Evaluating and optimising preoperative physical fitness to enhance postoperative outcome in major surgery

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. I agree to deposit this thesis in the University's open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

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Summary of Thesis

Higher levels of physical fitness are associated with numerous health benefits such as improved cardiovascular health, respiratory health, and musculoskeletal health (Heyward, 2010, Warburton et al., 2006). Current guidelines for perioperative risk assessment and modification lack any consensus on the role of preoperative physical fitness. For example, the NICE guidelines provide a number of recommendations for preoperative testing and report cardiopulmonary exercise testing (CPET) requires further research to justify its ability to predict perioperative risk (NICE, 2016). Furthermore, enhanced recovery after surgery (ERAS) pathways have been developed and implemented in a number of surgical specialities such as colorectal surgery (Khan et al., 2009). These pathways are designed to improve postoperative recovery, however they neglect to address the role of preoperative exercise therapy, which is a recognised component of the preoperative pathway in thoracic surgery (Nagarajan et al., 2011, Benzo et al., 2011). The aim of this thesis is to assess the role of preoperative physical fitness in influencing postoperative recovery.

In pursuing this aim, two systematic reviews and two original studies were completed. The first systematic review (Chapter 3) examined the validity of cardiopulmonary exercise testing and field tests of exercise tolerance as a risk assessment method in intra-abdominal surgery. Forty-two full text articles met the inclusion criteria and were included in the qualitative synthesis. The results showed that CPET is an objective measure of cardiorespiratory fitness that is able to identify patients at risk of poor postoperative outcome [morbidity, mortality and prolonged length of stay (LOS)] among various surgical procedures e.g. hepatic resection. Despite this, the areas of colorectal, renal transplant, upper gastrointestinal, and bariatric surgery require further research to draw conclusions concerning the ability of CPET to predict postoperative outcome. In addition, field tests of exercise tolerance offer a less robust method of identifying high-risk patients due to the small number of studies included (n=6).

The aim of the observational study in Chapter 4 was to address the findings of the previous review (Chapter 3) and identify a CPET derived cut-point predictive of postoperative outcome in colorectal surgery. In addition, this study assessed if other components of physical fitness such as muscle strength, could predict postoperative outcome. The results of this study demonstrated agreement with Chapter 3 reporting that lower cardiorespiratory fitness (Ventilatory threshold <11.95 ml/kg/min), measured using CPET, was significantly associated with postoperative complications and hospital LOS following colorectal surgery. The ability of CPET to predict mortality is unclear as there were no reported instances of mortality. Measures of physical fitness including grip strength, inspiratory muscle

strength and subjective levels of physical activity did not demonstrate significant relationships with postoperative outcome ($p<0.05$).

Patients with higher levels of preoperative physical fitness had a reduced risk of poor postoperative outcome, therefore the aim of Chapter 5 was to assess if preoperative exercise interventions designed to increase preoperative physical fitness translates to a reduction in postoperative risk. This systematic review identified nine studies and included them in a quantitative meta-analysis. Preoperative exercise interventions consisting of inspiratory muscle training, aerobic exercise, and resistance training decreases the incidence of all-cause postoperative complications in patients undergoing intra-abdominal surgery. This effect was strongest when prehabilitation was compared to usual care (no treatment or breathing exercises). Prehabilitation also significantly improved preoperative physical fitness as measured by inspiratory muscle strength and cardiopulmonary exercise testing. It is unclear if prehabilitation influenced postoperative LOS after intra-abdominal surgery, as the number of studies contributing to the Forest plot was low (n=4). Results should be interpreted with caution, as the quality of included studies measured via the GRADEPro was 'very low', demonstrating the need for high quality RCT's to validate the use of preoperative exercise programmes. Furthermore, current exercise prehabilitation protocols are longer (4-6 weeks) than the available duration between decision to treat and surgery as outlined by the National Health Service (31 days). Therefore, clinicians are presented with a difficult decision; proceed directly to surgery and forgo prehabilitation, or delay surgery to allow time for prehabilitation and risk metastatic spread.

Chapter 6 aimed to address this shortcoming of the literature by implementing a high intensity interval training (HIIT) programme within the current colorectal and thoracic surgery pathway. Exercise interventions of relatively high intensity have been reported to have low adherence rates (16% completion rates, Carli et al., 2010), therefore the feasibility of a preoperative HIIT programme should first be established to ensure this intervention will have adequate compliance and adherence rates. Subsequently, the PHIIT trial described in Chapter 6, demonstrated high adherence (84%) and compliance rates (88%) in a preoperative HIIT programme, among 16 patients scheduled for colorectal (n=7) and thoracic (n=9) cancer surgery. Furthermore, there were no adverse events related to the disease or exercise intervention. Cardiorespiratory fitness increased significantly as measured by VT (+1.55 ml/kg/min) and VO_{2peak} (+1.57 ml/kg/min) following a mean of 7 (SD: 3) preoperative HIIT sessions, however this was a secondary objective and the study was not sufficiently powered to detect true changes in cardiorespiratory fitness.

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Finally, I dedicate this thesis to Dad. I wish you could have been here for this.

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List of Publications from this Thesis

Publications in peer reviewed journals

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Publications under review

Moran, J., Guinan, E., McCormick, P., Larkin, J., Moriarty, J. & Hussey, J. Role of preoperative physical fitness in predicting postoperative outcome and recovery in colorectal surgery.

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Poster Presentations

Moran, J., Guinan, E., McCormick, P., Hussey, J., Moriarty, J., & Wilson, F. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Poster presented at *Association of Anaesthetists of Great Britain and Ireland (AAGBI) Annual Congress*, 23rd-25th September 2015, Edinburgh.

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Moran, J., Guinan, E., McCormick, P., Larkin, J., Mockler, D., Hussey, J., Moriarty, J., & Wilson, F. The ability of prehabilitation to influence postoperative outcome after intra-abdominal surgery: A systematic review and meta-analysis. *Association of Anaesthetists of Great Britain and Ireland (AAGBI) Annual Congress*, 14th-16th 2016, Birmingham.

Platform Presentations

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Moran, J., Guinan, E., McCormick, P., Larkin, J., Mockler, D., Hussey, J., Moriarty, J., & Wilson, F. The ability of prehabilitation to influence postoperative outcome after intra-abdominal surgery: A systematic review and meta-analysis. Platform presentation at *Irish Society of Chartered Physiotherapists (ISCP)*, 14th-15th October 2016, Wexford.

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Royal City of Dublin Hospital Trust (September 2016). Awarded €28,370 for the feasibility study entitled 'Preoperative High Intensity Interval Training in patients scheduled for colorectal and thoracic surgery: The PHIIT Trial'.

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List of Abbreviations

5-FU	5-fluorouracil
6MWT	Six minute walk test
95% C.I	95% Confidence intervals
ACCP	American College of Chest Physicians
ACSM	American College for Sports Medicine
AJCC	American Joint Committee on Cancer
AMNCH	The Adelaide & Meath Hospital Incorporating the National Children's Hospital
APR	Abdominal perineal resection
ASA	American Society of Anesthesiologists
ASA-PS	American Society of Anesthesiologists – Physical Status
ASHT	American Society of Hand Therapists
ASIS	Anterior superior iliac spine
AT	Anaerobic threshold
BMR	Basal metabolic rate
BPM	Beats per minute
BT	Bluetooth
BTS	British Thoracic Society
CAD	Coronary artery disease
CC	Closing capacity
CCI	Comprehensive Classifications Index
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CPM	Counts per minute
CRF	Clinical Research Facility
CR-POSSUM	Colorectal - Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity
CRT	Chair rise time
DBP	Diastolic blood pressure
DLCO	Diffusing capacity for carbon monoxide
DLW	Doubly labelled water
ECG	Electrocardiogram
ERAS	Enhanced Recovery After Surgery
ERS/ESTS	European Respiratory Society/European Society of Thoracic Surgeons

FEV_1	Forced expiratory volume in one second
FEV_1/FVC	Ratio of forced expiratory volume in one second to forced vital capacity
FRC	Functional residual capacity
FVC	Forced vital capacity
GCS	Glasgow Coma Scale
GI	Gastrointestinal
HDU	High Dependency Unit
HIIT	High intensity interval training
HR	Heart rate
HR_{max}	Maximum heart rate
HTN	Hypertension
ICC	Intra-class coefficients
ICU	Intensive Care Unit
IMT	Inspiratory muscle training
IQR	Interquartile range
ISWT	Incremental shuttle walk test
Kg	Kilogram
L	Litres
LCPCRT	Long course preoperative chemoradiation
LOS	Length of stay
LT	Lactate threshold
m	Meters
MAP	Maximal aerobic power
MEP	Maximal expiratory pressure
min	Minutes
MIP	Maximal inspiratory pressure
ml	Milliliters
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
PA	Physical activity

$PETCO_2$	End-tidal partial pressure of carbon dioxide
$PETO_2$	End-tidal partial pressure of oxygen
PFTs	Pulmonary function tests
PHIIT	Preoperative high intensity interval training
PMI	Postoperative morbidity index
POMS	Postoperative morbidity survey
POSSUM	Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity
PPC's	Postoperative pulmonary complications
PPMCC	Pearson Product Moment Correlation Coefficient
PPO	Peak power output
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSIS	Posterior superior iliac spine
Q	Perfusion
QUIPS	Quality in Prognosis Studies
RCT	Randomised controlled trial
RMR	Resting metabolic rate
ROC	Receiver operating characteristic
RPE	Rating of perceived exertion
s	seconds
SBP	Systolic blood pressure
SCLC	Small cell lung cancer
SCPRT	Short course preoperative radiotherapy
SCT	Stair climb test
SD	Standard deviation
SJH	Saint James's Hospital
SpO_2	Blood oxygen saturation levels
STROBE	Strengthening and Reporting of Observational studies in Epidemiology
t	Time
TT	Type and time
TEE	Total daily energy expenditure
TNF	Tumour necrosis factor
TUG	Timed up and go
V	Ventilation

VAS	Visual analogue scale
VATS	Video assisted thoracic surgery
V_E	Minute ventilation
V_E/VCO_2	Ventilatory equivalent for CO_2
V_E/VO_2	Ventilatory equivalent for O_2
VO_2	Oxygen uptake
VO_{2peak}	Peak oxygen uptake
VO_{2max}	Maximal oxygen uptake
VT	Ventilatory threshold
W	Watts
WHO	World Health Organisation
YPAS	Yale physical activity survey

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1 Chapter 1 Introduction

Major surgery carries substantial risk of postoperative morbidity, delayed recovery and increased risk of mortality, and requires significant healthcare resources (Royal College of Surgeons in Ireland, 2011). Major surgery is defined as all operations that require the following: (i) a general anaesthetic, (ii) opening into the great cavities of the body, (iii) severe haemorrhaging is a possibility, (iv) the life of the patient is at stake, (v) special anatomical knowledge and manipulative skills are required for proper performance (Earl, 1917). There are two broad categories of surgical procedures, elective and emergency. Patients admitted electively can have their surgery and admission at a predetermined time-point. Patients who are admitted under circumstances arising from emergency situations are unpredictable and require fast intervention either in an urgent or emergency setting. The focus of this thesis will be the examination of means of optimising physical performance for patients scheduled for elective surgery, particularly colorectal and thoracic surgery, as it allows time for effective planning, preparation, and preoperative intervention if necessary.

The identification of high-risk patients and implementing strategies to reduce postoperative risk would have high clinical utility as poor postoperative outcome can significantly impact patient recovery and hospital costs. Postoperative outcome is typically measured in terms of morbidity, mortality and length of stay (LOS), which can be further divided into general hospital stay, intensive care unit (ICU)/high dependency unit (HDU) admission and duration, and readmission rates. Complications post-gastrointestinal (GI) surgery are associated with a 2.4-fold increase in the risk of 30-day mortality [OR: 2.4, 95% Confidence Intervals (C.I): 1.1-5.7, $p<0.05$] (Jakobson et al., 2014). In addition, complications can significantly reduce overall, physical, and psychological quality of life (QOL) at 6 weeks post-colorectal surgery (Bosma et al., 2016). Furthermore, complications post colorectal surgery increase ICU expenditure and prolong LOS, leading to a 2.1 fold increase in costs from €12,405 to €25,680 (Zoucas and Lydrup, 2014). Therefore, reducing the risk of poor postoperative outcome would have high clinical impact as it may translate to an improvement in patient survival rates, quality of life and hospital costs.

The rate of postoperative complications varies depending on the type of surgery. In colorectal surgery postoperative complications occur in approximately 37%-48% of patients (West et al., 2014b, West et al., 2014c), in comparison thoracic surgery related complications range from 5-72% (Lang-Lazdunski, 2013, Galetta et al., 2012, Icard et al., 2013, Cho et al., 2012). The wide range in reported complications

is due to inconsistent definitions of postoperative complications (Feeney et al., 2010) and the difference in morbidity rates between the types of surgical procedures. For example, lobectomy complication rates are lower at 30-38% (Allen et al., 2006, Salati et al., 2013) compared to 47.2%-71% in the more invasive bilobectomy procedure (Lang-Lazdunski, 2013, Galetta et al., 2012, Icard et al., 2013, Cho et al., 2012).

Older and colleagues were the first group to publish a study identifying patients scheduled for major abdominal surgery with low levels of cardiorespiratory fitness as measured by cardiopulmonary exercise testing (CPET) were at higher risk for postoperative mortality (Older et al., 1993). Since the publication of this trial, the number of studies on the ability of preoperative CPET to identify patients at risk for poor postoperative outcome has grown. However there is no formal consensus on its ability to identify high-risk patients due to differences in outcomes (e.g. morbidity, length of stay and mortality) and time-points measured (e.g. 30 days, 90 days, 1 year etc.). The ability of CPET and other measures of physical fitness to identify high-risk patients will be examined through a systematic review in Chapter 3 and an observational study in Chapter 4. Preoperative exercise interventions or exercise prehabilitation aimed at increasing physical fitness offer the potential to reduce postoperative complications and improve postoperative outcome. Prehabilitation studies have been limited due to inadequate sample sizes. The majority of studies have been pilot studies with no sample size calculations (Dronkers et al., 2008, Kaibori et al., 2013a, Dronkers et al., 2010, Soares et al., 2013). Furthermore, studies with *a priori* sample size calculations have been powered to detect changes in physical fitness rather than differences in morbidity rates (Barbalho-Moulim et al., 2011, Carli et al., 2010). The ability of exercise prehabilitation to influence postoperative morbidity will be examined through a systematic review and meta-analysis in Chapter 5.

The pathophysiology of postoperative complications will be discussed and the theories of how preoperative physical fitness may influence postoperative outcome. Postoperative complications in colorectal and thoracic surgery are discussed in Section 1.8.

1.1 Pathophysiology of complications

The pathophysiology associated with surgery and anaesthesia that contributes to the development of postoperative complications is multifactorial. The effects of surgery that lead to postoperative complications can be broadly classified into primary and secondary injury (Scott and Miller, 2015).

Primary injury can be further sub-categorised into direct and indirect injury. Direct injury relates to the cellular dysfunction associated with organ resection and surgical incision. The location and size of the surgical incision is associated with postoperative outcome as the incision can have a detrimental effect on the surrounding musculature, with larger incisions typically having greater effects on the body. Indirect injuries arise from the effects of decreased oxygen and nutrient delivery due to blood loss, and reduced perfusion capability. Secondary injury is the body's response to the effects of surgery and is termed the stress response.

1.1.1 Stress response

Surgery creates a stress response in the body proportional to the type of injury and duration of insult (Scott and Miller, 2015). The stress response is a multi-system response initiated by the release of cytokine and inflammatory mediators due to localised tissue trauma, driving a complex process involving the metabolic, hormonal and immunologic systems. These changes include increased secretion of pituitary hormones from the hypothalamus, metabolic changes and activation of the sympathetic nervous system (Desborough, 2000, Finnerty et al., 2013).

Cellular injury causes the release of cytokines and inflammatory mediators such as interleukin IL-6, IL-1, IL-8, tumour necrosis factor-α (TNF-α), and C-reactive protein. The subsequent release of these inflammatory mediators causes local inflammation and stimulation of afferent neurons (Scott and Miller, 2015). Consequently, there is activation of the locus-coeruleus-noradrenergic system which stimulates the sympathetic nervous system and catecholamine release from the adrenal medulla (Scott and Miller, 2015). Activation of the sympathetic nervous systems increases secretion of the neurotransmitter, norepinephrine, which releases into the circulatory system and leads to tachycardia and hypertension (Desborough, 2000). Circulating catecholamines has a number of effects, most notable is an inhibition of insulin secretion from the pancreas (Scott and Miller, 2015).

Metabolic changes include the release of cortisol, a catabolic glucocorticoid hormone that mobilises energy stores in the liver to prepare the body for the 'fight or flight' response (Finnerty et al., 2013). Cortisol promotes gluconeogenesis and glycogenolysis in the liver which raises blood glucose levels and in combination with increased insulin resistance there is a state of hyperglycaemia which reduces the rate of wound healing and is associated with an increase in infections and other complications such as ischaemia, sepsis and mortality (Finnerty et al., 2013, Scott and Miller, 2015). Furthermore, pain and gastrointestinal dysfunction post-surgery leads to a state of fasting and immobility that can further

exacerbate the associated insulin resistance, reducing the availability of glucose and amino acids required for normal cellular function and repair. In severe cases, muscle wasting can occur as a result of the metabolic changes caused by surgical stress. Cortisol promotes protein breakdown in the liver and in cases of extreme surgical stress the rate of protein breakdown exceeds that of protein synthesis leading to muscle wasting (Finnerty et al., 2013).

Major surgery induces elevations in the body's metabolic rate to combat surgical trauma and maintain homeostasis and although this hypermetabolic state is initially beneficial, prolonged inflammatory, metabolic, and catabolic responses can lead to adverse outcomes such as postoperative complications (Finnerty et al., 2013). The stress response varies depending on the type of surgical procedure as cytokine release is proportional to primary surgical injury and blood loss. Therefore, surgical procedures with greater degrees of surgical injury and insult with higher risks of blood loss can have larger inflammatory responses, further impairing the restoration of normal homeostasis (e.g. open two-stage oesophagectomy) (Scott and Miller, 2015). Minimising the stress response can have a profound impact on postoperative recovery (Scott and Miller, 2015). Exercise is a promising intervention that may aid postoperative recovery by reducing the systematic inflammatory response through the release of anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines (Chapter 1.2.3).

1.1.2 Direct injury

In thoracic and colorectal surgery, direct injury through surgical incision detrimentally effects the integrity and function of the surrounding musculature, most notably of the respiratory muscles, through muscle or nerve damage. The mechanisms of respiration are further damaged through distortion of the chest wall, and diaphragmatic dysfunction (Siafakas et al., 1999). The subsequent surgery-related impairment of respiratory muscle function may lead to postoperative complications such as hypoxemia, hypoventilation and atelectasis, and in very severe cases respiratory failure and death (Siafakas et al., 1999).

Thoracic surgery involves a thoracotomy incision through the intercostal space and the subsequent intercostal muscles, which can lead to muscle or nerve damage (Siafakas et al., 1999). Surgery can also create distortion of the chest wall configuration. This may reduce the chest wall compliance and then increase the work of breathing leading to a decrease in the mechanical efficiency of the respiratory

muscles (Siafakas et al., 1999). In the presence of atelectasis, respiratory muscle efficiency experiences a further decline.

It has been theorised that respiratory muscle mass is reduced due to mechanical restriction of motion or by the muscle deconditioning associated with major surgery (Siafakas et al., 1999). This decrease in muscle mass further impairs the respiratory muscle response to an imposed load (Siafakas et al., 1999). Lung resection reportedly decreases maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) and these changes can last for up to four weeks postoperatively (Nomori et al., 1996). There is an increase in accessory inspiratory muscle use following thoracic surgery which is a sign of diaphragmatic dysfunction (Nomori et al., 1996). Furthermore, the chest wall damage during surgery appears to be critical in compromising respiratory muscle strength, as video assisted thoracic surgery (VATS) which produces less changes to chest wall also produces smaller postoperative decreases in MIP and MEP (Siafakas et al., 1999).

Upper abdominal surgery (incision site above the umbilicus) results in a higher incidence of postoperative pulmonary complications (PPC's) than lower abdominal surgery (incision site below the umbilicus) (PPC rates; Upper abdominal surgery: 20-40% vs. Lower abdominal surgery: 2-5%) as upper abdominal surgery is more likely to lead to diaphragmatic dysfunction (Siafakas et al., 1999). Abdominal surgery produces a decrease in MIP, MEP and transdiaphragmatic pressure which can last from 48 hours – 1 week postoperatively (Siafakas et al., 1999). Similarly to thoracic surgery, there is a shift towards using the accessory muscles of inspiration indicative of diaphragmatic dysfunction (Siafakas et al., 1999). The exact mechanism for diaphragm dysfunction is unknown, however it is most likely multifactorial, including side effects of anaesthesia and pain. The major factor for this dysfunction is theorised to be an inhibitory reflux of the phrenic nerve generated during the surgical procedure (Siafakas et al., 1999). Respiratory muscle dysfunction is greatly reduced when laparoscopic procedures are used (Rovina et al., 1996).

Laparoscopic surgery, often referred to as minimally invasive surgery or keyhole surgery is a modern surgical procedure in which small incisions are made and a flexible fibre-optic instrument is inserted and used to perform surgical resections. Video-assisted thoracoscopic surgery (VATS) is a minimally invasive surgery technique in thoracic surgery. Laparoscopic surgery minimises surgical incisions, contributes to a lower surgical stress response and reduces the requirements for oxygen postoperatively (Miyake et al., 2002, Scott and Miller, 2015). Patients undergoing laparoscopic procedures have reduced postoperative pain, complications, and length of stay compared to open

surgery (Kennedy et al., 2014, Abraham et al., 2004, Bartels et al., 2014). The surgery associated respiratory dysfunction can also be reduced through laparoscopic procedures (Siafakas et al., 1999). The combination of these benefits have been reported to aid in postoperative mobilisation and recovery (Kennedy et al., 2014).

1.1.3 Indirect injury

Indirect cellular injury arises from decreases in blood supply and oxygen and nutrient delivery (Scott and Miller, 2015). Blood loss reduces global oxygen delivery leading to a decrease in localised tissue oxygen delivery causing cellular dysfunction, and can also further increase the systematic inflammatory response associated with surgery. The ability of the body to deliver oxygen to the tissues is determined by the combination of cardiac output, haemoglobin concentration, and oxygen saturation (Scott and Miller, 2015). Exercise training may improve oxygen delivery through adaptations to cardiac output, increased haemoglobin concentration and improvements to oxygen unloading (Chapter 1.2.1).

Surgery creates changes in local tissue perfusion, arising from a multitude of factors. Retraction of tissue, clamping or coagulation of blood vessels and mobilisation of the gastrointestinal tract can reduce oxygen and nutrient delivery leading to cellular dysfunction (Scott and Miller, 2015). Alterations in microcirculatory blood flow around surgical sites have been shown to be impaired in the postoperative period even when there is sufficient global oxygen delivery (Scott and Miller, 2015). It is possible that exercise training can also improve microcirculatory blood flow as consistent exercise training increases capillary density in skeletal muscle (Chapter 1.2.1).

1.1.4 Anaesthesia

Anaesthesia significantly contributes to postoperative complications predominantly through interactions with the respiratory system. Patients scheduled for major abdominal or thoracic surgery undergo general anaesthesia, and although anaesthesia is necessary to perform surgery it has a number of side effects. Surgery has a detrimental effect on the respiratory system, and pulmonary dysfunction post abdominal and thoracic surgery is one of the leading causes of postoperative morbidity and mortality (Feeney et al., 2011, Rock and Rich, 2003, Kelkar, 2015). One of the most notable side effects of anaesthesia is respiratory impairment caused by a fall in functional residual capacity (FRC) due to loss of muscle tone (Wahba, 1991).

The reduction in FRC is reported to be primarily due to the loss of respiratory muscle tone resulting in a decreased elastic recoil of the chest wall (Wahba, 1991). Age and body position also have an effect on FRC. In most adults, the resting FRC is decreased by 800-1000 ml (millilitres) by moving from standing upright to supine lying, and there is a continued decrease with the introduction of general anaesthesia (Wahba, 1991). Mean FRC in adults is reduced from 3500 ml to 2000 ml perioperatively and increasing age equates to a further decrease in FRC, on the condition that weight and height remain unaltered (Wahba, 1991). Another theory for the fall in FRC during anaesthesia is a cranial displacement of the diaphragm due to increased abdominal pressure (Froese and Bryan, 1974).

The anaesthesia related reduction in FRC leads to airway closure and poor gas absorption, which may ultimately lead to atelectasis (Hedenstierna and Rothen, 2012). Atelectasis is a partial or full lung collapse occurring due to airway and alveolar collapse, which can also trigger inflammatory responses in the body (Nakos et al., 2003, van Kaam et al., 2004). During normal respiratory mechanisms airways may close during expiration and then reopen during inspiration, however while under general anaesthesia airways may remain closed. This closure occurs because of higher than normal intraluminal pressure. Pleural pressure increases in the dependent (lower) lung, and so airway closure occurs in the dependent lung first. This leads to a ventilation/perfusion mismatch which can lead to hypoxia (Davinson and Cottle, 2010). Ventilation/perfusion (V/Q) is a ratio used to assess the efficiency and adequacy of the matching of the two variables, ventilation and perfusion. Ventilation (V) is defined as the air that reaches the alveoli and perfusion (Q) is defined as the blood that reaches the alveoli via the capillaries (Hedenstierna and Edmark, 2015).

Closure of airways is the main cause of atelectasis, while resorption of gas that is trapped behind closed airways is the second factor that leads to atelectasis (Hedenstierna and Edmark, 2015). Closing capacity (CC) is the volume at which small airways collapse, and FRC typically exceeds CC and prevents collapse during normal expiration, however during anaesthesia CC can overtake the FRC, leading to small airway collapse (Davinson and Cottle, 2010). Airway closure leads to hypercapnia and impedes oxygenation, however administering higher oxygen concentration perioperatively increases oxygenation even in poorly ventilated areas (Gilbert et al., 1979). Pre-oxygenation allows the FRC to act as a reservoir of oxygen and help prevent hypoxia, however higher oxygen concentrations have a downside, and lead to faster resorption of gas which ultimately leads to faster atelectasis formation (Hedenstierna and Edmark, 2015). Therefore, atelectasis is caused by a reduction in FRC, gas reabsorption and higher oxygen concentrations.

The extent of atelectasis differs between surgical procedures, however anaesthesia causes a 10-20% collapse in the base of the lungs during uneventful anaesthesia before surgery has even begun (Hedenstierna and Edmark, 2015). Atelectasis is even greater post-thoracic surgery as there is a >50% lung collapse for up to several hours after surgery. Atelectasis post abdominal surgery is typically less than thoracic surgery, however atelectasis may persist for several days post abdominal surgery (Hedenstierna and Edmark, 2015).

1.2 Theories on the relationship between physical fitness and postoperative outcome

Preoperative physical fitness, assessed via cardiopulmonary exercise testing (CPET), is theorised to be predictive of postoperative complications, prolonged LOS and postoperative mortality. Cardiopulmonary exercise testing is a dynamic non-invasive assessment of an individual's cardiorespiratory system under stress and at rest, and is considered the gold-standard method of quantifying cardiorespiratory fitness. Older and colleagues pioneered using CPET as a method of predicting postoperative outcome in major abdominal surgery (Older et al., 1993). The results of this work demonstrated that patients with an anaerobic threshold (AT) <11 ml/kg/min on preoperative CPET had a higher risk of postoperative mortality. Since the publication of this study several authors have published positive findings in favour of preoperative CPET as a risk assessment method. The strength and limitations of the literature will be examined by systematic review in Chapter 3. The absolute mechanism for the relationship between preoperative physical fitness and postoperative outcome has not been concluded, however several theories report possible interactions between preoperative physical fitness and postoperative complications.

1.2.1 Cardiorespiratory fitness increases oxygen delivery

The most prominent theory suggests that preoperative cardiorespiratory fitness directly influences postoperative outcome as fitter patients are better able to cope with the sustained increase in oxygen demand perioperatively without outstretching their aerobic physiological parameters (Smith et al., 2009). The pathophysiology of postoperative complications is multifactorial, arising from a combination of deficits in global oxygen delivery, systematic inflammatory response, and hormonal and metabolic changes. The systemic inflammatory response increases global oxygen demand from an average of 110 ml/min/m at rest to an average of 170 ml/min/m in the postoperative period (Older

and Smith, 1988, Shoemaker et al., 1988). Therefore, it is likely that an improved ability to deliver oxygen would reduce the systematic inflammatory response post-surgery as discussed in Chapter 1.1.1.

An individual's ability to deliver oxygen to local tissue is determined by the combination of cardiac output, oxygen saturation, and haemoglobin concentration (Scott and Miller, 2015). Aerobic exercise training leads to increases in cardiac output, increased vascular conductance, a greater perfusion capacity of skeletal muscle and a greater ability to extract and deliver oxygen (Figure 1.1) (Hellsten and Nyberg, 2015). Cardiac output is the amount of blood pumped by the heart per minute, a product of heart rate (HR) [measured in beats per minute (bpm)] and stroke volume (ml/min). Cardiac output increases during exercise and trained individuals demonstrate higher cardiac outputs than sedentary individuals (Hellsten and Nyberg, 2015). Initially when exercising, heart rate increases so that cardiac output matches the demands of the working skeletal muscles, however heart rate is unable to further increase cardiac output when the maximum heart rate is reached. To match the oxygen demands of the working muscles unmet by heart rate, stroke volume increases with exercise training to further improve cardiac output (Hellsten and Nyberg, 2015).

Stroke volume increases through a combination of left ventricle improvements and increased blood volume (Kent and Kirtley, 2016, Hellsten and Nyberg, 2015). Aerobic endurance training creates eccentric left ventricle enlargement (increased left ventricle end-diastolic volume and mass) and enhances early diastolic filling, allowing for a more rapid filling of the heart during high-intensity exercise, which further improves stroke volume (Hellsten and Nyberg, 2015, Morganroth et al., 1975). Right ventricle improvements are similar to left ventricle enlargement post exercise training. Individuals with increased cardiorespiratory fitness tend to demonstrate lower heart rates (bradycardia) at rest compared to individuals with lower cardiorespiratory fitness. Systematic oxygen demand is similar between trained and sedentary individuals at rest and stroke volume increases to compensate for the lower heart rate in trained individuals and meet global oxygen demand (Beere et al., 1999, Stratton et al., 1994, Hellsten and Nyberg, 2015).

Aerobic exercise training further contributes to increased stroke volume by increasing erythrocyte volume and haemoglobin mass, which translates to an increase in the total amount of oxygen transported to cells (Hellsten and Nyberg, 2015, Mairbäurl, 2013). A review reported that 23 longitudinal studies reported exercise training increased blood volume (Sawka et al., 2000). Erythrocyte volume reportedly increases by 8-10% following 2-3 weeks of aerobic exercise training

(Sawka et al., 2000). Exercise stimulates erythropoiesis, however paradoxically exercise can also decrease the total amount of red blood cells through intravascular haemolysis, which is caused by mechanical rupture as red blood cells pass through contracting muscles. This mechanism also causes a decrease in the average age of circulating red blood cells and younger red blood cells have increased deformability and an improved ability to unload O_2 from haemoglobin to necessary cells due to a decreased Hb-O_2 affinity that occurs as a result of exercise (Mairbäurl, 2013). The combination of these characteristics improves tissue oxygen supply during exercise and may help combat the decrease in blood flow postoperatively (Chapter 1.1.3).

Increased cardiac output also increases the perfusion capacity of the working muscles through adaptations in arterial structure, specifically increased diameter and reduced wall thickness (Hellsten and Nyberg, 2015). Arteries allow for transport of oxygen and nutrients contained within the blood from the heart to different organs. The diameter and elastic properties of these arteries should be adequate so as not to limit oxygen delivery to local tissues. Exercise training increases luminal diameter and reduces arterial wall thickness through changes in shear stress (the force that blood applies to the endothelial cells) and transmural pressure to improve local perfusion of oxygen-enriched blood (Hellsten and Nyberg, 2015, Aalkjaer et al., 1987, Brown, 2003).

Exercise also improves perfusion of local tissue through increased capilliarisation (Hellsten and Nyberg, 2015). An increase in cardiac output, allows for an enhanced perfusion capacity of the muscle, however the consequent increase in velocity of the red blood cells would reduce the time for gas exchange and impair oxygen delivery to local tissue. To correct this, exercise increases local capilliarisation resulting in improvements to local perfusion to allow for sufficient time for off-loading oxygen by increasing the available area for gas exchange. It is likely that increased capillary density can improve local perfusion and combat indirect injury associated with surgery (Chapter 1.1.3). Capillary growth is stimulated by shear stress, which induces capillary growth by longitudinal splitting of the existing capillary, and passive stretch, which stimulates capillary growth by sprouting angiogenesis whereby a new capillary grows from an existing one (Egginton et al., 2001). Furthermore, tissue hypoxia that occurs due to exercise helps enhance capillary growth (Hellsten and Nyberg, 2015). Aerobic exercise is reportedly the most potent physiological stimulus for skeletal muscle capillary growth. Eight weeks of moderate intensity exercise at 65%-80% VO_{2max} (maximal oxygen uptake) can increase capillary density by 20-25% in young sedentary males (Gavin et al., 2007, Andersen and Henriksson, 1977). Furthermore, skeletal muscle capillary density has an inverse relationship with ageing, however the rate of capillary growth in response to exercise remains approximately the same between healthy young males (mean

age: 24 years) and healthy older males (mean age: 64 years) (Gavin et al., 2007). Capillary growth increased by 25% in the young sedentary cohort and 18% in the older sedentary cohort (Gavin et al., 2007).

Capillary growth is greatest in the first weeks of aerobic exercise training and then begins to level off after approximately four weeks (Hoier et al., 2013, Jensen et al., 2004), however capilliarisation does not typically exceed 2-2.5 fold increases from baseline (Hellsten and Nyberg, 2015). Capillary growth is similar in moderate intensity exercise and high intensity interval training (HIIT) (Cocks et al., 2013). Furthermore, aerobic exercise creates improvements in the oxidative efficiency of the muscle through improved mitochondrial capacity (Hellsten and Nyberg, 2015). The combination of an increased ability to transport oxygen through improvements in cardiac output and improved perfusion through increased capilliarisation (Figure 1.1) allow individuals with higher levels of cardiorespiratory fitness to meet the increased oxygen demand post-surgery. It is likely that this can reduce cellular dysfunction and improve postoperative outcome.

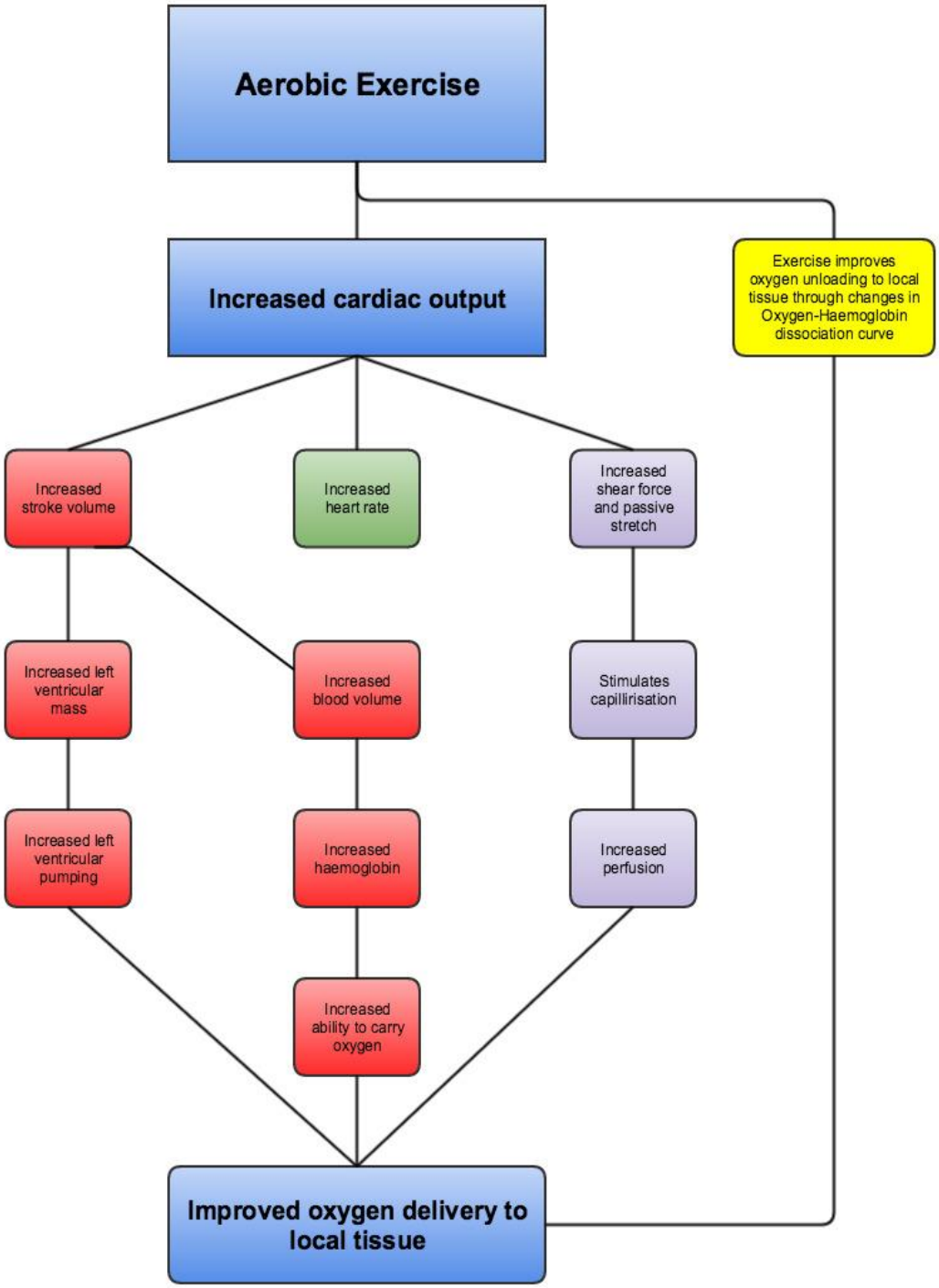


Figure 1.1: Mechanisms of aerobic exercise that improve oxygen delivery. Figure generated with data provided by Hellsten and Nyberg (2015).

1.2.2 Exercise and ischaemic preconditioning

Another theory suggests that regular exercise creates a systemic effect similar to ischemic preconditioning. This 'training effect' lessens the impact of any deficit in oxygen delivery and demand associated with surgery by increasing the body's ability to deal with an oxygen deficit or ischemic conditions (Smith et al., 2009). It is likely that this effect can reduce the indirect injuries that arise from lack of blood flow postoperatively (Chapter 1.1.3). Research has presented evidence for both a structural and biochemical link with this hypothesis. Endurance type exercise increases mitochondrial mass and may improve oxygen utilisation, thus delaying the onset of anaerobic respiration and ischaemia in human tissue during exercise (Robergs and Roberts, 2000). Studies in animals have demonstrated a second possible reason for this relationship. Exercise causes a number of physiological cardiac changes, such as an increase in the antioxidant capacity and number of sarcolemmal ATP-sensitive potassium channels (Powers and Jackson, 2008). These physiological changes are proposed to help tissues deal with ischaemic conditions and allow individuals to better tolerate periods of anaerobic metabolism perioperatively (Powers et al., 2008).

1.2.3 Exercise and inflammation

Higher levels of cardiorespiratory fitness are likely to reduce postoperative cellular dysfunction by matching the increased oxygen demand associated with the systemic inflammation response (Chapter 1.2.1), however exercise is also associated with anti-inflammatory effects. During exercise, IL-6 is released by muscle fibres via a TNF independent pathway (Petersen and Pedersen, 2005). IL-6 stimulates the release of other anti-inflammatory cytokines such as IL-1ra and IL-10 and inhibits the release of the pro-inflammatory cytokine TNF-α. Therefore, exercise can help reduce the systematic inflammatory response postoperatively through suppression of TNF-α (Petersen and Pedersen, 2005). In addition, lower levels of cardiorespiratory fitness are associated with higher neutrophil lymphocyte ratio (which is associated with postoperative complications) and absolute and relative lymphopenia (an abnormally low level of lymphocytes) suggesting that lower levels of cardiorespiratory fitness are associated with inflammatory dysregulation (Sultan et al., 2014). It is likely that the combination of the anti-inflammatory effect of exercise and improved oxygen delivery associated with higher levels of cardiorespiratory fitness can reduce the surgical stress response. Furthermore, TNF-α induces insulin resistance, which raises bloods glucose levels and contributes to poor postoperative healing (Chapter 1.1.1). Therefore, TNF-α suppression attributed to exercise is beneficial in postoperative recovery.

1.2.4 Exercise and lactate production

It has also been hypothesised that increased lactate production due to lower levels of cardiorespiratory fitness may contribute to postoperative complications as the body has a reduced ability to metabolise lactate postoperatively (Older, 2013). This theory is supported by evidence reporting that increased blood lactate levels can lead to increased mortality in a number of conditions (e.g. sepsis and myocardial infarction) (Bakker and de Lima, 2004).

Lactate is a hyrdoxycarboxylic acid produced as a by-product during anaerobic glycolysis when converting glucose into pyruvate to meet energy demands of cells under stress (e.g. exercise and surgery) (Adeva-Andany et al., 2014). Lactate is typically recycled into glucose through the Cori cycle when transported to the liver. However, the liver blood supply is typically poor as about 75% of blood received is deoxygenated via the hepatic portal system and surgery can reduce liver blood flow further (Chapter 1.1.3). Due to the reduced oxygen supply post-surgery, the liver may be unable to cope with the increased amounts of lactate leading to increased surgical stress and cellular dysfunction (Older, 2013).

To help offset liver lactate metabolism demands, lactate can also be metabolised at various other tissues (Adeva-Andany et al., 2014). Skeletal muscle simultaneously produces and consumes lactate at rest, however both lactate production and consumption are enhanced when the muscle is exercising. Consistent exercise training leads to improvements in the oxidative efficiency of cells. Consequently, this reduces non-aerobic glycolysis, mean lactate formation and ultimately may reduce surgical stress and cellular dysfunction arising from increased levels of circulating lactate (Adeva-Andany et al., 2014).

1.2.5 Effects of exercise on anaesthesia and direct injury

Inspiratory muscle training (IMT) may help combat the adverse effects of anaesthesia and direct injury on the respiratory system. Anaesthesia leads to a decrease in FRC due to a loss of muscle tone and increased muscle fatigue (Chapter 1.1.4). This leads to decreased elastic chest recoil and decreases in MIP (Nomori et al., 1994, Wahba, 1991, Siafakas et al., 1999). The surgical incision also leads to respiratory dysfunction through distortion of the chest wall configuration, which increases the work of breathing and mechanical efficiency of the respiratory muscles (Siafakas et al., 1999) (Chapter 1.1.2). Furthermore, respiratory muscle mass is reduced postoperatively leading to a further reduction in respiratory function (Siafakas et al., 1999).

The combination of these effects can lead to airway closure and poor absorption which can result in atelectasis and other postoperative complications. Inspiratory muscle training requires participants to inspire against a resistance produced by a mechanical or electronic pressure gauge. Preoperative IMT has been noted to increase mean inspiratory muscle strength and endurance, which can help offset the decrease in respiratory muscle mass postoperatively (Hulzebos et al., 2007, Siafakas et al., 1999). Furthermore, increases in muscle tone may help combat the anaesthesia related decrease in FRC by increasing respiratory muscle tone. It has also been reported that IMT helps with postoperative respiratory dysfunction through improved deep-breathing postoperatively and increasing the MIP (Katsura et al., 2015, Valkenet et al., 2011). Therefore, it is likely that IMT can help offset the adverse effects of anaesthesia and direct surgical injury on the respiratory system through improvements in muscle tone, strength and endurance.

1.2.6 Exercise and surgery conclusion

The mechanisms underlying the relationship between preoperative physical fitness and postoperative outcome are likely to be multifactorial. It is likely that increased levels of cardiorespiratory fitness can increase oxygen delivery through various adaptations (Figure 1.1) and combat the increased oxygen demand associated with the surgical stress response (Chapter 1.1.1) and indirect injury (Chapter 1.1.3). In addition, exercise has anti-inflammatory attributes which may reduce the stress response directly (Chapter 1.2.3). Furthermore, exercise may help cells cope with oxygen deficits through ischaemic preconditioning (Chapter 1.2.2) and decreasing mean lactate production (Chapter 1.2.4). Individuals with low levels of preoperative cardiorespiratory fitness may be at increased risk of postoperative dysfunction due to a reduced ability to deliver oxygen and/or tolerate ischaemic conditions and higher levels of circulating lactate. Preoperatively identifying these patients may allow time for effective preoperative intervention and prioritisation of limited resources to improve postoperative care.

1.3 Preoperative risk assessment

Preoperative identification of modifiable risk factors amenable to intervention and preparation of patients is essential to help improve quality of care and to help restore patients to baseline function postoperatively (Garcia-Miguel et al., 2003). Preoperative tests allow clinicians to gain additional information that cannot be obtained from a patient history. Furthermore, they can be used to identify patients with a high-risk of postoperative complications and inform the most effective treatment (NICE, 2016). Despite the value of preoperative tests and considering current economic and timing

constraints, performing unnecessary tests is in an inappropriate use of limited resources (Hepner, 2009). To improve standardisation of preoperative testing, the National Institute for Health and Care Excellence (NICE) recently published updated guidelines for preoperative care (NICE, 2016). The aim of this guideline is to reduce unnecessary preoperative testing by advising specific tests to perform depending on type of surgery and patient co-morbidities. The routine preoperative tests for elective surgery guideline recommends specific tests to be performed based on surgery grade (minor, intermediate and major) and American Society of Anaesthesiologists (ASA) Physical Status Classification System grade (Chapter 2.2.1) and are presented in (Figure 1.2). The evidence for using these tests is based on a combination of available studies and results of surveyed clinicians.

Test	ASA 1	ASA 2	ASA 3 or ASA 4
Minor surgery (**examples**: excising skin lesion; draining breast abscess)			
Full blood count	Not routinely	Not routinely	Not routinely
Haemostasis	Not routinely	Not routinely	Not routinely
Kidney function	Not routinely	Not routinely	Consider in people at risk of AKI[1]
ECG	Not routinely	Not routinely	Consider if no ECG results available from past 12 months
Lung function/arterial blood gas	Not routinely	Not routinely	Not routinely
Intermediate surgery (**examples**: primary repair of inguinal hernia; excising varicose veins in the leg; tonsillectomy or adenotonsillectomy; knee arthroscopy)			
Full blood count	Not routinely	Not routinely	Consider for people with cardiovascular or renal disease if any symptoms not recently investigated
Haemostasis	Not routinely	Not routinely	Consider in people with chronic liver disease • If people taking anticoagulants need modification of their treatment regimen, make an individualised plan in line with local guidance • If clotting status needs to be tested before surgery (depending on local guidance) use point-of-care testing[2]
Kidney function	Not routinely	Consider in people at risk of AKI[1]	Yes
ECG	Not routinely	Consider for people with cardiovascular, renal or diabetes comorbidities	Yes
Lung function/arterial blood gas	Not routinely	Not routinely	Consider seeking advice from a senior anaesthetist as soon as possible after assessment for people who are ASA grade 3 or 4 due to known or suspected respiratory disease
Major or complex surgery (**examples**: total abdominal hysterectomy; endoscopic resection of prostate; lumbar discectomy; thyroidectomy; total joint replacement; lung operations; colonic resection; radical neck dissection)			
Full blood count	Yes	Yes	Yes
Haemostasis	Not routinely	Not routinely	Consider in people with chronic liver disease • If people taking anticoagulants need modification of their treatment regimen, make an individualised plan in line with local guidance • If clotting status needs to be tested before surgery (depending on local guidance) use point of care testing[2]
Kidney function	Consider in people at risk of AKI[1]	Yes	Yes
ECG	Consider for people aged over 65 if no ECG results available from past 12 months	Yes	Yes
Lung function/ arterial blood gas	Not routinely	Not routinely	Consider seeking advice from a senior anaesthetist as soon as possible after assessment for people who are ASA grade 3 or 4 due to known or suspected respiratory disease

AKI, acute kidney injury
[1]See recommendation 1.1.8 of the NICE guideline on acute kidney injury
[2]Note that currently the effects of direct oral anticoagulants (DOACs) cannot be measured by routine testing.

Figure 1.2: NICE Guidelines for preoperative tests based on specific surgery grades and ASA classification (NICE, 2016). Currently there is not enough evidence to recommend preoperative cardiopulmonary exercise testing.

1.3.1 Current role of assessment of preoperative physical fitness

The NICE guidelines report there is currently insufficient evidence to recommended CPET as a preoperative risk stratification tool in elective surgery (NICE, 2016). In intra-abdominal surgery, there

is no consensus on the ability of preoperative exercise tests such as CPET to predict postoperative outcome. The evidence in support of CPET as a preoperative tool in thoracic surgery is strong and consequently both the British Thoracic Society (BTS) and American College of Chest Physicians (ACCP) recommend the use of preoperative CPET and field tests of exercise tolerance to identify high risk patients and prioritise limited perioperative resources (BTS, 2001, Brunelli et al., 2013). Other recommended tests employed in thoracic surgery include pulmonary function tests (PFTs), and gas exchange measurement tests.

The ACCP developed an algorithm to assess the level of perioperative risk for patients scheduled for thoracotomy and major anatomic resection (lobectomy or greater) based on lung function and exercise tolerance (Figure 1.3) (Brunelli et al., 2013). Patients are required to perform stair climb test (SCT) or incremental shuttle walk test (ISWT) as a first line preoperative assessment of cardiorespiratory fitness if they achieve a predicted postoperative forced expiratory volume in one second (FEV_1) or diffusing capacity for carbon monoxide (DLCO) <60%-30%. Formal CPET should be performed if predicted postoperative FEV_1 or DLCO are <30% (Brunelli et al., 2013). Despite the recommendations of the BTS and ACCP, the NICE Guidelines report that lung function tests should not be routinely performed, however lung function should be measured in patients with; (i) ASA grade 3 or 4 due to know or suspected respiratory disease and (ii) having intermediate/major/complex surgery (NICE, 2016).

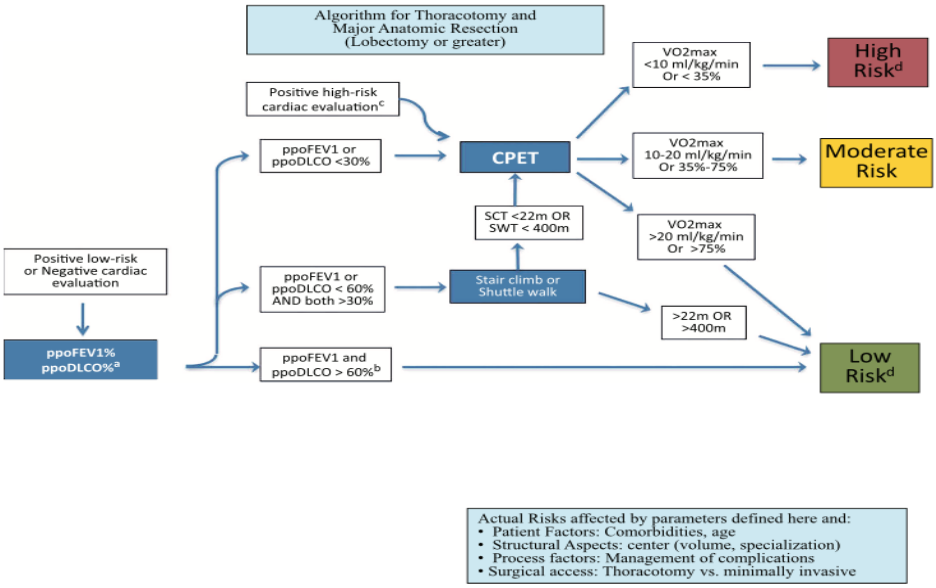


Figure 1.3: Algorithm for assessing perioperative risk for patients scheduled for thoracotomy and major anatomic resection based on preoperative lung function and exercise tolerance developed by the ACCP (Brunelli et al., 2013). CPET = Cardiopulmonary Exercise Testing, PPO = Predicted Postoperative, SCT = Stair Climb Test, SWT = Shuttle Walk Test.

1.3.1.1 Preoperative lung function tests

Both the BTS and ACCP recommend formal pulmonary function tests should be performed in all patients scheduled for lung cancer surgery, with an emphasis on the FEV_1 and the DLCO (Brunelli et al., 2013, BTS, 2001). Spirometry assess the individuals pulmonary function through maximal inspiration and expiration. Measures recorded during spirometry include FEV_1, functional vital capacity (FVC) and FEV_1/FVC. The FEV_1 is the total amount of air expired in one second, while the FVC is the total amount of air expired after a maximal inspiration. The FEV_1/FVC is a ratio between the two measures.

The FEV_1 is widely regarded as the spirometry measure with the greatest predictive ability, as it provides an indirect measure of pulmonary reserve, and has a high correlation with the severity of respiratory impairment in patients with chronic obstructive pulmonary disease (COPD) (Weinberger and King, 2016). The BTS recommends that no further pulmonary function tests are required if patients have a preoperative post-bronchodilator FEV_1 >1.5 litres for lobectomy, and >2.0 litres for a pneumonectomy (BTS, 2001). FEV_1 is an independent predictor of pulmonary morbidity (OR, 1.1 for every 10% decrease in FEV_1) and cardiovascular complications (OR, 1.13 for every 10% decrease in FEV_1) (Ferguson et al., 2008). DLCO measures the transfer of gas from the lungs to the red blood cells and is also recommended in conjunction with spirometry in the preoperative period (Macintyre et al., 2005). A study of 1,428 patients undergoing lung resection reported that the risk for development of postoperative pulmonary complications increases by approximately 10% for every 5% decrement in the predicted postoperative FEV_1 (OR: 1.11, 95% C.I: 1.01-1.20) and DLCO (OR: 1.11, 95% C.I: 1.01-1.17) (Alam et al., 2007). Spirometry data should be used to calculate predicted postoperative FEV_1 and DLCO, as patients with low predicted postoperative FEV_1 (<60%) and predicted postoperative DLCO (<60%) have an increased risk for postoperative complications and mortality (BTS, 2001).

1.3.1.2 Preoperative field tests

Field tests measure cardiorespiratory fitness indirectly by measuring distance or time to completion and are used as a preoperative assessment of exercise tolerance if predicted postoperative FEV_1 or DLCO are <60% in thoracic surgery (Brunelli et al., 2009a, Brunelli et al., 2013). The ACCP recommends two field tests of exercise tolerance to measure preoperative fitness in patients scheduled for thoracic surgery; the SCT and the ISWT. The stair climb test, requires patients to climb a set of stairs and the distance and time to completion is recorded. The SCT is an easy to administer field test and requires very little equipment, however it is not standardised as the stair case employed differs depending on

the environment. Despite the lack of standardisation, the SCT is reportedly well correlated with VO_{2peak} (peak oxygen uptake), and can predict patients at increased risk post-lung resection (Van Nostrand et al., 1968, Olsen et al., 1991, Brunelli et al., 2002, Brunelli et al., 2008, Brunelli et al., 2010). The incremental shuttle walk test is a field test of exercise tolerance that measures aerobic capacity indirectly through distance walked. This externally paced walking test requires patients to walk between two cones, set nine meters apart (ten meters when accounting for patient turns), in pace with auditory beeps. The patient walks at an increasing pace until they are no longer able to keep up with the auditory beeps.

Patients scheduled for thoracic surgery unable to climb 12 m during the SCT had an increased risk for morbidity and mortality. A study of 640 major anatomic lung resections (lobectomy and pneumonectomy) compared patients who were able to climb >22 m to patients unable to climb 12 m and reported the incidence of cardiopulmonary complications and mortality was 2.5 and 13-fold higher, respectively (Brunelli et al., 2008). The ACCP reports that data on the ability of the ISWT to predict postoperative outcome is limited, however a study of 125 patients scheduled for lung resection reported that a cut-off of 25 shuttles during the ISWT was significantly correlated to a VO_{2peak} of 15/ml/kg/min ($r=0.67$, $p<0.001$) (Brunelli et al., 2013, Win et al., 2006). Field tests provide several advantages over CPET, most notably they are cheaper, less resource heavy and are easy to administer, however they do not deliver an in-depth assessment of cardiopulmonary gas exchange provided by CPET. It is recommended that patients scheduled for thoracic surgery perform field tests such as the ISWT and SCT as a first line assessment of exercise tolerance and in the event that results are lower than recommended thresholds, patients should undergo formal CPET assessment (Brunelli et al., 2013). If patients are able to achieve a stair climbing altitude of >22m, they are regarded as low risk and should not be referred for formal cardiopulmonary exercise testing (Brunelli et al., 2013). For the ISWT, the ACCP suggests a cut-off of 40 shuttles (400m), as this reportedly corresponds to a VO_{2peak} of >15 ml/kg/min (Brunelli et al., 2013). Patients with preoperative distances <400m are recommended to undergo formal CPET (Brunelli et al., 2013).

1.3.1.3 Preoperative cardiopulmonary exercise testing

Cardiopulmonary exercise testing provides an in-depth assessment of an individual's cardiopulmonary system at rest and while exercising and is widely considered the gold-standard method of measuring an individual's cardiorespiratory fitness. The American College of Chest Physicians (ACCP) and the European Respiratory Society/European Society of Thoracic Surgeons (ERS/ESTS) consider patients with a VO_{2peak} of <10 ml/kg/min or <35% predicted measured via CPET to be at high risk for

postoperative morbidity and mortality (Brunelli et al., 2013, Brunelli et al., 2009b). In contrast, patients with a VO_2peak >20 ml/kg/min are suitable for any type of lung resection, including pneumonectomy. A study of 200 patients scheduled for lung resection reported that patients with a VO_2peak >20 ml/kg/min had no mortality and only a 7% morbidity rate. Patients scheduled for lung resection with a VO_2peak 10-20 ml/kg/min have a moderate amount of postoperative risk. In addition, the BTS report that a VO_2peak $\geq$15 ml/kg/min constitutes an average level of risk (BTS, 2001).

In accordance with good clinical practice and the NICE guidelines, the use of CPET for all patients would have high costs and be unnecessary. The development of a triage pathway in intra-abdominal surgeries (e.g. colorectal and pancreatic) using field tests and CPET would have high clinical utility as field tests are cheaper and easier to perform, while CPET can provide a more accurate and in-depth assessment of cardiorespiratory fitness that can be used in individuals if preoperative field test results are not ideal. The preoperative use of field tests and CPET would help identify high-risk patients and allow for the prioritisation of limited resources (e.g. ICU admission) to help reduce morbidity and LOS, which would be advantageous for both the patient and the hospital. This thesis will explore the effectiveness of cardiopulmonary exercise testing and field tests of exercise tolerance in intra-abdominal surgery through a systematic review in Chapter 3. Thoracic surgery will not be explored in the subsequent chapters as the ability of CPET and field tests to identify high-risk patients has been concluded by the ACCP and BTS. The development of a triage pathway, similar to Figure 1.3, in intra-abdominal surgery would help identify high-risk patients with low levels of cardiorespiratory fitness and allow time for preoperative interventions that can reduce postoperative risk. Patients with lower levels of physical fitness may be amenable to interventions designed to improve physical fitness. The addition of preoperative interventions, aimed at increasing physical fitness, to current perioperative pathways such as enhanced recovery after surgery (ERAS) protocols, may help reduce postoperative risk and improve perioperative outcomes.

1.4 Enhanced Recovery After Surgery

In the preoperative period effective surgical practices and interventions are needed to alter preoperative factors, optimise patient health, and improve postoperative risk (Hepner, 2009). Enhanced recovery after surgery programmes (also known as ERAS, fast track, multimodal, rapid or accelerated recovery programmes) aim to deliver the optimal perioperative care pathway through integrated multidisciplinary team goal-directed care plans. ERAS is a multimodal treatment pathway consisting of preoperative optimisation of nutritional status, preoperative counselling, preoperative

carbohydrate loading, early mobilisation, and standardised anaesthetic and analgesic regimens (epidural and non-opioid analgesia) (Khan et al., 2009). ERAS covers the preoperative, intraoperative, and postoperative periods and focuses on improving postoperative recovery and reducing length of stay (Paton et al., 2014). Originally ERAS was developed for patients undergoing colorectal surgery, and was shown to reduce postoperative complications and LOS (Bagnall et al., 2014). This programme has also been developed for other surgical procedures such as hepatic and gastrointestinal surgery (Hughes et al., 2014, Singh et al., 2017).

Enhanced recovery protocols improve postoperative outcome in colorectal surgery. A meta-analysis of 12 studies reported that ERAS protocols significantly reduced LOS [Mean Difference (MD): -2.28 days, 95% C.I: -3.09,-1.47] and overall morbidity (OR: 0.60, 95% C.I: 0.46-0.76) (Ljungqvist et al., 2017). The benefits of ERAS protocols can be applied to additional surgical procedures. A meta-analysis of 14 studies reported that ERAS protocols reduce LOS (MD: -4.17 days, 95% C.I: -5.72 to -2.61) and postoperative morbidity (OR: 0.63, 95% C.I: 0.54-0.74) in patients post-pancreaticoduodenectomy (Xiong et al., 2016). In addition, a meta-analysis of 8 studies concluded that ERAS protocols can reduce LOS (MD: -1.85, 95% C.I: -2.35 to -1.35) post-gastrectomy. Despite the abundance of literature supporting the implementation of ERAS in colorectal (Ljungqvist et al., 2017), gastric (Ding et al., 2017), and pancreatic surgery (Xiong et al., 2016), ERAS protocols for thoracic surgery have not been widely implemented. However, the limited amount of evidence available supports ERAS as a method of reducing postoperative morbidity (Muehling et al., 2008) and length of stay (Scarci et al., 2016) following lung resection.

Preoperative 'pulmonary rehabilitation', or preoperative exercise therapy, is a key component of thoracic surgery ERAS protocols (Nagarajan et al., 2011, Benzo et al., 2011). Preoperative exercise interventions aimed at improving preoperative cardiorespiratory fitness can reduce postoperative risk in thoracic surgery (Benzo et al., 2011). A study of 24 patients scheduled for lung cancer resection reported that preoperative exercise interventions significantly reduced the incidence of postoperative pulmonary complications [16.7% (intervention) vs. 77.8% (control), p=.01] and LOS [7.8±4.8 days (intervention) vs. 12.2±3.6 days (control), p=.04] compared to usual care (Morano et al., 2013). However, the optimal preoperative exercise intervention has not been concluded on. Despite the formal consensus of the importance of preoperative exercise prior to thoracic surgery, the widely established colorectal surgery ERAS protocols neglect to provide any recommendations for preoperative cardiopulmonary fitness. Therefore, this thesis will explore the ability of preoperative

exercise interventions to improve postoperative outcome in intra-abdominal surgical procedures through a systematic review and meta-analysis (Chapter 5).

Despite the implementation of ERAS protocols and guidelines for preoperative testing and risk stratification, the Health Service Executive (HSE) published a report stating that fundamental changes to the current surgical pathway are required to reduce waiting times and shorten hospital stays in Ireland (Royal College of Surgeons in Ireland, 2011). The HSE and the Acute Hospital Bed Capacity report that elective surgery has contributed to the hospital overcrowding problem, and suggests that this is due to inconsistent and inefficient practices and pathways being performed (Royal College of Surgeons in Ireland, 2011). Despite ERAS reducing postoperative complications, morbidity rates can remain relatively high at 15.1% post-colorectal surgery (Ljungqvist et al., 2017). Therefore, interventions that can reduce morbidity rates further would have high clinical utility. A reduction in complications may translate to a decrease in LOS postoperatively, which would lead to decreased hospital costs per patient. Furthermore, this could improve bed utilisation and decrease the overcrowding problem attributed to elective surgery. It is recommended that to improve bed utilisation, improved hospital care pathways are required (Group and Group, 2007).

This thesis will discuss the role of preoperative physical fitness in improving surgical pathways. The ability of testing preoperative physical fitness to identify high-risk surgical patients and predict postoperative morbidity, mortality and LOS will be explored (Chapter 3 and 4). Furthermore, this thesis will examine how preoperative exercise interventions aimed at increasing preoperative physical fitness can influence postoperative outcome and how these interventions may be included in future ERAS protocols (Chapter 5 and 6). Various abdominal and thoracic surgical procedures will be examined including oesophagectomy, hepatic resection, and abdominal aortic aneurysm (AAA) repair. However, there will be a particular emphasis on surgical resection for colorectal cancer and thoracic surgery for lung cancer. The following section will provide an overview of the incidence, surgical management and postoperative outcomes of colorectal and thoracic cancer surgery.

1.5 Cancer

Tumours can be described as either being benign or malignant. Benign tumours contain the disease within a well-defined capsule and do not spread, whereas malignant tumours spread and invade various tissues around the body (Brighton and Wood, 2005). Cancer is generally regarded as a multi-factorial disease, where normal body cells transform to become invasive malignant cells (Brighton and

Wood, 2005). Cancer is a state where normal cellular functions such as proliferation, apoptosis, and differentiation are unregulated (Brighton and Wood, 2005).

Cancer is usually treated through surgery, chemotherapy or radiotherapy, however these treatments may be used in combination with each other. Surgery is performed to remove the tumour and surrounding area (Brighton and Wood, 2005). Chemotherapy is a cytotoxic treatment that destroys rapidly dividing cells within the body, while radiotherapy is the use of ionizing radiation to control or kill malignant cells. Surgery is the main method of curative intervention for colorectal and lung cancer, however surgery carries substantial postoperative risk for both.

1.6 Colorectal Surgery

1.6.1 Colon and rectum anatomy

The colon comprises the large bowel proximal to the rectum and on average is 1.5 meters in length (MacKay G et al., 2010). The colon consists of the caecum, ascending colon, transverse colon, descending colon, and the sigmoid colon (MacKay G et al., 2010) (Figure 1.4). The rectum is connected to the sigmoid colon at the level of the third sacral vertebrae. The rectum concludes at the upper end of the anal canal and is variable in length, however it is commonly defined as a length of 15cm above the external anal margin (Stranding, 2016).

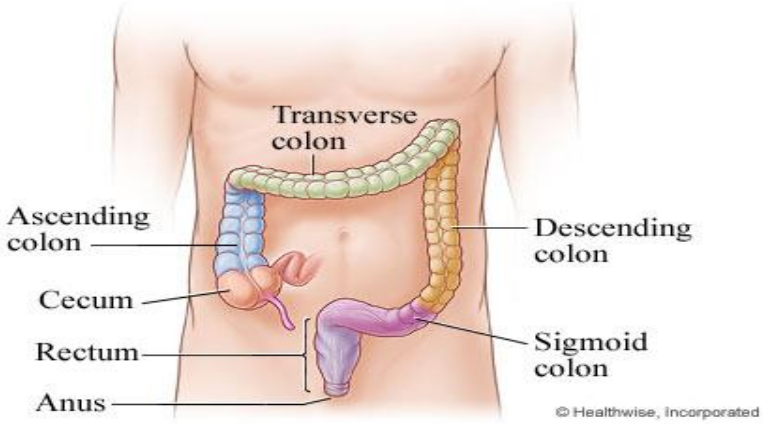


Figure 1.4: The colon and rectum anatomy

1.6.2 Colorectal cancer incidence and prevalence

Approximately 1.36 million new cases of colorectal cancer are diagnosed annually (Ferlay et al., 2015). Overall it is the third most common cancer worldwide with a higher incidence in men than woman (Torre et al., 2015, Rabeneck et al., 2015). In the Republic of Ireland, the reported incidence of colorectal cancer in 2011-2013 was 2,504 cases (Ireland, 2012). Colorectal cancer is the second most common type of cancer in males and females in Ireland and surgery remains the main form of curative treatment (Ireland, 2012). There are a reported 8.2 million cancer related deaths per year, and colorectal cancer contributes to 694,000 deaths, making up 8.5% of the total cancer related deaths (Ferlay et al., 2015). In Ireland, there was a total of 1,036 colorectal cancer related deaths in 2013 (441 in females and 595 in males), ranking as the 2nd most common cancer related death (Ireland, 2012), directly behind lung cancer (Ireland, 2016d).

