all cancers (1). Physical inactivity has a significant influence on colorectal cancer development; at least 15% of all colorectal cancer cases can be been attributed to insufficient physical activity (2). Supporting this, individuals who engage in higher levels of physical activity (>21 MET hours per week) are at a 24% reduced risk of developing colorectal cancer compared to those who engage in lower levels of physical activity (<2 MET hours per week) (3,4). Given that colorectal cancer survivors have a 1.4 fold increased risk for the development of second primary colorectal cancers compared to healthy persons (5), physical activity should be considered an essential adjuvant therapy for this population.

Physical activity has been shown to improve cardiovascular fitness and body composition in colorectal cancer survivors (6-8). Improvements in these measures are synonymous with decreased disease recurrence and lower mortality rates in this population (2). Specifically, there is convincing epidemiological evidence to suggest that vigorous activity (>85% of peak heart rate) is associated with a lower risk of colorectal cancer-specific mortality compared to moderate intensity (50-70% of peak heart rate) activity (9-11). Despite these findings, the optimal intensity of physical activity for preventing the development of colorectal cancer and reducing disease-specific mortality are yet to be established. This is, at least in part, due to an incomplete understanding of the biological mechanisms linking physical activity to colorectal cancer development and disease-specific mortality.

One mechanism that could potentially explain the relationship between physical activity and colorectal cancer risk is the insulin-like growth factor (IGF) axis; a family of proteins known to be associated with colorectal cancer pathology. Specifically, the IGF axis is believed to influence

cellular growth, proliferation regulation, differentiation and apoptosis (12,13). In light of this biological relationship, hyperinsulinemia has been implicated as a key host factor in colorectal cancer development due to the physiological similarities between insulin and the IGF axis (12,13). Insulin sensitivity, IGFs and their binding proteins have thus been a key research focus in colorectal cancer pathology (14).

The presence of diabetes in colorectal cancer survivors has been positively associated with heightened disease-specific mortality, with a relative risk of 1.36 compared to those who are non-diabetic (15). The insulin-like growth factor-1 (IGF-I) receptor is 60% homologous to the insulin receptor and is thus able to bind the insulin molecule and initiate cellular proliferation (16). Therefore, hyperinsulinemia leads to greater activation of the IGF-I receptor, and the subsequent mitogenic pathways it regulates. Physical activity has consistently been shown to improve insulin sensitivity, reduce hyperinsulinemia and the subsequent risk of disease-specific mortality in diabetics (17,18). A similar relationship between physical activity and insulin sensitivity has been found in colorectal cancer survivors; reductions in plasma insulin occurred in response to 12 weeks of moderate intensity exercise training (19).

Research findings from studies examining the relationship between physical activity and the IGF axis in cancer populations is mixed (20-22), however there is evidence showing positive changes in components of the IGF axis in response to regular exercise in colorectal cancer survivors (19,23). Haydon et al. (24), via prospective analysis of colorectal cancer-specific mortality, reported that a one standard deviation increase in insulin-like growth factor binding protein-III (IGFBP-III) was associated with a 51% reduction in premature mortality for those who were physically active. This association was not seen for inactive individuals (24). The researchers did not provide details relating to the specific intensity of exercise.

Recently, Lee et al. (19) measured changes in IGF-I and IGFBP-III following a 12-week home-based exercise intervention in colorectal cancer survivors. An increase in IGFBP-III was found in response to the intervention. To date, the aforementioned studies are the only ones to have examined the relationship between physical activity, insulin sensitivity and the IGF axis in colorectal cancer survivors. Research involving tightly controlled exercise interventions will advance understanding of the relationship between insulin sensitivity, the IGF axis and the risk of development of colorectal cancer. The 'Colon Health and Life-Long Exercise Change' (CHALLENGE) trial (25) is currently addressing this research gap. This ongoing randomised controlled trial incorporating a multicentre physical activity intervention is utilising instrumented measures of physical activity and aerobic fitness for people with stage II and III colon cancer. The primary outcomes of the CHALLENGE trial are disease-free survival and identification of key biological markers (insulin, insulin-like growth factors, and selected cytokines) believed to underpin the relationship between physical activity and survival after colorectal cancer diagnosis.

Emerging evidence suggests that high intensity exercise (HIE) is more effective than moderate intensity exercise (MIE) for improving insulin sensitivity in clinical populations characterised by impaired glucose control (17,26). This type of exercise training has proven to be safe and effective in cancer populations, with a reported 70% adherence to a high intensity exercise intervention, and no adverse events (27). It is therefore plausible that high intensity interval exercise may elicit superior improvements in insulin sensitivity in colorectal cancer survivors compared to moderate intensity exercise. The IGF axis is yet to be measured in response to high intensity interval training.

The aim of the study described in Chapter 3 of the present thesis was to compare the effect of high intensity interval training and moderate intensity exercise training on insulin sensitivity and the IGF axis in colorectal cancer survivors. It was hypothesised that high intensity interval training would result in greater increases in insulin sensitivity and IGFBP-III, and a greater reduction in IGF-I

compared to moderate intensity exercise training. Available evidence shows volumes of exercise that meet the current exercise oncology will reduce the risks of colon cancer. What is not clear is whether exercise completed at higher intensities to those aligned with current guidelines can confer potentially greater health benefits. Body composition and cardiorespiratory fitness were also assessed before and after the training programs to identify potential relationships between changes in insulin sensitivity, the IGF axis and these measures of health.

CHAPTER 2 REVIEW OF LITERATURE

2.1 Introduction

Of all cancers, colorectal cancer has the fourth highest incidence rate worldwide and it is estimated that colorectal cancer is responsible for the deaths of approximately 608,000 people each year (1). Due to improved detection and treatment protocols, mortality from this disease has decreased in recent years, with 5-year survival rates for localised tumours around 90% (28). However, the risk of second primary colorectal cancers in colorectal survivors is heightened up to 1.4 fold compared to healthy controls (5). Given this, preventing the development of primary colorectal cancers in current survivors is a public health priority.

Physical activity has been significantly associated with the prevention of colorectal cancers, whereby individuals who are physically active (>22 MET hours per week) have a 24% reduced risk of developing the malignancy compared to those who engage in lower levels of physical activity (<2 MET hours per week) (4). Further, epidemiological data show a significant decrease in disease-specific mortality for individuals who are physically active after diagnosis compared to those who are not (29,30). Though the biological mechanisms that underpin this association are not entirely clear, insulin and the IGF axis may be involved.

Insensitivity to insulin underpins the pathology of diabetes; a biological marker that responds favourably to physical activity. Diabetics have a 1.2-1.5 fold increased risk for the development of colorectal cancer compared to those without diabetes (31,32). Risk of mortality from colorectal cancer is also heightened (1.4 fold) in diabetics compared to non-diabetics (31,32). These associations premise investigation into the physiological connection between insulin, physical

activity and the development of second primary colorectal cancers. Due to its functional similarity to insulin, the IGF axis has also been implicated as a key host pathway potentially responsible for the association between physical activity and colorectal cancer (33-35).

Physical activity may represent an effective means of eliciting favourable changes in the insulin molecule and the IGF axis in colorectal cancer survivors. Presently, there is an absence of research investigating the effects of structured physical activity interventions on these biomarkers in colorectal cancer survivors. Available evidence surrounding the influence of physical activity on the development of colorectal cancer, insulin and the IGF axis will be reviewed in subsequent sections of this chapter.

2.2 Physical activity is protective for the development of primary colorectal cancers

An inverse relationship between physical activity and risk of developing colorectal cancer has been consistently reported in the literature (4,36,37). For those who are physically active (>22 MET hours per week), meta-analyses have calculated a 20-30% risk reduction for developing colorectal cancer compared to inactive persons (4,36,37). Furthermore, engaging in physical activity after colorectal cancer diagnosis is associated with a 50-60% reduction in disease-specific mortality (23,38-40). Comparatively, colorectal cancer patients who receive chemotherapy benefit from 40-50% reductions in mortality compared to those who receive surgery alone (41). With this in mind, physical activity is an essential therapy both for the prevention of colorectal cancer development, and reduction in mortality risk for those already diagnosed with the disease. Despite this recommendation, there is still much uncertainty surrounding the optimal prescription of physical activity required to elicit these changes.

2.2.1 Physical activity in the prevention of colorectal cancer

Over the past ten years, three meta-analyses (4,36,42) have confirmed an inverse relationship between both leisure time and occupational physical activity, and the risk for developing colon cancer. Samad et al. (36) analysed 19 cohort and 28 case-control studies and identified a relative risk for developing colon cancer when comparing the most to the least active individuals, of 0.78 and 0.79 in men for leisure time and occupational physical activity, respectively. For women, a relative risk for developing colorectal cancer of 0.71 was identified for leisure time physical activity only compared to no physical activity. More recently, Wolin et al. (4) found a lower relative risk for developing colorectal cancer (0.76) in both men and women when comparing the most to least active individuals. In the study by Wolin et al. (4), activity levels in the most active group equated to approximately 5-6 hours of brisk walking per week, whereas the least active group performed approximately 0.5 hours of brisk walking per week. The levels reported in the most active group (5-6 hours of brisk walking per week) are significantly greater than the current physical activity recommendations for cancer survivors, which advocate 1.5 hours of brisk walking (or equivalent) per week (43). For the prevention of colorectal cancer, greater quantities of physical activity than what is currently recommended may be required. This is of particular importance to colorectal cancer survivors who have a heightened risk (1.4) for the development of second primary colorectal cancers compared to healthy persons (5).

A meta-analysis by Boyle et al. (37) highlights the position that 'more is better', reporting an inverse dose-response relationship between physical activity level and colorectal cancer risk in 9 of the 13 studies included in their analysis. Apart from increasing the duration of physical activity, 'dose' can be modulated through activity intensity, whereby higher intensity activity upturns the overall dose. Three case-control studies (9,44,45) have highlighted a greater risk reduction for the development of colorectal cancer with vigorous intensity physical activity compared to moderate intensity activity. Boyle et al. (44) further supports the 'dose response' relationship reporting a

superior effect for >18 MET-hours per week (hazard ratio = 0.45, 95% CI = 0.24-0.85) compared to 6-18 MET-hours (hazard ratio = 0.51, 95% CI = 0.29-0.91) and <6 MET-hours (hazard ratio = 1.05, 95% CI = 0.64-01.71) of physical activity per week (P_{trend}=0.006).

The findings outlined above are promising for the prescription of high intensity, over moderate intensity physical activity in the prevention of colorectal cancer development. In light of the heightened risk of second primary cancers in colorectal cancer survivors (5), high intensity activity may also be beneficial for persons who have survived the disease. This is yet to be investigated in a controlled intervention. Given the substantial time and sample size requirements needed to measure colorectal cancer development as a primary outcome, it may be more feasible to initially investigate the impact of exercise intensity on biological markers that have been linked to the development of the disease. These will be discussed in section 2.3 of this review.

2.2.2 Physical activity in the prevention of colorectal cancer-specific mortality

Following conventional treatment, colorectal cancer survivors who remain or become physically active have a 50%-60% reduction in cancer-specific mortality compared to those who are inactive (38-40). Indeed, physical activity is recommended as an adjuvant to conventional treatment for those having been diagnosed with the disease (4,23,36,38-40,42).

Meyerhardt et al. (38) found an inverse relationship (p = 0.0002) between physical activity and colorectal cancer-specific mortality in male survivors. In a cohort of 661 men, engaging in more than 27 metabolic equivalent of task (MET) hours of physical activity per week was associated with a decreased risk of colorectal cancer-specific death (hazard ratio = 0.47, 95% CI = 0.24-0.92) compared to those who engaged in less than 3 MET hours per week (38). In a cohort of 573 female colorectal cancer survivors, a relative risk of 0.39 was found for those who engaged in at least 18 MET hours of physical activity per week compared to those who engaged in less than 3 MET hours

per week (39). Both studies found adjustment for cancer stage (I-III), body mass index and pre-diagnosis levels of physical activity did not affect the relationship. These robust findings highlight the importance of physical activity following diagnosis irrespective of pre-diagnosis activity levels. Although the specific intensity of physical activity required for reductions in colorectal cancer-specific mortality is not known, Meyerhardt et al. (38) indicated that a protective effect for colorectal cancer-specific mortality is likely to occur at approximately 9 MET hours per week. This volume of physical activity aligns well with the current physical activity recommendations for cancer survivors (43).

The majority of studies to have investigated the relationship between physical activity and colorectal cancer survival have not reported the intensity of activity performed by the participants (4,23,36,38-40,42). Rather, MET values have been reported, which are an amalgamation of frequency, duration and intensity of activity. To a large part, this can be attributed to the limitations of self-recall physical activity measures used in these studies, which typically estimate activity levels using assignment of MET values to specific tasks. Additionally, participants are more likely to over-report than under-report when recalling previous activity levels (46). This limits the conclusions that can be drawn from studies with respect to the optimal intensity of physical activity required to elicit a protective effect for colorectal cancer-specific mortality.

Research that involves structured physical activity interventions is required to better understand the relationships between colorectal cancer-specific mortality and physical activity. Particularly, these studies need to place a central focus on activity intensity, and how this variable implicates mortality. As discussed in section 2.2.1, there are difficulties associated with measuring mortality as a research outcome; namely, time required to track mortality. Rather, the measurement of biological markers that have been previously linked to disease-specific mortality in colorectal cancer survivors could be used as surrogate measures. The results from the previously mentioned CHALLENGE

trial (which will measures both biomarkers and mortality in response to a physical activity intervention for colorectal cancer survivors) will be extremely useful in supporting these insights.

2.2.4 Section summary

Physical activity has been consistently linked to a decreased risk for the development of colorectal cancer (4,36,37), and reductions in disease-specific mortality following diagnosis. Further, a dose-response relationship has been reported between physical activity and the development of colorectal cancer (44). This adds weight to the claim that high intensity activity (a derivative of activity dose) is more beneficial than moderate activity for the prevention of colorectal cancer development, and disease-specific mortality following diagnosis (9,44,45).

2.3 Insulin sensitivity and the insulin-like growth factor axis

Diabetes, which is characterised by insulin resistance, has been linked to the development of colorectal cancer (47,48). Further, individuals with colorectal cancer who also have diabetes have higher mortality rates compared to individuals who have colorectal cancer but not diabetes (49,50). In light of the already elevated risk for the development of second primary cancers in colorectal cancer survivors, insulin control in this population is an essential therapeutic target to limit the development of second cancers. Given this, investigating the effect of physical activity on insulin resistance and sensitivity in colorectal cancer survivors is warranted.

The IGF axis may also be involved in the relationship between physical activity, risk for developing colorectal cancer and disease-specific mortality (2,3). Specifically, the IGF axis plays a central role in cellular growth, proliferation regulation, differentiation and apoptosis (12,13). At a structural level, the insulin molecule bears a similar resemblance to certain members of the mitogenic IGF axis, specifically IGF-I. This allows the insulin molecule to initiate similar growth processes within

cancerous cells (12,13). Given these mechanisms, insulin, IGFs and their binding proteins have been identified as a key research focus in colorectal cancer pathology (14).

2.3.1 Physiology and mechanics of insulin and the insulin-like growth factor axis

The IGF axis consists of two polypeptide ligands (IGF-I and IGF-II), two cellular membrane receptors (IGF-IR and IGF-IIR), and six binding proteins (IGFBP-1 through IGFBP-6). IGF-I and IGF-II are produced via the endocrine, paracrine and autocrine systems (51). Growth hormone (GH) plays a dominant role in the upregulation of IGF-I with serum levels peaking around puberty and then decreasing throughout life (52,53). IGF-I levels are also influenced by sex and nutritional status with higher levels found in women (54), during periods of excess energy intake (55) and with obesity (52). Unlike IGF-I, the release of IGF-II is GH independent and levels remain stable after puberty (51). At a cellular level, IGF-I and IGF-II accelerate cell cycle progression through the growth phase where DNA replication occurs (56). Analogous to this growth-facilitating effect, IGF-I and IGF-II have the capacity to block cellular apoptosis. These processes have been reported in healthy (16) and malignant tissue (57), highlighting the potential role of IGF-I and IGF-II in the progression of colorectal cancer following diagnosis.

The biological actions of IGF-I and IGF-II are mediated via two cell-surface receptors; IGF-IR and IGF-IIR (16). Because of the structural similarities between IGF-I and IGF-II, the IGF-IR is able to bind both molecules albeit at different affinities. IGF-IR favours IGF-I, binding the molecule at a 2-15 fold higher affinity than IGF-II (58). Unlike the IGF-IR, the IGF-IIR does not bind IGF-I; this receptor specifically binds IGF-II, and at a 500-fold affinity greater than the IGF-IR (13). Because binding of IGF-II to the IGF-IIR results in degradation of the molecule, the intra-cellular actions of IGF-II are thought to be primarily mediated through the IGF-IR (59). This complex association underpins the uncertainty that exists for the role of the IGF axis within the relationship between physical activity and colorectal cancer.

The IGF-I receptor is 60% homologous to the insulin receptor and is able to bind the insulin molecule, albeit with a 1000-fold lower affinity than for IGF-I (16). Activation of the IGF-I receptor by the insulin molecule has the capacity to initiate downstream processes of cellular differentiation, proliferation and anti-apoptosis; mechanisms that have all been implicated in colorectal cancer prognosis (34). This pathway therefore recognises a biological link between hyperinsulinemia, insulin insensitivity and the IGF axis mediated pathways by which colorectal cancer is thought to develop and propagate.

It has been reported that insulin interaction with the IGF-I receptor only occurs at supraphysiologic levels, which may be far above what is observed even in hyperinsulinemic persons (34). What may be more apparent is an increase in plasma IGF-I and IGF-II as a result of hyperinsulinemia which, in turn, activates their respective receptors and initiates mitogenic behaviour within cancerous cells (60-62).

The majority (~75%) of IGF-I and IGF-II produced via the endocrine system are bound in a ternary complex with IGFBPs and an acid labile subunit (ALS) (63). The remaining IGF-I and IGF-II circulate in free form or in a binary unit with IGFBPs only (63). Because ALS only has an affinity for IGF-I/IGF-II that is bound in a IGFBP complex, IGFBPs are thought to control the bioavailability of IGF-I and IGF-II (64). Regulation of IGFs is achieved via three distinct pathways; 1) transportation, 2) prolonging the half-life of IGFs and protecting them from degradation, and 3) modulating the interaction between IGFs and their receptors (65). When combined in the ternary unit, IGF-I and IGF-II are unable to bind to the cell surface receptors, IGF-IR and IGF-IIR. This is due to the ~50 fold higher affinity of IGFBPs for IGF-I and IGF-II over their respective receptors (65). The outcome of this affinity is thought to be the inhibition of IGF receptor activation, which in turn prevents IGF-I and IGF-II mediated cellular proliferation and enhances apoptosis. In contrast,

IGFBPs prolong the half-life of IGF-I and IGF-II via the prevention of proteolytic degradation that would normally occur if IGF-I and IGF-II were circulating in isolation (63). This results in a lengthening of IGF-I and IGF-II bioavailability (66). Given these differing processes, IGFBPs can facilitate or inhibit the mitogenic actions of IGF-I and IGF-II. These mechanisms indicate that IGFBPs may be of similar importance to IGF-I and IGF-II in mediating cellular growth and understanding how physical activity influences colorectal cancer incidence and mortality.

In serum, IGFBP-III is the most abundant IGF binding protein, carrying approximately 90% of all bound and free circulating IGF-I and IGF-II (34). Independent to its association with IGF-I and IGF-II, IGFBP-III has been found to have a pro-apoptotic and anti-proliferative capacity (67). This has led to a focus on IGFBP-III as a mediator for the development and progression of colorectal neoplasms.

A limitation to the measurement of these biomarkers in existing cancer research is that they may not reflect downstream cellular growth. Assays used to measure IGF-I and IGF-II do not discriminate between free form IGF-I/IGF-II, and that which is bound in binary and ternary units (64). Because of this, current techniques may not reflect the bioactive IGF-I and IGF-II that are able to interact with cellular receptors. Furthermore, given that IGFBPs have both growth facilitating and inhibiting effects, direct measures of these biomarkers cannot accurately predict pro- or anti-proliferative processes. An assay that overcomes these limitations will enhance the understanding of how physical activity influences the IGF axis interaction with carcinomas. Identifying the action of intracellular growth processes rather than merely measuring circulating levels of these biomarkers is needed. Nonetheless, reductions in plasma IGF-I and IGF-II, and increases in IGFBP-III suggest a more favourable outcome for the prevention of colorectal cancer development and reductions in disease-specific mortality.

2.3.2 Epidemiology: insulin sensitivity

There is consistent evidence supporting a higher risk of colorectal cancer in people with diabetes compared to those with normal glucose control. A meta-analysis of 15 studies found a relative risk of 1.30 (95% CI = 1.20-1.40) for colorectal cancer development in individuals who were diagnosed with diabetes compared to individuals with colorectal cancer who were not diabetic (48).

Beyond the increased incidence of colorectal cancer in people with diabetes, individuals who have colorectal cancer with pre-existing diabetes have a higher risk of mortality (49). In a cohort of 1039 colorectal cancer patients, those with concurrent diabetes had a cancer-specific mortality hazard ratio of 1.36 compared to those without diabetes (68). These findings are supported by retrospective data from 469 diabetic colorectal cancer patients who had a mortality hazard ratio of 1.24 compared to those without diabetes (n=2293) (15). Within this cohort, persons with diabetes had a 5-year survival rate of 55.7% compared to 62.2% for those without diabetes.

The association between fasting insulin and glucose, and the incidence of colorectal cancer has also been investigated (69). Persons in the highest quartile of fasting glucose and insulin levels were reported to have a relative risk of 1.8 and 1.6, respectively, for colorectal cancer development when compared to the lowest quartile. Within a cohort of persons with and without recurrent colorectal adenomas it was found that persons in the highest quartile of both fasting insulin and glucose had a higher risk for recurrent adenomas compared to those in the lowest quartile. Odds ratios for the development of these recurrent adenomas for plasma glucose and insulin were 1.56 and 1.49, respectively, when comparing the highest versus lowest quartile. Further, longitudinal research has identified a predictive relationship between colorectal cancer-specific mortality and markers of insulin resistance (70). In a cohort of 718 men with colorectal cancer during 21.5 years of follow-up, it was found that those with higher levels of insulin resistance (measured via an oral glucose tolerance test) had a colorectal cancer-specific mortality hazard ratio of 1.65 compared to those with

normal insulin sensitivity. This positive association between diabetes and cancer-specific mortality has been reported across numerous cancer populations (71).

The weight of research evidence suggests the insulin molecule plays a central role in colorectal cancer pathology. Specifically, insensitivity to insulin increases a person's risk of developing colorectal cancer, and risk of disease-specific mortality for individuals already diagnosed with the cancer.

2.3.3 Epidemiology: IGF Axis

Unlike insulin sensitivity, findings from human *in vivo* research examining the IGF axis and colorectal cancer-specific mortality have produced varying results (14,72-75). These studies have focussed on tumour grade and metastasis, where a greater tumour grade and extent of metastasis infers a heightened colorectal cancer mortality risk (14,72,73,75,76). Across other cancer populations such as breast and prostate, a more consistent positive association between cancer-specific mortality and the IGF axis has been reported (56,77).

Prospective samples from men and women undergoing a colonoscopy identified high-risk adenomas to be positively associated with serum IGF-I and inversely associated with IGFBP-III (72). Supporting this, in a cohort of 125 colorectal cancer patients, higher serum concentrations of IGF-I were found in those with metastases compared to those with localised colorectal cancer (73). Similar associations for IGF-I and adenoma severity were reported by Jacobs et al. (74). IGF-II has also been linked to colorectal cancer severity with higher serum levels found in concurrence with secondary cancers (14). In contrast to these findings however, no significant differences in serum IGF-I were reported with patients who had moderate (adenoma) compared with more advanced (carcinoma) colon cancers (75). Nonetheless, the weight of the limited available evidence supports

a positive relationship between IGF-I/IGF-II and colorectal cancer-specific mortality and an inverse relationship between IGFBP-III and colorectal cancer-specific mortality.

In vitro research has been used to examine markers of the IGF axis after colorectal cancer diagnosis to determine the relationship with disease-specific mortality. Wolpin et al. (78) addressed this with 373 participants over 13 years and found no associations between pre-diagnostic IGF-I and IGFBP-III concentrations, and mortality in those who developed colorectal cancer. Given that lifestyle factors such as diet, obesity and physical activity are known to influence IGFs (52,64), failure to include these confounders into the analysis may have contributed to the lack of significant findings with regard to IGF-I and IGFBP-III. Following colorectal cancer diagnosis, higher circulating IGFBP-III has been correlated with a greater response to chemotherapy, arrested rate of tumour progression, and an increase in overall survival (79).