1.6.3 Colorectal polyps

A polyp is a growth of tissue projecting from the inner lining of the colon into the lumen of the colon. Types of polyps include adenomas, hamartomas, inflammatory and hyperplastic polyps. Polyps are benign, only a small amount (estimated at 10%) of benign adenomas progress to carcinomas (Research, 2011). Adenomas or adenomatous polyps, which are gland-like growths that develop on the mucous membrane lining the colon, are pre-malignant lesions present in ~30% of people aged 50 years old (MacKay G et al., 2010). Adenoma size is closely correlated with colorectal cancer, as larger polyps are more likely to develop into colorectal cancer (Strum, 2016). Evidence for the management of colorectal polyps is limited, however it is recognised that colon cancer prevention is the ultimate goal. The majority of adenoma polyps can be treated endoscopically, however large villous rectal polyps may be excised surgically (MacKay G et al., 2010).

1.6.4 Colorectal cancer staging

Cancer staging refers to the size of the primary tumour and the degree of spread (Institute, 2013). Correct and accurate cancer staging is important to help inform effective treatment decisions and predict outcome. The pathologist Cuthbert Dukes developed the first widely accepted staging classification of colorectal cancer (MacKay G et al., 2010). The Dukes Classification is outlined in Table 1.1 and is incorporated in the Colorectal-Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity (CR-POSSUM) risk prediction calculator (Chapter 2 - Methods). The American Joint Committee on Cancer (Cancer, 2010) developed an improved and internationally preferred method of classifying tumours (Appendix J).

Table 1.1: Dukes classification of tumour size and degree of spread.

Dukes' Classification	
Dukes A	Tumour confined to the innermost lining of the bowel/rectum or slightly growing into the muscle layer
Dukes B	Tumour invading through the muscle layer of the bowel/rectum.
Dukes C	Tumour has spread to at least one lymph node
Dukes D	Metastasis; the cancer has spread to elsewhere in the body.

1.6.5 Colorectal cancer treatment

Colorectal cancer treatment consists of a combination of chemotherapy, radiotherapy, and surgery. Surgery remains the only curative form of intervention for colorectal cancer (Steele, 2009). Although often mentioned together, the management of colon and rectal cancer differs. Rectal cancer is often treated with neoadjuvant chemoradiotherapy followed by surgery (Phillips, 2009). In contrast, colonic cancer is normally treated by surgical resection followed by adjuvant chemotherapy depending on disease stage (Steele, 2009). The implications of adjuvant therapy will not be discussed as this thesis will focus on the preoperative and immediate postoperative period (i.e. prior to discharge postoperatively). Management of colorectal cancer depends on cancer staging, primarily if the tumour is localised to the colon wall and/or regional nodes (localised), or spread to other organs (metastatic). Approximately 80% of cancers are localised to the colon and/or regional lymph nodes (Rodriguez-Bigas et al., 2016). Surgery is the main form of curative intervention for localised colorectal cancer (Steele, 2009). There are various surgical procedures detailed below that may be employed depending on tumour size, severity, and location.

Treatment for metastatic colorectal cancer (approximately 20% of colorectal cancer) can be broadly separated into resectable and unresectable. Surgery is the main method of treating resectable colorectal metastatic disease, metastectomy provides a mean 5-year survival of approximately 50%, however the 5 year results are superior for liver metastases (most common site of colon cancer metastases) than lung metastases (2nd most common site of colon cancer metastasis) (Lumachi et al., 2016). There are some instances when metastatic colorectal cancer cannot be treated. Neoadjuvant chemotherapy may be recommended as it may help patients who are borderline candidates for surgery (Grothey et al., 2016). Chemotherapy can be administered to reduce symptoms and prolong survival, however chemotherapy alone cannot cure metastatic colorectal disease, and treatment for patients with advanced colorectal cancer is limited (Grothey et al., 2016).

1.6.5.1 Colon cancer surgical management

Colon surgery can be completed via open repair or laparoscopically and the various procedures consist of segmental colectomy, ileocecectomy, right hemicolectomy, left hemicolectomy, sigmoid colectomy, transverse colectomy, sub-total or total colectomy, and the proctocolectomy and are defined in Appendix J. Some of the procedures are presented in Figure 1.5.

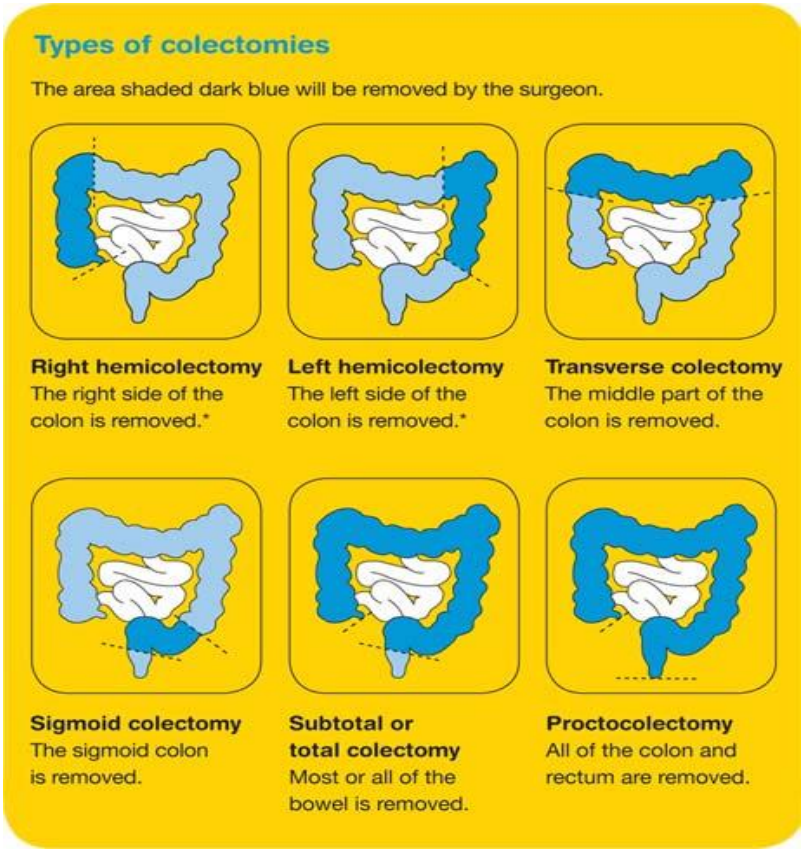


Figure 1.5: Types of colonic resections

1.6.5.2 Anastomosis

Following colorectal incision and removal of the diseased part of the organ, the remaining, disease-free sections are connected to form an anastomosis. An anastomosis is the reconnection of two hollow vessels, and occurs in post-colonic resection to reconnect the separated colon.

1.6.5.3 Neoadjuvant chemotherapy for colon cancer

Neoadjuvant chemotherapy is not typically performed in colon cancer, as it has not been widely investigated. There is evidence to support neoadjuvant chemotherapy in colon cancer, however further research is required (Jakobsen et al., 2015). Therefore, current treatment for colon cancer includes surgery as the primary method of treatment combined with adjuvant therapy depending on tumour staging.

1.6.6 Rectal cancer management

Surgical resection for rectal cancer include local excision, sphincter-sparing procedures, and abdominal perineal resection. The type of surgical intervention depends on a number of factors including, location of tumour, tumour staging, presence of lymph node involvement, and metastatic disease (Bleday and Shibata, 2016b).

The types of rectal surgery include local excision, sphincter-sparing resection, and abdominal perineal resection. Local excision removes the tumour and adjacent tissue without tumour fragmentation. Sphincter-sparing procedures include high anterior resection, low anterior resection, and ultra-low anterior resection (Figure 1.6). Low anterior resection is one of the most common procedures for rectal cancer, and includes sufficient removal of the sigmoid colon and rectum such that the distal margin is free of cancer (Bleday and Shibata, 2016a). Sphincter-sparing procedures create a colo-anal anastomosis, allowing preservation of the anal sphincter mechanism (Bleday and Shibata, 2016a). In addition, abdominal perineal resection (APR) includes the resection of the sigmoid colon, anus, and rectum, combined with construction of a permanent colostomy.

The overall aim of rectal cancer surgery is curative resection. To allow this, surgeons must perform a wide resection of the cancer by achieving histologically negative margins, using a total mesorectal excision (TME) technique and resection of lymph nodes combined with sphincter-sparing procedures or an APR. Total mesorectal excision involves the complete removal of the perirectal soft tissue (Parfitt and Driman, 2007, Bleday and Shibata, 2016a). In rectal cancer surgery, the proximal, distal, and radical surgical margins of resection must be histologically proven negative to reduce chances of local recurrence rates (Bleday and Shibata, 2016a).

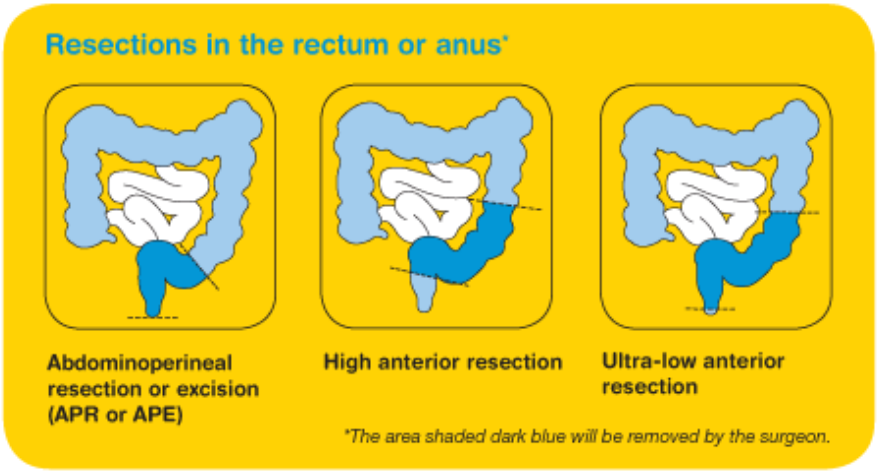


Figure 1.6: Abdominal perineal resections and sphincter sparing procedures of the rectum

1.6.6.1 Neoadjuvant treatment

Neoadjuvant treatment has become a 'gold standard approach' for rectal cancer management (Milinis et al., 2015). Neoadjuvant treatment is prescribed to preserve sphincter function, and can also be administered for patients with poor prognosis tumours with an at-risk circumferential resection margin, as defined by magnetic resonance imaging (MRI) (Brighton and Wood, 2005). Preoperative radiotherapy can be administered as a short or long course. Short course preoperative radiotherapy (SCPRT) consists of 25 Gy in five daily fractions over 1 week, while long course preoperative chemoradiation (LCPCRT), typically consists of 45-50.4 Gy in 1.8 Gy fractions over about 5 weeks with either 5-fluorouracil (5-FU) or capecitabine, followed by a recovery period of 6-8 weeks preoperatively.

1.6.6.2 Implications of neoadjuvant treatment on physical fitness

Chemotherapy leads to muscle weakness, fatigue and cardiopulmonary toxicity. In addition, neoadjuvant chemoradiotherapy leads to decreases in cardiorespiratory fitness due to cardiopulmonary toxicity (West et al., 2014a). West and colleagues reported a mean decrease in cardiorespiratory fitness of 1.4 ml/kg/min (95% C.I: −3.1, −1.0) post neoadjuvant chemoradiotherapy in 25 patients scheduled for rectal cancer surgery (West et al., 2014a). Cardiopulmonary toxicity due to chemotherapy is attributed to increased oxidative stress (Gilliam and St Clair, 2011). Doxorubicin (an antibiotic that exerts its antitumor activity by inhibiting DNA) induced chemotherapy increases oxidative stress through elevated levels of oxidants, markers of protein oxidation and decreased anti-oxidant activity (Gilliam and St Clair, 2011, Chatterjee et al., 2010). Doxorubicin-chemotherapy also increases the amount of circulating TNF-α (Bower et al., 2002). Subsequently, the elevated levels of the pro-inflammatory TNF-α caused by chemotherapy, increase oxidants and leads to cardiac muscle dysfunction (Gilliam and St Clair, 2011). The increase in oxidants leads to alterations of vital proteins which can change cardiac structure, leading to impaired contractile function, contributing to

cardiopulmonary toxicity (Gilliam and St Clair, 2011). It is likely that chemotherapy related alterations to cardiac muscle can affect cardiac output through impaired contractile function. This decrease in cardiac output may explain the chemotherapy related decrease in cardiorespiratory fitness, however future research is required to effectively conclude on the impact of chemotherapy on cardiorespiratory fitness.

Cancer induced cachexia can cause loss of up to 75% of skeletal muscle mass (Preston et al., 1986) leading to an increase in fatigue and mortality (Tisdale, 2001). Similar to cardiac muscle, chemotherapy can also lead to skeletal muscle weakness through reductions in size of both Type I and Type II fibres due to exposure to elevated levels of circulating oxidants (Gilliam and St Clair, 2011, Bonifati et al., 2000). Oxidative stress is further stimulated by elevated TNF-α levels caused by chemotherapy (Gilliam and St Clair, 2011). The influence of chemotherapy and TNF-α on circulating oxidants leads to skeletal muscle weakness. Furthermore, chemotherapy has additional adverse effects on the cardiorespiratory system, microcirculatory function, physical activity (PA) levels, and mitochondrial metabolism (West et al., 2014a).

Despite the adverse effects of chemotherapy on physical fitness, participants undergoing neoadjuvant treatment remain amenable to preoperative exercise interventions. A study of 39 patients with rectal cancer post neoadjuvant chemotherapy demonstrated that preoperative exercise interventions consisting of aerobic exercise can return cardiorespiratory fitness to baseline levels (West et al., 2015). Neoadjuvant chemotherapy reduced fitness by 1.9 ml/kg/min (95% C.I: -1.3, -2.6 ml/kg/min), however following a structured exercise regimen of three sessions a week for six weeks on a cycle ergometer, cardiorespiratory fitness returned to baseline levels (+2.1 ml/kg/min, 95% C.I: 1.3-2.9 ml/kg/min). Therefore, preoperative exercise interventions may help combat the neoadjuvant chemotherapy related reduction in cardiorespiratory fitness.

1.6.6.3 Inflammatory bowel disease

Colorectal surgery is not limited to the treatment of colorectal cancer, surgery may be performed in the treatment of inflammatory bowel disease (IBD). Inflammatory bowel disease comprises both Crohn's disease and ulcerative colitis, inflammatory conditions that affect mainly the colon and rectum (MacKay G et al., 2010, Abraham and Cho, 2009). Crohn's disease mainly affects the ileum and colon, however it may affect any region of the gastrointestinal tract (Abraham and Cho, 2009). In Crohn's disease the inflammation is often transmural, and it can be associated with intestinal granulomas,

strictures and fistulas. Ulcerative colitis is typically confined to the mucosa in the rectum and the colon. In the United States, approximately 1.4 million patients are affected by IBD with a peak onset in individuals of 15-30 years of age (Abraham and Cho, 2009). Treatment for IBD consists of a combination of lifestyle changes, medication, and surgical intervention (Abraham and Cho, 2009).

Patients with Crohn's disease who do not tolerate medical therapy or develop complications such as abscesses or malignancy, or suffer from pain, weight loss, anorexia, or malaise may be candidates for surgery (Torres et al., 2016). It is reported that 85% of patients with Crohn's disease will require surgery, however surgery is not a definitive cure, and 50% of these individuals will require a second operation (MacKay G et al., 2010). Approximately 33% of patients with ulcerative colitis will require surgery (MacKay G et al., 2010). Indications for surgery for patients with ulcerative colitis can be categorised into emergency and elective (MacKay G et al., 2010, Ungaro et al., 2016). Emergency surgery indications include uncontrolled haemorrhage, colon perforation and failed medical management (MacKay G et al., 2010). Indications for elective surgery for ulcerative colitis include disease resistant to medical management, advanced adenomas or colorectal cancer, and complications associated with medical therapy (MacKay G et al., 2010).

1.7 Thoracic surgery

1.7.1 Lung anatomy

The lungs are responsible for respiration and are situated on either side of the heart, occupying most of the thoracic cavity (Muresian, 2016). The lungs are attached via the hilum and pulmonary ligament to the mediastinum. The right and left lungs are divided into lobes. The right lung contains the superior, middle and inferior lobe separated by the oblique and horizontal fissures, while the left lung has a superior and inferior lobe, divided by the oblique fissure. Each lung contains 10 bronchopulmonary segments, each supplied by a segmental bronchus and artery.

1.7.2 Lung cancer incidence and prevalence

Lung cancer is the most common cancer worldwide and it is the 3rd most common cancer in Ireland, directly behind colorectal cancer (Lang-Lazdunski, 2013, Ireland, 2016d). Lung cancer is the leading cause of cancer death in the USA, and Ireland (Siegel et al., 2015, Ireland, 2016d), responsible for more than 350,000 deaths per year in Europe, and approximately 1,887 deaths in Ireland. The 5-year survival rate in Ireland between 2008-2012 averaged 15.3% (95% C.I: 14.4-16.2%) (Ireland, 2016d).

The majority of lung cancers are non-small cell lung cancer (NSCLC), accounting for approximately 85% of overall lung cancers, however only 25-30% of these tumours are suitable for surgical resection with curative intent (Lang-Lazdunski, 2013). This thesis will focus exclusively on those able to proceed to surgery. Tumour staging dictates treatment strategy for NSCLC. Patients with lung cancer of stage 1 or 2 and good functional status are suitable for surgical resection, the treatment of choice, however some patients with stage 3a, 3b or 4 may be unsuitable (Lang-Lazdunski, 2013).

Small cell lung cancer (SCLC) is a neuroendocrine tumour that occurs in approximately 15% of lung cancers, and occurs predominately in smokers (Kelly et al., 2016). SCLC has a higher growth fraction, and earlier development of metastases (Kelly et al., 2016). Surgery is not typically performed in SCLC, instead treatment focuses on systemic therapy (chemotherapy and radiotherapy), unless it is in the very early stages and patients are relatively fit (Society, 2016).

1.7.3 Surgical treatment

Surgical resection is the primary method of treating lung cancer, and surgical procedures include pneumonectomy and lobectomy (Lang-Lazdunski, 2013). Pneumonectomy, the largest lung resection possible, is the removal of the whole lung (Figure 1.7). A pneumonectomy is performed to remove central tumours with involvement of a mainstream bronchus, left or right pulmonary artery, and both superior and inferior pulmonary vein (Lang-Lazdunski, 2013). Pneumonectomy related morbidity is about 5-50%, however the right pneumonectomy has higher rates of complications and mortality, mainly due to bronchopleural fistula (Lang-Lazdunski, 2013).

Lobectomy is the surgical removal of a pulmonary lobe (upper, middle or lower), and is the most common approach for most patients with an operable lung cancer, accounting for 60-70% of lung resections (Lang-Lazdunski, 2013) (Figure 1.7). Lobectomy combined with complete mediastinal lymph node dissection for patients with early stage (1, 2, 3a) lung cancer is currently the most effective treatment (Donington et al., 2012). Postoperative morbidity rates are 30-38% (Allen et al., 2006, Salati et al., 2013), and 30-day mortality rates are 2-4% (Harpole et al., 1999, Treasure et al., 2003).

Less common surgical resections include wedge resection, and bilobectomy. The bilobectomy is a variant on the lobectomy procedure, and is performed exclusively for right lung cancers (Lang-Lazdunski, 2013). A bilobectomy involves the surgical excision of two lobes of the right lung, either the

upper and middle lobe or the middle and lower lobe. The mortality rates post bilobectomy are similar to lobectomy, however morbidity is substantially higher at 47.2-71% (Galetta et al., 2012, Icard et al., 2013, Cho et al., 2012, Lang-Lazdunski, 2013).

Wedge resection is a non-anatomic surgical resection of the lung tumour and the surrounding area, however this is not a recommended procedure for most patients with lung cancer (Lang-Lazdunski, 2013). Wedge resections may be acceptable for patients with poor pulmonary function, because wedge resections are used to minimise the surgery related reduction in pulmonary function. It is recommended that this procedure be avoided, and the surgeon should always try to perform a systematic lymph node dissection (Lang-Lazdunski, 2013). Despite the type of surgical procedure, pleural lavage cytology should be performed routinely to check for signs of malignancy within the pleural cavity (Lang-Lazdunski, 2013).

Video-assisted thoracoscopic surgery (VATS) is a minimally invasive surgical approach used in lung cancer surgery. VATS results in superior outcome compared to open thoracotomy and lobectomy, with patients experiencing less postoperative pain, shorter drainage duration, less complications, and fewer days in hospital (Lang-Lazdunski, 2013, Walker and Leaver, 2007, Whitson et al., 2008, Flores et al., 2009). Furthermore, in a meta-analysis of 39 articles, four-year survival rates were reported to be 17% higher in VATS lobectomy compared to open lobectomy (p=0.003) (Whitson et al., 2008).

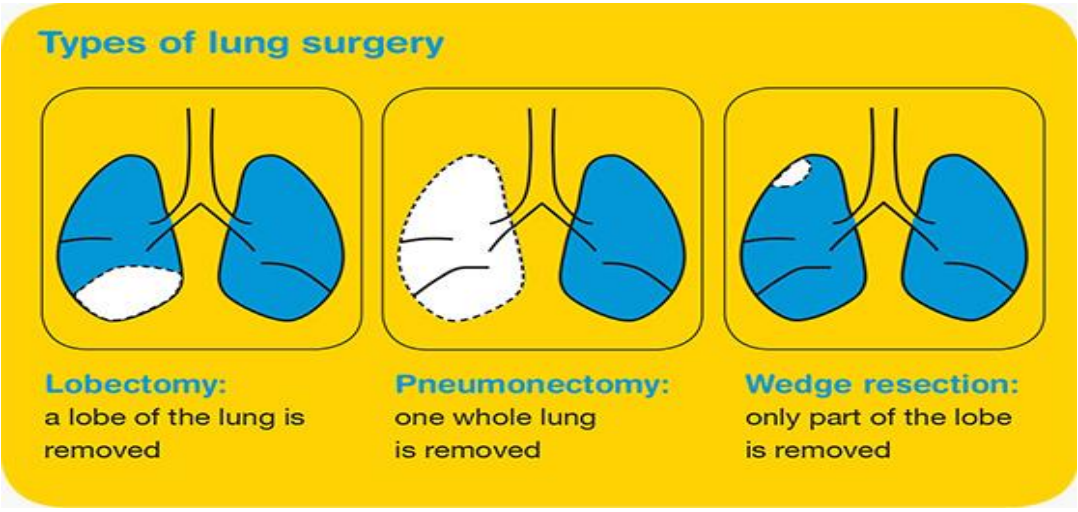


Figure 1.7: Types of lung surgery. Areas shaded in white will be removed

1.7.3.1 Neoadjuvant chemotherapy

The role of neoadjuvant chemotherapy in lung cancer is inconclusive. Currently, neoadjuvant chemotherapy is not recommended prior to lung cancer surgery due to the small number of published

trials (Lang-Lazdunski, 2013). Preoperative chemotherapy may delay potentially curative surgery (Lang-Lazdunski, 2013), however a recent meta-analysis of reported significant benefits observed in overall survival for patients that received neoadjuvant chemotherapy compared to patients who received surgery alone (Song et al., 2010). Patients scheduled for lung cancer surgery within St. James's Hospital, a national cancer centre, typically do not receive neoadjuvant chemotherapy with only 2% of patients receiving neoadjuvant chemotherapy between 2003-2012 (Hospital, 2003-2012).

1.8 Postoperative outcome

The pathophysiology and impact of postoperative complications were discussed in Section 1.1. This section will discuss the impact of poor postoperative outcome (complications, mortality and prolonged LOS) in colorectal and thoracic surgery.

1.8.1 Postoperative morbidity

Postoperative morbidity rates vary between surgeries, however the variation in postoperative complication rates is also due to inconsistent definitions of postoperative complications (Feeney et al., 2010). The lack of standardised definitions for postoperative complications leads to an underreporting of complications, which is a widely recognised global problem (Slankamenac et al., 2013). To improve the diagnosis and reporting of postoperative complications, objective measures of postoperative morbidity should be employed. Objective measures of measuring morbidity include the Postoperative Morbidity Survey (POMS), Clavien-Dindo Classification Score, and the Comprehensive Complications Index (CCI) and are discussed in Chapter 2.2.2.

Common types of complications to colorectal and thoracic surgery, and their effect on a patients quality of life (QOL) and hospital costs will be discussed. The definition and management of these complications will not be discussed as this thesis will examine the identification of high risk patients amenable to exercise based interventions that can prevent complications. The definition and management of a number of postoperative complications common to colorectal and thoracic surgery is provided in Appendix H. Types of postoperative pulmonary complications and their definitions will be discussed as they have high incidence rates and are common to both thoracic and colorectal surgery.

1.8.1.1 Complications in colorectal surgery

Colorectal complications occur in approximately 37-48% of patients (West et al., 2014b, West et al., 2014c). Types of complications include an anastomotic leak (2-7% cases) (Whitlow et al., 2010, Slieker et al., 2012, Kingham and Pachter, 2009, Hyman et al., 2007, Park et al., 2013), major anastomotic bleeding (0.5-4.2% cases) (Boushey and Williams, 2016, Cirocco and Golub, 1995, Malik et al., 2008, Martinez-Serrano et al., 2009, Lustosa et al., 2001), surgical site infection (17.9% cases) (MacKay G et al., 2010, Hubner et al., 2011), and deep venous thromboembolism (3% cases) (MacKay G et al., 2010).

Colorectal complications have a significant impact on patient's long term QOL. A study of 614 patients post colorectal resection reported significant differences in physical and social function, role functioning and body functioning between patients with and without complications at long term follow up (≥18 months) (Brown et al., 2014). Quality of life was measured using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (Cancer Core-30 and Colorectal-38 sub-scales) (Brown et al., 2014). Another study of 218 patients with complications post colorectal surgery demonstrated a decrease in overall QOL, physical QOL and psychological QOL at 6 weeks postoperatively according to the World Health Organization quality of life assessment instrument (Bosma et al., 2016). In contrast to Brown and colleagues, QOL returned to preoperative levels at 6 weeks in the study by Bosma and colleagues (Bosma et al., 2016). Differences in results between these studies may have arisen due to differences in recording complications and measuring QOL, as the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire is cancer specific and is further supplemented by disease specific subscales (e.g. Colorectal 38 sub-scale) (Aaronson et al., 1993). In comparison the World Health Organisation (WHO) QOL questionnaire was developed to assess QOL among a more general population (WHO, 1995). Furthermore, the study by Brown and colleagues did not use a standardised method of recording complications, compared to Bosma and colleagues who used the Clavien-Dindo Classifications Score. Despite these differences, postoperative complications significantly impact QOL with effects likely lasting from 6 weeks to ≥18 months.

In addition to the adverse effects of postoperative complications on a patients QOL, colorectal complications lead to a 2.1 fold increase in hospital costs from €12,405 to €25,680 (Zoucas and Lydrup, 2014). This retrospective study of 530 patients post-colorectal resection in the Netherlands demonstrated a significant increase in hospital costs due to prolonged LOS and ICU related expenditure. Readmissions resulted in a further mean increase in costs of €12,585. It is likely that interventions that can reduce postoperative complication rates would translate to a decrease in

hospital costs and an improvement in patient QOL. The ability of preoperative exercise interventions to reduce postoperative complications will be examined through a systematic review in Chapter 5.

1.8.1.2 Complications in thoracic surgery

Thoracic surgery complications occur in approximately 5-72% of patients (Lang-Lazdunski, 2013, Galetta et al., 2012, Icard et al., 2013, Cho et al., 2012). Types of complications include atrial fibrillation (10-40% cases) (Roselli et al., 2005), bronchopleural fistula (0.5-4% cases), pulmonary embolism (1-5%) (Di Nisio et al., 2015) and surgical site infections (1.5%) (Yoshida et al., 2006).

Similar to colorectal morbidity, thoracic complications have a noted effect on patient QOL. A study of health related quality of life in 44 patients scheduled for VATS for lung cancer reported patients with complications had worse QOL compared to patients without complications (Gazala et al., 2014). Health related QOL was measured using a combination of the Medical Outcomes Study Short Form-36 (SF-36) version 2, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) 30, the EORTC QLQ 13 and the utility index EQ-5D. Postoperative complications were recorded using the Clavien-Dindo score and QOL was compared in patients with high grade complications (grade 3 and 4) and minor (grade 1-2) or no complications (grade 0). General Health, Vitality and Mental Health were the main affected domains of the SF-36 generic measure at 12 weeks after surgery (Gazala et al., 2014). In addition, quality of life was significantly reduced at eight weeks after surgery as measured by the disease specific measures (QLQ 30 and QLQ 13). These results should be interpreted with caution due to the small sample size, however the literature regarding the effect of morbidity post-thoracic surgery on QOL is limited. It is likely that similar to colorectal surgery, thoracic surgery related morbidity adversely affects patient QOL.

Thoracic surgery complications also lead to an increase in hospital costs. A study of 503 patients post lung resection in the UK recorded the severity of postoperative complications using the Thoracic Mortality and Morbidity Classification System and recorded costs in US dollars (September 2016 exchange rates) (Gazala et al., 2014). This study demonstrated that hospital costs increased with the severity of postoperative complications (Gazala et al., 2014). The mean cost for a patient without complications was $3,560 (95% CI: $3,440 to $3,680). Hospital costs for patients with complications according to grade of severity were; $4,548 (95% C.I: $4,134-$4,962) for grade I, $4,909 (95% C.I: $4,537-$5,281) for grade II, $6,392 (95% C.I: $5,303-$7,483) for grade III and $14,547 (95% C.I: $6,334-$22,760) for grade IV. As preoperative exercise interventions can reduce postoperative complications in thoracic surgery (Morano et al., 2013, Benzo et al., 2011), it is likely that this effect translates to a decrease in hospital costs.

1.8.1.3 Postoperative pulmonary complications

Postoperative pulmonary complications may be defined as a 'pulmonary abnormality that produces identifiable disease or dysfunction that is clinically significant and adversely affects the patient's postoperative course' (O'Donohue, 1992). Postoperative pulmonary complications occur in both thoracic and colorectal resection, however PPC's are the main cause of postoperative morbidity following thoracic surgery with a reported incidence between (19-59%) (Garcia-Miguel et al., 2003). This is significantly higher than PPC rates in upper (16-17%) abdominal surgical procedures such as colorectal surgery (Garcia-Miguel et al., 2003). Reeve and colleagues developed an objective measure of PPC's that can be used to record PPC's (Table 1.2) (Reeve et al., 2008).

Table 1.2: Diagnostic criteria for postoperative pulmonary complications (Reeve et al., 2008).

Postoperative Pulmonary Complications	
1	Chest radiograph report of atelectasis/consolidation. In the event of no CXR being taken, the CXR report from the previous postoperative day will be used. If a CXR report is not available but a CXR has been taken, a ward medical officer will be asked to report
2	An otherwise unexplained WCC of >11.2 × 10^9/L or administration of respiratory antibiotics postoperatively (in addition to those administered routinely postoperatively)
3	Fever as seen by raised oral temperature >38°C with no focus outside of the lungs
4	Positive signs of infection on sputum microbiology
5	Production of purulent (yellow or green) sputum differing from preoperative status
6	SpO_2 > 90% on room air
7	Diagnosis of pneumonia/chest infection by attending physician
8	Readmission to the ITU/HDU with problems that are respiratory in origin or a prolonged stay in the ITU/HDU (over 36 h) with problems that are respiratory in origin
CXR: chest X-ray, PPC: postoperative pulmonary complication, SpO_2: blood oxygen saturation levels, WCC: white cell count, ITU: intensive treatment unit, HDU: high dependency unit	

Pneumonia (defined as a fever >38.5°C, purulent sputum, positive blood and/or sputum culture, as well as clinical and/or radiological evidence of consolidation postoperatively) is a significant concern post-pulmonary resection and post-abdominal surgery (Windsor and Hill, 1988). Prolonged air leak is defined as a leak lasting more than seven days after pulmonary resection (Ziarnik and Grogan, 2015). Atelectasis is defined as evidence of a fever, and clinical and radiological evidence of collapse (Windsor and Hill, 1988). Atelectasis is a serious complication that causes a ventilation/perfusion mismatch that

results in hypoxemia and respiratory decline (Ziarnik and Grogan, 2015). Treatment strategies include antibiotic treatment, chest physiotherapy, and in severe cases, ventilation support.

1.8.2 Length of stay

Length of stay is often used to measure the effectiveness of interventions aimed at improving surgical care. LOS is a general term that can be employed to encompass general hospital stay duration, ICU/HDU admission and duration of stay, and readmission rates. Programmes such as ERAS, aim to reduce LOS by preventing the development of complications, which can ultimately lower hospital costs (Stephen and Berger, 2003, Taheri et al., 2000, Dai et al., 2017).

1.8.2.1 Length of stay colorectal surgery

The National Health Service (NHS) Bowel Cancer Audit reported the LOS for 17,489 patients. The median LOS post colorectal cancer surgery was 7 days [Interquartile range (IQR): 5-12 days] (Braun et al., 2016). Median LOS increased according to patient age; patients ages <75 years had a median LOS of 7 days, compared to 8 days in patients aged 75-84 years, and 10 days in ≥85 years. Postoperative morbidity also contributes to increased LOS. A study of 23,098 patients in the United States compared LOS in patients with and without complications (Cohen et al., 2009). Patients with an event free postoperative recovery (n=20,039) had a mean LOS of 6.1 days [standard deviation (SD): 3.8] and a median LOS of 5 days. In comparison, patients with complications (n=3,059) had a mean LOS of 16.1 days (SD: 14.2) and a median LOS of 12 days.

1.8.2.2 Length of stay thoracic surgery

The Royal College of Physicians Lung Cancer Audit reported the LOS for 5,657 patients in the UK. The median LOS post lung cancer resection was 6 days (IQR: 5-10 days) (Physicians, 2016). Similar to colorectal surgery, postoperative complications contribute to prolonged LOS. A study in the United States of 4,979 patients post thoracic surgery reported the median LOS was 6 days (Wright et al., 2008). Prolonged LOS (defined as LOS ≥14 days) occurred in 351 patients (7%). The rate of postoperative complications were higher for patients with prolonged LOS compared to those without (3.4 vs. 1.2 complications, $p<0.0001$) (Wright et al., 2008).

1.8.3 Mortality

Surgery is associated with significant postoperative mortality rates. The NHS Bowel Cancer Audit reported the 90-day mortality rates for elective, urgent, and emergency colorectal surgery between

2014-2015 in the UK was 3.8% (Braun et al., 2016). When emergency and urgent surgery was excluded, elective 90-day colorectal surgery rates were 2.1%. The Royal College of Physicians Lung Cancer Audit reported the 90-day mortality rates of 5,657 patients in 2014 was 3.8% (Physicians, 2016). In addition, the 30-day mortality rates 2.1%. Furthermore, 90-day mortality rates based on type of surgical procedure were provided. Bilobectomy/lobectomy/sleeve resection 90-day mortality rates were 3.7% for 4,157 patients. Wedge/segmental resection 90-day mortality rates were 2.3% for 1,115 patients. Pneumonectomy 90-day mortality rates were highest at 10.3% in 302 patients. Finally, carinal resections/lung resection of the chest wall mortality rates were 3% (33 patients) and other resection mortality rates were 4% (50 patients).

1.9 Cancer centre

St. James's Hospital (SJH) is a national cancer centre for lung cancer and colorectal cancer and follows best practice for cancer management (Hospital, 2003-2012). In addition, SJH is one of eight nationwide rapid access centres specialising in lung cancer. The cardiothoracic team carries out >45% of curative lung cancer resections in Ireland. Colorectal cancer practice in SJH is defined and linked with the Association of Coloproctology of Great Britain and Ireland (Hospital, 2003-2012). The colorectal service is involved in the management of >9% of the national cancer workload. In addition, according to the SJH cancer audit, in-hospital morbidity and mortality are consistent with international benchmarks, however exact numbers were not provided (Hospital, 2003-2012). The National Health Service (NHS) require all patients with cancer to begin treatment within 31 days of diagnosis (Service, 2014). Ireland does not have strict cancer treatment requirements, however Ireland follows key performance indicators; in Ireland, colorectal cancer patients should be offered an admission date for surgery ≤20 working days from histological diagnosis (Service, 2012).

1.10 Abdominal Surgery

This thesis focused primarily on the effects of physical fitness in colorectal surgery and thoracic surgery, however this thesis also explored the effects of preoperative physical fitness in various abdominal surgical procedures. An overview of these abdominal operations is presented in Table 1.3 and more information is provided in Appendix J.

Surgery	Reasons for Surgery	Incidence and Prevalence	Treatment	Postoperative Morbidity Rates	Postoperative Complications	Length of Stay	Mortality Rates	Survival Rates
Abdominal Aortic Aneurysm Repair	Abdominal aortic aneurysm (AAA)	Affects approximately 4% of men and women aged 65-80 Higher incidence in males aged 65-80 (7.6%) (Scott et al., 1995)	Risk-factor modification Medical therapy Surgical intervention	Postoperative morbidity: 29% (Vemuri et al., 2004)	Complications include myocardial infarction, arrhythmias, pneumonia, and acute renal failure	Open Repair Mean LOS: 9 days EVAR Mean LOS: 3 days (Kent, 2014)	30-day mortality EVAR: 0.5-1.8% Open: 3.0-4.8% (Lederle et al., 2007, Greenhalgh et al., 2010, De Bruin et al., 2010, Lederle et al., 2012)	6-year survival rates EVAR: 31-34% Open: 30-35% (Lederle et al., 2012, Greenhalgh et al., 2010, De Bruin et al., 2010)
Gastric Bypass Surgery	Weight Loss	Approximately 113,000 cases a year in the USA (Livingston, 2010)	Restrictive and malabsorptive surgical procedures	Postoperative complications rates are approximately 11% (Hennis et al., 2012, McCullough et al., 2006)	Complications include: anastomotic strictures, gastrointestinal bleeding, anastomotic leak, sepsis, and bowel obstruction (Beaulac and Sandre, 2016)	Laparoscopic Roux-en-Y mean LOS: 1.8-4.5 days (Baker et al., 2006)	All gastric bypass procedures 30-day mortality rates: 0.1% Roux-en-Y gastric bypass 30-day mortality rates: 0.15% (Benotti et al., 2014)	N/a
Hepatic Resection & Liver Transplant	Liver Cancer End-stage Liver Disease	Globally, it is the 5th most common cancer in men (7.5%) and the	Resection and transplantation is the only method of curative intervention for	Hepatic resection morbidity rates: Laparoscopic: 18.31%	Complications include: atelectasis, pleural effusion, bile leakage, and liver	Median LOS: 6 days	30-day mortality rates are 0.4% and do not differ between laparoscopic and	Hepatic resection 5 year survival rates: 53.0% (Liu et al., 2016)

		ninth in women (3.4%) There were 6,139 liver transplants in the USA in 2006 (Goh, 2008)	liver cancer (Madkhali et al., 2015)	Open hepatic: 29.77% (Ciria et al., 2016)	failure (Jin et al., 2013)	IQR: 5-9 days (Dunne et al., 2014)	open resection (Ciria et al., 2016)	
Oesophageal Surgery	Oesophageal Cancer	Oesophageal cancer is the 8th most common cancer worldwide (Ferlay et al., 2015) 11th most common cancer in Ireland (12th in males and 14th in females) (Ireland, 2016a) Approximately 389 cancers diagnosed in Ireland annually (Ireland, 2016a)	Surgery remains the mainstay of treatment in conjunction with neoadjuvant chemoradiotherapy (Luketich, 2014)	Overall Complications: 22.9-50% (Connors et al., 2007, Rutegard et al., 2012) Postoperative Pulmonary Complications: 15-30% and are associated with a 4.5 fold increase in mortality, responsible for 45.5-55% of deaths (Feeney et al., 2011, Avendano et al., 2002, Ferguson and Durkin, 2002, Law et al., 2004, Whooley et al., 2001)	Complications include: anastomotic leak, atelectasis and pneumonia (D'Amico, 2007)	Mean LOS: 14 days (range 5-149 days) Median LOS: 10 days Mean ICU LOS: 5 days (range 0-139 days) (D'Amico, 2007)	30-day mortality: 11% (Ra et al., 2008)	5-year survival rate between 2008-2012 in Ireland is 18.1% (95% C.I: 16.0-20.2%) (Ireland, 2016a)

Pancreatic Surgery	Pancreatic Cancer	7th most common cancer in Ireland (9th in males, and 11th in females) (Ireland, 2016e) 2.4% of all invasive cancers (Ireland, 2016e)	Surgical resection is the only curative treatment for pancreatic cancer (Ho et al., 2005)	Postoperative morbidity rates are 18-64% (Buchler et al., 2003, Junejo et al., 2014)	Postoperative complications include pancreatic leak, post-pancreatectomy haemorrhage, and wound infection. (Buchler et al., 2003, Junejo et al., 2014)	Median LOS: 16 days (range 3-169 days) (Junejo et al., 2014)	Postoperative mortality is <5% (Bradley, 2002)	5-year survival rates in Ireland between 2008-2012 for pancreatic cancer is 8.7% (95% C.I: 7.2-10.1%) (Ireland, 2016e)
Radical Cystectomy	Bladder Cancer	9th ninth most common form of cancer worldwide and in Ireland (Ploeg et al., 2009, Ireland, 2016b) In men it is the eight most common and the fifteenth most common in females in Ireland (Ireland, 2016b) Incidence of 2.2% in Ireland (Ireland, 2016b)	Radial cystectomy (RC) with pelvic lymph node dissection and ileal conduit or orthotopic bladder reconstruction is the gold standard treatment (Bassi and Pagano, 2007, Prentis et al., 2013)	Postoperative morbidity (19-64%) (Prentis et al., 2013)	Major complications include, ileus, wound infection, pneumonia, and urinary tract infection (Prentis et al., 2013)	Median LOS: 17.5 days Patients with complications median LOS: 21 days Patients with no complications median LOS: 15 days (Prentis et al., 2013)	Mortality rates (6-11%) (Prentis et al., 2013)	The 5-year net survival rate between 2008-2012 in Ireland is 61.9% (95% C.I: 59.4-64.4%) (Ireland, 2016b)

Nephrectomy & Renal Transplant	Kidney Cancer Renal Failure Chronic Kidney Disease	In Ireland, Kidney cancer is the 5th most common cancer overall (Ireland, 2016c) In men it is the 6th most common (373 new cases per year) (Ireland, 2016c) 10th most common in females (197 new cases per year) (Ireland, 2016c) Kidney cancer is ranks as the 12th most common invasive cancer death (Ireland, 2016c)	Nephrectomy is the surgical removal of the kidney and is widely performed to treat renal tumours, which can be classified as renal cell carcinoma (RCC) or transitional cell carcinoma (TCCA) (Al-Qudah et al., 2007)	Major complications (Clavien-Dindo grade 3-4) post radical nephrectomy: 2.8% (Pierorazio et al., 2016) Major complications (Clavien-Dindo grade 3-4) post partial nephrectomy: 5.9% (Pierorazio et al., 2016)	Nephrectomy complications include; acute renal failure, wound infection, urinary tract infection, small bowel obstruction, arrhythmia, and pneumonia. Renal Transplant: Urologic complications (including urine leak and ureteral obstruction) occur in 4-8% of patients Vascular complications (including renal artery stenosis and infarction) occur in approximately 1-2% of patients (Akbar et al., 2005)	Nephrectomy Median LOS: 3 days (Lorentz et al., 2015) Renal Transplant Mean LOS: 9.48 days (Machnicki et al., 2011)	30 day mortality: 2.8% (Thoroddsen et al., 2003)	The net five-year survival rate between 2008-2012 in Ireland for kidney cancer is 57.4% (95% C.I: 54.8-59.9%) (Ireland, 2016c)

Table 1.3: Various surgical procedures included in this thesis. N/a=Not applicable

1.11 Thesis aims and objectives

The overall aim of this thesis was to explore the influence of preoperative physical fitness on postoperative outcome in major elective intra-abdominal and thoracic surgery. In pursuing this aim, a number of studies were completed. The aims and objectives of the studies included in this thesis are presented in Figure 1.8.

The ability of CPET and field tests of exercise tolerance to identify patients at high-risk of poor postoperative outcome in thoracic surgery has been firmly established, however a consensus on the use of preoperative CPET as a risk-stratification tool in intra-abdominal surgery has not been reached. The aim of Chapter 3 was to systematically review the available literature and assess the prognostic ability of CPET and field tests of exercise tolerance in predicting postoperative mortality, morbidity and LOS associated with non-cardiopulmonary intra-abdominal surgery. The aim of Chapter 4 was to assess if measures of physical fitness [sub-maximal CPET, six minute walk test (6MWT), hand-grip strength, IMT, and physical activity levels] are associated with postoperative outcome (morbidity, LOS and mortality) in colorectal surgery. It has been reported that additional studies are required to assess whether CPET derived variables can be used with other non-CPET markers to improve prediction of postoperative outcome and enhance perioperative risk assessment (West et al., 2016). Preoperative tests of physical fitness (such as the 6MWT and grip strength) that can be used in conjunction, or more importantly, independently of CPET would be beneficial as CPET is a labour intensive and expensive preoperative assessment that is not readily available in all clinics.

Exercise prehabilitation that improves preoperative physical fitness may translate to an improvement in postoperative outcome. To address this concept, Chapter 5 was a systematic review and meta-analysis that aimed to assess the ability of preoperative exercise therapy/exercise prehabilitation to improve postoperative outcome (mortality, morbidity and LOS). Based on the results of Chapter 5, it was identified that current preoperative exercise interventions were longer in duration than the available pathway for cancer surgery. High intensity interval training had been previously identified as an effective method of increasing cardiorespiratory fitness in healthy individuals, however when developing this study, HIIT had not been previously validated in a preoperative colorectal and thoracic surgery population. It has been reported that preoperative exercise interventions of relatively high intensity continuous exercise have demonstrated poor adherence and compliance. In accordance with these findings, Chapter 6, the PHIIT trial, aimed to examine the feasibility of a HIIT prehabilitation programme of 2-4 week duration prior to major abdominal and thoracic surgery.

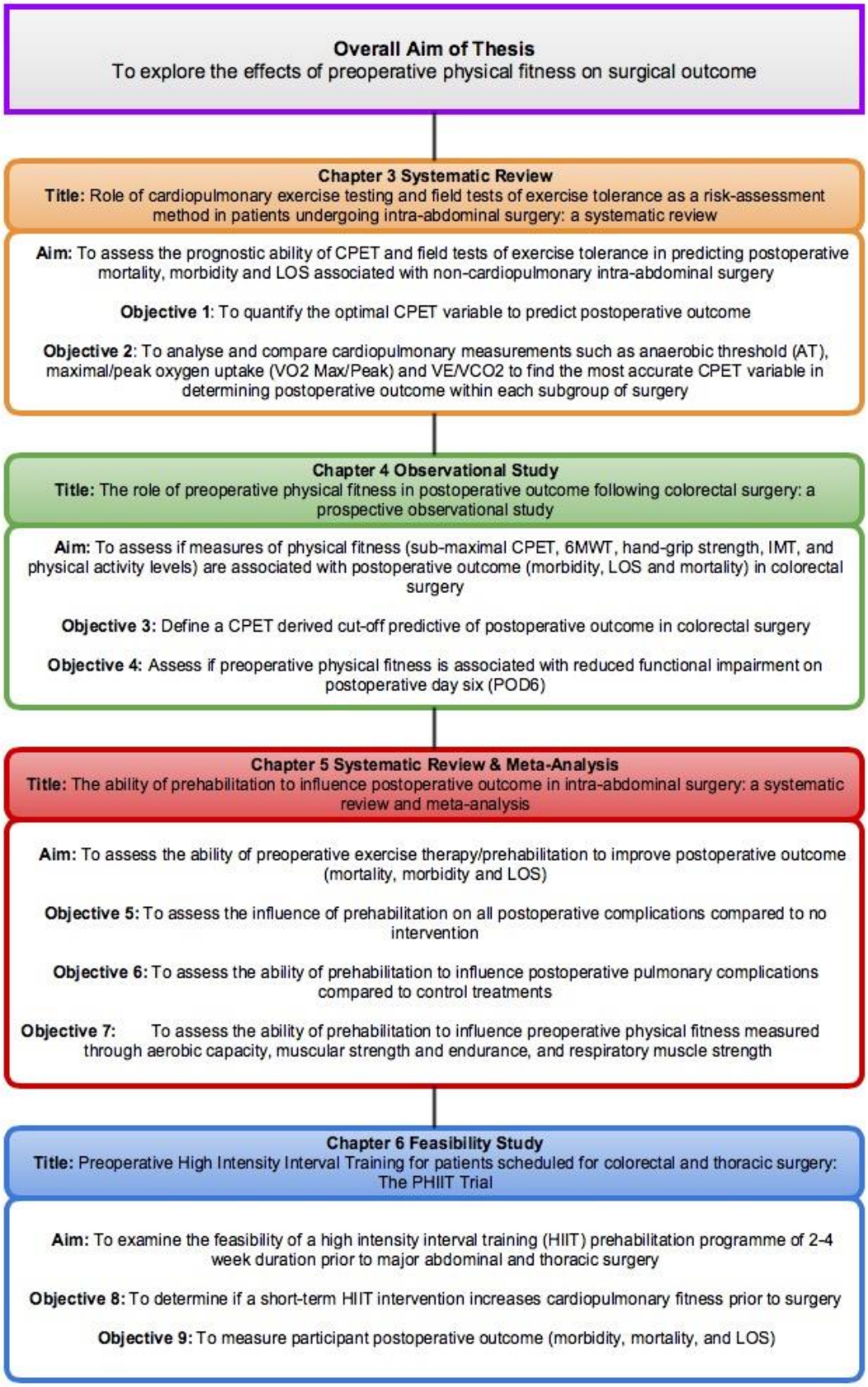


Figure 1.8: Overview of thesis aims and objectives

2 Chapter 2 Methods

This chapter will describe the methodology of study designs, sampling methods, data analysis and methods of assessments used in all studies. Section 1 will discuss the various study methodology relevant to this thesis. Section 2 will describe the various outcome measures used to calculate a patients' level of perioperative risk, and the objective measures of postoperative morbidity used to record the incidence of postoperative complications. Finally, Section 3 and 4 will focus on measures of physical fitness and physical activity, respectively, and describe the measurement protocols and validity of the chosen methods of measurement. The methods used in this thesis are outlined in Table 2.1. The measurements used in the observational study described in Chapter 4 and the feasibility study in Chapter 6 are outlined in Figure 2.1. Some of these methods are common among studies in this thesis and will be described in detail here. Subsequent chapters will refer back to the relevant sections in this chapter.

Table 2.1: Domains and instruments used in this thesis

Domain	Method Discussed
Section 1: Study Methodology	
Study Design	Systematic Review & Meta-Analysis Observational Studies Experimental Studies
Sampling & Sample Size	Sampling Sample Size
Measurement Properties	Reliability Validity
Principles of Data Analysis	Preliminary Data Analysis Types of Statistical Tests
Section 2: Clinical Outcomes	
Preoperative Risk	ASA-PS Grade POSSUM Score CR-POSSUM Score
Postoperative Complications	Postoperative Morbidity Survey Clavien-Dindo Classification Score Comprehensive Classifications Index
Section 3: Physical Fitness	
Body Composition	Body Mass Index (BMI) Circumferential measures (waist and hip)
Cardiopulmonary Fitness and Function	Maximal Exercise Test Sub-Maximal Exercise Test Six Minute Walk Test Incremental Shuttle Walk Test Stair Climb Test
Muscular Strength	Inspiratory Muscle Strength Hand-Grip strength
Pulmonary Function	Spirometry
Section 4: Physical Activity	
	Actigraph GT3X Yale Physical Activity Survey
ASA-PS: American society of anaesthesiologists physical status classification, POSSUM: Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity, CR-POSSUM: Colorectal- Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity. This table provides an overview of the study methodology and measurement instruments used in this thesis.	

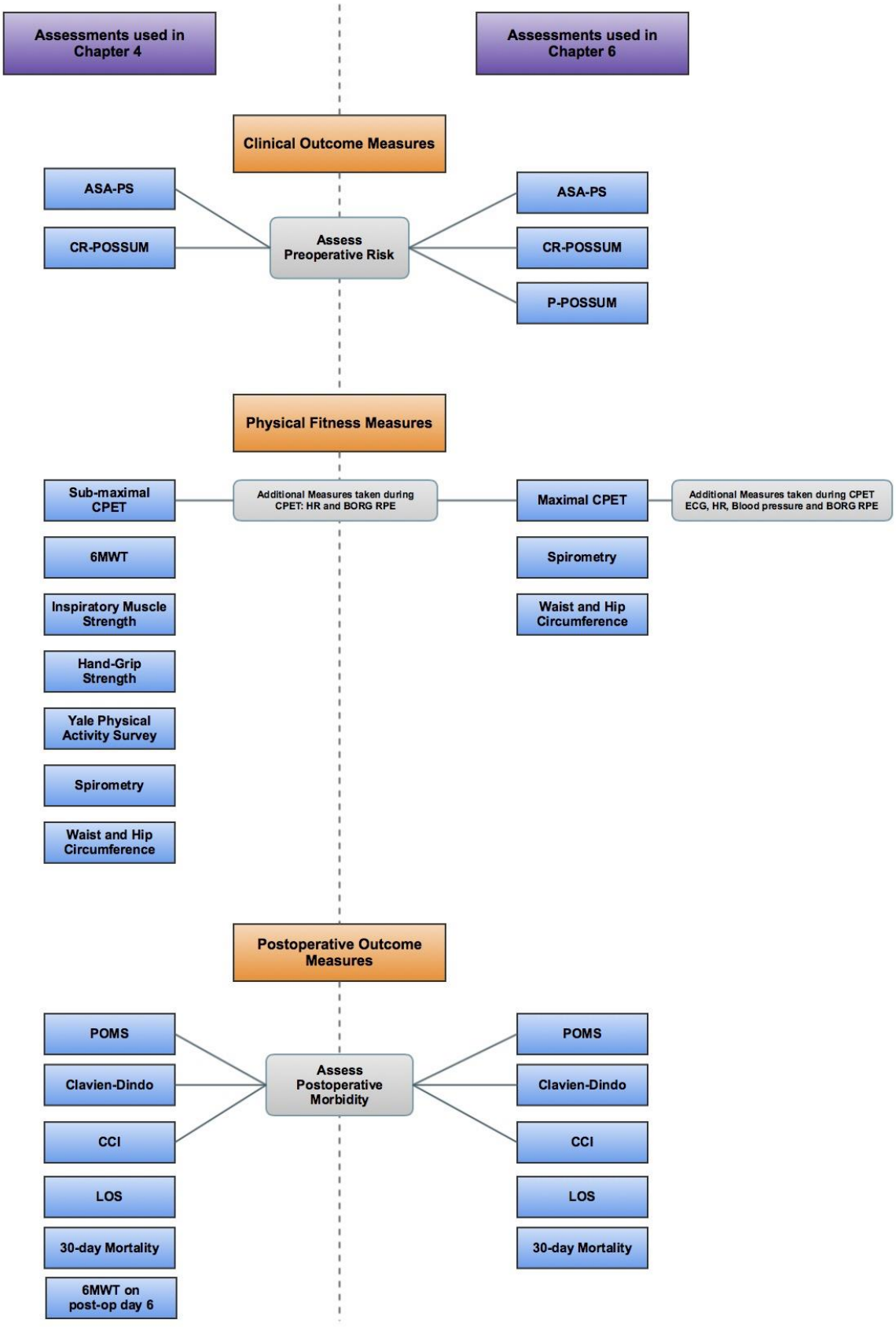

Assessments used in Chapter 4
Assessments used in Chapter 6
Clinical Outcome Measures
ASA-PS
CR-POSSUM
Assess Preoperative Risk
ASA-PS
CR-POSSUM
P-POSSUM
Physical Fitness Measures
Sub-maximal CPET
Additional Measures taken during CPET: HR and BORG RPE
Maximal CPET
Additional Measures taken during CPET ECG, HR, Blood pressure and BORG RPE
6MWT
Inspiratory Muscle Strength
Hand-Grip Strength
Yale Physical Activity Survey
Spirometry
Waist and Hip Circumference
Spirometry
Waist and Hip Circumference
Postoperative Outcome Measures
POMS
Clavien-Dindo
CCI
LOS
30-day Mortality
6MWT on post-op day 6
Assess Postoperative Morbidity
POMS
Clavien-Dindo
CCI
LOS
30-day Mortality

Figure 2.1: The assessment measures used in the observational study in Chapter 4 and the feasibility study in Chapter 6. Measures were used to assess postoperative risk, preoperative physical fitness and postoperative outcome. Some measures were shared between studies. 6MWT: Six minute walk test, ASA-PS: American Society of Anaesthesiologists-Physical Status, BORG RPE: BORG Rating of Perceived Exertion, CCI: Comprehensive Classifications Index, CPET: Cardiopulmonary Exercise Testing, CR-POSSUM: Colorectal-Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity, ECG: Electrocardiogram, HR: Heart rate, LOS: Length of stay, POMS: Postoperative morbidity Survey, P-POSSUM: Portsmouth-Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity

2.1 Section 1. Study Methodology

2.1.1 Study design

This section will examine the types of study designs used in this thesis including systematic review and meta-analysis, observational studies and experimental studies.

2.1.1.1 Systematic review and meta-analysis

Systematic reviews are an important cornerstone in evidence-based healthcare and are regarded as the highest level of clinical evidence (with or without a meta-analysis) (Evans, 2003, Khan et al., 2003). The objective of a systematic review is to methodically search and compile the available literature on a specific topic and formulate a conclusion based on the presented evidence. Systematic reviews include the formulation of a clear question to be addressed, followed by a thorough and systematic search for all relevant literature, a critical appraisal of the evidence, and interpretation of that evidence (Bigby, 2014). Systematic reviews use an explicit and systematic predefined methodology to minimise bias and to improve the precision of treatment effect measurements (Freeman et al., 2006). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is an evidence based set of minimum requirements for the conducting and reporting of a systematic review and meta-analysis. The PRISMA statement was published in 2009 and consists of a checklist and flow diagram to improve the quality of a systematic review (Antes and von Elm, 2009).

A meta-analysis is often used in conjunction with a systematic review and is a statistical technique, or set of techniques, for combining the results of several studies into a single estimate. A meta-analysis combines the effects observed across several relevant studies of similar methodology, pooling these effects to produce a single estimate of the effect, usually of a treatment or risk factor (Higgins and Green, 2008). A meta-analysis consists of three main parts: (i) a pooled estimate and confidence interval for the treatment effect after combining the treatment effects of all relevant studies, (ii) a

statistical significance test for the treatment or risk factor effect (iii) a test for heterogeneity of the effect on outcome between the included studies (Higgins and Green, 2008). Meta-analysis are beneficial as they provide a consolidated and quantitative review of the literature.

2.1.1.2 Observational studies

Clinical studies within medical research can be described as either experimental or observational. Experimental studies examine if a modification or change alters the development or course of an outcome among study participants (Hulley et al., 2013). In contrast, an observational study is defined as a study in which no intervention is performed, allowing for the measurement of events in their natural settings (Mann, 2003). In observational studies an investigator collects data on factors or exposures associated with the progression of an outcome of interest. Observational studies are beneficial in areas where performing experimental studies would be unethical or impractical. The main disadvantage of observational studies is that casual inference is challenging and interpretation is often obscured by confounding variables (Hulley et al., 2013).

Observational studies encompass cohort, cross-sectional, and case-control studies. A case-control study allows for pairing participants with a specific disease or outcome with an appropriate group of controls matched by certain demographic data e.g. age and gender (Mann, 2003). Data is extracted from the two groups and compared. A cross-sectional study examines the relationship between health related characteristics as they exist within a specific population at a particular point in time (Mann, 2003).

Cohort studies involve selecting a sample of participants (cohort) according to the presence or absence of an exposure and followed up over a selected period of time to determine the incidence of the outcome of interest (Bowling and Ebrahim, 2005). Cohort studies are ideal for determining the incidence and natural history of condition, and may be prospective or retrospective in nature. Prospective studies are generally ranked higher than retrospective studies on the hierarchy of evidence (Vandenbroucke, 2008). Prospective studies prevents the predictor measurements from being influenced by the outcome, thus allowing the investigator to measure variables more completely and accurately than is possible in a retrospective study, however prospective studies are subject to loss of participants to follow-up due to their long term nature. Retrospective studies eliminate this risk, however they often do not collect all relevant information due to missing or incomplete data (Hulley et al., 2013). Furthermore, retrospective studies are limited in the nature and quality of baseline measure, and are subject to recall bias. Patients with the outcome of interest are more likely to

remember the outcome of interest and exaggerate or belittle the risk factors (Hulley et al., 2013). An observational cohort study design was used in Chapter 4 to analyse the relationship between preoperative physical fitness and postoperative outcome in patients scheduled for colorectal surgery.

2.1.1.3 Experimental studies

The randomised clinical trial (RCT) tops the hierarchy of experimental study design for evaluating the intended effects of an intervention. An RCT design is advantageous in research as it reduces selection bias and allows comparison with a control group, however RCT's require a significant amount of resources, have high expenses, are time-consuming and usually require large sample sizes (Vandenbroucke, 2008). Non-randomised trials that compare groups are less effective in controlling for confounding variables compared to the gold standard RCTs, however in certain instances the feasibility and tolerability of the intervention should be assessed prior to implementing in an RCT (O'Cathain et al., 2015).

Feasibility studies are experimental studies conducted prior to a larger experimental study e.g. RCT. The main aim of feasibility studies is not to evaluate the outcome of interest, rather the role of feasibility studies is to estimate important parameters such as adverse events and recruitment, compliance, and adherence rates. Sample size calculations are often not required, however the sample size should be adequate to estimate the critical parameters such as compliance and adherence rates (O'Cathain et al., 2015). Feasibility studies are an important initial stage of developing and implementing an RCT.

Experimental studies such as an RCT often have an intervention and a control group to provide a comparison of the effects of the intervention. In comparison, single arm study's involve an intervention group only. In a time-series single arm design, measurements are made before and after the intervention is performed and participants act as their own matched control (Hulley et al., 2013). This provides an advantage as it eliminates confounding variables such as age and gender. The lack of control group also serves as a major disadvantage, as the recorded treatment effects might be due to learning effects (Hulley et al., 2013). Nevertheless, single arm time series designs may be beneficial in studies where the intervention feasibility needs to be assessed. A single time series design was used in Chapter 6 to examine the feasibility of a preoperative high intensity interval training intervention in patients scheduled for colorectal and thoracic surgery.

2.1.2 Sampling and sample size

2.1.2.1 Sampling

In quantitative research appropriate sampling methods and sample size are necessary to ensure that study results can be generalised to a larger population. A study sample must be representative of the population, allowing for results to be generalised beyond the study sample, therefore showing the study possess external validity (Fox et al., 2007). Unless the trait or disease of interest is very rare, it is impossible and expensive to test every individual with the trait of interest.

Sampling is a method of selecting a sample that is representative of the wider population and can be categorised as probability sampling and non-random sampling (Bland, 2015). Probability sampling is superior as it reduces systematic error, however non-random sampling is cheaper in time, resources and staffing requirements. The sampling frame is a random sample from a target population. Probability sampling ensures that every individual within the target population has an equal probability of being selected for participation (Fox et al., 2007).

Probability sampling techniques include simple random sampling, systematic random sampling, unrestricted random sampling, and stratified random sampling. Simple and unrestricted random sampling gives each of the potential participants in the target population an equal chance of being selected. Systematic sampling, selecting participants from a list, leads to a more even spread of the sample across a list than simple random sampling (Bowling and Ebrahim, 2005). Stratified random sampling divides the target population into layers (strata) and a sample is drawn from each stratum, using simple or systematic random sampling.

In the event that probability sampling is not possible, non-probability sampling techniques can be selected, however these sampling methods select participants non-randomly, therefore the degree to which they differ from the wider population is unknown (Bland, 2015). Convenience sampling is the most common type of non-random sampling. Participants are recruited based on availability until the target sample is achieved. While non-random samples are inherently biased, they may be required when probability sampling cannot be employed due to time constraints or cost issues (Schreuder and Gregoire, 2001).

Sampling error reports the amount by which a sample estimate can be expected to differ from the true mean of the population. Sampling error cannot be eliminated, however measures can be taken to reduce the possibility of Type I and II error such as having adequately powered sample sizes (Kang et

al., 2008). Type I error occurs when the null hypothesis is falsely rejected. Conversely, type II error occurs when the null hypothesis is falsely accepted. Error can occur from two main sources. Systematic error results when sampling is not performed adequately, resulting in a biased sample. The second main cause for error is random error, attributed to the chance factors that influence the sampling process. Increasing sample sizes, or adjusting study measures can reduce the likelihood of Type I and Type II error. In the observational study in Chapter 4 a sample size calculation was performed to reduce the risk of Type I and Type II error (Chapter 4.3.10).

2.1.2.2 Sample size

Adequate sample sizes are required to detect significant differences within or between groups and to be able to generalise study results to the wider population (Kang et al., 2008). When calculating sample size, a number of parameters must be defined such as the effect size, level of significance and the power of the study. The likelihood of detecting an association between a predictor and outcome variable depends on the magnitude of that association within the population, this is termed the effect size (Hulley et al., 2013). The effect size is typically estimated using data from previously published studies. The level of significance (α) defines the probability of type I error, and is typically 0.05 or 0.01, however lower significance levels require larger sample sizes. The probability of type II error (ß) occurring, defines the power of the study, as ß is the probability that the study will detect a significant change. Statistical power is typically defined at 80% or 90%, however higher power requires a larger sample size.

2.1.3 Measurement properties

2.1.3.1 Reliability

Reliability is a property of measurement and refers to the degree to which an outcome measure is free from random error (McDowell, 2006, Stokes, 2009). All observed scores using an outcome measure is the composite of the true score and random error. Random errors may occur during any part of the measurement process due to inaccuracy of the measurement device or inaccuracy of the assessor.

Reliability can be categorised as absolute or relative (Stokes, 2009). Absolute reliability is expressed as the standard error of the mean, the extent to which a score varies on repeated measurement. The standard error of the mean is used to detect the minimal detectable change, which is the minimal

amount of change in a measurement score required to ensure true change as opposed to change due to measurement error.

Relative reliability of an outcome measure can be reported as either inter-rater or intra-rater reliability (Stokes, 2009). Inter-rater reliability examines the consistency with which different investigators assign scores to the same measure. Intra-rater reliability examines the consistency between measures by the same investigator. Reliability provides an indication of the extent to which error may exist in an outcome measure and understanding the acceptable amount of absolute and relative reliability is essential in order to evaluate the extent of error influencing the results.

The reliability of measures can be analysed using a variety of statistical techniques (Stokes, 2009). The choice of statistical technique depends on the type of data i.e. ordinal or continuous. The level of agreement for between and within raters for ordinal data can be assessed with the kappa and weighted kappa coefficient. The kappa coefficient corrects for chance by calculating and taking into account the possibility of the agreement occurring by chance, while the weighted kappa coefficient allows for partial agreement between raters. For continuous data, the level of agreement between and within raters can be assessed using intra-class coefficients (ICC) or Pearson Product Moment Correlation Coefficients (PPMCC) (Stokes, 2009, McDowell, 2006). The intra-class coefficient is an indication of the variance due to error, and values closer to 1 indicate greater reliability (Stokes, 2009). The PPMCC assess internal consistency, which is also a measure of the homogeneity of the instrument. The PPMCC measures the degree to which two sets of continuous data have a linear relationship, not necessarily the level of agreement between the data. The reliability of the measurement tools used in this thesis is described in the various sections below.

2.1.3.2 Validity

Validity refers to the extent that an instrument or tool measures its intended outcome (Stokes, 2009). There are a number of domains of validity which require evaluation. Face validity examines if, “on the face of it”, the outcome measures its intended measurement, and is generally defined by professional consensus (Streiner et al., 2014, Stokes, 2009). Outcome measures with superior face validity are more likely to be used in practice. Content validity considers the individual items that are included and excluded from the outcome measure, ensuring that all relevant domains of interest are included (Stokes, 2009, Finch et al., 2002).

Criterion validity refers to the performance or accuracy of an outcome measure when compared to the relevant gold standard (Stokes, 2009). The gold standard measurement is often expensive, labour

intensive, and requires a significant amount of training, so measures with high criterion validity are ideal. Criterion validity can either be concurrent or predictive. Concurrent validity compares the outcome measure against the gold standard at a particular point in time. In comparison, predictive ability refers to relationship between the outcome measure and the gold standard to an assessment in the future. Criterion validity considers an outcomes sensitivity and specificity (Stokes, 2009). Sensitivity is the ability of an outcome measure in identifying correctly the presence of a disease/condition in an individual, while specificity refers to the precision of the outcome measure in correctly identifying that the disease/condition is not present.

Construct validity explores the constructs from which the hypothesis for the outcome measure is formed. Construct validity is an overarching term as it encompasses all other forms of validity e.g. face, and content, and is evaluated in terms of the individual factors (Stokes, 2009, Finch et al., 2002). Construct validity should be considered in terms of both, longitudinal and cross-sectional design, as an outcome measure may be validated at a particular point in time, however it may fail to effectively measure change over time (Stokes, 2009, Finch et al., 2002). Validity is a term widely used when evaluating outcome measures, and it is important to recognise the different categories of validity to ensure a tool or instrument measures its intended outcome. The validity of the measurement tools used in this thesis is described throughout various sections below.

2.1.4 Principles of data analysis

2.1.4.1 Preliminary data analysis

Preliminary data analysis involved examining and correcting missing or incorrect data. Descriptive statistics were performed for all variables. Descriptive statistics for nominal or ordinal variables state the frequency of the observation within the data set and the relative frequency within the dataset. Continuous variables (scale data) are described by a measure of central tendency (mean, median or mode) and a measure of variation about the mean, represented as standard deviation (σ) for normally distributed data or the inter-quartile range (IQR) for non-normally distributed data (Bland, 2015). Normality is an assumption underlying a number of statistical tests and is illustrated by a normal curve that is symmetrical about the mean and can be inspected visually using a histogram. Normally distributed data is an assumption required for various statistical tests such as regression and is illustrated by a normal distribution curve centred about the mean (Bland, 2015). Data disruption was assessed for normality using the Shapiro-Wilk test ($p>0.05$) and Kolmogorov-Smirnov test ($p>0.05$). In the event that distribution is non-normal, transformations can be applied to the non-normally

distributed data. Types of transformation include inverse and log transformations. The type of transformation employed depends if the data is positively or negatively skewed. If normality cannot be achieved through transformations, non-parametric tests can be used.

2.1.4.2 Types of statistical tests

The type of statistical test depends on the type of data, the study hypothesis and the underlying statistical assumptions (Mullins, 2003, Carter and Lubinsky, 2015, Bland, 2015). Statistical tests require a number of assumptions to ensure the tests are accurate. The exact assumptions differ between statistical tests, however some assumptions are shared between statistical tests.

To assess differences in continuous variables between groups methods available include independent-samples t-tests, and analysis of variance (ANOVA). Independent t-tests compare the mean difference in continuous variables between two groups without a special relationship at the same time point (Bland, 2015). Paired t-tests are used to assess differences in continuous variables within groups at different time points (Bland, 2015). ANOVA is used to compare measures between two or more groups, or two or more time points. The non-parametric equivalents of these tests include Mann-Whitney U test, Wilcoxon rank sum and Friedman's test, however these tests are inherently less robust than the parametric equivalents (Whitley and Ball, 2002). The underlying assumptions of these tests include; (i) independence of observations, (ii) there should be no significant outliers, (iii) the dependent variable should be approximately normally distributed for each group of the independent variable and (iv) homogeneity of variances. Homogeneity of variances ensures the variance is equal in each group of the independent variable and can be assessed using Levene's test for equality of variances. Differences in categorical variables can be assessed using the chi-squared test of independence however this test requires that all cells have expected counts ≥ 5. If the expected counts are <5, the Fishers exact test can be used as an alternative.

Relationships between variables can be explored through regression and correlation analysis. Regression analysis estimates the relationship among variables. Simple liner regression may be used to assess the relationship between a dependent and independent continuous variable (Bland, 2015). Binary linear regression is used for a dichotomous dependent variable, while ordinal regression is used for ordinal dependent variables (Bland, 2015). Multiple linear regression can be used if there are more than one independent variables that demonstrate a significant relationship with the dependent variable. Regression analysis requires certain assumptions to be true. The assumptions underlying regression include: (i) continuous dependent variable, (ii) continuous independent variable, (iii) there

is a linear relationship between the two variables, (iv) there is independence of observations, (v) there is homoscedasticity, (vi) there are no significant outliers and (vii) the residuals (errors) of the regression line are approximately normally distributed. The goodness of fit for regression models can be assessed using the Hosmer-Lemeshow, values that are significant ($p<0.05$) indicate the model is a poor fit (Statistics, 2013). Correlation analysis assess the strength and direction of a linear relationship between two variables (Bland, 2015). Types of correlation tests include Pearson's correlation (continuous variables), point-biseral correlation (one continuous and one dichotomous variable), and Spearman's correlation (two continuous or ordinal variables).

Evaluation of diagnostic tests is required to effectively identify and omit the presence of a disease or condition within an individual. The receiver operating characteristic (ROC) curve is a graphical plot that illustrates the performance of medical diagnostic tests of discriminating between two patient states. The ROC curve plots the sensitivity of the test against 1-specificity (Hajian-Tilaki, 2013). The area under the curve (AUC) is used to evaluate the diagnostic ability of the medical test. The AUC is used to evaluate the diagnostic ability of the medical test (in terms of sensitivity and specificity) across a range of threshold values. An AUC of 1.0 indicates a test with perfect predictive ability, in contrast an AUC of 0.5 is comparable to chance at identifying high-risk patients. An AUC of <0.7 is regarded as a poor predictive test, 0.7-0.8 is average accuracy and an AUC of >0.8 indicates good accuracy as a diagnostic test (Higgins et al., 2011).

Sample means provide an estimate of the true population mean, however random error suggests the sample mean differs from the true population mean. Confidence intervals provide an estimate of the true population mean and are calculated as mean $\pm$ 1.96 standard error (Guyatt et al., 1995). The standard error is the standard deviation of the sampling mean calculated as σ/n, where n is the sample population. Furthermore, confidence intervals can be used to describe the interval within which the mean change in a variable would lie, and for determining significance. Confidence intervals that cross the integer zero accept the null hypothesis that there is no significant difference in the variable being tested (Bland, 2015). In contrast, confidence intervals that do not contain zero, can be interpreted as significantly different from the null hypothesis. Furthermore, confidence intervals provide an estimate of the size of the treatment effect. Wide confidence intervals are regarded as being less precise, and larger sample sizes can improve confidence interval precision. In comparison, p-values only report if the observed result is significantly different from zero ($p<0.05$).

All efforts were made during outcome measurement to ensure all data as collected, however in this thesis there were some instances of missing data. In Chapter 4, there was missing data due to participants who had dropped out, or were unable to complete all measurements. In Chapter 6, there was missing data due to participants who dropped out from the study, or had their surgery rescheduled and could not complete all scheduled outcome measures. Participants with missing data were excluded from analysis in both studies.

2.2 Section 2. Clinical outcome measures of perioperative risk and postoperative outcome

2.2.1 Preoperative risk

Patients scheduled for surgical intervention should be screened for their level of postoperative risk. A number of clinical outcome measures or scoring systems have been developed to preoperatively predict outcomes after surgical intervention. These outcome measures calculate an individual's level of risk based on their physiologic and operative criteria. These outcome measures are simple, quick to administer and have been developed in surgical populations, however their clinical utility varies (Tiret et al., 1988, Chijiiwa et al., 1996). The most commonly used instruments and those used in this thesis include the American Society of Anaesthesiologists Physical Status (ASA-PS) classification, the Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM), and the Colorectal - Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity (CR-POSSUM).

2.2.1.1 American Society of Anaesthesiologists physical status Classification

The American Society of Anaesthesiologists (ASA) physical status classification is a subjective assessment of a patient's overall health that is based on five classes (Table 2.2).

Table 2.2: The American Society of Anaesthesiologists physical status classification

Grade:	Description:
I	Patient is a completely healthy fit patient
II	Patient has a mild systemic disease
III	Patient has severe systemic disease that is not incapacitating
IV	Patient has severe incapacitating disease that is a constant threat to life

V	A moribund patient who is not expected to live 24 hour with or without surgery
E.	Emergency surgery, E is placed after the grade

The ASA-PS is a simple and widely understood tool used for preoperative screening, however studies examining the ability of the ASA-PS to predict postoperative outcome have reported conflicting results. In non-emergency surgery cases in individuals over 40, the rate of postoperative complications was found to be closely related to the ASA-PS class (ASA-PS score I=0.41/1000; scores IV and V = 9.6/1000) (Tiret et al., 1988). Chiijiwa and colleagues report the ability of the ASA-PS to predict postoperative morbidity and mortality in 69 patients following pancreatoduodenectomy is poor (Chijiiwa et al., 1996). The inter-rater reliability of the ASA-PS was assessed between 160 specialists in Hong Kong and found the percentage of agreement varied greatly between 31 and 85% (Mak et al., 2002). One of the reasons for this inconsistency is the confusion between ASA-PS definitions such as 'systemic disease' (Daabiss, 2011).

The newly developed ASA 7 physical status, approved by the ASA House of Delegates on October 15, 2014, may have superior ability to predict the incidence of postoperative complications in surgical patients, however it has not been formally validated. The current version of the ASA-PS classification is described in

Table 2.3. The modified version of the ASA-PS provides examples for each grade to improve correct patient classification. The ASA-PS is advantageous to assess postoperative risk as it is easy to use, however further research is required to conclude on the ability of the ASA-PS to predict postoperative outcome. In this thesis, the ability of the modified version of the ASA-PS to predict postoperative risk in participants scheduled for colorectal surgery was assessed in Chapter 4 (Table 2.3). The ASA-PS was also used in Chapter 6, in participants scheduled for colorectal surgery participating in the PHIIT trial, however its predictive ability was not examined as it was beyond the aims of the feasibility study.

Table 2.3: The updated American Society of Anaesthesiologists Physical Status Classification

ASA-PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease

ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	
*The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part). BMI: Body Mass Index, CAD: Coronary Artery Disease, COPD: Chronic Pulmonary Disease, CVA: Cerebrovascular Accident, DM: Diabetes Mellitus, ESRD: End Stage Renal Disease, HTN: Hypertension, MI: Myocardial Infarction, TIA: Transient Ischaemic Attack.		

2.2.1.2 POSSUM

The POSSUM is a scoring system used to evaluate surgical outcome based on an individual's physiological and operative parameters. It was developed by Copeland and colleagues and numerous versions have been developed to evaluate outcome following specific surgical procedures (e.g. colorectal surgery) (Copeland et al., 1991). The POSSUM is divided into the physiologic score and the operative severity score. The physiologic score is a 12-factor, four grade score including age, cardiac status, pulse rate, systolic blood pressure, respiratory status, Glasgow Coma Score (GCS), serum concentration of urea, potassium, and sodium, haemoglobin concentration, white blood cell count and electrocardiogram (ECG) results. The operative severity score is a six factor, four grade score including type and number of procedures, total blood loss, peritoneal contamination, presence and extent of malignancy and timing of operation.

Studies examining the ability of the POSSUM to predict mortality have reported conflicting results. Originally the POSSUM over predicted death (Prytherch et al., 1998), and in an effort to correct this flaw the POSSUM equation was modified to the Portsmouth POSSUM (P-POSSUM). In this thesis the P-POSSUM was used to calculate the level of risk of participant's scheduled for thoracic surgery in the

PHIIT trial (Chapter 6). The P-POSSUM parameters are listed in Table 2.4. The results are placed in descending order of increasing risk.

Table 2.4: P-POSSUM Risk Calculator: descending values indicate increasing risk of mortality.

Physiological Parameters	Result
Age	<61 years old 61-70 years old >70 years old
Cardiac	No cardiac failure Diuretic, digoxin, treatment for angina or hypertension Peripheral oedema, warfarin, borderline cardiomyopathy Raised JVP, cardiomegaly
Respiratory	No dyspnoea Dyspnoea on exertion, mild COPD Limiting dyspnoea, moderate COPD Dyspnoea at rest, pulmonary fibrosis/consolidation on x-ray
ECG	ECG normal ECG = AF, rate 60-90 ECG = any other abnormal rhythm, >4/min ectopics, Q waves, ST/T changes
Systolic BP	110-130 mmHG 100-109 or 131-170 mmHG >170 or 90-99 mmHG <90 mmHG
Pulse Rate	50-80 bpm 40-49 or 81-100 bpm 101-120 bpm <40 or >120 bpm
Haemoglobin	13-16 g/dl 11.5 -12.9 or 16.1-17 g/dl 10.0-11.4 or 17.1-18 g/dl <10 or >18 g/dl
White Blood Cell Count	4-10 10.1-20 or 3.1-4 >20 or <3
Urea	<7.6 7.6-10 10.1-15 >15
Sodium	>135 mmol/l

	131-135 mmol/l 126-130 mmol/l <126 mmol/l
Potassium	3.5– 5mmol/l 3.2-3.4 or 5.1-5.3 mmol/l 2.9-3.1 or 5.4-5.9 mmol/l <2.9 or >5.9 mmol/l
Glasgow Coma Scale	15 12-14 9-11 <9
COPD; Chronic Obstructive Pulmonary Disease, JVP; Jugular Venous Pressure	

Operative Parameters	Result
Operation Type	Minor Operation Intermediate Operation Major Operation Complex Major Operation
Number of procedures	1 2 >2
Operative Blood Loss	<100 mls 101-500s 501-999s >1000 mls
Peritoneal Contamination	No soiling Minor soiling Local pus Free bowel content, pus or blood
Malignancy Status	Not malignant Primary malignancy only Malignancy and nodal metastasis Malignancy and distant metastasis
CEPOD	Elective Urgent Emergency (within 2 hours)
CEPOD; Daytime Efficacy of Emergency The P-POSSUM predicts postoperative morbidity and mortality based on operative and physiological variables, with descending values indicating an increased risk of mortality.	

2.2.1.3 CR-POSSUM Score

The Colorectal-Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity (CR-POSSUM), which is based on the original POSSUM score, was developed using data from 15 centres based on results from colorectal surgical operations and is outlined in Table 2.5.

Studies reporting the ability of the CR-POSSUM and P-POSSUM to predict postoperative outcome have reported conflicting results. The CR-POSSUM can identify patients undergoing enhanced recovery after surgery (ERAS) at risk of prolonged hospital LOS following colorectal surgery (Renz et al., 2015). In addition, the ability of the CR-POSSUM to predict morbidity and mortality was compared to the P-POSSUM in a single centre study of 204 patients post major colorectal cancer (Gomes et al., 2015). Although the CR-POSSUM was reported to be the best predictor of surgical mortality, the ROC curve analysis reported that the sensitivity of both risk calculators was <60% (CR-POSSUM: Sensitivity 52.9% and Specificity 70.5%, P-POSSUM: Sensitivity 58.8% and Specificity 71.9%). In contrast, a systematic review of 17 studies (6,576 patients scheduled for colorectal surgery) reported the P-POSSUM was better at predicting postoperative mortality with the weighted observed to expected ratio for mortality for the P-POSSUM was 0.90 compared to the CR-POSSUM (Richards et al., 2010). Further research is required to conclude on the ability of the CR-POSSUM and P-POSSUM to predict postoperative outcome.

In this thesis, the ability of the CR-POSSUM to predict postoperative risk in participants scheduled for colorectal surgery was assessed in Chapter 4. In addition, the CR-POSSUM also used in Chapter 6, in participants scheduled for colorectal or thoracic surgery participating in the PHIIT trial, however its predictive ability was not examined as it was beyond the aims of the feasibility study.

Table 2.5: CR-POSSUM risk score calculator: descending values indicates an increasing risk of mortality.

Physiological Parameters	Result
Age	<61 years old 61-70 years old 71-80 years old >80 years old
Cardiac	No/Mild cardiac failure Moderate cardiac failure Severe Cardiac Failure
Systolic BP	100-170 mmHG >171 or 90-99 mmHg <89 mmHg

Pulse Rate	40-100bpm 101-120 m >121 or <39 bpm
Haemoglobin	13-16 g/dl 10.0-12.9 or 16.1-18 g/dl <9.9 or >18.1 g/dl
Urea	<10 10.1-15 >15

Operative Parameters	Result
Operation Type	Minor Operation Intermediate Operation Major Operation Complex Major Operation
Peritoneal Contamination	None or serious fluid Local pus Free bowel content, pus or blood
Malignancy Status	No cancer/Dukes A/B Dukes C Dukes D
CEPOD	Elective Urgent Emergency (within 2 hours)
CEPOD; Daytime Efficacy of Emergency. The CR-POSSUM predicts postoperative morbidity and mortality based on operative and physiological variables, with descending values indicating an increased risk of mortality.	

2.2.2 Postoperative outcome

Mortality was traditionally the main focus of surgical outcome, however due to the subsequent reduction in mortality rates with improved surgical techniques, the use of laparoscopic procedures, and improved patient care, mortality is a poor discriminator of both the quality of care between institutions and the effectiveness of interventions (Slankamenac et al., 2013, Davies et al., 2013). Therefore morbidity, which is a more frequent occurrence post-surgery than mortality, is more commonly examined to evaluate postoperative outcome. Morbidity rates vary depending on surgical procedure and significantly impact the patient's recovery, quality of life, and hospital costs (Zoucas and Lydrup, 2014).

Postoperative complications are subject to inconsistent definitions, and so rates of complications vary between studies and institutions (Feeney et al., 2010). In addition, about 80% of studies describing complications fail to report the severity of postoperative complications. The underreporting of postoperative complications due to a lack of a standardized methodology is recognised as a global hindrance to surgical research (Slankamenac et al., 2013).

To combat these issues, there are a number of objective morbidity measures including the Postoperative Morbidity Survey (POMS), the Clavien-Dindo classification score, and the recently developed Comprehensive Classifications Index (CCI). The use of objective morbidity measures reduces inconsistencies in the definition of postoperative complication definitions and allows for comparison between studies (Feeney et al., 2010). The following sections will describe these measures of postoperative morbidity.

2.2.2.1 Postoperative morbidity survey

The postoperative morbidity survey (POMS) is a nine-domain tool that prospectively describes and records in-hospital postoperative complications following major surgery (Bennett-Guerrero et al., 1999). It is recommended the POMS is performed on specific days during the postoperative period (e.g. postoperative day 3, day 5 and day 7). The POMS provides defined criteria for complications in nine categories classified by organ system including pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound and pain. The POMS definitions of complications is provided in Table 2.6.

Table 2.6: Postoperative Morbidity Survey

Morbidity Type	Criteria	Source of data
Pulmonary	Has the patient developed a new requirement for oxygen or respiratory support	Patient Observation Treatment Chart
Infectious	Currently on antibiotics and/or has had a temperature of >38°C in the last 24 hr	Treatment Chart Observation Chart
Renal	Presence of oliguria <500mL/24hr; increased serum creatinine (>30% from preoperative level); urinary catheter in situ.	Fluid Balance Chart Biochemistry Result Patient Observation
Gastrointestinal	Unable to tolerate an enteral diet for any reason including nausea, vomiting and abdominal distension (use of antiemetic).	Patient Questioning Fluid Balance Chart Treatment Chart

Cardiovascular	Diagnostic tests or therapy within the last 24 hr for any of the following: new myocardial infarction or ischemia, hypotension (requiring fluid therapy >200mL/hr or pharmacological therapy), atrial or ventricular arrhythmias, cardiogenic pulmonary edema, thrombotic event (requiring anticoagulation).	Treatment Chart Note Review
Neurological	New focal neurological deficit, confusion, delirium or coma	Note Review Patient Questioning
Haematological	Requirement for any of the following within the last 24 hr: packed erythrocytes, platelets, fresh-frozen plasma or cryoprecipitate	Treatment Chart Fluid Balance Chart
Wound	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms	Note Review Pathology Result
Pain	New postoperative pain significant enough to require parenteral opioids or regional analgesia	Treatment Chart Patient Questioning
If a patient presents with any of the above criteria on a specific day postoperatively (e.g. day 5) then the type of complication is recorded. Patients can have more than one complication.		

A number of studies have demonstrated the POMS has good inter-rater reliability (97.7% agreement between observers) (Davies et al., 2013), and is accurate in the assessment of postoperative complications (Grocott et al., 2007). The POMS is also associated with LOS (Grocott et al., 2007, Snowden et al., 2010, West et al., 2014b), and complications on postoperative day 5 are associated with an eight fold increase in patients having a prolonged LOS (Davies et al., 2013).

There are limitations to using the POMS, the most significant limitation is that severity of postoperative complication is not quantified (Davies et al., 2013). Furthermore, the POMS provides criteria for recording complications, however many of these therapies are considered routine (e.g. oxygen therapy) (Davies et al., 2013).

2.2.2.2 Clavien-Dindo classification score

The Clavien-Dindo classification score, addresses one of the main limitation of the POMS, and measures the most severe complication in the postoperative period. The Clavien-Dindo score is a modified version of recording postoperative complications proposed by Clavien et al. (1992) (Clavien

et al., 1992). The ordinal scale is divided into seven grades (Grade I-V) with 2 subgroups for grade 3 and 4, and grade 5 represents patient mortality (Table 2.7).

Table 2.7: The Clavien-Dindo Classification Score

Grades:	Definition:
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drug as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and total parental nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention
III-A	Intervention not under general anaesthesia
III-B	Intervention under general anaesthesia
IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management
IV-A	Single organ dysfunction (including dialysis)
IV-B	Multi-organ dysfunction
V	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge, the suffix "d" (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication
The Clavien-Dindo measures the single most severe complication during the postoperative period using the above criteria.	

The Clavien-Dindo score is a simple and convenient tool for measuring postoperative complications. This particular tool is used worldwide and has reportedly been validated in hundreds of studies across a wide variety of surgeries (Clavien et al., 2009, Permpongkosol et al., 2007, Haynes et al., 2009, Slankamenac et al., 2013). A number of studies use the Clavien-Dindo classification score due to its simplicity and reproducibility, its correlation with LOS, and the degrees of severity of complications also correlate with the perceptions of severity of medical staff and patients (Dindo et al., 2004, Clavien et al., 2009).

A limitation of the Clavien-Dindo is that the entire postoperative course is summed up in the single most severe complication. It has been argued that patients who experience a number of smaller grade complications (e.g. four grade 2 complications) in the postoperative period may have a worse postoperative recovery compared to a patient with a single grade 3 complication, however according

to the Clavien-Dindo score the patient with a grade 3 complication had a worse recovery (Slankamenac et al., 2013).

2.2.2.3 Comprehensive Complications Index

In an attempt to better summarise the overall morbidity, including the type, number and severity of each complication experienced during the postoperative period, Slankamenac and colleagues developed the Comprehensive Complications Index (CCI) (Slankamenac et al., 2013). During the development of the CCI, 227 patients and 245 doctors rated the severity of 30 individual complications via a questionnaire, using a numerical analogue scale from 0 (no complication or best outcome), and 100 (worst complication).

The validity of the CCI was compared to the Clavien-Dindo score and it was reported that the CCI discriminates between patients with a different number and severity of complications better than the Clavien-Dindo (Slankamenac et al., 2013). This study reported that due to the high discriminatory ability of the CCI, future studies may be able to more easily detect clinically relevant differences in complication incidence, this could potentially reduce the large amount of studies reporting 'negative results'. It was also recommended to use both the CCI and Clavien-Dindo together because both scoring systems are closely related, and the CCI can be easily calculated based on the Clavien-Dindo defined complications (www.assesssurgery.com). The CCI grading criteria is outlined in Table 2.8.

Table 2.8: The Comprehensive Classifications Index Scoring Criteria. N/a=Not applicable

Grades:	Definition:	CCI Score
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drug as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	**8.7**
II	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and total parental nutrition are also included.	**20.9**
III	Requiring surgical, endoscopic or radiological intervention	**N/a**
III-A	Intervention not under general anaesthesia	**26.2**
III-B	Intervention under general anaesthesia	**33.7**
IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management	**N/a**

IV-A	Single organ dysfunction (including dialysis)	**42.4**
IV-B	Multi-organ dysfunction	**46.2**
V	Death of a patient	**100**
The CCI measures the number and severity of each complication experienced during the postoperative period using the Clavien-Dindo criteria. An overall score is calculated at www.assesssurgery.com		

2.3 Section 3. Physical fitness

Physical fitness is "the ability to perform occupational, recreational and daily activities without becoming unduly fatigued" (Heyward and Gibson, 2014). It is an overall term encompassing cardiopulmonary fitness, musculoskeletal fitness, body weight and composition, flexibility and balance. For the purpose of this thesis, the following measures of physical fitness were primarily dealt with: cardiopulmonary fitness, musculoskeletal fitness, and body weight and composition.

2.3.1 Cardiopulmonary fitness

Cardiopulmonary fitness is defined as "the ability of the heart, lungs and circulatory system to supply oxygen and nutrients efficiently to working muscles" (Heyward and Gibson, 2014). Cardiopulmonary fitness can be measured in the laboratory or in field setting, depending on the demographic of the patient being tested, the available equipment and skills of the tester. There are two main methods of assessing cardiopulmonary fitness; cardiopulmonary exercise testing (CPET) and field tests of exercise tolerance.

2.3.1.1 Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing is a non-invasive, dynamic assessment of the cardiovascular, pulmonary, haemotopoetic, neuropsychologic and skeletal muscle systems at rest and under stress. Cardiopulmonary exercise testing is the gold standard method of measuring an individual's aerobic capacity and involves the measurement of respiratory gas exchange: oxygen uptake (VO_2), carbon dioxide output (VCO_2) and minute ventilation (VE). CPET may also involve measurement of blood pressure, pulse oximetry, electrocardiograph and blood lactate. CPET is a safe procedure with the risk of mortality between 2 and 5 patients per 100,000 CPET's (ATS/ACCP, 2003). Cardiopulmonary fitness can be evaluated by either maximal or sub-maximal CPET. The definitions of a number of CPET variables used throughout this thesis are presented in Table 2.9.

This section will provide an outline of the types of CPET performed (e.g. maximal and sub-maximal CPET), the equipment used during CPET (e.g. treadmill and cycle ergometer) and CPET protocols used in the observational study in Chapter 4 and the feasibility study in Chapter 6.

Table 2.9: Cardiopulmonary Exercise Test Variables and Definitions (Wasserman et al., 2005)

CPET Variable	Definition
Anaerobic threshold (AT)	The exercise VO_2 above which anaerobic high-energy phosphate production supplements aerobic high-energy phosphate production, with consequential lowering of the cellular redox state, increase in lactate/pyruvate (L/P) ratio, and net increase in lactate production at the site of anaerobiosis. Exercise above the AT is reflected in the muscle effluent and central blood by an increase in lactate concentration, L/P ratio and metabolic acidosis.
Maximal oxygen uptake (VO_2 max)	Describes the VO_2 when it reaches a plateau value during a single maximum work rate test. Repeated measurements are necessary to obtain the VO_2 that cannot be exceeded by the subject.
Oxygen pulse (O_2 pulse)	The oxygen uptake divided by the heart rate. Hence, this represents the amount of oxygen extracted by the tissue of the body from the O_2 carried in each stroke volume.
Oxygen uptake (O_2)	The amount of oxygen extracted from the inspired gas in a given period of time (ml or L per minute).
Peak oxygen uptake (VO_2peak)	The highest oxygen uptake achieved during a maximum work rate test.
Ventilatory Equivalents for CO_2 and O_2 (VE/VCO_2 and VE/VO_2)	The ventilatory equivalents for CO_2 and O_2 are measurements of the ventilatory requirement for a given metabolic rate.
Minute ventilation (VE)	The volume of air taken into or exhaled from the body in one minute.

2.3.1.2 Graded exercise test protocols

The goal of CPET is to evaluate the organs and systems involved in the exercise response under a progressively increasing workload (ATS/ACCP, 2003). Exercise testing involves large muscle groups (usually the lower extremities) during running on a treadmill or pedalling on a cycle ergometer. It is advisable to perform a graded exercise test protocol so that a range of exercise intensities can be studied within a short time period (ATS/ACCP, 2003). A variety of treadmill or cycle ergometer protocols are available for both maximal and sub-maximal graded exercise tests. The protocols usually involve an incremental test which terminates when a participant reaches volitional exhaustion (maximal testing), reaches a predetermined requirement such as a percentage of maximum heart rate

(submaximal testing), requests to stop, or experiences any adverse signs or symptoms such as those listed in Table 2.10.

Table 2.10: Indications for stopping exercise (ATS/ACCP, 2003)

Indicators for Stopping Exercise

Absolute indications for Stopping Exercise:
• Suspicion of a myocardial infarction or acute myocardial infarction (heart attack)
• Onset of moderate-to-severe angina (chest pain)
• Drop in systolic blood pressure (SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms
  ○ Hypotensive response resulting in SBP <60mmHg
• Signs of poor perfusion (circulation or blood flow) including pallor (pale appearance to the skin), cyanosis (bluish discoloration) or cold and clammy skin
• Severe or unusual shortness of breath
• CNS (central nervous system symptoms
  ○ Ataxia (failure of muscular coordination)
  ○ Vertigo (an illusion of dizzying movement)
  ○ Visual or gait (pattern of walking or running) problems
  ○ Confusion
• Patient's request to stop
• Irregular pulse
• Extreme fatigue

Relative Indications: • Increasing chest pain • Physical or verbal manifestations of shortness of breath or severe fatigue • Wheezing • Leg cramps or intermittent claudication (grade 3 on a 4-point scale) • Hypertensive response

2.3.1.3 Treadmill tests

Treadmills provide a common form of exercise that can accommodate deconditioned individuals and individuals with higher levels of aerobic capacity (ACSM, 2013). The primary exercise modality for CPET has traditionally been the cycle ergometer, however a treadmill based CPET may also be administered. In addition, it has been reported that treadmills are more suitable for older adults as walking is a more familiar and functional exercise modality than cycling (Huggett et al., 2005).

Treadmill based CPET's create higher VO_2peaks when compared to cycle ergometer, however exercise on a treadmill may not be suitable for individuals with balance deficits or mobility impairing conditions such as arthritis and hemiplegia (Huggett et al., 2005). VO_2max levels average 11% lower (range, 8%-15%) compared to results measured on a cycle ergometer (Hermansen et al., 1970) (Hermansen and Saltin, 1969, Kamon and Pandolf, 1972, McKay and Banister, 1976). The American College of Sports

Medicine (ACSM) recommends that treadmill stages last 3 minutes or longer to ensure a steady state HR response during each stage (ACSM, 2013). The HR values are extrapolated to age-predicted maximal HR to estimate VO_2max.

Chapter 4 used the Modified Bruce Protocol to measure cardiopulmonary fitness. The Modified Bruce Protocol is an adaptation of the original Bruce Protocol (Bruce et al., 1973, Bruce, 1971). The Modified Bruce Protocol is a treadmill based graded exercise protocol. The treadmill protocol initially begins at 2.7 km/hr at an incline of 0%. This starting speed (a walking pace) does not change for the first three stages, however the incline increases at the beginning of a new stage, and each stage lasts 3 minutes. The protocol is outlined in Table 2.11. The Modified Bruce Protocol is comparable to the Bruce Protocol in healthy individuals as it is found to elicit similar physiological responses, particularly in heart rate, at equivalent workloads (Trabulo et al., 1994). This protocol is more suitable for a clinical population due to the more gradual start (ATS/ACCP, 2003).

Table 2.11: Modified Bruce Protocol

Stage	Speed (kmph)	Gradient (%)	Duration (min)
0	2.7	0	3
0.5	2.7	5	3
1	2.7	10	3
2	4.0	12	3
3	5.5	14	3
4	6.8	16	3
5	8	18	3
6	8.9	20	3
7	9.7	22	3

2.3.1.4 Cycle ergometers

Exercise tests may also be performed on a cycle ergometer (ATS/ACCP, 2003). Participants on a cycle ergometer are prone to less movement than a treadmill and allows for more accurate measurement of vitals and produces less artefacts (e.g. ECG and blood pressure cuff). A significant advantage of the cycle ergometer over the treadmill walking is that the cycle ergometer allows for the quantification of the external work rate. In addition, the cycle ergometer is generally less expensive and requires less space than a treadmill.

There are two types of cycle ergometers, differing in the types of brakes. Mechanically braked cycle ergometers regulate external work using adjustable frictional bands, and electronically braked

ergometers increase pedalling resistance electromagnetically. Electromagnetically braked cycle ergometers offer superior precision in controlling work rate settings compared to friction braked ergometers. Mechanical ergometers require the subject to pedal at a fixed cadence to maintain a constant work rate (ATS/ACCP, 2003). Electromagnetically braked ergometers may be computer controlled, allowing for the work rate to be increased incrementally and continuously. An advantage of electromagnetically braked cycle ergometers is that changes in cadence does not influence the work rate performed (ATS/ACCP, 2003).

2.3.1.5 Cycle ergometer protocols

Cycle ergometer protocols can be divided into two main groupings: incremental and ramp protocols. Ramp protocols provide a constant and continuous increase in workload, while the work rate in an incremental protocol can change at regular intervals. A drawback of incremental protocols is the relatively long increment duration (e.g. 3 minutes), making it difficult to assess non-invasive anaerobic threshold (ATS/ACCP, 2003). It is recommended to use an exercise protocol in which work rate increases at a constant rate because the key variables of interest (VE, VCO_2 and VO_2) lag behind changes in work rate (ATS/ACCP, 2003). For the same reason it is best to begin the incremental phase of exercise from a baseline of unloaded pedalling (0 W) rather than rest. A ramp protocol was chosen in Chapter 6 and the ramp gradient was set to 10-25 W/min based on a calculation using predicted unloaded VO_2, predicted VO_2 at peak exercise, height and age (Wasserman et al., 2005). The American Thoracic Society/American College of Chest Physician (ATS/ACCP) recommends a work rate increment of 25-30 W/min may be selected for participants who appear to have high cardiopulmonary fitness, while for deconditioned participants work rate increments as low as 5 W/minute can be selected (ATS/ACCP, 2003). The calculation is shown below in Figure 2.2.

Equation 1: Unloaded VO_2 (ml/min) = 150 + [6 x weight (kg)]

Equation 2: Peak VO_2 (ml/min) = [height (cm) – age (years)] x 20 (sedentary men) [or x 14 (sedentary women)]

Equation 3: Work rate increment (W/min) = [Peak VO_2 (ml/min) – Unloaded VO_2 (ml/min)]/100

Figure 2.2: Work rate increment prediction calculations.

2.3.1.6 Maximal cardiopulmonary exercise test

A maximal CPET, which demands high patient motivation to exercise to volitional exhaustion, measures an individual's maximum oxygen consumption (VO_2max). VO_2max is the maximal amount of oxygen consumed during exercise and reflects the capacity of the heart, lungs and blood to transport oxygen to working muscles during exercise. An individual's VO_2max is characterised by the plateau in oxygen consumption despite the increase in workload during exercise, and is widely considered the gold standard measure of cardiopulmonary fitness.

VO_2max is expressed in absolute or relative terms and absolute terms are expressed in litres per minute (L/min) or millimetres per minute (ml/min). VO_2max is directly related to body size and is more widely expressed in relative terms (ml/kg/min), allowing for ease of comparison between individuals and it can be used to classify an individual's cardiopulmonary fitness level (Heyward, 2010).

Current research suggests that the incidence of plateau in VO_2 during incremental exercise testing is highly variable ranging from 16-94% (Day et al., 2003, Magnan et al., 2013, Mier et al., 2012, Rossiter et al., 2006, Yoon et al., 2007). In the likely event that a VO_2 plateau is not reached, the term VO_2peak is often used. VO_2peak is the highest oxygen consumption attained during a graded exercise test i.e. the highest rate of VO_2 measured during CPET. This is a common measure and is considered a valid index of VO_2max, (Heyward and Gibson, 2014) and is often used in preoperative CPET (Noonan and Dean, 2000, West et al., 2014b, Snowden et al., 2010).

During a maximal CPET, patients should be verbally encouraged to continue to exercise until achieving physiologic limitation, or volitional exhaustion. The CPET may also be terminated if any of the following five criteria are reached:

1. The patient achieves predicted peak oxygen uptake and/or a plateau is observed
2. Predicted maximal work rate is achieved
3. Predicted maximal heart rate is achieved
4. There is evidence of ventilator limitation, that is, peak exercise ventilation approaches or exceeds maximal ventilator capacity
5. Respiratory Exchange Ratio (RER) greater than 1.15

To ensure safe practice, there are a number of acceptable criteria for terminating an exercise test before symptom limitation (Table 2.10).

Measuring VO_{2max} and VO_{2peak} is dependent on a number of factors, as patient motivation and musculoskeletal impairments are likely to impact VO_{2max} and VO_{2peak} (Noonan and Dean, 2000). VO_{2max} and VO_{2peak} are measured directly using expensive gas analysis equipment operated by trained staff. The use of maximal CPET may be restricted in people whose performance is limited due to fatigue or musculoskeletal impairments. In the event that maximal CPET is contraindicated or deemed unsafe, VO_{2max} can be predicted through a sub-maximal graded exercise test. This thesis used a sub-maximal treadmill based CPET in the observational study in Chapter 4 and a maximal cycle ergometer based CPET in the PHIIT trial described in Chapter 6.

2.3.1.7 Sub-maximal cardiopulmonary exercise test

Sub-maximal CPETs can be performed using either single stage or multistage protocols. Sub-maximal exercise testing provides a less accurate assessment of VO_{2max} compared to maximal exercise testing. However, submaximal graded exercise tests can be used to predict VO_{2max} when maximal exercise testing is contraindicated. Sub-maximal CPETs can be used for individuals who are deconditioned or are physically limited by pain or fatigue, and is a valid and reliable method of predicting cardiorespiratory fitness without reaching volitional exhaustion (Noonan and Dean, 2000).

Sub-maximal tests rely on a number of equations to predict VO_{2max}, such as a linear relationship between HR and oxygen uptake (Marsh, 2012). This requires a number of assumptions, for example, it is assumed that a steady-state HR is achieved for each workload and that there is a constant linear relationship between HR and VO_2. VO_{2max} is predicted by linear extrapolation of the slope of the submaximal HR and submaximal VO_2 (or work rate) to an estimated maximal heart rate (HR_{max}) (Noonan and Dean, 2000). The linear relationship between HR and VO_2 is maintained at light-to-moderate workloads, however as the workload moves to a vigorous intensity the HR-VO_2 relationship becomes curvilinear (Heyward and Gibson, 2014). In instances when gas analysis is not used, VO_2 can be estimated from work rate; this makes a further assumption that VO_2 for a given work load is identical between individuals. However inter-individual variability at a given work rate does exist, and it is influenced by a number of factors including running economy, gender, age, and body mass (Marsh, 2012). Sub-maximal tests also assume that HR_{max} is similar between individuals of the same age, however there is a significant inter-individual variability ($\pm$10-15%) in predicting VO_{2max} (Marsh, 2012, Heyward and Gibson, 2014). Heart rate was measured during CPET using the Polar T31 coded heart rate monitor, and BORG rating of perceived exertion (RPE) scores were recorded at three minute intervals. Sub-maximal CPET was used in Chapter 4 using the Modified Bruce Protocol.

The American College of Sports Medicine's (ACSM) metabolic equations were used to estimate VO_2max, presented below (ACSM, 2013). HR_{max} is estimated using equation 1, and VO_2max can be predicted by using equation 2 and 3 in Figure 2.3. The ratio of the difference between the VO_2 recorded during the final two completed stages and the corresponding change in HR was used to calculate the slope (*b*). The slope was then used to predict VO_2max by extrapolating the VO_2:HR values from the final completed stage to the estimated HR_{max} (Equation 3).

Equation 1: HR_{max} = 220-age

Equation 2: *b* = (VO_2 last stage – VO_2 penultimate stage) / (HR last stage – HR penultimate stage)

Equation 3: VO_2max = VO_2 last stage + *b*(HR_{max} - HR last stage)

Figure 2.3: Prediction equations for calculating maximal heart rate and maximal oxygen consumption

2.3.1.8 Anaerobic threshold

Both maximal and sub-maximal CPET can measure anaerobic threshold (AT), an important component in predicting postoperative outcome. AT is defined as an intensity of exercise above which measurement of oxygen uptake cannot account for all the required energy (Svedahl and MacIntosh, 2003). AT is an overall term encompassing the lactate threshold (substantial increase in blood lactate during exercise) and ventilatory threshold (increase in ventilation becomes disproportional to the increase in power output during exercise) and AT is used to reference both lactate threshold (LT) and ventilatory threshold (VT) (Svedahl and MacIntosh, 2003).

Anaerobic threshold can be measured using either invasive or non-invasive methods. The former consists of determining AT through measurement of lactic acid and standard bicarbonate through assessment of blood. Non-invasive methods of determining AT include ventilator equivalents method, V-slope method, and the modified V-slop method determined by the change in slope of the relationship of VCO_2 to VO_2 (ATS/ACCP, 2003).

2.3.1.8.1 Lactic acid

Lactic acid is measured in plasma, whole blood, or lysed blood (Zeballos and Weisman, 1994, Wasserman et al., 1986) and blood samples can be obtained from arterial, capillary, or arterialised venous blood (Robergs et al., 1990, Davis et al., 1983, Simon et al., 1986, McLoughlin et al., 1992). To determine AT, blood samples should be taken intermittently thorough the exercise test, with at least five data points' available (including resting value). AT is determined by plotting arterial lactate concentration against VO_2.

In this thesis, in the feasibility study described in Chapter 6, lactic acid was assessed via a pin prick blood sample collected on the Lactate Pro Portable Blood Lactate Analyser (KDK). The Lactate Pro was compared to three other lactate analysers: the ABL 700 Series Acid-Base analyser (n=172 cases), the Accusport Lactate Meter (n=118 cases), and the YSI 2300 Stat lactate analyser (n=22 cases) (Pyne et al., 2000). Versatility was assessed in elite athletes in the field and the level of agreement was determined over the range of 1-18mM. The correlations between the Lactate Pro and the ABL 700 series Acid-Base analyser, YSI 2300 and Accusport were r=0.98, r=0.99, r=0.97, respectively.

Participants performed a resting ECG prior to maximal exercise testing in supine lying. While resting a blood sample was taken from the index or middle finger of the participants hand using the Bayer microlet lancets, the sample was collected onto a Lactate Pro Reagent strip and placed in the Lactate Pro Analyser. A sixty second analysis time is required prior to obtaining the result. The resting lactate value was recorded and during exercise a lactate result was taken at three minute intervals (allowing for 60 seconds to calculate lactic acid concentration and time to prepare for next lactate sample).

2.3.1.8.2 Ventilatory threshold analysis

This particular method involves the simultaneous analysis of ventilatory equivalents for O_2 (VE/VO_2), and CO_2 (VE/VCO_2) and end-tidal partial pressure of oxygen ($PETO_2$) and carbon dioxide ($PETCO_2$). The AT is defined as the moment when all of the following events occur simultaneously: the VO_2 at which VE/VO_2 and $PETO_2$ reach a minimum and thereafter begin to rise consistently, coinciding with an unchanged VE/VCO_2 and $PETCO_2$ (ATS/ACCP, 2003).

AT is determined as the point in which the change in slope of the relationship of VCO_2 to VO_2 occurs (ATS/ACCP, 2003). VCO_2 increase as a relatively linear function of VO_2 early in an incremental protocol and this slope is termed S1. As exercise intensity increases, there is a subsequent increase in the slope, referred to as S2. To confirm that this change of slope is not occasioned by hyperventilation,

monitoring ventilatory equivalent and end-tidal PCO_2 is necessary. Consequently, the ventilatory equivalents for O_2 and end-tidal O_2 reach their nadir and begin to rise in concert with the S1-S2 transition, without an increase in the ventilator equivalent for CO_2 and/or decrease in end-tidal PCO_2. The V-slope method is complex and has been replaced in most conventional systems by a simplified approach. The modified V-slope method, in turn, determines the point of the change in slope of the relationship of VO_2 above which VCO_2 increases faster than VO_2 without hyperinflation (ATS/ACCP, 2003).

The accuracy of AT determined by non-invasive methods reported in the literature appears to be related to the investigator's experience, the protocol used, the system utilised for the collection of data, the subjects studied, and the peculiarities and variances of the methods used (Matsumura et al., 1983, Patessio et al., 1993, Caiozzo et al., 1982, Gladden et al., 1985, Yeh et al., 1983). In this thesis, in the studies described in Chapter 4 and 6, anaerobic threshold was determined by an experienced assessor using the COSMED ergospirometry software using the modified V-slope method (Figure 2.4).

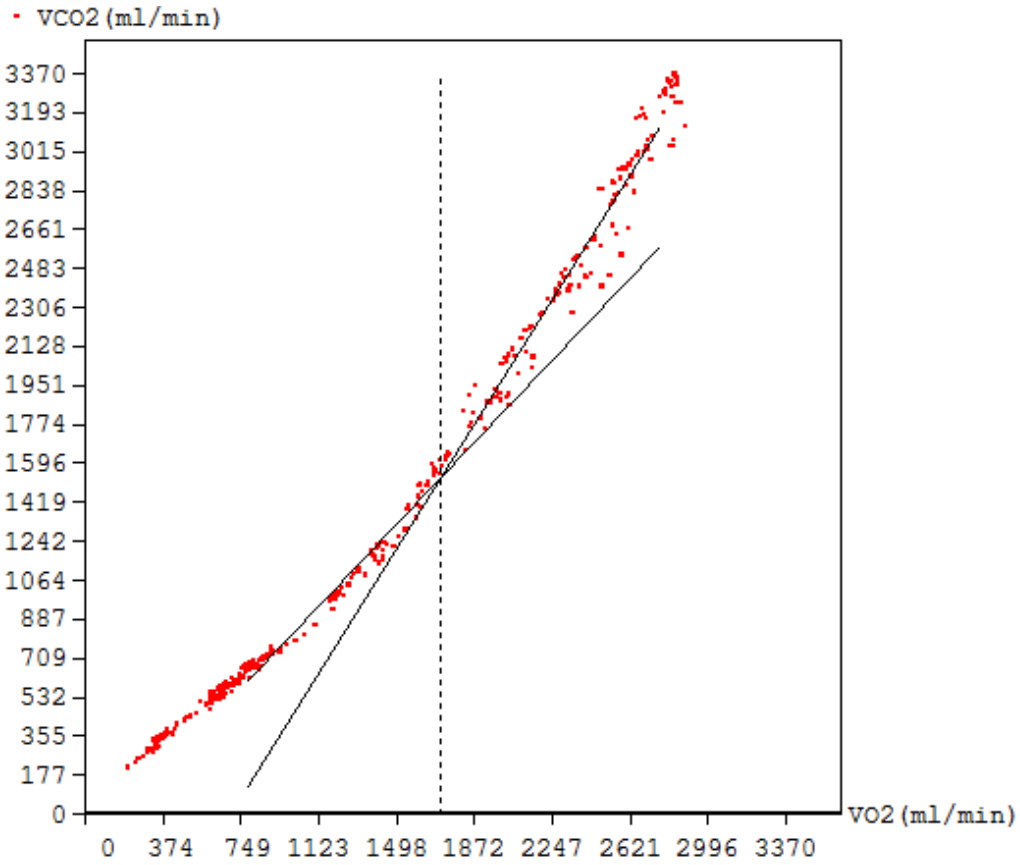


Figure 2.4: Modified V-slope graph as produced using the COSMED ergospirometry software. The ventilatory threshold is indicated by the change in slope of the relationship of VCO_2 to VO_2.

2.3.1.9 Breath-by-breath analysis

Oxygen uptake (VO_2) and carbon dioxide output (VCO_2) both represent the difference between the volume of gas (O_2 and CO_2, respectively) inhaled and the volume exhaled per unit of time. VO_2 and VCO_2 are equal to the rate of metabolic O_2 consumption and CO_2 creation under steady state conditions (ATS/ACCP, 2003). VCO_2 and VO_2 can be recorded on a breath-by-breath basis thanks to digital computer analysis of physiologic measurements (Beaver et al., 1973). As the breath-by-breath method is convenient and flexible, it has become attractive and widely utilised, however, there is potential for error. These metabolic indicators are calculated based on the combined measurement errors of determined values and so great care must be taken with the calibration of sensors as these errors can accumulate. Although breath-by-breath collection and analysis can be used for CPET purposes, it is recommended that this method be compared to the Douglas bag method (ATS/ACCP, 2003).

The Douglas bag method is considered the gold standard for determining VO_2 and VCO_2. The COSMED $K4b^2$ has been compared to the Douglas bag method at a range of exercise intensities between rest and 250 watts. The $K4b^2$ values were significantly higher than the DB at 50 w, 100 w, 150 w and 200 w, however the magnitude of these differences was small (0.088, 0.092, 0.096, and 0.088 L/min, respectively) and only reached statistical significance due to extremely small standard errors. In conclusion, the $K4b^2$ portable ergospirometry system is acceptable for measuring VO_2 across a wide range of exercise intensities (McLaughlin et al., 2001) and was used in the studies described in Chapter 4 and 6 to measure cardiorespiratory fitness.

2.3.1.10 CPET Testing protocols

Maximal cardiopulmonary exercise testing was performed in the feasibility study in Chapter 6. Maximal CPET was used to assess changes in VO_{2peak}, as it is considered a more important measure in participants scheduled for thoracic surgery. In comparison, a sub-maximal CPET was used in the observational study in Chapter 4. Sub-maximal CPET has not been effectively studied in a colorectal surgery population and is easier to perform. Therefore, sub-maximal CPET may have higher clinical utility in preoperative risk assessment for a colorectal surgery population, however it provides only an estimate of VO_{2peak} and its role is limited in a thoracic surgery population. The protocols for maximal CPET and sub-maximal CPET are outlined separately below, however resting blood pressure assessment and the COSMED set-up are common to both protocols.

2.3.1.10.1 Resting blood pressure

Resting blood pressure (BP) measurement is an essential component of pre-exercise test assessment. Blood pressure represents the force or pressure exerted by the blood against the arterial walls during

a cardiac cycle (ACSM, 2013). Two phases of blood pressure are assessed: systolic blood pressure (SBP) measures the maximum pressure in the arteries upon contraction of the heart, the second phase of blood pressure represents the diastolic blood pressure (DBP), this is the minimum pressure in the arteries during the relaxation phase of the heart. Arterial blood pressure is represented as systolic blood pressure over diastolic blood pressure, measured in millimetres of mercury (mmHg). Measuring an individual's blood pressure through intra-arterial pressure using a catheter is considered the gold standard method, however this is considered unnecessary in asymptomatic individuals (ACSM, 2010).

Blood pressure can be measured in the clinical setting through auscultation and oscillometric methods. The auscultatory method uses either an aneroid or mercury sphygmomanometer that has been calibrated previously. An inflatable cuff is placed on the right or left arm, above the elbow. The pressure is increased to occlude the brachial artery. As the pressure is released from the cuff, the assessor listens through a stethoscope placed over the brachial artery at the cubital fossa for Korotkoff sounds. Korotkoff sounds are described as the audible sounds produced by turbulent blood flow when taking non-invasive blood pressure.

Electronic devices using the oscillatory method for blood pressure have been developed (Alpert et al., 2014). The speed and simplicity of these devices has made their use in clinical practice widespread. A cuff is inflated to a target pressure, and systematically decreased using a valve. Small oscillations of intra-cuff pressure, which are caused by heartbeat-induced pulse volume changes, are sensed by the cuff and measured by a pressure transducer. A proprietary algorithm then calculates values for SBP and DBP. The Welch Allyn, Connex Clinical Surveillance System was used to measure resting BP in the experimental studies in this thesis.

Individuals were required to sit quietly for at least five minutes in a chair with back support with their feet placed firmly on the floor and their arm supported at heart level using a table (ACSM, 2013). The cuff was wrapped firmly around the upper left arm unless contraindicated (e.g. bloods taken from left arm). The cuff was aligned with the brachial artery and placed 1-2 cm above the elbow. The assessor pressed start on the monitor to inflate the cuff and begin the blood pressure measurement. An automatic pressure release valve controlled deflation of the cuff, and systolic and diastolic BP were reported in mmHG. In the study described in Chapter 4, blood pressure was recorded three times, twice in sitting and the third time in standing. In the PHIIT trial (Chapter 6), blood pressure was recorded twice (once in sitting and once in standing). When measuring standing blood pressure the arm was relaxed by the participant's side.

2.3.1.10.2 COSMED set-up

During CPET, breath-by-breath analysis was conducted using the COSMED K4b^2 portable ergospirometry system (COSMED, Rome, Italy). Breath-by-breath systems integrate the product of continuously measured flow and gas concentration to obtain expired gas volumes. Calibrations were performed prior to each test session in accordance with manufacturer guidelines. Firstly, a sampling line was connected to the K4b^2 unit and was calibrated against room air and then against reference gases. Secondly, the sampling line was connected to a turbine flowmeter, which was calibrated with a 3-litre calibration syringe. The final calibration was the VO_2/VCO_2 delay, the assessor synchronised their breathing with the K4b^2. An inspection was performed to ensure all values were within the recommended reference ranges.

Participants were sized for a face mask with the top of the mask placed midway on the bridge of the nose and underneath the mandible. The integrity of the seal was checked for air leaks by asking the participant to inhale. The assessor would then place their hand over the turbine hole and ask the participant to exhale sharply. Pressure was held on the face mask for less than one second to see the face mask inflate. The face mask was adjusted if any air escaped through the sides of the mask. The turbine flowmeter was attached to the mask. Participants were fitted with a HR monitor (POLAR, T31 Coded); conducting gel was used to improve contact with the thorax. A participant with the COSMED K4b^2 is presented in Figure 2.5. Participant's gender, date of birth, height and weight were inputted into the K4b^2 computer software. The COSMED K4b^2 software was used to calculate CPET defined variables such as VO_{2peak}, VO_{2max} and AT. Anaerobic threshold was assessed using the modified V-slope method.



Figure 2.5: Participant fitted with portable COSMED K4b^2 used for breath-by-breath analysis of cardiorespiratory fitness.

2.3.1.11 Maximal CPET assessment protocol

This protocol was used in the feasibility study in Chapter 6 when performing maximal CPET in participants scheduled for colorectal and thoracic surgery. A number of additional measurements were performed in conjunction with maximal CPET (ECG, blood pressure and BORG RPE). Participants were required to sit quietly for three minutes to establish baseline ventilatory values. A warm-up was then performed in accordance with the ATS/ACCP guidelines (ATS/ACCP, 2003). Participants performed three minutes of free-wheel pedalling (Figure 2.6). Following the warm-up, the ramp protocol began. The resistance increased depending on the protocol chosen previously based on the equations mentioned in Figure 2.2.

The testing protocol was explained to the participants prior to test initiation. Breath-by-breath gas analysis, HR and heart rhythm were recorded during exercise. Participants were asked to rate their effort using the Borg Rate of Perceived Exertion in the final ten seconds of each minute (Appendix I). Blood pressure was manually measured by an experienced assessor at 3 minute intervals. Blood lactate was measured by a separate experienced assessor at three minute intervals at staggered time points to blood pressure assessment. Participants were advised not to talk during the test unless to communicate problems occurred during the test. The test was terminated when participants reached volitional exhaustion, requested to stop, or experienced any of the indicators for stopping exercise in Table 2.10.

A cool down was performed at a resistance of 30 watts for three minutes and participants were monitored for signs of distress (pallor, chest pain, dyspnoea). Participants were transferred to the plinth and asked to rest in supine, and continued to wear the ECG monitor until HR had returned to within 10 bpm of resting levels.

2.3.1.11.1 ECG

Heart rate and rhythm were monitored using 12 lead ECG in accordance with the ATS/ACCP guidelines (ATS/ACCP, 2003). The ATS/ACCP recommend that for optimal detection of myocardial ischaemia and cardiac arrhythmias during exercise that serial 12-lead electrocardiograms should be used during CPET. A key requirement of ECG measurement is that the electrodes and the detection electronics be specially designed for movement artefact rejection. The COSMED Quark T12x wireless ECG machine was used during maximal exercise testing. This wireless ECG machine allows for resting and exercise ECG measurement and interpretation and provides real time displays of ECG data. In Chapter 6, ECG was performed during maximal CPET. Participants lay in supine on a plinth while the assessor placed the ECG electrodes on the bare chest. Participants were asked to rest for 10 minutes to establish baseline ECG heart rate and rhythm. An experienced medical doctor checked ECG recordings for irregularities or artefacts.

2.3.1.11.2 Non-invasive blood pressure

Auscultation of blood pressure is difficult during exercise because of the increase in ambient noise and movement artefacts, nevertheless blood pressure was assessed manually at three minute intervals by an experienced assessor during maximal CPET (Myers et al., 2009). Manual blood pressure was performed as it is inexpensive, easy to use and the recommended method (Myers et al., 2009, Sharman and LaGerche, 2015). Participant's blood pressure was measured in sitting (posture of exercise), the cuff was measured using manufacturer recommendations, and placed on the bare arm 2-3 cm above the point of brachial artery auscultation. The diaphragm of the stethoscope was placed on the brachial artery for better coverage (the bell was used if superior sound production was required). The arm was kept at the level of the heart and measured every 3 minutes during exercise. Immediately post-exercise BP was measured in supine position until BP returned to within 10% of resting values.

Blood pressure was monitored for the incidence of hypertension, or less commonly, hypotension. In the event blood pressure reached >250 mmHg systolic or >120 mmHG diastolic then the test was stopped. If there was a drop in systolic pressure >20 mmHG from the highest value during the test, then the test was stopped and the patient was monitored until vitals returned to within 10% of resting values.

2.3.1.11.3 BORG Score

Levels of perceived exertion were monitored using the Category Ratio (CR-10) BORG Rating of Perceived Exertion (RPE) Scale. The BORG scale is a psychophysiological, quantitative measure of perceived exertion. The CR-10 scale incorporates nonlinear spacing of verbal descriptors of severity corresponding to specific numbers. Each participant was given clear and concise instructions for rating dyspnoea using the CR-10 BORG scale during exercise testing (Appendix I). In both Chapter 4 and 6, the BORG RPE scale was administered pre and post-CPET and every minute during CPET assessment.

It is possible to use a visual analog scale to rate dyspnoea during exercise testing, however there are several theoretical advantages of the CR-10 scale. As the CR-10 scale is open ended, patients' can select a number greater than 10 on the CR-10 scale. The use of descriptors (e.g. moderate) allows for direct comparisons between individuals and is easier to prescribe exercises at an intensity marked on the CR-10 scale rather than the VAS (ATS/ACCP, 2003).



Figure 2.6: Participant preparing for maximal CPET on cycle ergometer with COSMED K4b^2 and COSMED Quark T12x wireless ECG attached.

2.3.1.12 Sub-maximal CPET assessment protocol

Sub-maximal CPET was performed in the observational study in Chapter 4. Participants were offered a familiarisation period of up to 5 minutes with the treadmill. The speed of the treadmill was set to 2.7 kmph at a grade of 0% (equivalent to the first stage of the Modified Bruce Protocol). Following the optional familiarisation period, participants performed a 3 minute warm-up also equivalent to the first

stage of the Modified Bruce Protocol (Figure 2.7). The pre-programmed Modified Bruce Protocol was selected on the treadmill (Viasys LE 100CE, H/P Cosmos sports & medical gmbh, Nussdorf-Traunstein, Germany).

The testing protocol was explained to the participants prior to starting the test. Blood pressure and SpO_2 were measured at rest. The speed and grade increased as previously outlined in Table 2.11. Breath-by-breath gas analysis and HR were recorded during exercise. Participants were asked to rate their effort using the Borg RPE scale in the final ten seconds of each 3 minute stage (Appendix I). Participants were advised not to talk during the test unless to communicate problems that occurred during the test. Participants were advised not to hold on to the hand rail during the CPET to ensure accuracy of the metabolic work (ATS/ACCP, 2003). The test was terminated when 85% of age-predicted HR_{max} was attained, or if the participant requested to stop due to physical problems such as dyspnoea, pain, fatigue or dizziness. A cool-down was performed at a self-selected speed on the treadmill upon completion of the test. Participants were monitored for signs of distress (pallor, chest pain, dyspnoea) and continued to wear the HR monitor until HR had returned to within 10 bpm of resting levels.



Figure 2.7: Participant preparing for sub-maximal CPET on treadmill with COSMED K4b^2

2.3.1.13 Setting for CPETs

All cardiopulmonary exercise tests were performed in the Clinical Research Facility (CRF) in St James's Hospital. A medical doctor was on call for sub-maximal testing sessions and on site for maximal testing

sessions. In the event that the patient felt unwell or ill the medical doctor assessed and treated the patient. The exercise physiology room in the CRF, where all sessions were performed, has emergency call buttons and pulleys to contact staff.

The CRF has trained personnel and crash cart facilities in case of emergency e.g. myocardial infarction or ventricular tachycardia. Services and equipment provided in the CRF include full time on site nurse, oxygen and suction equipment, pocket face mask in each room, resuscitation trolley including defibrillator, anaphylaxis kit, first aid kit, basic drug list, glucometer and ECG machine. The CRF is part of the St. James's Hospital corridor and has access to the crash team in case of cardiac arrest. In the event of a major adverse event the CRF emergency services can be contacted by pulling the emergency cord. In the event of a cardiac arrest the crash team on site can be contacted. Sessions were performed during CRF opening hours only.

2.3.2 Field tests

Field tests of exercise tolerance provide an objective evaluation of an individual's functional exercise capacity. Field tests are practical, cheap and easy to administer. CPET requires specialised equipment, increased safety precautions and extra staff which limit wide clinical application (Balady et al., 2010, Oliver et al., 2015), consequently, field tests are often employed in the clinical setting as they do not require previous training by the clinician and require little equipment. Examples of field exercise tests include the 20 metre shuttle test, (Leger and Lambert, 1982) self-paced walking test, (Bassey et al., 1976) bag and carry test, (Posner et al., 1995) and the 12 minute walk test (McGavin et al., 1976). The field tests discussed in this thesis were the SCT, ISWT and the six minute walk test (6MWT).

2.3.2.1 Six Minute Walk Test (6MWT)

The 6MWT was adapted from the 12 minute walk test (Butland et al., 1982). The self-paced 6MWT is a sub-maximal assessment of exercise tolerance. The test does not require any exercise equipment or previous experience for clinicians (ATS, 2002). Patients are required to walk and cover as much distance as possible over a flat, hard surfaced 30-metre stretch of corridor in six minutes. The 6MWT is a dynamic, non-invasive method of assessing the cardiopulmonary system, neuromuscular units and muscle metabolism. Compared to CPET, the 6MWT does not provide an in-depth assessment of the cardiorespiratory system under stress. The 6MWT has been reported to be easy to administer, more

easily tolerated and more reflective of everyday activities compared to other walk tests (Solway et al., 2001). The 6MWT is significantly correlated with VO_{2peak} as measured by CPET in chronic heart failure patients and middle-aged and older adults (Pulz et al., 2008, Sperandio et al., 2015). The 6MWT is a simple method of measuring functional capacity and can be administered in the immediate postoperative setting as a method of measuring functional recovery (Pecorelli et al., 2016).

2.3.2.1.1 Six minute walk test assessment protocol

The 6MWT was used in the observational study described in Chapter 4 of this thesis as a measure of preoperative and postoperative functional capacity. The ATS/ACCP guidelines were followed in the conducting of the 6MWT (ATS, 2002). Participants rested for five minutes in a chair, blood pressure was assessed using the Welch Allyn, Connex Clinical Surveillance System as described in Chapter 2.3.1.10.1. A portable pulse oximeter was placed on the index finger of the preferred hand to measure HR and oxygen saturation levels. Participants were asked to walk as quickly as possible without running or jogging along a 30 metre corridor with cones placed at three metre intervals. When participants reached the end of the 30 metres they were instructed to turn quickly and continue walking, trying to cover as much distance as possible within six minutes. Participants were allowed to rest during the test, however the timer was not stopped. Participants were allowed stop the test completely if they felt they could not continue. All participants were monitored for any indications for terminating exercise as listed in Table 2.10, and HR and O_2 saturation levels were recorded in the last ten seconds of each minute. The final distance covered in metres was recorded upon completion of six minutes.

2.3.2.2 Incremental Shuttle Walk Test (ISWT)

The externally paced ISWT is a maximal exercise test and is controlled by a series of pre-recorded signals (Holland et al., 2014, EACTA, 2014). Two cones are placed nine metres apart. Participants are required to cover a distance of ten metres (to account for the turns around the cones) in time set to auditory cues. The time between cues progressively decreases requiring the patient to increase walking speed. The test is terminated when the patient can no longer keep up with the auditory cues. The maximum duration of the test is six minutes. The ISWT is also significantly correlated with VO_{2peak} in chronic heart failure patients (Pulz et al., 2008). This thesis does not use the ISWT for testing purposes, however it is examined in detail in the systematic review in Chapter 3.

2.3.2.3 Stair Climb Test (SCT)

The stair climb test is a test of an individual's ability to ascend and descend a flight of stairs. The test is timed (in seconds) and the number of stairs will depend on the environment. The SCT has been reported to be predictive of PPC's in non-cardiac thoracic surgery (Ambrozin et al., 2013). The SCT demonstrates high correlation with VO_2peak in patients with chronic obstructive pulmonary disease (COPD) and patients scheduled for spirometry (Pollock et al., 1993, Cataneo and Cataneo, 2007). This thesis does not employ the SCT for testing purposes, however it is examined in detail in the systematic review in Chapter 3.

2.3.3 Muscular strength

Muscular strength is defined as the ability of a muscle group to develop a contractile force against a resistance in a single contraction (Caspersen et al., 1985, Heyward and Gibson, 2014). Muscular strength can be assessed for static and dynamic contractions. A static (or isometric) contraction is one in which there is no visible movement at the joint and a dynamic contraction is one in which movement is visible at the joint. A concentric contraction occurs when the resistance is less than the force produced by a muscle, or muscle group, and the muscle shortens. The opposite occurs when the resistance is more than the force produced, the muscle produces a braking force and the muscle lengthens.

Assessment of muscular strength offers a number of challenges. For instance, the various types of contractions, previously outlined, result in different muscular performance. Muscular performance can also vary with technique and the method of loading applied. A number of standardised laboratory, gym and field tests have been developed to facilitate assessment of muscular fitness (ACSM, 2013). Static strength may be measured using dynamometers and strain gauges. Free weights (barbells, dumbbells) or field-tests of muscular strength and endurance (push-up test or curl-up test) may be used to assess dynamic strength. However, the type of assessment may also be dictated by the equipment available. For the purpose of the studies in this thesis one measure of peripheral muscular strength was performed, grip strength using a hand-held dynamometer, and one measure of inspiratory muscle strength using a portable electronic inspiratory muscle trainer.

2.3.3.1 Grip strength

A hand-held dynamometer is commonly used to measure static hand grip strength (Roberts et al., 2011, Heyward and Gibson, 2014). Grip strength is an objective measure of upper limb strength. Hand grip strength has a strong association with overall muscle strength and has been reported to be

associated with all-cause mortality, cardiovascular disease and death (Bohannon, 2015, Leong et al., 2015).

The Jamar hydraulic hand dynamometer is a widely used instrument of measuring hand grip strength, with established reliability when a standardised test protocol is followed. The Jamar Plus is an electronic version of the hydraulic dynamometer and differs in that it uses electronic loads cells to measure isometric grip strength and displays output on a digital screen; there are no other differences (Roberts et al., 2011, Trampisch et al., 2012).

2.3.3.1.1 Grip strength assessment protocol

In this thesis, grip strength was measured in Chapter 4 using the Jamar Plus digital hand dynamometer, according to the American Society of Hand Therapists (ASHT) guidelines (Fess, 1982). Participant's sat in a chair with lumbar support (no armrests) with both feet placed flat on the floor. An adjustable handle on the dynamometer was fitted to the size of the participant's hand. The test arm was placed with the shoulder in neutral rotation, elbows close to the thorax and flexed to 90° (Figure 2.8). The forearm was in mid-position and the wrist extended to between 0° and 30°. The assessor demonstrated the grip squeeze manoeuver. Participants alternatively performed three maximal isometric contractions on each hand, with a one minute recovery between contractions. Verbal encouragement to 'squeeze' was given. The mean value for each hand was recorded, in kilograms.