Within animal models, research has identified significant associations between tumour severity and IGF-I, IGF-II and IGFBP-III (14,72,73,75,76). IGF-I has been found to influence colon cancer tumour growth and metastasis in liver IGF-I deficient (LID) mice, which have approximately 75% less endogenous IGF-I than controls (76). Following transplantation of colon adenocarcinomas, LID mice had smaller and fewer tumours with less liver metastases than controls. Further, exogenous IGF-I administration in both controls and LID mice increased the rate of tumour progression and metastases compared to mice treated with saline (76).

Given the pathways by which IGF-I and IGF-II stimulate cellular proliferation, expression of IGF-I receptor (IGF-IR) and IGF-II receptor (IGF-II R) in colonic carcinomas likely influences tumour progression. A high presence of these receptors in tissues would allow for enhanced activation of intracellular growth via IGF signalling. Positive tissue staining for IGF-IR has been more frequently identified in primary and high risk colorectal cancers in comparison to non-cancerous adenomas

and normal tissue (80,81). Further research has identified IGF-IR and IGF-IIR gene expression to be 2.5 and 4.0 times higher, respectively, in malignant tissue compared to adjacent non-cancerous tissue (82). Despite this finding, the IGF-IIR is not thought to influence tumorigenic potential as it lacks the capacity to initiate mitogenic behaviours (59).

2.3.4 Section summary

Epidemiological insights into to the association between diabetes and the development of, and mortality from colorectal cancer have identified insulin as a key marker in the pathology of colorectal cancer. Bearing structural similarities to insulin, IGF-I and its biological mediator, IGFBP-III have also been linked to the development of, and mortality from colorectal cancer in numerous population studies.

Reflecting the epidemiological data, *in vivo* and *in vitro* research has identified insulin and the IGF axis as facilitators of neoplastic growth in the colon and rectum. From a clinical perspective, these processes indicate that heightened levels of IGF-I and reduced IGFBP-III and insulin increase ones risk for the development of colorectal cancer, and disease-specific mortality in those with a pre-existing diagnosis.

2.4 Insulin and insulin-like growth factor responses to physical activity

Reductions in plasma insulin and improvements in insulin sensitivity can occur in response to a physical activity interventions in both healthy and clinical populations (83). The response of the IGF axis to a chronic exercise exposure is more variable, however reductions in IGF-I and increases in IGFBP-III in response to physical activity in cancer populations have been reported (19,20,84).

2.4.1 Insulin sensitivity changes in response to physical activity in cancer survivors

Changes in insulin sensitivity in response to a physical activity intervention re reported in Appendix B of this thesis. The only intervention to investigate changes in insulin sensitivity with colorectal cancer survivors following a chronic exposure to exercise was published by Lee et al. (19). Following 12 weeks of home-based exercise comprising of moderate intensity exercise, such as walking, hiking, stationary cycling, swimming and resistance training, fasting plasma insulin decreased by ~40% (19). A limitation of this study was that the participants self-monitored their exercise intensity. Given that participants historically over-report rather than under-report their activity levels (46), a potential relationship between specific exercise intensity and changes in insulin sensitivity could not be accurately assessed in this study.

Due to the lack of research exploring the insulin response to a controlled physical activity intervention in colorectal cancer survivors, the evidence from other cancer populations will be reviewed. Sixteen weeks of combined aerobic and resistance-based physical activity resulted in significant reductions in fasting plasma insulin in a cohort of breast cancer survivors (85). A similar trend was found in response to a 26-week aerobic activity-based intervention in breast cancer survivors, however this did not reach statistical significance ($p = 0.089$) (20). Decreases in insulin have not been reflected across all interventions that have explored biological responses to physical activity in cancer survivors. Following a 26-week resistance training intervention in breast cancer survivors, no within-group changes in fasting insulin or insulin sensitivity were reported (22). The reason for this disparity may be related to the mode of exercise used. Generally, aerobic-based physical activity has resulted in greater reductions in fasting insulin and improvements in insulin sensitivity compared with resistance training in healthy persons (83).

2.4.2 Insulin-like growth factor axis responses to physical activity

Similar to the insulin molecule, physiological responses of the IGF axis to physical activity are inconsistent; increases, decreases and no change in the IGF axis have been reported in cancer and non-cancer populations (20,21,84,86-89) (Appendix B). While the reason for this inconsistency is not clear, some researchers believe that negative energy balance may underlie the mechanism/s (88), while others purport that it may be more closely related to energy flux (86) and physical conditioning (87). Although limited, there is evidence from trials involving colorectal cancer populations to indicate that changes in these biomarkers in response to physical activity can have favourable outcomes for disease-specific mortality (23).

Only one intervention has investigated the influence of physical activity on the IGF axis in a colorectal cancer population. Following 12 weeks of unsupervised physical activity of 18 to 27 MET-hours per week, significant increases in IGF-I and IGFBP-III were found (19). Given that the intervention was unsupervised and adherence to the protocol was measured via a self-reported questionnaire, the precise intensity of physical activity required to elicit these changes is unclear. This limitation is a reprise of what has been consistently overlooked in physical activity interventions for persons with colorectal cancer and/or survivors; a lack of supervision and measurement of precise intensity of physical activity. Since participants notoriously over-report rather than under-report activity levels, these concerns need to be addressed in future interventions.

Prospective evidence demonstrated that a one standard deviation increase in IGFBP-III was associated with a 51% reduction in colorectal cancer-specific mortality for those who were physically active (24). The same association was not seen for inactive individuals or for IGF-I (24). This indicates that physical activity is capable of eliciting a clinically meaningful shift in disease-specific mortality that is manifested by a measureable change in IGFBP-III. Whilst it cannot be concluded without further research why the IGF-I response did not reflect changes in IGFBP-III,

there likely exists a delicate interplay between the IGF axis and other exercise-induced biochemical responses.

Research in other cancer types has examined the relationship between the IGF axis and physical activity. In a cohort of 26 men diagnosed with prostate cancer and currently receiving androgen deprivation therapy, it was found that IGFBP-3 significantly increased and IGF-I significantly decreased in men undertaking a six-month resistance training program (21). No significant changes in these biomarkers were reported for men in the aerobic training arm. Although no analysis of this dissonance was mentioned in the paper, it is interesting to note differences with regard to the exercise prescription in both treatment arms. Those in the resistance training group were given a set of exercises to complete in the program whereas those in aerobic group were encouraged to exercise at 60-80% of their age-predicted maximum heart rate via feedback from a wristwatch monitor. No baseline test was completed to confirm this heart rate range, therefore the intensity range completed by participants in the aerobic group may have been inadequate to elicit similar changes in the IGF axis experienced by the resistance training group.

Several studies have measured the response of IGFs to a physical activity intervention in breast cancer survivors. Fairey et al. (84) tracked the changes in IGF-I, IGF-II and IGFBP-III following 15 weeks of moderate intensity aerobic exercise; significant increases in IGFBP-3 and decreases in IGF-I were found, including decreases in their molar ratio, which is thought to reflect bioactive IGF-I. More recent research by Irwin et al. (20) tracked breast cancer survivors over a 6 month randomised controlled trial, and found similar results for IGF-I but significant decreases in IGFBP-III compared to pre-intervention levels. Schmitz et al. (22) investigated the role of resistance training on the IGF axis in breast cancer survivors. Six months of resistance training resulted in significant reductions in IGF-II however no significant changes in IGF-I were reported. Compared to Fairey et al. (84), a higher percentage of participants in this study were undergoing

chemotherapy, which is known to alter IGF-I levels and therefore may have muted the biochemical response to physical activity.

2.4.3 Confounds to the insulin sensitivity and insulin-like growth factor response to physical activity

In addition to physical activity, negative energy balance through dietary restriction may lead to a improvement in insulin sensitivity (90) and a reduction in IGF-I (55). Several studies involving healthy populations have attempted to address this by employing rigorous dietary controls in addition to a physical activity intervention. Nemet and colleagues (88) found IGF-I only decreased following seven days of aerobic exercise when participants were in a negative energy balance (assisted via dietary restriction). In contrast, plasma insulin decreased in both positive and negative energy balance groups, highlighting that physical activity was enough stimulus to elicit a response in this group (88). Smith et al. (91) found no differences in IGF-I between two groups who experienced the same negative energy balance through physical activity or diet alone. These findings are in contrast to those of Smith et al. (91), further confounding the relationship between physical activity and the IGF axis in particularly.

Given that dietary intake influences insulin sensitivity and IGF-I levels, controlling for this variable in the days preceding testing is crucial to understanding the precise impact of physical activity on the IGF axis (55). Many of the studies investigating the physical activity/IGF association (20,21,84,86-89) (Appendix B) have not reported dietary intake control prior to testing. Further, redistribution of body composition may be fundamental to changes in insulin and the IGF axis that occur following a physical activity intervention. Chronic exposure to physical activity has repeatedly been associated with changes in body composition in cancer survivors. Namely, an increase in lean body mass and/or a decrease in fat mass, depending on the type of activity utilised during the intervention (92,93).

Presently there is limited evidence investigating associations between lean and fat mass with changes in insulin sensitivity and the IGF axis in cancer survivors. Following a 15-week resistance training intervention in 30-50 year old women, lean mass increased significantly and fat mass decreased significantly compared to baseline (22). This change occurred concurrently with a decrease in fasting insulin and total IGF-I. Unfortunately, no p-value was reported for this correlation. Following a combined physical activity and dietary intervention, underfed individuals who experienced significant losses in fat mass ($p < 0.0005$) also showed significant decreases in insulin ($p < 0.044$) and IGF-I ($p < 0.0005$) (88). Total body mass change was positively correlated with IGF-I ($R = 0.65$, $p < 0.02$); unfortunately no distinction was made between fat and lean mass in this sub-analysis. In light of available evidence, future interventions should consider potential changes in both lean and fat mass when interpreting insulin sensitivity and IGF axis responses to physical activity.

2.4.4 Section summary

The evidence reviewed above highlights insulin and the IGF axis as potential biological mediators linking physical activity to the development of colorectal cancer, and disease-specific mortality in persons already diagnosed with the disease. Decreases in plasma insulin and IGF-I, and increases in IGFBP-3 in response to a physical activity intervention have the potential to reduce the risk of second primary colorectal cancers in colorectal cancer survivors, along with disease-specific mortality in this population. Changes in fat and lean body mass in response to exercise training may also be related to changes in these biological markers and to risk of colorectal cancer development and mortality.

2.5 High intensity exercise

High intensity exercise has, in recent years, attracted the attention of researchers involved in the management and prevention of a number of chronic diseases. Indeed, high intensity exercise has emerged as an effective means of improving functional capacity and health in persons with type II diabetes, primarily via changes in insulin sensitivity (17). These improvements in insulin sensitivity have been identified following as little as two weeks of high intensity training (17,18).

Although adopting different training protocols and methods of analysis, the available research highlights a superior effect of high intensity exercise over moderate intensity exercise for improvements in fasting insulin and insulin sensitivity (26,94-96) (Appendix B). Within clinical populations such as type II diabetes, coronary artery disease and heart failure, the '4x4' high intensity exercise approach (97) has been most commonly utilised, and shown to be safe (26,97-99). Specifically, no adverse events have been reported in response to this mode of training (26,97-99). This protocol involves exercising at 85-95% of a person's peak heart rate for four minute intervals interspersed with three minute periods of active recovery (including warm-down following the forth interval) at 50-70% of peak heart rate (97). This combination repeats four times with the inclusion of a 10-minute warm-up, to total 38-minutes of exercise.

Although the aforementioned '4x4' protocol is yet to be utilised in cancer populations, Adamsen et al. (27) investigated the effect of a six week high intensity exercise intervention with 269 cancer survivors. The intervention incorporated three 90-minute sessions of combined resistance and aerobic training. The resistance-training component required participants to complete 3 sets of 8 repetitions at 70% of their 1-repetition maximum weight. Aerobic training involved intervals on a stationary bike at 85-95% of each participant's maximum heart rate, similar to the '4x4' protocol described above (26,97-99). The intervention group reported a 10.7% improvement in cardiorespiratory fitness measured via a maximum oxygen uptake (VO_2max) test after six weeks of

training; no changes were reported in the control group. Further, muscular strength improved by 29.6% in the intervention group, although this was not reflected by changes in lean mass. No changes in muscular strength were reported in the control group. Additionally, the intervention group reported no adverse events and a 70% adherence rate. This study provides preliminary support for the safety and feasibility of high intensity exercise in cancer survivors.

In light of the reviewed evidence, a high intensity exercise intervention over as few as two weeks may improve insulin sensitivity. Further, it is plausible that high intensity exercise may deliver superior improvements in insulin sensitivity and the IGF axis compared to moderate intensity exercise. Whether these aforementioned changes in response to high intensity exercise occur in colorectal cancer survivors remains to be elucidated. Increases in insulin sensitivity and IGFBP-III, and decreases in IGF-I, indicate clinically meaningful responses such as a reduced risk for the development of colorectal cancer, along with decreased mortality in persons already diagnosed with the disease. Given that the current physical activity recommendations for cancer survivors recommends 150 minutes of only 'moderate intensity' exercise per week (43), the benefits of brief, high intensity exercise needs to be explored.

2.6 Summary

While the benefits of physical activity for reduction in disease-specific mortality following colorectal cancer diagnosis are well established, the physiological mechanisms by which physical activity can mediate these outcomes remain to be determined. Of the several biological pathways that may be involved, insulin and the IGF axis are the most plausible mechanisms and have subsequently received the most interest. Following diagnosis from colorectal cancer, there is evidence to suggest that a decrease in IGF-I and an increase in IGFBP-III can reduce disease-specific mortality. In addition, the insulin molecule bears a strong structural similarity to IGF-I, and therefore has the capacity to mediate colorectal cancer-specific survival. Given that colorectal

cancer survivors who have diabetes are at a heightened risk of disease-specific mortality, improving insulin sensitivity through physical activity also warrants investigation.

Evidence from epidemiological studies have highlighted that high intensity physical activity has a greater protective effect for the development of colorectal cancer compared to moderate intensity activity. This is of particular importance to colorectal cancer survivors, given their increased risk of second primary colorectal cancers compared to healthy persons.

There is evidence to suggest that physical activity may influence insulin sensitivity, IGF-I and IGFBP-3 in persons with colorectal cancer. Further, IGF changes in response to physical activity have been associated with significant reductions in disease-specific mortality for persons with colorectal cancer. Despite these encouraging findings that explore the nexus between physical activity, insulin and the IGF axis, and colorectal cancer, the evidence is still limited and inconsistent. Intervention studies involving a structured high intensity physical activity regime for colorectal cancer survivors that examine changes in insulin sensitivity and IGF-I, IGFBP-III are clearly warranted.

CHAPTER 3 RANDOMISED CONTROLLED TRIAL

3.1 Introduction

Of all cancers, colorectal cancer has the fourth highest incidence rate worldwide and it is estimated that colorectal cancer is responsible for the deaths of approximately 608,000 people each year (1). Due to improved detection and treatment protocols, mortality from this disease has decreased in recent years, with 5-year survival rates for localised tumours around 90% (28). However, the risk of second primary colorectal cancers in colorectal survivors is heightened compared to healthy controls, with an estimated risk reported to be up to 1.4 fold (5). Given this, preventing the development of primary colorectal cancers in current survivors is a public health priority.

Physical inactivity has a significant influence on colorectal cancer development; at least 15% of all colorectal cancer cases have been attributed to insufficient physical activity (2). There is convincing epidemiological evidence to suggest that vigorous activity elicits a greater risk reduction for the development of colorectal cancer than activity performed at a moderate intensity (9-11). Despite these findings, the optimal intensities of physical activity for preventing the development of colorectal cancer are yet to be established. This limitation is, at least in part, due to an incomplete understanding of the biological mechanisms linking physical activity to colorectal cancer development and disease-specific mortality.

The IGF axis is believed to influence cellular growth, proliferation regulation, differentiation and apoptosis (12,13). Further, poor insulin sensitivity has been implicated as a key host factor in colorectal cancer development due to the physiological similarities between insulin and the IGF axis (12,13). These biological markers are yet to be examined in response to a regimen of high intensity physical activity in colorectal cancer survivors.

The aim of this study was to compare the effect of different exercise intensities on insulin sensitivity and the IGF axis in colorectal cancer survivors. Secondary measures such as body composition and cardiorespiratory fitness were measured to enable investigation of potential relationships among insulin sensitivity, the IGF axis and previously validated measures of health in colorectal cancer survivors. It was hypothesised that HIE would result in superior improvements in insulin sensitivity, the IGF axis, body composition and cardiorespiratory fitness compared to MIE.

3.2 Methods

3.2.1 Study design

This study was a 4-week randomised controlled trial of high intensity and moderate intensity exercise in colorectal cancer survivors. The data for this study were extracted from a longer intervention assessing identical physiological markers (along with psychosocial markers) over a period of 12-weeks. The details of this intervention are described on the Australian and New Zealand Clinical Trials Registry (ACTRN12615000908538). Participants were stratified according to age and gender before being randomly assigned to: 1) a 4-week program of HIE on a cycle ergometer, or 2) a 4-week program of MIE on a cycle ergometer. Computer generated randomisation was performed by a researcher not involved with the testing or training aspects of the study. The allocation ratio for the HIE and MIE groups was 2:1. This randomisation ratio was implemented for two reasons: firstly to account for a potentially higher dropout rate (approximately 20%) in the HIE group as the feasibility of HIE in this population has not been reported; and secondly to allow for appropriate sample sizes for outcomes included in the larger trial as described above. Dropout refers to withdrawal of participants from the intervention following randomisation and prior to the final testing session. Assuming a similar dropout in our study, this would allow us to maintain equal numbers in the groups for the final analysis. Group allocation was concealed from the tester and participant until after baseline testing was completed.

3.2.2 Participants

Women and men who had been diagnosed with colorectal cancer and were living in southeast Queensland, Australia were invited to participate in the study. Inclusion criteria were as follows:

Participants must have been:

i. Diagnosed with colon and/or rectal cancer at some point in their lifetime.
ii. Over the age of 18 years.
iii. Not medicated with exogenous insulin or taking insulin-sensitising medication.
iv. Free of any musculoskeletal, neurological, respiratory, metabolic or cardiovascular conditions that may have prevented safe completion of the exercise demands of the study. This criterion was determined via screening of the participants' medical history form and general practitioner consent form.
v. Completed treatment at least one month prior to commencing baseline testing and anticipated not undergoing further treatment for the 8-week duration on the study.

3.2.3 Recruitment Procedures

Participants were recruited from an existing Cancer Council Queensland (CCQ) colorectal cancer registry. Eligibility according to criteria 'i', 'ii' and 'v' as outlined above was determined during registry case screening by the CCQ. The Principal Investigator (Andrew Sax) determined eligibility according to inclusion criteria 'iii' and 'iv' during phone contact with the individual.

Phase one of recruitment: August 2013-January 2014

1. In collaboration with the CCQ, participants were recruited from an existing cohort of colorectal cancer survivors who participated in a longitudinal study exploring quality of life in colorectal cancer survivors (101). This study has been in progress for the past 6 years. The cohort was initially matched with mortality records from the Queensland Cancer Registry to identify members who had died. A letter introducing the study (Appendix C) and inviting participation was then sent to potential participants by Professor Joanne Aitken, the Principal Investigator of CCQ's longitudinal study. CCQ did not provide names or contact details of any cohort member directly to The

University of Queensland researchers for this study. Colorectal cancer survivors who were interested in participating in the study were invited to contact the Principal Investigator directly at The University of Queensland. Reasons for participant inclusion and exclusion as a result of this recruitment process are shown in Figure 1.

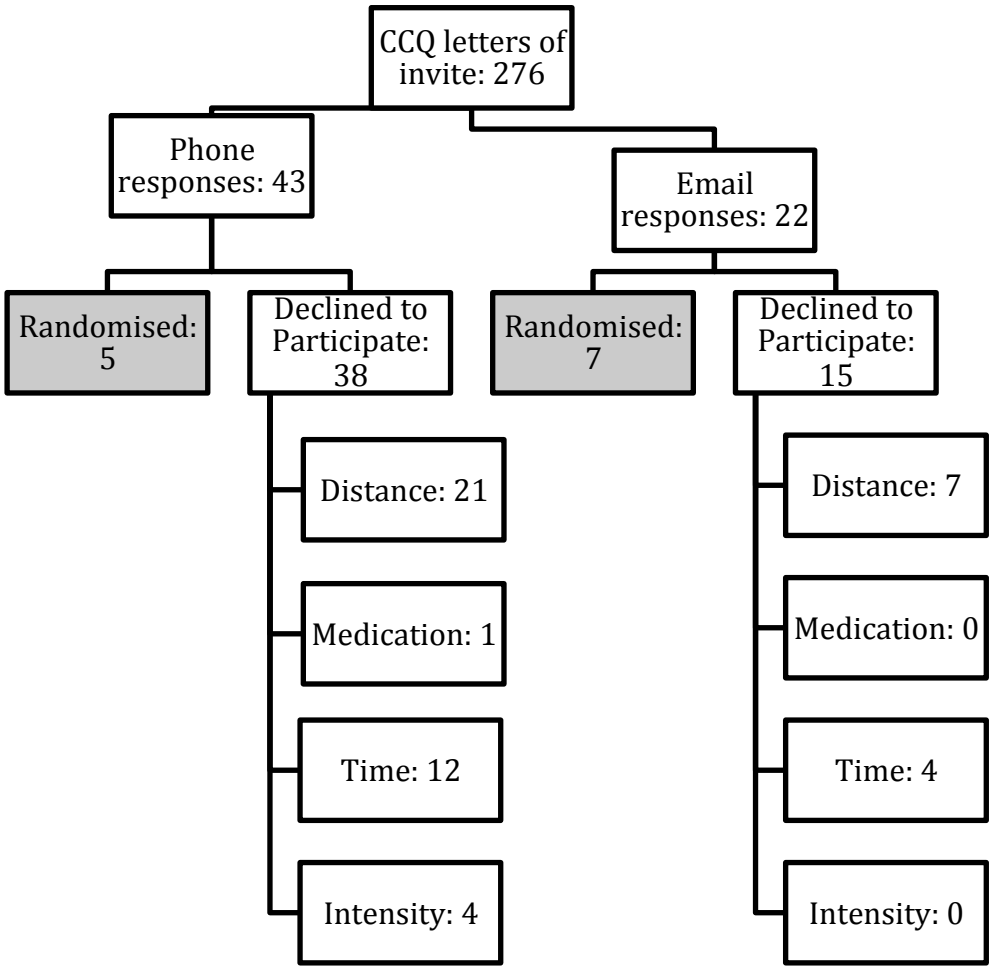


Figure 1: Consort diagram outlining responses from phase one of recruitment. Reasons for non-involvement in the study as reported by individuals who contacted the principal study investigator include; Distance – individual commented that the location of the intervention was too far from their place of residence, Medication – individual was taking medication that made them ineligible to participate, Time – individual was unable to commit to the time requirements of the study, Intensity – individual stated that they believed that the intensity of the exercise involved in the study would be too great for them. CCQ; Cancer Council Queensland.

Phase two of recruitment: April 2014-October 2014

1. CCQ Cancer Helpline: Cancer Council Helpline staff identified potential participants who fulfilled the inclusion criteria above during phone calls, provided a brief explanation of the study and asked them to consider participating in the study. Callers who expressed an interest were mailed a study information flyer (Appendix D) from the Head of Research at CCQ. The information flyer included details and instructions for contacting the Principal Investigator to discuss the study details, eligibility criteria and their possible participation.

2. Queensland Cancer Registry: This is a population-based register including all individuals diagnosed with cancer in Queensland since 1982. For the purposes of this phase of recruitment within the study, details of participants diagnosed with colorectal cancer from 2011 onwards only were drawn from the registry. Further, southeast Queensland residents only (postcodes 4000-4207, 4300-4305, 4500-4519) were extracted from the database via this recruitment pathway as the primary reason for non-involvement by participants contacted through *'Phase one'* of recruitment was too great a travelling distance (Figure 2). All cases were extracted from the database in April 2014. Cases were then checked against the CCQ death register to ensure no deceased patients were selected. Finally, cases were checked against the names of the individuals contacted during phase 1 of recruitment to avoid unnecessarily contacting an individual a second time.

Once case extraction was completed, patient names and the names of their treating doctor were obtained from the Queensland Cancer Registry database. Invitation letters (Appendix E) and information sheets (Appendix F) were sent to the treating doctor requesting his or her permission to contact their patient. The mail-out included a total of 280 patient invitations sent to 130 doctors. This occurred on the 2nd of July 2014. Following the doctor's consent, patients were forwarded a study information sheet (Appendix G) and a letter from their

doctor (Appendix H) informing them of the details of the study. The first patient mail-out occurred on the 9th of July 2014.

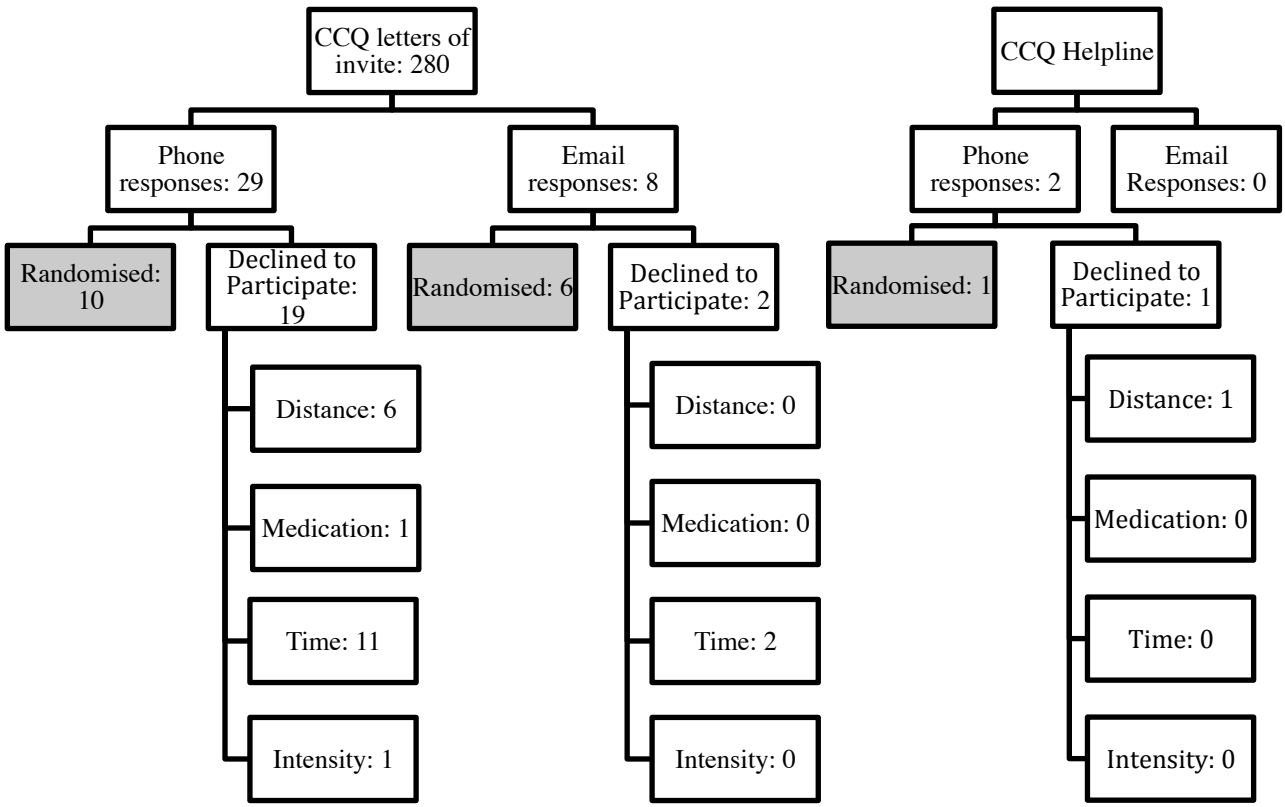


Figure 2: Consort diagram outlining responses from phase two of recruitment. Reasons for non-involvement in the study as reported by individuals who contacted the principal study investigator include; Distance – individual commented that the location of the intervention was too far from their place of residence, Medication – individual was taking medication that made them ineligible to participate, Time – individual was unable to commit to the time requirements of the study, Intensity – individual stated that they believed that the intensity of the exercise involved in the study would be too great for them. CCQ; Cancer Council Queensland.

All individuals who contacted the Principal Investigator were first assessed to determine whether they met the eligibility criteria. Those deemed eligible for the study and were willing to participate were mailed a copy of the participant information sheet, medical history form, and the general physician consent forms. All participants deemed eligible by the study investigators required further consent by their medical practitioner prior to the initial testing session. Ethics approval (2013000749) was obtained for this project by the Principal Investigator through The University of Queensland's Medical Research Ethics Committee and by the CCQ through the Queensland Public Health Act (RD004946); written informed consent was provided by all participants.

3.2.4 Study outline

Following recruitment, participants were invited to attend an initial face-to-face consultation with the Principal Investigator at the Exercise Physiology Research Laboratories within the School of Human Movement and Nutrition Sciences at The University of Queensland. During this consultation, the pre-testing requirements were discussed with the participant followed by the completion of a familiarisation peak cardiorespiratory fitness test. Testing procedures are discussed in sections *3.2.5.1* and *3.2.5.3*, respectively. Participants performed a baseline testing session prior to completing 12 exercise sessions over a 4-week period. All sessions were supervised by an Accredited Exercise Physiologist and are described in section *3.2.6*. Following the 12 exercise sessions, participants completed a final testing session involving the same procedures that were included in the baseline testing session.

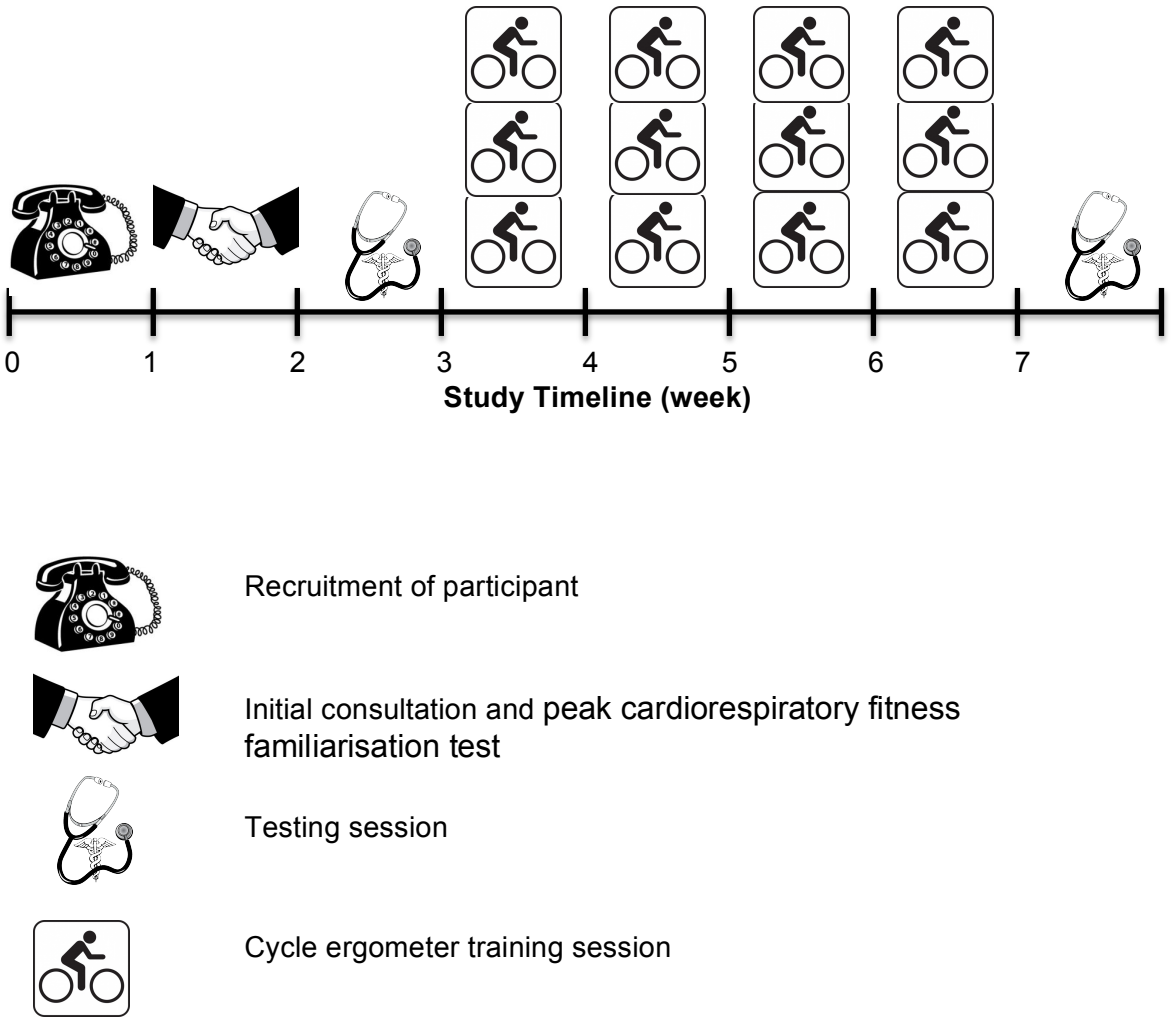


Figure 3: Time-course of study from participant recruitment to endpoint testing

3.2.5 Testing Sessions

Insulin sensitivity, IGF-I, IGFBP-III concentrations, soft tissue composition, peak heart rate and peak cardiorespiratory fitness were assessed at baseline and following the 4-week exercise intervention. Testing occurred following a 12-hour fast and required participants to adhere to pre-testing preparation requirements as outlined in section *3.2.5.1*. The start time of the testing session differed for each participant, depending on his or her preference and/or availability. Start time was the same for baseline and endpoint testing.

3.2.5.1 Participant Preparation

In advance of the testing sessions, participants were required to:

- Refrain from food and liquid (other than water) for 12 hours prior to the testing session start time (first blood draw).
- Refrain from caffeinated beverages (coffee, tea, selected soft drinks) and alcohol for 24 hours prior to the testing session.
- Refrain from vigorous or higher intensity activity for 48 hours prior to the testing session. Definitions of 'vigorous intensity' and examples of activities that fall within and above this category were discussed with the participants to ensure complete understanding.
- Consume 2-3 cups of water (1 cup = 250 mL) in the 2-3 hours preceding the beginning of the testing session.

Food and liquid intake prior to baseline and endpoint testing were recorded using a 3-day food diary (Appendix I). Participants were given a copy of their baseline food diary and asked to replicate it prior to the endpoint testing session. In the instance that it was not replicated exactly, participants edited the copy of their baseline diary to include any deviations. All participants were asked to maintain their pre-intervention level of physical activity outside of the training sessions for the duration of the study. Self-reported physical activity was assessed using a validated questionnaire (Godin Leisure time Physical Activity Index; Appendix J) (102) at baseline and endpoint testing sessions.

Upon arrival for testing at the laboratory, each participant was asked to confirm via a checklist and signature that all the pre-exercise criteria had been met. If the above procedures were not met, the testing session was rescheduled.

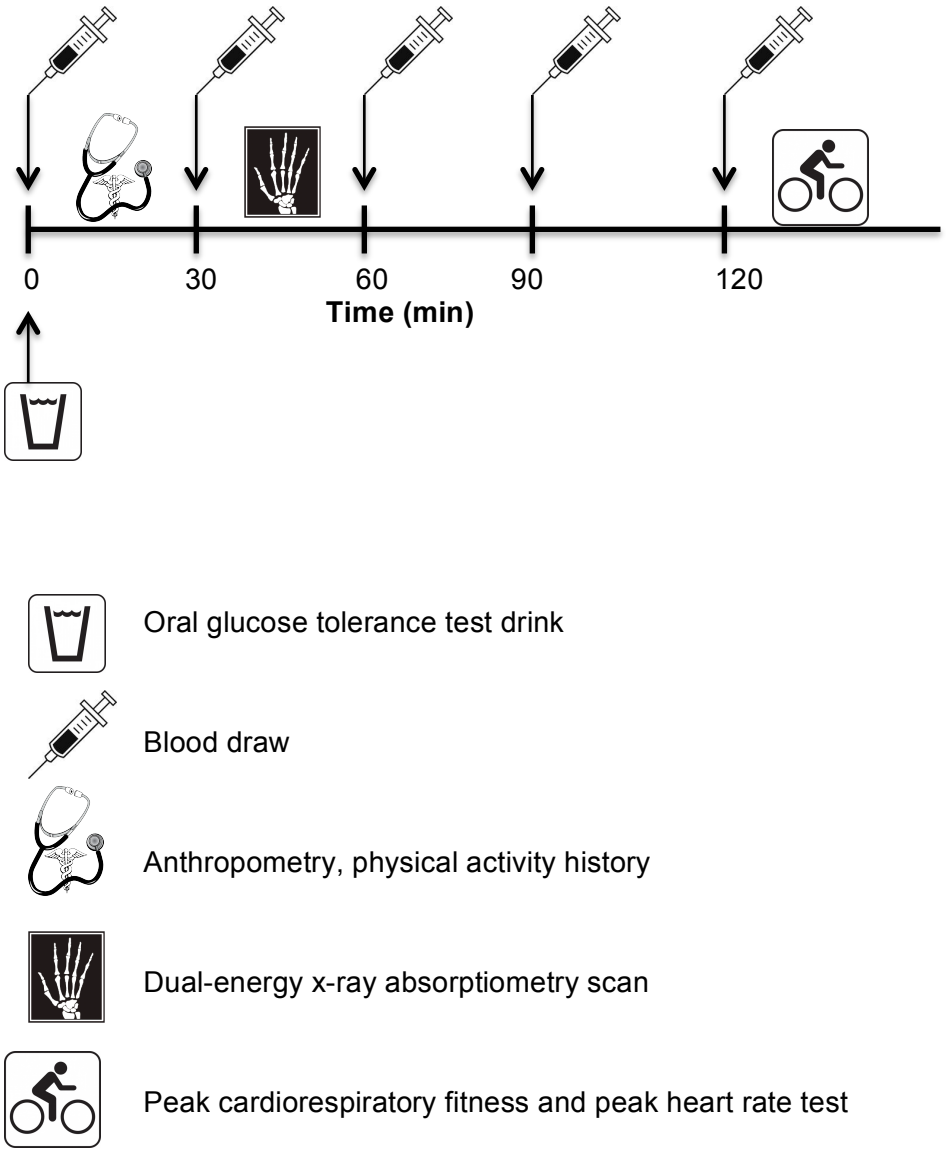


Figure 4: Time-course of tests completed during baseline and endpoint testing sessions

3.2.5.2 Primary Endpoints

Blood Collection Procedures

Upon arrival for baseline testing, fasting blood (12 mL) was sampled by a qualified phlebotomist from an antecubital vein using a 21 G 'BD Vacutainer Precision Glide' needle (Becton, Dickinson and Company, New Jersey, USA), 'BD Vacutainer Cage' (Becton, Dickinson and Company, New

Jersey, USA) and 2 x 6 ml plasma EDTA Vacutainers (Becton, Dickinson and Company, New Jersey, USA) and immediately centrifuged for 10 minutes at 500 x g. Plasma was then extracted and stored in 5 x 500 μL aliquots in 600 μL Eppendorf collection tubes (Eppendorf, Hamburg, Germany) at -80 degrees until analysis.

An OGTT was used to estimate insulin sensitivity. This procedure required a 1 mL fasting blood sample followed by a 300 mL drink containing 75 g of sugar (Fronine, Australia). Subsequent 1 mL blood samples were collected every 30 minutes over a 2-hour period (30, 60, 90, and 120 minutes). Participants were required to rest quietly for the 2-hour sampling period. Blood was sampled from an antecubital vein using an indwelling 25 G 'BD Precision Glide' needle (Becton, Dickinson and Company, New Jersey, USA) and 1 mL syringe (Becton, Dickinson and Company, New Jersey, USA). Blood was immediately transferred into a 1 ml plasma EDTA collection tube (Becton, Dickinson and Company, New Jersey, USA) and centrifuged for 10 minutes at 500 x g. Plasma was then extracted and stored in 1 x 500 μL aliquot in a 600 μL Eppendorf collection tubes (Eppendorf, Hamburg, Germany) tube at -80 degrees until analysis.

Insulin Sensitivity

Insulin and glucose were analysed using commercially available reagents (R&D Systems, Minneapolis, USA) on a Cobas E411 (Roche Diagnostics, Castle Hill, AUS) and RX Daytona Plus (Randox, Crumlin, UK) system, respectively. Prior to analysis, samples were thawed and centrifuged at 500 x g for 20 seconds. Standard curves were fitted for insulin and glucose and the values for each biomarker calculated accordingly. All sample values recorded were within the range of the standards used during analysis. The coefficient of variation (CV) in our laboratory for insulin and glucose are 1.48% and 1.19%, respectively. Insulin sensitivity was reported using two previously validated methods; the homeostasis model for assessing insulin resistance (HOMA-IR) (103) and the Matsuda index for insulin sensitivity (Matsuda ISI) (104). The HOMA-IR and

Matsuda ISI indices correlate well with whole body insulin sensitivity measured via the hyperinsulinemic-euglycemic clamp (r=0.691 and r=0.732, respectively), the current gold standard measurement of insulin sensitivity (104,105).

Insulin-like Growth Factor Axis

IGF-I and IGFBP-3 concentrations were analysed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, USA). Prior to analysis, samples were thawed and centrifuged at 500 x g for 20 seconds. For analysis of IGF-I and IGFBP-3, 50 μL and 100 μL plasma, respectively, were incubated in 96-well antibody-coated plates according to the manufacturer's instructions. Standard curves were fitted for each protein and the values for each protein calculated accordingly. All sample values recorded were within the range of the standards used during analysis. The CV in our laboratory for IGF-I and IGFBP-3 are 2.25% and 3.71%, respectively.

3.2.5.3 Secondary Endpoints

Peak Cardiorespiratory Fitness ($\dot{V}O_2$peak)

The $\dot{V}O_2$peak test required participants to progressively cycle to volitional fatigue. Expired air was analysed for fraction of expired oxygen and fraction of expired carbon dioxide every 15 seconds during exercise (ParvoMedics TrueOne 2400, Sandy, USA) from a mixing chamber, while minute ventilation was recorded every 15 seconds using a turbine ventilometer (Morgan, Model 096, Kent, England). The gas analysers were calibrated immediately prior to testing and validated after each test using a certified beta gas mixture (BOC, Brisbane, Australia). The ventilometer was also calibrated before and validated after each test using a 3 L syringe (Hans Rudolph series-5530) in accordance with the manufacturer's instructions. Sub-maximal oxygen uptakes were calculated by averaging the 30-second readings of fraction of expired oxygen recorded during each minute.

$\dot{V}O_2$peak was recorded as the mean of the two highest 15-second $\dot{V}O2$ epochs during the test. This is in contrast to $\dot{V}O2$max, which requires a plateau in oxygen uptake with an increase in work rate; $\dot{V}O2$max was not used as a measure of cardiorespiratory fitness for any participant in this intervention. The CV in our laboratory for $\dot{V}O_2$peak is 3.98%. The coefficient of variation refers to the variability of duplicate tests on participants from our laboratory; this is repeat $\dot{V}O_2$peak tests on consecutive days under the same conditions.

The cycle test was completed on an electromagnetically braked 'Excalibur Sport' cycle ergometer (Lode, Groningen, The Netherlands). The testing protocol, modified from that of Balke and Ware (106), began with three minutes of rest for respiratory normalisation and was followed by four minutes of warm up at a resistance of 50 watts. Thereafter the resistance applied to the cycle ergometer increased incrementally by 25 watts each minute. Participants were required to maintain a cycling cadence between than 60-70 revolutions per minute throughout the test. The cycle ergometer and test protocol were controlled via computer interface linkage (Dell, Texas, USA) and software provided with the ergometer (Lode, Groningen, Netherlands). Heart rate, blood pressure, and rating of perceived exertion were monitored prior to, and during the test. Heart rate was recorded every minute using a Suunto Ambit2 S heart rate monitor (Suunto Oy, Vantaa, Finland). Participant's peak heart rate (HR_{peak}) was used to inform training intensities during the intervention. This was calculated via the maximum heart rate achieved during the fitness test. Blood pressure was monitored every two minutes using a DuraShock Sphygmomanometer (Welch Allyn, New York, USA). Participants were also asked each minute to indicate their rating of perceived exertion according to the Borg Scale (107). The test was terminated when the participant reached volitional fatigue or at the discretion of the researchers with consideration for exercise testing termination criteria as outlined by the American College of Sports Medicine (100).

Body Composition

Standing height and body mass were measured using a fixed stadiometer (Seca, Birmingham, UK) and an analogue scale (Seca, Birmingham, UK), respectively. These measures were used to calculate body mass index [body mass in kg divided by height in metres squared (kg/m^2)] for each participant.

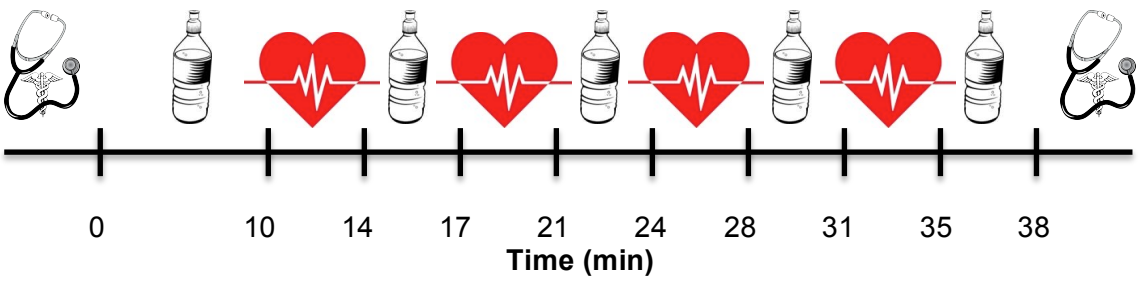
Whole body and regional lean and fat mass for each participant were measured using a 'Discovery W Series' dual energy x-ray absorptiometry machine (Hologic, Bedford, USA). Participants lay on the scanning table for approximately 10 minutes while a scanning arm moved above their body. A low-dosage x-ray passed from underneath the table to the scanning arm. Scans were analysed using the software (APEX Version 3.3) provided with the machine (Hologic, Bedford, USA) and according to the manufacturer's instructions. The coefficient of variation in our laboratory for regional and whole body lean and fat mass is <1.1%. The CV refers to the variability of duplicate scans on participants from our laboratory; this is on-off table repeat scans of older adults.

3.2.6 Exercise Intervention

The training intervention required participants to exercise three days per week for four weeks comprising either; 1) a program of HIE on a cycle ergometer, or 2) a program of MIE on a cycle ergometer. Training sessions were conducted on an air- and magnetically-braked cycle ergometer (Wattbike Pro™, Wattbike Ltd., Nottingham, England) in the Exercise Physiology Research Laboratories within the School of Human Movement and Nutrition Sciences at The University of Queensland. Exercise sessions were scheduled on non-consecutive days to allow for adequate recovery and all sessions were supervised with a ratio no greater than one Exercise Physiologist for every three participants.

3.2.6.1 High Intensity Exercise Group

The high intensity exercise (HIE) group followed the same protocol as outlined previously by Tjonna et al. (26). A complete time-course of the HIE group is shown in Figure 5. HR_{peak} ranges used for participants were calculated as a percentage of the HR_{peak} recorded during the aerobic fitness test as described in section *3.2.5.3*. The HIE group session began with a cycling warm-up at 50-70% of HR_{peak} for 10 minutes followed by 4 x 4 minute bouts of cycling at an intensity corresponding to 85-95% of the participants HR_{peak}. Each 4 min interval was interspersed with three minutes of active recovery, cycling at 50-70% HR_{peak}. The session ended with a three minute cool down, cycling at an intensity of 50-70% HR_{peak}. The total duration of each HIE session was 38 minutes.



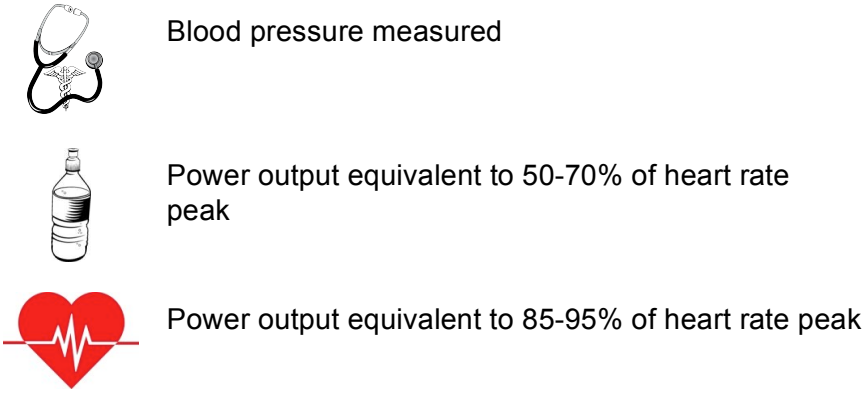


Figure 5: Time-course of high intensity exercise session

Power output during the session was self-selected as a function of cadence and workload, to allow participants to maintain a heart rate within the prescribed intensity range. Rating of perceived exertion was recorded at the end of each interval using the Borg scale (107). If a participant reached a Borg rating of '20', the exercise session was terminated to minimise the potential of any adverse events related to the HIE.

3.2.6.2 Moderate Intensity Exercise Group

Participants assigned to the moderate intensity exercise (MIE) group cycled continuously at 50-70% HR_{peak} for 50 minutes. This duration (150 minutes per week) and intensity is consistent with the current exercise oncology guidelines (43). Rating of perceived exertion was recorded at 10 minute intervals during the session using the Borg scale (107). If a participant reached a Borg rating of '15', the power output on the cycle ergometer was reduced to ensure a moderate intensity was maintained. The total duration of each MIE session was 50 minutes.