Figure 2.8: Participant performing hand-grip strength assessment

2.3.3.2 Inspiratory muscle strength

The strength of the respiratory muscles is measured by the maximal inspiratory pressure (MIP) produced within the lungs by an individual using a mechanical or electronic pressure gauge (ATS/ERS, 2002). The pressure developed by the inspiratory muscles should be viewed as global respiratory muscle 'output' rather than a direct measures of the muscles contractile properties. To test respiratory muscle properties, pressures can be measured either during voluntary or involuntary respiration (ATS/ERS, 2002). Voluntary respiration tests the synergistic action of several inspiratory or expiratory muscle groups, and in involuntary respiration, such as stimulation of the phrenic nerve, the pressure developed is specific to the contracting muscle(s) (ATS/ERS, 2002).

The main advantages of volitional tests is that they give an estimate of inspiratory muscle strength, are easy to perform, and are well tolerated by patients (ATS/ERS, 2002). A significant disadvantage is it is difficult to ensure that the subject is performing a truly maximal effort. To produce a maximal effort requires participants to activate peripheral and respiratory muscles fully during voluntary movements, however even experienced assessors cannot do this reliably for respiratory efforts and naïve subjects or participants with respiratory difficulties may have even greater difficulty (ATS/ERS, 2002).

The measurement of the maximum static inspiratory pressure that an individual can generate at the mouth is a simple method of gauging inspiratory muscle strength. This pressure is reflective of the pressure developed by contraction of the diaphragm and other respiratory muscles, and the passive elastic recoil pressure of the respiratory system including the lung and the chest wall (Valkenet et al., 2011). Maximal inspiratory pressure was assessed using the POWERbreathe K series, a portable electronic inspiratory muscle training and monitoring system, and measured in cmH_2O (Langer et al., 2013).

2.3.3.2.1 Inspiratory muscle strength assessment protocol

In this thesis, inspiratory muscle strength was measured in the observational study in Chapter 4. Participants were seated in a chair with lumbar support, one hand on their thigh, and feet planted firmly on the ground. The POWERbreathe was inputted with the participant's height, weight and date of birth, and a sterile mouthpiece was placed on the POWERbreathe. Participants were instructed in the use of the POWERbreathe prior to use and to wear a nose clip when performing maximal inspiration (Figure 2.9). Participants placed the POWERbreathe in their mouth, forming a tight seal over the rubber mouthpiece and then performed a maximal exhalation for at least 1.5 seconds (ATS/ERS, 2002). Participants repeated this measure three times in total and the average result was

recorded. Values were aimed to be within 10% of each other, if not, participants were instructed to repeat the measure until three values were within 10% of each other.

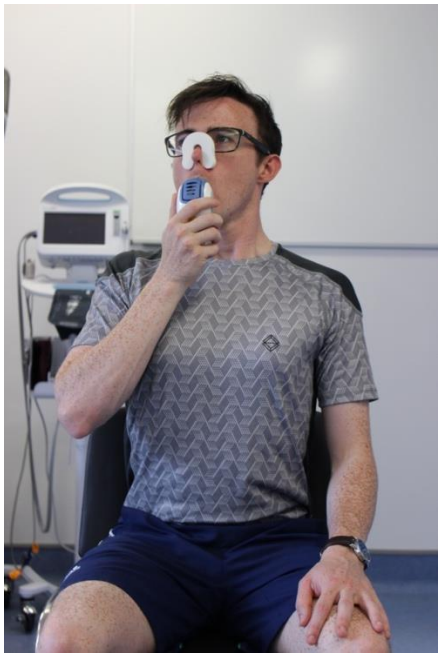


Figure 2.9: Participant performing inspiratory muscle strength assessment with the POWERbreathe K series

2.3.4 Body composition

2.3.4.1 Body mass index

Body mass index (BMI) was calculated using the following formula: weight (kg)/height (m^2). Participants were then classified according to their BMI as underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9) or obese (≥30).

2.3.4.2 Waist circumference and waist/hip ratio

Waist circumference and waist-hip ratio are simple, inexpensive measures of abdominal adiposity, which have been validated against MRI and CT (Ross et al., 1992, Pouliot et al., 1994, World Health Organisation, 2008). Body mass index has been the most popular measurement of body fat distribution, however measurements such as waist circumference and waist/hip ratio have been increasingly used for their ability to measure body fat distribution (Kartheuser et al., 2013).

Waist circumference has been reported to correlate strongly with total body adipose tissue mass and is a superior measure of intra-abdominal adipose tissue than BMI. The assessment of waist

circumference provides a measure of abdominal fat distribution that cannot be obtained by BMI only. Waist to hip ratio compares the circumferences between the two measures and describes the relative distribution of abdominal to gluteal adipose tissue. A study by Kartheuser and colleagues argued that these studies may have used inappropriate measures of obesity (Kartheuser et al., 2013). The authors measured waist circumference and WHR in 1349 patients (754 males) and reported WHR was associated with postoperative morbidity and mortality. The authors reported that waist/hip ratio has a directly proportional relationship to the amount and severity of complications following colorectal surgery and it should be incorporated in clinical practice and in future risk-estimating systems.

2.3.4.2.1 Waist and hip circumference assessment protocol

In the observational study in Chapter 4 of this thesis, the World Health Organisation (WHO) recommendations for measuring waist and hip circumference were followed (World Health Organisation, 2008). According to the WHO (2008) the waist circumference is measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Participants stood with their feet positioned close together, arms by their sides, and weight distributed evenly across the feet. Measurements were performed through one layer of clothing and at the end of normal expiration to standardise the extent of fullness of the lungs and position of the diaphragm. The tape was positioned perpendicular to the long axis of the body, and parallel to the floor. The hip circumference was measured at the widest portion of the buttocks with the tape parallel to the floor. Circumferences were measured to the nearest 0.1 cm.

2.3.5 Pulmonary function testing

Ventilation is one of the primary functions of the pulmonary system – i.e. the movement of air in and out of the lungs. The volume of gas in the lungs and intrathoracic airways is determined by the properties of the lung parenchyma and surrounding organs and tissues, surface tension, the force exerted by respiratory muscles, by lung reflexes and by the properties of airways.

Pulmonary function tests (PFTs) can evaluate the ventilation properties of the pulmonary system. Other less common methods of measuring lung capacity and gas flow include pneumotachometers, gas dilution methods, whole body plethysmography, or radiographic determination (Quanjer et al., 1993). Pulmonary function tests or spirometry is the method of choice for assessing lung function in clinic as these methods require fewer resources (Miller and Enright, 2012).

Spirometry assesses the ability of the patient to inspire and exhale as a function of time. Spirometry may be useful as a preoperative screening or diagnostic tool, for monitoring lung function, response to treatment, establishing a prognosis and evaluating disability (Quanjer et al., 1993). Spirometry measures total lung volume and gas flow. Forced vital capacity (FVC) is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration. The forced expiratory volume in one second (FEV_1) is the volume delivered in the first second of an FVC manoeuvre.

Preoperative spirometry may have a role at identifying high-risk patients. A study of 538 gastric cancer patients reported that abnormal pulmonary function (FEV_1/FVC) was significantly associated with local (anastomosis leakage and wound complication) and systemic postoperative complications (complications not associated with the incision site) (Jeong et al., 2013). The authors recommended that preoperative spirometry be implemented to assess the operative risk and aid in post-operative treatment planning. The ATS/ERS have produced guidance documents to standardise the spirometry tests to reduce variability (Miller and Enright, 2012, Miller et al., 2005). These recommendations have been adopted in the equipment selection and spirometry procedures performed in this thesis.

2.3.5.1 Spirometry testing protocol

In Chapter 4, pulmonary function tests were performed using the Micro 1 spirometer (Micro1, CareFusion, USA). This portable spirometer demonstrates good accuracy ±3% to ATS recommendations. Prior to each test, individual gender, date of birth, height, weight and ethnic origin are inputted into the spirometer.

Testing was performed seated, with participants wearing a nose clip (Figure 2.10). Subjects performed a full inspiration and inserted the portable spirometer mouthpiece ensuring their lips formed a seal. Following a pause of <1 second at total lung capacity, participants exhaled maximally until no more air could be expelled. The procedure was performed at least 3 times. In the event that a result was ± 10% of other values, participants repeated the manoeuvre. Coaching and encouragement was provided throughout (Miller et al., 2005). Outcomes recorded included FVC, FEV1, and FEV_1/FVC ratio.

In Chapter 6, the COSMED $K4b^2$ was used to measure pulmonary function prior to CPET, using similar methods to the Micro 1 spirometer (Micro1, CareFusion, USA). The main difference in assessment procedures was participants using the $K4b^2$ for pulmonary function testing were sized for a face mask, as described in Chapter 2.3.1.10.2.

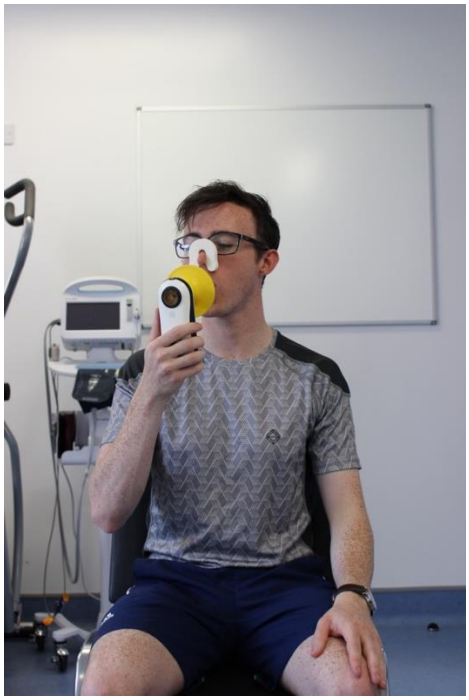


Figure 2.10: Participant performing spirometry assessment

2.4 Section 4. Physical activity

Physical activity (PA) includes any bodily movement produced by skeletal muscles that results in energy expenditure (Caspersen et al., 1985). Consequently, measurement of PA is multi-dimensional, including duration, frequency, intensity and type of activity. Measurement of PA is difficult due to the often unregulated nature of PA, incorporating a range of activity domains including exercise, household activity, transport and occupation (Plasqui and Westerterp, 2007).

The doubly-labelled water (DLW) technique of measuring energy expenditure is widely regarded as the gold standard measure of free-living PA. Physical activity related energy expenditure can be estimated by determining the difference between total daily energy expenditure (TEE) measured by DLW and basal metabolic rate (BMR) and the thermic effect of food measured by indirect calorimetry (Starling et al., 1999). Unfortunately, doubly labelled water is limited in its use due to the relatively high price of the oxygen-18 water, mass spectrometer instrumentation, and the need for technical expertise in sample preparation and measurement. Additionally, while information on TEE can be measured, other aspects of PA, such as frequency and intensity, cannot be measured using DLW technique (Plasqui and Westerterp, 2007). Methods of measuring PA may be subjective or objective. Subjective methods of measuring PA include questionnaires and measures which correlate well with DLW are favourable.

Objective measures of physical activity include pedometers and accelerometers. This section will describe the methods used in this thesis to measure physical activity levels.

2.4.1 Yale Physical Activity Survey

The Yale Physical Activity Survey (YPAS) is an interview-administered physical activity questionnaire which takes approximately 20 minutes to complete (Dipietro et al., 1993). The YPAS is divided into two sections. The first section of the survey contains a work, yard work, caretaking exercise, and recreational checklist to assess time spent in groups of related activities during a typical week in the past month. The second section of the YPAS consists of questions with categorical responses based on physical activity in the past month. These questions assess current participation in several different types of activities (vigorous activity, leisurely walking, moving, standing and sitting).

The YPAS measures the following outcomes; (1) Total time: The time for each activity in section one of the YPAS checklist was summed over all activities to create a total time summary index, expressed as hours per week, for each participant (2) Energy expenditure: The time for each YPAS checklist activity in section one was multiplied by an intensity code (kcal/min) according to Taylor et al. (1978) or McArdle et al. (2010) and then summed for all activities to create an energy expenditure summary index, expressed kcal/wk (Taylor et al., 1978, McArdle et al., 2010). These intensity codes are based on a resting metabolic rate (RMR) of 60 kcal/min for a subject weighting 60 kg and, thus, are independent of individual variation in body weight and RMR. (3) Activity dimensions: Individual scores for the categorical questions in section two about activities in the past month were created by multiplying a frequency score for each of five specific activities [i.e. vigorous activity (questions 1, 2), leisurely walking (questions 3, 4), moving (question 5), standing (question 6), and sitting (question 7)] and multiplying again by a weighting factor. The YPAS prescribed weights are based on the relative intensity of the activity. The final score is the sum of these five indices. The test-retest correlation coefficient of the YPAS over a 2 week period has been shown to be 0.42-0.65 in 71 year old men and women, and compares favourably with the gold standard of energy expenditure DLW, TEE and physical activity related energy expenditure (Starling et al., 1999).

2.4.2 Actigraph

The Actigraph GT3X-BT (Pensacola, FL, USA) is a tri-axial accelerometer with Bluetooth (BT) support that uses a capacitive micro-electro-mechanical system and an ambient light sensor that detects static

and dynamic accelerations. A capacitive accelerometer, such as the Actigraph GT3X, detects change in acceleration through changes in capacitance of the sensing element (i.e. variations in the sensor's electric charge storage potential). The change, an analog signal, in capacitance causes specific changes in voltage to the existing electric flow proportional to the detected acceleration. The signal is then both amplified and digitised to determine the direction of the acceleration. Directions are categorised along the vertical, antero-posterior, or medio-lateral axes (John and Freedson, 2012). The acceleration data is sampled by a 12 bit analog and digital converter at rates ranging between 30 and 100 Hz (user selected) and stored in a raw, unfiltered data file. Physical activity is measured via counts per minute (cpm) of whole-body movement, a similar measure to pedometers using steps per minute. Activity counts are provided as a composite vector-magnitude of these three axes.

A number of studies have investigated the ability of the GT3X to record physical activity in healthy adults. The GT3X accelerometer output correlated strongly with indirect calorimetry (Kelly et al., 2013, Sasaki et al., 2011, Romanzini et al., 2014). In comparisons with the previous generation of validated Actigraph accelerometers (the GT1M), the GT3X showed good agreement with vertical axis activity counts, but dissimilarities in counts reported in the antero-posterior axis (Vanhelst et al., 2012). Direct comparisons of counts between the two generations of Actigraph accelerometers should be avoided. It is a reliable instrument with high inter-monitor and intra-monitor reliability (Santos-Lozano et al., 2012). The Actigraph GT3X demonstrates a significant correlation in adult oxygen consumption (VO_2) measured using a metabolic system (Parvo-Medics: True One 2400 Metabolic System, Sandy Utah US) ($r=0.810$, $p<0.001$) (Kelly et al., 2013).

The Actigraph also includes an inclinometer function to measure body position. When worn on the hip or anterior superior iliac spine (ASIS) body positions are categorised into: lying, sitting and standing. The validity of the inclinometer function is location dependant, however the hip is the superior location when compared to the posterior superior iliac spine (PSIS) and the lateral thigh (Moran et al., 2016).

2.4.2.1 Measurement protocol

The Actigraph GT3X was used in the observational study described in Chapter 4. The Actigraph GT3X was initialised based on patient characteristics, including date of birth, height and weight. Actigraph activity monitors were initialised to a sample acceleration of 30 Hz. The device was secured via an elastic belt across the participant's waist and worn on the hip (in line with axillary line of the iliac crest) on the dominant side of their body. Participants were required to wear the device for one week. The GT3X was worn during all waking hours, participants were requested to remove the activity monitor when going to sleep and when partaking in water based activities e.g. showering and swimming. Participants used log diaries to document non-wear time. A stamped addressed envelope was also

provided to facilitate return of the monitor and non-wear time activity log to the research team. Due to timing constraints during the study described in Chapter 4, the Actigraph could not be used to measure all participants physical activity (Chapter 4.5.1).

3 Chapter 3 Role of cardiopulmonary exercise testing and field tests of exercise tolerance as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review

Material presented in this chapter has been disseminated in the following publications:
Moran J., Wilson F., Guinan E., McCormick P., Hussey J., Moriarty J. (2016) Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. *British Journal of Anaesthesia.* 116: 177-191

Moran J., Wilson F., Guinan E., McCormick P., Hussey J., Moriarty J. (2016) The preoperative use of field tests of exercise tolerance to predict postoperative outcome in intra-abdominal surgery: a systematic review. *Journal of Clinical Anesthesia*. 35: 446-455
See Appendix A for full manuscripts

3.1 Introduction

Cardiopulmonary exercise testing is a dynamic, non-invasive assessment of an individual's cardiopulmonary system at rest and under stress and is widely considered the gold-standard method of measuring an individual's aerobic capacity. Cardiopulmonary exercise testing measures several physiological variables, including ventilatory parameters, HR, and inspiratory and expiratory gases.

Cardiopulmonary exercise testing can be implemented to aid clinical decision-making. These uses include assessing patients with significant complaints of exercise intolerance and dyspnoea and determining the severity of impairment related to heart failure and chronic obstructive pulmonary disease (Stringer et al., 2012, Weisman and Zeballos, 2001). Cardiopulmonary exercise testing was first used to predict postoperative mortality in 187 patients scheduled for major abdominal surgery (Older et al., 1993). The authors identified that patients with a preoperative AT of <11 ml/kg/min had an increased risk of postoperative mortality compared to those with an AT ≥11 ml/kg/min (18% vs. 1%, respectively, $p<0.001$). Since the publication of this paper, the literature examining the ability of preoperative cardiopulmonary exercise testing to predict postoperative mortality, LOS, and morbidity has grown, however its role requires validation.

Field tests of exercise tolerance such as the 6MWT and ISWT differ from CPET as they do not directly assess the relationship between pulmonary gas exchange during exercise, however they provide an objective measure of physical fitness when CPET is not readily available. Field tests are practical, cheap and easy to administer. CPET requires specialised equipment, considerable safety precautions and extra staff which limit wide clinical application (Oliver et al., 2015, Balady et al., 2010). Consequently, field tests are often used in the clinical setting as they are do not require previous training by the clinician and require little equipment. The field tests of exercise tolerance used in the articles included for review in this chapter were the SCT, the ISWT and the 6MWT.

Numerous studies have reported that physical fitness is a valid prognostic measure of postoperative outcome in cardiopulmonary surgery (Mancini et al., 1991, Beckles et al., 2003, Brunelli et al., 2009a). There have been four previous reviews of CPET in non-cardiopulmonary surgery (Hennis et al., 2011, Levett and Grocott, 2015, Smith et al., 2009, West et al., 2011). All reviews concluded that CPET may be a strong predictor of postoperative outcome. These reviews also concluded that: (i) CPET-derived cut-points need to be refined and optimised for different surgical procedures and (ii) the validity of CPET variables, such as O_2 pulse and the ventilatory equivalent for carbon dioxide (V_E/VCO_2), needs to be analysed; and (iii) further studies need to be performed to obtain a greater understanding of the role of CPET as a preoperative risk-stratification method. Since the publication of these reviews, the number of studies analysing CPET has grown.

The aim of this chapter is to assess the prognostic ability of CPET and field tests of exercise tolerance in predicting postoperative mortality, morbidity and LOS associated with non-cardiopulmonary intra-abdominal surgery. The objectives are as follows: (i) to quantify the optimal CPET variable and/or field test to predict postoperative outcome; and (ii) to analyse and compare cardiopulmonary measurements such as anaerobic threshold (AT), maximal/peak oxygen uptake ($VO_{2max/peak}$) and V_E/VCO_2 to find the most accurate CPET variable capable of determining postoperative outcome within each subgroup of surgery.

Postoperative outcome includes all-cause mortality, morbidity, and LOS. Morbidity after surgical intervention includes all-cause complications; pulmonary, infectious, renal, gastrointestinal (GI), cardiovascular, neurological, and haematological. The outcome LOS covers the overall length of stay in hospital, intensive care unit (ICU), high-dependency unit (HDU), and critical care unit (CCU) admission and length of stay.

3.2 Methods

A protocol outlining the planned search strategy and methods of analysis for this review was registered online with a registry of systematic reviews (PROSPERO ID: 42014009561) (Appendix E). The PRISMA guidelines were used to standardize the methods of conducting and reporting this review (Antes and von Elm, 2009) (Chapter 2.1.1.1).

3.2.1 Literature search

An experienced medical librarian was consulted and a comprehensive search strategy was developed with all keywords and subject headings included (Appendix F). The databases CINAHL, AMED, PEDro, EMBASE, The Cochrane Library, and PubMed were searched up to May 2015. In addition, the abstracts from the annual European Anaesthesiology Congress (2004–2014), the Anaesthetic Research Society (2007–2015), the Society of Academic & Research Surgery (2012–2015), the Vascular Society (2005–2012), the International Anaesthesia Research Society (2003–2015), the World Federation of Society of Anaesthesiologists (2008–2012), and the American Society of Anaesthesiologists (2000–2014) were reviewed for eligibility. A hand search of reference lists of the studies of interest was conducted to identify extra articles.

3.2.2 Eligibility criteria

The inclusion criteria consisted of the following: (i) prognostic studies of intra-abdominal surgery among adult populations; (ii) the use of a preoperative CPET or field test of exercise tolerance; (iii) measurement of postoperative outcome (mortality, morbidity, or length of stay); and (iv) comparison of preoperative CPET variables (e.g. anaerobic threshold) or field tests with postoperative outcome. Studies were excluded if they contained the following: (i) a cardiopulmonary surgical procedure; (ii) paediatric surgery; (iii) head and neck surgery; (iv) orthopaedic surgery; (v) spinal surgery; (vi) transfusion procedures, (e.g. blood or stem cells); (vii) preoperative interventions (e.g. preoperative exercise programmes); or (viii) were systematic reviews, meta-analyses, case studies, letters to the editor, or abstracts with no full text available.

Studies which included both intra-abdominal surgeries and other surgical procedures were included if results pertaining to the intra-abdominal surgical group could be extracted and analysed in isolation. Procedures involving multiple incisions which included major intra-abdominal resection were included (e.g. oesophagectomy).

3.2.3 Data extraction

A data extraction template was developed based on the Cochrane Collaboration recommendations and the template was piloted on two randomly selected studies and modified accordingly (Higgins and Green, 2008). Data extraction was performed independently by the lead investigator (J. Moran). All data were reviewed blind by another author (F.Wilson). The type of data extracted is included in Table 3.1. The data extracted included author, patient characteristics, study setting, surgery type, postoperative outcome measure, method of CPET, and CPET variables assessed and is presented in Table 3.2.

Table 3.1: Data extraction template used by authors to extract data from relevant studies. Data extracted included: participant characteristics, study methodology, cardiopulmonary exercise testing characteristics and postoperative outcome measures

Variable	Description/units/examples
Participant Characteristics:	
Number of participants	Number
Age	Years
Gender	Males/Female ratio, %
Surgery type	Colorectal, abdominal aortic aneurysm, hepatic resection or transplant
Neoadjuvant chemo/radiotherapy	Participants undergoing neoadjuvant chemo/radiotherapy
Study Methodology	
Location	Setting and country
Study Design	Prospective, retrospective
Study Duration	Study recruitment duration
Group Allocation	Participants allocated to groups based on: Fitness levels or surgery type

CPET Characteristics*	
CPET Assessment Type	Maximal vs. sub-maximal
CPET Protocol	Ramped vs. Incremental
CPET Assessment Equipment	Treadmill/Cycle Ergometer/Arm Ergometer
CPET Variables Measured	AT, VO_2peak, VO_2max, VE/VO_2 , VE/VCO_2
Type of Field Test of Exercise Tolerance	ISWT, SCT, 6MWT
Postoperative Outcomes:*	
Postoperative Morbidity	POMS, Clavien-Dindo, CCI, self-defined morbidity
Length of stay	General hospital stay, ICU stay, HDU stay, CCU stay, readmission rates
Mortality	Yes/No
Duration of follow-up	In hospital, 30 day, 90 day, 1 year
*Examples listed are not exhaustive, they served to guide the reviewer when extracting data for each variable.	

Table 3.2: Demographic details of included studies exploring the ability of CPET to predict postoperative outcome. AT = Anaerobic Threshold, HR = Heart Rate, N/R = Not Reported, RER = Respiratory Exchange Ratio, VE = Minute Ventilation

Author	Surgery	Sample Size (n=)	Age (years)	Gender	Geographical Location	Outcome	CPET Type	CPET Variables Reported
Ausania et al. (2012a)	Pancreaticoduodenectomy	124	66 (37-82)	67 Male, 57 Female	Newcastle Upon Tyne, UK	Mortality, Morbidity, LOS	Cycle Ergometer	VO_2peak, AT, VE/VCO_2
Ausania et al. (2012b)	Pancreatic (Palliative Double Bypass) Surgery	50	64 (39-79)	33 Male, 17 Female	Newcastle Upon Tyne, UK	Mortality, Morbidity	N/R	AT
Bernal et al. (2014)	Liver Transplant	223	56 (42-61)	151 Male, 72 Female	London, UK	Mortality, LOS	Cycle Ergometer	VO_2peak, AT
Carlisle and Swart (2007)	Abdominal Aortic Aneurysm Repair	130	N/R	N/R	Torquay, UK	Mortality	Cycle Ergometer	VO_2peak, AT, VE/VCO_2, VE/VO_2
Chandrabalan et al. (2013)	Pancreatic Surgery	100	≤65=47, >65=53	60 Male, 40 Female	Glasgow, UK	Mortality, Morbidity, LOS	Cycle Ergometer	AT
Colson et al. (2012)	Major Thoraco-Abdominal Surgery	1,725	71 (36-93)	1,121 Male, 604 Female	Geelong, Australia	Mortality	Cycle Ergometer	AT
Dunne et al. (2014)	Liver Surgery	197	70 (64-75)	138 Male, 59 Female	Liverpool, UK	Morbidity, LOS	Cycle Ergometer	VO_2peak AT, VE/VCO_2, HR
Epstein et al. (2004)	Liver Transplant	59	46	35 Male, 24 Female	Boston, USA	Mortality	Cycle Ergometer	VO_2peak, AT, O_2 pulse
Forshaw et al. (2008)	Oesophagectomy	78	65 (9) (40-81)	64 Male, 14 Female	London, UK	Mortality, Morbidity, LOS	Cycle Ergometer	VO_2peak, AT
Grant et al. (2015)	Abdominal Aortic Aneurysm Repair	506	73.4 (44-90)	418 Male, 88 Female	Manchester, UK	Mortality	Cycle Ergometer	VO_2peak, AT, VE/VCO_2

Hartley et al. (2012)	Abdominal Aortic Aneurysm Repair	415	N/R	349 Male, 66 Female	Manchester, UK	Mortality	Cycle Ergometer	VO_2peak, AT, VE/VCO_2
Hennis et al. (2012)	Gastric Bypass Surgery	106	43 (41-44.9)	18 Male, 88 Female	London, UK	Morbidity, LOS	Cycle Ergometer	VO_2peak, AT
Hightower et al. (2010)	Major Abdominal Surgery	32	63 (22-80)	21 Male, 11 Female	Texas, USA	Morbidity	Cycle Ergometer	VO_2peak, AT
James et al. (2013)	Intra-Abdominal	83	68 (63-75)	60 Male, 23 Female	London, UK	Morbidity	Cycle Ergometer	VO_2peak, AT
Junejo et al. (2012)	Hepatic Resection	94	71 (24-85)	N/R	Manchester, UK	Mortality, Morbidity, LOS	Cycle Ergometer	VO_2peak, AT, VE/VCO_2, Peak VO_2 pulse
Junejo et al. (2014)	Pancreaticoduodenectomy	64	64 (45-80)	38 Male, 26 Female	Manchester, UK	Mortality, Morbidity	Cycle Ergometer	VO_2peak, AT, VE/VCO_2, VE/VO_2
Kaibori et al. (2013)	Hepatectomy	61	70 (9)	45 Male, 16 Female	Osaka, Japan	Mortality	Cycle Ergometer	VO_2peak, AT
Lai et al. (2013)	Colorectal Surgery	269	N/R	N/R	Plymouth, UK	Mortality, LOS	Cycle Ergometer	VO_2peak, AT
Lee et al. (2013)	Colorectal Surgery	112	59.9 (15.5)	65 Male, 47 Female	Montreal, Canada	Morbidity	Cycle Ergometer	VO_2peak, Distance
McCullough et al. (2006)	Bariatric Surgery	109	46 (10.4)	27 Male, 82 Female	Michigan, USA	Mortality, Morbidity, LOS	Treadmill	VO_2peak, AT, VE/VCO_2, RER
Moyes et al. (2013)	Oesophagogastric Cancer Surgery	108	66 (SD: 9, IQR: 38-84)	83 Male, 25 Female	Glasgow, UK	Morbidity	Cycle Ergometer	VO_2peak, AT
Nagamatsu et al. (2001)	Oesophagectomy and Lymphadenectomy	91	59 (38-74)	88 Male, 3 Female	Fukuoka, Japan	Morbidity	Cycle Ergometer	VO_2peak, AT

Neviere et al. (2014)	Liver Transplant	263	58.8 (8.5)	198 Male, 65 Female	Lille, France	Mortality	Cycle Ergometer	VO_2peak, AT, VE/VCO_2, VE/VO_2, O_2 pulse
Nugent et al. (1998)	Abdominal Aortic Aneurysm Repair	30	71.3 (57-85)	24 Male, 6 Female	Belfast, UK	Mortality, Morbidity	Treadmill	VO_2peak, AT, O_2 pulse
Older et al. (1993)	Major Abdominal	187	70 (7)	102 Male, 85 Female	Victoria, Australia	Mortality	Cycle Ergometer	AT
Older et al. (1999)	Major Abdominal Surgery	548	69	N/R	Victoria, Australia	Mortality, Morbidity, LOS	Cycle Ergometer	AT
Prentis et al. (2012a)	Liver Transplant	60	N/R	N/R	Newcastle Upon Tyne, UK	Mortality, LOS	Cycle Ergometer	VO_2peak, AT, VE/VCO_2
Prentis et al. (2012b)	Abdominal Aortic Aneurysm Repair	185	73.4 (SD: 8.2)	161 Male, 24 Female	Newcastle Upon Tyne, UK	Morbidity, LOS	Cycle Ergometer	VO_2peak, AT, VE/VCO_2
Prentis et al. (2013)	Radical Cystectomy	69	N/R	48 Male, 21 Female	Newcastle Upon Tyne, UK	Mortality, LOS	Cycle Ergometer	VO_2peak, AT, VE/VCO_2, Peak VO_2 pulse
Snowden et al. (2010)	Major Surgery	123 (7 excluded from analysis)	69.2 (9.3)	78 Male, 45 Female	Newcastle Upon Tyne, UK	Morbidity, LOS	Cycle Ergometer	VO_2peak, AT
Snowden et al. (2013)	Non-Laparoscopic Hepatobiliary Surgery	389	65.8 (10.3)	218 Male, 171 Female	Newcastle Upon Tyne, UK	Mortality, LOS	Cycle Ergometer	VO_2peak, AT, VE/VCO_2
Ting et al. (2013)	Kidney Transplant	70	41.7 (14.5)	42 Male, 28 Female	Coventry, UK	LOS	Cycle Ergometer	VO_2peak, AT, VE/VCO_2, VO_2/HR

Tolchard et al. (2015)	Radical Cystectomy	105	71 (38-90)	88 Male, 17 Female	Bristol, UK	Mortality, Morbidity, LOS	Cycle Ergometer	VO_2peak, VE/VCO_2	AT,
Ulubay et al. (2010)	Renal Transplant	16	30.3 (6.5)	10 Male, 6 Female	Ankara, Turkey	Mortality	Cycle Ergometer	VO_2peak, VE/VCO_2	AT,
West et al. (2013)	Rectal Cancer Surgery	95	66 (10)	72 Male, 23 Female	Liverpool, UK	Mortality, Morbidity	Cycle Ergometer	VO_2peak, VE/VCO_2, VE/VO_2	AT,
West et al. (2014)	Major Colonic Surgery	136	71 (62-77)	89 Male, 47 Female	Liverpool, UK	Mortality, Morbidity, LOS	Cycle Ergometer	VO_2peak, VE/VCO_2, Pulse peak	AT, O_2
Wilson et al. (2010)	Colorectal Resection, Radical Nephrectomy or Cystectomy	847	N/R	506 Male, 341 Female	York, UK	Mortality, LOS	Cycle Ergometer	AT, VE/VCO_2	

3.2.4 Study selection

A total of 1086 titles were identified using the search strategy on the previously mentioned databases. Of these, 1044 studies were excluded (Figure 3.1). Two authors (J. Moran and F.W.) excluded articles based on titles and abstracts. Disagreements between reviewers were resolved through discussion. If disagreements could not be resolved through discussion, an independent third author was asked to intervene (J.H.). Forty-two full-text articles were included in the data extraction and synthesis (Figure 3.1). The authors of abstracts and conference posters were contacted to provide the full text. If full-text articles were not acquired then abstracts were excluded because of the potential high risk of bias and lack of a detailed methodology.

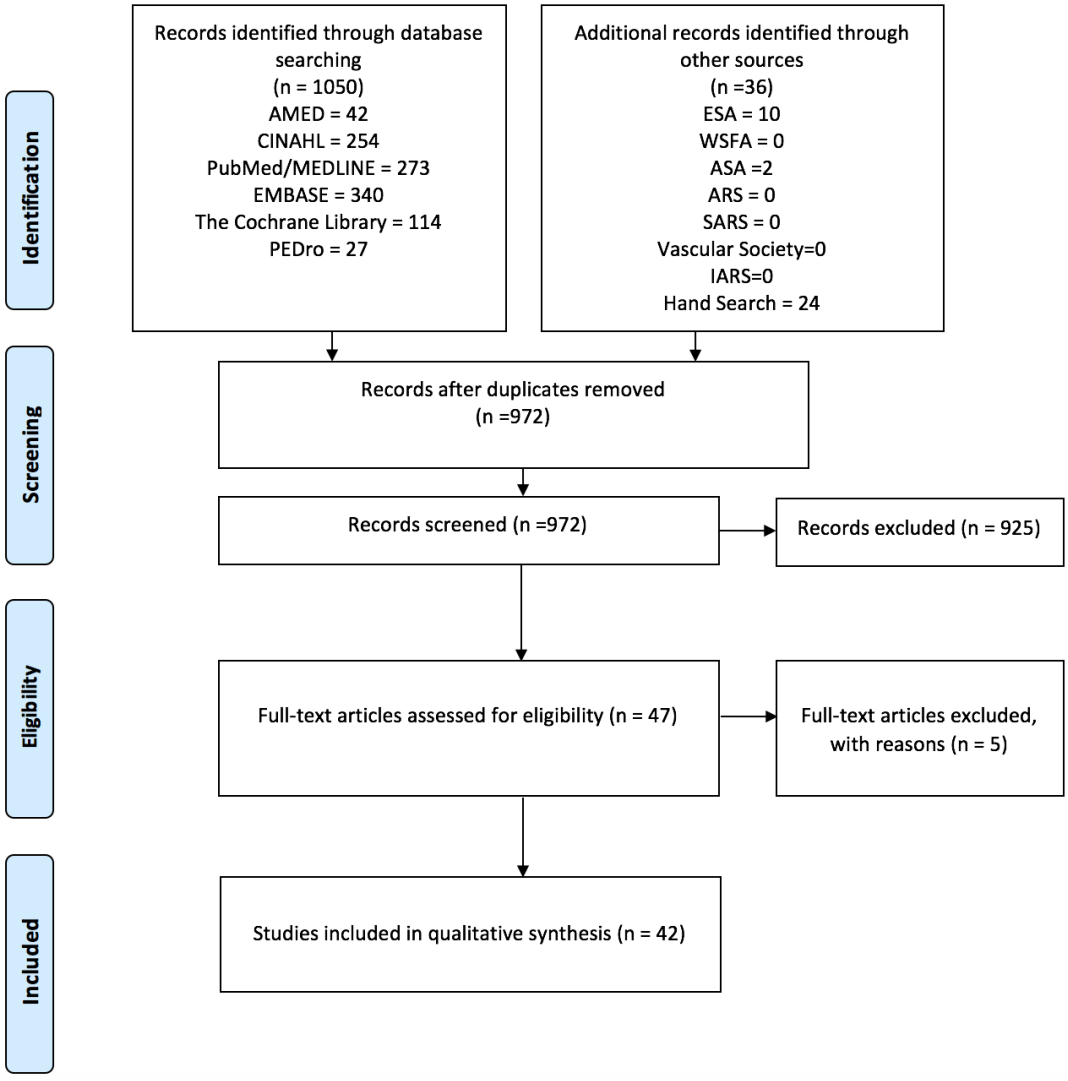


Figure 3.1**:** PRISMA flow diagram demonstrating the article inclusion process. ARC = Anaesthetic Research Society, ASA = American Society of Anaesthesiologists, EAC = European Anaesthesiology Congress, IARS = International Anaesthesia Research Society, SARS = Society of Academic & Research Society, VS = Vascular Society, WFSA = World Federation of Society of Anaesthesiologists

3.2.5 Assessment of risk of bias

The risk of bias in studies was assessed using the Quality in Prognosis Studies (QUIPS) tool (Hayden et al., 2013) (Appendix H). The recently developed tool is informed by basic epidemiologic principles and is based on recommendations of quality assessment in prognosis systematic reviews. The QUIPS tool analyses the risk of bias in observational prognostic studies in six key areas, as follows: study participation, attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each area contained several criteria described in detail below.

The study participation domain addresses the sensitiveness of the study sample. It allows the assessor to judge whether the study's reported association is a valid estimate of the true relationship between the prognostic factor and the outcome of interest in the source population. To make this decision, the assessor considers the proportion of eligible persons in the study to ensure this proportion is a true reflection of the source population. Furthermore, the study attrition domain allows the assessor to judge whether the reported relationship between the prognostic factor and outcome is biased towards the group who completed the study based on the level of drop outs during the study period. There are several criteria to aid the decision process; the withdrawal rate, information about why participants are lost to follow up and observed differences between persons lost to follow-up and those who completed the study.

The prognostic factor measurement domain addresses the adequacy of the prognostic factor measurement used in the study. To have a low risk of bias, the method of prognostic factor measurement must be similar between individuals and performed in a valid and reliable method. To make this decision, the assessor considers the definition of the prognostic factor measurement and the evidence for the reliability and validity of the measurement approach.

The outcome measurement domain assesses if the study outcome measure is adequate. The assessor considers whether the study measured the outcome in an objective, reliable and valid way between all individuals for the duration of the study. The study confounding section examines the level of bias imparted by confounding factors. To effectively judge this, the assessor considers the validity, reliability, and similarity of measurement of potential confounders (defined *a priori*) for all study participants. The assessor also considers if all important confounders were accounted for in the study design or analysis e.g. patient comorbidities.

The final domain, statistical analysis and reporting addresses the appropriateness of the study's statistical analysis and reporting or results. The assessor must judge whether results are likely to be spurious or biased because of analysing or reporting. The assessor considers the data presented to determine the adequacy of the analytic strategy and model-building process and investigates concerns about selective reporting.

The QUIPS tool systematically rates each of the six domains as low, medium or high risk of bias. If a study failed to address one or fewer criteria within an area, it was deemed to have a low risk of bias. Two authors (J. Moran and F.W.) independently assessed the risk of bias in each study. An independent third author (J.H.) was asked to intervene if any disagreements could not be resolved through discussion. The overall risk of bias is presented in Table 3.3.

The tool is relatively recent and so there have been no studies on validity, however the QUIPS tool is the first risk of bias assessment tool for observational prognostic studies, which are subject to considerable bias (Jepsen et al., 2004). The QUIPS tool allows for several areas of bias to be effectively assessed and reported, allowing for readers to judge the amount of bias potentially influencing results.

Table 3.3: Risk of bias assessment. Overall risk of bias was low.

Authors	The QUIPS Tool					
	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Arruda et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Ausania et al. (2012a)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Ausania et al. (2012b)	Low Bias	Low Bias	High Bias	High Bias	High Bias	Low Bias
Bernal et al. (2014)	Low Bias	Low Bias	Low Bias	Low Bias	High Bias	Low Bias
Carlisle and Swart (2007)	High Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Chandrabalan et al. (2014)	High Bias	Low Bias	Low Bias	Low Bias	High Bias	Low Bias
Colson et al. (2012)	Moderate Bias	High Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Dunne et al. (2014)	Moderate Bias	High Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Epstein et al. (2004)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Forshaw et al. (2008)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Grant et al. (2015)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Hartley et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Hennis et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Hightower et al. (2010)	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
James et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Junejo et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Junejo et al. (2014)	Low Bias	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Kaibori et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
Lai et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Lee et al. (2013)	Low Bias	Low Bias	Low Bias	Moderate Bias	Moderate Bias	Low Bias
McCullough et al. (2006)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias

Moriello et al. (2008)	Moderate Bias	Low Bias	Low Bias	Low Bias	High Bias	Low Bias
Moyes et al. (2008)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Murray et al. (2007)	Low Bias	High Bias	Low Bias	Low Bias	High Bias	Moderate Bias
Nagamatsu et al. (2001)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Neviere et al. (2014)	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
Nugent et al. (1998)	Moderate Bias	Low Bias	Low Bias	High Bias	Moderate Bias	Low Bias
Nutt and Russel (2012)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Older et al. (1993)	Moderate Bias	Moderate Bias	Low Bias	Low Bias	High Bias	Low Bias
Older et al. (1999)	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Moderate Bias	High Bias
Paisani et al. (2012)	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Moderate Bias	Low Bias
Prentis et al. (2012a)	Low Bias	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Prentis et al. (2012b)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Prentis et al. (2013)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Snowden et al. (2010)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Snowden et al. (2013)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Ting et al. (2013)	Moderate Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
Tolchard et al. (2015)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Ulubay et al. (2010)	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Moderate Bias	Low Bias
West et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
West et al. (2014)	Low Bias	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Wilson et al. (2010)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias

3.3 Results

Studies examining the predictive ability of CPET were separated from studies involving field tests of exercise tolerance.

3.3.1 Cardiopulmonary exercise testing

The studies included in this review were categorized by surgical procedures, as follows: hepatic transplant and resection (n=7), abdominal aortic aneurysm (AAA) repair (n=5), colorectal surgery (n=4), pancreatic surgery (n=4), renal transplant (n=2), upper gastrointestinal surgery (n=3), bariatric surgery (n=2), and intra-abdominal surgery (studies that did not differentiate between surgical procedures; n=10). A total of 7,852 patients were included.

A meta-analysis was deemed inappropriate because of the large heterogeneity of the data. The studies included varied in the type of surgery, CPET variable analysed, outcome, time to outcome, and the use of hazard ratios and odds ratios, resulting in an inability to pool data effectively. A qualitative synthesis of the results was deemed most appropriate.

Table 3.4-3.6 provide a streamlined version of the CPET variable results deemed significant that predict postoperative mortality (Table 3.4), length of stay (Table 3.5) and morbidity (Table 3.6). A more detailed analysis of preoperative CPET and postoperative outcome is provided in the Appendix G.

3.3.1.1 Hepatic transplant and resection

3.3.1.1.1 Mortality

Six studies reported CPET as a significant predictor of mortality after hepatic surgery (Junejo et al., 2012, Prentis et al., 2012a, Bernal et al., 2014, Kaibori et al., 2013a, Neviere et al., 2014, Epstein et al., 2004) (Table 3.4). Junejo and colleagues (Junejo et al., 2012) reported an AT of 9.9 ml/kg/min to be predictive of survival 30 days after surgery, whereas at 90 days after surgery an AT cut-off point of 9.0 ml/kg/min was shown to be significant ($p<0.05$) and had a 90.7% sensitivity and 83.3% specificity rate (Prentis et al., 2012a). Bernal and colleagues reported that survivors had a median AT of 11.7 ml/kg/min compared with non-survivors (median, 9.8 ml/kg/min) at 1 year post-transplant ($p=0.04$) (Bernal et al., 2014). Kaibori and colleagues followed patients for 2 (range 1–3) years and found an AT ≥11.5 ml/kg/min to be predictive of survival ($p<0.05$) (Kaibori et al., 2013a). From the results of these

four studies, a minimal AT of 9 ml/kg/min can predict short-term mortality (up to 90 days), but an AT of at least 11.5 ml/kg/min may predict long-term mortality (≥1 year).

Peak oxygen uptake (VO_{2peak}) has also been shown to be beneficial at predicting mortality after liver surgery. Neviere and colleagues reported that survivors of liver transplant at 1 year had a VO_{2peak} of 18.6 (SD: 2.8) ml/kg/min when compared with non-survivors 17.1 (SD 3.3) ml/kg/min (p=0.04) (Neviere et al., 2014). Kaibori and colleagues presented a cut-off of ml/kg/min as predictive of survival at 24 months after surgery (p<0.05). Epstein and colleagues (Epstein et al., 2004) reported that both predicted VO_{2peak} and AT were effective at predicting mortality at 100 days. Peak oxygen uptake appears to be beneficial at predicting mortality, but the evidence for its use is weaker than that for AT.

3.3.1.1.2 Length of stay

The relationship between AT and LOS is unclear. Junejo and colleagues and Prentis and colleagues found no relationship between AT and LOS (Junejo et al., 2012, Prentis et al., 2012a). In contrast, Dunne and colleagues reported that patients with higher AT (in litres per minute) were more likely to be discharged early; however, this AT cut-off was not quantified (Hazard Ratio: 2.16; 95% C.I: 1.18–3.96; p<0.05) (Dunne et al., 2014). An AT <9.2 ml/kg/min was associated with a LOS of 21 days (IQR: 14–30) compared with patients with an AT ≥9.2 ml/kg/min [LOS of 15 days (IQR: 13–23); p<0.03] (Bernal et al., 2014).

Junejo and colleagues reported that an AT of <9.9 ml/kg/min was associated with increased unplanned ICU stay (1.2 vs. 0.3 days, p<0.05) (Junejo et al., 2012). In agreement, Prentis and colleagues demonstrated that an AT of 11 ml/kg/min was significantly correlated with CCU LOS (p<0.05) (Prentis et al., 2012a).

The evidence for VO_{2peak} as a predictive factor of LOS and ICU admission is weaker than that for AT. Dunne and colleagues reported that VO_{2peak} was associated with LOS (p<0.05) (Dunne et al., 2014). Peak oxygen consumption may also be predictive of ICU LOS stay in liver transplant surgery (p<0.05) (Bernal et al., 2014). Anaerobic threshold appears to be predictive of ICU or CCU admission after liver surgery (Junejo et al., 2012, Prentis et al., 2012a). Further studies are required to draw a definite conclusion about the ability of CPET to predict postoperative LOS after liver surgery (Table 3.5).

3.3.1.1.3 Morbidity

Many studies did not examine postoperative morbidity. Kaibori and colleagues grouped morbidity with mortality and analysed outcome as event-free survival (Kaibori et al., 2013a). This latter parameter will

not be included in the analysis of this section. Both Junejo and colleagues and Dunne and colleagues analysed the possible relationship between CPET and postoperative complications (Junejo et al., 2012, Dunne et al., 2014). In a multivariable predictive regression model, a V_E/VCO_2 threshold of 34.5 at AT was predictive of postoperative cardiopulmonary complications (Junejo et al., 2012). Dunne and colleagues reported that HR at AT ($p<0.05$) and HR at VO_2peak ($p<0.05$) were associated with all-cause postoperative complications (Dunne et al., 2014).

Preoperative CPET shows possible benefit for predicting postoperative complications after liver surgery, but further studies are required to validate the prognostic ability of CPET (Table 3.6).

3.3.1.2 Abdominal aortic aneurysm repair

3.3.1.2.1 Mortality

Four full-text articles analysing the potential predictive ability of CPET in AAA repair were reviewed (Nugent et al., 1998, Grant et al., 2015, Hartley et al., 2012, Carlisle and Swart, 2007). In a small cohort (n=30), with only two documented deaths, Nugent and colleagues reported no difference in preoperative VO_2peak between patients who did and did not experience postoperative morbidity and mortality.

Grant and colleagues found in the multivariable analysis that $V_E/VCO_2>42$ at AT was predictive of mortality ($p<0.05$) as was VO_2peak <15 ml/kg/min ($p<0.05$). Anaerobic threshold was not included in this study because values were missing in >10% of patients (Grant et al., 2015). An AT of <10.2 ml/kg/min was reported to be predictive of 30 day mortality ($p<0.05$), and VO_2peak <15 ml/kg/min was predictive of 90 day mortality ($p<0.05$) (Hartley et al., 2012). The V_E/VCO_2 was predictive of 30 ($p<0.05$) and 90 day mortality ($p<0.05$) after AAA repair (Hartley et al., 2012). In a univariable analysis, Carlisle and Swart reported that V_E/VCO_2 ($p<0.01$), ventilatory equivalent for oxygen (V_E/VO_2; $p<0.01$), AT ($p<0.01$), and VO_2peak ($p<0.01$) were predictive of mortality (Carlisle and Swart, 2007). In the multivariable analysis, V_E/VCO_2 and AT were predictive of postoperative survival ($p<0.01$ and $p=0.03$, respectively).

The prognostic ability of CPET in determining postoperative mortality after AAA repair appears useful but requires further validation. Only one study did not find VO_2peak to be predictive (Nugent et al., 1998). The variables and cut-off points used between studies vary or are not reported (Nugent et al., 1998, Carlisle and Swart, 2007). The length of postoperative follow-up also differs; therefore, further studies will need to examine the prognostic ability of CPET and mortality at specific time points to allow

for suitable comparison (e.g. 30 and 90 days and 5 years). A VO_{2peak} cut-off point of 15 ml/kg/min is a good starting point because it is predictive of 90 day mortality and 26 month (median) survival (Hartley et al., 2012, Grant et al., 2015).

3.3.1.2.2 Length of stay

Anaerobic threshold was reported to be predictive of CCU and overall hospital LOS in open AAA repair, but not endovascular aneurysm repair (Prentis et al., 2012b).

3.3.1.2.3 Morbidity

Nugent and colleagues reported no statistically significant relationship between VO_{2peak} and postoperative complications. An AT of 10 ml/kg/min has been reported to be predictive of postoperative morbidity (Prentis et al., 2012b).

3.3.1.3 Colorectal surgery

3.3.1.3.1 Mortality

Lai and colleagues stratified patients into the following three categories: fit (AT ≥11 ml/kg/min), unfit (AT <11 ml/kg/min), and unable (unable to generate an AT) (Lai et al., 2013). This study compared mortality at 30 and 90 days and 2 years between fit and unfit and between unfit and unable and reported that mortality was significantly different between groups ($p<0.01$).

West and colleagues reported that seven patients (total n=95) died within 1 year after rectal surgery, all of whom had a VO_{2peak} of <10.6 ml/kg/min (West et al., 2014c). In contrast, West and colleagues were unable to conclude whether CPET was predictive of mortality after major colonic surgery because there were only two deaths (1.5%) (West et al., 2014b). Anaerobic threshold and VO_{2peak} appear to be beneficial in predicting postoperative mortality, but owing to the low rate of mortality it is difficult to draw conclusions.

3.3.1.3.2 Length of stay

Patients with higher AT values (≥11 ml/kg/min) had a significantly shorter LOS in hospital compared with unfit (AT <11 ml/kg/min) and unable groups (unable to generate an AT; $p<0.01$) (Lai et al., 2013). West and colleagues reported that patients with low AT ($p<0.01$) or VO_{2peak} ($p<0.01$) or with high VE/VCO_2 ($p<0.01$) were susceptible to an increased hospital stay (West et al., 2014b). The prognostic ability of CPET appears viable; however, more research is needed to validate the ability of AT to determine postoperative LOS.

3.3.1.3.3 Morbidity

Peak oxygen uptake and AT have been reported to be associated with postoperative complications using the POMS on day 5 after rectal cancer surgery and major colonic surgery (West et al., 2014c, West et al., 2014b). After major colonic surgery, West and colleagues reported that VO_{2peak}, AT, and V_E/VCO_2 were independently predictive of morbidity. Lee and colleagues reported that VO_{2peak} was associated with occurrence of medical complications ($p<0.01$) but not surgical and all-cause complications (Lee et al., 2013).

The data regarding preoperative CPET as a predictor of postoperative morbidity are strong, but further research is needed to quantify a level of aerobic fitness that is protective against complications.

3.3.1.4 Pancreatic surgery

3.3.1.4.1 Mortality

Three studies exclusively reported on the ability of AT to predict postoperative mortality following pancreatic surgery and concluded that there was no significant relationship. Ausania and colleagues reported similar mortality rates between groups, AT ≤10.1 and >10.1 ml/kg/min ($p=1.00$) (Ausania et al., 2012a). Anaerobic threshold was not associated with postoperative mortality ($p=0.74$) (Chandrabalan et al., 2013). Ausania and colleagues performed Cox regression analysis and reported that AT was not associated with long-term survival ($p=0.5$) (Ausania et al., 2012b). Their study failed to quantify the length of long-term survival. Junejo and colleagues reported V_E/VCO_2 to be a significant predictor of both 30 day ($p=0.03$) and in-hospital mortality ($p=0.02$) (Junejo et al., 2014).

Preoperative AT is not predictive of postoperative mortality after pancreatic surgery; however, V_E/VCO_2 may be able to predict postoperative survival. Further studies are required to determine the validity of V_E/VCO_2 to predict postoperative mortality in pancreatic surgery.

3.3.1.4.2 Length of stay

Only two studies examined LOS and CPET variables. Chandrabalan and colleagues reported that an AT <10 ml/kg/min was predictive of a median of 6 days longer LOS than those of AT ≥10 ml/kg/min ($p<0.01$) (Chandrabalan et al., 2013). Likewise, Ausania and colleagues reported that an AT value of ≤10.1 ml/kg/min resulted in a median LOS of 29.4 days, whereas patients with an AT >10.1 ml/kg/min had a median LOS of 17.5 days ($p<0.01$) (Ausania et al., 2012a).

An AT of 10–10.1 ml/kg/min appears to be predictive of LOS after pancreatic surgery. This may be used in current practice to guide postoperative care. Future studies will be required to validate this CPET result.

3.3.1.4.3 Morbidity

Junejo and colleagues reported that no CPET variable was related to postoperative morbidity following pancreatic surgery ($p<0.05$). Ausania and colleagues reported that patients with a mean AT of 14.1 (range 10.3–16.9) ml/kg/min experienced no complications, whereas patients who did develop complications had a mean AT of 11.3 (range 6.2–15.4) ml/kg/min ($p=0.02$) (Ausania et al., 2012b). In contrast, Chandrabalan and colleagues reported that an AT <10 ml/kg/min was significantly related to postoperative pancreatic fistula ($p=0.03$) and major intra-abdominal abscesses ($p=0.04$), but not cardiac ($p=0.31$) or pulmonary complications ($p=0.66$). Ausania and colleagues reported that the postoperative complication rate was significantly lower in the group with AT >10.1 ml/kg/min ($p=0.01$) (Ausania et al., 2012a).

3.3.1.5 Renal transplant

3.3.1.5.1 Mortality

Ulubay and colleagues were unable to determine whether CPET was predictive of postoperative mortality after renal transplant surgery because there were no deaths in the relatively small sample size (n=16) (Ulubay et al., 2010).

3.3.1.5.2 Length of stay

No single study examined whether there was a relationship between CPET variables and LOS after renal transplant. Ting and colleagues reported that mean AT was significantly lower in the CCU admission group vs the non-CCU admission group ($p<0.01$) (Ting et al., 2013).

3.3.1.5.3 Morbidity

There was no study that examined the prognostic ability of CPET for postoperative morbidity after renal transplant.

3.3.1.6 Upper gastrointestinal surgery

3.3.1.6.1 Mortality

Forshaw and colleagues could not conclude whether CPET was predictive of postoperative mortality because there was only one death after oesophagectomy (Forshaw et al., 2008).

3.3.1.6.2 Length of stay

Forshaw and colleagues reported that there was no apparent correlation with AT and LOS (p=0.89). Cardiopulmonary exercise testing appears unable to determine LOS after upper GI surgery, but there have been few studies in this area.

3.3.1.6.3 Morbidity

Nagamatsu and colleagues reported that VO_2 Max m^{-2} was lower in patients with cardiopulmonary complications compared to patients without complications (p<0.01) after oesophagectomy with lymphadenectomy (Nagamatsu et al., 2001). In contrast, Moyes and colleagues reported that VO_{2peak} was not associated with cardiopulmonary complications (14 vs 16 ml/kg/min, p=0.07) but that AT was associated with morbidity (p=0.05) (Moyes et al., 2013).

There have been too few studies to conclude whether CPET is predictive of postoperative morbidity after upper GI surgery, but the results are optimistic. The present review expresses the need for more high-quality CPET prognostic studies in upper GI surgery.

3.3.1.7 Bariatric surgery

3.3.1.7.1 Mortality

McCullough and colleagues (total n=99) reported that VO_{2peak} was predictive of morbidity and mortality (grouped together); however, there was only one death, and the results of this study cannot solely predict postoperative mortality (McCullough et al., 2006).

3.3.1.7.2 Length of stay

McCullough and colleagues reported that VO_{2peak} was predictive of LOS (p<0.01) (McCullough et al., 2006). The AT of patients with LOS >3 days was lower than that of patients with LOS ≤3 days after gastric bypass surgery (p=0.02) (Hennis et al., 2012). The literature suggests that CPET can identify patients subject to increased LOS, but a consensus on the optimal CPET variable and cut-point is required.

3.3.1.7.3 Morbidity

Hennis and colleagues reported that AT was significantly lower in patients with complications compared with those without complications (p<0.05) (Hennis et al., 2012). McCullough and colleagues presented a multivariable model using VO_{2peak} as a continuous variable and included smoking status that was a significant predictor of complications (OR: 1.61, 95% CI 1.19–2.18, p<0.01) (McCullough et al., 2006).

Cardiopulmonary exercise testing shows potential for determining patients at risk of postoperative complications in the preoperative period, but further studies are required to quantify the optimal CPET variable and cut-off point.

3.3.1.8 Intra-abdominal surgery

3.3.1.8.1 Mortality

Anaerobic threshold has been reported in four studies to be a significant predictor of mortality following intra-abdominal surgery (Snowden et al., 2013, Wilson et al., 2010, Older et al., 1999, Older et al., 1993). Snowden and colleagues reported an AT of 10.9 ml/kg/min to be predictive of postoperative survival; however, their follow-up was limited to in-hospital stay. An AT of 10.9 ml/kg/min was reported to be predictive of survival up to 90 days (p=0.03) (Wilson et al., 2010). Two studies presented an AT <11 ml/kg/min to be predictive of postoperative mortality (Older et al., 1999, Older et al., 1993).

Colson and colleagues concluded that AT was not a statistically significant predictor of mortality (Colson et al., 2012). Prentis and colleagues reported only two postoperative deaths, and no statistical analysis was performed (Prentis et al., 2013). Tolchard and colleagues could not conclude on the effectiveness of CPET due to an insufficient sample size (Tolchard et al., 2015).

The present review suggests that an AT of 10.9 ml/kg/min may have good clinical utility. It may also be beneficial to explore the prognostic ability of other CPET variables. A V_E/VCO_2 of 34 has been reported to be associated with postoperative mortality at 90 days (p=0.02) (Wilson et al., 2010).

3.3.1.8.2 Length of stay

Tolchard and colleagues reported that a lower mean oxygen uptake was correlated with ICU admission following intra-abdominal surgery (14.9 vs 16.5 ml/kg/min, $p<0.05$) and $V_E/VCO_2 \geq 33$ correlated with LOS ($p<0.01$). Wilson and colleagues reported that the overall median LOS was lower in the group with AT ≥11 ml/kg/min (8 vs 9 days, $p<0.01$) (Wilson et al., 2010). Snowden and colleagues reported that cardiovascular fitness was a significant independent predictor of hospital and critical care LOS (Snowden et al., 2013). The prognostic ability of CPET in predicting LOS after intra-abdominal surgery is strong; however, a consensus needs to be reached on the optimal CPET variable.

3.3.1.8.3 Morbidity

Hightower and colleagues reported that HR at AT ($p<0.01$), the difference between HR at rest and at AT ($p=0.01$), and the percentage AT achieved ($p=0.02$) to be predictive of postoperative morbidity (Hightower et al., 2010). Tolchard and colleagues, using Mann–Whitney U-tests, compared patients who experienced complications with those who did not and showed VO_2peak ($p=0.02$) and VE/VCO_2 ($p<0.01$) to be predictive of complications. The following AT cut-off values have been reported: 12, 11, 10.6, and 10.1 ml/kg/min (Prentis et al., 2013, Tolchard et al., 2015, Hightower et al., 2010, Snowden et al., 2010).

Anaerobic threshold is the strongest predictor of postoperative morbidity in intra-abdominal surgery. Patients with an AT of <10.1 ml/kg/min should have appropriate measures adopted to ensure a smooth postoperative outcome. Any patients with an AT between 10.1 and 12 ml/kg/min should be considered with caution.

Table 3.4: Preoperative cardiopulmonary exercise testing and mortality. CPET-derived cut-offs predictive of postoperative mortality. AT = Anaerobic Threshold, * = No value was given for VE/VCO_2, † = Only one death

Cardiopulmonary Exercise Testing and Mortality							
Author	**Sample Size**	**In-hospital**	**30 day**	**90 days**	1 year	≥ 2 years	Duration of follow-up not reported
Hepatic Resection and Transplant							
Bernal et al. (2014)	223	-	-	-	**AT 9.8 (non-survivors) vs. 11.7 (survivors) ml/kg/min**	-	-
Dunne et al. (2014)	197	-	-	-	-	-	-
Epstein et al. (2004)	59	-	-	**(100 days) Predicted VO_{2peak} <60% Predicted AT <50%**	-	-	-
Junejo et al. (2012)	94	-	**AT <9.9 ml/kg/min**	-	-	-	-
Kaibori et al. (2013)	61	-	-	-	-	**AT <11.5 ml/kg/min**	-
Neviere et al. (2014)	263	-	-	-	**VO_{2peak}; 18.6 vs. 17.1 ml/kg/min**	-	-
Prentis et al. (2012a)	60	-	-	**AT of 9.0 ml/kg/min**	-	-	-

Abdominal Aortic Aneurysm Repair							
Carlisle and Swart (2007)	130	-	-	-	-	**VE/VCO_2 and AT**	-
Grant et al. (2015)	506	-	-	-	-	**VO_{2peak} <15 ml/kg/min and VE/VCO_2 >42 at AT**	-
Hartley et al. (2012)	415	-	**AT <10.2 ml/kg/min and VE/VCO_2**	**VO_{2peak} <15 ml/kg/min and VE/VCO_2**	-	-	-
Nugent et al. (1998)	30	-	-	-	**VO_{2peak} - Not Significant**	-	
Colorectal Surgery							
Lai et al. (2013)	269	-	**AT <11.0 ml/kg/min**	**AT <11.0 ml/kg/min**	-	**AT <11.0 ml/kg/min**	-
West et al. (2013)	95	-	-	-	**VO_{2peak} of <10.6 ml/kg/min**	-	-
West et al. (2014)	136	-	-	-	-	-	-
Pancreatic Surgery							
Ausania et al. (2012a)	124	-	**AT <10.1 ml/kg/min - Not Significant**	-	-	-	-
Ausania et al. (2012b)	50	-	-	-	-	-	**AT - Not Significant**

Chandrabalan et al. (2013)	100	**AT – Not Significant**	-	-	-	-	-
Junejo et al. (2014)	64	**VE/VCO_2***	**$VE/VCO_2 > 41$**	-	-	-	-
Renal Transplant							
Ulubay et al. (2010)	16	-	-	-	-	-	-
Upper Gastrointestinal Surgery							
Forshaw et al. (2008)	78	-	-	-	-	-	-
Bariatric Surgery							
McCullough et al. (2006)	109	-	**VO_{2peak}†**	-	-	-	-
Intra-Abdominal Surgery							
Colson et al. (2012)	1,725	-	**AT – Not Significant**	-	**AT – Not Significant**	**AT – Not Significant**	-
Older et al. (1993)	187	-	-	-	-	-	**AT <11 ml/kg/min**
Older et al. (1999)	548	-	-	-	-	-	**AT <11 ml/kg/min**
Snowden et al. (2013)	389	**AT <10 ml/kg/min**	-	-	-	-	-
Wilson et al. (2010)	847	-	-	**AT of 10.9 ml/kg/min and VE/VCO_2 of 34**	-	-	-

Table 3.5: Preoperative cardiopulmonary exercise testing and length of stay. CPET-derived cut-offs predictive of LOS. AT = Anaerobic Threshold, CCU = Critical Care Unit, EVAR = Endovascular Aneurysm Repair, ICU = Intensive Care Unit, LOS = Length of Stay

Cardiopulmonary Exercise Testing and Length of Stay				
Author	**Sample Size**	**Hospital LOS**	**ICU/CCU Admission**	**ICU/CCU LOS**
Hepatic Transplant and Resection				
Bernal et al. (2014)	223	**AT <9.2 ml/kg/min,**	**-**	**VO_{2peak} <13.4 ml/kg/min**
Dunne et al. (2014)	197	**AT, VO_{2peak} (L/min)**	**-**	**-**
Junejo et al. (2012)	94	**-**	**-**	**AT <9.9 ml/kg/min**
Prentis et al. (2012a)	60	**-**	**-**	**AT <11 ml/kg/min**
Abdominal Aortic Aneurysm Repair				
Prentis et al. (2012b)	185	**AT <10 ml/kg/min (Open Repair and EVAR)**	**-**	**AT <10 ml/kg/min (Open Repair)**
Colorectal Surgery				
Lai et al. (2013)	269	**AT <11 ml/kg/min**	**-**	**-**
West et al. (2014)	136	**AT, VO_{2peak}, VE/VCO_2**	**-**	**-**
Pancreatic Surgery				
Ausania et al. (2012a)	124	**AT ≤10.1 ml/kg/min**	**-**	**-**

Chandrabalan et al. (2013)	100	**AT <10 ml/kg/min**	**-**	**-**
Renal Transplant				
Ting et al. (2013)	70	**-**	**AT**	**-**
Upper Gastrointestinal Surgery				
Forshaw et al. (2008)	78	**AT <11 ml/kg/min – Not Significant**	**-**	**-**
Bariatric Surgery				
McCullough et al. (2006)	109	**VO_{2peak}***	**-**	**-**
Hennis et al. (2012)	106	**AT <11.4 ml/kg/min**	**-**	**-**
Intra-Abdominal Surgery				
Snowden et al. (2013)	389	**AT <10 ml/kg/min**	**-**	**AT <10 ml/kg/min**
Tolchard et al. (2015)	105	**AT, V_E/VCO_2**	**VO_{2peak}***	**-**
Wilson et al. (2010)	847	**AT <11 ml/kg/min**	**-**	**-**

Table 3.6: Preoperative cardiopulmonary exercise testing and morbidity. CPET-derived cut-offs predictive of postoperative morbidity. AT = Anaerobic Threshold, ISGPF = International Study Group on Pancreatic Fistula, POMS = Postoperative Morbidity Survey *= No value was given

Cardiopulmonary Exercise Testing and Morbidity								
Author	**Sample Size**	**Morbidity Measure**	**In-hospital**	**7 days**	**30 day**	**90 day**	**>90 Days**	**Not Reported**
Hepatic Resection and Transplant								
Dunne et al. (2014)	197	Clavien-Dindo	-	-	**Heart Rate at AT and Heart Rate at VO_{2peak}**	-	-	-
Junejo et al. (2012)	94	POMS, Clavien-Dindo	-	-	**VE/VCO_2 at AT**	-	-	-
Kaibori et al. (2013)	61	Clavien-Dindo	-	-	-	-	**AT <11.5 ml/kg/min**	-
Abdominal Aortic Aneurysm Repair								
Nugent et al. (1998)	30	Self-Defined		-	-	-	**VO_{2peak} – Not Significant**	-
Prentis et al. (2012b)	185	Self-Defined	**AT ≤10 ml/kg/min, VO_{2peak}* and VE/VCO_2**	-	-	-	-	-
Colorectal Surgery								
Lee et al. (2013)	112	Clavien-Dindo	-	-	**VO_{2peak}***	-	-	-

West et al. (2013)	95	POMS, Clavien-Dindo	-	-	**AT <10.1 ml/kg/min and VO_{2peak} 16.7 ml/kg/min**	-	-	-
West et al. (2014)	136	POMS, Clavien-Dindo	-	-	-	-	**VO_{2peak} <18.6 ml/kg/min and AT <10.6 ml/kg/min**	-
Pancreatic Surgery								
Ausania et al. (2012a)	124	POMS, ISGPF	-	-	**AT ≤10.1 ml/kg/min**	-	-	-
Ausania et al. (2012b)	50	POMS	-	-	-	-	-	**AT ≥14.1 ml/kg/min**
Chandrabalan et al. (2013)	100	Clavien-Dindo and ISGPF	**AT <10 ml/kg/min**					
Junejo et al. (2014)	64	ISGPS for pancreatic complications Non-pancreatic complications were self-defined.	-	-	-	-	**No CPET variable was significant**	-
Upper Gastrointestinal Surgery								
Moyes et al. (2013)	108	Cardio-pulmonary complications defined according to the Common	-	-	-	-	-	**AT 9.9 (complications) vs. 11.2 (no**

		Terminology Criteria for Adverse Events. Non-cardio-pulmonary complications were self-defined.						**complications) ml/kg/min**
Nagamatsu et al. (2001)	91	Self-Defined	-	-	-	-	-	**VO_2 Max/m² ***
Bariatric Surgery								
Hennis et al. (2012)	106	POMS	**AT <11 ml/kg/min**	-	-	-	-	-
McCullough et al. (2006)	109	Self-Defined	-	-	**VO_{2peak} <18.5 ml/kg/min**	-	-	-
Intra-Abdominal Surgery								
Hightower et al. (2010)	32		-	**Heart Rate at AT, Difference between Heart Rate from rest to AT and Percentage of predicted AT achieved (<75% vs. ≥75%)**	-	-	-	-
James et al. (2013)	83	Major adverse cardiac events and self-defined	-	-	**AT <10.6 ml/kg/min and VO_{2peak}**	-	-	-

					<14.0 ml/kg/min			
Prentis et al. (2013)	69	Clavien-Dindo	**AT <12 ml/kg/min**	**-**	**-**	**-**	**-**	**-**
Snowden et al. (2010)	116	POMS	**AT (POMS ≤1) 11.9 vs. 9.1 ml/kg/min (POMS >1)**	**-**	**-**	**-**	**-**	**-**
Tolchard et al. (2015)	105	Clavien-Dindo	**-**	**-**	**-**	**AT (complications) 10.6 vs. 11.8 ml/kg/min (no complications), VO_{2peak} (complications) 14.3 vs. 15.4 ml/kg/min (no complications), V_E/VCO_2 (complications) 33.3 vs. 30.3 (no complications)**	**-**	**-**

3.3.2 Field tests of exercise tolerance

3.3.2.1 Six minute walk test

Four studies assessed the ability of the 6MWT to predict postoperative outcome (Table 3.7). Moriello and colleagues reported 31, out of a total of 63, patients developed postoperative complications following colorectal resection and found no statistically significant difference in terms of 6MWT distance between patients with and without complications (Moriello et al., 2008). The raw data describing preoperative 6MWT distances between groups with and without complications was not reported. Lee and colleagues noted that in a multivariate analysis containing nine variables, such as age, sex, BMI and comorbidities, the 6MWT correlated with medical ($p=0.033$) and any (medical and surgical) complication ($p=0.012$) but not surgical complications post colorectal surgery (Lee et al., 2013). Medical complications included urinary tract infections, cardiopulmonary complications, upper gastrointestinal bleeding, clostridium difficil infection and deep vein thrombosis. Surgical complications included surgical site infection, ileus, anastomotic leak and haematoma requiring transfusion.