3.2.6.3 Safety and Attendance

Upon arriving at the laboratories for the exercise training session, participants had their baseline heart rate and blood pressure measured using a Suunto 'Ambit2S' heart rate wrist monitor and chest strap (Suunto, Finland) and DuraShock Sphygmomanometer (Welch Allyn, New York, USA), respectively. The heart rate monitor and chest strap were kept on the participant for the duration of the session. These values were recorded and used as a resting threshold that participants needed to return to before they were discharged after their exercise session. An Accredited Exercise Physiologist (Andrew Sax) supervised all sessions during the intervention. Heart rate ranges were continuously monitored during each session to ensure participants were conforming to their prescribed heart rate intensities. If participants were not meeting their prescribed heart rate intensities they were encouraged to alter their power output (via cadence or workload) to meet this criteria.

Participants were asked to report any adverse events experienced during the exercise sessions to the Exercise Physiologist, and these were recorded over the duration of the study. Attendance during the intervention was measured via total number of sessions attended (out of 12 possible sessions).

3.2.6.4 Statistical analysis

To achieve 80% power at an alpha level of 0.05 (two-tailed), three participants per group were required to demonstrate a 1 standard deviation (SD) difference in the primary outcome (insulin sensitivity) between groups at the end of the 4-week intervention. Sample size calculations were based on the homeostasis model of assessment for insulin sensitivity data from Tjonna et al. (26) using G*Power version 3.1 software (G*Power Software, University of Düsseldorf, Germany). To account for 25% attrition, which has previously been reported from our laboratory, a minimum of five participants were needed to be randomised to each group.

Data was analysed using the SPSS statistical software package (version 20.0, SPSS, Inc., Chicago, IL). Data were assessed for normality using the Kolmogorov-Smirnov test. Where data were not normally distributed (i.e. fasting insulin, fasting glucose and the HOMA-IR), log-transformations were performed and rechecked for normality prior to analysis. In the instances that log transformed data were not normally distributed ($\dot{V}O_2$peak), non-parametric analyses were used on the raw (untransformed) data. Analyses included standard descriptive statistics, t tests, analysis of covariance, and Wilcoxon-signed rank tests where appropriate. Statistical analyses were based on an intention-to-treat approach, however as the exercise session attendance was 100% this was synonymous with per protocol analysis. Missing data points were not replaced. Analyses also included Pearson or Spearman correlation coefficients, as appropriate, to examine the association between insulin sensitivity, IGF axis, body composition and cardiorespiratory fitness. Partial correlations controlling for age, sex, cancer stage, cancer location, cancer treatment, time since

diagnosis and baseline biological variables were performed. Analysis of covariance adjusted for baseline values was used for the primary and secondary endpoints. All tests were two-tailed and an alpha level of 0.05 was applied as the criterion for statistical significance. Results are given as the mean ± SD unless otherwise stated.

3.3 Results

3.3.1 Participant characteristics

A consort diagram of the participant flow through the intervention is detailed in *Figure* 6. Baseline characteristics of the 29 participants are presented in Table 1a. Participants in the HIE and MIE groups were aged 33-84 and 44-82 years, respectively. At baseline, there were no significant differences between groups for participant characteristics (i.e. age, sex, BMI, cancer history, cancer stage, cancer treatment; Table 1a) or any of the outcome measures (Table 1b).

3.3.2 Attendance, safety and adherence

Of the total 348 exercise sessions, attendance was 100%. There were no adverse events in response to the exercise sessions reported or observed during the intervention. The total combined time participants' spent exercising during the intervention was approximately 260 hours. A total of 228 sessions were completed by the HIE group during the intervention; this equates to 912 individual high-intensity intervals. Over the course of these intervals, the average time it took for participants to reach their prescribed HRpeak (85% - 95% HRpeak) intensity range was 38±39 seconds. Thus, in each of the training sessions, participants in the HIE group spent approximately 14 minutes in the target training zone, equating to a total of 168 minutes per participant over the duration of the entire training intervention.

3.3.3 Physical activity outside intervention

There were no significant between-group differences in the amount of physical activity completed by participants outside of the intervention at baseline (p = 0.542) or at the end of the 4-week intervention (p = 0.946). Physical activity completed by participants in either group outside the intervention did not change from baseline to the end of the study (HIE, p = 0.879; MIE, p = 0.878).

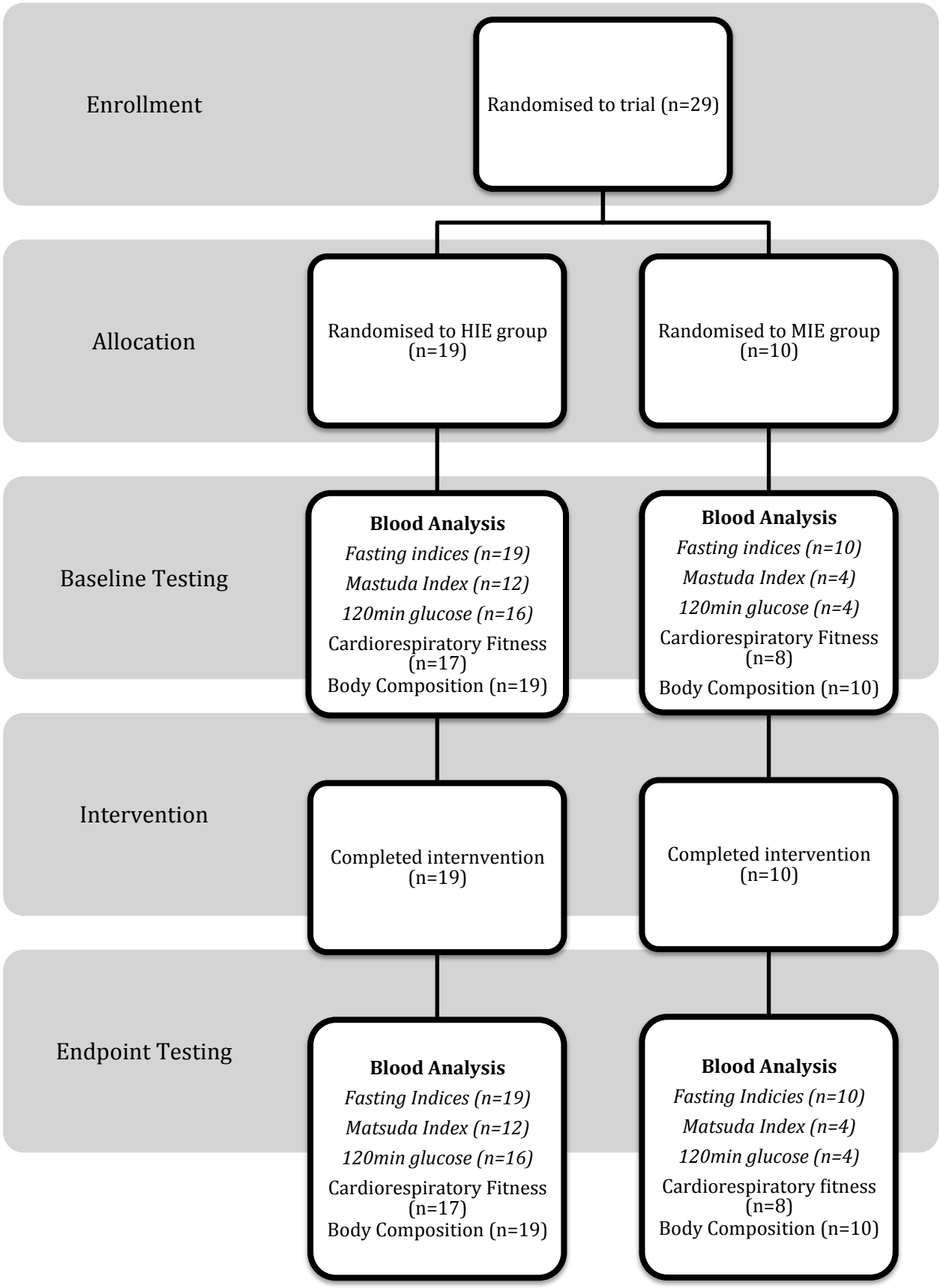


Figure 6: CONSRT diagram outlining participant flow through the intervention.

Table 1a: Baseline characteristics of participants randomised to the HIE and MIE groups.

	HIE *(n=19)*	MIE *(n=10)*	*p* value
Age (years) ‡	60.9 ± 13.2	61.2 ± 10.6	0.959
Male	13 (68.4)	4 (40.0)	0.140
Body mass (kg) ‡	78.53 ± 16.43	77.96 ± 19.51	0.564
BMI (kg/m^2) ‡	26.17 ± 4.61	27.03 ± 4.03	0.625
Physical activity	21.00 (23.00)	30.50 (29.80)	0.542
Cancer History			
Colon cancer †	17 (89.5)	9 (90.0)	0.965
Rectal cancer †	2 (10.5)	1 (10.0)	0.965
Time since diagnosis (years) #	2.0 (7.0)	3.3 (7.1)	0.353
Time since final treatment (years) #	2.0 (7.5)	2.3 (3.2)	0.982
Cancer Stage			
Stage A †	3 (15.8)	4 (40.0)	0.148
Stage B †	10 (52.6)	3 (30.0)	0.244
Stage C †	4 (21.1)	3 (30.0)	0.593
Stage D †	2 (10.5)	0 (0.0)	0.288
Cancer Treatment			
Surgery †	7 (36.8)	4 (40.0)	0.868
Surgery & chemotherapy †	8 (42.1)	3 (30.0)	0.713
Surgery & radiation †	1 (5.3)	0 (0.0)	0.460
Surgery, chemotherapy & radiation †	2 (10.5)	3 (30.0)	0.187
Chemotherapy & radiation †	1 (5.3)	0 (0.0)	0.460

Values reported as [n (%)] unless otherwise specified, ‡ Values reported as mean ± standard deviation, # Values reported as median (inter-quartile range), † Chi squared analysis used to determine significance between groups, HIE: High Intensity Exercise, MIE: Moderate Intensity Exercise, BMI: Body Mass Index. Physical activity level reported in Godin Minutes (102).

Table 1b: Baseline testing data of participants randomised to the HIE and MIE groups.

	HIE *(n=19)*	MIE *(n=10)*	*p* value
Insulin Sensitivity			
Fasting Glucose (mmol/L) ‡	5.6 (1.0)	5.7 (0.9)	0.821
Fasting Insulin (pmol/L) ‡	72.4 (56.6)	57.9 (36.9)	0.727
HOMA-IR ‡	2.7 (1.6) *(n=12)*	2.1 (1.4) *(n=4)*	0.705
Matsuda Index	5.1 ± 3.3 *(n=16)*	5.0 ± 1.3 *(n=4)*	0.572
120 min Glucose (mmol/L)	6.9 ± 1.9	5.8 ± 1.2	0.284
IGF Axis	*(n=19)*	*(n=10)*	
IGF-I (ng/mL)	74.6 ± 21.1	75.3 ± 22.8	0.899
IGFBP- III (ng/mL)	2354.6 ± 705.1	2465.0 ± 656.5	0.685
Body Composition	*(n=19)*	*(n=10)*	
Lean Mass (kg)	45.9 ± 10.2	41.9 ± 13.8	0.371
Fat Mass (kg)	24.5 ± 8.2	27.9 ± 10.3	0.326
Body Fat (%)	33.4 ± 6.9	39.0 ± 8.1	0.064
Cardiorespiratory Fitness	*(n=17)*	*(n=8)*	
Relative VO_2peak ($ml.kg^{-1}.min^{-1}$) ‡	23.3 (6.7)	20.9 (5.2)	0.120

Values reported as mean ± standard deviation unless otherwise stated,‡ Values reported as median (inter-quartile range), HIE: High Intensity Exercise, MIE: Moderate Intensity Exercise, IGF-I: Insulin-like Growth Factor I, IGFBP-III: Insulin-like Growth Factor Binding Protein III, HOMA-IR: Homeostatic Model Assessment - Insulin Resistance, VO2peak: Peak Volume of Oxygen Consumed.

3.3.4 Insulin sensitivity

There were no significant differences between groups for fasting glucose ($p = 0.626$), fasting insulin ($p = 0.583$), HOMA-IR ($p = 0.367$), Matsuda Index ($p = 0.490$), or 120 min glucose ($p = 0.372$) at baseline. Changes in all measures of insulin sensitivity over four weeks did not significantly differ between the groups (Table 2). Furthermore, no significant differences were found between groups for fasting glucose ($p = 0.494$), fasting insulin ($p = 0.356$), HOMA-IR ($p = 0.327$), Matsuda Index ($p = 0.870$), or 120 min glucose ($p = 0.488$) at the end of the 4-week intervention.

There was a significant within-group change in the 120 min blood glucose concentration of -7.1% in the HIE ($p = 0.037$) but not MIE (+0.8%, $p = 0.866$) group (Table 3). Within-group changes in the HIE and MIE groups for fasting glucose were +2.2% ($p = 0.863$) and -2.1% ($p = 0.598$), for fasting insulin -10.6% ($p = 0.179$) and -16.9% ($p = 0.064$), for HOMA-IR -13.7% ($p = 0.174$) and -15.1% ($p = 0.107$), and for Matsuda Index +13.8% ($p = 0.142$) and +0.8% ($p = 0.933$), respectively.

Aggregated or training-group specific changes in insulin sensitivity were not significantly ($p > 0.05$) correlated with changes in fat mass, lean mass, or body fat percentage (Table 4). Between group differences in insulin sensitivity were also not significantly different after controlling for age, sex, cancer stage, cancer location, cancer treatment, time since diagnosis or baseline biological variables.

Pre- and post-intervention HOMA-IR levels of each participant are shown in Figure 7. Matsuda Index could not be calculated for 13 participants (HIE n = 7, MIE n = 6) and 120 min glucose for 9 participants (HIE n = 3, MIE n = 6) due to an inability to obtain the blood samples required to complete the respective analyses.

Table 2: Insulin sensitivity and IGF axis values and change over four weeks

	MIE: Baseline	HIE: Baseline	MIE: Endpoint	HIE: Endpoint	Difference between groups in mean change (95% CI)	*p* value
Insulin Sensitivity	*(n=10)*	*(n=19)*	*(n=10)*	*(n=19)*		
Fasting Glucose (mmol/L) ‡	5.7 (0.9)	5.6 (1.0)	5.6 (0.9)	5.7 (0.8)	-0.1 (-0.6-0.3)	0.511
Fasting Insulin (pmol/L) ‡	57.9 (36.9)	72.4 (56.6)	48.1 (59.9)	64.7 (26.2)	-5.5 (-23.5-12.5)	0.536
HOMA-IR ‡	2.1 (1.4)	2.7 (1.6)	1.7 (1.9)	2.3 (1.3)	-0.2 (-0.9-0.5)	0.518
	(n=4)	*(n=12)*	*(n=4)*	*(n=12)*		
Matsuda Index	5.0 ± 1.3	5.1 ± 3.3	5.1 ± 1.6	5.9 ± 3.9	-0.6 (-2.2-1.1)	0.482
	(n=4)	*(n=16)*	*(n=4)*	*(n=16)*		
120 min Glucose (mmol/L)	5.8 ± 1.2	6.9 ± 1.9	5.9 ± 0.6	6.4 ± 1.5	0.2 (-0.6-1.0)	0.563
IGF Axis	*(n=10)*	*(n=19)*	*(n=10)*	*(n=19)*		
IGF-I (ng/mL)	75.3 ± 22.8	74.6 ± 21.1	68.7 ± 18.7	79.9 ± 22.1	-11.8 (-26.5-2.9)	0.112
IGFBP-III (ng/mL)	2465.0 ± 656.5	2354.6 ± 705.1	2539.6 ± 674.4	2395.8 ± 802.3	68.3 (-423.1-559.7)	0.777

Values reported as mean ± standard deviation unless otherwise stated,‡ Values reported as median (inter-quartile range), CI: Confidence Interval, HIE: High Intensity Exercise, MIE: Moderate Intensity Exercise, IGF-I: Insulin-like Growth Factor I, IGFBP- III: Insulin-like Growth Factor Binding Protein III, HOMA-IR: Homeostatic Model Assessment - Insulin Resistance.

Table 3: Within-group comparisons for insulin sensitivity and IGF axis values over four weeks

	MIE: Baseline	MIE: Endpoint	*p* value	HIE: Baseline	HIE: Endpoint	*p* value
Insulin Sensitivity	*(n=10)*	*(n=10)*		*(n=19)*	*(n=19)*	
Fasting Glucose (mmol/L) ‡	5.7 (0.9)	5.6 (0.9)	0.598	5.6 (1.0)	5.7 (0.8)	0.863
Fasting Insulin (pmol/L) ‡	57.9 (36.9)	48.1 (59.9)	0.064	72.4 (56.6)	64.7 (26.2)	0.179
HOMA-IR ‡	2.1 (1.4)	1.7 (1.9)	0.107	2.7 (1.6)	2.3 (1.3)	0.174
	(n=4)	*(n=4)*		*(n=12)*	*(n=12)*	
Matsuda Index	5.0 ± 1.3	5.1 ± 1.6	0.933	5.1 ± 3.3	5.9 ± 3.9	0.142
	(n=4)	*(n=4)*		*(n=16)*	*(n=16)*	
120 min Glucose (mmol/L)	5.8 ± 1.1	5.9 ± 0.6	0.866	6.9 ± 1.9	6.4 ± 1.5	0.037*
IGF Axis	*(n=10)*	*(n=10)*		*(n=19)*	*(n=19)*	
IGF-I (ng/mL)	75.3 ± 22.8	68.7 ± 18.7	0.301	74.6 ± 21.1	79.9 ± 22.1	0.299
IGFBP- III (ng/mL)	2465.0 ± 656.5	2539.6 ± 674.4	0.642	2354.6 ± 705.1	2395.8 ± 802.3	0.800

Values reported as mean ± standard deviation unless otherwise stated, ‡ Values reported as median (inter-quartile range), * $p \leq 0.05$, HIE: High Intensity Exercise, MIE: Moderate Intensity Exercise, IGF-I: Insulin-like Growth Factor I, IGFBP- III: Insulin-like Growth Factor Binding Protein III, HOMA-IR: Homeostatic Model Assessment - Insulin Resistance.

Table 4: Relationships among absolute changes in insulin sensitivity, IGF axis and body composition over four weeks

	Δ IGF-I (ng/mL)	Δ IGFBP-III (ng/mL)	Δ Fasting Glucose (mmol/L)	Δ Fasting Insulin (pmol/L)	Δ HOMA-IR	Δ Matsuda Index ‡	Δ 120min Glucose (mmol/L)	Δ Lean Mass (kg)	Δ Body Fat %
Δ IGF-I (ng/mL)	1								
Δ IGFBP-III (ng/mL)	0.472 (0.010)**	1							
Δ Fasting Glucose (mmol/L)	0.445 (0.016)*	-0.016 (0.933)	1						
Δ Fasting Insulin (pmol/L)	0.306 (0.106)	0.210 (0.274)	0.288 (0.130)	1					
Δ HOMA-IR	0.352 (0.061)	0.226 (0.239)	0.480 (0.008)**	0.961 (0.000)**	1				
Δ Matsuda Index ‡	-0.446 (0.029)*	-0.137 (0.522)	-0.289 (0.171)	-0.580 (0.003)**	-0.606 (0.002)**	1			
Δ 120min Glucose (mmol/L)	0.071 (0.766)	0.401 (0.079)	-0.080 (0.738)	0.052 (0.829)	0.100 (0.675)	-0.059 (0.806)	1		
Δ Lean Mass (kg)	0.107 (0.582)	-0.113 (0.561)	0.346 (0.066)	0.096 (0.620)	0.162 (0.401)	0.237 (0.266)	0.011 (0.964)	1	
Δ Body Fat %	-0.036 (0.851)	0.092 (0.637)	-0.002 (0.993)	-0.024 (0.900)	-0.039 (0.841)	-0.329 (0.116)	-0.203 (0.392)	-0.791 (0.000)**	1
Δ Fat mass (kg)	-0.103 (0.594)	0.191 (0.320)	-0.046 (0.812)	-0.075 (0.699)	-0.082 (0.671)	-0.297 (0.158)	0.007 (0.977)	-0.644 (0.000)**	0.891 (0.000)**

Values reported as [Correlation (*p* value)], * $p \leq 0.05$, ** $p \leq 0.01$, ‡ Spearman correlation used for non-parametric data, IGF-I: Insulin-like Growth Factor I, IGFBP-III: Insulin-like Growth Factor Binding Protein III, HOMA-IR: Homeostatic Model for the Assessment of Insulin Resistance, VO_2peak: Peak Volume of Oxygen Consumed.

3.3.5 Insulin-like growth factor axis

There were no significant between-group differences in IGF-I ($p = 0.717$) or IGFBP-III ($p = 0.292$) at baseline. Changes in IGF-I and IGFBP-III over 4-weeks did not significantly differ between the groups (Table 2). There were also no significant between-group differences for IGF-I ($p = 0.183$) and IGFBP-III ($p = 0.633$) following the 4-week intervention. Pre- and post-intervention IGF-I and IGFBP-III levels of each participant are shown in Figure 7. There were no significant within-group changes for IGF-I (HIE +6.5%, $p = 0.299$; MIE -8.9%, $p = 0.301$) or IGFBP-III (HIE +1.7%, $p = 0.800$; MIE +3.0%, $p = 0.642$) from baseline to endpoint testing (Table 3). Aggregated or training-group specific changes in the IGF axis were not significantly ($p \geq 0.05$) correlated with changes in fat mass, lean mass, or body fat percentage (Table 4). Between group differences for the IGF-I and IGFBP-III were also not significantly different when controlling for age, sex, cancer stage, cancer location, cancer treatment, time since diagnosis or baseline biological variables.

When data was subdivided by time since last treatment (≤5 years >5 years), no significant within-group differences were found for IGF-I (≤5 years, MIE, $p = 0.288$; >5 years, MIE, $p = 0.827$; ≤5 years, HIE, $p = 0.205$; >5 years, HIE, $p = 0.325$) or IGFBP-III (≤5 years, MIE, $p = 0.851$; >5 years, MIE, $p = 0.717$; ≤5 years, HIE, $p = 0.205$; >5 years, HIE, $p = 0.126$). The same stratification showed no significant between-group differences at baseline (≤5 years, IGF-I, $p = 0.976$; >5 years, IGF-I, $p = 0.328$; ≤5 years, IGFBP-III, $p = 0.689$; >5 years, IGFBP-III, $p = 0.063$), or endpoint (≤5 years, IGF-I, $p = 0.678$; >5 years, IGF-I, $p = 0.358$; ≤5 years, IGFBP-III, $p = 0.817$; >5 years, IGFBP-III, $p = 0.304$).

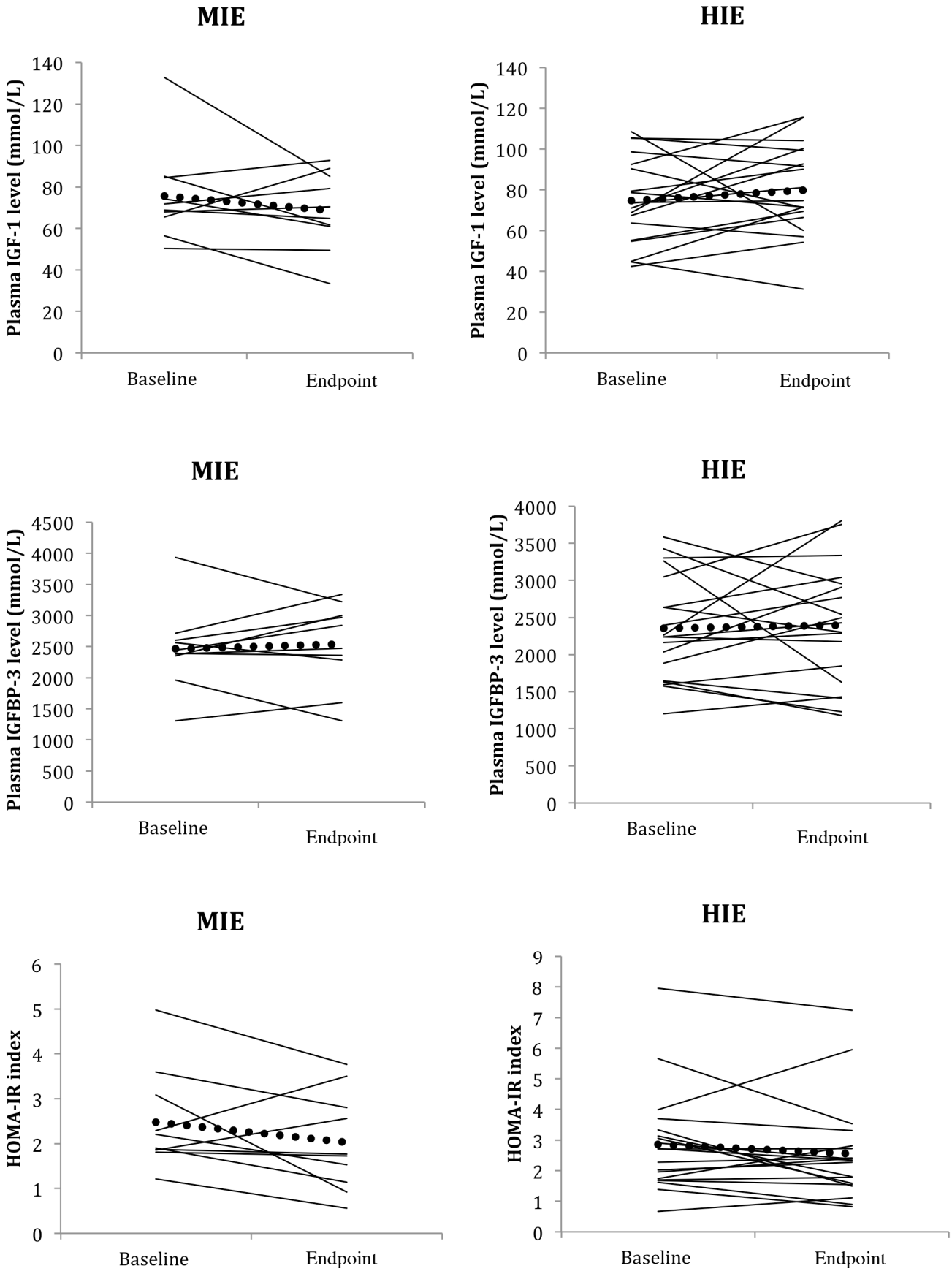


Figure 7: Individual participant pre- to post-intervention IGF-1 *(top)*, IGFBP-3 *(middle)* and HOMA-IR *(bottom)* values. The *dotted* lines represent the mean value. IGF-I: Insulin-like Growth Factor I. IGFBP- III: Insulin-like Growth Factor Binding Protein III. HOMA-IR: Homeostatic Model for the Assessment of Insulin Resistance. HIE: High Intensity Exercise. MIE: Moderate Intensity Exercise.

3.3.6 Cardiorespiratory fitness

There were no significant between- group differences for $\dot{V}O_2$peak ($p = 0.140$) at baseline. Changes in $\dot{V}O_2$peak did not significantly differ between groups (Table 5). There were no significant between-group differences for $\dot{V}O_2$peak ($p = 0.124$) following the 4-week intervention.

There were significant within-group differences in absolute $\dot{V}O_2$peak values for both the HIE (23.0%, $p = 0.013$) and MIE (1.7%, $p = 0.025$) groups over the 4-week intervention (Table 6). Changes in $\dot{V}O_2$peak were not significantly correlated ($p > 0.05$) with insulin sensitivity, the IGF axis or body composition (Table 4). Pre- and post-intervention $\dot{V}O_2$peak levels of each participant are shown in Figure 9.

Relative $\dot{V}O_2$peak data were unable to be obtained for four participants (HIE n = 2, MIE n = 2); two participants (MIE) experienced nausea and vomiting in response to the OGTT glucose drink and had their testing session terminated prior to the cardiorespiratory fitness test. One participant (HIE) was not comfortable wearing the mouthpiece required to measure relative $\dot{V}O_2$peak data. A technical error was experienced during the endpoint cardiorespiratory fitness test of one participant (HIE) and their data had to be excluded.

Table 5: Body composition and cardiorespiratory fitness values and change over four weeks

	MIE: Baseline	HIE: Baseline	MIE: Endpoint	HIE: Endpoint	Difference between groups in mean change (95% CI)	*p* value
Body Composition	*(n=10)*	*(n=19)*	*(n=10)*	*(n=19)*		
Lean Mass (kg)	41.9 ± 13.8	45.9 ± 10.2	42.5 ± 14.4	46.8 ± 10.5	-0.0 (-0.6-0.6)	0.975
Fat Mass (kg)	27.9 ± 10.3	24.5 ± 8.2	27.6 ± 10.5	23.7 ± 8.2	0.4 (-0.3-1.1)	0.227
Body Fat (%)	39.0 ± 8.1	33.4 ± 6.9	38.3 ± 8.7	32.3 ± 7.4	0.1 (-0.8-1.1)	0.767
Cardiorespiratory Fitness	*(n=8)*	*(n=17)*	*(n=8)*	*(n=17)*		
Relative $\dot{V}O_2$peak ($ml.kg^{-1}.min^{-1}$) ‡	20.9 (5.2)	23.3 (6.7)	21.3 (8.5)	28.6 (10.7)	-1.5 (-4.9-1.9)	0.361

Values reported as [mean ± standard deviation] unless otherwise stated. ‡ Values reported as median (inter-quartile range). CI: Confidence Interval, HIE: High Intensity Exercise. MIE: Moderate Intensity Exercise. $\dot{V}O_2$peak: Peak Volume of Oxygen Consumed.

Table 6: Within-group comparisons in body composition and cardiorespiratory fitness over four weeks

	MIE: Baseline	MIE: Endpoint	*p* value	HIE: Baseline	HIE: Endpoint	*p* value
Body Composition	*(n=10)*	*(n=10)*		*(n=19)*	*(n=19)*	
Lean Mass (kg)	41.9 ± 13.8	42.5 ± 14.4	0.071	45.9 ± 10.2	46.8 ± 10.5	0.001**
Fat Mass (kg)	27.9 ± 10.3	27.6 ± 10.5	0.263	24.5 ± 8.2	23.7 ± 8.2	0.001**
Body Fat (%)	39.0 ± 8.1	38.3 ± 8.7	0.132	33.4 ± 6.9	32.3 ± 7.4	0.001**
Cardiorespiratory Fitness	*(n=8)*	*(n=8)*		*(n=17)*	*(n=17)*	
Relative $\dot{V}O_2$peak ($ml.kg^{-1}.min^{-1}$) ‡	20.9 (5.2)	21.3 (8.5)	0.025*	23.3 (6.7)	28.6 (10.7)	0.013*

Values reported as mean ± standard deviation unless otherwise stated. * $p \leq 0.05$. ** $p \leq 0.001$. ‡ Values reported as median (inter-quartile range). HIE: High Intensity Exercise. MIE: Moderate Intensity Exercise. $\dot{V}O_2$peak: Peak Volume of Oxygen Consumed.

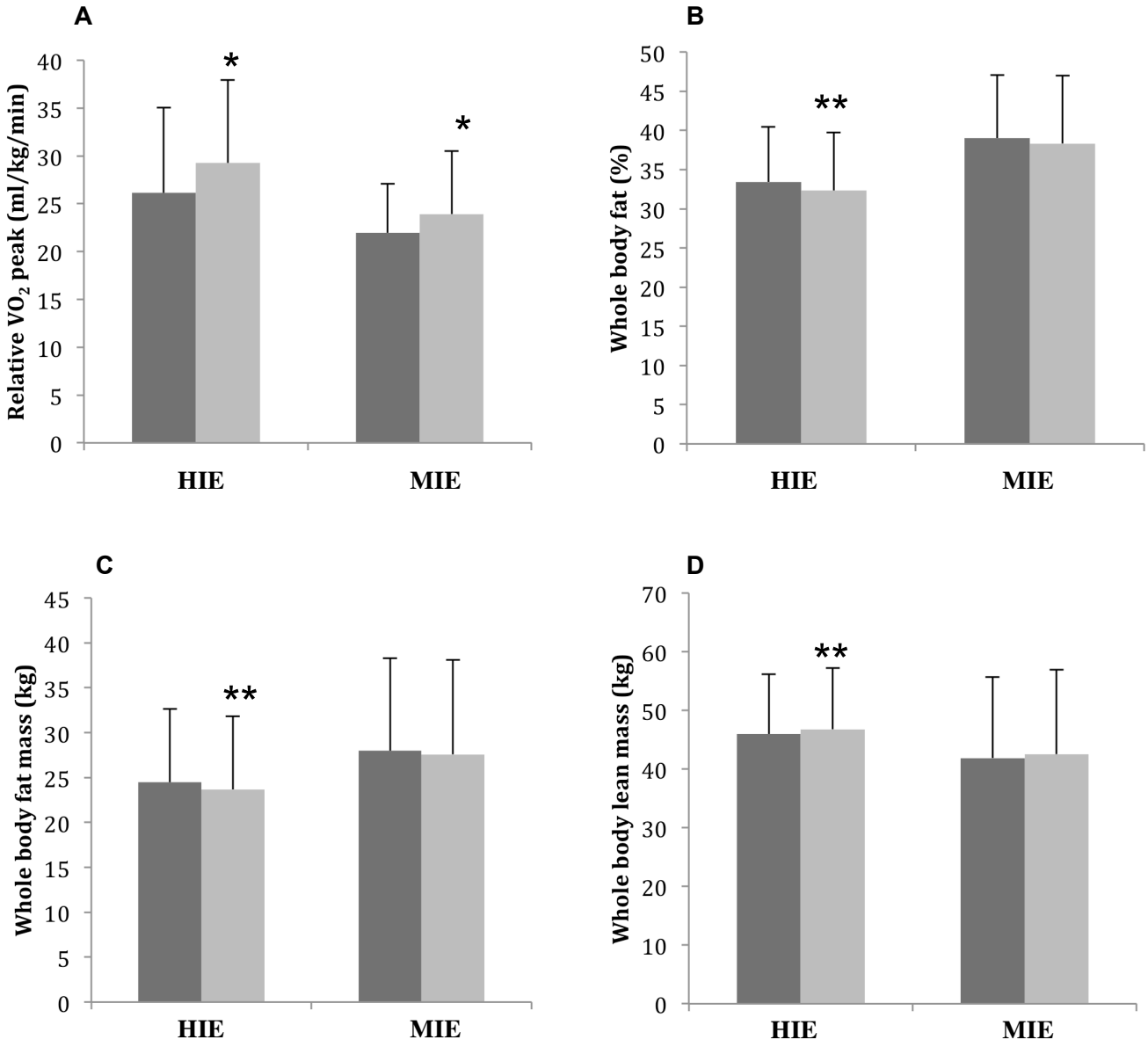


Figure 8: Pre and post-intervention mean values for *A)* relative VO_2 peak; *B)* whole body fat percentage; *C)* whole body fat mass; *D)* and whole body lean mass. *Dark grey* denotes baseline values; *light grey* denotes endpoint values. *Error bars* denote SD. * $p \leq 0.05$ versus baseline. ** $p \leq 0.001$ versus baseline. VO_2peak: Peak Volume of Oxygen Consumed. HIE: High Intensity Exercise. MIE: Moderate Intensity Exercise.

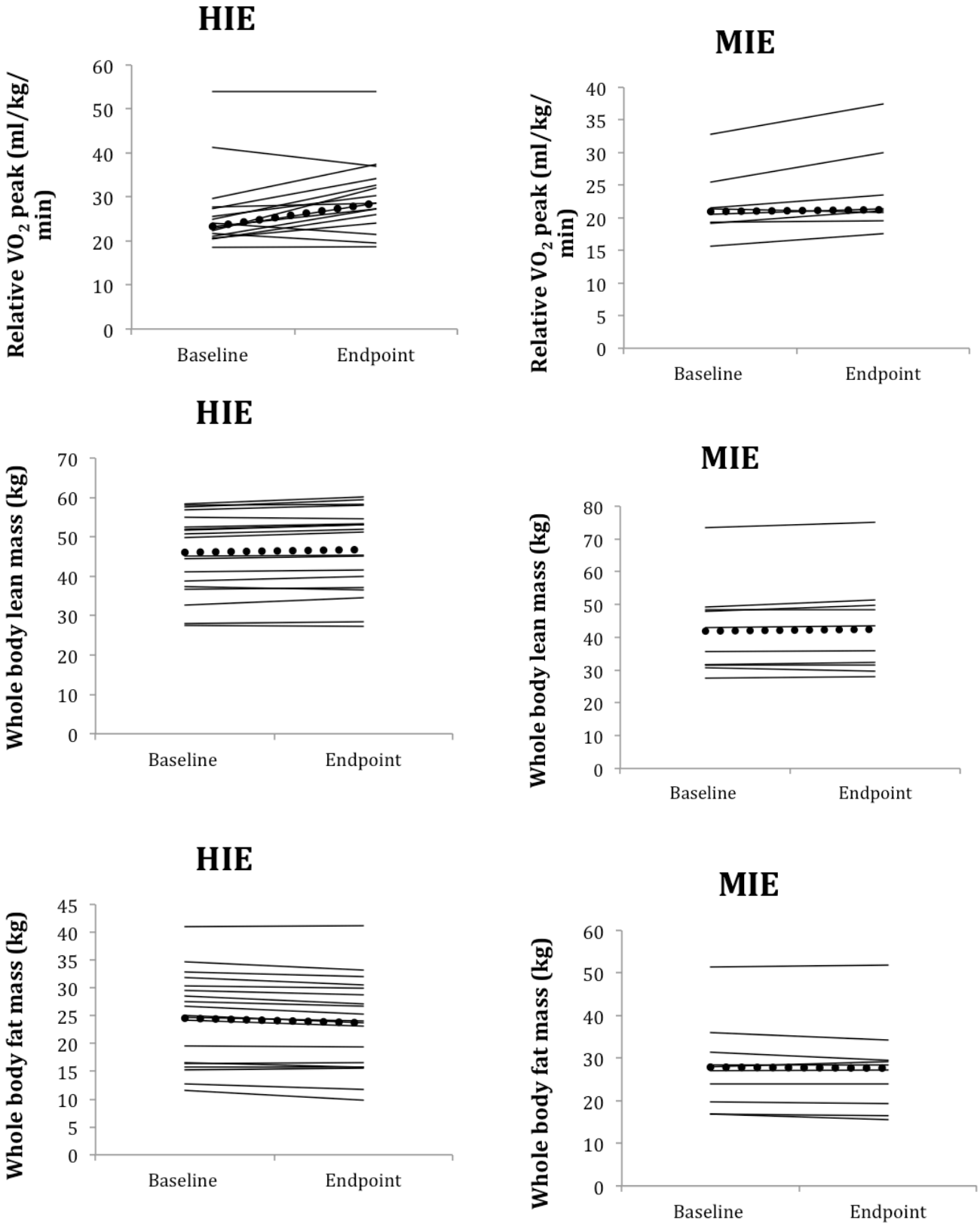


Figure 9: Individual participant pre- to post-intervention $\dot{V}O_2$peak *(top)*, whole body lean mass *(middle)* and whole body fat mass *(bottom)* values. The *dotted* lines represent the mean value. $\dot{V}O_2$peak: Peak Volume of Oxygen Consumed. HIE: High Intensity Exercise, MIE: Moderate Intensity Exercise.

3.3.7 Body composition

There were no significant between-group differences for whole body lean mass (p = 0.371), fat mass (p = 0.326), and fat percentage (p = 0.064) at baseline. There were no significant between-group differences for lean mass (p = 0.370), fat mass (p = 0.277), and body fat percentage (p = 0.061) following the 4-week intervention (Table 5). There were significant within-group changes for the HIE but not MIE group in lean mass (HIE +1.8%, $p \leq 0.001$; MIE +1.6%, $p = 0.071$), fat mass (HIE -3.3%, $p \leq 0.001$; MIE -1.4%, $p = 0.263$), and body fat percentage (HIE -3.3%, $p \leq 0.001$ MIE +1.7%, p = 0.132) from baseline to endpoint testing (Table 6) (Figure 8). Pre- and post-intervention lean mass and fat mass levels of each participant are shown in Figure 9. Changes in each measure of body composition were not significantly correlated with changes in insulin sensitivity or the IGF axis (Table 4).

3.4 Discussion

The primary aim of the present study was to examine the influence of exercise intensity on insulin sensitivity and the IGF axis in colorectal cancer survivors. In addition, changes in body composition and cardiovascular fitness were assessed in response to the two different training intensities. Following the 4-week intervention, there were no significant between-group differences for any measure at the end of the 4-week intervention. There were significant improvements in 120 min glucose concentrations in the HIE group only following the intervention. No significant within-group changes were found for other measures of insulin sensitivity, IGF-I, or IGFBP-III. Significant improvements were found for VO_2peak in both the HIE and MIE groups, and for lean mass, fat mass, and fat percentage in the HIE group only.

Insulin Sensitivity

It was hypothesised that HIE training would result in greater improvements in measures of insulin sensitivity compared to MIE training due to the higher recruitment and activation of neuromuscular motor units associated with HIE (108). However, apart from lower 120 min glucose concentrations for the HIE group following the intervention, there were no other significant changes in insulin sensitivity as measured by fasting glucose, fasting insulin, HOMA-IR or Matsuda index in response to training for either the HIE or MIE group.

Blood was sampled in the present study approximately 170-hours (1 week) after the final exercise session. Acute improvements in insulin sensitivity are known to diminish after 48-hours and this may explain why no significant changes in fasting glucose, insulin, HOMA-IR or Matsuda index were reported following the intervention (109). Despite this, exercise has been linked to chronic improvements in insulin sensitivity that extend beyond this 48-hour window (109), and this

suggests that the non-significant changes reported in this study may be due to factors other than the timing of sampling; these will be discussed in the following sections.

Currently, only one study has investigated changes in insulin sensitivity following an exercise intervention in colorectal cancer survivors (n = 17) (110). The study by Lee et al. (110) involved 12 weeks of home-based moderate intensity exercise such as hiking, swimming and stationary cycling equating to 27 MET-hours of exercise per week. Following the intervention, significant reductions in fasting insulin (p = 0.006) and HOMA-IR (p = 0.017) were observed, representing an improvement in whole body insulin sensitivity (104). Baseline fasting insulin and HOMA-IR in the study by Lee at al. (110) were 46.3 pmol/L (SD = 31.8) and 1.7 (SD = 1.2), respectively; in comparison, baseline fasting insulin and HOMA-IR for participants in the HIE group in the present study were 72.4 pmol/L (SD = 56.6) and 2.1 (SD = 1.6) respectively. This indicates that participants in our study had poorer insulin sensitivity at baseline than the colorectal cancer survivors examined by Lee et al. (110). The disparity in baseline insulin sensitivity across studies may, in part, be explained by differences in average body fat percentage, with participants from the study by Lee et al. (110) reporting 26.6% body fat compared to 33.4% within the present study. The method used to determine body composition in the study by Lee et al. (110) was not reported. Compared to people with high baseline insulin sensitivity, those with poor baseline insulin sensitivity have been found to experience greater improvements in insulin sensitivity following a 16-week exercise intervention (111). In light of this and the findings from Lee et al. (110), it was reasonable to expect that there would be significant improvements in fasting insulin and HOMA-IR following the current intervention. The absence of improvement in fasting insulin and HOMA-IR in response to the current intervention suggests that factors other than the participants' baseline values need to be explored. Factors such as the duration of the intervention and the intensity of the training program are discussed below.

Mean fasting glucose for participants in the present HIE group at baseline was 5.6 mmol/L; this falls within the limits defined by the American Diabetes Association for 'pre-diabetes' (5.6-6.9 mmol/L) (112). Physical activity has consistently been shown to reduce fasting glucose in both pre-diabetic and diabetic populations (113). Apart from the present trial, the only other study to have measured changes in fasting glucose in response to an exercise intervention in colorectal cancer survivors also found no significant change in fasting insulin following the intervention (110). A plausible explanation for the non-significant changes in fasting glucose following in the current intervention may be related to the measure itself. It has been reported that simple indices of insulin sensitivity, based on fasting plasma measures alone, cannot always reliably estimate insulin resistance (105). This is due to a biological variance (day-to-day changes under the same conditions) that exists for fasting measures of insulin sensitivity, which becomes more pronounced in persons who are pre-diabetic, such as those in the present study (105). Specifically, when comparing HOMA-IR measures on separate occasions, Jayagopal et al. (114) reported greater intra-individual variation for those with type 2 diabetes (CV = 1.05) compared to normoglycemic controls (CV = 0.15) ($p = 0.001$). Indeed, this biological variability for fasting indices may also explain, at least in part, the non-significant changes in fasting insulin and HOMA-IR reported in the present study. More reliable measures of assessing insulin sensitivity such as the OGTT and the euglycemic hyperinsulinemic clamp are available; the strengths and limitations of these are discussed below.

An OGTT was utilised in the present study in order to account for the limitations associated with simpler measures of insulin sensitivity (e.g. fasting glucose, fasting insulin, HOMA-IR) that were mentioned above. The Matsuda index and 120 min glucose indices were extrapolated from the OGTT to determine insulin sensitivity. To date, the Matsuda index and measures of 120 min glucose have not been utilised in exercise interventions for any population of cancer survivors, limiting the comparisons that can be made between the present findings and those of others. Whilst

missing data due to difficulties obtaining sufficient quantities of blood at various time points limited our ability to interpret findings from the OGTT-derived Matsuda index and 120 min (Table 1b) glucose measures, significant improvements were reported in the HIE group for the 120 min glucose, but not Matsuda index following the intervention. The 120 min glucose measure used in the present study has previously been reported to correlate well with insulin sensitivity measured via the euglycemic hyperinsulinemic clamp (115). Based on the 120min glucose measure alone, this suggests that participants in the HIE group improved their insulin sensitivity following the 4-week intervention. However, given that there were no changes in any other measure of insulin sensitivity, it is not possible to conclude with certainty that improvements in glucose control occurred in response to the HIE intervention. .

The Matsuda index is currently considered the best alternative to the euglycemic hyperinsulinemic clamp with a Pearson's correlation of 0.732 ($p = 0.0001$) (116). However, the Matsuda index is considered to be more precise in persons with normal glucose tolerance ($r = 0.73$, $p = 0.0001$) compared to those with impaired glucose tolerance ($r = 0.66$, $p = 0.0001$) (116), such as the participants in the present study. This reduced reliability may, in part at least, explain the non-significant findings in insulin sensitivity in the present study.

The intensity and/or duration of the exercise programs used in the present study may have contributed to the lack of improvement (apart from 120 min glucose) observed across the insulin sensitivity measures. The 4-week duration of the intervention was chosen in light of previous research that reported significant improvements in markers of insulin sensitivity after only 2-weeks (6 sessions) of high intensity interval training (18,117). In these trials, pre-intervention fasting glucose concentrations for obese men (n = 10) (18) and sedentary but otherwise healthy adults (n = 12) (117) were 2% and 21% 'better', respectively, than the values for participants in the present study. As mentioned previously, individuals with lower baseline insulin sensitivity are likely to

improve to a greater degree following an exercise intervention when compared to those with poor baseline insulin sensitivity (111). Given that baseline insulin sensitivity measures observed in the current trial were 'worse' than the values reported by Whyte et al. (18) and Richards et al. (117), we expected to see significant changes following the intervention. Reasons for differences in the findings between the present study and those of Whyte et al. (18) and Richards et al. (117) may therefore be related to the intensity of the training protocol utilised by these trials. Both of these previous exercise protocols involved a series of 4-7 'all out' cycle ergometer sprints for a total duration of 30 seconds each. While the specific exercise intensity was not reported in these trials, given that it was repeated 'all out' efforts, it is reasonable to assume that the exercise intensity was above the 85-95% HRpeak achieved by those in the present HIE group (118).

In comparison to the 27 MET-hours of exercise per week completed by participants in the study by Lee et al (110), participants in the current study completed 19 and 17 MET-hours per week for the HIE and MIE group, respectively. This suggests that, at least for colorectal cancer survivors, a greater quantity of exercise is required for significant changes in insulin sensitivity to occur.

Improvements in insulin sensitivity following HIE have been associated with a larger increase in skeletal muscle blood flow compared to MIE (118). To achieve the power outputs required in the studies by Whyte et al. (18) and Richards et al. (117), the exercise intensity was likely greater than the present study and therefore may have involved a greater recruitment of motor units (i.e. and incurring a higher physiological cost) and higher blood flow to the active muscle. This may explain why 'all out' HIE sprint ergometer cycling resulted in significant improvements in insulin sensitivity in 2-weeks (18,117), compared to the non-significant findings from the current 4-week intervention at an intensity of 85-95% HRpeak.

Another potential explanation for why six sessions of 'all out' cycle ergometer sprints resulted in significant improvements in insulin sensitivity, as opposed to the lower intensity exercise protocols utilised in the present study, may arise from glucose uptake following exercise. Burgomaster et al. (119) previously reported a significant 20% increase in vastus lateralis GLUT4 content following two weeks of 'all out' repeated cycle ergometer sprints. Enhanced GLUT4 content and subsequent improvements in glucose uptake have been reported to improve insulin sensitivity (118). Indeed, these changes are likely to be positively correlated with exercise intensity given that glucose (mobilised via GLUT4-related pathways) becomes the primary fuel for cellular metabolism when exercise transitions from moderate (50-70% HRpeak) to high (> 80% HRpeak) intensity (120). With this in mind, the disparate findings for insulin sensitivity between the current study and those involving 2-weeks of 'all out' cycle ergometer sprints (18,117) may result from the intensity prescribed for each interval. From this it could be surmised that for significant improvements in insulin sensitivity to occur in 4-weeks or less, the intensity of each HIE interval may need to be 'all out' (118). If the intensity of exercise training is lower, then the duration of the training program may need to be longer than the present 4-weeks (121,122).