Paisani and colleagues reported there was no difference in preoperative 6MWT distance in subjects who developed PPC's compared to those without PPC's ($p=0.57$) post upper abdominal surgery (Paisani et al., 2012). Arruda and colleagues reported the 6MWT was unable to predict postoperative cardiopulmonary complications in upper abdominal surgery (Arruda et al., 2013).

No study examined the ability of the 6MWT to predict postoperative mortality and LOS. Paisani and colleagues reported that mortality and LOS following upper abdominal surgery was higher in patients who developed PPC's compared to those who did not ($p<0.01$) (Paisani et al., 2012). The authors did not report if preoperative 6MWT distance was predictive of postoperative mortality or LOS.

3.3.2.2 Incremental shuttle walk test

Two studies required patients to perform the ISWT prior to surgery. The surgical procedures included colorectal resection and oesophagogastrectomy. The ability of the ISWT to predict mortality post colorectal surgery is limited due to the low rate of mortality reported in included studies. Nutt and Russell (2012) reported one death in their cohort of 120 patients (Nutt and Russell, 2012). Murray and colleagues reported patients undergoing oesophagogastrectomy who walked ≥350m or more during the ISWT reported no deaths within 30 days of operation; however there was no statistical analysis performed (Murray et al., 2007).

Patients undergoing colorectal surgery with higher preoperative ISWT distances had shorter stays in hospital. Patients with a preoperative ISWT distance <250m had a LOS of 14 (IQR: 9-24) days, compared to patients with a distance >250m who had a LOS of 8 (IQR: 6-10) days ($p<0.01$). In the study by Murray et al. (2007) there was insufficient statistical analysis performed to assess if the ISWT can predict hospital LOS following oesophagogastrectomy (Murray et al., 2007).

In terms of morbidity, Nutt and Russell (2012) reported patients undergoing colorectal surgery who developed postoperative complications, as measured by Clavien-Dindo classification score, had a mean preoperative ISWT distances of 256.8m (SD: 113.8) compared to those without complications who had a mean distance of 382.7m (SD: 145.3) (Nutt and Russell, 2012).

3.3.2.3 Stair climb test

Only one study assessed the ability of the stair climb test to predict postoperative outcome. Arruda et al. (2013) reported the SCT was unable to predict postoperative cardiopulmonary complications post upper abdominal surgery (Arruda et al., 2013).

Table 3.7: Field tests and postoperative outcomes. 6MWD = 6 Minute Walk Distance, 6MWT = 6 Minute Walk Test, CI = Confidence Interval, ISWT = Incremental Shuttle Walk Test, LOS = Length of Stay, N/A = Not Applicable, PPC = Postoperative Pulmonary Complications, SCT = Stair Climb Test, SD = Standard Deviation

Author	Surgery	Mortality	LOS	Morbidity
Six Minute Walk Test				
Arruda et al. (2013)	Upper Abdominal and Thoracic Surgery	N/A	N/A	Duration of follow-up: In-hospital stay Morbidity Measure: Self-defined cardiopulmonary complications No exercise variable presented a significant correlation with complications in Upper Abdominal Surgery. There was a significant correlation between complications in Thoracic surgery and the 6MWT distance (p=0.0062) and SCT time (p=0.0012).
Lee et al. (2013)	Colorectal Surgery	N/A	N/A	Duration of follow-up: 30 days Morbidity Measure: Clavien-Dindo 6 min vs. VO_2peak, for each meter increase in distance, VO_2peak increased by 0.042 (95% C.I=0.035-0.050) ml/kg/min. Multivariate Analysis: 6MWD and Any complication; 0.51 (95% C.I: 0.30-0.87, p=0.012), 6MWD and Medical Complication; 0.49 (95% C.I: 0.25-0.94, p=0.033). No statistically significant correlation with surgical complication. VO_2peak and Medical Complication; 0.31 (95% C.I: 0.13-0.71, p=0.006). No statistically significant correlation with All-cause or Surgical Complications.
Moriello et al. (2008)	Colon Resection	N/A	N/A	Duration of follow-up: 6 weeks Morbidity Measure: Self-defined complications No statistically significant difference in terms of 6MWT distance between the group with postoperative complications and the group without complications.
Paisani et al. (2012)	Upper Abdominal Surgery	N/A	N/A	Duration of follow-up: In-hospital stay Morbidity Measure: Self-Defined Postoperative Pulmonary Complications

				PPC's group (6 minute walk test distance = 466.0 ± 97.0 m) vs. No PPC's group (6 minute walk test distance = 485.3 ± 107.1); p=0.57
Incremental Shuttle Walk Test				
Murray et al. (2007)	Oesophagogastrectomy	Duration of follow-up: 30 days No patient who walked 350m or more died within 30 days. No statistical analysis performed.	Statistical analysis was insufficient Destination at 30 days (median): Home; 540 m, Ward; 445 m, Critical Care; 370 m	N/A
Nutt and Russell (2012)	Colorectal Surgery	Duration of follow-up:30 days One postoperative death (0.8%)	ISWT Distance <250 m LOS was 14 days (IQR: 9-24) vs. >250 m was 8 days (IQR: 6-10) p <0.0001.	Duration of follow-up: 30 days Patients suffering major complication mean distance 256.8 m (SD: 113.8) compared to patients without complication, mean distance 382.7 m (145.3). ROC Curve Analysis, ISWT Distance cut-point of 250m, AUC=0.74, 95% C.I: 0.64-0.83, p <0.0001, 88% specificity and 58% sensitivity
Stair Climb Test				
Arruda et al. (2013)	Upper Abdominal and Thoracic Surgery	N/A	N/A	Duration of follow-up: In-hospital stay Morbidity Measure: Self-defined cardiopulmonary complication There was no significant difference in time to complete stair climb test between patients who developed complications and those who did not post-upper abdominal surgery (p=0.212)

3.4 Discussion

Previous reviews concluded that CPET is a valuable predictor of postoperative outcome, but more research is needed to determine its validity in non-cardiopulmonary surgery (Hennis et al., 2011, Smith et al., 2009). The area has grown since the publication of these reviews, and the present review has analysed considerably more studies and is the largest systematic review of preoperative CPET published to date. Given that a qualitative synthesis approach was undertaken, definite conclusions cannot be drawn from the present review regarding the ability of CPET to predict postoperative outcome after surgery, but certain areas can be highlighted and suggestions can be made.

3.4.1 Main findings

This review recommends that CPET may be useful in the preoperative assessment of liver, pancreatic, and intra-abdominal surgery and AAA repair and that the following cut-points are predictive of clinical outcomes.

- Hepatic transplant and resection: 90 day survival, AT 9 ml/kg/min; 3 year survival, AT 11.5 ml/kg/min; and ICU/CCU admission, AT <9.9–11 ml/kg/min.
- Abdominal aortic aneurysm repair: 90 day survival, VO_{2peak} 15 ml/kg/min.
- Pancreatic surgery: LOS and morbidity, AT 10–10.1 ml/kg/min.
- Intra-abdominal surgery: mortality, AT of 10.9 ml/kg/min; morbidity, AT <10.1 ml/kg/min; and patients with an AT of 10.1–12 ml/kg/min should be treated with caution.

In regards to field tests of exercise tolerance the ISWT was significantly associated with LOS and complications post-colorectal surgery and a cut-off of 250m may help predict the postoperative requirements of colorectal surgery patients (Nutt and Russell, 2012). In addition, Murray and colleagues reported that patients who walked a preoperative distance <350m during the ISWT had an increased risk of mortality post-oesophagogastrectomy, however this cut-off requires further validation, as this study was found to have the highest risk of bias of all studies reviewed (Murray et al., 2007) (Table 3.3). Studies examining the 6MWT produced conflicting results regarding its ability to identify high-risk patients and the evidence examining the predictive ability of the SCT is lacking. Overall the evidence behind field tests is weaker compared to CPET.

3.4.2 Cardiopulmonary exercise testing

CPET has been reported to be able to predict postoperative outcome, however it is unclear how higher levels of cardiorespiratory fitness can influence postoperative complications. As discussed in Chapter 1, it is likely that patients with higher levels of cardiorespiratory fitness are better able to meet the greater oxygen demands postoperatively. However, in this review, anaerobic threshold was identified as the optimal predictor of outcome in liver, pancreatic, and intra-abdominal surgery compared to other CPET variables such as VO_{2peak} and VE/VCO_2. Increases in lactate production post-surgery are theorised to lead to postoperative dysfunction (Chapter 1.2.4) and it is likely that patients with a lower anaerobic threshold are unable to manage the subsequent increase in net lactate production, leading to increased postoperative risk.

Studies were divided based on surgery type, similar to previous reviews and the strength of relationship between CPET variable and postoperative outcome varied between surgical interventions (Hennis et al., 2011, Smith et al., 2009, West et al., 2011). The variation in cut-points between surgeries may be because of the possibility that certain surgical procedures require a greater physiological demand, or the pre- and postoperative management varies between surgical procedures (Levett and Grocott, 2015).

The relationship between morbidity after pancreatic surgery has produced conflicting results. One study reported no relationship between AT and morbidity (Junejo et al., 2014). In contrast, two studies reported that an AT of 10-10.1 ml/kg/min was predictive of postoperative morbidity (Ausania et al., 2012a, Chandrabalan et al., 2013), while one study reported an AT of ≥14.1 ml/kg/min was predictive of postoperative morbidity (Ausania et al., 2012b). The present review suggests using an AT of 10–10.1 ml/kg/min as a cut-point for morbidity after pancreatic surgery (Ausania et al., 2012a, Chandrabalan et al., 2013) instead of 14.1 ml/kg/min as reported by Ausania and colleagues because it was found to have a relatively high risk of bias using the QUIPS tool, which is likely to have biased results (Ausania et al., 2012b).

3.4.3 Field tests of exercise tolerance

Studies examining the 6MWT reported conflicting results in regards to its ability to predict postoperative outcome. In comparison, the ISWT was reported to be predictive of postoperative outcome in colorectal and oesophagogastrectomy (Nutt and Russell, 2012, Murray et al., 2007). The ISWT is an externally paced field test during which patients are stressed to a symptom-limited maximal performance and is therefore similar to a maximal CPET. The ISWT generates higher metabolic and

ventilatory levels compared to self-paced tests such as the 6MWT (Oliver et al., 2015). The 6MWT is susceptible to biased results as patients can regulate their physical effort during the test. The ISWT is more demanding than the 6MWT and so may be a superior method of assessing cardiopulmonary fitness when CPET is unavailable. Furthermore, the ISWT has a higher correlation with AT (r=0.775) than either the 6MWT (r=0.587) and the SCT (r=0.592) (Khan et al., 2011, Irisawa et al., 2014). The ISWT may be better than the 6MWT and SCT to predict postoperative outcome following abdominal surgery due to higher correlations with AT. This is in agreement with the results of this review, which reported that the ISWT was able to predict postoperative morbidity and LOS in colorectal surgery and postoperative mortality following oesophagogastrectomy.

The ability of the SCT to predict postoperative outcome in abdominal surgery has only been investigated by one study (Arruda et al., 2013). Arruda and colleagues reported the SCT was not correlated with postoperative complications; however this study only assessed PPC's and not all-cause complications e.g. renal and gastrointestinal (Arruda et al., 2013). The SCT is better correlated with VO_2peak than AT, therefore the SCT may be useful in predicting outcome in surgeries that use VO_2peak as a predictive variable e.g. thoracic and abdominal aortic aneurysm (Pollock et al., 1993, Cataneo and Cataneo, 2007, Khan et al., 2011).

3.4.4 Methodological quality

There are four main reasons for associations in observational studies between cardiopulmonary fitness and postoperative outcome: bias, confounding, chance, and cause (Jepsen et al., 2004). The level of bias and confounding was assessed using the QUIPS tool (Hayden et al., 2013). The level of chance of association is summed up by the 95% CIs and p-value (Appendix G). The CPET-derived cut-points are similar between studies; as the level of bias, chance, and confounding have been accounted for, it is likely that a cause of poor postoperative outcome is cardiorespiratory fitness below these cut-points.

There is large heterogeneity between studies; therefore, results could not be pooled to complete a meta-analysis. All surgeries were grouped together by surgical intervention (or grouped into the intra-abdominal cohort when no distinctions were made) to improve homogeneity. Despite this, there is considerable variation in areas such as surgical procedure (e.g. laparoscopic vs. open), the outcome measures used (e.g. postoperative morbidity survey vs. self-defined morbidity), and accounting for co-morbidities. A number of important variables, such as type of anaesthesia and length of surgery, were not reported in most studies (n=34). The choice of statistical approaches also varied between studies.

The present review included studies that did not have *a priori* power calculation. The sample sizes of the included studies may be underpowered and could potentially influence results. In order for future studies to have sufficient power to determine the ability of an AT <11 ml/kg/min to predict mortality at 90 days, we estimate that a sample size of 406 patients above and below AT <11 ml/kg/min is required, and for 2 year mortality a sample size of 253 above and below AT <11 ml/kg/min is required (α=0.05, β=0.80). The calculations were based on data reported by Lai and colleagues (Lai et al., 2013).

A robust methodology should also be used for future studies (Grocott and Pearse, 2010). This review recommends that future studies consist of the following: (i) report all measured CPET variables (e.g. VO_2peak, AT, VE/VCO_2, and HR); (ii) predetermined outcome time points should be used, including 30 day, 90 day, 1, 3, and 5 year time points for mortality and morbidity, and LOS should include overall hospital stay, ICU/HDU/CCU admission, and length of stay along with readmission; (iii) morbidity should be measured using a combination of the Clavien–Dindo classification scoring system (Dindo et al., 2004) and the Postoperative Morbidity Survey (Bennett-Guerrero et al., 1999); and (iv) odds ratios should be determined for mortality and morbidity outcomes to allow results to be pooled in a future meta-analysis. Length of stay should be recorded with means, standard deviations, and 95% CIs.

Many studies conclude separate CPET-defined cut-points that predict postoperative outcome. Perhaps a single cut-point cannot be recommended; instead, subgroups based on fitness could be created to stratify patients before surgery based on the risk of poor surgical outcome (McCullough et al., 2006). It is also possible that the variation between CPET variables and strength of relationship with outcome between studies is subject to the inconsistent methodology coupled with data analysis and presentation.

3.4.5 Future research

The areas of colorectal, renal transplant, upper GI, and bariatric surgery require further research to draw conclusions concerning the ability of CPET to predict postoperative outcome. In hepatic surgical intervention, the postoperative morbidity has not been well analysed; currently, there is no consensus on the CPET variable and cut-point to use. The ability of AT to predict LOS after hepatic surgery produces a divided opinion. The VO_2peak shows potential, but evidence in its support is weak. It is recommended that future studies examine the possible link between preoperative aerobic fitness and morbidity and LOS. A number of studies have examined CPET and survival after AAA repair, but time

points to survival vary and so future studies will need to use specific time points, such as 1 and 5 year survival. The present review suggests future research should examine the possible relationship between CPET and LOS and morbidity after AAA repair because research in this area is lacking.

Higher levels of physical fitness are correlated with improved postoperative outcome. Patients with cardiopulmonary fitness below the recommended cut-points are susceptible to postoperative complications and mortality. Preoperative exercise programmes may improve fitness before surgery (Dronkers et al., 2010). The ability of preoperative exercise interventions to improve postoperative outcome requires further validation.

3.5 Conclusion

Cardiopulmonary exercise testing provides a good objective measure of a patient's preoperative fitness, which in turn is a strong predictor of postoperative outcome. Cardiopulmonary exercise testing has been well documented in certain surgical interventions (liver, AAA, pancreatic, and intra-abdominal), but it is less well defined in other areas (colorectal, renal transplant, upper GI, and bariatric). The CPET variables AT and VO_2peak are the most commonly analysed. Anaerobic threshold is a stronger predictor of outcome in hepatic, pancreatic, and intra-abdominal surgery, whereas VO_2peak is superior in AAA repair. Variables such as VE/VCO_2 show emerging significance but continue to be underused. Future studies should use a robust methodology to clarify further the role of CPET in preoperative risk prediction.

CPET is a superior method of predicting postoperative outcome following intra-abdominal surgery compared to field tests of exercise tolerance. The evidence behind field tests of exercise tolerance is weaker, and so future research is needed to justify their use. In addition field tests are more relevant to clinical practice as they are cheaper and easier to use compared to CPET. The ISWT demonstrates the greatest predictive ability compared to the 6MWT and the SCT. The ISWT is externally paced, therefore patients are more likely to reach their maximal exercise tolerance as opposed to the 6MWT which is subject to patients regulating their physical activity. The 6MWT requires further studies to validate its use at predicting postoperative outcome due to the conflicting results of the studies in this review. In addition, the SCT requires further research to justify its use in an abdominal surgery cohort.

4 Chapter 4 The role of preoperative physical fitness in postoperative outcome following colorectal surgery: an observational study

4.1 Introduction

Patients following colorectal surgery are subject to considerable postoperative risk, and the incidence of postoperative complications can significantly increase hospital costs and adversely affect an individual's quality of life (Chapter 1.8.1.1). Therefore, the preoperative identification of patients at high-risk of poor postoperative outcome can help clinicians to develop effective treatment plans and allocate limited resources, such as ICU admission, based on level of postoperative risk.

The results of the systematic review in Chapter 3 conclude that cardiopulmonary exercise testing can predict postoperative outcome and identify high-risk patients (Chapter 3.3). However the evidence in support of CPET in colorectal surgery is limited as there is no definitive CPET derived cut-point predictive of postoperative outcome (Chapter 3.3.1.3). In addition, only maximal CPET has been used in a colorectal surgery cohort, which requires a significant amount of resources and is more labour intensive compared to the easier to perform, sub-maximal CPET (Noonan and Dean, 2000). To the authors knowledge, the ability of sub-maximal CPET to predict postoperative morbidity, mortality and LOS in a colorectal surgical cohort has not been studied.

Furthermore, it has been reported that more studies are required to assess whether CPET derived variables can be used with other non-CPET markers to improve prediction of postoperative outcome and enhance perioperative risk assessment (West et al., 2016). Preoperative tests of physical fitness that can be used in conjunction, or more importantly, independently of CPET would be beneficial as CPET is a labour intensive and expensive preoperative assessment that is not readily available in all clinics. Cardiorespiratory fitness is a component of physical fitness that also includes muscular strength and endurance, and body composition. Therefore, it is possible that other tests of physical fitness can be used to identify high-risk patients scheduled for colorectal surgery.

Field tests such as the 6MWT indirectly measure cardiorespiratory fitness (Chapter 2.3.2.1), and are cheaper and easier to administer compared to CPET, however studies investigating the ability of the 6MWT to predict postoperative outcome have reported conflicting results (Chapter 3.3.2.1). These results justify the need for further research to validate its efficacy in identifying high-risk patients. The

6MWT is a simple method of measuring functional capacity that is more easily tolerated than CPET, and can also be administered in the immediate postoperative setting as a method of measuring functional recovery (Pecorelli et al., 2016). Functional impairment is a common consequence of surgery with patients experiencing a significant and clinical decrease in functional capacity while in hospital (Gannon et al., 2015) and although higher levels of preoperative physical fitness are protective against poor postoperative outcome, the relationship between preoperative fitness and postoperative functional recovery is unclear.

In colorectal surgery, frailty has been identified as a risk factor for poor postoperative outcome (Tan et al., 2012). Frailty is defined as a state of vulnerability characterised by an age-associated decline in physiological function and reserve leading to an increased risk of adverse outcomes, and is measured through a combination of function, cognition, nutrition, and geriatric assessments (Fagard et al., 2016, Chen et al., 2014). Hand grip strength is a recognised component of measuring frailty and is a simple measure reflective of overall muscle strength with wide clinical utility, commonly used by therapists (Fagard et al., 2016, Reuter et al., 2011). There is conflicting evidence regarding the ability of grip strength to predict postoperative outcome independently (Chen et al., 2011, van Egmond et al., 2016). Chen and colleagues reported that low grip strength was predictive of postoperative complications in a cohort of 68 patients scheduled for oesophagectomy, however in contrast van Egmond and colleagues reported that low hand grip strength was not associated with complications as measured using the Clavien-Dindo score in a cohort of 94 patients scheduled for oesophagectomy. These results justify the need for further research into the predictive ability of grip strength.

Cardiopulmonary exercise testing can identify all-cause postoperative complications, however it is unable to identify specific types of complications such as postoperative pulmonary complications, which are a major source of morbidity post-colorectal surgery (8.8%-13.7%) (West et al., 2014b, West et al., 2014c). Measures that can specifically target patients at risk of PPC's may help to prepare appropriate treatments to reduce the risk of PPC's. Inspiratory muscle training has previously been identified as beneficial in reducing the incidence of PPC's, however it is unclear if patients with lower inspiratory muscle strength are at higher risk of PPC's (Dronkers et al., 2008). Furthermore, higher levels of physical activity have been identified as protective against poor postoperative outcome in oesophageal surgery (Feeney et al., 2011, Feeney et al., 2010), however their role in colorectal surgery has been underexplored.

4.2 Aims and objectives

It is hypothesised that measures of physical fitness such as hand-grip strength and physical activity levels, that are cheaper and easier to administer than CPET, may be predictive of outcome following colorectal surgery. The aim of this study was to assess if measures of physical fitness (sub-maximal CPET, 6MWT, hand-grip strength, IMT, and physical activity levels) are predictive of postoperative outcome (morbidity, LOS and mortality) in colorectal surgery. The objectives of this study were to: (i) define a CPET derived cut-off predictive of postoperative outcome in colorectal surgery, and (ii) assess if preoperative physical fitness is associated with reduced functional impairment, assessed using the 6MWT, on postoperative day six (POD6).

4.3 Methods

4.3.1 Study design

This was a prospective, observational cohort study undertaken between October 2014 and December 2015. Approval for the study was granted by the SJH/Adelaide & Meath Hospital Incorporating the National Children's Hospital (AMNCH) Research Ethics Committee, Dublin (Appendix B). The 'Strengthening and Reporting of Observational studies in Epidemiology' (STROBE) guidelines for reporting observational studies were followed in preparing this chapter (von Elm et al., 2014). Participants attended a single preoperative assessment of baseline physical fitness prior to surgery. Postoperatively participants were followed up for the presence of complications, LOS and mortality. In addition, participants completed a functional walking test on POD6.

4.3.2 Participants & centre

Participants scheduled for colorectal surgery in the Colorectal & General Surgery Clinic in St. James's Hospital, Dublin who met the eligibility criteria were invited to take part. A participant information leaflet and consent form were extended to attendees of the clinic who met the recruitment criteria (Appendix C). Participants had up to three days to provide informed consent, as the window between assessment and surgery is limited (approximately 2 weeks).

4.3.3 Eligibility criteria

Eligible participants were at least 18 years of age, scheduled for colorectal surgery and able to provide written informed consent. Suitable participants were identified by consultants and nurse coordinators. Exclusion criteria consisted of the ATS/ACCP contraindications to CPET (Table 4.1), emergency surgery situations and participants unable to walk independently (ATS/ACCP, 2003). CPET is a safe procedure with the risk of mortality between 2 and 5 patients per 100,000 CPET's (ATS/ACCP, 2003). Despite this, CPET is a test that requires the patient to exercise to sub-maximal or maximal effort and places the cardiorespiratory system under stress. The ATS/ACCP report that the risk of medical complications is related to the underlying disease. Therefore, there are a number of absolute contraindications to CPET. As CPET is performed in a laboratory with trained personal, with monitoring and resuscitation equipment available, there are only a few absolute contraindications. These criteria are to ensure that only the most high-risk patients do not perform CPET. The ATS/ACCP developed absolute and relative contraindications to CPET and to ensure safe practice and to be in line with good clinical practice, this study employed these contraindications as exclusion criteria.

Table 4.1: The ATS/ACCP absolute and relative contraindications for exercise testing.

ATS/ACCP Absolute and Relative Contraindications to Exercise Testing:
Absolute Contraindications
• Acute myocardial infarction • Unstable angina • Uncontrolled arrhythmias causing symptoms or hemodynamic compromise • Syncope • Active endocarditis • Symptomatic severe aortic stenosis • Uncontrolled heart failure • Acute pulmonary embolus or pulmonary infarction • Thrombosis of lower extremities • Suspected dissecting aneurysm • Uncontrolled asthma • Pulmonary oedema • Room air desaturation at rest ≤85% • Respiratory failure • Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis) • Cognitive impairment leading to inability to cooperate
Relative Contraindications

- Left main coronary stenosis or equivalent
- Moderate stenotic valvular heart disease
- Severe untreated arterial hypertension at rest (>200 mmHg systolic, >120 mmHg diastolic)
- Tachyarrhythmias or bradyarrhythmias
- High-degree atrioventricular block
- Hypertrophic cardiomyopathy
- Significant pulmonary hypertension
- Pregnancy
- Electrolyte abnormalities
- Orthopaedic impairment that compromises exercise performance

4.3.4 Preoperative assessment protocol

Participants attended a single preoperative session in the Wellcome-Trust Health Research Board Clinical Research Facility in St. James's Hospital. A standardised test protocol was used for all assessments. Participants underwent a comprehensive physical fitness assessment undertaken by the same experienced physiotherapist. Participant sociodemographic and clinical outcome measures were also performed by the same physiotherapist. Prior to beginning testing, participant resting HR, SpO_2, and blood pressure were measured. In accordance with ATS/ACCP guidelines for CPET, participants were requested to (i) avoid smoking 8 hours prior to testing (ii) take their prescribed medications (iii) avoid exercise on the day of testing and (iv) have a light meal no less than 2 hours before testing.

4.3.5 Demographic outcomes

Participant age, gender, comorbidities, and smoking and alcohol history were obtained at baseline assessment from the participant. The following surgery specific measures were also recorded from the medical chart; diagnosis, type of surgery, and treatment regimen (e.g. neoadjuvant chemoradiotherapy). All participants were enrolled on the standard institutional ERAS protocol, similar to the ASGBI guidelines (Khan et al., 2009). Preoperative carbohydrate loading was not performed due to logistical restraints at the institution (SJH).

4.3.6 Clinical outcomes

To assess preoperative risk each participant was assessed using the ASA and the CR-POSSUM score as outlined in Chapter 2.2.1.

4.3.7 Preoperative assessment of physical performance

Participant height and weight were measured using a stadiometer and SECA weighing scale and used to calculate BMI. Participant waist and hip circumference, cardiorespiratory fitness, muscular strength, inspiratory muscle strength, and physical activity levels were measured using the following methods and protocols:

- Waist and hip circumference (see Chapter 2.3.4.2.1)
- Sub-maximal cardiopulmonary exercise test (see Chapter 2.3.1.12)
- The six-minute walk test (see Chapter 2.3.2.1.1)
- Pulmonary function testing (see Chapter 2.3.5.1)
- Hand grip dynamometry (see Chapter 2.3.3.1.1)
- Inspiratory muscle strength (see Chapter 2.3.3.2.1)
- Physical activity levels using the YPAS and Actigraph accelerometer (see Chapter 2.4)

The 6MWT was performed in accordance with the ATS/ACCP guidelines (ATS, 2002) to measure preoperative functional capacity and postoperative functional recovery. In the preoperative assessment participants were given up to 30 minutes to rest prior to initiating the 6MWT. Postoperatively, participants were requested to complete the 6MWT to measure the level of return to baseline functional capacity, on POD6, as the average length of stay post-colorectal resection is 6 days (Miller et al., 2014). If participants were unable to perform the 6MWT on POD6 for any reason (e.g. complications) the 6MWT was performed on the next available day, however these results were excluded from analysis. The 6MWT was performed on day of discharge in the event a participant was discharged prior to POD6. The preoperative assessment measures are outlined in Figure 4.1.

4.3.8 Postoperative assessment

Following surgical resection, participants were monitored for postoperative morbidity, mortality and length of stay. Postoperative complications were recorded using the Clavien-Dindo Classification Score, the POMS and the CCI (Dindo et al., 2004, Bennett-Guerrero et al., 1999, Slankamenac et al., 2013) (Chapter 2.2.2). LOS included general hospital stay from surgery to discharge, ICU/HDU admission rates and ICU/HDU LOS. Hospital readmission rates within 30 days were also recorded. Mortality was recorded until day 30 post-op. The postoperative assessment measures are outlined in Figure 4.1.

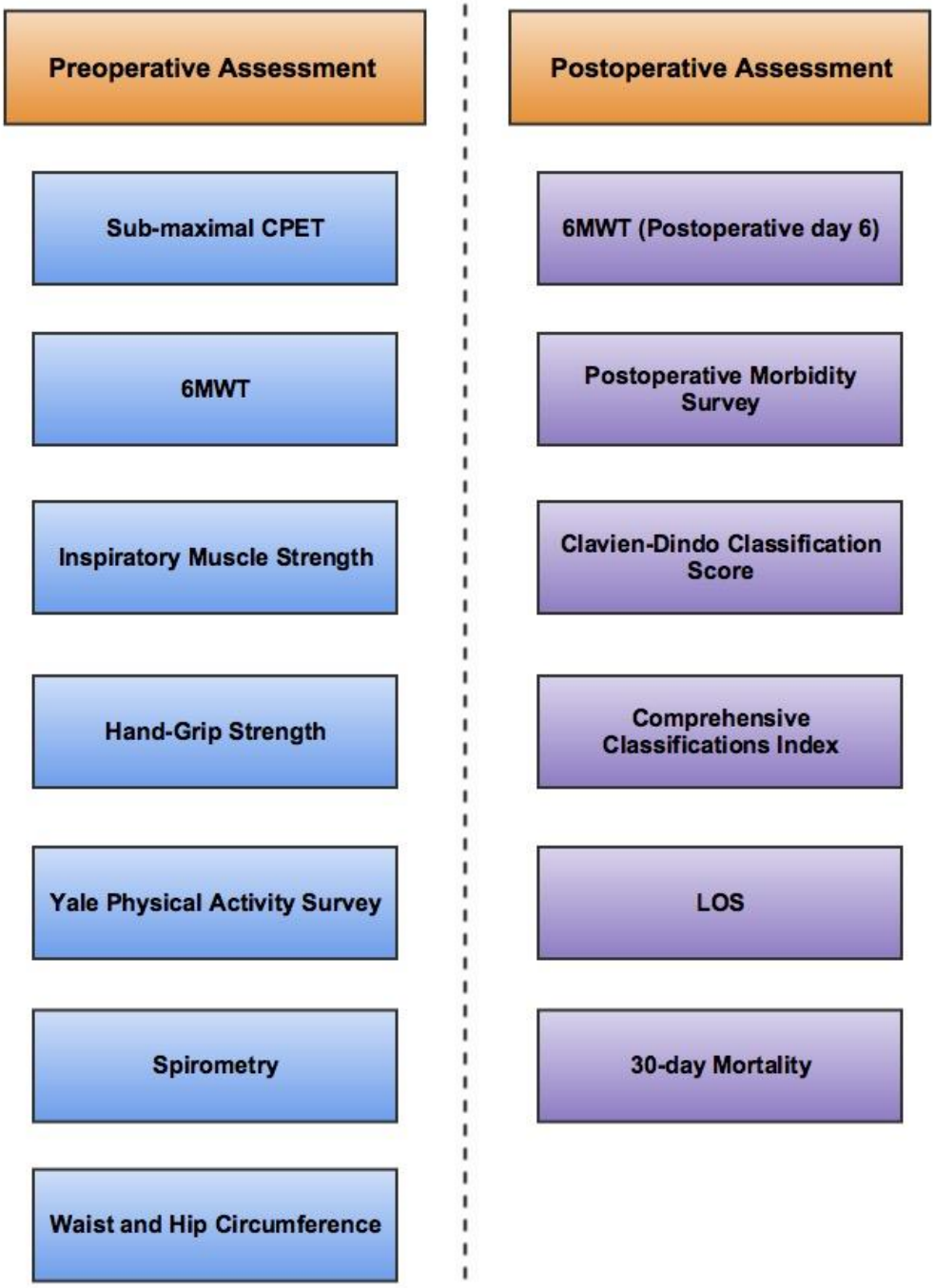


Figure 4.1: Preoperative and postoperative assessment measures used in this study. 6MWT: Six Minute Walk Test, CPET: Cardiopulmonary Exercise Testing, LOS: Length of Stay

4.3.9 Statistical analysis

Statistical analysis was performed using SPSS v.23.0. Normality was assessed using the Shapiro-Wilk test. Normally distributed data was presented as mean and standard deviation. Non-normally distributed data was transformed to resemble normally distributed data. Participants were categorised

based on presence of morbidity on POD6 as measured by the POMS. Differences in continuous data were assessed using independent t-tests and differences in categorical data were assessed using chi-square tests. Differences between pre- and postoperative 6MWT scores were assessed using paired t-tests. The relationship between preoperative characteristics and binary variables such as POMS defined complications were analysed using binary logistic regression, while categorical variables such as the Clavien-Dindo classification score were assessed using ordinal regression. Relationships between preoperative characteristics and continuous variables such as postoperative 6MWT scores were assessed using linear regression and point-biserial correlation. Regression models were assessed for goodness of fit using the Hosmer-Lemeshow test. ROC curve analysis was performed for preoperative ventilatory threshold (VT) (Chapter 2.1.4.2) to assess its ability to discriminate between participants with, and without complications. Significance was set at $p<0.05$.

Following univariate analysis, a multivariate analysis was performed on the relationship between preoperative characteristics and POMS defined complications. Three variables were identified as candidates for multivariate analysis, to satisfy the 'one predictor per ten events rule' (van Belle, 2008). As there were 25 events (POMS defined complications), this was rounded up to allow three variables to be included in the model. Variables included in the multivariate analysis were: VT, comorbidities and laparoscopic vs. open surgery.

4.3.10 Sample size calculation

Physical fitness data was taken from previously published CPET results as it is more widely available. Lai and colleagues assessed preoperative physical fitness in patients scheduled for colorectal surgery. They separated patients into categories of fit (AT >11 ml/kg/min), unfit (AT <11 ml/kg/min) and unable to complete CPET. Patients deemed as fit, had a mean VO_2peak of 22.31 (SD: 6.1) ml/kg/min, compared to a mean VO_2peak of 15.1 (SD: 3.7) ml/kg/min, representing a mean difference of 7.21 ml/kg/min (Lai et al., 2011). This data was used to inform the sample size calculation for this study. A statistician was consulted prior to performing sample size calculations. To examine a difference in physical fitness of 7 ml/kg/min (SD: 5 ml/kg/min) between those with postoperative complications and those without complications, for 90% power, 22 participants per arm was needed for a total of 44 participants (Lai et al., 2011). An additional nine subjects were recruited with an anticipated dropout of 20%, a total of 53 participants were needed. Significance was set at 0.05.

4.4 Results

A total of 55 participants were recruited and completed preoperative screening. Valid CPET's were performed on 46 participants. Nine participants did not perform CPET for the following reasons; technical difficulties (n=3), could not walk at the minimum treadmill speed (n=3), refused to wear the face mask (n=1), blood pressure >200 mmHg systolic (n=1) and diagnosis of severe heart block (n=1). No adverse events were recorded during or after CPET. One participant did not complete all measurements (waist and hip circumference, grip strength, MIP and spirometry values not recorded) due to unavoidable restraints with appointment duration. Participant surgery and assessment pathway are presented in a flow diagram in Figure 4.2. All participants completed testing within 3 weeks of surgery, and participants undergoing neoadjuvant chemoradiotherapy (n=16) performed testing post treatment. Neoadjuvant therapy has previously been reported to reduce cardiorespiratory fitness due to effects of cardiotoxicity (Section 1.6.6.2). All patients in this study performed preoperative assessment post-neoadjuvant therapy. Therefore, participants likely experienced a decrease in fitness between commencement and completion of neoadjuvant treatment (West et al., 2014a), however as neoadjuvant therapy was concluded by the time of assessment, it is likely cardiorespiratory fitness did not reduce further.

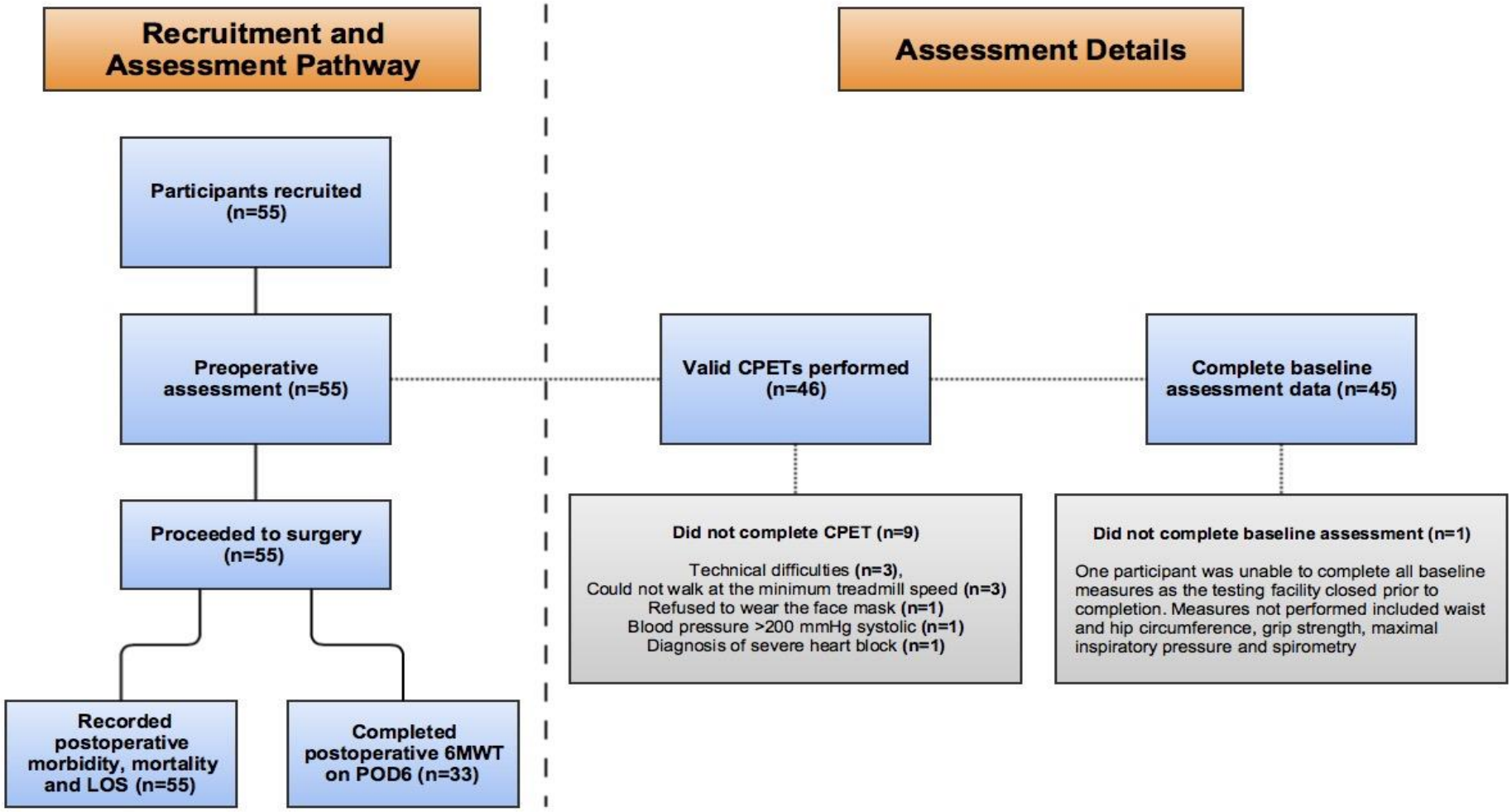


Figure 4.2: Participant flow diagram through the surgery and assessment pathway. 6MWT = Six minute walk test, LOS = Length of stay, POD6 = Postoperative da

4.4.1 Participant characteristics

Participants characteristics are presented in Table 4.4. A total of 37 males and 18 females were included. Males [mean age 65.35 (SD: 9.38) years] had a mean BMI of 28.13 (4.04) kg/m^2, while females [mean age 60.28 (SD: 13.07) years] had a mean BMI of 30.36 (7.45) kg/m^2. Accordingly, 73% of males were overweight or obese and 72% of females were overweight or obese. In this study, males had a mean predicted VO_2max of 26.30 ml/kg/min and women had a mean predicted VO_2max of 22.89 ml/kg/min. The American College of Sports Medicine (ACSM) report that males aged 60-69 years with a VO_2max <26.6 ml/kg/min as having poor cardiorespiratory fitness (ACSM, 2013). In contrast females with a VO_2max of 21.2-24.5 ml/kg/min are reported to have good cardiorespiratory fitness. Therefore, in this study males had poor cardiorespiratory fitness and females had good cardiorespiratory fitness according to normative data.

Table 4.2: Participant baseline characteristics. Values are means and standard deviations *One participant (male) was missing a complete data set

	Male	Female
Total (n=)	37	18
Age (years)	65.35 (9.38)	60.28 (13.07)
Height (cm)	172.07 (7.36)	159.78 (6.90)
Weight (kg)	83.07 (12.59)	77.63 (21.31)
BMI (kg/m^2)	28.13 (4.04)	30.36 (7.45)
VT (ml/kg/min)	15.28 (5.54)	11.74 (4.84)
VO_2peak (ml/kg/min)	20.80 (5.59)	17.63 (6.15)
Predicted VO_2max (ml/kg/min)	26.30 (4.38)	22.89 (5.50)
Waist Circumference (cm) *	101.74 (11.52)	99.62 (17.83)
Hip Circumference (cm)*	103.91 (6.23)	110.42 (13.38)
Waist/Hip Ratio:*	.98 (.08)	.90 (.08)

4.4.2 Morbidity

Twenty-five participants (45%) experienced a complication measured using the POMS on POD6 and are compared to those with no morbidity in

Table 4.3-Table 4.5. The three most common complications measured using the POMS in descending order were; renal (n=15, participants, characterised by the presence of oliguria <500mL/24hr; increased serum creatinine; urinary catheter in situ), infectious (n=11, participants, characterised by prescribed antibiotics and/or has had a temperature of >38°C in the last 24hr) and gastrointestinal complications (n=9, characterised by inability to tolerate an enteral diet for any reason including nausea, vomiting and abdominal distension or use of antimetic).

	Morbidity (n=25)	No Morbidity (n=30)	OR	95% C.I	P-value
Age (years)	63.6 (13.72)	63.77 (8.02)	0.999	0.951-1.049	0.954
Height (cm)	168.88 (8.89)	167.35 (9.58)	1.019	0.961-1.080	0.539
Weight (kg)	83.82 (18.59)	79.18 (13.38)	1.019	0.984-1.055	0.286
BMI (kg/m^2)					
Male	27.82 (4.15)	28.40 (4.04)	0.964	0.819-1.136	0.663
Female	33.01 (8.04)	28.24 (6.59)	1.102	0.955-1.273	0.184
Waist Circumference (cm) *					
Male	102.16 (12.93)	101.40 (10.59)	1.006	0.949-1.006	0.843
Female	105.89 (22.35)	94.61 (12.22)	1.043	0.978-1.113	0.2
Hip Circumference (cm) *					
Male	103.34 (6.90)	103.97 (5.90)	0.996	0.895-1.109	0.996
Female	114.35 (14.87)	107.27 (11.89)	1.045	0.967-1.128	0.266
Waist/Hip Ratio*					
Male	.98 (.09)	.97 (.07)	4.4	0.001-23415	0.735
Female	.92 (.1)	.88 (.07)	404.8	0.001-15700	0.361

Values are means and standard deviations and comparisons were made using Independent t-Tests. *One participant data set missing. BMI = body mass index. There was no significant differences in the above variables between patients with complications and patients without complications.

Twenty-eight participants experienced a complication measured using the Clavien-Dindo Classification Score. The majority of complications were assigned grade 2 (n=14, requiring pharmacological treatment with medication other than antimetics, antipyretics, and analgetics). The types of complications measured using the POMS and Clavien-Dindo scores are listed in Table 4.6 and complications measured using the CCI are listed in Table 4.7. The median LOS was 8 days (range 4-74 days).

4.4.3 Relationship between preoperative physical fitness and morbidity

All measures of preoperative physical performance were examined as predictors of postoperative morbidity. The only measure of preoperative physical fitness that was associated with POMS defined morbidity was aerobic capacity, specifically VT assessed via CPET (p=0.03, 95% C.I:0.76-0.99). Participants who experienced any POMS defined complications on POD6 had significantly lower preoperative VT compared to participants without postoperative complications (12.20 vs. 15.91 ml/kg/min, respectively, p=0.03). No other measure of physical fitness was associated with POMS defined morbidity (p<0.05). There was no association in preoperative 6MWT distance and postoperative complications (OR: 0.99, 95% C.I: 0.99-1.00, p>0.05). The preoperative 6MWT demonstrated a significant relationship with VT (OR: 0.40, 95% C.I: 0.01-0.04, p=0.007), however the correlation was low (r=0.399). In ROC curve analysis a VT value of 11.95 ml/kg/min had a sensitivity of 84% and a specificity of 60% (AUC: 0.71, 95% C.I: 0.56-0.87) to predict POMS defined morbidity (Figure 4.3).

When VT was included in a multivariate analysis of POMS defined morbidity including comorbidities and laparoscopic vs. open surgery, VT was not significant (OR: -0.14, 95% C.I: 0.75 – 1.01, p=0.07). Neither comorbidities nor laparoscopic vs. open surgery were associated with POMS defined complications (p=0.64 and p=0.69, respectively). In addition, this model was a poor fit as measured by Hosmer & Lemeshow (p=0.03). An assessment of multicollinearity was performed using Variance Inflation Factor (VIF), however there was no evidence of multicollinearity as results were within normal ranges for VIF (range: 1-10).

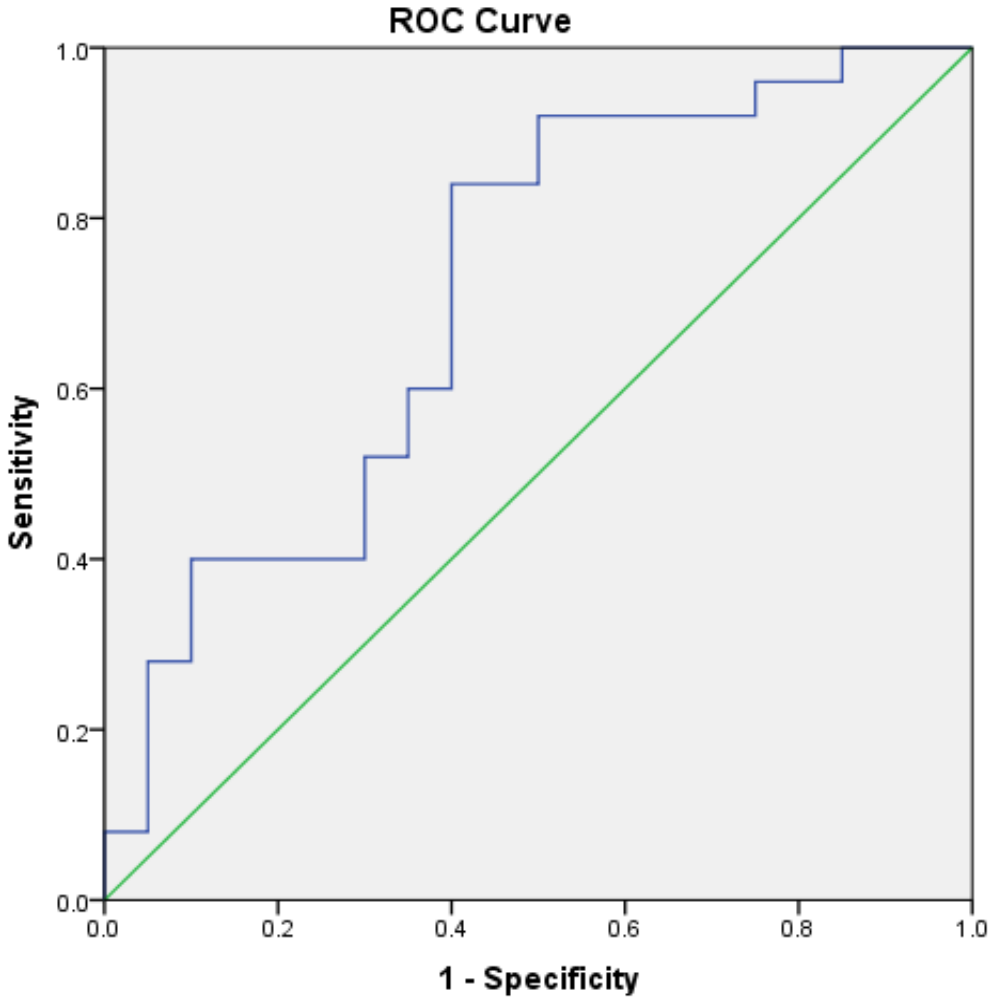


Figure 4.3: ROC curve analysis of ventilatory threshold and POMS morbidity on day six post-op. A preoperative VT value of 11.95 ml/kg/min had a sensitivity of 84% and a specificity of 60% (AUC: 0.71, 95% C.I: 0.56-0.87) to predict POMS defined morbidity indicating average predictive ability (Higgins et al., 2011).

Similar to the results for POMS defined morbidity, VT was the only measure of physical fitness that predicted complications as measured using both the Clavien-Dindo score (OR: 0.89, 95% C.I: 0.78-0.99, p=0.03) and the CCI (OR: 0.88, 95% C.I: 0.78-0.99, p=0.03). V_E/VO_2 (the ratio of minute ventilation to oxygen uptake by the lungs) was significantly associated with both the Clavien-Dindo score (OR: 1.09, 95% C.I: 1.01-1.18, p=0.03), CCI (OR: 1.09, 95% C.I: 1.01-1.17) and POMs score on POD6 (p=0.02), however this model was a poor fit, limiting the utility of V_E/VO_2 to predict postoperative outcome (Hosmer-Lemeshow, p=0.04).

Table 4.3: Participant baseline characteristics separated based on the presence of morbidity as assessed using the Postoperative Morbidity Survey (POMS) on day 6 post colorectal surgery.

	Morbidity (n=25)	No Morbidity (n=30)	OR	95% C.I	P-value
Age (years)	63.6 (13.72)	63.77 (8.02)	0.999	0.951-1.049	0.954
Height (cm)	168.88 (8.89)	167.35 (9.58)	1.019	0.961-1.080	0.539
Weight (kg)	83.82 (18.59)	79.18 (13.38)	1.019	0.984-1.055	0.286
BMI (kg/m^2)					
Male	27.82 (4.15)	28.40 (4.04)	0.964	0.819-1.136	0.663
Female	33.01 (8.04)	28.24 (6.59)	1.102	0.955-1.273	0.184
Waist Circumference (cm) *					
Male	102.16 (12.93)	101.40 (10.59)	1.006	0.949-1.006	0.843
Female	105.89 (22.35)	94.61 (12.22)	1.043	0.978-1.113	0.2
Hip Circumference (cm) *					
Male	103.34 (6.90)	103.97 (5.90)	0.996	0.895-1.109	0.996
Female	114.35 (14.87)	107.27 (11.89)	1.045	0.967-1.128	0.266
Waist/Hip Ratio*					
Male	.98 (.09)	.97 (.07)	4.4	0.001-23415	0.735
Female	.92 (.1)	.88 (.07)	404.8	0.001-15700	0.361

Values are means and standard deviations and comparisons were made using Independent t-Tests. *One participant data set missing. BMI = body mass index. There was no significant differences in the above variables between patients with complications and patients without complications.

Table 4.4: Preoperative physical fitness variables separated based on the presence of morbidity as assessed using the Postoperative Morbidity Survey (POMS) on day 6 post colorectal surgery.

	Morbidity (n=25)	No Morbidity (n=30)	OR	95% C.I	P-value
VT (ml/kg/min) (n=45) †	12.20 (5.02)	15.91 (5.47)	0.87	0.76-0.99	0.03
VO_{2peak}	19.55 (5.02)	20.02 (6.61)	1.035	0.942-1.137	0.473
V_E/VO_2 @ VT (n=45)	34.03 (8.14)	28.63 (6.16)	1.123	1.013-1.246	0.027
V_E/VCO_2 @ VT (n=45)	34.99 (6.66)	31.59 (6.03)	1.096	9.84-1.221	0.096
Predicted VO_{2max}	25.63 (4.68)	24.93 (5.24)	1.03	0.912-1.162	0.637
6MWT (m)	477.08 (126.13)	516.08 (95.91)	0.997	0.992-1.002	0.199
Right Grip Strength (kg)*	30.1 (9.04)	31.76 (10.76)	0.983	0.930-1.038	0.53
Left Grip Strength (kg)*	27.33 (9.09)	31.29 (10.4)	0.959	0.906-1.015	0.147
FEV_1 (l)*	2.45 (0.78)	2.78 (0.89)	0.623	.321-1.209	0.162
FVC (l)*	3.23 (0.82)	3.48 (1.04)	0.753	.420-1.352	0.343
MIP (cm/H_2O)*	50.98 (28.17)	48.84 (27.04)	1.003	0.983-1.024	0.778
YPAS 1 (minutes/week)	1007.50 (1979)	1080.50 (1443)	0.999	0.967-1.033	0.975
YPAS 2 (kcal/week)	3236.5 (5937)	3803.63 (5845.25)	0.993	0.976-1.011	0.442
YPAS 3 (units)‡	38 (26)	44.5 (32.75)	0.979	0.951-1.008	0.156

Values are means and standard deviations and comparisons were made using Independent t-Tests. †One participant did not reach their Ventilatory Threshold. *One participant data set missing. VT = Ventilatory threshold, 6MWT = Six minute walk test, FEV_1 = Forced expiratory volume in one second, FVC = Forced vital capacity, MIP = Maximal inspiratory pressure, YPAS = Yale physical activity survey (divided into three outcomes). Preoperative VT was significantly different between patients with complications and patients without complications.

Table 4.5: Surgical and comorbidity variables separated based on the presence of morbidity assessed using the Postoperative Morbidity Survey (POMS) on day 6 post colorectal surgery.

	Morbidity (n=25)	No Morbidity (n=30)	P value
Laparoscopic	20 (80)	25 (83)	0.75
Open	5 (20)	5 (17)	
ASA Grade*°	2.00	2.00	0.129
CR-POSSUM Score†°	3.24	1.91	0.204
Neoadjuvant Chemoradiotherapy	7 (28)	9 (30)	0.871
Smoking	5 (20)	4 (13)	0.508
Cancer			0.718
• **Benign**	5 (20)	7 (23)	
• **Inflammatory Bowel Disease**	1 (4)	0 (0)	
• **Colon**	10 (40)	13 (43)	
• **Rectal**	9 (36)	10 (33)	
Arial Fibrillation	0 (0)	1 (3)	1
Coronary Artery Bypass Graft	0 (0)	1 (3)	1
Chronic Obstructive Pulmonary Disease	1 (4)	0 (0)	1
Diabetes Type 2	4 (16)	2 (7)	0.283
Ischaemic Heart Disease	1 (4)	0 (0)	1
Congestive Cardiac Failure	1 (4)	0 (0)	1
Myocardial Infarction	1 (4)	1 (3)	0.896
Defibrillator	1 (4)	0 (0)	1
Co-morbidities	9 (36)	5 (17)	0.184
Surgical Intervention			1
• **Abdominoperineal Resection**	1 (4)	1 (3)	
• **Anterior Resection**	13 (52)	19 (63)	
• **Ileocolic Resection**	0 (0)	1 (3)	
• **Ileorectal Anastomosis**	1 (4)	0 (0)	
• **Loop Ileostomy**	1 (4)	0 (0)	
• **Right Hemicolectomy**	6 (24)	9 (30)	
• **Total Colectomy**	3 (12)	0 (0)	

Values are number of participants (percentages in parentheses). Comparisons were made using Chi-Square tests. *Values are median †Values are mean. °Comparisons with mean data were made using Independent t-Tests. ASA = American Society of Anaesthesiologists, CR-POSSUM = Colorectal Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity. There was no significant differences in the above variables between patients with complications and patients without complications.

Table 4.6: Postoperative morbidity assessed by the Postoperative Morbidity Survey (POMS) and Clavien-Dindo Classification Score.

POMS		Clavien-Dindo	
Type	Number (n=25)	**Grade**	Number (n=55)
Cardiac	2	**0**	27
Gastrointestinal	9	**1**	8
Haemotologic	1	**2**	14
Infectious	11	**3a**	1
Pain	3	**3b**	3
Pulmonary	3	**4a**	2
Renal	15	**4b**	0
Wound	2	**5**	0
Associations were assessed using binary logistic (POMS) and ordinal (Clavien-Dindo) regression. Type of complications are presented using the POMS and increasing severity of complications measured using the Clavien-Dindo score are presented as grades.			

Table 4.7: Postoperative morbidity assessed using the Comprehensive Complications Index (CCI).

Comprehensive Complications Index	
Grade	Number (n=55)
0	27
8.70	8
20.90	10
22.60	1
24.20	2
25.70	1
33.70	3
35.90	2
42.40	1
Associations were assessed using ordinal regression. Increasing grade of complications represents increasing severity and number of complications.	

4.4.4 Length of stay

VT was the only variable significantly associated with LOS (p=0.01, 95% C.I: 0.02-0.12), however the 6MWT was trending towards significance with LOS (t=1.99, p=0.05). Participants with a VT <11.95 ml/kg/min had a median LOS of 11.5 days (IQR: 4-31.5 days) compared to 6 days (IQR: 4-8 days) for participants with a VT ≥11.95 ml/kg/min. No other measure of preoperative fitness predicted LOS, unplanned ICU admissions (total n=4) or hospital readmission rates (total n=3). When a multivariate analysis of LOS was performed including VT, comorbidities and laparoscopic vs. open surgery, VT was not significant (p=0.11). Furthermore, comorbidities and laparoscopic surgery were not associated with LOS (p=0.84 and p=0.77, respectively).

4.4.5 Mortality

There was no mortality within 30 days of surgery.

4.4.6 Postoperative functional recovery

Participants experienced a statistically significant and clinically meaningful decline in 6MWT from preoperative assessment to POD6 (values) (Mean difference: -139.91m, 95% C.I: 115.78-164.04m, p=<0.001). Thirty-three participants performed the 6MWT on POD6, the mean distance walked was 390.58 m (18.68 m). Participants who could not complete the 6MWT on POD6 for any reason were excluded from this analysis and postoperative complications were the main reason for not performing the 6MWT on POD6 (p<0.001).

Participants with higher preoperative 6MWT experienced a greater decline between pre and postoperative 6MWT on POD6 (OR: 0.37, 95% C.I: 0.02, 0.59, p=0.036). However, postoperative 6MWT scores remained high (OR: 0.64, 95% C.I: 0.43-0.84, p=<0.001). Participants with a VT <11.95 ml/kg/min experienced a mean difference between preoperative and postoperative 6MWT of 171.4m (SD: 86.36m) and a median difference of 220m. In contrast, participants with a VT ≥11.95 ml/kg/min had a mean 6MWT difference of 146.61m (SD: 89.95m) and a median difference of 134m. However, there was no significant difference between postoperative functional capacity (measured using the 6MWT) between participants with a VT of ≥11.95 ml/kg/min and participants with a VT <11.95 ml/kg/min. Increased waist circumference and BMI were significantly associated with lesser functional capacity assessed via the 6MWT, however the 95% C.I's indicate large uncertainty (Table 4.8).

Table 4.8: Preoperative measures of physical fitness associated with differences between preoperative and postoperative 6MWT results on POD6.

6MWT on POD6 (n=33)	OR	95% C.I:	P-value
Age (years)	-0.17	-4.369, 1.60	0.351
Height (cm)	0.007	-3.029, 3.139	0.971
Weight (kg)	-0.316	-3.687, 0.210	0.078
BMI (kg/m^2)	-0.358	-11.397, -0.152	0.044
Waist Circumference (cm)	-0.397	-4.446, -0.331	0.024
Hip Circumference (cm)	-0.293	-6.335, 0.624	0.104
Waist/Hip Ratio	-0.336	-614.422, 13.118	0.060
6MWT (m)	0.372	0.021, 0.590	0.036
Right Grip Strength (kg)	-0.147	-4.218, 1.820	0.424
Left Grip Strength	-0.103	-3.846, 2.178	0.576
FEV1 (l)	-0.113	-46.712, 24.811	0.536
FVC (l)	0.071	-25.257, 37.135	0.700
MIP (cm/H_2O)	0.299	-0.169, 1.955	0.096
VT (ml/kg/min)	-0.138	-8.364, 4.139	0.493
VO_{2peak}	0.136	-2.942, 5.990	0.489
VE/VO_2 @ VT	0.272	-1.34, 7.231	0.169
VE/VCO_2 @ VT	0.246	-1.827, 7.699	0.216
Predicted VO_{2max}	0.228	-2.652, 10.0	0.243
YPAS 1 (minutes/week)	0.123	-0.017, 0.034	0.501
YPAS 2 (kcal/week)	-0.05	-0.007, 0.005	0.787
YPAS 3 (units)	-0.22	-2.279, 0.561	0.226

BMI = Body mass index, 6MWT = Six minute walk test, VT = Ventilatory threshold, FEV1 = Forced expiratory volume in one second, FVC = Forced vital capacity, MIP = Maximal inspiratory pressure, YPAS = Yale physical activity survey (divided into three outcomes). Preoperative 6MWT results were significantly associated with postoperative 6MWT results.

4.5 Discussion

The results of this study are consistent with current literature reporting that lower cardiorespiratory fitness (VT of <11.95 ml/kg/min), measured by CPET, was significantly associated with postoperative complications (POMS, CCI, and Clavien-Dindo classification scores) and hospital LOS following colorectal surgery. The CPET derived variable VT was a more consistent predictor of outcome compared to V_E/VCO_2 and V_E/VO_2. Other measures of physical fitness including grip strength, IMT and subjective levels of physical activity were not associated with postoperative outcome. It is unclear if there is a relationship between preoperative physical fitness and ICU admissions, and readmission rates due to the low rates recorded in this study (n=4 and n=3, respectively). As there was no mortality within 30 days of surgery it is unclear if preoperative physical fitness can predict postoperative mortality.

Preoperative VT, measured by sub-maximal CPET, was significantly associated with postoperative morbidity (OR: 0.87, 95% C.I: 0.76-0.99). The cut-point for VT to predict postoperative morbidity reported in this study (11.95 ml/kg/min) is slightly higher when compared to a previously published cut-point for this cohort; 10.1 ml/kg/min (West et al., 2014b). It is possible these differences arose because West and colleagues measured lactate threshold, which was not reported in this study, however both lactate threshold and ventilatory threshold are significantly associated with postoperative outcome (Chapter 3.4.1) (West et al., 2014b). Furthermore, the variance in cut-point values could have occurred due to differences in CPET protocols as this study used sub-maximal CPET, which is easier to perform and less labour intensive than maximal CPET, used by West and colleagues.

Ventilatory threshold was the only variable that was significantly associated with postoperative complications measured using the POMS, Clavien-Dindo and CCI scores. Ventilatory threshold is when the increase in ventilation becomes disproportional to the increase in power output during exercise, it represents the point in which anaerobic glycolysis contributes to meet the energy demands of a system under stress. It is likely that the VT which signals when non-aerobic glycolysis occurs, identifies patients who may be unable to meet the postoperative oxygen demands aerobically. This is further discussed in Chapter 7.2.3.

The ROC curve analysis, in this study using sub-maximal CPET, (AUC: 0.71, 95% C.I: 0.56-0.87) was higher compared to West and colleagues who used maximal CPET in a cohort of 198 patients scheduled for major colonic surgery (AUC: 0.63, 95% C.I: 0.54–0.73) (West et al., 2014b). The ROC curve analysis assesses the performance of CPET at discriminating between two patient states (patients with

complications and patients without complications) and the AUC is a combined measure of the sensitivity and specificity. An area under the curve of 0.7-0.8 is regarded as a diagnostic test with average accuracy, compared to <0.7 which has poor accuracy (Chapter 2.1.4.2) (Higgins et al., 2011). The AUC in this study was higher indicating a superior ability to identify patients at risk of postoperative complications measured using the POMS. However, the ROC curve analysis in this study was lower than the AUC reported in another study by West and colleagues that used maximal CPET in a cohort of 703 patients scheduled for colorectal surgery (AUC: 0.79, 95% C.I: 0.76-0.83) (West et al., 2016). Despite this, both tests are regarded as having average accuracy (AUC=0.7-0.8) (Higgins et al., 2011). Although the ability of sub-maximal CPET is lower compared to the result reported by West et al. (2016), sub-maximal provides several advantages compared to maximal CPET and therefore may have higher clinical utility (Noonan and Dean, 2000). As previously discussed in Chapter 2, sub-maximal CPET can be used for participants who are deconditioned or are physically limited by pain or fatigue (Chapter 2.3.1.7). In addition, it provides a valid and reliable method of predicting cardiorespiratory fitness without reaching volitional exhaustion and is cheaper and less labour intensive than maximal CPET.