Insulin-like growth factor axis

It was hypothesised that exercise training would reduce IGF-I and increase in IGFBP-III. Further, these changes were expected to be greater in the HIE group compared to the MIE group due to the potentially greater improvements in insulin sensitivity that were also expected to occur in the HIE group. In contrast to our hypothesis, no significant differences within or between training groups were found for IGF-I or IGFBP-III at the end of the 4-week intervention.

A possible explanation for the non-significant findings from our study may be related to a 'normalisation' effect of exercise, whereby plasma IGF-I and IGFBP-III will increase/decrease following an exercise intervention depending on whether the baseline measures are below/above

normative values. This hypothesis has been briefly suggested by Schmitz et al. (89) to explain non-significant changes in IGF-I following a 12 month resistance training intervention in breast cancer survivors.

In support of this theory, previous trials have reported significant decreases in plasma IGF-I and IGFBP-III following 6-months of moderate intensity exercise in breast cancer survivors (123), and 24-weeks of resistance training in men with prostate cancer treated with androgen deprivation therapy (21). The authors of these studies attributed the significant reductions in IGF-I and IGFBP-III to improvements in body composition, however neither study was appropriately powered to conclude this with certainty (21,123). Interestingly, baseline IGF-I and IGFBP-III measures in the trials by Santa Mina et al. (21) and Irwin et al. (123) were well above values that have been reported in healthy individuals of a comparable age and gender (124), adding support for the hypothesis by Schmitz et al. (89) that exercise can shift IGF axis levels into the range reported for healthy persons.

Only one trial has previously investigated the IGF-I and IGFBP-III response to an exercise intervention in colorectal cancer survivors; significant increases in IGF-I and IGFBP-III following 12-weeks of moderate intensity activity were found (110). In this study, pre-intervention values for both IGF-I and IGFBP-III were lower than those previously reported by healthy persons of a comparable age and gender (124). In line with the changes reported by Santa Mina et al. (21) and Irwin et al. (123), this provides further support for the hypothesis that exercise shifts IGF-I and IGFBP-III concentrations more in line with normal levels comparable to those in healthy individuals.

In the present study, pre-intervention IGF-I and IGFBP-III concentrations were well below what has previously been reported in healthy individuals of a comparable age and gender (124). The non-

significant findings from our study therefore conflict with the mechanism of exercise-mediated IGF axis shift postulated by Schmitz et al. (89) and research findings from the trial by Lee et al. (110).

Within the literature, there is currently no consensus on the mechanisms by which exercise mediates changes in IGF-I and IGFBP-III (125,126). Further, there is less certainty regarding the direction of shift in IGF-I and IGFBP-III following a chronic exercise exposure; increases, decreases and no change in the IGF axis have been reported in cancer and non-cancer populations (21,22,87,110,123,127). IGF-I and IGFBP-III released via the endocrine system are directly mediated via hepatic growth hormone (GH) release (126). Due to financial restrictions, GH was not measured in our study, limiting some of the conclusions that can be made to explain why no significant changes in IGF-I and IGFBP-III were reported. Despite these limitations, several theories to explain the non-significant changes in IGF-I and IGFBP-III in the present study are discussed below.

One of the major determinants of IGF-I reductions in response to a physical activity intervention is thought to be related to fat loss (128), although there is still some disagreement concerning this (125). Participants in the present HIE group had a significant reduction in fat mass over the 4 weeks, however no relationship between changes in IGF-I, IGFBP-III and any measure of body composition over the 4-week intervention was found. This suggests that a potential relationship between fat mass and components of the IGF axis is influenced by other factors.

Apart from body composition, mechanisms to explain the relationship between exercise and changes in the IGF axis include changes in muscle composition, increased glucose transporter protein, increased fatty acid clearance and increased post-receptor insulin signalling (123). Although none of these markers were measured in our study, collectively, improvements in these measures will generally result in greater insulin sensitivity and lower plasma insulin levels (126).

Insulin regulates the hepatic synthesis of IGFBP-1 and IGFBP-2, whereby a decrease in plasma insulin will up-regulate the production of IGFBP-I and IGFBP-II. Although IGFBP-III (as measured in our study) is the most abundant IGF-I binding protein controlling bioactive IGF-I, IGFBP-I and IGFBP-II also play a role in controlling IGF-I bioavailability (13). Up-regulation of IGFBP-I and IGFBP-II (via a reduction in plasma insulin) will cause a subsequent down-regulation in the hepatic production of IGF-I (13). This cascade happens independent of changes in body composition. The non-significant changes in insulin within the present study may therefore explain why no significant changes in IGF-I were observed.

Similarly to the discussion surrounding insulin sensitivity, the length of the intervention may explain the non-significant changes in the insulin-like growth factor axis found in our study. Indeed, our trial was the first to explore changes in these biomarkers via a 4-week physical activity intervention within cancer survivors. Previous studies that have reported significant changes in the insulin-like growth factor axis in response to a physical activity intervention in cancer survivors have been 6-months (123), 24-weeks (21), and 12-weeks (110) in duration.

Apart from systemic (endocrine) production, IGF-I and IGFBP-III are also produced locally via paracrine and exocrine mechanisms. Research identifying increased muscular performance following an exercise intervention without a concurrent change in endocrine-produced IGF-I has concluded that exercise-induced IGF-I changes are likely to be locally produced (exocrine/paracrine) (126). IGF-I and IGFBP-III measured via plasma (as in our study) would therefore not reflect changes that occur outside of the circulatory system. This may explain why in the present study no significant changes in IGF-I or IGFBP-III were reported following the intervention.

Based on the non-significant findings relating to the IGF axis in the present study trial and the subsequent exploration of why our results did not support our initial hypothesis, future trials would benefit from to using biochemical techniques that measure both paracrine and exocrine IGF-I and IGFBP-III. As discussed by Sax et al. (129), the IGF axis is a plausible mechanism linking physical activity to improved survival following colorectal cancer diagnosis. It may however be apparent that the IGF components responsible for this association are produced exclusively via paracrine/exocrine, rather than by endocrine mechanisms.

Body composition

It was expected that lean mass would increase significantly in the HIE group in comparison to the MIE group due to the potentially greater recruitment of motor units during exercise compared to that for the MIE group. Further, it was expected that there would be similar decreases in fat mass for both groups; this is consistent with the current position that for weight loss moderate and vigorous intensity exercise are equally as effective (130). In the present study, significant improvements were reported for lean mass, fat mass, and body fat percentage at the end of the 4-week intervention for the HIE group only.

For the HIE group only the present findings are in contrast to trials in other cancer survivors, which have failed to report improvements in fat mass, lean mass and body fat percentage in response to an exercise intervention (110,123). In colorectal cancer survivors, no significant improvements in body fat, lean mass, or body fat percentage were reported in response to a 12-week moderate intensity aerobic exercise intervention (110). Similarly, however with breast cancer survivors (123), 6 months of moderate intensity aerobic training did not significantly alter body fat percentage. These investigations utilised DEXA to analyse body composition; the same technique used in our trial. The reason for the disparity between the current study and previous reports may be due to the physiological response to the high intensity interval protocol used in our trial. No other studies

utilising the present '4x4' high intensity interval protocol (122,131,132) have included measures of body composition (121).

The significant within-group decrease in fat mass reported by the HIE group may be due to a number of mechanisms including increased fat oxidation and decreased appetite following exercise. Beta-oxidation (133) and lactate production (134) have been found to be 24% and 80% greater, respectively, after HIE compared to MIE. Further, catecholamine (135) and growth hormone production (136) following acute bouts of HIE have been reported as being higher than levels produced after MIE (137). Collectively, these biochemical responses indicate a superior degree of fat-oxidation following an acute bout of HIE compared to MIE. In the present study, no significant between-group differences were found for fat mass following the intervention, however the physiological mechanisms outlined above may, in part, explain the significant reductions in fat mass reported for the HIE group only.

The changes in body composition found for the HIE group in the current trial are clinically significant. Colorectal cancer survivors have a 1.4 fold increased risk for the development of second primary colorectal cancers compared to healthy populations (5). Epidemiologic data have shown that a 10 kg gain in fat mass increases, in a linear fashion, the risk of developing colorectal cancer by 33% (138). Participants in the present HIE group decreased their fat mass by 0.8 kg, which would reasonably lead to a decrease in relative risk for the development of second primary colorectal cancers (138). Although the cohort described by MacInnis et al. (138) did not include survivors of colorectal cancer, their findings suggest that as a result of their fat loss, participants in the present 4-week study may have decreased their relative risk for the development of second primary colorectal cancers by ~3%.

The significant increase in lean mass for the HIE group following the 4-week intervention also warrants discussion. In previous exercise interventions for colorectal cancer survivors involving resistance (139) and aerobic (19) training, no significant changes have been reported in lean mass. Despite both these trials being much longer than our trial (12-weeks), the intensity of exercise prescribed in the aforementioned interventions was below the intensity utilised in our HIE protocol (50-70% HRpeak versus 85-95% HRpeak). This disparity likely underpins the marked improvement reported for lean mass in our HIE group. Mechanistically, the significant within group increase in lean mass from baseline for those in the HIE group is likely due to the greater degree of muscle fibre recruitment compared to MIE training (118). The significant improvements in lean mass reported for the HIE group may also underpin the reductions in fat mass via an increase in basal metabolic rate (140).

From a clinical perspective, improvements in lean body mass have been inversely correlated with mortality risk (141). A one standard deviation increase in lean mass has been associated with a 19% and 31% decrease in mortality risk for women and men, respectively ($p < 0.001$) (141). Beyond this, increases in lean mass have been consistently related to improvements in mobility and independence, reductions in falls, and decreases in hospital admissions; factors that all contribute to quality of life in older individuals (142,143).

To the author's knowledge, this is the first trial to report significant within-group changes in body composition following 4-weeks of HIE in colorectal cancer survivors. Whilst further research is required, the current findings support engagement, where possible, of colorectal cancer survivors in HIE for beneficial changes in whole body fat and lean tissue mass. Currently, the American College of Sports Medicine recommends people engage in 250 minutes per week of MIE in order to achieve ~1.0 kg loss in fat mass per week (100). In light of this, the significant 0.8kg mean loss in fat mass reported for the HIE group following only 114 minutes of exercise per week is clinically

meaningful. Future research should utilise the same HIE protocol as the present study to determine if these changes are transferrable to other clinical populations.

Cardiorespiratory fitness

It was hypothesised that VO_2peak would increase in both training groups following the interventions. In support of previous findings from a systematic review of HIE for persons with cardiometabolic disease (121), it was further hypothesised that the changes in VO_2peak would be significantly greater in the HIE group. Over the 4-week intervention, significant within-group improvements were reported for VO_2peak in both HIE and MIE groups (23.0% and 1.9%, respectively).

The absolute increase in VO_2peak of 5.3 mL/kg/min for the HIE group in our study is greater than improvements reported previously in colorectal cancer survivors (144). As described by Sellar et al. (144), 12-weeks of moderate intensity aerobic and resistance based exercise accounting for a total of 18-MET hours per week resulted in a 3.0 mL/kg/min VO_2peak improvement. Compared to the findings of Sellar et al. (144), the absolute improvement in VO_2peak of 5.3ml/kg/min reported for the present HIE group may have been due to the higher exercise intensity employed.

The proposed mechanisms potentially responsible for the significant improvements in VO_2peak for the HIE group include changes in mitochondrial density (145) and cardiac stroke volume (146). Following 6 sessions of 'all out' sprinting, healthy males and females (n = 8) significantly increased intramuscular citrate synthase (a marker of oxidative potential and mitochondrial function) by 38% ($p < 0.05$) compared to pre-intervention values (145). Further, in a cohort of male university students (n = 10), 16 sessions of HIE at an intensity of 90-95% HRpeak significantly improved cardiac stroke volume by 13% ($p < 0.01$) compared to pre-intervention values. Collectively, these

physiological changes will result in a greater presentation and utilisation of oxygen at an intercellular level which will, in turn increase ones VO_2peak (118).

For the present HIE group, the significant within-group improvement in VO_2peak may be associated with a decreased risk for cancer-specific mortality. A 1-MET increase in cardiorespiratory fitness (equivalent to a VO_2peak change of 3.5 mL/kg/min) has been equated to a 5% decreased risk for cancer-specific mortality (147). It is uncertain whether these improvements are linear. However, the present findings for the HIE group suggest a decreased their risk for cancer-specific mortality by at least 5% based on their VO_2peak improvements. Beyond cancer-specific health, longitudinal research has identified an inverse association between cardiovascular fitness and all-cause mortality in men (148). A 1-MET improvement in VO_2peak has been shown to be correlated with a 15% reduction in risk for all-cause mortality in a cohort of approximately 15,000 men (149). In light of these data, participants in the present HIE group may have reduced their risk for all-cause mortality by ~ 15% in only 4-weeks.

Our findings support those from a recent systematic review and meta-analysis investigating the benefits of HIE for persons with cardiometabolic disease (121). In nine of the ten studies reviewed, VO_2peak increased by an average of 19.4%; comparable to the 23% reported in the present trial. Of these trials, three utilised the same '4x4' training protocol (122,131,132), however the mode of intervention was restricted to uphill walking on a treadmill rather than stationary cycling. The duration of these trials were 10 (132), 12 (131), and 16 weeks (122), highlighting the novelty of the current 4-week intervention. Further, the present data show that significant changes in VO_2peak can be gained through cycling; an important consideration particularly for persons who are unable to walk due to a variety of limitations.

Safety and Adherence to Intervention

The present study is the first to incorporate the '4x4' high intensity exercise protocol in a cancer population. Given this, safety, attendance and adherence to the intervention were key areas of interest. There were no adverse events in response to exercise reported or observed during the intervention; this includes events that occurred outside the training and testing sessions. This is consistent with findings from previous research that utilised the same exercise protocol, and found no adverse events in person with heart failure (131), metabolic disease (122) and coronary artery disease (132). The use of appropriate screening and risk stratification procedures along with supervision of each training and testing session by an Accredited Exercise Physiologist in our trial is a likely explanation for the absence of adverse events. This was also the case in the trials for persons with heart failure (131), metabolic disease (122) and coronary artery disease (132).

Given the higher physiological demands of the HIE compared to MIE training programs, attendance rates during HIE training sessions have, in other studies, been slightly lower. In persons with heart failure, metabolic disease and coronary artery disease, attendance to training sessions has been reported as 92% (131), 90% (122) and 94% (132), respectively. In the present study participant attendance was 100%. The disparities in attendance reported between the present study and previous studies utilising the same protocol may be due to the length of the intervention. The aforementioned interventions were all substantially longer exercise trials, requiring commitments of 10 (132), 12 (131) and 16 (122) weeks.

An important aspect with regard to the '4x4' high intensity exercise protocol is the reporting of adherence to the heart rate zones during the intervals. Participants are required to maintain a heart rate between 85% and 95% of their peak during the 4-minute intervals. Presently, no studies utilising the '4x4' approach have reported the time taken for participants to actually achieve their prescribed heart rate intensity. In the current study, the average time taken to reach the prescribed

heart rate intensity in the HIE group was 38-seconds. Anecdotally, the Norwegian Cardiac Exercise Research Group (CERG) who developed the '4x4' protocol have advised that heart rate prescription should be reached within 2-minutes of the high intensity interval. By comparison, persons in the present study were within prescribed heart rate ranges for approximately 68% longer than what is recommended by this group.

The safety and adherence outcomes from our trial support the findings from existing research utilising HIE interventions in clinical (but not cancer) populations (122,131,132,150). To the author's knowledge, only one other trial has incorporated aerobic HIE at an intensity of 85-95% HRpeak in cancer survivors (150). The present findings therefore give weight to the claim that HIE is safe, feasible and effective for colorectal cancer survivors, and potentially for other cancer survivors.

Limitations and future recommendations

A key limitation of the present study was the method used to assess insulin sensitivity. The euglycemic hyperinsulinemic clamp is currently the most robust measure of insulin sensitivity; however this was not utilised in the present study due to cost and participant time requirements. If feasible, future investigations with the primary outcome of insulin sensitivity should attempt to use this technique over surrogate measures such as fasting glucose, insulin and the HOMA-IR index, which were all utilised in the present study. This is of particular importance when participants are pre-diabetic or diabetic prior to the intervention; simple indices such fasting glucose, insulin and HOMA-IR have been reported to be less precise for these people compared to those with normal insulin sensitivity (105,116).

In light of the non-significant changes in the present measures of the IGF axis (despite sound theory supporting their mediation via physical activity), future interventions should consider measuring

these markers in skeletal muscle. This may allow for the measurement of IGF-I and IGFBP-III produced via autocrine and paracrine (rather than endocrine) pathways. If exercise indeed mediates the IGF axis through these pathways (as opposed to endocrine), significant changes are more likely to be reported following a controlled HIE intervention when using biopsy-based IGF-I and IGFBP-III measures.

Future studies should also aim to provide a more accurate assessment of total energy expenditure outside of the supervised intervention. Indeed, participants from the present study were advised to continue their pre-intervention level of activity outside of the intervention until the conclusion of the trial. However, an instrumented measure of activity such as accelerometer could be used to assess all physical activity performed during the intervention period – activity that could potentially influence the outcome measures.

Presently, there is no evidence to support the conclusion that moderate intensity exercise is more beneficial than no exercise for the insulin-like growth factor axis in colorectal cancer survivors. While the absence of a non-exercising control group in this study may be considered a limitation, the MIE group met the current exercise oncology guidelines; comparison of the HIE training responses to the MIE training responses involved the MIE essentially assuming a control condition.

It would be useful to include a participant follow-up component in future studies. In the present trial, no additional correspondence was made with participants subsequent to their discharge from the intervention. It therefor remains unclear as to whether participants continued to engage in HIE after the intervention, and as a consequence, preserve the physiological improvements that were developed during the study.

Finally, one of the key limitations presented by this study was recruitment of suitable participants. I was able to recruit 29 participants from the 556 people invited to participate (5%). The inclusion criteria in relation to age, was wide to encourage recruitment, which is notoriously difficult in this clinical patient group. Therefore, the results of the study should be treated with caution when translating them to particular age groups.

Additionally- and unfortunately we weren't powered to run the sub-analyses by age groups. Larger trials would be needed for this to be possible. Future trials targetting specific age groups are required to determine the effects of the different types of exercise on younger and older colorectal cancer survivors.

Based on the results from our trial, the following sample sizes would be required to achieve an 80% power (two tailed, alpha level of 0.05) in future trials utilising the same population and intervention;

HOMA-IR: effect size = 0.3685771, sample size = 117/group.

Fasting insulin: effect size = 0.4165356, sample size = 92/group.

IGF-I: effect size = 0.5471232, sample size = 54/group.

IGFBP-III: effect size = 0.1943924, sample size = 417/group.

Conclusions

The present study found no change in markers of insulin sensitivity (apart from 120 min glucose), IGF-I or IGFBP-III in response to 4-weeks (12 exercise sessions) of moderate- and high-intensity exercise training with colorectal cancer survivors. This was despite there being significant improvements in VO_2max and body composition – improvements that are known to be associated with decreases in all-cause mortality (including cancer).

CHAPTER 4 CONCLUSIONS

While the benefits of physical activity for the prevention of colorectal cancer and reduction in disease-specific mortality post-diagnosis are well established, the physiological mechanisms by which physical activity can mediate these outcomes remains to be determined. The increased incidence of colorectal cancer in persons with diabetes has developed interest in hyperinsulinemia as a potential mediating factor for the development of first and second primary cancers. Apart from insulin sensitivity, the IGF axis is the most plausible mechanism; there is evidence to suggest that a decrease in IGF-I and an increase in IGF-III can reduce disease-specific mortality. In colorectal cancer survivors, there is evidence to suggest that physical activity can deliver a positive effect on insulin sensitivity and the IGF axis. Given that colorectal cancer survivors are at a heightened risk for the development of a second primary colorectal cancer (compared to persons without a previous cancer diagnosis), understanding how physical activity can mediate these biological markers is crucial.

The current physical activity recommendations for cancer survivors suggest 150 minutes of moderate intensity exercise each week (43). There is however developing evidence suggesting that high intensity exercise is more beneficial for improvements in cardiorespiratory fitness and insulin sensitivity. Prior to the study included in chapter 3 of this thesis, insulin sensitivity and the IGF axis were yet to be measured in response to a high intensity exercise protocol in colorectal cancer survivors.

The aim of the randomised controlled trial included within chapter 3 of this thesis was thus to compare the effect of moderate versus high intensity exercise on insulin sensitivity and the IGF axis in colorectal cancer survivors. Although no changes were consistently reported in all measures of

insulin sensitivity and the IGF axis, significant improvements were reported in body composition for the high intensity exercise group only. Beyond the novelty of these changes in only 4-weeks, improvements in fat and lean mass correlate with reductions in cancer-specific and overall mortality.

In light of the findings from this thesis, future investigations should continue to investigate the effect of HIE on various biomarkers in CRC survivors. Indeed, physical activity has been shown to have a protective effect for the development of colorectal cancers, with higher intensity exercise being even more beneficial. Identifying the physiological mechanism supporting this association will broaden our understanding of the nexus between physical activity and the development of colorectal cancers.

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CHAPTER 6 APPENDICES

Appendix A The insulin-like growth factor axis: A biological mechanism linking physical activity to colorectal cancer survival

Title

The insulin-like growth factor axis: a biological mechanism linking physical activity to colorectal cancer survival

Authors and Affiliations

Andrew T Sax, David G Jenkins, James L Devin, Gareth I Hughes, Kate A Bolam, Tina L Skinner

School of Human Movement Studies, The University of Queensland, Australia.

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Corresponding Author

Andrew Sax

Level 5, Building 26, School of Human Movement Studies, The University of Queensland, St Lucia, QLD, Australia, 4072

a.sax@uq.edu.au (+61) 430 060 872

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Abstract

Physical activity (PA) is related to colorectal cancer (CRC) mortality, with approximately 15% of CRC deaths worldwide attributable to physical inactivity. Moreover, higher levels of PA in CRC survivors have been associated with a reduced risk of the disease recurring. Despite the recognised nexus between PA and the risk of CRC, the physiological mechanisms underlying the inverse relationship between PA and mortality following CRC diagnosis are less apparent, with evidence primarily drawn from epidemiological studies. The insulin-like growth factor (IGF) axis plays a central role in cellular growth, proliferation regulation, differentiation and apoptosis. Specifically, high levels of insulin-like growth factor 1 (IGF-1) have been consistently linked to the severity of CRC tumours. Further, insulin-like growth factor binding protein 3 (IGFBP-3) regulates the bioavailability of IGF-I and therefore plays a central role in CRC prognosis. Decreasing levels of IGF-1 and increasing levels of IGFBP-3 may thus be a plausible mechanism underlying the inverse association between PA and CRC survival.

Introduction

Of all cancers, colorectal cancer (CRC) has the fourth highest incidence rate worldwide and it is estimated that CRC is responsible for the deaths of approximately 608,000 people each year (1). Given these statistics, reducing CRC incidence, recurrence and improving survival have emerged as major public health priorities.

Physical activity (PA) has been specifically linked to CRC mortality, with approximately 15% of CRC deaths worldwide being attributable to physical inactivity (151) Further, epidemiological data show a significant decrease in disease-specific mortality for individuals who are physically active after diagnosis compared to those who are not (29,30). However beyond recognising a relationship between PA and CRC survival, the biological mechanisms that underpin this association are not entirely clear. Given that the insulin-like growth factor (IGF) axis has been implicated as a key host pathway responsible for the association between PA and CRC specific mortality (33-35), using PA to influence the IGF axis may represent an effective means of reducing CRC mortality and improving survival. This paper will review the available evidence relating to PA following CRC diagnosis, the IGF axis and survival from the disease.

1.0 Physical Activity and Colorectal Cancer

An inverse relationship between PA and the incidence of CRC has consistently been reported in the literature (4,36,37). Furthermore, engaging in PA after CRC diagnosis is associated with 50-60% reductions in disease-specific mortality (23,38-40). Despite the important role PA has for the health of survivors following CRC diagnosis, specific PA guidelines for reducing the risk of CRC-related mortality following diagnosis do not yet exist.