Ventilatory threshold was significantly associated with POMS defined complications using univariate regression. When included in a multivariate analysis, VT was no longer significant ($p<0.05$). It is likely that due to the relatively small sample, some known risk factors for postoperative complications such as comorbidities (Kirchhoff et al., 2010), have a reduced effect on this cohort and that the lack of significance in the model is due to sampling error. One potential reason for the model being insignificance is multicollinearity, however based on the VIF results there was no multicollinearity present.

Participant comorbidities were not significantly associated with postoperative outcome in this study. Nine participants (36%) with comorbidities had postoperative complications, assessed using the POMS, on POD6. In comparison, five participants (17%) with comorbidities had no complications on POD6. Although this study was powered to detect a difference in physical fitness between those with postoperative complications and those without complications for 90% power, it is likely this study was not powered to detect the influence of comorbidities on complications. As the percentage of participants with comorbidities and postoperative complications is higher (36% vs. 17%), it is likely that with a larger sample size, the influence of comorbidities on complications may be significant.

Cardiorespiratory fitness assessed using VT was predictive of postoperative outcome, however the 6MWT, which is an indirect measure of cardiorespiratory fitness was unable to predict postoperative

complications or LOS. It is likely that the 6MWT did not predict postoperative outcome in the current study due to its low correlation with VT (r=0.399). As discussed in Chapter 3.3.2.2, the ISWT is able to predict postoperative outcome in colorectal surgery (Nutt and Russell, 2012). It is likely that ISWT demonstrates a superior ability to predict postoperative outcome in comparison to the 6MWT due to its higher correlation with VT (r=0.775) (Irisawa et al., 2014). Furthermore, the results of the 6MWT are confounded by the fact that participants are able to walk at a self-selected speed, compared to the ISWT and CPET, which are externally paced meaning patients are more likely to reach a maximal level of physical exertion.

Participants with higher preoperative 6MWT scores experienced a greater decrease between preoperative and postoperative 6MWT results (OR: 0.37, 95% C.I: 0.02, 0.59, p=0.036). Despite this, participants with higher preoperative 6MWT results also had higher postoperative 6MWT scores (OR: 0.64, 95% C.I: 0.43-0.84, p=<0.001). The mean difference between preoperative and postoperative 6MWT scores was -139.91m. This represents both a statistically and clinically significant result as a clinically meaningful difference in 6MWT is estimated at between 30-80 meters in patients with respiratory disease (Wise and Brown, 2005, Holland et al., 2014). To the authors knowledge the clinically meaningful difference in 6MWT for a surgical population is unknown. Participants with a VT ≥11.95 ml/kg/min experienced a smaller decrease between preoperative and postoperative 6MWT (median: 134m) compared to participants with a VT <11.95 ml/kg/min (median: 220m), representing a clinically significant difference of 86m. The majority of the literature has explored the link between cardiorespiratory fitness and postoperative complications, LOS and mortality. However, surgery also leads to a well-documented decrease in functional capacity and ability to mobilise, and the link between preoperative physical fitness and postoperative functional capacity has been underexplored (Gannon et al., 2015, Minnella et al., 2017). This study reported that postoperative complications were the main reason for not performing the 6MWT on POD6 and as cardiorespiratory fitness influences postoperative complications it is likely that preoperative physical fitness can improve functional capacity. This is supported by interventions aimed at increasing preoperative physical fitness that have demonstrated improvements in functional capacity as measured using the 6MWT (Minnella et al., 2017). Despite this, further research is required to explore this association between cardiorespiratory fitness and postoperative functional capacity.

A particular strength of this study is that clinicians were blinded to results of the CPET, however the investigator performing and interpreting CPET was not blinded. Other strengths of this study included, measuring functional recovery via the 6MWT, the use of objective measures of postoperative

morbidity (POMS, Clavien-Dindo) and the use of the relatively new Comprehensive Complications Index (Slankamenac et al., 2013). The objective morbidity measures reduces inconsistencies in the definition of postoperative complications and allows for comparison between studies (Feeney et al., 2011).

4.5.1 Limitations

Limitations of this study include the use of a treadmill to perform CPET. A cycle ergometer is more widely applicable, as the treadmill requires participants to be able to walk independently and a number of potentially suitable participants were excluded for this reason, potentially introducing a source of bias as this study sample may not be representative of the true population. Despite this, a systematic review reported the treadmill is a more appropriate method of assessing cardiorespiratory fitness than a cycle ergometer in older adults because walking is a more familiar activity (Huggett et al., 2005). Therefore, the treadmill is a valid alternative method for performing CPET when a cycle ergometer is not available. A final limitation was physical activity was measured subjectively using YPAS. An objective measure of physical activity such as accelerometry would be more reliable, however following pilot testing, accelerometry was deemed unfeasible as a number of participants were unable to be prescribed the accelerometer at least one week prior to surgery.

4.6 Conclusion

Cardiorespiratory fitness, measured using sub-maximal CPET, is predictive of postoperative outcome in colorectal surgery. In the current study, no other measure of physical fitness was associated with postoperative outcome. Although an expensive tool, CPET, particularly ventilatory threshold, is able to predict postoperative complications and LOS following colorectal surgery, which is in agreement with current literature. Participants with a VT of less than 11.95 ml/kg/min are subject to an increased risk of postoperative complications. It is unclear if patients with higher levels of cardiorespiratory fitness experience less functional impairment postoperatively.

5 Chapter 5 The ability of prehabilitation to influence postoperative outcome in intra-abdominal surgery: a systematic review and meta-analysis

Material presented in this chapter has been disseminated in the following publications:

Moran J., Guinan E., McCormick P., Larkin J., Mockler D., Hussey J., Moriarty J. & Wilson F. (2016) The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis. *Surgery,* 160, 1189-1201

Moran J., Guinan E., McCormick P., Larkin J., Mockler D., Hussey J., Moriarty J. & Wilson F. (2017) Response to: Is prehabilitation limited to preoperative exercise? *Surgery* [Epub ahead of print]. *See Appendix A for full manuscripts*

5.1 Introduction

Globally, an estimated 230 million surgical procedures are performed annually (Weiser et al., 2008). Surgery carries substantial postoperative risk and the number of patients undergoing elective surgery is increasing (Glance et al., 2014). In major abdominal surgery 30 day postoperative mortality is 3.7% for all patients (Finan et al., 2011). Postoperative complications are more common than mortality with a rate of 35% following abdominal surgery (Pouwels et al., 2014). Postoperative morbidity is a significant burden on health systems and patients, can prolong hospital length of stay and may lead to repeated hospital admissions, chronic ill-health and a decline in functional capacity and quality of life (Khuri et al., 2005, Ghaferi et al., 2009, Finlayson et al., 2012, Rhodes et al., 2010).

As discussed in Chapter 3 and 4, preoperative physical fitness (an individual's level of physical fitness prior to surgery) is predictive of postoperative outcome (Smith et al., 2009, Valkenet et al., 2011, Mans et al., 2015, Kartheuser et al., 2013, Chen et al., 2011). Optimising preoperative physical fitness, through exercise 'prehabilitation', may improve postoperative outcome and ultimately reduce surgery associated hospital costs and enhance the patient's quality of life. Prehabilitation is defined as the course of improving the functional capacity of an individual to facilitate them to withstand a stressful event (Ditmyer et al., 2002, Topp et al., 2002).

One previous review by Pouwels and colleagues, concluded that preoperative exercise therapy may improve physical fitness of patients prior to major abdominal surgery (Pouwels et al., 2014). This review concluded that the ability of exercise prehabilitation to improve postoperative outcomes is unclear, and that further RCT's are needed to determine its effect. Since the publication of that review, the number of trials has grown and an updated review should be performed to analyse the effect of exercise prehabilitation on postoperative outcome. In addition, a meta-analysis has not been previously performed.

The aim of this review was to assess the ability of preoperative exercise therapy/exercise prehabilitation to improve postoperative outcome (mortality, morbidity and LOS). The objectives were to (i) assess the influence of exercise prehabilitation on all-cause postoperative complications compared to no intervention, (ii) to assess the ability of exercise prehabilitation to influence postoperative pulmonary complications compared to control treatments, and (iii) to assess the ability of exercise prehabilitation to influence preoperative physical fitness measured through aerobic capacity, muscular strength and endurance, and respiratory muscle strength.

5.2 Methods

A protocol outlining the planned search strategy and methods of analysis for this review was registered online with a registry of systematic reviews (PROSPERO ID: 42015020546) (Appendix E). The PRISMA guidelines were used to standardize the methods of conducting and reporting this review (Antes and von Elm, 2009).

Patients scheduled for intra-abdominal surgery undergoing preoperative exercise interventions or 'prehabilitation' were included. Randomised controlled trials examining exercise modalities such as aerobic or strength training including inspiratory muscle training, aimed at increasing musculoskeletal, cardiovascular or respiratory muscle function were included. All causes for surgical intervention were included (e.g. cancerous or inflammatory conditions). Patients undergoing any non-abdominal or orthopaedic based surgical intervention were excluded.

Intervention groups consisted of patients scheduled for major non-cardiopulmonary intra-abdominal surgery who received a preoperative exercise programme. Patients scheduled for intra-abdominal surgery who received usual care only were considered a passive control group. Usual care consisted of no treatment (Barbalho-Moulim et al., 2011, Gillis et al., 2014, Kulkarni et al., 2010, Soares et al., 2013)

or breathing exercises such as diaphragmatic breathing, deep inspirations with incentive spirometry and coughing and forced expiration techniques (Dronkers et al., 2008). Incentive spirometry was considered a passive control treatment as it has been reported to not influence postoperative outcome (do Nascimento Junior et al., 2014). Similarly, incentive spirometry in combination with breathing exercises were considered a passive control group. Patients prescribed an exercise intervention with a lower volume/intensity compared to the intervention group were considered an active control group. Active control interventions prescribed simpler exercise interventions such as walking and were considered less likely to improve preoperative physical fitness and influence postoperative outcome compared to the intervention groups. Exercise interventions prescribing preoperative pelvic floor exercises only were excluded.

5.2.1 Primary outcomes

- Postoperative mortality: All-cause mortality in the postoperative period
- Length of stay (LOS): Includes, general LOS in hospital, intensive care unit (ICU)/critical care unit (CCU)/high dependency unit (HDU) admission and length of stay and hospital readmission
- Morbidity: All-cause postoperative complications, as defined by study authors (listed in Table 5.2) but preferably objectively measured using the POMS, CCI, Clavien-Dindo classification score or the Postoperative Morbidity Index (PMI).

Table 5.1: Study characteristics: C=Control, HDU=High Dependency Unit, I=Intervention, ICU=Intensive Care Unit, IQR=Inter-Quartile Range, PPC's=Postoperative Pulmonary Complications.

Author	Surgical Procedure	Gender (Male/Female)	Age Mean (SD)	Outcomes
Barbalho-Moulim et al. (2011)	Open Roux-en-Y gastric bypass surgery. Preoperative pathway not reported.	Female only I: 15 C: 17	I: 36.13 (8.12) C: 34.8 (9.47)	Morbidity: PPC's ***Pneumonia:*** Body temperature ≥38 degrees Celsius, productive cough with purulent sputum, presence of pulmonary infiltration on chest X-ray examination and increased leukocyte count ***Atelectasis*** with clinical implications (evidence of pulmonary atelectasis in the chest X-ray associated with respiratory discomfort) ***Acute respiratory failure:*** Acute inability of the lungs to promote gas exchange, demanding the use of mechanical ventilation
Carli et al. (2010)	Resection of benign or malignant colorectal lesions, or colonic reconstruction of non-active inflammatory bowel disease ± neoadjuvant chemoradiotherapy. Preoperative pathway not reported.	I: 34/24 C: 31/23	I: 61 (16) C: 60 (15)	LOS: General hospital stay Morbidity: Clavien-Dindo
Dronkers et al. (2008)	Abdominal aortic aneurysm surgery. Preoperative pathway not reported.	I: 3/7 C: 2/8	I: 70 (6) C: 59 (6)	Morbidity: ***Atelectasis*** diagnosed on X-ray by a blinded radiologist
Dronkers et al. (2010)	Colon surgery. Preoperative pathway not reported	I: 15/7 C: 16/4	I: 71.1 (6.3) C: 68.8 (6.4)	Morbidity: Self-defined; **Post-op complications:** Oxygen saturation, fever, pain medication, sputum retention, coughing, and delayed patient mobilisation **Post-op pulmonary complications:** Hypoxia, atelectasis, pneumonia, and respiratory failure LOS: General hospital length of stay

Gillis et al. (2014)	Colorectal surgery. All patients followed the Enhanced Recovery programme	I: 38 C: 39	I: 65.7 (13.6) C: 66.0 (9.1)	LOS: General hospital stay and 30 day readmission Morbidity: Clavien-Dindo
Kaibori et al. (2013)	Hepatic surgery. Preoperative pathway not reported	I: 17/8 C: 19/7	I: 68.0 (9.1) C: 71.3 (8.8)	Mortality: 6 months post-op Morbidity: Method of measuring morbidity not reported LOS: General hospital stay
Kulkarni et al. (2010)	Major abdominal surgery Colorectal resection: n=32 Upper GI resection: n=22 Vascular procedures: n=11 General surgery: n=10 Urological surgery: n=1 Preoperative pathway not reported.	I: 11/9 C: 12/8	I: 60 (N/a) C: 65 (N/a)	Morbidity: Postoperative pulmonary complications – Method of measuring PPC's not reported LOS: General hospital stay, Time in HDU/ICU
Soares et al. (2013)	Open abdominal surgery, defined as the opening of the peritoneal cavity. Surgical site Gastric: n=9 Oesophagus: n=13 Biliary Tract: n=10	I: 8/8 C: 9/7	I: 58.5 (IQR: 51.3-63.5) C: 55.0 (IQR: 49.3-64.3)	Morbidity: PPC's (Self-Defined) ***Respiratory Failure:*** Need for endotracheal intubation and mechanical ventilation ***Atelectasis:*** Pleural effusion/pneumothorax on chest radiographs ***Pneumonia:*** Clinical, laboratory and imaging findings and institution of antibiotic therapy

	Preoperative pathway not reported.			LOS: General hospital stay
Van Adrichem et al. (2014)	Oesophagectomy (Total, n=39) Left-sided thoraco-phreno-laparotomy with intrathoracic anastomosis (n=15) Right-sided thoraco-laparotomy with cervical anastomosis (McKeown) (n=24) Neoadjuvant chemoradiotherapy (n=36)	I: 15/5 C: 14/5	I: 62.7 (7.1) C: 61.3 (7.3)	LOS: General hospital stay, ICU LOS Morbidity: PPC's defined by Kroenke et al. (1992) **Grade 1**: Cough, dry Microatelectasis: abnormal lung findings and temperature of 37.5°C without other documented cause; results of chest roentgenogram either normal or unavailable Dyspnea, not attributable to other documented cause **Grade 2:** Cough, productive, not attributable to other documented cause Bronchospasm: new wheezing or pre-existent wheezing resulting in change in therapy Hypoxemia: alveolar-arterial gradient of 29 and symptoms of dyspnea or wheezing Atelectasis: radiologic confirmation plus either temperature of 37.5°C or abnormal lung findings Hypercapnia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation Adverse reaction to pulmonary medication **Grade 3:** Pleural effusion requiring thoracentesis Pneumonia, suspected: radiologic evidence without bacteriologic confirmation Pneumonia, proved: radiologic evidence and documentation of pathologic organism by Gram staining or culturing Pneumothorax Reintubation, period of ventilator dependence does not exceed 48 h **Grade 4**: Ventilatory failure: postoperative ventilator dependence exceeding 48 h or intubation with subsequent period of ventilator dependence exceeding 48 h

5.2.2 Literature Search

The databases CINAHL, AMED, PEDro, EMBASE, The Cochrane Library and PubMed/MEDLINE were searched up until August 2015. A search strategy was defined with all keywords and subject headings included (Appendix F). A search of relevant grey literature was performed. The abstracts from the annual European Anaesthesiology Congress (2004-2014), the Anaesthetic Research Society (2007-2015), the Society of Academic & Research Surgery (2012-2015), the Vascular Society (2005-2012), the International Anaesthesia Research Society (2003-2015), the World Federation of Society of Anaesthesiologists (2008-2012) and the American Society of Anaesthesiologists (2000-2014) were reviewed for eligibility. A hand search of reference lists of the studies of interest was conducted to identify extra articles.

Two review authors (J. Moran and F.W) selected trials for inclusion independently based on the titles, keywords and abstracts (generated from the search strategy) to determine eligibility in terms of intervention, participants and design. The full text versions of all relevant trials were retrieved. If a full text version could not be retrieved then the study was excluded due to the lack of a detailed methodology and possibility of a high risk of bias.

Data extraction was performed independently by the lead author (J. Moran). All data was reviewed blind by another author (F.W). Extracted data included details of methods, surgical interventions, exercise interventions, control group and outcome measures. The data extraction form was piloted on two randomly selected studies. Upon completion, the form was deemed appropriate for data extraction. Any disagreements were discussed, if a conclusion could not be reached upon discussion a third party was asked to intervene (J.H).

Two review authors (J. Moran and F.W) assessed the risk of bias in included studies independently using The Cochrane Collaboration's 'Risk of bias' tool (Higgins et al., 2011). Each study was graded for risk of bias in each of the following domains: sequence generation; allocation concealment; blinding (participants and personnel and outcome assessment); incomplete outcome data; selective outcome reporting and other source of bias. Any disagreements were discussed, if a conclusion could not be reached, an independent third reviewer was asked to intervene (JH).

5.2.3 Measures of treatment effect

Dichotomous data was reported as odds ratios and 95% confidence intervals. For continuous data the mean difference and standard deviation with 95% confidence intervals was calculated using RevMan software (version 5.3).

5.2.4 Dealing with missing data

Authors were contacted via email to request access to missing data. All relevant data were reviewed.

5.2.5 Assessment of heterogeneity

Clinical heterogeneity was based on information from the participants of each study, interventions and outcome measurements. Statistical heterogeneity was assessed by visual inspection of the overlap of the confidence intervals on the forest plots, and consideration of the Chi-squared test (p value <0.1 was interpreted as significant heterogeneity) and the I^2 statistic. I^2 results were interpreted as: 0-40% might not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity and 75-100% may represent considerable heterogeneity (Higgins and Green, 2008). The results of comparable groups were pooled using random-effects models.

5.2.6 Assessment of methodological quality

The GRADEpro (http://tech.cochrane.org/revman/other-resources/gradepro/download) software was used to assess the methodological quality of included studies (Figure 5.1). The GRADEpro highlights key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on important outcomes in a summary of findings table.

Preoperative exercise in the prevention of postoperative morbidity

Patient or population: patients with postoperative morbidity

Settings:

Intervention: preoperative exercise

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk **Control**	Corresponding risk **Preoperative exercise**	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Morbidity	**Study population**		**OR 0.59** (0.38 to 0.91)	435 (9 studies)	⊕⊖⊖⊖ **very low**[1,2,3,4,5]	
	359 per 1000	**249 per 1000** (176 to 338)				
	Moderate					
	400 per 1000	**282 per 1000** (202 to 378)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias (Fig. 2).
[2] I2=43%, p=0.02
[3] There was a wide variety of surgeries included
[4] Most studies had small sample sizes. Only Barbalho-Moulim et al. (2011) and Carli et al. (2010) performed sample size calculations
[5] Unable to detect publication bias due to small number of studies

Preoperative exercise to reduce postoperative length of stay

Patient or population: patients with to reduce postoperative length of stay

Settings:

Intervention: preoperative exercise

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Preoperative exercise**				
Length of Stay Scale from: 0 to 45.	The mean length of stay ranged across control groups from **2.11-21.6 Days**	The mean length of stay in the intervention groups was **1.62 lower** (7.57 lower to 4.33 higher)		232 (4 studies)	⊕⊖⊖⊖ **very low**[1,2,3,4,5]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias (Fig. 2).
[2] I2=53%, p=0.59
[3] There was a wide variety of surgeries included
[4] Most studies had small sample sizes. Only Barbalho-Moulim et al. (2011) and Carli et al. (2010) performed sample size calculations
[5] Unable to detect publication bias due to small number of studies

Figure 5.1: GRADEpro assessment of methodological quality of included studies examining the ability of preoperative exercise interventions to reduce morbidity and length of stay. Prehabilitation can reduce postoperative morbidity (OR: 0.59, 95% C.I: 0.38-0.91). There were no significant differences in LOS between exercise and control groups (mean difference: -1.62 days, 95% C.I: -7.57, 4.33). The quality of evidence is graded as 'very low' suggesting these results should be interpreted with caution.

5.3 Results

The database search was completed in August 2015. The search strategy yielded a total of 906 articles; AMED (n=24), CINAHL (n=142), The Cochrane Library (n=153), EMBASE (n=325) and PubMed/MEDLINE (n=262). Three articles were identified through searching conference abstracts, and six more articles by searching the reference lists of key studies. A total of 204 duplicates were removed and 687 articles excluded based on title and abstract.

Fifteen studies were excluded as they did not meet the inclusion criteria. Three were excluded as they were not RCT's, four studies were excluded as participants had no surgical intervention, two were excluded as there was no preoperative intervention, three abstracts were excluded because there was no full-text available, one study was excluded as there was no postoperative follow-up, one study did not include participants undergoing a laparotomy incision of the abdomen and one article was excluded as it was a reanalysis of previously included data. A total of nine studies were included (Figure 5.2).

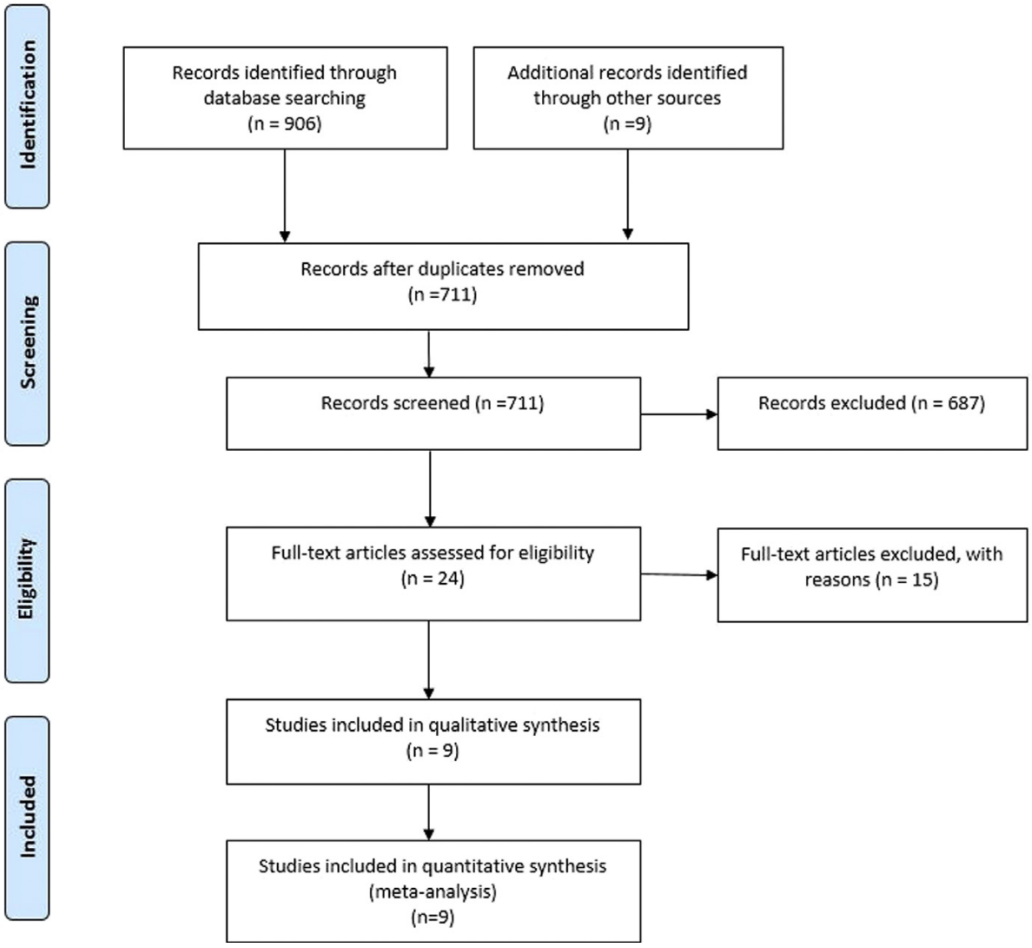


Figure 5.2: PRISMA flow diagram

5.3.1 Participants

A total of 435 patients scheduled for surgical resection were included. Surgeries included colorectal (Carli et al., 2010, Gillis et al., 2014, Dronkers et al., 2010), abdominal (Dronkers et al., 2008, Kulkarni et al., 2010, Soares et al., 2013), upper gastrointestinal (Van Adrichem et al., 2014), hepatectomy (Kaibori et al., 2013b) and open bariatric surgery (Barbalho-Moulim et al., 2011). The mean age of participants between groups ranged from 34.8-71.3 years. One study recruited females only (Barbalho-Moulim et al., 2011). The remaining eight studies recruited males and females (Table 5.2).

5.3.2 Interventions

Exercise interventions consisted of a variety of methods such as aerobic training, resistance training, inspiratory muscle training or a combination of all. The frequency, intensity, time and type of intervention were recorded from each study (Table 5.2). Five studies compared exercise interventions to no treatment or usual care. Usual care consisted of no treatment (Barbalho-Moulim et al., 2011, Gillis et al., 2014, Kulkarni et al., 2010, Soares et al., 2013) or preoperative breathing exercises; deep breathing exercises, incentive spirometry and forced expiration techniques (Dronkers et al., 2008). Four studies compared exercise prehabilitation to a lower impact intervention group, this group was considered a control group. The lower impact interventions consisted of walking (Carli et al., 2010, Dronkers et al., 2010), endurance based IMT (Van Adrichem et al., 2014), and a diet based intervention (Kaibori et al., 2013b).

Included studies are described in detail in Table 5.1 & 5.2. Four studies prescribed inspiratory muscle training (IMT) only preoperatively (Barbalho-Moulim et al., 2011, Dronkers et al., 2008, Kulkarni et al., 2010, Van Adrichem et al., 2014). Two studies prescribed a combination of IMT and aerobic exercise (Dronkers et al., 2010, Soares et al., 2013). Two studies prescribed a combined aerobic and resistance exercise intervention (Carli et al., 2010, Gillis et al., 2014). One study prescribed a walking based intervention (Kaibori et al., 2013b). Six studies delivered a mix of supervised and unsupervised programmes (Barbalho-Moulim et al., 2011, Soares et al., 2013, Dronkers et al., 2008, Dronkers et al., 2010, Carli et al., 2010, Kaibori et al., 2013b). Unsupervised sessions were expected to be completed at home. In two studies, participants were educated about the exercise protocol during an initial session and then completed the remaining sessions unsupervised (Gillis et al., 2014, Kulkarni et al., 2010).

Table 5.2: Study interventions and outcomes: AT = Anaerobic Threshold, F = Frequency, HDU = High Dependency Unit, HTN = Hypertension, I = Intensity, ICU = Intensive Care Unit, IMT = Inspiratory Muscle Training, IQR = Inter-Quartile Range, LOS = Length of Stay, TT = Type and Time of Exercise.

Author	Intervention	Control	Compliance/Adherence:	Results: Mean (SD)
Barbalho-Moulim et al. (2011)	**Inspiratory Muscle Training** **F**: 6 times a week **I**: Initial load was 30% MIP and recalculated at each visit to the physiotherapist **TT**: One daily session for 15 minutes, 2-4 weeks before surgery. Two times supervised by physiotherapist, four times unsupervised	No intervention	Not reported	No post-op complications in intervention or control group **LOS:** • Intervention: 2 days (0.0) • Control: 2.11 (0.33)
Carli et al. (2010)	**Aerobic Exercise & Resistance Training** **F:** Bike every day, weights x3/7 **I:** 50% HR max, increase by 10% each week if tolerable. Weights: Based on weight until volitional fatigue in 8 reps, increase to 12 reps **TT:** Bike and weight training (push-ups, sit-ups, lunges). Bike 20-30 mins, Weights; 10-15 min, 3.5 hrs a week, 14 hrs in 4 weeks, total bike and weight training	**F:** Everyday **I:** N/a **TT:** Deep breathing at full vital capacity, diaphragmatic breathing, huffing and coughing, ankle rotations and pumping, static quad contractions and bridging. **Walk;** minimum of 30 mins a day, Breathing 5-10 mins a day, additional exercise; 5-10 mins for 4 weeks All participants were visited once at home to demonstrate the programme and at least once to verify	21 participants did not undergo colorectal surgery at the McGill University Health Centre and were excluded. 14 participants dropped out and missing data was imputed. Only 16% of patients were fully adherent to the bike/strengthening group. Adherence rates of walk/breathing group were not reported.	**Morbidity**: Clavien-Dindo grade of most severe complication: Intervention: • 0=34/56 • 1=9/56 • 2=7/56 • ≥3=6/56 Control: • 0=36/54 • 1=4/54 • 2=11/54 • ≥3=3/54 **LOS:** • Intervention (n=56): 11.9 days (34.6) • Control (n=53): 6.6 days (3.6)

Dronkers et al. (2008)	**Inspiratory Muscle Training** **F:** 6 sessions, 6 days a week for at least two weeks **I:** 20% MIP at baseline. The resistance was increased incrementally, based on the rate of Borg Rating of Perceived Exertion Scale, if <5, MIP increased by 2 cmH_2O **TT:** One session supervised, 5 sessions unsupervised for 15 minutes a day	**Control:** Usual Care, diaphragmatic breathing, deep inspirations with incentive spirometry, coughing and forced expiration techniques *Received one day before surgery*	2 participants in the control group drooped out. 2 patients in the intervention group could not be followed up during the first seven days after surgery because of acute reoperation for blood vessel occlusion in the leg. All participants reported their daily IMT in their diaries. No participants dropped out and no adverse events were reported. Adherence rates for IMT was not reported.	**Atelectasis:** • Intervention: 3/10 • Control: 8/10
Dronkers et al. (2010)	**Aerobic Exercise & Resistance Training** **F:** Everyday, two supervised sessions and 5 home-based sessions **I:** *Supervised*: warm-up, resistance training of lower limb extensors (with a maximum of one set of 8-15 reps consistent with 60-80% of the one rep max), IMT (10-60% of MIP for), aerobic training (55-75% of max heart rate) or perceived exertion (between 11-13 on the borg scale), training functional activities (depending on patients' needs) *Home-Based*: Walking or cycling, IMT; 20% MIP baseline, increase by 10% MIP if BORG <13 **TT:** Two supervised sessions, 5 home-based sessions a week *Supervised*: IMT; 15 mins/240 breathing cycles, Aerobic; 20-30 mins. *Home-Based*: Aerobic; 30 mins, IMT; 15 mins	**Control:** Walking for a minimum 30 mins a day, monitored by a pedometer *Both groups received instruction in:* *Diaphragmatic breathing* *Deep inspirations with incentive spirometry* *Coughing and forced expiration techniques*	The adherence rate for the supervised intervention sessions was 97%. The mean number of steps performed during the pre-op period are as follows: Intervention: 4980 steps Control: 5003 steps	**Post-op Complications:** • Intervention: 9/22 • Control: 8/20 **Pulmonary complications:** • Intervention: 5/22 • Control: 5/20 **LOS:** • Intervention: 16.2 days (11.5) • Control: 21.6 (23.7)

Gillis et al. (2014)	**Aerobic Exercise & Resistance Training** *Intervention received this treatment at the pre-op stage. Control received it in the post-op stage* **F:** 3 days a week **I: Aerobic exercise**; walking, jogging, swimming or cycling. *Resistance*; eight exercises targeting major muscle groups, 8-12 reps, increase when pt could complete the aerobic exercise with mild exertion (BORG 12) and/or when the patient could complete 15 reps of a given resistance exercise. **TT:** 50 min of home-based unsupervised exercise consisting of a 5 min warm-up, 20 min aerobic, 20 min resistance, 5 min cool-down Pt's also received nutritional advice and coping strategies to reduce anxiety	No preoperative intervention. This group received the same intervention in the postoperative period.	12 participants were excluded because either they did not undergo resection, required emergency surgery, were operated at a different hospital, withdrew consent or were lost to follow-up. Compliance during preoperative period (SD): 1. Prehab: 78% (21) 2. Control: N/A Compliance from surgery to 4 weeks: 1. Prehab: 53% (30) 2. Control: 31% (26) Compliance from 4 to 8 weeks: 1. Prehab: 53% (33) 2. Control: 40% (31)	**Morbidity:** Clavien-Dindo (Grade of most severe complication): Intervention: • Grade 1: 5/38 • Grade 2: 3/38 • Grade 3: 4/38 • Grade 4: 0/38 Control: • Grade 1: 5/39 • Grade 2: 6/39 • Grade 3: 4/39 • Grade 4: 2/39 **LOS:** • Intervention: 4 days (IQR: 3-7) • Control: 5 days (IQR: 3-9) **30 Day Readmission Rates:** • Intervention: 6/38 • Control:5/39

Kaibori et al. (2013)	**Aerobic Exercise** Exercise and Diet (same diet as the control group) **F:** 3 sessions a week **I:** Walking based on the AT of each patient, **TT:** 60 mins a session, from diagnosis (up to 1 mth pre-op) and resumed post-op for 6 mth. Sessions consisted of 5 mins of stretching, 30 mins of walking, 20 mins of targeted stretching and 5 min stretching cool-down	Diet: **Patients with chronic hepatitis or liver cirrhosis** (1 mth preop- 6mths post-op): Daily energy intake; 25-30 kcal/kg body weight (BW) with a daily protein intake of 1.0-1.2 g/kg of BW and daily sodium intake of 5-7 g/kg of BW. **Patients with diabetes or fatty livers:** Daily energy intake was set at 20-25 kcal/kg of BW Daily sodium was 6 g/kg of BW for patients with HTN	The specific adherence rates were not reported for the intervention or control groups. Patients in the exercise group showed 2 patterns at 6 months postoperatively, a highly active group and a less active group. We stratified the patients according to the frequency of exercise as standard (3 times a week) or high (5 or 6 times a week).	**Mortality:** • Intervention: 0/25 • Control: 0/26 **Morbidity:** • Intervention: 2/23 • Control: 3/23 **LOS:** • Intervention: 13.7 days (SD: 4.0) • Control: 17.5 days (SD: 11.3)
Kulkarni et al. (2010)	**Inspiratory Muscle Training** IMT for 14 days (median; range: 8-28) with grade 3 difficulty (median; range: 1-4) Difficulty was self-assessed on a scale of 1-5 (1 being very easy and 5 being very difficult).	No intervention received	Sessions were performed at home and participants undertook self-assessment of training method. Patients in the control group did not train. Patients in the IMT group trained for 14 days (median; range, 8–28 days) with grade 3 difficulty (median; range, 1-4)	**Complications/Chest Infection:** • Intervention: 0/18 • Control: 2/19 **LOS:** • Intervention: 4 days (median; range: 1-13) • Control: 6 days (median; range 1-14) **HDU/ICU Stay:** • Intervention: 0 days (median; range: 0-3) • Control: 0 days (median; range: 0-5)
Soares et al. (2013)	**Inspiratory Muscle Training** **F:** Two supervised sessions a week, four unsupervised sessions a week **I:** IMT at 20% baseline MIP, increase by 2 cmH_2O a week. Walk on flat ground, fast but -<15 on BORG scale (6-20) **TT:** IMT for 15 mins a day. Walk, 10 mins. Stretching, trunk rotation (dissociation of	No intervention	9 patients did not complete the final assessment on the 30th postoperative day. The reason for this was not reported. Adherence rates were not reported.	**Morbidity:** • Intervention: 5/16 • Control: 11/16 **LOS:** • Intervention: 8.5 days (median; IQR: 4.8-12.3) • Control: 8.5 days (median; IQR: 6.5-17.3)

	pelvis and shoulder girdle), deep breathing, respiratory muscle training, active upper and lower extremity exercises and relaxation			
Van Adrichem et al. (2014)	**Inspiratory Muscle Training – High Intensity** **F:** 6 cycles of 6 inspiratory manoeuvres on an IMT, 3 sessions a week **I:** 60% of MIP, increased to 80% during first week. Increased by 5% if BORG <5. Resting cycles progressively reduced, 60s, 45, 30, 15, 5s **TT:** Supervised, MIP measured weekly for 3 weeks	**Inspiratory Muscle Training - Endurance** **F:** Seven sessions a week **I:** 30% of MIP. Increased by 5% if BORG <5 **TT:** Supervised and unsupervised; 20 min sessions for 3 weeks	**Average compliance:** IMT-High Intensity: 98% (minimum 84.6-maximum 100%) IMT-Endurance: 99.4% (minimum 93.6%-maximum 100%).	**Morbidity:** • Intervention: 4/20 • Control: 11/20 **LOS:** • Intervention: 13.5 days (median; IQR: 11-16) • Control: 18.0 days (median; IQR: 14.0-28.0) **ICU:** • Intervention: 0.5 days (median; IQR: 0.5-2.0) • Control: 1.5 days (median; IQR: 0.5-5.5)

5.3.3 Outcomes

The primary outcome measures of the review were; mortality, morbidity and length of stay. Only one study reported on postoperative mortality (Kaibori et al., 2013b). Length of stay was regarded as time of surgery to discharge from hospital, ICU admission, ICU LOS, and hospital readmission rates. This was assessed in eight studies. Morbidity was assessed using the Clavien-Dindo Classification Score (Dindo et al., 2004), postoperative pulmonary complications (Kroenke et al., 1992), and self-defined complications (complications based on criteria determined by study authors). Morbidity was measured in nine studies.

5.3.4 Risk of bias of included studies

Risk of bias was assessed for all studies using the Cochrane risk of bias tool and used to assess methodological quality using the GRADEPro software (Higgins et al., 2011). The risk of bias is presented in Figure 5.3. Due to the nature of exercise interventions it is difficult for studies to blind participants and personnel and this led to a high risk of bias in six studies. It was unclear if blinding was attempted in the remaining studies.

5.3.4.1 Allocation (selection bias)

Allocation concealment was often deemed 'unclear' as many studies did not report if envelopes used were opaque. The randomisation process was largely unclear as many studies did not report on the method of randomisation used. Three studies reported the method employed, of which, two were a sufficient method (computer generated randomisation) and were deemed low risk. One study reported using an independent research assistant to stratify patients into two groups (Dronkers et al., 2008). This was deemed high risk.

5.3.4.2 Blinding (performance bias and detection bias)

Overall performance bias was high as it is difficult to blind participants and personnel to exercise based interventions. The risk of detection bias was less than performance bias with four studies scoring a low risk of bias (Dronkers et al., 2008, Dronkers et al., 2010, Gillis et al., 2014, Van Adrichem et al., 2014), however three studies scored unclear (Carli et al., 2010, Kaibori et al., 2013b, Soares et al., 2013) and two scored high (Barbalho-Moulim et al., 2011, Kulkarni et al., 2010).

5.3.4.3 Incomplete outcome data (attrition bias)

Attrition bias was generally low with seven studies receiving a low risk of bias.

5.3.4.4 Selective reporting (reporting bias)

Reporting bias was mostly unclear as many trials did not publish protocols in which to check the original outcomes intended for study. One study scored a high risk of bias as there were certain outcomes (baseline AT and VO_{2peak}) not presented in the articles (Kaibori et al., 2013b).

5.3.4.5 Other potential sources of bias

The authors were unclear if studies were free from potential sources of bias in four studies. Four studies scored a high risk, while only one study scored a low risk of bias. Potential sources of bias included significant differences in baseline between intervention and control groups (Barbalho-Moulim et al., 2011, Dronkers et al., 2008, Dronkers et al., 2010) and walking interventions were not well monitored (Carli et al., 2010, Soares et al., 2013). One author had a royalty share in the 'POWERbreathe' inspiratory muscle trainer, a device used by the intervention group (Kulkarni et al., 2010).

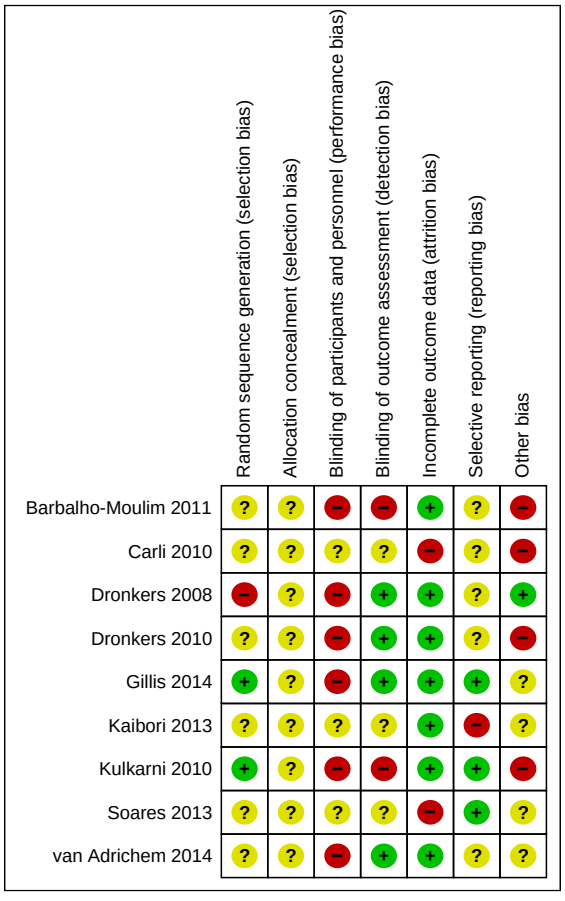


Figure 5.3: Risk of bias assessment. Green symbol indicates low risk of bias, yellow symbol represents an unclear risk of bias and a red symbol indicates a high risk of bias. Generally, risk of bias was unclear.

5.3.5 Morbidity

All studies included in this review examined the impact of preoperative interventions on all-cause postoperative complications and were included in the forest plot (Figure 5.4). Exercise prehabilitation resulted in a significant reduction in postoperative complications (OR: 0.59, 95% C.I: 0.38-0.91, p=0.03). Interventions consisted of a mixture of IMT, aerobic exercise and resistance training. Control groups consisted of no treatment, breathing exercises, lower intensity IMT and walking. Moderate heterogeneity existed between studies I^2=43% and the quality of evidence was very low, as measured using the GRADEpro.

Study or Subgroup	Exercise Events	Exercise Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Barbalho-Moulim 2011	0	15	0	17		Not estimable
Carli 2010	22	56	18	54	20.3%	1.29 [0.59, 2.82]
Dronkers 2008	3	10	8	10	10.2%	0.11 [0.01, 0.84]
Dronkers 2010	9	22	8	20	9.0%	1.04 [0.30, 3.57]
Gillis 2014	12	38	17	39	20.9%	0.60 [0.24, 1.52]
Kaibori 2013	2	23	3	23	5.0%	0.63 [0.10, 4.21]
Kulkarni 2010	0	18	2	19	4.3%	0.19 [0.01, 4.22]
Soares 2013	5	16	11	16	13.8%	0.21 [0.05, 0.92]
van Adrichem 2014	4	20	11	19	16.5%	0.18 [0.04, 0.76]
Total (95% CI)		**218**		**217**	**100.0%**	**0.59 [0.38, 0.91]**
Total events	57		78			

Heterogeneity: $Chi^2 = 12.38$, df = 7 (P = 0.09); $I^2 = 43\%$

Test for overall effect: Z = 2.41 (P = 0.02)

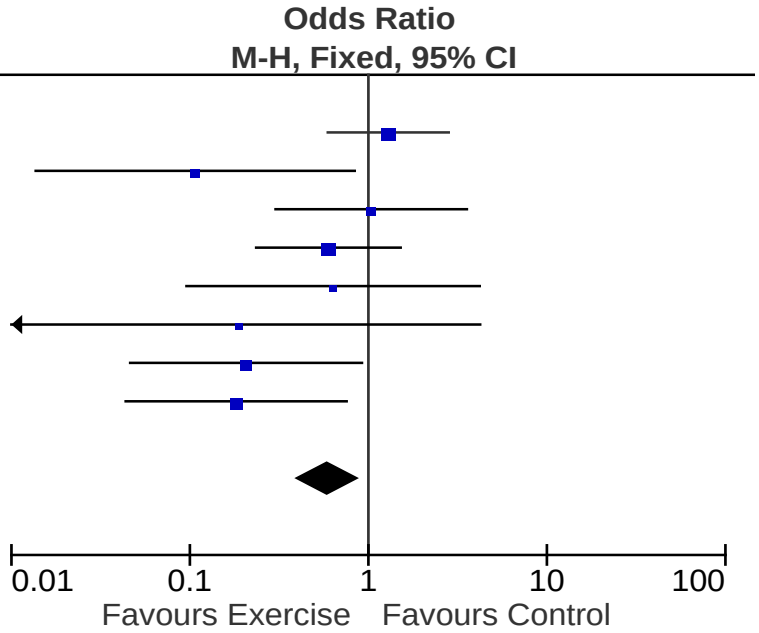


Figure 5.4: Preoperative exercise interventions were compared to control treatments in terms of postoperative morbidity for all included studies.

5.3.6 Exercise versus usual care

Five of the nine studies reviewed compared preoperative interventions to *usual care* or passive control groups. Usual care consisted of no treatment or standard preoperative breathing exercises (Barbalho-Moulim et al., 2011, Gillis et al., 2014, Kulkarni et al., 2010, Soares et al., 2013) (Table 5.2). In contrast, three studies included an active control group which received an exercise based intervention. These exercise interventions prescribed lower intensity activities such as walking for 30 minutes a day, and endurance based IMT [(Seven sessions of IMT at 30% maximal inspiratory pressure (MIP)] (Carli et al., 2010, Dronkers et al., 2010, Van Adrichem et al., 2014). One study compared exercise to preoperative dietary advice (Kaibori et al., 2013b). Patients were reported to have a daily energy intake; 25-30 kcal/kg body weight (BW) with a daily protein intake of 1.0-1.2 g/kg of BW and daily sodium intake of 5-7 g/kg of BW. These control groups were not considered usual care.

When studies were examined which compared exercise training to usual care only, there was a significant decrease in the number of postoperative complications in favour of exercise prehabilitation (OR: 0.35, 95% C.I: 0.17-0.71) (Figure 5.5). There was low heterogeneity between studies I^2=5%. This reduction in postoperative morbidity with exercise training compared to usual care was far stronger than the results reported in Figure 5.4 which compared exercise training to a mix of usual care and active control groups (OR: 0.59, 95% C.I: 0.38-0.91).

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Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Barbalho-Moulim 2011	0	15	0	17		Not estimable
Dronkers 2008	3	10	8	10	20.7%	0.11 [0.01, 0.84]
Gillis 2014	12	38	17	39	42.5%	0.60 [0.24, 1.52]
Kulkarni 2010	0	18	2	19	8.8%	0.19 [0.01, 4.22]
Soares 2013	5	16	11	16	28.0%	0.21 [0.05, 0.92]
Total (95% CI)		**97**		**101**	**100.0%**	**0.35 [0.17, 0.71]**
Total events	20		38			

Heterogeneity: Chi² = 3.16, df = 3 (P = 0.37); I² = 5%

Test for overall effect: Z = 2.94 (P = 0.003)

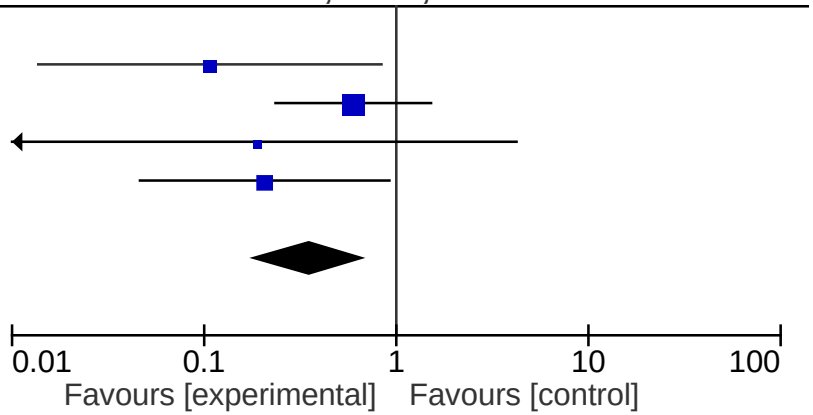


Figure 5.5: Preoperative exercise interventions were compared to usual care (breathing exercises or standard treatment only) in terms of postoperative morbidity

5.3.7 Exercise and postoperative pulmonary complications

Six studies examined the effect of exercise training on the incidence of postoperative pulmonary complications only. All interventions were compared to a control group involving lower intensity training or usual care. Of these, four studies prescribed preoperative IMT only, while two studies prescribed multimodal interventions involving a combination of IMT, aerobic exercise and resistance training of the lower limbs (Dronkers et al., 2010, Soares et al., 2013). Preoperative training resulted in a significant reduction in postoperative pulmonary complications (OR: 0.27, 95% C.I: 0.13-0.57) (Figure 5.6).

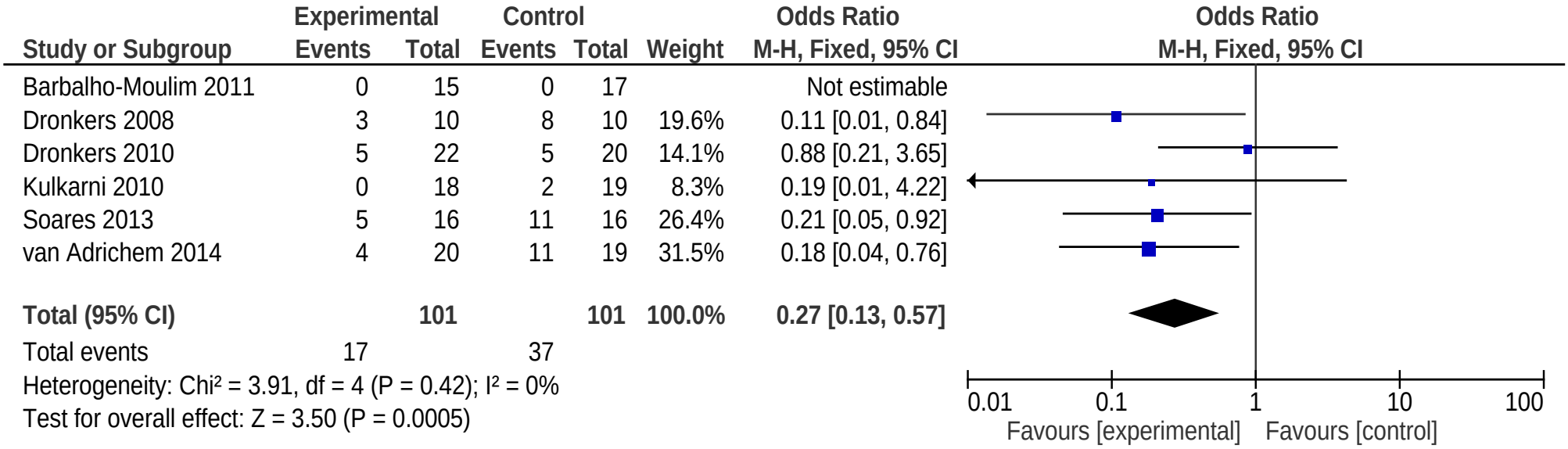


Figure 5.6: Preoperative exercise interventions were compared to control treatments in terms of postoperative pulmonary complications only

5.3.8 Exercise and other complications

Four studies measured all types of complications (e.g. anastomotic leak and wound infection) and reported no difference between intervention and control groups. Two of these studies assessed complications with the Clavien-Dindo classification score (Carli et al., 2010, Gillis et al., 2014), while Kaibori and colleagues did not report how complications were measured (Kaibori et al., 2013b). Dronkers and colleagues reported no significant difference between the intervention and control group in terms of self-defined complications (9 vs. 8, p=0.65) (Dronkers et al., 2008).

5.3.9 Length of stay

A total of eight studies examined the influence of preoperative exercise therapy on general LOS. Of these, four studies reported mean LOS and were pooled for meta-analysis. Exercise prehabilitation consisted of IMT, aerobic and resistance exercise (Table 5.2). It was not possible to estimate the results by Barbalho-Moulim et al. (2011) due to the standard deviation of zero and therefore only three studies were weighted in the meta-analysis. There were no significant differences in LOS between exercise and control groups (Mean difference: -1.62 days, 95% C.I: -7.57, 4.33) (Figure 5.7)

Four studies were unable to be pooled in the meta-analysis as LOS was non-normally distributed. Van Adrichem et al. (2014) reported that patients who completed high intensity IMT (3 sessions a week of IMT at 60-80% MIP) as opposed to a lower intensity endurance based IMT (7 sessions a week of IMT at 30% MIP) had a significantly shorter LOS (13.5 vs. 18 days, p=0.01). Furthermore, the high intensity IMT group showed a trend towards a shorter stay in ICU (0.5 vs. 1.5 days, p=0.07). In contrast, Kulkarni et al. (2010), Soares et al., (2013) and Gillis et al. (2014) reported no difference in LOS between intervention and control groups. The exercise interventions prescribed in these four studies included IMT, aerobic and resistance exercise (Table 5.2). The GRADEpro classifies the methodological quality of these studies as very low (Figure 5.1) and the overall risk of bias of these studies is presented in Figure 5.3. Gillis and colleagues reported there was no significant difference in readmission rates between the prehabilitation group and the control group [6 (15%) vs. 5 (13%), respectively, p=0.780] (Gillis et al., 2014). No other study reported readmission rates.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barbalho-Moulim 2011	2	0	15	2.11	0.33	17		Not estimable
Carli 2010	11.9	34.6	55	6.5	3.6	52	27.2%	5.40 [-3.80, 14.60]
Dronkers 2010	16.2	11.5	22	21.6	23.7	20	20.0%	-5.40 [-16.84, 6.04]
Kaibori 2013	13.7	4	25	17.5	11.3	26	52.8%	-3.80 [-8.42, 0.82]
Total (95% CI)			**117**			**115**	**100.0%**	**-1.62 [-7.57, 4.33]**

Heterogeneity: Tau² = 11.88; Chi² = 3.38, df = 2 (P = 0.18); I² = 41%

Test for overall effect: Z = 0.53 (P = 0.59)

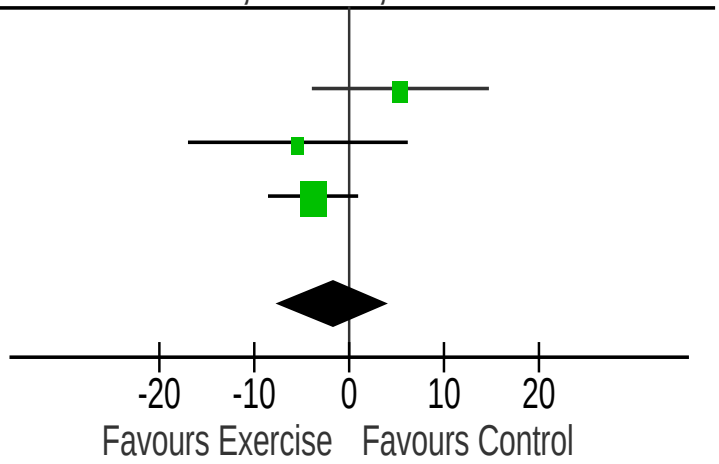


Figure 5.7: Preoperative exercise interventions were compared to control treatments in terms of LOS. Only four studies had normally distributed LOS

5.3.10 Mortality

There was no reported mortality in any of the studies reviewed and therefore this analysis was not completed.

5.3.11 Preoperative physical fitness

Due to the heterogeneity of data, it was not appropriate to complete a meta-analysis to assess if preoperative exercise interventions resulted in changes in preoperative physical fitness (Table 5.3). Two studies reported conflicting results in terms of improvements in preoperative aerobic capacity as measured by the 6MWT. Gillis and colleagues reported a significant difference in the improvement of 6MWT in the intervention group (25.2 ± 50.2m) compared to the deterioration in the control group (-16.4 ± 46.0, $p<0.001$). In comparison, Carli and colleagues reported no change in 6MWT distance in the intervention group preoperatively (494.1 ± 15.5 pre-intervention vs. 502.8 ± 15.8 post-intervention, $p=0.203$), however there was a significant difference in VO_{2peak}, as measured by CPET, in both the intervention (1395 $\pm$ 76 vs. 1529 $\pm$ 88 ml/min, $p=0.003$) and the control group (1400 $\pm$ 71 vs. 1511 $\pm$ 84 ml/min, $p=0.007$) (Carli et al., 2010). Dronkers and colleagues reported no differences in physical fitness as measured by functional exercise tests such as the timed up and go test (TUG) and the chair rise time test (CRT) in either the intervention or control group (Dronkers et al., 2010).

Five studies prescribed IMT to increase respiratory muscle strength as assessed by MIP. With the exception of Dronkers and colleagues who reported no change in post-intervention MIP, all studies reported improvements in MIP (Dronkers et al., 2008). Three studies reported a significant difference in MIP between baseline and pre-surgery (Dronkers et al., 2010, Kulkarni et al., 2010, Barbalho-Moulim et al., 2011). Soares and colleagues reported a non-significant improvement in MIP during the preoperative period in the intervention group (62 vs. 88 cmH_2O $p>0.05$), however there was a significant difference in post-intervention MIP between the intervention (88 cmH_2O) and the control group (64 cmH_2O) ($p=0.049$) (Soares et al., 2013).

Table 5.3: Changes in physical fitness during preoperative period: Values are presented as mean ± SD unless otherwise stated *values are median and IQR. 6MWT; Six Minute Walk Test, CRT; Chair Rise Time, IME; Inspiratory Muscle Endurance, MEP; Maximal Expiratory Pressure, MIP; Maximal Inspiratory Pressure, RME; Respiratory Muscle Endurance, TUG; Timed Up and Go

Author	Exercise Intervention	Baseline	Pre-op	Baseline and Pre-op differences	Between intervention and control group differences
Inspiratory Muscle Training					
Barbalho-Moulim et al. (2011)	Inspiratory Muscle Training	MIP (cmH_2O): 93.33 ± 23.80 MEP (cmH_2O): 117.33 ± 34.53	MIP (cmH_2O): 120.00 ± 20.35 MEP (cmH_2O): 142.66 ± 28.90	MIP: p<0.05 MEP: p>0.05	
	Control	MIP (cmH_2O): 92.94 ± 18.63 MEP (cmH_2O): 116.47 ± 32.39	MIP (cmH_2O): 91.76 ± 20.38 MEP (cmH_2O): 135.29 ± 34.11	MIP: p>0.05 MEP: p>0.05	
Dronkers et al. (2008)	Inspiratory Muscle Training	MIP (cmH_2O): 68 ± 19 IME (cmH_2O): 32 ± 8	MIP (cmH_2O): 72 ± 22 IME (cmH_2O): 43 ± 14	MIP: p=0.32 IME: p=0.05	MIP: p=0.29
	Control	MIP (cmH_2O): 83 ± 15 IME (cmH_2O): 39 ± 10	MIP (cmH_2O): 80 ± 24 IME (cmH_2O): 43 ± 9	MIP: p=0.60 IME: p=0.36	IME: p=0.12
Kulkarni et al. (2010)	IMT	MIP (cmH_2O): 51.5 (33-97)*	MIP (cmH_2O): 68.5 (44-121)*	MIP: p<0.01	
	Control: No intervention	MIP (cmH_2O): 55 (30-93)*	MIP (cmH_2O): 48 (21-94)*	MIP: p=0.25	MIP: p<0.01
	IMT – High Intensity	MIP (cmH_2O): 93.5 (69-120.5)*	MIP (cmH_2O): 104.5 (95.5-136.3)*	MIP: p=0.001	MIP: p=0.316

Van Adrichem et al. (2014)	IMT - Endurance	MIP (cmH_2O): 84.0 (67-94)*	MIP (cmH_2O): 113 (86-126)*	MIP: p<0.001	
Aerobic Exercise, Resistance Training and Inspiratory Muscle Training Combination					
Carli et al. (2010)	Bike and strengthening	6MWT (m): 474.3 ± 15.1 VO_{2peak} (ml/min): 1395 ± 76	6MWT (m): 463.6 ± 18.5 VO_{2peak} (ml/min) 1529 ± 88	6MWT: p=0.148 VO_{2peak}: P=0.003	
	Walk and breathing	6MWT (m): 494.1 ± 15.5 VO_{2peak} (ml/min): 1400 ± 71	6MWT (m): 502.8 ± 15.8 VO_{2peak} (ml/min): 1511 ± 84	6MWT: p=0.203 VO_{2peak}: P=0.007	
Dronkers et al. (2010)	Intervention	TUG (s): 8.0 ± 3.6 CRT (s): 26.3 ± 6.7 MIP (cmH_2O): 78 ± 33	TUG (s): 7.8 ± 3.3 CRT (s): 26.6 ± 6.2 MIP (cmH_2O): 92 ± 26	TUG (s): p=0.29 CRT (s): p=0.74 MIP (cmH_2O): p<0.001	TUG (s): p=0.34 CRT (s): p=0.87 MIP (cmH_2O): p=0.09
	Control	TUG (s): 6.4 ± 1.3 CRT (s): 21. 6 ± 4.7 MIP (cmH_2O): 93 ± 25	TUG (s): 6.6 ± 1.2 CRT (s): 21.2 ± 6.1 MIP (cmH_2O): 98 ± 26	TUG (s): p=0.28 CRT (s): p=0.81 MIP (cmH_2O): p=0.33	

Gillis et al. (2014)	Prehab	Mean change in 6MWT during pre-op period (m): 25.2 ± 50.2 8 weeks post-surgery (m): 24.4 ± 54.8		Pre-op period: p<0.001 8 weeks post-op: p=0.02	
	Rehab	Mean change in 6MWT during pre-op period (m): -16.4 ± 46.0 8 weeks post-surgery (m): -21.8 ± 80.7			
Kaibori et al. (2013)	No measure or baseline and pre surgery. Measures performed are baseline and 6 months after surgery				
Soares et al. (2013)	Intervention	MIP (cmH_2O): 62 (50-83)* RME (cmH_2O): 18 (17-22)* 6MWT (m): 126 (124-126)*	MIP (cmH_2O): 88 (66-103)* RME (cmH_2O): 28 (22-32)* 6MWT (m): 126 (120-126)*	MIP (cmH_2O): p>0.05 RME: p<0.05 6MWT (m): p>0.05	MIP (cmH_2O): p=0.049 RME (cmH_2O): p=0.006 6MWT (m): p=0.349

5.4 Discussion

The results of this meta-analysis demonstrate that exercise prehabilitation consisting of inspiratory muscle training, aerobic exercise, and resistance training decreases the incidence of all-cause postoperative complications in patients undergoing intra-abdominal surgery (OR: 0.59, 95% C.I: 0.38-0.91). This effect was strongest when exercise prehabilitation was compared to usual care or breathing exercises only (OR: 0.35, 95% C.I: 0.17-0.71). Furthermore, exercise prehabilitation significantly decreased the incidence of postoperative pulmonary complications (OR: 0.27, 95% C.I: 0.13-0.57), which was measured as the primary complication of interest in the majority of studies reviewed. The methodological quality of these studies was ranked as 'very low' according to the GRADEPro, it is possible that with further research these results could change. Therefore further research is needed to conclude on the ability of preoperative exercise interventions to reduce postoperative complications. Exercise prehabilitation also significantly improved preoperative physical fitness as measured by inspiratory muscle strength and cardiopulmonary exercise testing, however further research is needed to definitely conclude on the ability of prehabilitation to increase preoperative cardiorespiratory fitness due to the low number of studies measuring VO_2peak (n=1) (Carli et al., 2010) (Table 5.3). Exercise prehabilitation did not influence postoperative LOS after intra-abdominal surgery, however the number of studies contributing to the Forest plot was low (n=4) (Figure 5.7). Due to the low readmission rates and no reported mortality, this review cannot conclude if exercise prehabilitation influences these important postoperative outcomes.

This review demonstrates that exercise prehabilitation decreases the risk of postoperative complications (Figure 5.4), however this effect was strongest for postoperative pulmonary complications (Figure 5.6). Preoperative inspiratory muscle training is an effective form of reducing postoperative pulmonary complications (Katsura et al., 2015), however it is unclear if the combination of inspiratory muscle training and aerobic and resistance exercise (n=3) leads to greater reductions in postoperative pulmonary complications compared to inspiratory muscle training alone (n=3). Three studies reported no effect of exercise prehabilitation on medical or surgical complications (Carli et al., 2010, Gillis et al., 2014, Dronkers et al., 2010). It is likely that exercise exerts a stronger effect on pulmonary and general medical complications compared to surgical complications such as ileus, due to the effect of exercise on the ability to deliver oxygen and meet the global oxygen demand post-surgery (Chapter 1.2.1).

In two of the studies reviewed, control groups performing low intensity walking for 30 minutes a day preoperatively experienced less postoperative complications (non-significant) compared to

intervention groups consisting of aerobic exercise, resistance training, and/or inspiratory muscle training (Dronkers et al., 2010, Carli et al., 2010). Dronkers and colleagues reported 9 patients in the intervention group had postoperative complications compared to 8 in the active control group. In addition, Carli and colleagues reported 22 patients in the intervention group had complications, as measured using the Clavien-Dindo score, compared to 18 in the active control group. Walking is often prescribed preoperatively, however its ability to increase aerobic capacity is not well reported (Englesbe et al., 2015). For example, Englesbe and colleagues prescribed a preoperative walking programme to 500 participants scheduled for various surgical procedures with the goal of increasing walking distance. Physical activity levels increased by 85%, however, it is unclear if this improved preoperative aerobic capacity (Englesbe et al., 2015). Walking can increase aerobic capacity (Murphy et al., 2002) and while the walking interventions in the studies included in this review were designed to serve as control groups it could be argued that they acted as effective preoperative interventions. The effect size generated by the Forest plot comparing postoperative complications between preoperative exercise and active and passive control groups in Figure 5.4 was reduced compared to the Forest plot comparing postoperative complication rates between preoperative exercise and usual care (Figure 5.5). Therefore, it is likely that preoperative walking interventions influenced postoperative complications through increases in preoperative fitness. The ability of walking interventions to increase fitness in the preoperative setting is underexplored and warrants further investigation.

The results of this meta-analysis do not suggest that exercise prehabilitation influences LOS after intra-abdominal surgery (p=0.24). Theoretically, a decrease in overall postoperative complications may translate to a decrease in LOS and even small decreases in LOS may translate to cost savings. Amongst the studies reviewed, a mean decrease of 1.6 days was observed (Figure 5.7). In the United States, the average cost of one inpatient day is $2,157 (Foundation, 2013), and therefore, a mean decrease of 1.6 days would create a cost saving of $3,451.2 per surgical procedure.

Three studies in this review included patients undergoing neoadjuvant chemoradiotherapy (Van Adrichem et al., 2014, Carli et al., 2010, Gillis et al., 2014). There were no differences in postoperative complication rates between patients treated with neoadjuvant chemoradiotherapy and those who were not and no adverse events were reported. Van Adrichem and colleagues delayed commencing prehabilitation by 1-2 weeks to allow for completion of neoadjuvant chemoradiotherapy, while two studies did not report if prehabilitation was performed during or after neoadjuvant chemoradiotherapy (Gillis et al., 2014, Carli et al., 2010). Neoadjuvant chemoradiotherapy leads to cardiopulmonary toxicity and decreases in aerobic capacity (West et al., 2014a). In one report, West

and colleagues observed a mean decrease in aerobic capacity of 1.4 ml/kg/min (95% C.I: −3.1, −1.0 ml/kg/min) post neoadjuvant chemoradiotherapy in 25 patients scheduled for rectal cancer surgery (West et al., 2014a). In oesophagogastric surgery, decreases in aerobic capacity during neoadjuvant chemotherapy are associated with increased rates of mortality at one year post surgery (Jack et al., 2014). Therefore, the need for prehabilitation in cohorts receiving neoadjuvant therapies may be greater than those treated with surgery alone. The studies in this review, consistent with current literature, report that exercise prehabilitation post neoadjuvant chemo(radio)therapy is safe and can increase aerobic capacity (West et al., 2015).

Current standards in cancer care demand minimal delay between cancer diagnosis and treatment commencement. As surgery is often the first line intervention in cancer treatment, this poses a challenge to incorporating exercise prehabilitation into a time restricted clinical pathway. For example, the median time between colorectal diagnosis and surgery is 30 days (IQR: 18-42) and the mean duration of prehabilitation in the study by Carli and colleagues was 40 days (SD: 30) (Redaniel et al., 2014, Carli et al., 2010). The potential for interventions that achieve maximum results over short periods should be explored. A recent meta-analysis concluded that high intensity interval training (bursts of high intensity exercise interspersed with periods of rest) was more effective than continuous training at increasing both VO_{2peak} ($p<0.01$) and AT ($p<0.01$) and demonstrated a similar safety profile to moderate-intensity training (Elliott et al., 2015). A preoperative supervised high intensity interval training programme may increase a patient's aerobic capacity prior to surgery, within a short time frame. An easier alternative is a walking based intervention, as it is likely to influence postoperative complication rates and can be performed by patients at home. However, this type of moderate intensity exercise may not create the improvements necessary within a short time frame. The ability of these programmes to improve aerobic fitness should be compared in future research.

Exercise prehabilitation and ERAS pathways aim to minimise surgical stress and complications, however the two are not often combined (Findlay et al., 2014). Only one study in this review reported treating patients with an ERAS program with prehabilitation and a recent review found that the literature specific to ERAS and prehabilitation is limited (Gillis et al., 2014, Levett and Grocott, 2015). Preoperative interventions included in ERAS approaches include, preoperative nutrition, and haemoglobin optimisation and the potential to include exercise prehabilitation as part of ERAS to further reduce postoperative complications should be explored.

There were several aspects of the included studies that may have influenced the results of this review. Two studies prescribed an exercise based intervention as a control, therefore, the influence that they

had to protect against postoperative complications is unclear. The physical fitness of patients prior to beginning preoperative interventions may have introduced bias to the results. Two studies reported that participants who consented may have been slightly fitter and healthier compared to the normal population (Kulkarni et al., 2010, Kaibori et al., 2013b). In contrast, Dronkers and colleagues reported participants were 60% less active compared to normative data (Dronkers et al., 2010) therefore, it is unclear if the physical fitness of patients in these interventions was comparative to the normal population.

Inconsistencies in the definition of postoperative complication definitions across the studies reviewed made comparison between studies challenging. Future studies should use a combination of the Clavien-Dindo classification scoring system, the POMS, and the CCI to objectively measure postoperative morbidity (Dindo et al., 2004, Bennett-Guerrero et al., 1999, Slankamenac et al., 2013). The methodologic quality of included studies was 'very low', as measured by the GRADEPro, this result was largely driven by lack of blinding and ambiguity regarding allocation concealment. The low quality of evidence in this meta-analysis reiterates the need for further high quality exercise prehabilitation RCT's. One of the limitations of exercise-based interventions is the inability to blind participants and personnel to the true intervention, however, sham inspiratory muscle training can be used in future research to blind participants and improve methodologic quality. While the results of this meta-analysis should be considered with caution, it provides interesting results that small pilot RCT's produced favourable results towards exercise interventions.

5.5 Conclusion

Exercise prehabilitation can improve postoperative outcome by decreasing all-cause and pulmonary complications. The effect of exercise prehabilitation is strongest when compared to no treatment or breathing exercises. The ability of exercise prehabilitation to decrease postoperative mortality and LOS is inconclusive due to the low rate of mortality and low number of studies reporting on postoperative LOS. Although exercise prehabilitation can decrease postoperative complications the results of this meta-analysis should be considered with caution due to the relatively low methodologic quality of the included studies. Further RCT's are needed to validate the protective effects of exercise prehabilitation.

6 Chapter 6 Preoperative High Intensity Interval Training for patients scheduled for colorectal and thoracic surgery: The PHIIT Trial

6.1 Introduction

Preoperative exercise interventions can reduce the incidence of postoperative complications in intra-abdominal (Chapter 5) and thoracic surgery (Benzo et al., 2011), however the evidence in support of these interventions is of low quality and high quality studies are needed to justify the inclusion of such interventions in preoperative surgical pathways (Chapter 5) (Mainini et al., 2016). Exercise prehabilitation studies have previously prescribed a combination of moderate intensity aerobic exercise, inspiratory muscle training, and resistance exercises (Soares et al., 2013, Dronkers et al., 2010). As cardiorespiratory fitness is an important component in protecting against poor postoperative outcome, exercise prehabilitation models focusing on improving preoperative protocols is a notable limitation to their implementation within clinical practice. The National Health Service (NHS) requires patients with cancer undergo treatment within 31 days of decision to treat and current moderate intensity exercise prehabilitation protocols are longer than the available time frame between decision to treat and surgery (4-6 weeks) (Ireland, 2007, Service, 2014). Therefore, clinicians are presented with a difficult decision, proceed directly to surgery and forgo prehabilitation, or delay surgery to allow time for prehabilitation and risk disease progression.

The PHIIT trial explores HIIT as a method of achieving a therapeutic increase in cardiorespiratory fitness within current surgical pathway timelines. HIIT requires participants to exercise at high levels of VO_2peak (≥80% VO_2peak) for short intervals followed by periods of rest of equal or lesser duration. A review by Guiraud et al. (2012) reported HIIT programmes to be safe in individuals with coronary artery disease and stable heart failure (Guiraud et al., 2012). Furthermore, HIIT leads to greater improvements in cardiorespiratory fitness compared to continuous moderate intensity exercise. In one meta-analysis comprising ten studies of 472 patients with coronary artery disease (CAD), participants exercising according to HIIT protocols experienced a +1.78 (95% CI: 0.45-3.11) ml/kg/min greater improvement in cardiopulmonary fitness compared to continuous moderate intensity training (Liou et al., 2015). In addition, HIIT has been reported to create similar improvements in cardiorespiratory fitness compared to continuous moderate intensity exercise, despite a lower total exercise period (2.5 hours vs. 10 hours, respectively) (Gibala et al., 2006). Therefore, HIIT is a more time-efficient method of improving cardiorespiratory fitness compared to continuous moderate intensity exercise.

There are a number of factors to take into account when designing a HIIT programme e.g. duration and intensity of exercise phase and type of recovery period (active vs. passive). The time spent at a high level of VO_2 (e.g. >80% VO_{2peak}) appears to be one of the most important factors for increasing cardiorespiratory fitness (Guiraud et al., 2012). Two studies compared a selection of HIIT protocols for safety and time at a high percentage of VO_{2peak} (≥80% VO_{2peak}) (Table 6.1) (Meyer et al., 2012, Guiraud et al., 2010). Protocols with rest periods (passive recovery) allowed patients to exercise for longer and had lower perceived difficulties (Meyer et al., 2012, Guiraud et al., 2010). In one study of 20 patients with CAD, HIIT was prescribed with 15s exercise and passive recovery intervals at 100% Peak Power Output (PPO) or Maximal Aerobic Power (MAP) with no adverse events (Guiraud et al., 2010). Peak Power Output or MAP is the maximum resistance achieved during the last completed stage of a maximal cardiopulmonary exercise test (watts). This intervention had the highest duration of time above 80% VO_{2peak} (819s) and a high completion rate of 63%. This protocol was chosen for this study.

Preoperative exercise interventions of relatively high intensity continuous exercise have poor adherence rates (16% completion) (Carli et al., 2010) (Table 5.2). It is likely that these high intensity interventions can be difficult to complete and may be perceived as intimidating for untrained individuals. In accordance with best practice, a feasibility study should be performed to assess if the adherence rates of a preoperative HIIT are adequate prior to implementing an RCT (Tickle-Degnen, 2013, Research, 2012)**.** Therefore, the aim of this study was to examine the feasibility of a HIIT prehabilitation programme of 2-4 week duration prior to major abdominal and thoracic surgery. Secondary objectives included: (i) to determine if a short-term HIIT intervention increases cardiopulmonary fitness prior to surgery and (ii) to measure participant postoperative outcome (morbidity, mortality, and LOS).

Table 6.1: High Intensity Interval Training (HIIT) programmes and their relative intensities and the time above a high percentage (>80% VO_2peak).

Author	Intervention	Duration of exercise cycle	Intensity (MAP= PPO)	Recovery	Duration of recovery	Number completing programme	Mean % of VO_2 peak	Time above 80% VO_2 Peak (s)	Total exercise/ Time to exhaustion (s)
Meyer et al. 2012	HIIT in CHF 30 min	30 s	100% PPO	Passive	30 s	75%	75 (9)	688 (543)	1651
		30 s	100% PPO	Active	30s	20%	87 (10)	711 (505)	986
		90 s	100% PPO	Passive	90s	50%	73 (9)	600 (345)	1,574
		90 s	100% PPO	Active	90s	25%	88 (8)	748 (473)	961
Guiraud et al. 2010	HIIT in CAD 30 min	15 s	100% MAP	Passive	15s	63%	-	819 (578)	1724
		15 s	100% MAP	Active	15s	16%	-	635 (443)	733
		60 s	100% MAP	Passive	15s	42%	-	585 (370)	1525
		60 s	100% MAP	Active	15s	0	-	654 (366)	836

The highlighted protocol was selected due to the highest time >80% VO_2peak. The time spent at a high level of VO_2 (e.g. >80% VO_2peak) appears to be one of the most important factors for increasing aerobic capacity (Guiraud et al., 2012). CAD; Coronary Artery Disease, CHF; Chronic Heart Failure, MAP; Maximal Aerobic Power, PPO; Peak Power Output.

6.2 Methods

6.2.1 Study design

This was a prospective, single arm feasibility conducted in the Wellcome Trust-HRB Clinical Research Facility in St. James' Hospital between March 2016 and December 2016. Approval for this study was granted by the SJH/AMNCH Research Ethics Committee Dublin (Appendix B). The study protocol was registered with a trial registry (ClinicalTrials.gov; identifier: NCT02674815; see Appendix E). The United Kingdom Medical Research Council guidelines for feasibility studies were followed in drafting this chapter (O'Cathain et al., 2015).

6.2.2 Participants

Potential participants were recruited from the Colorectal & General Surgery Clinic and the Cardiothoracic Surgery Clinic at St. James' Hospital. Suitable participants were identified by consultant surgeons and thoracic and colorectal surgical coordinator nurses in St. James's Hospital. The lead investigator (J. Moran) discussed all study details with potential participants and screened for eligibility. All participants were provided with participant information leaflets, consent forms, time for questions and given 24 hours to provide informed consent. Written informed consent was obtained for each subject prior to participation, in compliance with the Declaration of Helsinki.

6.2.3 Participant eligibility

Inclusion criteria consisted of (i) patients scheduled for thoracic or colorectal surgery, (ii) able to give informed consent, and (iii) ability to understand English. Exclusion criteria consisted of (i) the ATS/ACCP contraindications to exercise testing (Table 4.1) (ATS/ACCP, 2003), (ii) individuals with pacemakers or defibrillators, (iii) epilepsy, (iv) past-history or MRI evidence of brain damage, (v) ASA-PS grade of 4 or 5, (vi) acute illness, fever, or thyroiditis and (vii) emergency surgery or surgery scheduled <2 weeks. The exclusion criteria are based on best practice guidelines and ensure only the most high-risk patients are excluded from performing CPET (Table 4.1). These criteria were used to ensure safe practice while also warranting the study population were as representative of the true study population as possible. P

6.2.4 Feasibility outcomes

To examine the feasibility of a preoperative HIIT programme the following feasibility outcomes were included (i) adherence and compliance (ii) programme safety and (iii) costs. Adherence (percentage of sessions attended) and compliance (percentage of sessions completed) were measured by recording the number of appointments each participant attended, and successfully completed, respectively. Furthermore, the safety of this programme was explored. Adverse events were assessed at every visit and the following details recorded: type, incidence, severity, timing, seriousness, and relatedness to a) disease and b) the intervention. Hospital resources and costs were investigated to highlight the likelihood of future implementation of preoperative HIIT programmes. To achieve this, the PHIIT trial examined the resources available, and recorded the expected costs. Expected costs included, parking, room rental charges and equipment purchasing. Participant's views on the PHIIT trial were recorded using a questionnaire administered postoperatively (Appendix D) and participants highlighted what they liked and didn't like about the programme and provided suggestions for improvement.

6.2.5 Assessment protocol

All sessions were performed in the Wellcome Trust-HRB Clinical Research Facility (CRF) in St. James's Hospital by the same physiotherapist. A standardised test protocol was used for all assessments and is outlined in Table 6.2. Participants attended a pre-intervention session to measure baseline characteristics, including; age, gender, surgical procedure, and co-morbidities. Preoperative clinical outcome measures recorded included ASA-PS classification, CR-POSSUM score and P-POSSUM score, as outlined in (Chapter 2.2.1).

Participants completed a comprehensive physical fitness assessment undertaken by the same experienced physiotherapist. Prior to beginning testing, participant resting HR, SpO_2, and blood pressure were measured. Participant height and weight were measured using a stadiometer and SECA weighing scale and used to calculate BMI. The participant's waist and hip circumference was assessed according to the WHO guidelines using a tape measure (World Health Organisation, 2008). Prior to CPET and in accordance with ATS/ACCP guidelines, participants were requested to (i) avoid smoking 8 hours prior to testing (ii) take their prescribed medications (iii) avoid exercise on the day of testing and (iv) have a light meal no less than 2 hours before testing prior to exercise testing. Cardiopulmonary exercise testing was conducted according to the ATS/ACCP recommendations (ATS/ACCP, 2003) as outlined in (Chapter 2.3.1.11). Ventilatory threshold was calculated using the modified V-slope method (Schneider et al., 1993) and VO_2peak was calculated as the mean VO_2 over the last 30 seconds of exercise. Furthermore, spirometry was assessed prior to CPET and in accordance with ATS/ACCP guidelines (Chapter 2.3.5.1).

Prior to surgery and following completion of HIIT intervention, participants attended a post-intervention assessment. All measurements performed in the initial pre-intervention assessment were repeated (Table 6.2). Participants then proceeded for surgery and were followed up postoperatively. In-hospital postoperative morbidity was assessed using a combination of the Postoperative Morbidity Survey (POMS) (type and number of complications on a specific day), the Clavien-Dindo Classification Score (most severe complication) and the Comprehensive Complications Index (CCI) (the number and severity of complications). POMS was performed on Day 3, 5, and 7. Length of stay included general hospital stay from time of operation to discharge, ICU/HDU admission rates and length of stay as well as 30-day readmission rates. Finally, 30-day and in-hospital mortality rates were also recorded.

6.2.6 HIIT training protocol

Following baseline assessment all participants were scheduled to complete HIIT sessions performed on a stationary cycle ergometer. The PHIIT trial followed an established HIIT protocol incorporating 15 seconds of exercise at 100% PPO and passive recovery intervals at 0 watts (Guiraud et al., 2012) (Table 6.1). Each session consisted of a warm-up phase for 5 minutes at 50% PPO, the HIIT phase lasted for 30 minutes or until exhaustion and upon completion participants performed 3 min active recovery period (30 W) and a 7-minute passive recovery. Participants were monitored upon completion until baseline variables (HR, SpO_2 and blood pressure) were within 10% of recorded resting measurements.

Participants attended up to ten exercise sessions preoperatively within a 2-4 week period, aiming to perform 3-5 sessions a week. All classes were supervised by a qualified physiotherapist. Heart rate, blood pressure and SpO_2 were recorded prior to exercise. Heart rate was recorded throughout using a POLAR HR monitor and watch (FT7, Finland). The resistance, PPO, was increased by 5-10 watts if heart rate did not reach within 10% of maximal heart rate recorded during CPET.

Table 6.2: PHIIT trial assessment timeline detailing assessment measures at each time-point with highlighted areas indicating assessment measures completed at relevant time-points. ECG; Electrocardiography, LOS; Length of stay

		Screening (Pre-study)	First Visit (1st Session)	Intervention (2nd-11th Session)	Final Visit (12th Session)	Post-op Assessment
Initial Study Procedures	Explain Study	X				
	Screen Eligibility Criteria	X				
	Sign Consent Form	X				
Pre and Post Intervention Assessment	Explanation of Testing Procedure		X		X	
	Height, weight, body composition, waist and hip circumference		X		X	
	Spirometry Assessment		X		X	
	Resting vital signs, ECG and maximal exercise test		X		X	
Preop Exercise Intervention Sessions	Resting vitals, heart rate monitor set-up, warm-up			X		
	High intensity interval training			X		
	Cool-down and resting vitals			X		
Postoperative Assessment	Postoperative Morbidity Survey					X
	Clavien-Dindo Classification Score					X
	Comprehensive Complications Index					X
	LOS					X
	Mortality					X

6.2.7 Statistical Analysis

This sample size of 20 participants, was similar to a previous prehabilitation pilot randomized controlled trial (Dronkers et al., 2008). Statistical analyses were performed using SPSS v.23.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean and standard deviation. Normality was assessed using the Sharpio-Wilk test (>0.05). Transformations were performed to ensure all data was normally distributed. Paired t-tests were used to assess differences between pre-and post-intervention cardiorespiratory fitness variables. Significance was set at 0.05.

6.3 Results

6.3.1 Recruitment rates

Potential participants were identified by the colorectal and thoracic surgical teams and screened by the research team for eligibility criteria. Initially 51 participants met eligibility screening and were invited to participate (37 thoracic and 14 colon), and of these, 21 declined due to living too far from the hospital (>2 hour return commute). Of the remaining 10 participants, 6 believed they had an acceptable level of physical fitness and four participants refused to participate. A total of 20 participants were recruited (12 scheduled for thoracic surgery, 8 scheduled for colon surgery) of 51 identified, representing a recruitment rate of 39.2%. Two participants dropped out following registration (Thoracic n=1; Colorectal n=1), and two participants had their surgery rescheduled and couldn't complete the programme (Thoracic n=2). Therefore, there was a drop-out rate of 20% (n=4/20 participants).

6.3.2 Baseline characteristics

Baseline demographic characteristics of participants are presented in Table 1.2. The mean age of participants (n=16) was 66.31 years (SD: 7.12). Nine participants were scheduled for lung surgery, while seven participants were scheduled for colorectal intervention. The majority of participants (n=11) were classified as Grade 2 (participants with mild systemic disease) according to the ASA-PS. Participants were classified as overweight [BMI: 28.33 (SD: 5.41) kg/m^2]. Mean preoperative ventilatory threshold (VT) was 10.35 ml/kg/min (SD: 2.86), which is lower than the recommended preoperative AT (<10.9 ml/kg/min) reported in Chapter 3.4.1 for intra-abdominal surgery. Furthermore, cardiorespiratory fitness in participants scheduled for thoracic surgery was lower [VO_2peak: 13.70 ml/kg/min (SD: 2.06)] than the recommended cut-off of 15.0 ml/kg/min (BTS, 2001).

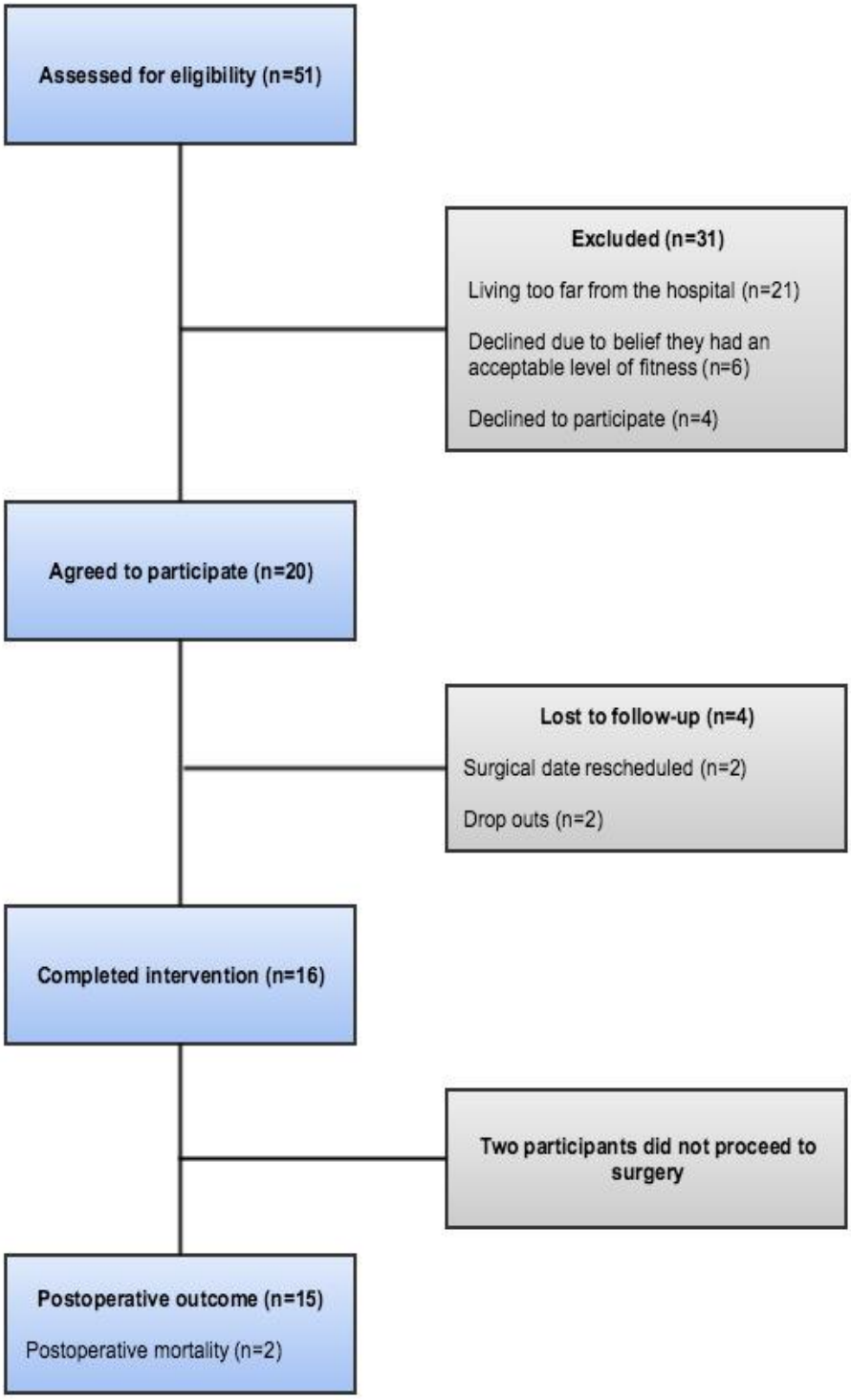


Figure 6.1: Flow diagram of participants through the PHIIT trial

Table 6.3: Baseline demographic characteristics.

	Mean (SD)
Participant Characteristics	
Age	66.31 (7.12) years
~Gender	
Female	9
Male	7
Height	163.68 (10.49) cm
Weight	76.45 (19.36) kg
BMI	28.33 (5.41) kg/m^2
Waist Circumference	101.08 (14.68) cm
Hip Circumference	105.12 (9.97) cm
Waist/Hip Ratio	
Female	0.91 (0.05)
Male	0.97 (0.09)
Surgical Characteristics	
~Planned Intervention	
Thoracic Surgery	9
Colon Surgery	7
~Cancer Staging^	
Colon Polyps	2
Stage 1	7
Stage 2	1
Stage 3A	2
Stage 3B	2
Stage 4	1
~Type of Surgery*^ (n=14)	
Right Lower Lobectomy	3
Right Upper Lobectomy	2
Right Upper Lobectomy and Mediastinal Lymph Node Dissection	1
VATS Right Upper Lobectomy	1
Right Wedge Resection	1
Low Anterior Resection	1
High Anterior Resection	1
High Anterior Resection and Hepatectomy	1
Right Hemicolectomy	2
Abdominal Perineal Resection	1
~Open vs. Laparoscopic	
Open	9
Laparoscopic	5
~ASA Grade	
1	4
2	11
3	1
P-POSSUM^	
Morbidity	24.64% (5.13)
Mortality	1.15% (0.35)

CR-POSSUM Mortality*	2.47% (1.15)
Sociodemographic Characteristics	
~Employment status	
Full time	1
Part time	1
Retired	13
Sick Leave	1
~Co-morbidities	
Diabetes Type II	1
Coronary artery bypass graft	1
Myocardial infarction	2
Chronic obstructive pulmonary disease	1
Abdominal aortic aneurysm repair	1
Hypertension	7
Hyperlipidemia	4
Data is presented as mean (standard deviation) unless otherwise stated ~Categorical data is presented as number of participants *One participant scheduled for colorectal surgery did not proceed to surgery ^One participant scheduled for thoracic surgery did not proceed to surgery and did not have cancer staging performed.	

6.3.3 Feasibility outcomes

6.3.3.1 Compliance and adherence

Mean adherence and compliance rates were high at 84% (SD: 34.17%) and 88% (SD: 26.15%), respectively. Only three participants had a compliance rate of <100% and this was due to the uncomfortable seat of the cycle ergometer.

6.3.3.2 Safety

There were no adverse events related to the intervention or participant's disease. One participant experienced an adverse event prior to completing the post-intervention CPET, resulting in a delay in surgery and change in treatment plan. This event, which was a fall resulting in a hip fracture, was not considered to be related to the disease or prehabilitation programme. The treatment plan for this participant changed from planned surgical resection to radiosurgery. Postoperative outcome was not recorded for this participant, however post-intervention CPET data from this participant was collected prior to the adverse event.

6.3.3.3 Costs analysis

The total costs of the PHIIT Trial are presented in Table 6.4. Costs of this preoperative HIIT intervention included; staff costs, exercise facility room rental, exercise equipment costs and participant parking costs. Exercise prehabilitation sessions lasted one hour (including set-up time) and were performed on

a 1:1 basis, supervised by a physiotherapist. Staff costs are based on the median salary of a basic grade physiotherapist (€42,742) within the Irish healthcare system (2016 data). The Wellcome-Trust HRB CRF was used to perform all exercise sessions, and the room rental costs were calculated at €12.50 per hour. Exercise equipment costs included a HR monitor and watch (€169.80), and a programmable cycle ergometer (€3,700). Participants were subsidised for their car parking charges, which equated to €2.50 per hour.

The costs of the PHIIT trial were calculated on a per class, per participant and total cost basis. Per class costs were the total costs for one participant, for one session that lasted one hour in duration. In addition, per participant costs were calculated based on the mean number of sessions attended per participant. This equated to 7 classes per participant. Finally, the total costs for the PHIIT trial is presented in Table 6.4. The total costs were based on the total number of classes, 112, multiplied by the per class cost.

Table 6.4: Costs associated with the PHIIT trial

Costs:	Per class (€)	Per participant (€)	Intervention total (€)
Staff	20.55	143.85	2,301.6
Exercise Facility Rental	12.50	87.5	1,400
Equipment	34.55	241.86	3,869.8
Parking	2.50	17.5	280
Total	**70.1**	**490.7**	**7,851.4**

6.3.3.4 Feedback questionnaire

Fourteen participants completed a feedback questionnaire postoperatively and results showed that that participants enjoyed the intervention (Table 6.5). Overall participants rated the programme highly (Excellent, n=8; Great, n=2; Good, n=3). The majority of participants (n=5) reported that increasing the number of sessions from a mean of 7 sessions to 11-14 sessions would be appropriate, 4 participants reported a total of 10 sessions would be ideal, two participants suggested increasing preoperative HIIT sessions to 15 or more, and the remaining two suggested the optimal number of sessions was 6-9.

Participants were asked to report what they enjoyed about the programme and areas for improvement. Participants enjoyed the 'close supervision', 'pleasant surroundings', and 'the feeling of helping myself get fitter and prepare for surgery, while at the same time helping the research'. The PHIIT trial helped improve subjective levels of fitness as one participant reported 'the programme was

truly appropriate to my needs. I learned to push myself under supervision and attain new levels of fitness that surprised myself'. The 'uncomfortable' cycle ergometer saddle was a noted area for improvement, while one participant felt using the 'treadmill for 10 minutes as a warm-up' would be beneficial. Participants were also asked a number of questions regarding safety and convenience, presented in Table 6.5, and responses were highly positive.

Table 6.5: Feedback questionnaire results. Data is presented as number of participants and their response for each question. Feedback was generally very positive.

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
Was it convenient to attend the scheduled sessions?	7	5	1	0	0
Was the information clearly presented before starting the intervention?	8	5	0	0	0
Were the investigators helpful?	7	6	0	0	0
Did the intervention help prepare you for surgery?	4	9	0	0	0
Did you feel safe throughout the intervention?	10	3	0	0	0

6.3.4 Physical fitness outcomes

Participants experienced a significant increase in VT (10.35 vs. 11.80 ml/kg/min, p=0.003) and VO_2peak (15.39 vs. 16.89 ml/kg/min, p=0.023) following a median number of 8 (range: 2-11) HIIT sessions over a median of 19 days. Participants also achieved a higher peak power output (PPO) on maximal CPET (85.63 vs. 98.63 W, p=0.005). Participants scheduled for thoracic surgery experienced a significant increase in VT (9.42 vs. 10.91 ml/kg/min, p=0.015) and participants scheduled for colorectal surgery experienced a significant improvement in VO_2peak (17.57 vs. 19.31 ml/kg/min, p=0.020) (

Table 6.7). Participants scheduled for thoracic surgery only experienced an increase in VO_2peak (13.7 vs. 15.00 ml/kg/min) however this was not significant (p=0.170). Pulmonary function, measured by spirometry, did not change over the course of the intervention (Table 6.6).

Table 6.6: Pre- and post-intervention change in cardiopulmonary fitness. *One participant had incomplete CPET data.

Outcome (n=16)	Pre-HIIT Mean (SD)	Post-HIIT Mean (SD)	Mean Difference	95% C.I	P-value
VT*	10.35 (2.86)	11.80 (3.34)	1.45	0.57, 2.31	0.003
VO_2peak	15.39 (4.32)	16.89 (4.37)	1.50	0.33, 2.65	0.022
VE/VCO2 at AT*	35.30 (7.57)	34.94 (6.94)	-0.36	-1.89, 1.16	0.620
VE/VCO2 at VO_2peak *	33.09 (6.39)	33.47 (6.19)	0.38	-1.80, 2.56	0.714
PPO/MAP	85.63	98.63	13.0	5.33, 20.67	0.005
FEV1*	1.80 (0.72)	1.91 (0.62)	0.11	-0.07, 0.29	0.218
FVC*	3.28 (1.12)	2.98 (0.93)	-0.30	-0.20, 0.80	0.184

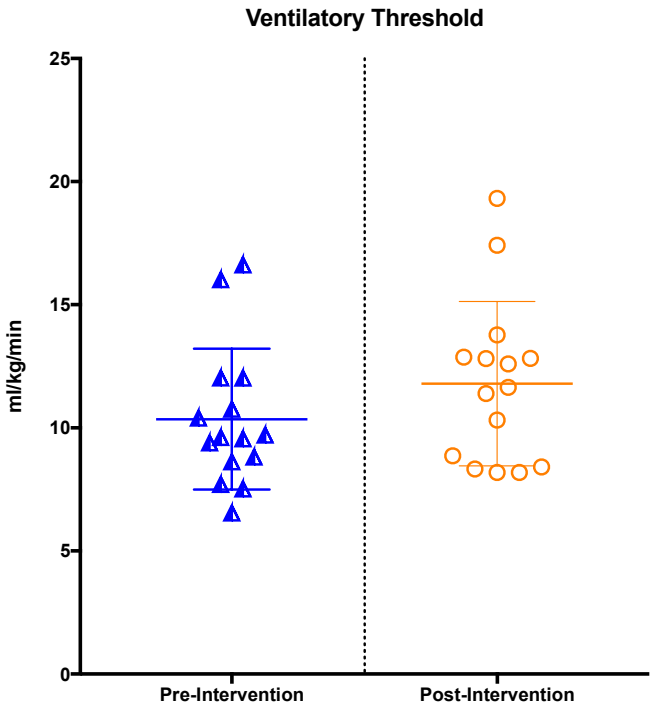


Figure 6.2: Comparison of pre-and post-intervention ventilatory threshold. There was a significant increase in VT (10.35 vs. 11.80 ml/kg/min, p=0.003), representing a mean difference of 1.45 ml/kg/min. Post-intervention VT is missing for one participant.

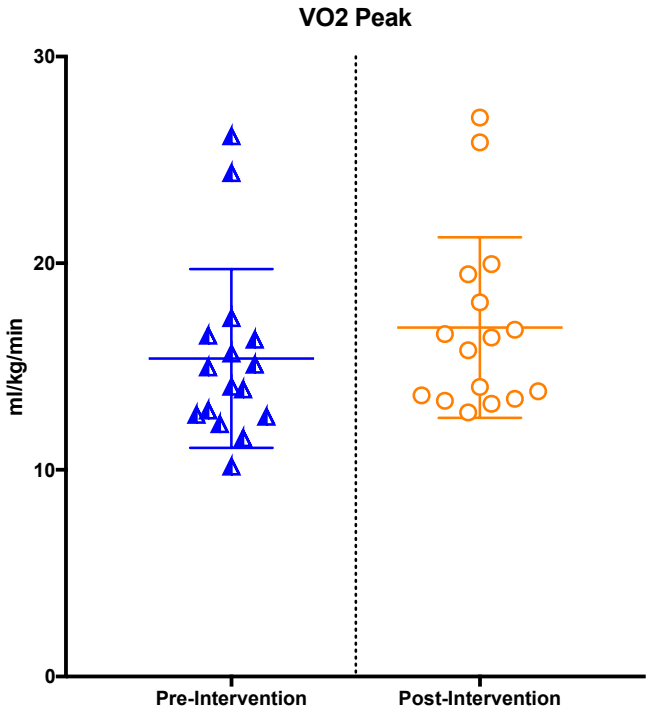


Figure 6.3: Comparison of pre- and post-intervention VO_2peak. There was a significant improvement in VO_2peak between (15.39 vs. 16.89 ml/kg/min, p=0.023), representing a mean difference of 1.50 ml/kg/min.

Table 6.7: Pre- and post-intervention cardiorespiratory fitness data separated based by participants scheduled for colorectal and thoracic cancer surgery. *One participant had incomplete post-intervention CPET data.

Outcome	Pre-HIIT Mean (SD)	Post-HIIT Mean (SD)	Mean Difference	95% C.I	P-value
Colorectal Surgery					
VT	11.42 (3.75)	12.80 (4.16)	1.38	-0.40, 3.17	.107
VO_2peak	17.57 (5.59)	19.31 (5.36)	1.74	0.58, 2.90	.020
Thoracic Surgery					
VT*	9.42 (1.49)	10.91 (2.36)	1.49	0.40, 2.59	.015
VO_2peak	13.70 (2.06)	15.00 (2.25)	1.30	-0.82, 3.42	.170

6.3.5 Postoperative outcome

The relationship between preoperative physical fitness and postoperative outcome was not examined in this study because this study was not adequately powered and did not have a control group, however postoperative outcome for all participants is presented below (Table 6.8-6.10).

The mean LOS of stay was 26.5 days (SD: 50.97) and the median LOS was 7.5 days. Morbidity rates post-colorectal surgery were 50% and 75% post-thoracic surgery according to the Clavien-Dindo classification score and the CCI. The single most severe complication for each participant assessed using the Clavien-Dindo classification score are presented in Table 6.8, and the CCI assessed the severity of all-cause postoperative complications experienced while in-hospital (Table 6.9). The types of complications as measured using the POMS postoperative day 3, 5 and 7 and are presented in Table 6.10. Two participants died in the postoperative period (one participant scheduled for colorectal and one participant scheduled for thoracic surgery). One participant was readmitted within 30 days of colorectal surgery with a wound infection.

Table 6.8: Postoperative complications as measured by the Clavien-Dindo Classification Score reporting the number of patients and the grade of complication.

Clavien-Dindo Classification Score	No. of Participants (n=14)
0	5
I	1
II	4
III (A)	1
IV	1
V	2

Table 6.9: Postoperative complications as measured by the Comprehensive Complications Index reporting the number of patients and the grade of complication.

Comprehensive Complications Index Grade	No. of Participants (n=14)
0	5
8.7	1
20.9	3
26.2	1
29.6	1
60	1
100	2

Table 6.10: Postoperative complications as measured by the Postoperative Morbidity Survey reporting the number of patients and types of complication on a specific day. *One participant died on postoperative day 5.

Type of Complication	Day 3 (n=14)	Day 5* (n=13)	Day 7* (n=13)
Pulmonary	7	4	4
Infectious	2	3	2
Renal	9	6	4
Gastrointestinal	6	4	3
Cardiovascular	3	2	2
Neurological	2	1	1
Haematological	1	1	1
Wound	0	0	0
Pain	1	0	0

6.4 Discussion

This HIIT prehabilitation intervention is feasible to perform in patients scheduled for major abdominal and thoracic surgery, and was well received by participants. The main barrier to recruitment was distance from hospital. Daily supervision of this programme was required as this was a novel intervention of high intensity exercise for high-risk patients. The drop-out rate was 20%, and there were no adverse events. Furthermore, there was a significant improvement in preoperative cardiopulmonary fitness characterised by increases in both AT and VO_{2peak}.

Clinical pathways for curative cancer involving surgical resection demand an efficient transition from diagnosis to surgery. The NHS guidelines require that patients with cancer to be treated within 31 days of decision to treat (Service, 2014). A particular strength of the HIIT prehabilitation programme was specifically designed to adhere to these timelines and therefore did not delay surgery. Current exercise prehabilitation programmes discussed in the systematic review and meta-analysis described in Chapter 5 force clinicians to choose between delaying treatment and increasing risk of cancer spread, or cancelling prehabilitation and increasing risk of postoperative morbidity and mortality. In comparison, the PHIIT intervention allows for exercise prehabilitation to be performed without delaying surgery due to the ability of HIIT to increase cardiorespiratory fitness within a short time frame. This trial demonstrated high compliance rates (88%) that compare favourably with compliance rates (70%) reported by a systematic review of exercise interventions in patients with cancer (Stevinson et al., 2004).

Recruiting patients with cancer to exercise interventions is challenging and time consuming (Sygna et al., 2015). Data for recruitment rates for preoperative exercise interventions are limited, however recruitment rates in this study (39.2%) compare favourably to exercise interventions for patients with breast cancer undergoing adjuvant chemotherapy (33%) (Courneya et al., 2007), further highlighting the clinical utility of this preoperative HIIT programme.

Surgery is the only form of curative treatment for lung and colorectal cancer, however surgery carries substantial perioperative risk, and patients with low levels of cardiorespiratory fitness are at increased risk (Chapter 3.4.1). Preoperative exercise interventions have the potential to increase cardiorespiratory fitness above established thresholds. In abdominal surgical interventions, such as colorectal surgery, VT ≤10.9 ml/kg/min is associated with increased postoperative risk (Chapter 3.4.1). Mean VT pre-intervention in this study was 10.35 ml/kg/min, and post-intervention VT increased to 11.80 ml/kg/min, suggesting that this prehab intervention can increase physical fitness above the risk threshold defined as ≤10.9 ml/kg/min. It is likely this increase in preoperative physical fitness may translate into improved postoperative outcomes (e.g. reduced postoperative complications and shorter LOS), however further research is required to conclude on the ability of exercise prehabilitation to improve postoperative outcome.

The observational study presented in Chapter 4 reported that a VT of <11.95 ml/kg/min was indicative of high postoperative risk. In the PHIIT trial, participants scheduled for colorectal surgery had a baseline VT of 11.42 (SD: 3.45) ml/kg/min. Following HIIT intervention, VT significantly increased to 12.80 (SD: 4.16) ml/kg/min, therefore this preoperative exercise intervention successfully reduced the level of risk for participants scheduled for colorectal surgery. Furthermore, a VO_{2peak} threshold of 15 ml/kg/min can predict postoperative outcome as VO_{2peak} is a superior predictor of outcome in patients scheduled for thoracic intervention (BTS, 2001). The mean VO_{2peak} for all participants (n=16) prior to beginning the intervention was 15.32 ml/kg/min. Participants scheduled for thoracic surgery only (n=9) had a mean VO_{2peak} <15ml/kg/min pre-intervention and had a high level of postoperative risk according to the BTS guidelines (BTS, 2001). Post-intervention mean VO_{2peak} scores increased to 15 ml/kg/min, therefore these participants have ascended from a high level of risk to an average level as defined by the BTS guidelines. Therefore, further investigation is warranted to examine the potential for this intervention to reduce the incidence of postoperative complications, prolonged LOS and postoperative mortality among colon and thoracic surgical cohorts. It was beyond the scope of this feasibility study to examine the relationship between postoperative outcome and preoperative aerobic capacity. It is possible that with further investigation and validation in an adequately powered

randomised controlled trial (RCT), this exercise prehabilitation intervention can reduce the risk of poor postoperative outcome.

Participants scheduled for colorectal surgery had a baseline cardiorespiratory fitness of VT; 11.42 (SD: 3.75) ml/kg/min and VO_2peak; 17.57 (SD: 5.59) ml/kg/min. In comparison, participants scheduled for thoracic surgery had a lower baseline cardiorespiratory fitness of VT; 9.42 (SD: 1.49) ml/kg/min and VO_2peak; 13.70 (SD: 2.06) ml/kg/min. It is likely that participants scheduled for thoracic surgery had a lower baseline fitness as decreased cardiorespiratory fitness is associated with lung cancer (Pletnikoff et al., 2016). Following HIIT intervention, VO_2peak significantly increased in participants scheduled for colorectal surgery. In comparison, VT significantly increased in participants scheduled for thoracic surgery. Subsequently, VT did not significantly increase in participants scheduled for colorectal surgery and VO_2peak did not significantly increase in participants scheduled for thoracic surgery. This is likely due to this study not being adequately powered to detect changes in cardiorespiratory fitness. Future research should investigate the ability of a HIIT intervention to influence preoperative cardiorespiratory fitness among different clinical populations.

The PHIIT trial demonstrates favourable results compared to other preoperative HIIT trials. A preoperative HIIT study in a colorectal and thoracic surgery population had not been performed when conducting this trial, however there have been a number of recently published preoperative HIIT studies reflecting the desire to develop a time-efficient preoperative exercise intervention. Licker and colleagues conducted a similar HIIT protocol (patients completed two 10-minute series of 15 sec high intensity intervals interspersed by 15 sec periods of rest) in 74 patients scheduled for thoracic surgery and reported an increase in VO_2peak of +2.9 ml/kg/min (95% C.I: 1.1-4.2), however this programme was a longer duration (median: 26 days) compared to this study (median: 19 days) (Licker et al., 2017). Therefore the PHIIT trial is more likely to fit within the time restrained preoperative pathway. Dunne and colleagues performed a preoperative HIIT protocol in 20 patients scheduled for liver resection (Dunne et al., 2016). Both VO_2peak (2.0 ml/kg/min, 95% C.I: 0.4-3.6) and AT (+1.0 ml/kg/min 95% C.I: -0.2-2.1) significantly increased from baseline following 12 sessions over a 4-week period. The PHIIT trial demonstrated similar improvements in aerobic capacity, with a lower number of sessions compared to the trial by Dunne and colleagues (7 vs. 12 sessions, respectively) and a lower overall duration (median 19 vs. 26 days, respectively) compared to the programme prescribed by Licker and colleagues. In addition, the PHIIT trial demonstrated a shorter duration to a preoperative HIIT programme with a mean duration of 28 days in patients scheduled for colorectal surgery (Boereboom et al., 2016). Therefore, the PHIIT trial may have higher clinical utility compared to other HIIT protocols

as it requires a lower number of overall sessions to demonstrate a significant increase in cardiorespiratory fitness.

6.4.1 Future directions

Exercise is beneficial in reducing postoperative complications in abdominal surgery, however the evidence is of low quality and further research is justified (Chapter 5). This trial has established HIIT as a feasible method of increasing cardiorespiratory fitness, with high adherence and compliance rates, that can be used within the current surgical pathway. The results of this trial warrant the investigation of the ability of HIIT to improve preoperative cardiorespiratory fitness through an adequately powered RCT.

Supervised exercise programmes allow a great deal of control over the exercise load imposed in the intervention, a feature that participants of the PHIIT trial appreciated, however one of the largest barriers to recruitment in supervised hospital-based exercise interventions is participant distance from hospital (Liou et al., 2015). Future studies should compare hospital-based exercise to community or home-based exercise programmes. HIIT leads to greater improvements in cardiorespiratory fitness than moderate intensity exercise, however it is unlikely that HIIT interventions can be implemented at home. Community-based HIIT classes should be explored as a potential alternative to hospital-based interventions for patients unable to commute to hospital regularly.

6.4.2 Limitations

The single arm design limits the interpretation of secondary outcomes including cardiopulmonary fitness, however the design is appropriate for answering the primary question of programme feasibility. In relation to cardiopulmonary fitness, while results are interpreted with caution, the increase in fitness to levels above safe thresholds for complex surgical resection warrants further investigation and validation of the efficacy of this HIIT intervention, ideally within an RCT. Blood lactate was recorded during CPET as outlined in Chapter 2.3.1.8.1, in an attempt to measure lactate threshold, however due to inconsistent and missing results lactate threshold was not measured for all patients. Despite this ventilatory threshold was measured which is part of the overall term, anaerobic threshold (Chapter 2.3.1.8.2).

A limitation to this study was the participant recruitment rate of 39%. This result is comparable with previously published prehab feasibility studies (37% recruitment rate in patients scheduled for

gastrointestinal surgery) (Valkenet et al., 2016) and exercise programmes in cancer survivors (33%) (Courneya et al., 2007). However, there is potential selection bias present as the participants of the PHIIT trial were limited to urban dwelling individuals within close proximity to the hospital site. Another limitation of this study was patients completed a feedback questionnaire upon discharge from hospital. This questionnaire was administered by the same physiotherapist who completed the preoperative HIIT sessions, therefore patients may have been unlikely to report negative comments about the PHIIT trial. A final limitation is that this study did not demonstrate a clinically meaningful change in cardiorespiratory fitness. An increase in cardiorespiratory fitness of 2.0 ml/kg/min has been reported as clinically meaningful difference in cardiorespiratory fitness (Kothmann et al., 2009). It is likely that a clinically meaningful change could not be detected as this study was underpowered. Adequately powered RCT's are required to conclude on the ability of this HIIT programme to produce clinically meaningful improvements in preoperative cardiorespiratory fitness.

6.5 Conclusion

The PHIIT trial demonstrated that a preoperative HIIT intervention for patients scheduled for major abdominal or thoracic surgery is feasible. There were no adverse events associated with the exercise intervention and compliance and adherence rates were high. Furthermore, this intervention was not associated with delays to surgery, emphasising its ability to fit within the current surgical pathway. The PHIIT trial also demonstrated a significant increase in preoperative aerobic capacity, warranting the need for further RCT's to validate the efficacy of a preoperative HIIT programme to increase preoperative aerobic capacity and prevent poor postoperative outcome.

7 Chapter 7 Discussion

7.1 Introduction and main findings

Major elective surgery carries substantial postoperative risk. Postoperative complications occur in 37%-48% of patients scheduled for colorectal surgery (West et al., 2014b, West et al., 2014c) and 5-72% of patients post-thoracic surgery (Lang-Lazdunski, 2013, Galetta et al., 2012, Icard et al., 2013, Cho et al., 2012). The NICE guidelines provide recommendations for preoperative testing to identify patients at high risk of poor postoperative outcome which enables clinicians to develop and implement effective treatment plans (NICE, 2016). Furthermore, ERAS programmes aim to improve postoperative outcome by maintaining preoperative organ function and reducing the profound stress response following surgery (Khan et al., 2009). Despite these risk reduction strategies, postoperative risk is still high and therefore identifying methods of optimising modifiable risk factors amenable to intervention will aid perioperative care.

Preoperative physical fitness assessed using CPET is theorised to predict postoperative outcome (Smith et al., 2009, Hennis et al., 2011). Despite this, the NICE guidelines state that cardiopulmonary exercise testing as a method of predicting perioperative risk does not have sufficient evidence to recommend its use in clinical practice (NICE, 2016). Furthermore, preoperative exercise interventions aimed at increasing preoperative physical fitness are not implemented in current ERAS protocols (Khan et al., 2009). The aim of this thesis was to evaluate the ability of preoperative physical fitness to protect against poor postoperative outcome in abdominal and thoracic surgery.

Consistently, the work of this thesis showed that preoperative cardiorespiratory fitness is predictive of postoperative outcome, as patients with lower levels of cardiorespiratory fitness were at an increased risk of postoperative complications, prolonged LOS and postoperative mortality. Chapter 3 reported that CPET is able to predict postoperative outcome and may be used as a preoperative risk assessment tool. In addition, anaerobic threshold was shown to be a superior predictor of postoperative outcome in intra-abdominal surgery compared to VO_2peak/VO_2max (except for AAA repair) and a number of AT cut-points were identified that are predictive of postoperative outcome in various abdominal surgery procedures e.g. an AT of $\leq$10.9 ml/kg/min is predictive of mortality post intra-abdominal surgery (Chapter 3). These findings were supported by the results of Chapter 4 which provided further evidence that lower cardiorespiratory fitness, specifically a lower VT (<11.95 ml/kg/min) rather than

VO_{2peak}, was significantly associated with postoperative complications (POMS, CCI, and Clavien-Dindo classification scores) and hospital LOS following colorectal surgery, however the ability of CPET to predict mortality post-colorectal surgery is unclear due to the low rates of mortality (Chapter 3 and 4).

Cardiorespiratory fitness assessed using field tests of exercise tolerance offer a less robust method of identifying patients at risk of postoperative complications. In Chapter 3 there were conflicting results from studies examining the ability of the 6MWT walk test to predict postoperative outcome. In addition, the results of an observational study in Chapter 4 reported the 6MWT was unable to predict postoperative outcome (OR: 0.997, 95% C.I: 0.992-1.002, p=0.199). Furthermore, measures of physical fitness such as muscle strength (grip strength and inspiratory muscle strength) and physical activity levels (measured subjectively using the YPAS) did not relate to postoperative outcome.

If higher levels of preoperative physical fitness are associated with improved postoperative outcomes, it seems likely that increasing preoperative physical fitness through preoperative exercise interventions, or prehabilitation, may reduce postoperative risk. The aim of Chapter 5 was to assess if preoperative exercise interventions designed to increase preoperative physical fitness translated to a reduction in postoperative risk. The results of the meta-analysis demonstrated that prehabilitation consisting of inspiratory muscle training, aerobic exercise, and resistance training decreases the incidence of all postoperative complications in patients undergoing intra-abdominal surgery (OR: 0.59, 95% C.I: 0.38-0.91, p=0.03). This effect was strongest when prehabilitation was compared to usual care (no treatment or breathing exercises) (OR: 0.35, 95% C.I: 0.17-0.71, p=0.02). It is unclear if prehabilitation influenced postoperative LOS after intra-abdominal surgery, as the number of studies contributing to the Forest plot was low (n=4). Furthermore, there were no documented cases of postoperative mortality in the studies included in the meta-analysis (n=9) so it remains unclear whether prehabilitation can influence postoperative mortality rates. Results should be interpreted with caution, as the quality of included studies measured via the GRADEPro was 'very low', demonstrating the need for high quality RCT's to validate the use of preoperative exercise programmes.

While exercise prehabilitation improved preoperative physical fitness in patients scheduled for major intra-abdominal surgery (Table 5.3), the exercise prehabilitation protocols included in this review were longer (4-6 weeks) than the available duration between decision to treat and cancer surgery (31 days) (Service, 2014). Therefore, clinicians are presented with a difficult decision; proceed directly to surgery and forgo prehabilitation, or delay surgery to allow time for prehabilitation and risk disease

progression. Interventions that can increase cardiorespiratory fitness within the timeframe of the current surgical pathway (≤31 days) would have high clinical utility.

High intensity interval training programmes create greater improvements in cardiorespiratory fitness compared with more commonly prescribed moderate intensity aerobic exercise, however preoperative exercise interventions of relatively high intensity continuous exercise have been reported to have low patient adherence (16% completion rates, Carli et al., 2010). Therefore, Chapter 6 aimed to assess the feasibility of a preoperative HIIT programme through measurement of adverse events and analysis of compliance and adherence rates. The PHIIT trial demonstrated high adherence (84%) and compliance rates (88%) in a preoperative HIIT programme, among 16 patients scheduled for colorectal (n=7) and thoracic (n=9) cancer surgery. Furthermore, there were no adverse events related to the disease or exercise intervention. Cardiorespiratory fitness increased significantly as measured by VT (+1.45 ml/kg/min) and VO_{2peak} (+1.50 ml/kg/min) following a mean of 7 (SD: 3) preoperative HIIT sessions, highlighting the need for further research through an adequately powered RCT to determine the ability of HIIT to improve preoperative cardiorespiratory fitness.

7.2 Analysis of key points

7.2.1 Identifying patients with low cardiorespiratory fitness

Consistently, the results of this thesis showed that patients scheduled for major elective surgery with lower levels of cardiorespiratory fitness, assessed using CPET are at increased risk of postoperative complications, prolonged LOS and postoperative mortality (Chapter 3 and 4). It is likely that CPET can predict postoperative outcome by identifying individuals unable to meet the postoperative global oxygen demand by providing a direct measure of an individual's ability to consume and utilise oxygen (VO_2) (Chapter 1.2.1). CPET may be used as a preoperative assessment to aid in identifying modifiable risk factors amenable to intervention and preparation, which is essential to improve the quality of care and to help minimise the impact of surgery on patients (Garcia-Miguel et al., 2003) (Chapter 1.3).

Maximal CPET is a relatively safe procedure particularly in healthy individuals, however underlying comorbidities can increase the risk of mortality in CPET. The ATS/ACCP report the rate of mortality is 2-5 deaths per 10,000 CPETs (ATS/ACCP, 2003). Maximal CPET is considered the gold standard method of measuring cardiorespiratory fitness, however cardiorespiratory fitness can also be evaluated sub-maximally, which reduces the risks associated with maximal CPET as it does not require patients to exercise until volitional exhaustion (Chapter 2.3.1.7). Maximal CPET also requires additional

monitoring equipment (e.g. ECG machine) and is more labour intensive compared to sub-maximal CPET (Noonan and Dean, 2000). The results from this thesis demonstrated that sub-maximal CPET is a valid alternative to maximal CPET in assessing preoperative risk and patients with a VT <11.95 ml/kg/min have an increased risk of postoperative complications and prolonged LOS (Chapter 4.4.3). Maximal CPET is required to measure VO_2max, as submaximal CPET can only provide an estimate of VO_2max. The ability of VO_2max to predict postoperative outcome in thoracic surgery is well established, however the evidence supporting its use in intra-abdominal surgery is weaker (Brunelli et al., 2013).

Consistently this thesis has demonstrated that anaerobic threshold is a superior predictor of postoperative outcome compared to VO_2max or VO_2peak in CPET assessment in patients scheduled for intra-abdominal surgery (Chapter 3.4.1 and 4.4.3). Sub-maximal CPET is a suitable method of measuring the ventilatory or anaerobic threshold as it occurs at a relatively low level of VO_2max (45%-60% of VO_2max) (Schneider et al., 1993, Ghosh, 2004). In addition, the ROC curve analysis in this study (AUC: 0.71, 95% C.I: 0.56-0.87) produced a higher result compared to West and colleagues (AUC: 0.63, 95% C.I: 0.54-0.73) who used maximal CPET (Chapter 4.4.3) (West et al., 2014b). ROC curve analysis illustrates the performance of medical diagnostic tests of discriminating between two patient states. An area under the curve (AUC) of <0.7 is regarded as a poor predictive test, while an AUC of 0.7-0.8 is regarded as having average accuracy (Higgins et al., 2011) (Chapter 2.1.4.2). The higher AUC of this study indicates a superior ability to identify patients at risk of postoperative complications compared to the study by West and colleagues. Maximal CPET may be more suitable in surgical cohorts where VO_2peak is a superior predictor of outcome e.g. thoracic and AAA repair (Brunelli et al., 2013, Grant et al., 2015, Carlisle and Swart, 2007). However, in surgical cohorts where AT is associated with postoperative outcome (e.g. colorectal and pancreatic surgery), sub-maximal CPET can be used which offers a number of advantages to maximal CPET such as requiring fewer resources and is less labour intensive.

Despite the reported benefits of maximal and sub-maximal CPET in identifying high-risk patients, CPET is not readily available in all clinics. In addition, CPET is an expensive preoperative assessment tool and the cost of a cardiopulmonary exercise laboratory is estimated at $85,735 plus annual expenses (Diamond, 2007). Field tests of exercise tolerance provide attractive alternatives to the more demanding CPETs as field tests are cheap, require little equipment and are easy to administer. Lee and colleagues reported that in a multivariate analysis of nine other variables including age, sex, BMI and comorbidities, the 6MWT was significantly associated with medical and any (medical or surgical) postoperative complications, however the 6MWT was not independently associated with medical (OR:

0.73, 95% C.I: 0.44-1.20), surgical (OR: 0.81, 95% C.I: 0.53-1.23) or any (OR: 0.77, 95% C.I: 0.51-1.14) postoperative complications. This thesis also reported that the 6MWT was not independently predictive of postoperative complications or prolonged LOS in a univariate analysis and this result is supported by additional research (Arruda et al., 2013, Moriello et al., 2008, Paisani et al., 2012). It is likely that the 6MWT is unable to predict postoperative complications and prolonged LOS due to its relatively low correlation with VT (r=0.399) (Chapter 4.4.3) and as patients can regulate their physical effort, due to the self-selected walking speed (Chapter 2.3.2.1), the 6MWT is susceptible to biased results.

The ACCP recommends that field tests of exercise tolerance, specifically the ISWT and SCT, are used to assess cardiorespiratory fitness prior to thoracic surgery (Chapter 1.3.1.2) (Brunelli et al., 2013). If patients obtain a result lower than pre-defined thresholds (ISWT: <400m, SCT: <22m) then CPET is required. In Chapter 3.3.2.3, the SCT was not found to be predictive of postoperative outcome in intra-abdominal surgery, however the ISWT was able to predict postoperative complications and LOS in colorectal surgery (Nutt and Russell, 2012, Arruda et al., 2013). Furthermore, patients with an ISWT <350m had a higher risk of postoperative mortality in oesophagogastric surgery, however the statistical analysis was insufficient to definitively conclude on the ability of the ISWT to predict postoperative mortality (Murray et al., 2007). It is likely that the ISWT is better able to predict postoperative outcome in intra-abdominal surgery due to its higher correlation with VT (r=0.775), compared to the 6MWT (r=0.399) (Irisawa et al., 2014, Nutt and Russell, 2012). In addition, as the ISWT is externally paced, patients are more likely to reach their maximal exercise tolerance as opposed to the self-selected pace of the 6MWT, which is subject to patients regulating their physical effort. The ISWT has considerable potential to predict postoperative outcome in intra-abdominal surgery, however further research is needed to conclude on the use of the ISWT in the preoperative setting.

CPET can be used to help identify patients with a high-risk of postoperative complications, however performing unnecessary CPETs on all patients scheduled for intra-abdominal surgery would be an inappropriate use of limited resources as it is an expensive, and resource and personal heavy measure of perioperative risk that is not readily available in all clinics (Hepner, 2009). Field tests of exercise tolerance provide a cheaper and easier to administer alternative of measuring preoperative cardiorespiratory fitness, however further research is needed to justify their ability to predict postoperative outcome. Therefore, future research should further examine the predictive ability of field tests. A triage pathway for intra-abdominal surgery, similar to that developed by the ACCP in thoracic surgery in which field tests of exercise tolerance are used as a first line assessment of

preoperative cardiorespiratory fitness, followed by a more in-depth assessment of cardiorespiratory fitness via CPET if necessary would have high clinical utility (Brunelli et al., 2013) (Figure 1.3).

7.2.2 The ability of cardiorespiratory fitness to influence postoperative complications

Postoperative complications can be described as either medical complications (e.g. DVT, urinary tract infection and postoperative pulmonary complications) or surgical complications (e.g. ileus and anastomotic leak) (Lee et al., 2013). Preoperative cardiorespiratory fitness has previously been reported to have a significant association with medical complications (e.g. pneumonia) only (Lee et al., 2013), however this thesis reported that preoperative cardiorespiratory fitness demonstrated a significant relationship with all complications measured via the POMS, CCI and Clavien-Dindo classification scores (Chapter 4.4.3). This result is in agreement with current research, reporting that patients with lower levels of cardiorespiratory fitness were more likely to develop medical complications, such as pneumonia (West et al., 2014b) and surgical complications (e.g. pancreatic leak and ileus) (Ausania et al., 2012a, Snowden et al., 2010). Primary cellular injury consisting of direct cellular injury through surgical incision and indirect cellular injury arising from blood loss and reduced perfusion capacity are likely to contribute to the incidence of surgical complications. It is likely that individuals with higher levels of cardiorespiratory fitness offset indirect cellular injury through increases in blood volume and perfusion capacity (Figure 1.1). Medical complications are more likely to arise due to the stress response and increase in global oxygen demand associated with surgery (Chapter 1.1.1). Individuals with higher levels of cardiorespiratory fitness may be better able to match the postoperative increase in oxygen demand. Furthermore, exercise releases anti-inflammatory mediators, therefore is it likely that exercise reduces the total stress response associated with surgery (Chapter 1.2.3). The combination of these factors are likely to contribute to the relationship between higher levels of preoperative cardiorespiratory fitness and reduction in all postoperative complications.

Despite the association between cardiorespiratory fitness and all complications, several studies have reported that prehabilitation programmes aimed at increasing physical fitness did not influence all complications (Carli et al., 2010, Gillis et al., 2014, Dronkers et al., 2010). In the meta-analysis in Chapter 5, preoperative exercise reduced all-cause complications, however three studies that recorded all-cause complications (medical and surgical) reported no significant differences in complication rates between the intervention and control groups. Carli et al. (2010) and Gillis et al. (2014) used the Clavien-Dindo classification score to measure postoperative morbidity and Dronkers et al. (2010) measured postoperative complications using the following criteria: oxygen

supplementation, saturation, fever, pain medication, sputum retention, coughing and mobilisation (Carli et al., 2010, Gillis et al., 2014, Dronkers et al., 2010). Preoperative exercise interventions may not have influenced all complications in these three studies as the methods of measuring complications may have confounded results. The Clavien-Dindo score is a widely used objective measure of postoperative morbidity, however it records only the single most severe complication (Chapter 2.2.2.2). The Clavien-Dindo ignores the complications of lesser severity, and so may underreport the overall morbidity (Slankamenac et al., 2013). The method of recording complications used by Dronkers and colleagues mainly addressed pulmonary complications and failed to address other complications. Therefore, it is likely that these three studies failed to comprehensively record and analyse all postoperative complications.

Furthermore, these studies lacked sufficient statistical power to detect a difference in all-cause complications postoperative. In two trials, sample sizes were powered to detect differences in postoperative fitness instead of complications (Carli et al., 2010, Gillis et al., 2014) and Dronkers and colleagues performed a pilot study which did not provide a sample size calculation (Dronkers et al., 2010). Studies require large sample sizes to show an effect of prehabilitation reducing the incidence of complications. For example, the ongoing PREPARE-ABC trial aims to establish if a preoperative exercise programme prior to colorectal surgery can reduce complications, and this study requires a sample size of 1146 patients (Hernon, 2016). The studies included in this meta-analysis were not effectively powered to detect reductions in postoperative complications, therefore it is likely that these studies were underpowered and unable to measure the true effect of preoperative exercise on the incidence of postoperative complications (Button et al., 2013).

In addition, two of the studies included in the meta-analysis lacked a true control group which may have confounded results. Carli et al. (2010) and Dronkers et al. (2010) prescribed an exercise programme with a lower volume/intensity for the control group as opposed to no treatment or usual care (Dronkers et al., 2010). This is likely to have confounded results by increasing the control group's physical fitness and reducing the incidence of complications. In contrast, Gillis and colleagues included a control group that received no treatment. Further high quality adequately powered RCTs with true control groups and effective methods of measuring morbidity are required to effectively conclude on the ability of preoperative exercise to positively influence both medical and surgical complications.

7.2.3 Anaerobic threshold as a predictor of outcome in intra-abdominal surgery

VO_{2peak} is a well-established predictor of postoperative outcome in thoracic surgery. In contrast, the results from this thesis demonstrate that the anaerobic threshold (measured by ventilatory threshold or lactate threshold) is a superior predictor of postoperative outcome in intra-abdominal procedures (with the exception of AAA repair) (Chapter 3.4.1 and 4.4.3). There is further evidence in support of this as the SCT is predictive of postoperative outcome in thoracic surgery and is correlated with VO_{2peak} (r=0.707) (Cataneo and Cataneo, 2007), while the ISWT is predictive of postoperative complications and LOS in colorectal surgery and demonstrates a strong correlation with AT (r=0.775) (Irisawa et al., 2014).

The systemic inflammatory response post-surgery increases global oxygen demand and postoperative cellular dysfunction occurs when the global oxygen demand is not met (Chapter 1.1.1). VO_{2peak} represents the highest amount of oxygen delivered to metabolically active tissue, suggesting that in thoracic surgery the global oxygen demand must be met postoperatively to ensure normal cellular function. In comparison to abdominal surgery, thoracic surgery is likely to incur greater postoperative oxygen demands due to the more invasive incision and mobilisation of organ tissue therefore creating greater cellular injury and subsequently a larger systemic inflammatory response (Scott and Miller, 2015). Furthermore, VO_{2peak} may play a more vital role in patients scheduled for thoracic surgery as patients will need to meet the global oxygen debt with the disadvantage of having reduced lung capacity postoperatively. In contrast, global oxygen demands in abdominal surgery may be less as laparoscopic surgery is a more commonly used technique and is a less invasive surgery. This is supported through the results of the systematic review in Chapter 3 and observational study in Chapter 4, which reported that VO_{2peak} (Chapter 3.3) and predicted VO_{2max} (Table 4.4) were not the optimal CPET derived variables predictive of postoperative outcome in intra-abdominal surgery. Laparoscopic surgery causes less cellular injury and subsequently a lower stress response (Scott and Miller, 2015, Miyake et al., 2002). Therefore, it is likely that the oxygen requirements may be lower in laparoscopic abdominal surgery compared to open thoracic surgery (Buunen et al., 2004).

Chapter 3 identified that anaerobic threshold was consistently a superior predictor of postoperative outcome in intra-abdominal surgery compared to VO_{2peak} (Chapter 3.3). This was further supported through the results of an observational study (Chapter 4.4) which reported VT was associated with postoperative complications measured using the POMS (OR: 0.87, 95% C.I: 0.76-0.99, p=0.03). In comparison, VO_{2peak} and predicted VO_{2max} were not associated with postoperative complications measured using the POMS (VO_{2peak}: OR: 1.035, 95% C.I: 0.942-1.137, p=0.473, VO_{2max}: OR: 1.03, 95%

C.I: 0.912-1.162, p=0.637). Anaerobic threshold represents the point in which anaerobic glycolysis contributes to meet the energy demands of a system under stress and is measured by the ventilatory threshold (increase in ventilation becomes disproportional to the increase in power output during exercise) or lactate threshold (substantial increase in blood lactate during exercise) (Svedahl and MacIntosh, 2003, ATS, 2002, Ghosh, 2004). Both ventilatory threshold and lactate threshold have been identified as predictors of postoperative outcome by this thesis (Chapter 3.4.1 and 4.4.3). Lactate is produced during anaerobic glycolysis when converting glucose into pyruvate and is typically transported to the liver (Adeva-Andany et al., 2014). During periods of decreased blood and oxygen supply to the liver it is theorised that increased blood lactate can lead to cellular dysfunction (Chapter 1.2.4). This theory is supported by evidence reporting that increased blood lactate levels can lead to higher mortality in a number of conditions (e.g. sepsis and myocardial infarction), however lactate can also be metabolised at various other tissues (Adeva-Andany et al., 2014). Skeletal muscle simultaneously produces and consumes lactate, but both are enhanced when the muscle is exercising compared to resting state. Exercising increases lactate release, however mean lactate release decreases with training as oxidative efficiency of cells is improved. Improvements in the oxidative efficiency of cells, reduces non-aerobic glycolysis, increasing the anaerobic threshold and subsequently reducing lactate formation (Adeva-Andany et al., 2014).