1.1 Physical Activity and Colorectal Cancer Incidence

Over the past ten years, three meta-analyses (4,36,42) have reported an inverse relationship between PA and the incidence of colon cancer. Samad et al. (36) analysed nineteen cohort and twenty-eight case-control studies and identified a relative risk (RR) for developing colon cancer of 0.79 when comparing the recreational PA of the most to the least active men. For women, a RR of 0.71 was identified for recreational PA when comparing the most active to least active (36). More recently, Wolin et al. (4) found a RR of 0.76 for both men and women when comparing the most to the least physically-active individuals. Further, Boyle et al. (37) highlighted an inverse dose-response relationship between PA and colon cancer risk in eleven of the twenty-one studies included in their analysis.

Whilst these results offer support for the promotion of PA to reduce the risk of colon cancer, there is little evidence that PA can decrease the risk of developing rectal cancer (4,36,42). The reason for this disparity is unknown. The closest understanding to the relationship between PA and rectal cancer is derived from studies that demarcate the colon into proximal and distal sub-sites during statistical analysis. However, findings from these studies offer no significant differences between proximal and distal colon regions with a RR of 0.73 and 0.74, respectively, when comparing the most to the least physically-active individuals (37). A greater understanding of the physiological link between PA and colon cancer from a survival perspective may explain why rectal cancer incidence does not appear to be mediated by PA.

1.2 Physical Activity and Colorectal Cancer Survivorship

Following conventional treatment, CRC survivors who remain or become physically active have a > 50% reduction in cancer-specific mortality over those who are inactive (38-40). Indeed, researchers recommend exercise as an adjuvant to conventional treatment for those diagnosed with the disease (4,23,36,38-40,42).

Meyerhardt et al. (38) found an inverse relationship between PA and hazard ratio for CRC-specific mortality in male survivors. In a cohort of 661 men, those who engaged in more than 27 metabolic equivalent of task (MET) hours of PA per week had a CRC specific mortality hazard ratio of 0.47

compared to those who engaged in less than 3 MET-hours per week (38). In a cohort of 573 female CRC survivors, a RR of 0.39 was found for those who engaged in at least 18 MET-hours of PA per week compared to those who engaged in less than 3 MET-hours per week (39). Both studies found no change in statistical significance following adjustment for cancer stage (I-III), body mass index (BMI) and pre-diagnosis levels of PA. Such evidence highlights the importance of PA following diagnosis irrespective of pre-diagnosis activity levels. Although the specific frequency, intensity, type and mode of PA required for reductions in CRC specific mortality is uncertain, Meyerhardt et al. (38) have indicated that a protective effect for this measure occurs at approximately 9 MET-hours per week. This volume of PA aligns well with the current adult PA guidelines for health benefits (152).

The majority of studies that have investigated the relationship between PA and CRC survival have not reported the frequency, intensity, duration and/or mode of activity of the participants (4,23,36,38-40,42). To a large part, this can be attributed to the limitations of self-report PA measures used in these studies, which typically estimate activity levels using MET values. It has been shown that participants tend to over-report than under-report PA when recalling previous activity levels (46). This limits the conclusions that can be drawn from studies with respect to the 'dose' of PA required to elicit a protective effect. Research that involves structured PA interventions is required to better understand the relationships between CRC survival and PA that have been identified in prospective, case-control studies. Results from these intervention trials will help to determine the optimal 'dose' of exercise required to reduce CRC incidence and disease-specific mortality post-diagnosis. The Colon Health and Life-Long Exercise Change trial (CHALLENGE) (25) aims to address this limitation; this ongoing randomised controlled trial incorporates a multicentre PA intervention utilising instrumented measures of PA and aerobic fitness for people with stage II and III colon cancer. The primary outcome of this trial is disease-free survival, with cardiovascular fitness a secondary endpoint. This study will also track key biological markers believed to underpin the relationship between PA and colon cancer risk.

2.0 Insulin-like Growth Factors and Colorectal Cancer

Changes in gastrointestinal transit time, inflammation, immune function, genetic mutations, insulin and the IGF axis have all been suggested as mediators to explain the relationship between PA and CRC incidence and disease-specific mortality (2,3). Specifically, it is believed that the IGF axis plays a central role in cellular growth, proliferation regulation, differentiation and apoptosis (12,13). Given these mechanisms, IGFs and their binding proteins (IGFBPs) have been identified as a key research focus in CRC pathology (14).

The IGF axis has been linked to the incidence of CRC, along with the risk of tumour metastases following diagnosis (35,153). Cross-sectional research has also found associations between the IGF axis and the graded severity of CRC carcinomas (14,72,73). Manipulation of the IGF axis through PA may therefore be a promising therapy for preventing CRC, as well as reducing the likelihood of CRC-specific mortality post-diagnosis.

2.1 Insulin-like Growth Factor Axis

The IGF axis consists of two polypeptide ligands (IGF-I and IGF-II), two cellular membrane receptors (IGF-IR and IGF-IIR), and six binding proteins (IGFBP-1 through IGFBP-6). IGF-I and IGF-II are produced via the endocrine, paracrine and autocrine systems (51). Growth hormone (GH) plays a dominant role in the upregulation of IGF-I with serum levels peaking around puberty and then decreasing throughout life (52,53). IGF-I levels are also influenced by sex and nutritional status with higher levels found in females (54), periods of excess energy intake (55) and obesity (52). Unlike IGF-I, the release of IGF-II is GH independent and levels remain stable after puberty (51). At a cellular level, IGF-I and IGF-II accelerate cell cycle progression through the growth phase where DNA replication occurs (56). Analogous to this growth-facilitating effect, IGF-I and IGF-II have the capacity to block cellular apoptosis. These processes have been reported in healthy (16) and malignant tissue (57), highlighting the potential role of IGF-I and IGF-II in the progression of CRC following diagnosis.

The biological actions of IGF-I and IGF-II are mediated via two cell-surface receptors; IGF-IR and IGF-IIR (16). Because of the structural similarities between IGF-I and IGF-II, the IGF-IR is able to

bind both molecules albeit at different affinities. IGF-IR favours IGF-I, binding the molecule at a 2-15 fold higher affinity than IGF-II (58). Unlike the IGF-IR, the IGF-IIR does not bind IGF-I; this receptor specifically binds IGF-II, and at a 500-fold affinity greater than the IGF-IR (13). Because binding of IGF-II to the IGF-IIR results in degradation of the molecule, the intra-cellular actions of IGF-II are thought to be primarily mediated through the IGF-IR (59). This complex association underpins the uncertainty that exists for the role of the IGF axis within the relationship between PA and CRC.

The majority (~75%) of IGF-I and IGF-II produced via the endocrine system are bound in a ternary complex with IGFBPs and an acid labile subunit (ALS) (63). The remaining IGF-I and IGF-II circulates in free form or in a binary unit with IGFBPs only (63). Because ALS only has an affinity for IGF-I/IGF-II that is bound in a IGFBP complex, IGFBPs are thought to control the bioavailability of IGF-I and IGF-II (64). This is actioned via three distinct pathways; 1) transportation, 2) prolonging the half-life of IGFs and protecting them from degradation, and 3) modulating the interaction between IGFs and their receptors (65). When combined in the ternary unit, IGF-I and IGF-II are unable to bind to the cell surface receptors, IGF-IR and IGF-IIR. This is due to the up to 50 fold higher affinity of IGFBPs for IGF-I and IGF-II over their respective receptors (65). The outcome of this affinity is thought to be the inhibition of IGF receptor activation, which in turn prevents IGF-I and IGF-II mediated cellular proliferation and reduces anti-apoptosis. In contrast, IGFBPs prolong the half-life of IGF-I and IGF-II via the prevention of proteolytic degradation that would normally occur if IGF-I and IGF-II were circulating in isolation (63). This results in a lengthening of IGF-I and IGF-II bioavailability (66). Given these differing processes, IGFBPs can facilitate or inhibit the mitogenic actions of IGF-I and IGF-II. These mechanisms indicate that IGFBPs may be of equal importance to IGF-I and IGF-II in mediating cellular growth and understanding how PA influences CRC incidence and mortality.

In serum, IGFBP-3 is the most abundant IGF binding protein, carrying approximately 90% of all bound and free circulating IGF-I and IGF-II (34). Independent to its association with IGF-I and IGF-II, IGFBP-3 has been found to have a pro-apoptotic and anti-proliferative capacity (67). This has

led to a focus on this specific binding protein as a mediator for the development and progression of colorectal neoplasms.

A limitation to the measurement of these biomarkers in existing cancer research is that they may not reflect downstream cellular growth. Assays used to measure IGF-I and IGF-II do not discriminate between free form IGF-I/IGF-II, and that which is bound in binary and ternary units (64). Because of this, current techniques may not reflect the bioactive IGF-I and IGF-II that are able to interact with cellular receptors. Furthermore, given that IGFBPs have both growth facilitating and inhibiting effects, direct measures of these biomarkers cannot accurately predict pro- or anti-proliferative processes. An assay that overcomes these limitations will enhance the understanding of how exercise influences the IGF axis interaction with carcinomas. Identifying the action of intracellular growth processes rather than merely measuring circulating levels of these biomarkers is needed. Nonetheless, reductions in plasma IGF-I and IGF-II, and increases in IGFBP-3 suggest a more favourable outcome for the prevention of CRC and reductions in disease-specific mortality.

2.2 Insulin-like Growth Factors and Colorectal Cancer Survival

There is strong epidemiological evidence linking IGF-I, IGF-II and IGFBP-3 to the incidence of CRC (35,153-157). What is less apparent is the nexus between the IGF axis, tumour metastasis and tumour recurrence. Although 5-year relative survival for isolated CRC is promising (89.9%), those who experience regional and distant tumour metastasis following diagnosis have a poorer prognosis, with expected survival rates of 69.6% and 11.9%, respectively (158).

Research has identified significant associations between tumour severity and IGF-I, IGF-II and IGFBP-3 (14,72,73,75,76). These studies have focussed on tumour grade and metastasis, where a greater tumour grade and extent of metastasis infers a heightened CRC-specific mortality risk (14,72,73,75,76). In an animal model, IGF-I has been found to influence colon cancer tumour growth and metastasis in liver-IGF-I deficient (LID) mice, which have approximately 75% less endogenous IGF-I than controls (76). Following transplantation of colon adenocarcinomas, LID

mice had smaller and fewer tumours with less liver metastases than controls. Further, exogenous IGF-I administration in both controls and LID mice increased the rate of tumour progression and metastases compared to mice treated with saline (76).

Findings from human *in vivo* research examining IGF and CRC staging have produced varying results (14,72-75). Prospective samples from men and women undergoing a colonoscopy identified high-risk adenomas were positively associated with serum IGF-I and inversely associated with IGFBP-3 (72). Supporting this, in a cohort of 125 CRC patients, higher serum concentrations of IGF-I were found in those with metastases compared to those with localised CRC (73). Similar findings for IGF-I and adenoma severity were reported by Jacobs et al. (74). IGF-II has also been linked to CRC severity with higher serum levels found in concurrence with secondary cancers (14). In contrast to these results, no significant differences in serum IGF-I were reported with patients who had moderate adenomas compared to advanced carcinomas (75). Nonetheless, the weight of the limited available evidence tends to support a positive relationship between IGF-I/IGF-II and CRC specific mortality and an inverse relationship between IGFBP-3 and CRC specific mortality.

Given the pathways by which IGF-I and IGF-II stimulate cellular proliferation, the expression of IGF-IR and IGF-IIR in colonic carcinomas is likely to influence tumour progression. A high presence of these receptors in tissues would allow for enhanced activation of intracellular growth processes via IGF signalling. Positive tissue staining for IGF-IR has been more frequently identified in primary and high risk CRCs in comparison to non-cancerous adenomas and normal tissue (80,81). Further research has identified IGF-IR and IGF-IIR gene expression to be 2.5 and 5 times higher, respectively, in malignant tissue compared to adjacent non-cancerous tissue (82). Despite this finding, the IGF-IIR is not thought to influence tumorigenic potential as it lacks the capacity to initiate mitogenic behaviours (59).

In vivo research has examined markers of the IGF axis after CRC diagnosis to determine their relationship with disease-specific mortality. Wolpin et al. (78) addressed this among 373

participants over 13 years, and found no associations between pre-diagnosis IGF-I and IGFBP-3, and mortality in those who developed CRC. Given that lifestyle factors such as diet, obesity and PA are known to influence IGFs (52,64), failure to include these confounders into the analysis may have contributed to the lack of significant findings with regard to IGF-I and IGFBP-3. Following CRC diagnosis, higher circulating IGFBP-3 has been correlated with a greater response to chemotherapy, arrested rate of tumour progression, and an increase in overall survival (79).

The varied physiological findings reviewed above highlight the need for robust interventional designs to clarify the relationships between IGF-I, IGFBP-3 and CRC mortality. Larger sample sizes coupled with improved assays that more precisely measure how IGF-I, IGF-II and IGFBP-3 influence cellular growth will advance the understanding of these relationships. In addition, confounding factors such as energy intake and PA following CRC diagnosis need to be either controlled for or accurately monitored. Notwithstanding these limitations, there is strong evidence to support a mechanistic link between IGFs and heightened CRC mortality following diagnosis, whereby increased levels of IGFBP-3 and decreased circulating levels of IGF-I and IGF-II are associated with reduced disease-specific mortality.

3.0 Physical Activity and the Insulin-like Growth Factor Axis

The physiological response of IGFs to PA is inconsistent; increases, decreases and no change in the IGF axis have been reported in cancer and non-cancer populations (20,21,84,86-89). While the reason for this inconsistency is not clear, some researchers believe that negative energy balance may underlie the mechanism/s (88), while others purport that it may be more closely related to energy flux (86) and physical conditioning (87). Although limited, there is evidence from trials involving CRC populations to indicate that changes in these biomarkers driven by PA can have favourable outcomes for disease-specific mortality (23).

Only one intervention study has investigated the influence of PA on the IGF axis in a CRC population. Following 12 weeks of unsupervised PA of 18 to 27 MET-hours per week, significant increases in IGF-I and IGFBP-3 were found (19). Given that the intervention was unsupervised

and adherence was measured via a self-reported questionnaire, the precise quantity and intensity of PA completed is unknown. Furthermore, prospective evidence demonstrated a one standard deviation increase in IGFBP-3 was associated with a 51% reduction in cancer-specific death for those who were physically active (24). The same association was not seen for inactive individuals or for IGF-1 (24). This indicates that PA is capable of eliciting a beneficial shift in disease-specific mortality that is manifested by a measureable biochemical change. Whilst it cannot be concluded without further research why the IGF-I response does not reflect that of IGFBP-3, there likely exists a delicate interplay between the IGF axis and other exercise-induced biochemical responses.

Although not within the subset of CRC, research in other cancer pathologies has examined the relationship between the IGF axis and PA. In a cohort of 26 males diagnosed with prostate cancer and currently receiving androgen deprivation therapy, it was found that IGFBP-3 significantly increased and IGF-I significantly decreased in men undertaking a six month resistance training program (21). No significant changes in these biomarkers were reported for men in the aerobic training arm. Although no analysis of this dissonance was mentioned in the paper, it is interesting to note the discrepancy with regard to the exercise prescription in both treatment arms. Those in the resistance training group were given a set of exercises to complete in the program whereas those in aerobic group were encouraged to exercise at 60-80% of their age-predicted maximum heart rate via feedback from a wristwatch monitor. No baseline test was completed to confirm this heart rate range, therefore the intensity range completed by participants in the aerobic group may have been inadequate to elicit changes in the IGF axis that those in the resistance training group experienced.

Several studies have measured the response of IGFs to a PA intervention in breast cancer survivors. Fairey et al. (84) tracked the changes in IGF-I, IGF-2 and IGFBP-3 following 15 weeks of moderate intensity aerobic exercise; significant increases in IGFBP-3 and decreases in IGF-I were found, including decreases in their molar ratio, which is thought to reflect bioactive IGF-I. More recent research by Irwin et al. (20) tracked breast cancer survivors over a 6 month

randomised controlled trial, and found similar results for IGF-I but significant decreases in IGFBP-3 compared to pre-intervention levels.

Schmitz et al. (22) investigated the role of resistance training on the IGF axis in breast cancer survivors. Six months of resistance training resulted in significant reductions in IGF-II however no significant changes in IGF-I were reported. Compared to Fairey et al. (84), a higher percentage of participants in this study were undergoing chemotherapy, which is known to alter IGF-I levels (Bonani, 2001) and therefore may have muted the biochemical response to PA.

In addition to PA, negative energy balance through dietary restriction may lead to a reduction in IGF-I (55). Several studies involving healthy populations have attempted to address this by employing dietary controls in addition to a PA intervention. Nemet and colleagues (88) found IGF-I to only decrease following seven days of aerobic exercise when participants were in a negative energy balance (assisted via dietary restriction). In agreement, Smith et al. (91) found no differences in groups who experienced the same negative energy balance through PA or diet alone. The volume and intensity of PA required to lower IGF-I is not known and it may be that without a negative energy balance, longer interventions at a higher intensity or volume of PA are required for significant IGF-I changes to occur. Rarick et al. (86) addressed this idea of energy flux which accounts for the absolute level of energy expenditure and intake under conditions of energy balance. They found that energy balance and baseline aerobic fitness had no impact on IGF-I or IGFBP-3 response. These findings are in contrast to those of Smith et al. (91) and Nemet et al. (88), further confounding the relationship between PA and the IGF axis.

Given that dietary intake influences IGF-I levels, controlling for this variable in the days preceding blood sampling is crucial to understanding the precise impact of PA on the IGF axis (55). Many of the studies investigating the PA/IGF association have not reported dietary intake control prior to testing. Further, assays that only measure total IGF-I in circulation rather than free IGF-I or IGF-IR activation have generally been used. This measure does not differentiate between IGF-I that is

free/bioactive or bound in binary and ternary units (and therefore unable to interact with cell surface receptors).

4.0 Conclusions and Future Directions

While the benefits of PA for the prevention of CRC and reduction in disease-specific mortality post-diagnosis are well established, the physiological mechanisms by which PA can mediate these outcomes remains to be determined. Of the several biological pathways that have been considered, the IGF axis is the most plausible mechanism and has subsequently received the most interest. Following diagnosis from CRC, there is evidence to suggest that a decrease in IGF-I and an increase in IGFBP-3 can reduce disease-specific mortality. While there is evidence to suggest that PA may influence IGF-I and IGFBP-3, intervention studies involving a structured PA regime for CRC populations examining changes in the IGF axis are required. Understanding the frequency, intensity, duration and mode of exercise that each will potentially influence the IGF axis, reduce the incidence of CRC and improve survival is needed to inform the development of specific PA guidelines for CRC survivors - guidelines that currently do not exist.

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Appendix B Review of literature outlining the effects of exercise on insulin sensitivity and the insulin-like growth factor axis

Insulin responses to a chronic high intensity exercise intervention in clinical and non-clinical populations					
Reference	Cohort	Exercise Mode (M) and Interval Intensity (I)	Intervals (INT) and Recovery Periods (R)	Frequency (F) and Duration of Intervention (D)	Insulin (I) and Insulin Sensitivity Changes (ISI)
Richards et al. 2010 (117)	Sedentary, or recreationally active males and females 13 cases (Ä=29 y) 10 controls (nil rx) (Ä=24 y)	M) Cycling I) Maximal	INT) 30 s x 4-7 R) 240 s	F) 3 / week D) 2 weeks	ISI) ↑ Insulin sensitivity measured via hyperinsulinemic euglycemic clamp improved 4.5 fold compared to the control group *
Nybo et al. 2010 (159)	Sedentary males 8 cases (Ä=37 y) 9 controls (mod rx) (Ä=31 y)	M) Running, jogging, walking I) >95% HRmax	INT) 120 s x 5 R) Not measured	F) 2 / week D) 12 weeks	ISI) ↑ Insulin sensitivity measured via oral glucos tolerance test improved by 16% in the high intensity group compared to baseline *
Sandvei et al. 2012 (160)	Sedentary, or recreationally active males and females 11 cases	M) Running, jogging, walking I) Maximal	INT) 30 s x 5-10 R) 180 s	F) 3 / week D) 8 weeks	ISI) ↑ Insulin sensitivity measured via oral glucos

	(Ä=not reported) 12 controls (mod rx) (Ä=not reported)				tolerance test improved by 6% in the high intensity group compared to baseline *
Tjonna et al. 2008 (122)	Males and females with metabolic syndrome 12 cases (Ä=55 y) 10 controls (mod rx) (Ä=52 y)	M) Running, jogging, walking I) 75-85% HRmax	INT) 240 s x4 R) 180 s	F) 3 / week D) 16 weeks	ISI) ↑ Insulin sensitivity measured via homeostasis assessment model for insulin sensitivity improved by 24% in the high intensity group compared to baseline *
Harmer et al. 2007 (161)	Males and females with type 1 diabetes 8 cases (Ä=25 y)	M) Cycling I) Maximal	INT) 30 s x 4-8 R) 240 s	F) 3 / week D) 7 weeks	I) ←→
Whyte et al. 2010 (18)	Sedentary, overweight or obese males 10 cases (Ä=32 y)	M) Cycling I) Maximal	INT) 30 s x 4-6 R) 270 s	F) 3 / week D) 2 weeks	ISI) ↑ Insulin sensitivity measured via oral glucos tolerance test improved by 19% compared to baseline *
Babraj et al. 2008 (162)	Sedentary, or recreationally active males 16 cases (Ä=21 y)	M) Cycling I) Maximal	INT) 30 s x 4-6 R) 240 s	F) 3 / week D) 2 weeks	ISI) ↑ Insulin sensitivity measured via oral glucos tolerance test improved by 23% compared to

					baseline **
Little et al. 2011 (163)	Males and females with type 2 diabetes 8 cases (Ä=63 y)	M) Cycling I) 90% HRmax	INT) 60 s x 10 R) 60 s	F) 3 / week D) 2 weeks	ISI) ↑ Insulin sensitivity measured via area under 24-hour glucose curve improved by 14% compared to baseline *

Ä; Mean Age. *Rx;* Exercise Treatment. * $p \leq 0.05$. ** $p \leq 0.001$.

IGF-I and IGFBP-3 responses to a chronic exercise exposure in non-cancer populations						
Reference	Cohort	Exercise Mode (M) and Intensity (I)	Exercise Duration (D) and Frequency (F)	Duration of Intervention	IGF-1 Changes	IGFBP3 Changes
Arikawa et al. 2010 (164)	Sedentary, but otherwise healthy women 166 cases (Ä=25 y) 153 controls (Ä=25 y)	M) Various aerobic weight bearing activities I) 80-85% HRmax	D) 30 mins/session F) 5 sessions/week	16 weeks	↔	↔
Barnard et al. 2003 (165)	Sedentary males at elevated risk of prostate cancer 12 cases (Ä=60 y) 14 controls (Ä=55 y)	M) Walking I) 70-85%	D) 30-60 mins/session F) 4-6 sessions/week	11 days	↓ Total IGF-1 decreased 59% compared to control *	Not measured
Chicharro et al. 2001 (166)	Trained male cyclists 17 cases (Ä=17 y)	M) Cycling I) Competition Intensity	D) >3500 km (~90 h over 3 weeks F) Not measured	3 weeks	↑ Total IGF-1 increased 78% above baseline levels **	↔
Eliakim et al. 1996 (167)	Recreationally-active adolescent females 10 cases (Ä=16 y) 6 controls (Ä=16 y)	M) Various aerobic activities (e.g. running, dance, team sports) I) Not measured	D) 2 h/session F) 5 sessions/week	5 weeks	↓ Total IGF-1 decreased by 14% compared to control *	↓ IGFBP-3 decreased by 10% compared to pre-intervention and 15% compared to control *
Eliakim et al. 1998 (168)	Recreationally-active adolescent males 10 cases	M) Various aerobic activities (e.g. running, dance, team	D) 2 h/session F) 5 sessions/week	5 weeks	↓ Total IGF-1 decreased by 13% compared to	↔

	(Ä=16 y) 6 controls (Ä=16 y)	sports) I) Not measured			baseline and 9% compared to control *	
Filaire et al. 2003 (169)	Elite adolescent female gymnasts 7 cases (Ä=15 y)	M) Gymnastics training I) Not measured	D) 4.5 h/session F) 6 sessions/week	16 weeks	↓ Total IGF-1 decreased by 50% compared to baseline **	↓ IGFBP-3 decreased by 20% compared to pre-intervention levels *
Hellenius et al. 1995 (170)	Recreationally-active healthy males 39 cases (Ä=46 y) 39 controls (Ä=47 y)	M) Various aerobic activities (e.g. walking, jogging) I) 60-80% HRmax	D) 30-45 mins/session F) 2-3 sessions/week	6 months	↔	Not measured
Koziris et al. 1999 (171)	Trained male and female swimmers 14 cases divided into 3 teams (Ä=18-22 y)	M) Swimming training I) Not measured	D) NR F) 5-6 sessions/week	5 months	↑ Total IGF-1 increased by 76% *, 68% *, no significant change for third team	↑ IGFBP-3 increased by 30% 97% and 53% compared to baseline *
Manetta et al. 2003 (172)	Trained male cyclists & sedentary controls 8 cases (Ä=24 y) 8 controls (Ä=25 y)	M) Competitive Cycling I) Month 1: HR=120-160 bpm Months 2-4: HR >170 bpm	D) Not measured F) 6 sessions/week (~17 h total/week)	4 months	↑ Total IGF-1 of cyclists post training higher than controls *	↑ IGFBP-3 increased by 20% compared to baseline values * IGFBP-3 post training higher than controls *
Nindl et al. 2010 (173)	Healthy females 13 cases	M) Endurance and interval	D) 20-30 mins/session	8 weeks	↔	↔

	(Ä=20 y) 20 controls (Ä=20 y)	jogging I) 70-85% HRmax	F) 3 sessions/week			
Nindle et al. 2004 (174)	Male and female dialysis patients with end stage renal disease 10 cases (Ä=43 y)	M) Resistance exercise I) 10-15 reps, 2-3 sets	D) 9 exercises/session F) 2 sessions/week	12 weeks	↓ Total IGF-1 decreased by 15% compared to baseline *	↔
Nishida et al. 2010 (175)	Sedentary, but otherwise healthy males 14 cases (Ä=23 y)	M) Cycling I) ~50% VO_2max	D) 60 mins/session F) 5 sessions/week	6 weeks	↓ Total IGF-1 decreased by 9% compared to baseline *	↔
Ounis et al. 2010 (176)	Sedentary, obese girls and boys 14 cases (M=13 y) 14 controls (Ä=13 y)	M) Various aerobic activities (e.g. running, jumping, balloon games) I) Not measured	D) 90 mins/session F) 4 sessions/week	8 weeks	↓ Total IGF-1 decreased 17% compared to baselines and 22% compared to control **	↓ IGFBP-3 decreased 10% compared to baseline and 14% compared to control **
Poehlman et al. 1994 (177)	Sedentary, but otherwise healthy males and females 18 cases (Ä=66 y)	M) Cycling I) 60-75% HRmax	D) 150-300 kcal/session F) 3 sessions/week	8 weeks	↑ Total IGF-1 increased by 14% compared to baseline *	↔

Rosendal et al. 2002 (87)	Trained healthy males and untrained healthy controls 12 cases (Ä=20 y) 7 controls (Ä=20 y)	M) Military style training I) Not measured	D) 2-4 h/session F) 7 sessions/week	11 weeks	↓ Total IGF-1 decreased in untrained group by 15% compared to baseline * Total IGF-1 decreased in the trained group by 9% at week 4 compared to baseline *, but returned to baseline at 11 weeks	←→
Schmitz et al. 2002 (22)	Recreationally-active healthy females 27 cases (Ä=41 y) 27 controls (Ä=42 y)	M) Resistance exercise I) 8-10 reps @ 3 sets	D) 9 exercises (~50 mins)/session F) 2 sessions/week	15 weeks	↓ Total IGF-1 decreased by 14% compared to baseline and 24% compared to control *	←→

Ä; Mean Age. *Rx;* Exercise Treatment. * $p \leq 0.05$. ** $p \leq 0.001$.

Appendix C Letter of invitation from phase 1 of recruitment

<Date>

«Title» «Given_names» «Surname»
«Current_Address»
«Current_Locality»

Dear «Title» «Surname»

Thank you for your participation in The Cancer Council Queensland's *Colorectal Cancer and Quality of Life* study. This research project has provided us with a wealth of information on the health and well-being of colorectal cancer survivors over time with over 20 publications to date in national and international scientific journals. The research has significantly improved our understanding of the issues faced by many colorectal cancer patients and it will contribute to the ongoing development of better services and support.

We are contacting you at this time to invite you to participate in a new project being conducted by the University of Queensland in conjunction with Cancer Council Queensland. The study is examining the health benefits of different types of exercise for people who have had colorectal cancer. The project is being conducted by qualified exercise physiologists.

Please find enclosed a flyer which provides information on the study and what your participation would involve.

If you are interested in taking part in this exciting new study, or if you would like more information, please contact Andrew Sax, the study coordinator and Principal Investigator, at the University of Queensland.

Andrew's contact details are: Telephone: 0456 746 938.
Email: a.sax@uq.edu.au

Thank you once again for your time and help with improving our understanding of the impact of colorectal cancer.

Yours sincerely

Professor Joanne Aitken
Head of Research
Cancer Council Queensland

Appendix D Recruitment flyer

EXERCISE PROGRAM FOR COLORECTAL CANCER SURVIVORS

The Project

In conjunction with Cancer Council Queensland, the University of Queensland is running an exercise and health research project for colorectal cancer survivors. The eight-week exercise program will take place at the University of Queensland St Lucia campus and will be supervised by qualified exercise physiologists. This project will be the first of its kind to investigate the influence of different modes of exercise and how they impact on the holistic health of colorectal cancer survivors.

What's involved?

Participation will involve attendance at three group exercise sessions per week over an eight-week period. Participants will also be required to undergo a health and fitness assessment several times during the program. Free parking will be provided to all participants directly outside the training facility.

What do I get out of it?

You will receive eight weeks of supervised exercise training in an enjoyable and stimulating group environment. You will also receive gold standard measures of cardiorespiratory fitness, insulin sensitivity, body composition, bone density, fatigue and psychosocial health.

Can I be involved?

To be involved you must be over the age of 18 and have been diagnosed with colon and/or rectal cancer at some point in your life and not be currently receiving treatment. Participants will also be required to have no uncontrolled cardiovascular disease or be taking medication for the treatment of diabetes or metabolic disease. Consent from your primary care physician will be required prior to entry into the program.

What's Next?

For more detailed information on this research project please contact the project coordinator listed below.

Andrew Sax | Exercise Physiologist
School of Human Movement Studies, UQ
a.sax@uq.edu.au

Cancer Council Queensland

The University Of Queensland AUSTRALIA

Appendix E Invitation letter to doctors from phase 2 of recruitment

< Doctors Name >
< Doctors Address >
< >
< Date >

Dear «LU_Doctors_Title» < >,

As you know, the Queensland Cancer Registry collects information on all cases of cancer diagnosed in Queensland, as required under the Public Health Act 2005. One of the most important roles of the Cancer Registry is to facilitate research into cancer.

Two studies titled 'The impact of high intensity interval training on insulin sensitivity in colorectal cancer survivors' and 'The optimal exercise mode and intensity for colorectal cancer survivors' health' are being conducted by the University of Queensland in collaboration with the Cancer Council Queensland to collectively determine

1. the most effective intensity and type of exercise for colorectal cancer survivors to inform the development of guidelines;
2. whether high intensity (exercise) training results in greater improvements compared to moderate intensity training in colorectal cancer survivors;
3. the effect of dosage, tapering and detraining on the maintenance of these improvements following exercise training in colorectal cancer survivors; and
4. the effect of exercise training on cancer related fatigue in colorectal cancer survivors.

I am writing to seek your permission to approach your patient(s) who is/are registered with the Queensland Cancer Registry as having been diagnosed with colorectal cancer. These studies have received ethics approval from the University of Queensland Human Research Ethics Committee. These studies have been considered and approved under Part 4 'Research' of the Public Health Act 2005 to use the information in the Registry. Following your written approval, the Queensland Cancer Registry would send your patient(s) a personal letter signed by you (letter is enclosed for your signature) and an information flyer about the studies. Should your patient(s) wish to participate they are asked to contact the researchers directly to discuss the studies in more detail.

If you agree to your patient(s) being invited to participate in either of these studies, I would be grateful if you would:

- Complete the enclosed consent form
- Sign the letter to your patient(s) (the Queensland Cancer Registry requires that this letter to your patient(s) is signed by you).
- Return to us in the reply paid envelope
  - the consent form and
  - the signed letter.

If you do not wish your patient(s) to be approached, please indicate on the enclosed consent form and return this to us in the reply paid envelope.

It is important for the scientific validity of the research to include responses from as many patients as possible. I greatly appreciate your assistance in this regard. I would be pleased to discuss any queries you may have about this request on (07) 3634 5333.

With thanks,
Yours sincerely

Appendix F Doctor information sheet

The impact of high intensity interval training on insulin sensitivity in colorectal cancer survivors

and

Optimal exercise mode and intensity for colorectal cancer survivors' health

Introduction
Colorectal cancer is second only to lung cancer as the leading cause of cancer death in Australia, with age, family history, diet, inactivity and smoking identified as being significant risk factors for the disease. Research has found that Colorectal Cancer (CRC) survivors with Type 2 Diabetes have heightened disease specific and overall mortality rates compared to survivors without this associated condition. Moderate intensity physical activity has been found to result in significant improvements in insulin sensitivity in this population. High intensity exercise has, in recent years, attracted the attention of researchers involved in the management and prevention of a number of chronic diseases and improvements in insulin sensitivity have been shown to result from as little as two weeks of high intensity training. Whilst these results are promising for the prognosis of Type 2 Diabetes, the benefits from high intensity exercise are yet to be investigated in colorectal cancer survivors.

Further, research indicates that colorectal cancer survivors experience elevated levels of fatigue following diagnosis and treatment. Whilst physical activity interventions in this population have been found to significantly lower levels of cancer related fatigue, little is known about the influence of high intensity training on this measure.

These randomised clinical trials will examine the dose-response effects of physical activity and exercise on insulin sensitivity, other identified biological markers associated with colorectal cancer risk, and cancer related fatigue. Thus, these studies have the potential to improve our understanding of how disease mortality risk can be reduced, particularly for those at risk of Type 2 Diabetes.

What are the expected outcomes from these projects?
These studies will enable us to:

1. Determine the most effective intensity and type of exercise for CRC survivors to inform the development of guidelines aiming to reduce the risk of cancer recurrence and improve the overall health of CRC survivors;
2. Determine whether high intensity (exercise) training results in greater improvements compared to moderate intensity training in CRC survivors;
3. Determine the effect of dosage, tapering and detraining on the maintenance of these improvements following exercise training in CRC survivors; and
4. Determine the effect of exercise training on cancer related fatigue in CRC survivors.

Study 1: The impact of high intensity interval training on insulin sensitivity in colorectal cancer survivors

How could your patients help?

If your patient consents to take part in this study, they will be randomly assigned to one of three groups: (1) high intensity aerobic interval training – continued, (2) high intensity aerobic interval training – tapered, (3) moderate intensity aerobic continuous training. Groups (1) and (3) will exercise three times per week for 8 weeks, whereas group (2) will exercise three times per week for weeks 1-4, then one time per week for weeks 5-8. Following the 8-week intervention, participants will be re-assessed after 4 weeks of no training (week 12).

All exercise sessions will be undertaken at the School of Human Movement Studies on The University of Queensland's St Lucia campus.

What will testing involve?

Patients will be assessed at baseline, 4 weeks, 8 weeks and 12 weeks following the start of training. We will measure your patient's body composition, and cardiorespiratory fitness, as well as conduct a blood analysis. Your patient will also be asked to complete a self-administered questionnaire to collect information about their quality of life, fatigue and dietary habits.

Study 2: Optimal exercise mode and intensity for colorectal cancer survivors' health

How could your patients help?
If your patient consents to participate in this study they will be required to perform three types of singular exercise sessions: (1) high intensity interval exercise session, (2) moderate intensity exercise session and (3) circuit weight training. The aim of this study is to understand the acute response of insulin sensitivity and other biological markers associated with CRC to a single session of exercise. This will help determine the optimal exercise mode and intensity to induce favourable biological changes to improve the health of colorectal cancer survivors.

What will testing involve?
Patients will undergo baseline testing consisting of body composition, and cardiorespiratory fitness, as well as a blood analysis. Patients will then undergo three exercise testing sessions with blood analysis being performed prior to and following exercise to map the duration of exercise-induced improvements in biological markers associated with CRC.

Who is eligible to participate in these studies?
We require men and women who have been diagnosed with Colorectal Cancer. Participants must not have any musculoskeletal, neurological, respiratory, or cardiovascular conditions that prevent them from safely completing the exercise demands of the study. Participants will also be excluded if they are receiving pharmacological treatment to increase their insulin sensitivity and/or exogenous insulin therapy.

Are there any risks for my patient?
Your patient will be exposed to a dual energy x-ray absorptiometry (DXA) to determine body composition and bone mass. The amount of radiation is very small and the corresponding risk from participating in this study is extremely low. Patients may experience some initial muscle soreness as the result from testing and training. Patients will also be exposed to the normal discomfort and risks associated with the blood drawing procedures.

Will my patient's information remain confidential?
All information collected in the study will be used for medical research purposes only. No identifiable information that your patient provides will be passed on to any other person who is not directly involved in the research. Results will be presented to the scientific community and to the public in ways that protect the identity of participants.

The conduct of this research involves access to your patient's identified personal information. The information collected is completely confidential and will not be disclosed to third parties without their consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your patient's anonymity will at all times be safeguarded. This study has been cleared by one of the human ethics committees of the University of Queensland in accordance with the National Health and Medical Research Council's guidelines. If you would like to speak to an officer of the University not involved in the study, you may contact the Ethics Officer on 3365 3924.

Your patient's participation in this project is entirely voluntary and has no bearing on his or her medical care. If you would like further information at any other time, please contact me on 3634 5333.

Yours sincerely

Ms Carly Scott
Registrar, Queensland Cancer Registry

Research Team

Andrew Sax, BExSS (ClinExPhys) (Hons1)	PhD Candidate, School of Human Movement Studies, Accredited Exercise Physiologist, University of Queensland
James Devin, BExSS (ClinExPhys) (Hons1)	PhD Candidate, School of Human Movement Studies, Accredited Exercise Physiologist, University of Queensland
Gareth Hughes, BExSS (ClinExPhys) (Hons1)	MPhil Candidate, School of Human Movement Studies, Accredited Exercise Physiologist, University of Queensland
Kate Bolam, BScApp (Hons)	PhD Candidate, School of Human Movement Studies, University of Queensland
A/Prof David Jenkins, PhD, MSc, BA	Lecturer, School of Human Movement Studies, University of Queensland
Dr Tina Skinner, PhD, BScApp (Hons)	Lecturer, School of Human Movement Studies, University of Queensland
Prof Suzanne Chambers, PhD	Australian Research Council Future Fellow, Griffith University
Prof Joanne Aitken	Head of Research and Director Cancer Registries, Cancer Council Queensland
Prof Jeff Dunn	CEO, Cancer Council Queensland

Appendix G Participant information sheet

The impact of high intensity interval training on insulin sensitivity in colorectal cancer survivors.

Principal Investigator:

Andrew Sax, BExSS (Hons)	PhD Candidate, School of Human Movement Studies, Accredited Exercise Physiologist, University of Queensland **E-mail: a.sax@uq.edu.au** **Phone: 0456 746 938**

Co-Investigators:

Kate Bolam, BScApp (Hons)	PhD Candidate, School of Human Movement Studies, University of Queensland
A/Prof David Jenkins, PhD, MSc, BA	Lecturer, School of Human Movement Studies, University of Queensland
Dr Tina Skinner, PhD, BScApp (Hons)	Lecturer, School of Human Movement Studies, University of Queensland
Prof Suzanne Chambers, PhD	Australian Research Council Future Fellow, Griffith University
Prof Joanne Aitken	Head of Research and Director Cancer Registries, Cancer Council Queensland
Prof Jeff Dunn	CEO, Cancer Council Queensland

Why are we conducting this study?

Research has found that Colorectal Cancer survivors with Type 2 Diabetes have heightened disease specific and overall mortality rates compared to survivors without this associated condition. Moderate intensity physical activity has been found to result in significant improvements in insulin sensitivity in this population. High intensity exercise has, in recent years, attracted the attention of researchers involved in the management and prevention of a number of chronic diseases and improvements in insulin sensitivity have been shown to result from as little as two weeks of high intensity training. The benefits from high intensity exercise are yet to be investigated in colorectal cancer survivors. Further, research indicates that colorectal cancer survivors experience elevated levels of fatigue following diagnosis and treatment. Whilst physical activity interventions in this population have been found to significantly lower levels of cancer related fatigue, little is known about the influence of high intensity training on this measure.

Are you eligible to participate in this study?

We require participants who have been diagnosed with Colorectal Cancer.
Participants must not have any musculoskeletal, neurological, respiratory, or cardiovascular conditions that prevent them from safely completing the exercise demands of the study. Participants will also be excluded if they are receiving pharmacological treatment to increase their insulin sensitivity and/or exogenous insulin therapy. In addition, participants will need to obtain consent from their doctor (GP) before participating in the study.

What does the exercise program involve?
Participants will be randomly assigned to one of three groups: (1) high intensity aerobic interval training – continued, (2) high intensity aerobic interval training – tapered, (3) moderate intensity aerobic continuous training. Groups (1) and (3) will exercise three times per week for 8 weeks, whereas group (2) will exercise three times per week for weeks 1-4, then one time per week for weeks 5-8. Following the 8-week intervention, participants will be re-assessed after 4 weeks of no training (week 12). All sessions will be completed on stationary bicycles.

High intensity groups will exercise at 90% of their maximum capacity for 4x4minute intervals, interspersed by 3 min periods of recovery at a lower intensity. Moderate intensity groups will exercise at 70% of their maximum capacity for the duration of the session (50 minutes). All exercise sessions will include a 10min warm-up and 5min cool-down. With warm-ups and cool-downs, each exercise session will last approximately 60 minutes in total.

All exercise sessions will be undertaken at the School of Human Movement Studies on The University of Queensland's St Lucia campus. All sessions will be conducted in small groups of 3-4 participants under direct supervision of a qualified exercise physiologist.

The type of exercise training used in this study has been previously investigated in clinical populations including patients with heart failure and type 2 diabetes. No adverse events were reported in these trials; high intensity exercise training is safe to use in this population. Blood pressure, heart rate and perceived exertion will be monitored during exercise testing and training sessions to further ensure the safety of all participants.

What will testing involve?

Assessments at baseline (i.e., before the training starts), then again 4 weeks, 8 weeks and 12 weeks following the start of training will include all the measures listed below. All testing will be completed by an accredited exercise physiologist trained to conduct each measure. Testing sessions take approximately 3 hours to complete and you will need to be 12-hours fasted prior to each session (water is fine).

Body composition

- Height and body weight.

- Muscle and fat mass of the whole body will be measured by dual energy x-ray absorptiometry (DXA), a routine technique for the measurement of body composition. You will lie on a specially designed table *(as shown in the adjacent photo)* for approximately 7 minutes and a scanning arm will move above your entire body.

There is no pain or discomfort associated with these measures.

Cardiorespiratory (aerobic) fitness

- Aerobic fitness will be measured via a maximal cardiorespiratory fitness test. The test will involve cycling on an exercise bike for 10-15 minutes whilst you breathe through an apparatus that measures your oxygen consumption *(as shown in the adjacent photo).*

Blood Analysis: glucose, insulin and other biomarkers of colorectal cancer growth

- Blood will be sampled for us to assess insulin sensitivity and other markers that have been linked to Colorectal Cancer growth. All blood will be sampled and be analysed at The University of Queensland's School of Human Movement Studies biochemistry laboratory by a qualified phlebotomist. You will be required to avoid food and drink (except water) for twelve hours before those sessions where your blood will be sampled. On the day of testing, you will be required to consume a 75g glucose drink in order to assess your insulin sensitivity. This will be followed by 4 blood samples over the subsequent 2 hours. Following blood sampling, you will be given an energy snack to minimise the impact of fasting on your exercise training/testing.

Questionnaires

- Your health history and other general information will be assessed using questionnaires that you can complete at home. Quality of life and cancer related fatigue will be assessed by questionnaires that can be completed at home. Levels of self-reported physical activity will be assessed by the leisure score index from the Godin Leisure-Time Exercise Questionnaire that you can complete at home. Dietary information will be collected using a 3-day food diary.

Will I need to provide any medical information?

We would also like your permission to access important medical information about you throughout the study period. In particular, we would like your permission to access your medical and Cancer Registry records for research purposes only in order to obtain important medical information about your colorectal cancer diagnosis.

Are there any risks associated with being involved in this study?

DXA uses very low energy x-rays to determine body composition and bone mass. The total dose associated with the scans you will undergo in this study is approximately 12 μSv. In comparison, an individual receives approximately 7 μSv for daily natural background exposure, 80 μSv for a return trans-Pacific flight, 100 μSv for a chest x-ray, and 2000 μSv for a lumbar spine x-ray. Therefore, although radiation is used in the scan, the amount of radiation is very small and the corresponding risk from participating in this study is extremely low.

It is possible that some initial muscle soreness may result from testing and training; however, all participants will undertake a warm-up prior to, and cool-down immediately following each session. In the event that an emergency occurs, medical assistance will be available from the university health service according to our established emergency procedures.

Lastly, the discomfort associated with the blood drawing procedures is minimal. There is a risk that bruising and infection may occur and that the arm might become sore. Risk of bruising or infection from the blood draws will be minimized because all blood will be sampled by a trained phlebotomist. The total amount of blood drawn during each testing session will not exceed 12 ml which is equivalent to approximately 2 teaspoons. No syringes, lancets, needles or other devices capable of transmitting infection from one person to another shall be reused. All of these items, which are disposable, will be destroyed after each use. As an additional safeguard in preventing contamination, new disposable gloves will be worn for all blood draws. All contaminated items will be disposed of promptly in sharps containers.

All information will be strictly confidential and kept safely locked in a filing cabinet in the principal investigator's office. Should publications result from this study, no reference will be made to any individuals. There is no financial reimbursement for participating in this study.

On completion of the intervention and measurements, a summary of study findings and individual results will be made available to all participants.

PARTICIPATION IS VOLUNTARY AND SUBJECTS ARE FREE TO WITHDRAW FROM THIS STUDY AT ANY TIME, FOR ANY REASON.

This study has been cleared by one of the human ethics committees of the University of Queensland in accordance with the National Health and Medical Research Council's guidelines. You are of course free to discuss your participation in this study with project staff **(Andrew Sax contactable on 0430 060 872)**. If you would like to speak to an officer of the University not involved in the study, you may contact the Ethics Officer on 3365 3924.

Thank you for your interest in this study.

Appendix H Invitation letter to participant from doctor

< Patient Name >
< Patient Address >
< >

< Date >

Dear < Patient Title and Name >,

The Queensland Cancer Registry has contacted me about a series of research projects that are being conducted by researchers at the University of Queensland in collaboration with the Cancer Council Queensland, to help determine the impact of exercise training on the health, wellbeing, cancer related fatigue and other factors in colorectal cancer survivors. Information collected during the studies will:

- Inform the development of exercise-specific guidelines that may reduce the risks of colorectal cancer recurrence in survivors of the disease
- Specifically assess the influence of exercise intensity and type on biological factors that have been associated with the risks of colorectal cancer and also evaluate the relationship between exercise intensity and psychological stress among colorectal cancer survivors.

The Queensland Cancer Registry collects, by law, information on all cases of cancer diagnosed or treated in Queensland. All information in the Registry is kept strictly confidential and is held under tight security.

There are currently two studies being conducted:

- The effect of a single exercise session on the health of colorectal cancer survivors
- The impact of 8 weeks of exercise training on the health of colorectal cancer survivors

One of the most important roles of the Registry is to assist cancer research. These studies have been approved under the Public Health Act 2005 to use the information in the Registry. With your consent, the researchers undertaking these studies would like to invite you to participate in this research. Would you be willing to take part in these research projects?

Please find enclosed an information flyer that explains a little more about the studies. If you are willing to take part, please contact the project coordinator at the University of Queensland whose contact details are included in the information flyer. The project coordinator will provide you with more information about the study and determine your eligibility to participate.

Participation in this research is entirely voluntary and any information you provide will be treated as strictly confidential.

If you have any questions please call a registry staff member on (07) 3634 5333.

Thank you for your assistance.

Yours sincerely

< Doctors Name >

Appendix I Food Diary

▪ **Please try to replicate your dietary intake from your baseline testing as accurately as possible (attached)** ▪ **If you cannot exactly replicate a single meal or day for any reason, please record the alternative dietary intake in the corresponding box**		
DECLARATION	I declare that I have tried to replicate my baseline dietary intake to the best of my ability, except in the circumstances that have been outlined below.	**Signature: -** _____ **Date: -** _____

3 DAY FOOD DIARY

*Please provide as much detail as possible and include all drinks (excluding water).
*Keep in mind you will be required to follow this diet at 3 other time points during study.

Day	Brkfst	Snack	Lunch	Snack	Dinner	Snack
Eg.	-Toast with honey (2 slices). -Fruit juice (1 glass).	-Chocolate biscuit (2 units). -Coffee with milk. -1 banana.	-1 Meat pie with tomato sauce. -Can of coke (350mL).	N/A	-Lasagne (medium portion). -Caesar salad (half plate).	-Skim milk (1 glass). -Cadbury chocolate (10 squares). -1 apple.
1						
2						
3						

Appendix J Godin leisure time physical activity index

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week / Duration (mins)
a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____ / _____
b) MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____ / _____
c) MILD EXERCISE (MINIMAL EFFORT) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____ / ____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. ☐	2. ☐	3. ☐