Decreases in oxygen delivery due to surgery lead to tissue hypoxia, therefore anaerobic glycolysis contributes to meet the energy demands of oxygen deprived cells, however this also increases lactate production (Adeva-Andany et al., 2014). Patients with higher levels of cardiorespiratory fitness are better able to tolerate and metabolise the increase in lactate due to improved oxidative efficiency in the cells and less lactate being formed (Adeva-Andany et al., 2014). This is supported with the results of this thesis that consistently identified patients with higher levels of cardiorespiratory fitness had a decreased incidence of postoperative complications, mortality and reduced LOS (Chapter 3.4.1 and 4.4.3). It is likely then that the anaerobic threshold, which signals when non-aerobic glycolysis occurs, identifies patients who may be unable to meet the postoperative oxygen demands aerobically. Exercise at an intensity above the anaerobic threshold cannot be maintained for extended periods of time due to the increase in lactic acid in the blood stream and subsequent change in pH balance, and depletion of energy stores (Knuttgen, 2007). As this intensity cannot be maintained for extended periods of time it is likely that patients with a low AT are unable to match the increase in oxygen demand associated with surgery, subsequently leading to cellular dysfunction (Chapter 1.2.1) and an increase in the incidence of complications identified in the observation study (Chapter 4.4). It has been reported through an observational study of 502 patients scheduled for cardiac surgery that high levels

of lactate in the immediate postoperative period were predictive of postoperative complications post cardiac surgery (Hajjar et al., 2013). It is likely that the increase in lactate serves as an indicator for the presence of oxygen debt (tissue hypoxia). Previously discussed theories suggest that a low anaerobic threshold is associated with inflammatory dysregulation which may contribute to increased postoperative morbidity and mortality (Sultan et al., 2014) (Chapter 1.2.3) or fitter patients have an improved ability to tolerate tissue hypoxia and subsequent physiological changes allow these individuals to better tolerate prolonged periods of anaerobic metabolism (Chapter 1.2.2). Preoperative exercise interventions that increase the AT such as the PHIIT trial (VT: +1.45 ml/kg/min, 95% C.I: 0.57-2.31) are likely to reduce lactate formation. This thesis adds to the body of evidence supporting AT as an independent predictor of postoperative outcome in intra-abdominal surgery. The exact mechanisms for this interaction require further research, however it is likely the role of anaerobic threshold in protecting against poor postoperative outcome is multi-factorial.

7.2.4 High intensity interval training as a preoperative intervention

Improving cardiorespiratory fitness prior to surgery should be a key component of future prehabilitation programmes, however the time frame between diagnosis and treatment presents a barrier for effective moderate intensity exercise interventions. The ACSM states that a period of 16 weeks or longer is the recommended duration to increase cardiorespiratory fitness in middle-aged and older adults (≥60% of pre-training VO_{2max}) (Chodzko-Zajko et al., 2009). Current cancer care demands minimal delay between diagnosis and treatment and the NHS requires all patients begin treatment within 31 days of decision-to-treat (Service, 2014). The discrepancy between the optimal duration for exercise interventions and the clinical timelines for cancer treatment presents an almost unfeasible challenge to exercise prehabilitation.

HIIT is a time efficient method of increasing cardiorespiratory fitness that can fit within the current surgical pathway (≤31 days from decision to treat to surgery). The PHIIT trial led to significant improvements in preoperative VT and VO_{2peak} following a median duration of 8 (range: 2-11) HIIT sessions over a median of 19 days, a comparatively shorter period than the required 31 days and other preoperative exercise interventions with median durations of 24.5 (Gillis et al., 2014) and 38 days (Carli et al., 2010). Improvements in cardiorespiratory fitness attributed to HIIT have been compared to the improvements in exercise performance and skeletal muscle oxidative capacity associated with continuous exercise, however the total time commitment of HIIT is much shorter. For example, in a healthy cohort, similar improvements in cardiorespiratory fitness were reported following 2.5 hours of HIIT compared to 10.5 hours of continuous exercise over a two-week training period (Gibala et al.,

2006). One of the main barriers to participants performing exercise is a perceived lack of time (Godin et al., 1994), HIIT addresses this limitation as it leads to similar improvements in fitness to continuous exercise over a shorter time period (Gibala et al., 2006). The reduced amount of total exercise time attributed to HIIT provides an attractive incentive for current surgical pathways that demand minimal disruption to their planned course. Pre-admission clinics can play a role in future clinical practice by identifying high-risk patients through appropriate exercise testing and prescribing preoperative exercise, such as HIIT to improve cardiorespiratory fitness within the current surgical pathway (Hepner, 2009).

The PHIIT trial significantly improved preoperative cardiorespiratory fitness (10.35 vs. 11.80 ml/kg/min, p=0.003), above the recommended cut-points protective against poor postoperative outcome for intra-abdominal surgery (≤10.9 ml/kg/min) (Chapter 3.4.1). Other studies report that HIIT leads to greater improvements in VO_{2peak} than moderate intensity continuous exercise in healthy participants (+1.2 ml/kg/min, 95% C.I: 0.3-2.1 ml/kg/min) and patients with coronary artery disease (+1.78 ml/kg/min, 95% CI: 0.45-3.11) (Milanovic et al., 2015, Liou et al., 2015). It is theorised that HIIT elicits rapid changes in skeletal muscle oxidative capacity through high level of muscle fibre recruitment and its ability to stress Type II muscle fibres (Gibala and McGee, 2008). Broadly, exercise is classified as strength or endurance training, with high intensity exercise associated with increased skeletal muscle mass through recruiting Type II fibres and low-moderate intensity endurance exercise typically leading to increased mitochondrial mass and oxidative enzyme activity through recruiting Type I fibres. HIIT is unusual in that it is not characterised by skeletal muscle hypertrophy typical with other high intensity exercise, rather the metabolic adaptations of HIIT are associated with endurance training related changes, such as increased stroke volume and capilliarisation, further supporting its use as a method of increasing preoperative cardiorespiratory fitness to aid in addressing the oxygen demand post-surgery (Chapter 1.1.1 and Figure 1.1) (Gibala and McGee, 2008).

In addition, when patients in the PHIIT trial were examined by type of operation, patients scheduled for colorectal surgery (n=7) increased preoperative VT from 11.42 ml/kg/min to 12.80 ml/kg/min, above the recommended cut-point of 11.95 ml/kg/min (AUC: 0.71, 95% C.I: 0.56-0.87) identified in Chapter 4.4.3. Similarly, patients scheduled for thoracic surgery (n=9) increased VO_{2peak} from 13.70 ml/kg/min, indicative of a cohort at high perioperative risk, to VO_{2peak} of 15 ml/kg/min, which is considered an average level of perioperative risk (BTS, 2001). While the absolute change in VT for patients scheduled for colorectal surgery (+1.38 ml/kg/min) and VO_{2peak} for patients scheduled for thoracic surgery (+1.30 ml/kg/min) was not statistically significant, these results are of considerable

clinical importance. An increase in cardiorespiratory fitness above CPET derived thresholds will increase the number of patients eligible for surgical intervention and reduce the incidence of postoperative complications, mortality and prolonged LOS (Gibala and McGee, 2008). The results of the PHIIT trial are promising and it is hoped that in an RCT powered to detect change in fitness, that a statistically significant and clinically meaningful change in fitness would be observed. HIIT is likely to further influence postoperative outcome as it increases resting glycogen content, decreases the rate of glycogen utilisation, and perhaps most importantly reduces the rate of lactate production (Burgomaster et al., 2007, Burgomaster et al., 2006). It is likely that lactate accumulation perioperatively can adversely affect postoperative recovery (Chapter 1.2.4). In a cohort of eight healthy men, HIIT helps reduce net lactate release through increases in muscle oxidative capacity, ranging from approximately 15% to 35% after six sessions of HIIT over 2 weeks as measured through muscle needle biopsy (vastus lateralis) (Burgomaster et al., 2006, Burgomaster et al., 2005, Gibala et al., 2006). Increases in cardiorespiratory fitness through HIIT would likely improve postoperative outcome by increasing oxygen delivery, however another potential benefit is reduced lactate production.

One of the main limitations of high intensity preoperative exercise programmes is low patient compliance. Previous preoperative interventions with relatively high intensity continuous exercise have reported low adherence rates (16% completion rate) (Carli et al., 2010). Participants in the exercise intervention prescribed by Carli and colleagues were required to exercise initially at 50% of their maximal HR for 20 minutes on a cycle ergometer, HR was increased by 10% each week if tolerable and duration was increased to 30 minutes daily. Weight training, three times per week was also prescribed. Participants were instructed to do push-ups, sit-ups, and lunges for 12 reps or until participants reached volitional fatigue. In comparison, the PHIIT trial had a higher intensity (100% PPO), yet demonstrated higher adherence (84%) and compliance (88%) rates. It is likely that patients scheduled for surgery prefer HIIT compared to continuous exercise which would be in agreement with current evidence (Cassidy et al., 2017). A group of 40 women with obesity (20 with type 2 diabetes) perceived interval training as being easier than continuous exercise (Coquart et al., 2008). Similarly, a group of 20 patients with stable coronary heart disease preferred HIIT to continuous exercise (Guiraud et al., 2011). It is likely that interval training breaks up the monotony of continuous exercise and gives patients a chance to rest between periods of high intensity work. Furthermore, as discussed in Chapter 6.3.4, the PHIIT trial demonstrated significant improvements in cardiorespiratory fitness within a shorter time frame compared to other preoperative HIIT interventions.

Postoperative complications significantly increase total hospital costs, therefore interventions that can reduce the incidence of complications will have a considerable impact (Zoucas and Lydrup, 2014). The occurrence of any complication post-colorectal surgery can increase hospital costs from a mean of €12,405 to €25,680 (Zoucas and Lydrup, 2014). In the PHIIT trial, the impact of preoperative HIIT to reduce complications was not recorded, as feasibility was deemed the primary outcome, it is likely from previous research that preoperative exercise interventions can reduce the incidence of postoperative complications (Chapter 5.4). A reduction in postoperative complications would ultimately reduce total hospital costs as the cost of running a supervised hospital based HIIT intervention was relatively low, calculated at €490.70 per patient (Chapter 6.3.3.3). A cost analysis investigation in future research is warranted to effectively determine if a preoperative exercise intervention can reduce postoperative costs attributed to poor postoperative outcome. The PHIIT trial demonstrated that HIIT is a relatively low cost and feasible preoperative intervention with high compliance rates. Its ability to increase cardiorespiratory fitness should be assessed with an adequately powered RCT.

7.2.5 Role of muscle strength in postoperative outcome

Isometric grip strength assessed using hand held dynamometry, which demonstrates a strong association with overall muscle strength (Chapter 2.3.3.1), was not predictive of functional impairment, LOS, or postoperative complications (OR 0.98, 95% C.I 0.93-1.04, p=0.53) in Chapter 4.4.3. It is possible that grip strength is not an independent predictor of postoperative outcome because resistance training stimulates different bodily responses and does not improve oxygen delivery compared to aerobic exercise (Knuttgen, 2007, Gibala and McGee, 2008). Aerobic exercise stimulates Type I (slow twitch) muscle fibres and improves oxygen delivery through increases in oxidative enzyme concentration, mitochondrial size, myogloblin content, stroke volume, and capilliarisation (Knuttgen, 2007). Resistance training does not improve oxygen delivery mechanics as oxygenation and refuelling of muscle cells occurs immediately post-exercise (Knuttgen, 2007, Hellsten and Nyberg, 2015). Furthermore, resistance training incurs increases in size of Type II (fast twitch) muscle fibres leading to muscle hypertrophy. Subsequently, the muscle capillaries are separated due to the increase in muscle fibre cross-sectional area, a situation described as capillary dilution resulting in decreased perfusion (Bell and Jacobs, 1990, Brown, 2003).

To the authors knowledge this is the first study to examine grip strength as an independent predictor of postoperative outcome in colorectal surgery, however preoperative grip strength has been examined in a number of surgeries. Overall the ability of preoperative hand grip strength to

independently predict postoperative outcome is unclear. A recent systematic review reported that low preoperative hand grip strength may be associated with postoperative complications, however these results should be interpreted with caution. This review included 19 studies examining preoperative grip strength in patients scheduled for a wide number of operations including hip replacement, coronary artery bypass graft and liver transplant (Sultan et al., 2012). In addition, none of the included studies used a validated measure of postoperative morbidity. Therefore, the strong heterogeneity and lack of a standardised method of measuring complications is likely to weaken external validity of the results (Sultan et al., 2012). A number of studies have been published since this review, however the results remain conflicting. In a cohort of 68 patients undergoing oesophagectomy, grip strength was predictive of postoperative complications, however this study also did not use a standardised method of measuring morbidity (Chen et al., 2011). Sato and colleagues retrospectively analysed the preoperative grip strength of 293 patients scheduled for gastrectomy and reported low grip strength was associated with an increased incidence of postoperative complications. Although this study used the Clavien-Dindo classification score to measure complications, it only recorded Grade 2 or higher (Sato et al., 2016). Finally, a study of 94 patients scheduled for oesophagectomy reported low hand grip strength was not associated with complications as measured using the Clavien-Dindo score (van Egmond et al., 2016).

Grip strength may be a useful preoperative risk assessment tool as a composite measure of measuring sarcopenia and frailty. Sarcopenia is characterised by a progressive and generalised loss of skeletal muscle mass and strength and is predominantly associated with ageing but can also occur due to cancer treatment (Makiura et al., 2016, Prado et al., 2011). Patients with sarcopenia have an increased postoperative inflammatory response, and sarcopenia is a risk factor for prolonged LOS and infections post-colorectal resection (Reisinger et al., 2016, Lieffers et al., 2012, Lauretani et al., 2003). The European Working Group on Sarcopenia in Older People (EWGSOP) describe grip strength cut-offs for measuring sarcopenia, which is based on BMI and gender (Fried et al., 2001, Tan et al., 2012). Grip strength measures of sarcopenia for male patients is defined as a hand-grip strength <32 kg with a BMI >28 kg/m^2, and female participants is <21 kg with a BMI >28 kg/m^2. In Chapter 4, male participants scheduled for colorectal surgery had a preoperative mean BMI of 28.26 kg/m^2 and a mean right hand grip strength of 35.36 kg, and female participants had a mean BMI of 30.36 kg/m^2 and a mean right grip strength of 22.28kg. Therefore, it is unlikely that the patients in the observational study had sarcopenia and were therefore unlikely to have an increased sarcopenia related stress response.

Frailty is another risk factor for poor postoperative outcome in colorectal surgery (Fagard et al., 2016) and is similar to sarcopenia as it is defined as a state of vulnerability characterised by an age-associated decline in physiological function and reserve leading to an increased risk in adverse outcomes (Chapter 4.1). The Fried criteria is a widely accepted measure of frailty that combines measures of weight loss, physical exhaustion, physical activity levels, walking speed and grip strength and is associated with major postoperative complications (grade 2 and higher Clavien-Dindo classification score) (Tan et al., 2012). Low gait speed is a criterion for frailty and is defined by a gait speed of >0.65 m/s and a height ≤173cm (males) or ≤159cm (females). Only three patients in the observational study (Chapter 4) could not complete the first stage of the Modified Bruce Protocol, which has a minimum walking speed of 0.75 m/s. It is unlikely that patients included in Chapter 4 were frail as patients exceeded the grip strength cut-offs to measure frailty, which are similar to those used by the EWGSOP to measure sarcopenia. Furthermore, the mean physical activity levels recorded by the YPAS in Chapter 4 (males: 5447 kcal/week, females: 4483 kcal/week), exceeded the energy expenditure requirements for a diagnosis of frailty (males: <383 kcal/week, females: <270 kcal/week). It is unlikely that grip strength can independently predict postoperative outcome, however it is a recognised component of measuring sarcopenia and frailty. In Chapter 4 patients were unlikely to have sarcopenia or be diagnosed as frail, therefore, the predictive ability of grip strength is limited in this cohort.

Similarly, in the observational study, inspiratory muscle strength did not predict postoperative pulmonary complications (OR: 1.003, 95% C.I: 0.983-1.024, p=0.778) (Chapter 4.4.3), it is likely that this was due to the relatively low incidence of pulmonary complications (n=3) measured using the POMS on POD6. Despite the lack of predictive ability, the results of the meta-analysis demonstrate that preoperative interventions consisting of IMT can reduce the incidence of postoperative complications (Figure 5.4). Respiratory muscle function correlates with pulmonary function (Nomori et al., 1994). Anaesthesia causes reductions in FRC due to a loss of muscle tone and increased muscle fatigue resulting in decreased elastic chest recoil, and decreases in MIP (Nomori et al., 1994, Wahba, 1991, Siafakas et al., 1999). This leads to airway closure and poor absorption which can result in atelectasis and other postoperative complications. It is reported that IMT improves muscle tone, MIP and deep-breathing post-surgery, resulting in a reduction in the incidence of postoperative pulmonary complications (Katsura et al., 2015). Studies examining the role of IMT have produced conflicting results. Chapter 5 demonstrated that interventions consisting of IMT can reduce PPC's, however these results should be interpreted with caution as the GRADEPro analysis concluded that the methodological quality of these studies is 'very low' and that results are likely to change with further research. In addition, a large scale RCT demonstrated no differences in postoperative pneumonia post-

oesophagectomy between preoperative IMT and usual care (Valkenet, 2017). In contrast, a Cochrane review concluded that preoperative IMT based intervention can reduce the incidence of postoperative atelectasis in 222 patients (RR: 0.53, 95% C.I: 0.34-0.82) and pneumonia in 358 patients (RR: 0.44, 95% C.I, 0.26-0.77) scheduled for abdominal and cardiac surgery (Katsura et al., 2015).

The role of preoperative muscle strength as a predictor of postoperative outcome requires further study. It is likely that interventions aimed at improving inspiratory muscle strength can reduce postoperative complications by increasing respiratory muscle tone and prevent airway closure by improving the body's ability to withstand helping the muscle tone reducing effects of anaesthesia (Chapter 1.1.4), however the results are conflicting and further research is required. General muscle strength is unlikely to influence postoperative complications as resistance training does not improve oxygen delivery mechanics to the same extent as aerobic exercise, however muscle strength may play an important role in patients with frailty or sarcopenia and reducing the postoperative inflammatory response.

7.2.6 Preoperative exercise recommendations

There is a growing body of evidence that prehabilitation consisting of a mix of IMT, aerobic and resistance training is more effective at reducing complications than usual care (no treatment and breathing cases) and can be used clinically (Figure 5.5). Cardiorespiratory fitness has a positive effect on postoperative outcome and interventions aimed at improving aerobic capacity should be prescribed. Clinicians aiming to increase preoperative cardiorespiratory fitness can prescribe the HIIT interventions included in the PHIIT trial, however this intervention requires further validation in an adequately powered RCT. Clinicians may seek to use the exercise interventions included in Chapter 5. Carli et al. (2010) and Gillis et al. (2014) prescribed an aerobic exercise programme for 3-7 days a week during the preoperative period at 50-75% heart rate max for 20-30 minutes which was safe and improved aerobic fitness (Carli et al., 2010, Gillis et al., 2014). IMT can be prescribed to reduce PPC's, however it should be noted that IMT is not effective at reducing pneumonia in patients scheduled for oesophagectomy (Valkenet, 2017). If prescribing IMT, clinicians should consider using high intensity IMT (60-80% MIP) as it is more effective in reducing PPC's, requires few sessions (3 sessions a week for 3 weeks) and has a high compliance rate (98%) (Van Adrichem et al., 2014).

Preoperative exercise interventions require a certain amount of exercise equipment and supervision and can be costly. The PHIIT trial demonstrated adequate recruitment rates of 39.2%, however 41.2% of patients declined to participate due to living too far from the hospital. For patients and clinicians

without easy access to the necessary resources walking presents a viable alternative. Walking is advantageous as it easy to prescribe, requires very little to no equipment, and it can be performed at home unsupervised. Two studies in the meta-analysis had an active control group (Carli et al., 2010, Dronkers et al., 2010). Both studies instructed patients to walk for a minimum of 30 minutes a day in the preoperative period. Dronkers and colleagues advised patients to walk for a minimum of 30 minutes a day and reported no significant difference in the number of steps performed by the aerobic exercise and resistance training intervention (4980 steps per day) and the control group (5003 steps per day). Carli and colleagues reported that in the walking (control) group, VO_2peak significantly increased (1400-1511 ml/min, p=0.007) and there was no significant difference in VO_2peak between the bike/strengthening (intervention) and walking/breathing (control) group (1529 vs. 1511 ml/min, respectively) (Carli et al., 2010). Clinicians wishing to prescribe preoperative exercise interventions that do not have access to exercise equipment such as a cycle ergometer should consider prescribing a walking-based intervention. Further research should examine the ability of a home-based unsupervised exercise programme following the physical activity guidelines (e.g. 30 minutes of moderate intensity exercise for five days a week) (Haskell et al., 2007). Preoperative exercise programmes such as this would have high clinical utility.

7.3 Critical analysis of work

The limitations of the two original studies and two systematic reviews have been discussed in the relevant chapters (Chapter 2, 4, 5, 6). There are a number of further limitations to the work in this thesis. The sample size of the observational study in Chapter 4 is smaller than previously published observational studies on the predictive ability of CPET in colorectal surgery (West et al., 2016, Lai et al., 2011), however this study had a notably smaller catchment area and less resources available. Although the sample size of the PHIIT trial presented in Chapter 6 is more comparable in size to previously published feasibility studies, there is a possibility of selection bias as the majority of this research was conducted on samples of convenience. Participants were recruited from the colorectal and thoracic surgery clinics of St. James's Hospital, Dublin, and while this cohort is somewhat representative of the national population, because of transport limitations there is a bias towards the inclusion of urban dwelling over rural dwelling participants. Another limitation is studies investigating physical fitness are likely to recruit participants who are interested in exercise; participants recruited into the observational and feasibility study may had increased levels of cardiorespiratory fitness, limiting the external validity of these results.

A strength of this thesis was publishing two systematic reviews with strict adherence to the PRISMA guidelines. Both reviews performed a thorough search of the literature with the aid of a medical librarian and Chapter 3 provided objective CPET derived cut-points to inform clinicians of an individuals perioperative risk and all time to develop effective treatments. Another strength of this thesis was the use of the GRADEPro software, according to best practice, to formulate a summary of findings table (Chapter 5.2.6). A summary of findings table is recommended by the Cochrane Group to present the main findings of a systematic review of RCTs in a transparent and simple tabular format. A summary of findings table provides key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of all available data on the main outcomes. Previously published reviews of preoperative exercise interventions have neglected to effectively quantify the quality of the evidence, a limitation that this meta-analysis addressed (Chapter 5.2.6)

The ability of grip strength to independently predict postoperative outcome has previously been discussed. To effectively assess preoperative muscle strength and endurance isokinetic dynamometry could been used in combination with hand-held dynamometry to improve measurement of muscle strength. Isokinetic dynamometry is the gold standard method of measuring muscle strength and endurance, and allows for isometric, isotonic (fixed load and changing angular velocity) or isokinetic (fixed angular velocity and changing load) testing of muscle strength and endurance for multiple peripheral joints and trunk muscle groups. Isokinetic dynamometry would provide a more in depth analysis of muscle strength and endurance, however isokinetic dynamometry was not available at time of testing and handheld dynamometry is strongly correlated with lower extremity muscle power and has good clinical utility (Lauretani et al., 2003).

The PHIIT trial presented a novel exercise intervention in a high-risk population that increased cardiorespiratory fitness and demonstrated high compliance and adherence rates that were superior to other high intensity preoperative programmes (Carli et al., 2010). A limitation of the PHIIT trial was the lack of a control group, however as the main aim of the this study was to determine the feasibility of a preoperative HIIT programme, the single arm design was deemed appropriate.

A final limitation was the lack of blinding in the PHIIT trial. The same physiotherapist was responsible for recruiting, testing, performing HIIT sessions and assessing postoperative outcome. Therefore, it is possible that an element of bias was introduced in analysing changes in cardiorespiratory fitness, however this was a secondary objective of the study and the main aim was to assess feasibility.

Furthermore, this trial was not effectively powered to detect true changes in preoperative cardiorespiratory fitness.

7.4 Future research

There are a number of areas to be addressed through further research. The research and development of a triage pathway similar to thoracic surgery that identifies patients with a low cardiorespiratory fitness would have high clinical utility. Future research should further assess the predictive ability of field tests of exercise tolerance, which provide clinicians with a quick and easy to administer method of measuring cardiorespiratory fitness. The identification of high-risk patients would aid clinical decision making and allow clinicians time to implement effective treatment interventions such as exercise based prehabilitation.

Prehabilitation requires adequately powered RCT's to determine its effectiveness at increasing preoperative fitness and reducing perioperative risk. High intensity interval training represents a time efficient exercise intervention with considerable potential to improve preoperative cardiorespiratory fitness that should be assessed through an adequately powered RCT. In addition, preoperative exercise interventions have the potential to reduce total hospital costs by reducing postoperative complications. Consequently, a grant application is currently being developed to determine the ability of HIIT to increase preoperative cardiorespiratory fitness in patients scheduled for a thoracotomy (oesophagectomy and thoracic surgery) and the cost-effectiveness of a preoperative exercise intervention. An increase in physical fitness would most likely translate to a reduction in postoperative complications, however investigation of this would require a larger sample size.

The PREPARE-ABC trial aims to determine if a preoperative exercise intervention can effectively reduce the incidence and severity of complications prior to colorectal surgery (Hernon, 2016). This international, UK-based, multi-centre trial aims to recruit 1146 patients scheduled for colorectal surgery. Patients will be randomised to one of three groups, a supervised hospital based exercise programme, home-based exercise programme, and a control group. Participants in the hospital-based supervised exercise programme will be offered three sessions per week of aerobic interval exercise on a cycle ergometer 3-4 weeks before surgery, with the aim of achieving 12 sessions preoperatively. In addition, there will be twice weekly resistance training sessions. The home-based intervention will encourage participants to comply with current physical activity recommendations; 150 minutes of moderate intensity aerobic exercise per week and two resistance training sessions per week. Finally, the control group will receive treatment as usual and no information related to perioperative exercise

will be offered. The PREPARE-ABC trial team and the author of this thesis are in collaboration to bring this trial to St James's Hospital.

The role of preoperative muscle strength as a predictor of postoperative outcome requires further study (Chapter 4.4.3). It is likely that individuals with sarcopenia would benefit from interventions aimed at increasing muscles mass due to the increased stress response associated with sarcopenia (Reisinger et al., 2016). Future research should examine the ability of preoperative exercise interventions consisting of resistance training to influence postoperative outcome in patients with sarcopenia.

Current research suggests prehabilitation should not be limited to preoperative exercise interventions, instead prehabilitation should encompass a multimodal treatment pathway including preoperative exercise, nutrition and psychosocial support (Le Roy and Slim, 2016). Although nutritional and psychosocial support are reported to be effective preoperative interventions, there is currently a lack of evidence to support this (Balstad et al., 2014, Burden et al., 2012, Tsimopoulou et al., 2015). Currently, the majority of the literature supports exercise as key component of prehabilitation (Chapter 5). There are a number of factors which influence postoperative outcome, and prehabilitation should be aimed at addressing these specific needs, however the effectiveness of unimodal interventions such as exercise and nutrition should first be validated prior to introducing multimodal interventions.

A final area for future research would be examining the perceived barriers and beliefs to exercise prior to surgery. In recruiting for the two original studies (Chapter 4 and 6) potential participants refused to take part in these studies as they believed that exercise prior to surgery would be too exhaustive and would have a detrimental effect on their postoperative outcome. If preoperative exercise is to become a component of future ERAS protocols then the perceived barriers must be addressed to improve future recruitment rates. In comparison, there was a belief among some potential participants that they already had an acceptable level of fitness, however what this exact level was is unclear. Therefore, a study aiming to explore the attitudes towards preoperative exercise and physical fitness would allow for future prehabilitation programmes to address the needs and concerns of patients scheduled for major surgery.

7.5 Conclusion

International guidelines for preoperative cardiopulmonary exercise testing report that there is insufficient evidence to recommend the use of cardiopulmonary exercise testing as a preoperative risk-assessment tool. Furthermore, ERAS guidelines neglect to mention the role of preoperative exercise in colorectal surgery. In comparison, preoperative exercise capacity is a recognised component of perioperative thoracic surgery care, however the quality of evidence is weak and further research is required to determine the optimal preoperative exercise programme.

Cardiorespiratory fitness as measured through CPET is predictive of postoperative outcome in hepatic, abdominal aortic aneurysm repair, pancreatic, and intra-abdominal surgery, and colorectal surgery. Measures of physical fitness such as muscle strength, and body composition do not predict postoperative outcome in colorectal surgery, suggesting that the protective effects of increased cardiorespiratory fitness arise from the improved ability to extract oxygen and match the global oxygen deficit post-surgery. There is currently insufficient evidence to conclude on the role of field tests of exercise tolerance to predict postoperative outcome.

Preoperative exercise interventions aimed at increasing preoperative physical fitness can reduce postoperative complications. Despite the amount of evidence in favour of preoperative exercise, the methodological quality of the studies included in the meta-analysis was deemed 'very low' citing the need for further high quality RCT's to determine if preoperative exercise interventions can protect against poor postoperative outcome. Furthermore, it is unclear if preoperative exercise interventions can influence LOS and mortality.

The exercise interventions included in Chapter 5 were longer than the current surgical colorectal and thoracic surgery pathway and present cancer care demands minimal delay between decision to treat and surgery. Interventions that can create minimal disruption to the current surgical pathways would have high clinical utility. The feasibility of such a programme was explored in the PHIIT trial which concluded that a preoperative high intensity interval training programme was safe and had high adherence and compliance rates. A significant increase in preoperative cardiorespiratory fitness was reported, however adequately powered RCT's are required to validate HIIT's ability to improve cardiorespiratory fitness within a short time frame.

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Appendices

A. Publications resulting from this thesis

A.1 Moran, J., Guinan, E., McCormick, P., Hussey, J., Moriarty, J., & Wilson, F. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. *British Journal of Anaesthesia*, 116, 177-191. http://dx.doi.org/10.1093/bja/aev454

A.2 Moran, J., Guinan, E., McCormick, P., Hussey, J., Moriarty, J., & Wilson, F. The preoperative use of field tests of exercise tolerance to predict postoperative outcome in intra-abdominal surgery: a systematic review. *Journal of Clinical Anesthesia*, 35, 446-455. doi: http://dx.doi.org/10.1016/j.jclinane.2016.09.019

A.3 Moran, J., Guinan, E., McCormick, P., Larkin, J., Mockler, D., Hussey, J., Moriarty, J., & Wilson, F. The ability of prehabilitation to influence postoperative outcome after intra-abdominal surgery: A systematic review and meta-analysis. *Surgery*, 160,1189-1201. doi: http://dx.doi.org/10.1016/j.surg.2016.05.014

A.4 Moran, J., Guinan, E., McCormick, P., Larkin, J., Mockler, D., Hussey, J., Moriarty, J., & Wilson, F. 2017. Response to: Is prehabilitation limited to preoperative exercise? *Surgery.* http://dx.doi.org/10.1016/j.surg.2017.01.008. [Epub ahead of print]

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Review Article

Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review

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Abstract

Background: Cardiopulmonary exercise testing (CPET) is used as a preoperative risk-stratification tool for patients undergoing non-cardiopulmonary intra-abdominal surgery. Previous studies indicate that CPET may be beneficial, but research is needed to quantify CPET values protective against poor postoperative outcome [mortality, morbidity, and length of stay (LOS)].

Methods: This systematic review aimed to assess the ability of CPET to predict postoperative outcome. The following databases were searched: PubMed, EMBASE, PEDro, The Cochrane Library, Cinahl, and AMED. Thirty-seven full-text articles were included. Data extraction included the following: author, patient characteristics, setting, surgery type, postoperative outcome measure, and CPET outcomes.

Results: Surgeries reviewed were hepatic transplant and resection (n=7), abdominal aortic aneurysm (AAA) repair (n=5), colorectal (n=6), pancreatic (n=4), renal transplant (n=2), upper gastrointestinal (n=4), bariatric (n=2), and general intra-abdominal surgery (n=12). Cardiopulmonary exercise testing-derived cut-points, peak oxygen consumption ($\dot{V}_{O_2}$ peak), and anaerobic threshold (AT) predicted the following postoperative outcomes: 90 day–3 yr survival (AT 9–11 ml kg^{-1} min^{-1}) and intensive care unit admission (AT <9.9–11 ml kg^{-1} min^{-1}) after hepatic transplant and resection, 90 day survival after AAA repair ($\dot{V}_{O_2}$ peak 15 ml kg^{-1} min^{-1}), LOS and morbidity after pancreatic surgery (AT <10–10.1 ml kg^{-1} min^{-1}), and mortality and morbidity after intra-abdominal surgery (AT 10.9 and <10.1 ml kg^{-1} min^{-1}, respectively).

Conclusions: Cardiopulmonary exercise testing is a useful preoperative risk-stratification tool that can predict postoperative outcome. Further research is needed to justify the ability of CPET to predict postoperative outcome in renal transplant, colorectal, upper gastrointestinal, and bariatric surgery.

Key words: exercise test/methods; general surgery; health status indicators; postoperative complications; preoperative care/methods; preoperative period; prognosis; risk; risk assessment/methods

Cardiopulmonary exercise testing (CPET) is a dynamic, non-invasive assessment of the cardiorespiratory system at rest and under stress. Cardiopulmonary exercise testing is the gold-standard method of measuring an individual's aerobic capacity. Cardiopulmonary exercise testing measures several physiological variables, including ventilatory parameters, heart rate (HR), and inspiratory and expiratory gases (the definitions for CPET variables are provided in Supplementary material, Table S1).

Cardiopulmonary exercise testing can be implemented to aid clinical decision-making. These uses include assessing patients

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with significant complaints of exercise intolerance and dyspnoea[1] and determining the severity impairment related to heart failure and chronic obstructive pulmonary disease.[2] Cardiopulmonary exercise testing is used as a preoperative risk-stratification tool to predict postoperative mortality, length of stay (LOS), and morbidity; however, its role requires validation.

Numerous studies have reported that CPET is a valid prognostic measure of postoperative outcome in cardiopulmonary surgery.[3–5] There have been four previous reviews of CPET in non-cardiopulmonary surgery.[6–9] All reviews concluded that CPET may be a strong predictor of postoperative outcome. These reviews also concluded that: (i) CPET-derived cut-points need to be refined and optimized for different surgical procedures and (ii) the validity of CPET variables, such as O_2 pulse and the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$), needs to be analysed; and (iii) further studies need to be performed to obtain a greater understanding of the role of CPET as a preoperative risk-stratification method. Since the publication of these reviews, the number of studies analysing CPET has grown.

The aim of the present review is to assess the prognostic ability of CPET in predicting postoperative outcome associated with non-cardiopulmonary intra-abdominal surgery. The objectives are as follows: (i) to quantify the optimal CPET variable to predict postoperative outcome; and (ii) to analyse and compare cardiopulmonary measurements such as anaerobic threshold (AT), maximal oxygen uptake ($\dot{V}_{O_2}$ max) and $\dot{V}_E/\dot{V}_{CO_2}$ to find the most accurate CPET variable in determining postoperative outcome within each subgroup of surgery.

Postoperative outcome includes all-cause mortality, morbidity, and LOS. Morbidity after surgical intervention includes all complications; pulmonary, infectious, renal, gastrointestinal (GI), cardiovascular, neurological, and haematological. The outcome LOS covers the overall length of stay in hospital, intensive care unit (ICU), high-dependency unit (HDU), and critical care unit (CCU) admission and length of stay.

Methods

Literature search

The preferred reporting items for systematic reviews (PRISMA) standardized reporting guidelines were used to standardize the methods of conducting and reporting this review.[10] The databases CINAHL, AMED, PEDro, EMBASE, The Cochrane Library, and PubMed were searched up to May 2015. A search strategy was defined with all keywords and subject headings included (Supplementary data, Appendix S1). In addition, the abstracts from the annual European Anaesthisiology Congress (2004–2014), the Anaesthetic Research Society (2007–2015), the Society of Academic & Research Surgery 2012–2015, the Vascular Society (2005–2012), the International Anaesthesia Research Society (2003–2015), the World Federation of Society of Anaesthesiologists (2008–2012), and the American Society of Anaesthesiologists (2000–2014) were reviewed for eligibility. A hand search of reference lists of the studies of interest was conducted to identify extra articles.

The inclusion criteria consisted of the following: (i) prognostic studies of intra-abdominal surgery among adult populations; (ii) the use of a preoperative CPET; (iii) measurement of postoperative outcome (mortality, morbidity, or length of stay); and (iv) comparison of preoperative CPET variables (anaerobic threshold etc.) with postoperative outcome.

Studies were excluded if they contained the following: (i) a cardiopulmonary surgical procedure; (ii) paediatric surgery; (iii) head and neck surgery; (iv) orthopaedic surgery; (v) spinal surgery; (vi) transfusion procedures, (e.g. blood or stem cells); (vii) preoperative interventions (e.g. preoperative exercise programmes); or (viii) were systematic reviews, meta-analyses, case studies, letters to the editor, or abstracts with no full text available.

If studies had split the analysis of intra-abdominal and cardiopulmonary surgery then the subgroup containing intra-abdominal surgery was taken and the cardiopulmonary surgery group was excluded. Procedures involving multiple incisions which included major intra-abdominal surgery were included (e.g. oesophagectomy).

Data extraction

Data extraction was performed independently by the lead investigator (J. Moran). All data were reviewed blind by another author (F.W.). The data extracted included author, patient characteristics, study setting, surgery type, postoperative outcome measure, method of CPET, and CPET variables assessed (Table 1).

A total of 1086 titles were identified using the search strategy on the above-mentioned databases. Of these, 1049 studies were excluded (Fig. 1). The authors (J. Moran and F.W.) excluded articles based on titles and abstracts. If any disagreements could not be resolved through discussion, an independent third author was asked to intervene (J.H.). Thirty-seven full-text articles were included in the data extraction and synthesis (Fig. 1). The authors of abstracts and conference posters were contacted to gain the full text. If full-text articles were not acquired then abstracts were excluded because of the potential high risk of bias and lack of a detailed methodology.

Assessment of the risk of bias

The methodological quality of the studies was assessed using the Quality in Prognosis Studies (QUIPS) tool[11] (Supplementary material, Appendix S2). The QUIPS tool analyses the risk of bias in observational prognostic studies in six key areas, as follows: study participation, attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each area contained several criteria. If a study failed to address one or fewer criteria within an area, it was deemed to have a low risk of bias. Two authors (J. Moran and F.W.) independently assessed the risk of bias in each study. An independent third author (J.H.) was asked to intervene if any disagreements could not be resolved through discussion. The overall risk of bias is presented in Table 2.

Results

The papers included in this review were categorized by surgical procedures, as follows: hepatic transplant and resection (n=7), abdominal aortic aneurysm (AAA) repair (n=5), colorectal surgery (n=4), pancreatic surgery (n=4), renal transplant (n=2), upper gastrointestinal surgery (n=3), bariatric surgery (n=2), and intra-abdominal surgery (studies that did not differentiate between surgical procedures; n=10). A total of 7852 patients were included.

A meta-analysis was deemed inappropriate because of the large heterogeneity of the data. The studies included varied in the type of surgery, CPET variable analysed, outcome, time to outcome, and the use of hazard ratios and odds ratios, resulting in an inability to pool data effectively. A quantitative synthesis of the results was deemed most appropriate.

Tables 3–5 show the outcomes and CPET variables deemed significant that predict poor postoperative outcome. Supplementary material, Tables S2–S4 provide a more detailed Results section.

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Table 1: Demographic details of included studies

Author	Surgery	Sample Size (n=)	Age	Gender:	Location	Outcome	CPET Type	Variables Reported
Ausania et al. (2012)	Pancreaticoduodenectomy	124	66 (Range: 37–82)	67 M, 57 F	Newcastle Upon Tyne, UK	Mortality, Morbidity, LOS	Cycle Ergometer	Vo_2 Peak, AT, V_E/Vco_2
Ausania, Vallance et al. (2012)	Pancreatic (Palliative Double Bypass) Surgery	50	64 (Range: 39–79)	33 M, 17 F	Newcastle Upon Tyne, UK	Mortality, Morbidity	N/R	AT
Bernal et al. (2014)	Liver Transplant	223	56 (Range: 42–61)	151 M, 72 F	London, UK	Mortality, LOS	Cycle Ergometer	Vo_2 Peak, AT
Carlisle and Swart (2007)	Abdominal Aortic Aneurysm Repair	130	N/R	N/R	Torquay, UK	Mortality	Cycle Ergometer	Vo_2 Peak, AT, V_E/Vco_2, V_E/Vo_2
Chandrabalan et al. (2013)	Pancreatic Surgery	100	≤65=47, >65=53	60 M, 40 F	Glasgow, UK	Mortality, Morbidity, LOS	Cycle Ergometer	AT
Colson et al. (2012)	Major Thoraco-Abdominal Surgery	1,725	71 (Range: 36–93)	1,121 M, 604 F	Geelong, Australia	Mortality	Cycle Ergometer	AT
Dunne et al. (2014)	Liver Surgery	197	70 (IQR: 64–75)	138 M, 59 F	Liverpool, UK	Morbidity, LOS	Cycle Ergometer	Vo_2 Peak AT, V_E/Vco_2, HR
Epstein et al. (2004)	Liver Transplant	59	46	35 M, 24 F	Boston, USA	Mortality	Cycle Ergometer	Vo_2 Peak, AT, o_2 Pulse
Forshaw et al. (2008)	Oesophagectomy	78	65 (SD: 9) (Range: 40–81)	64 M, 14 F	London, UK	Mortality, Morbidity, LOS	Cycle Ergometer	Vo_2 Peak, AT
Grant et al. (2015)	Abdominal Aortic Aneurysm Repair	506	73.4 (Range: 44–90)	418 M, 88 F	Manchester, UK	Mortality	Cycle Ergometer	Vo_2 Peak, AT, V_E/Vco_2
Hartley et al. (2012)	Abdominal Aortic Aneurysm Repair	415	N/R	349 M, 66 F	Manchester, UK	Mortality	Cycle Ergometer	Vo_2 Peak, AT, V_E/Vco_2
Hennis et al. (2012)	Gastric Bypass Surgery	106	43 (IQR: 41–44.9)	18 M, 88 F	London, UK	Morbidity, LOS	Cycle Ergometer	Vo_2 Peak, AT
Hightower et al. (2010)	Major Abdominal Surgery	32	63 (Range: 22–80)	21 M, 11 F	Texas, USA	Morbidity	Cycle Ergometer	Vo_2 Peak, AT
James et al. (2013)	Intra-Abdominal	83	68 (IQR: 63–75)	60 M, 23 F	London, UK	Morbidity	Cycle Ergometer	Vo_2 Peak, AT
Junejo et al. (2012)	Hepatic Resection	94	71 (Range: 24–85)	N/R	Manchester, UK	Mortality, Morbidity, LOS	Cycle Ergometer	Vo_2 Peak, AT, V_E/Vco_2, Peak Vo_2 Pulse
Junejo et al. (2014)	Pancreaticoduodenectomy	64	64 (Range: 45–80)	38 M, 26 F	Manchester, UK	Mortality, Morbidity	Cycle Ergometer	Vo_2 Peak, AT, V_E/Vco_2, V_E/Vo_2
Kaibori et al. (2013)	Hepatectomy	61	70 (SD: 9)	45 M, 16 F	Osaka, Japan	Mortality	Cycle Ergometer	Vo_2 Peak, AT
Lai et al. (2013)	Colorectal Surgery	269	N/R	N/R	Plymouth, UK	Mortality, LOS	Cycle Ergometer	Vo_2 Peak, AT
Lee et al. (2013)	Colorectal Surgery	112	59.9 (SD: 15.5)	65 M, 47 F	Montreal, Canada	Morbidity	Cycle Ergometer	Vo_2 Peak, Distance
McCullough et al. (2006)	Bariatric Surgery	109	46 (SD: 10.4)	27 M, 82 F	Michigan, USA	Mortality, Morbidity, LOS	Treadmill	Vo_2 Peak, AT, V_E/Vco_2, RER
Moyes et al. (2013)	Oesophagogastric Cancer Surgery	108	66 (SD: 9, IQR: 38–84)	83 M, 25 F	Glasgow, UK	Morbidity	Cycle Ergometer	Vo_2 Peak, AT

Continued

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Table 1: *Continued*

Author	Surgery	Sample Size (n=)	Age	Gender:	Location	Outcome	CPET Type	Variables Reported
Nagamatsu et al. (2001)	Oesophagectomy and Lymphadenectomy	91	59 (Range: 38–74)	88 M, 3 F	Fukuoka, Japan	Morbidity	Cycle Ergometer	V_{O_2} Peak, AT
Neviere et al. (2014)	Liver Transplant	263	58.8 (SD: 8.5)	198 M, 65 F	Lille, France	Mortality	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}, V_E/V_{O_2}, O_2 Pulse
Nugent et al. (1998)	Abdominal Aortic Aneurysm Repair	30	71.3 (Range: 57–85)	24 M, 6 F	Belfast, UK	Mortality, Morbidity	Treadmill	V_{O_2} Peak, AT, O_2 Pulse
Older et al. (1993)	Major Abdominal	187	70 (SD: 7)	102 M, 85 F	Victoria, Australia	Mortality	Cycle Ergometer	AT
Older et al. (1999)	Major Abdominal Surgery	548	69	N/R	Victoria, Australia	Mortality, Morbidity, LOS	Cycle Ergometer	AT
Prentis et al. (2012)	Liver Transplant	60	N/R	N/R	Newcastle Upon Tyne, UK	Mortality, LOS	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}
Prentis et al. (2012)	Abdominal Aortic Aneurysm Repair	185	73.4 (SD: 8.2)	161 M, 24 F	Newcastle Upon Tyne, UK	Morbidity, LOS	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}
Prentis et al. (2013)	Radical Cystectomy	69	N/R	48 M, 21 F	Newcastle Upon Tyne, UK	Mortality, LOS	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}, Peak V_{O_2} Pulse
Snowden et al. (2010)	Major Surgery	123 (7 excluded from analysis)	69.2 (SD: 9.3)	78 M, 45 F	Newcastle Upon Tyne, UK	Morbidity, LOS	Cycle Ergometer	V_{O_2} Peak, AT
Snowden et al. (2013)	Non-Laproscopic Hepatobiliary Surgery	389	65.8 (SD: 10.3)	218 M, 171 F	Newcastle Upon Tyne, UK	Mortality, LOS	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}
Ting et al. (2013)	Kidney Transplant	70	41.7 (SD: 14.5)	42 M, 28 F	Coventry, UK	LOS	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}, V_{O_2}/HR
Tolchard et al. (2015)	Radical Cystectomy	105	71 (Range: 38–90)	88 M, 17 F	Bristol, UK	Mortality, Morbidity, LOS	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}
Ulubay et al. (2010)	Renal Transplant	16	30.3 (SD: 6.5)	10 M, 6 F	Ankara, Turkey	Mortality	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}
West et al. (2013)	Rectal Cancer Surgery	95	66 (SD: 10)	72 M, 23 F	Liverpool, UK	Mortality, Morbidity	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}, V_E/V_{O_2}
West et al. (2014)	Major Colonic Surgery	136	71 (IQR: 62–77)	89 M, 47 F	Liverpool, UK	Mortality, Morbidity, LOS	Cycle Ergometer	V_{O_2} Peak, AT, V_E/V_{CO_2}, O_2 Pulse Peak
Wilson et al. (2010)	Colorectal Resection, Radical Nephrectomy or Cystectomy	847	N/R	506 M, 341 F	York, UK	Mortality, LOS	Cycle Ergometer	AT, V_E/V_{CO_2}

AT = Anaerobic Threshold, V_E = Minute Ventilation, N/R = Not Reported

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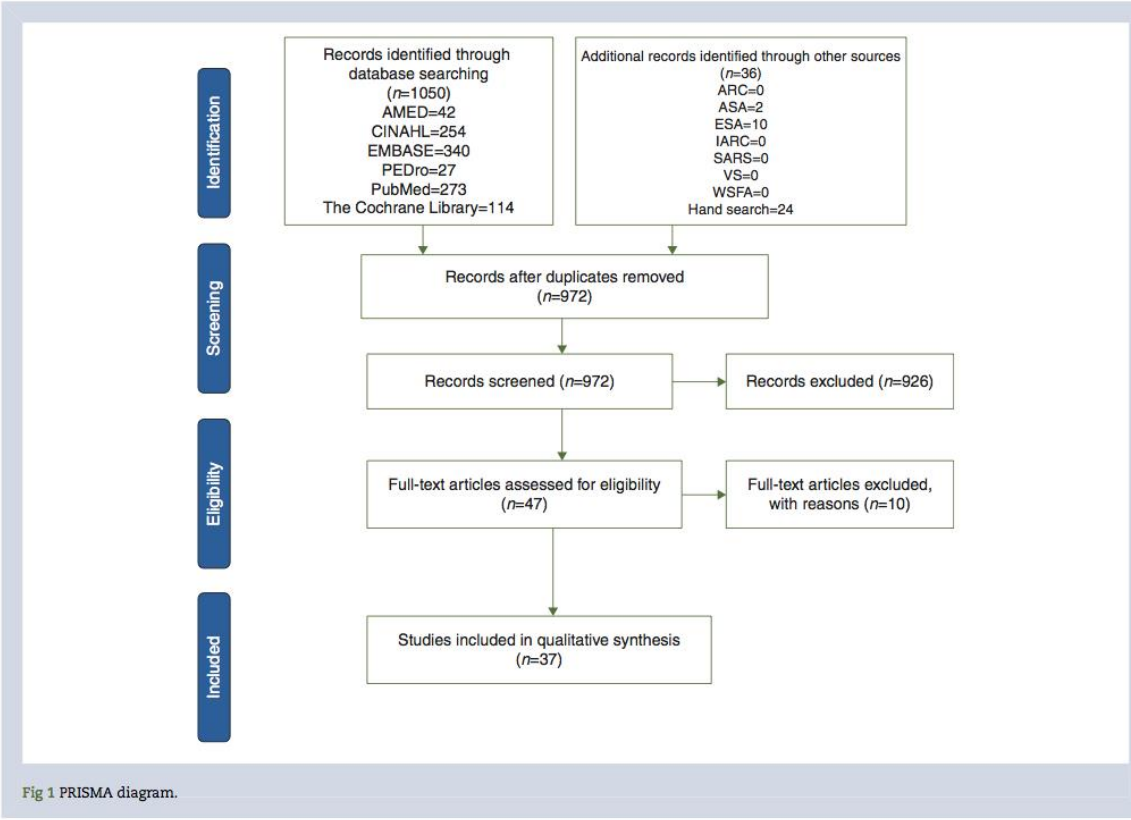


Fig 1 PRISMA diagram.

Hepatic transplant and resection

Mortality

Six studies reported CPET as a significant predictor of mortality after hepatic surgery[12–17] (Table 3). Junejo and colleagues[12] reported an AT of 9.9 ml kg^{-1} min^{-1} to be predictive of survival 30 days after surgery, whereas at 90 days after surgery an AT cut-off point of 9.0 ml kg^{-1} min^{-1} was shown to be significant ($P<0.05$) and had a 90.7% sensitivity and 83.3% specificity rate.[13] Bernal and colleagues[14] reported that survivors had a median AT of 11.7 ml kg^{-1} min^{-1} compared with non-survivors (median, 9.8 ml kg^{-1} min^{-1}) at 1 yr post-transplant ($P=0.04$). Kaibori and colleagues[15] followed patients for 2 (range 1–3) yr and found an AT ≥11.5 ml kg^{-1} min^{-1} to be predictive of survival ($P<0.05$). From the results of these four studies, a minimal AT of 9 ml kg^{-1} min^{-1} can predict short-term mortality (up to 90 days), but an AT of at least 11.5 ml kg^{-1} min^{-1} may predict long-term mortality (≥1 yr).

Peak oxygen uptake ($\dot{V}_{O_2}$ peak) has also been shown to be beneficial at predicting mortality after liver surgery. Neviere and colleagues[16] reported that survivors of liver transplant at 1 yr had a $\dot{V}_{O_2}$ peak of 18.6 (SD 2.8) ml kg^{-1} min^{-1} when compared with non-survivors 17.1 (SD 3.3) ml kg^{-1} min^{-1} ($P=0.04$). Kaibori and colleagues[15] presented a cut-off of ≥16.5 ml kg^{-1} min^{-1} as predictive of survival at 24 months after surgery ($P<0.05$). Epstein and colleagues[17] stated that both predicted $\dot{V}_{O_2}$ peak and AT were effective at predicting mortality at 100 days. Peak oxygen uptake appears to be beneficial at predicting mortality, but the evidence for its use is weaker than than that for AT.

Length of stay

The relationship between AT and LOS is unclear. Junejo and colleagues[12] and Prentis and colleagues[13] found no relationship between AT and LOS. In contrast, Dunne and colleagues[18] reported that patients with higher AT (in litres per minute) were more likely to be discharged early; however, this AT cut-off was not quantified [hazard ratio 2.16; 95% confidence interval (CI) 1.18–3.96; $P<0.05$]. An AT <9.2 ml kg^{-1} min^{-1} was associated with a LOS of 21 days (inter-quartile range 14–30) compared with patients with an AT ≥9.2 ml kg^{-1} min^{-1} [LOS of 15 days (inter-quartile range 13–23); $P<0.03$].[14]

Junejo and colleagues[12] reported that an AT of <9.9 ml kg^{-1} min^{-1} was associated with increased unplanned ICU stay (1.2 *vs* 0.3 days, $P<0.05$). In agreement, Prentis and colleagues[13] demonstrated that an AT of 11 ml kg^{-1} min^{-1} was significantly correlated with CCU LOS ($P<0.05$).

The evidence for $\dot{V}_{O_2}$ peak as a predictive factor of LOS and ICU admission is weaker than that for AT. Dunne and colleagues[18] reported that $\dot{V}_{O_2}$ peak was associated with LOS ($P<0.05$). Peak oxygen consumption may also be predictive of ICU LOS stay in liver transplant surgery ($P<0.05$).[14] Anaerobic threshold appears to be predictive of ICU or CCU admission after liver surgery.[12 13] Further studies are required to draw a definite conclusion about the ability of CPET to predict postoperative LOS after liver surgery.

Morbidity

Many studies did not examine postoperative morbidity. Kaibori and colleagues[15] grouped morbidity with mortality and analysed

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Table 2: Risk of Bias Assessment

Authors	The QUIPS Tool					
	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Ausania et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Ausania, Vallance et al. (2012)	Low Bias	Low Bias	High Bias	High Bias	High Bias	Low Bias
Bernal et al. (2014)	Low Bias	Low Bias	Low Bias	Low Bias	High Bias	Low Bias
Carlisle and Swart (2007)	High Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Chandrabalan et al. (2014)	High Bias	Low Bias	Low Bias	Low Bias	High Bias	Low Bias
Colson et al. (2012)	Moderate Bias	High Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Dunne et al. (2014)	Moderate Bias	High Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Epstein et al. (2004)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Forshaw et al. (2008)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Grant et al. (2015)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Hartley et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Hennis et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Hightower et al. (2010)	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
James et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Junejo et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Junejo et al. (2014)	Low Bias	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Kaibori et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
Lai et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Lee et al. (2013)	Low Bias	Low Bias	Low Bias	Moderate Bias	Moderate Bias	Low Bias
McCullough et al. (2006)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Moyes et al. (2008)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Nagamatsu et al. (2001)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Neviere et al. (2014)	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
Nugent et al. (1998)	Moderate Bias	Low Bias	Low Bias	High Bias	Moderate Bias	Low Bias
Older et al. (1993)	Moderate Bias	Moderate Bias	Low Bias	Low Bias	High Bias	Low Bias
Older et al. (1999)	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Moderate Bias	High Bias
Prentis et al. (2012)	Low Bias	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Prentis et al. (2012)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Prentis et al. (2013)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Snowden et al. (2010)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Snowden et al. (2013)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Ting et al. (2013)	Moderate Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
Tolchard et al. (2015)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Ulubay et al. (2010)	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Moderate Bias	Low Bias
West et al. (2013)	Low Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
West et al. (2014)	Low Bias	Moderate Bias	Low Bias	Low Bias	Moderate Bias	Low Bias
Wilson et al. (2010)	Moderate Bias	Low Bias	Low Bias	Low Bias	Moderate Bias	Low Bias

outcome as event-free survival. This latter parameter will not be included in the analysis of this section. Both Junejo and colleagues[12] and Dunne and colleagues[18] analysed the possible relationship between CPET and postoperative complications. In a multivariable predictive regression model, a $\dot{V}_E/\dot{V}_{CO_2}$ threshold of 34.5 at AT was predictive of postoperative cardiopulmonary complications.[12] Dunne and colleagues[18] reported that heart rate at AT ($P<0.05$) and HR at $\dot{V}_{O_2}$ peak ($P<0.05$) were associated with all postoperative complications.

Preoperative CPET shows possible benefit for predicting postoperative complications after liver surgery, but further studies are required to validate the prognostic ability of CPET.

Abdominal aortic aneurysm repair

Mortality

Four full-text articles analysing the potential predictive ability of CPET in AAA repair were reviewed.[19–22] In a small cohort ($n=30$), with only two documented deaths, Nugent and colleagues[19] reported no difference in preoperative $\dot{V}_{O_2}$ peak between patients who did and did not experience postoperative morbidity and mortality.

Grant and colleagues[20] found in the multivariable analysis that $\dot{V}_E/\dot{V}_{CO_2}$ >42 at AT was predictive of mortality ($P<0.05$) as was $\dot{V}_{O_2}$ peak <15 ml kg^{-1} min^{-1} ($P<0.05$). Anaerobic threshold was not included because of missing values. An AT of <10.2 ml kg^{-1} min^{-1} was reported to be predictive of 30 day mortality ($P<0.05$), and $\dot{V}_{O_2}$ peak <15 ml kg^{-1} min^{-1} was predictive of 90 day mortality ($P<0.05$).[21] The $\dot{V}_E/\dot{V}_{CO_2}$ was predictive of 30 ($P<0.05$) and 90 day mortality ($P<0.05$) after AAA repair.[21] In a univariable analysis, Carlisle and Swart[22] reported that $\dot{V}_E/\dot{V}_{CO_2}$ ($P<0.01$), ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}_{O_2}$; $P<0.01$), AT ($P<0.01$), and $\dot{V}_{O_2}$ peak ($P<0.01$) were predictive of mortality. In the multivariable analysis, $\dot{V}_E/\dot{V}_{CO_2}$ and AT were predictive of postoperative survival ($P<0.01$ and $P=0.03$, respectively).

The prognostic ability of CPET in determining postoperative mortality after AAA repair appears useful but requires further

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Table 3: Preoperative Cardiopulmonary Exercise Testing and Mortality

Cardiopulmonary Exercise Testing and Mortality							
Author	**Sample Size**	**In-hospital**	**30 days**	**90 days**	**1 year**	**≥ 2 years**	**Duration of follow-up not reported**
Hepatic Resection and Transplant							
Bernal and colleagues[14]	223	–	–	–	AT 9.8 (non-survivors) vs. 11.7 (survivors) ml/kg/min	–	–
Dunne and colleagues[18]	197	–	–	–	–	–	–
Epstein and colleagues[17]	59	–	–	(100 days) Predicted Vo_2 Peak <60% Predicted AT <50%	–	–	–
Junejo and colleagues[12]	94	–	AT <9.9 ml/kg/min	–	–	–	–
Kaibori and colleagues[15]	61	–	–	–	–	AT <11.5 ml/kg/min	–
Neviere and colleagues[16]	263	–	–	–	Vo_2 Peak; 18.6 vs. 17.1 ml/kg/min	–	–
Prentis and colleagues[13]	60	–	–	AT of 9.0 ml/kg/min	–	–	–
Abdominal Aortic Aneurysm							
Carlisle and Swart[22]	130	–	–	–	–	V_E/ Vco_2 and AT	–
Grant and colleagues[20]	506	–	–	–	–	Vo_2 Peak <15 ml/kg/min and V_E/ Vco_2 >42 at AT	–
Hartley and colleagues[21]	415	–	AT <10.2 ml/kg/min and V_E/ Vco_2	Vo_2 Peak <15 ml/kg/min and V_E/ Vco_2	–	–	–
Nugent and colleagues[19]	30	–	–	–	Vo_2 Peak - Not Significant	–	
Colorectal							
Lai and colleagues[24]	269	–	AT <11.0 ml/kg/min	AT <11.0 ml/kg/min	–	AT <11.0 ml/kg/min	–
West and colleagues[25]	95	–	–	–	Vo_2 Peak of <10.6 ml/kg/min	–	–
West and colleagues[26]	136	–	–	–	–	–	–
Pancreatic							
Ausania and colleagues[28]	124	–	AT <10.1 ml/kg/min - Not Significant	–	–	–	–
Ausania and colleagues[30]	50	–	–	–	–	–	AT - Not Significant
Chandrabalan *and colleagues*[29]	100	AT – Not Significant	–	–	–	–	–
Junejo and colleagues[31]	64	$V_E/Vco_2^{\cdot}$	V_E/Vco_2 > 41	–	–	–	–
Renal Transplant							
Ulubay and colleagues[32]	16	–	–	–	–	–	–
Upper Gastrointestinal							
Forshaw and colleagues[34]	78	–	–	–	–	–	–

Continued

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Table 3: Continued

Cardiopulmonary Exercise Testing and Mortality							
Author	Sample Size	In-hospital	30 days	90 days	1 year	≥ 2 years	Duration of follow-up not reported
Bariatric							
McCullough and colleagues[37]	109	–	V_{O_2} Peak†	–	–	–	–
Intra-Abdominal							
Colson and colleagues[43]	1,725	–	AT – Not Significant	–	AT – Not Significant	AT – Not Significant	–
Older and colleagues[42]	187	–	–	–	–	–	AT <11 ml/kg/min
Older and colleagues[41]	548	–	–	–	–	–	AT <11 ml/kg/min
Snowden and colleagues[48]	389	AT <10 ml/kg/min	–	–	–	–	–
Wilson and colleagues[40]	847	–	–	AT of 10.9 ml/kg/min and V_E/V_{CO_2} of 34	–	–	–

AT = Anaerobic Threshold; * = No value was given for V_E/VCO_2; † = Only one death

validation. Only one study did not find $\dot{V}_{O_2}$ peak to be predictive.[19] The variables and cut-off points used between studies vary or are not reported.[19 22] The length of postoperative follow-up also differs; therefore, further studies will need to examine the prognostic ability of CPET and mortality at specific time points to allow for suitable comparison (e.g. 30 and 90 days and 5 yr). A $\dot{V}_{O_2}$ peak cut-off point of 15 ml kg^{-1} min^{-1} is a good starting point because it is predictive of 90 day mortality[21] and at (median) 26 months.[20]

Length of stay

Anaerobic threshold was reported to be predictive of CCU and overall hospital LOS in open AAA repair, but not endovascular aneurysm repair.[23]

Morbidity

Nugent and colleagues[19] reported no statistically significant relationship between $\dot{V}_{O_2}$ peak and postoperative complications. An AT of 10 ml kg^{-1} min^{-1} has been reported to be predictive of postoperative morbidity[13] (Table 5).

Colorectal surgery

Mortality

Lai and colleagues[24] stratified patients into the following three categories: fit (AT ≥11 ml kg^{-1} min^{-1}), unfit (AT <11 ml kg^{-1} min^{-1}), and unable (unable to generate an AT). This study compared mortality at 30 and 90 days and 2 yrs between fit and unfit and between unfit and unable and reported that mortality was significantly different between groups ($P<0.01$).

West and colleagues[25] reported that seven patients (total n=95) died within 1 yr after surgery, all of whom had a $\dot{V}_{O_2}$ peak of <10.6 ml kg^{-1} min^{-1}. West and colleagues[26] were unable to conclude whether CPET was predictive of mortality after major colonic surgery because there were only two deaths (1.5%; Table 3). Anaerobic threshold and $\dot{V}_{O_2}$ peak appear to be beneficial in predicting postoperative mortality, but owing to the low rate of mortality it is difficult to draw conclusions.

Length of stay

Patients with higher AT values (≥11 ml kg^{-1} min^{-1}) had a significantly shorter LOS in hospital compared with unfit (AT <11 ml kg^{-1} min^{-1}) and unable groups (unable to generate an AT; $P<0.01$).[24] West and colleagues[26] reported that patients with low AT ($P<0.01$) or $\dot{V}_{O_2}$ peak ($P<0.01$) or with high $\dot{V}_E/\dot{V}_{CO_2}$ ($P<0.01$) were susceptible to an increased hospital stay. The prognostic ability of CPET appears viable; however, more research is needed to validate the ability of AT to determine postoperative LOS.

Morbidity

Peak oxygen uptake and AT have been reported to be associated with postoperative complications using the Postoperative Morbidity Survey (POMS) on day 5 after rectal cancer surgery and major colonic surgery.[25 26] After major colonic surgery, West and colleagues[26] reported that $\dot{V}_{O_2}$ peak, AT, and $\dot{V}_E/\dot{V}_{CO_2}$ were independently predictive of morbidity in rectal cancer surgery and major colonic surgery. Lee and colleagues[27] reported that $\dot{V}_{O_2}$ peak was associated with occurrence of medical complications ($P<0.01$) but not surgical and all complications (Table 5).

The data regarding preoperative CPET as a predictor of postoperative morbidity are strong, but further research is needed to quantify a level of aerobic fitness that is protective against complications.

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Table 4: Preoperative Cardiopulmonary Exercise Testing and Length of Stay

Cardiopulmonary Exercise Testing and Length of Stay				
Author	**Sample Size**	**Hospital LOS**	**ICU/CCU Admission**	**ICU/CCU LOS**
Hepatic Transplant and Resection				
Bernal and colleagues[14]	223	AT <9.2 ml/kg/min,	–	Vo_2 Peak <13.4 ml/kg/min
Dunne and colleagues[18]	197	AT, Vo_2 Peak (L/min)	–	–
Junejo and colleagues[12]	94	–	–	AT <9.9 ml/kg/min
Prentis and colleagues[13]	60	–	–	AT <11 ml/kg/min
Abdominal Aortic Aneurysm				
Prentis and colleagues[23]	185	AT <10 ml/kg/min (Open Repair and EVAR)	–	AT <10 ml/kg/min (Open Repair)
Colorectal				
Lai and colleagues[24]	269	AT <11 ml/kg/min	–	–
West and colleagues[26]	136	AT, Vo_2 Peak, V_E/Vco_2	–	–
Pancreatic				
Ausania and colleagues[28]	124	AT ≤10.1 ml/kg/min	–	–
Chandrabalan and colleagues[29]	100	AT (<10 ml/kg/min	–	–
Renal Transplant				
Ting and colleagues[33]	70	–	AT	–
Upper Gastrointestinal				
Forshaw and colleagues[34]	78	AT <11 ml/kg/min – Not Significant	–	–
Bariatric				
McCullough and colleagues[37]	109	Vo_2 Peak*	–	–
Hennis and colleagues[38]	106	AT <11.4 ml/kg/min	–	–
Intra-Abdominal				
Snowden and colleagues[39]	389	AT <10 ml/kg/min	–	AT <10 ml/kg/min
Tolchard and colleagues[45]	105	AT, V_E/Vco_2	Vo_2 Peak*	–
Wilson and colleagues[40]	847	AT <11 ml/kg/min	–	–

AT = Anaerobic Threshold, CCU = Critical Care Unit, EVAR = Endovascular Aneurysm Repair, ICU = Intensive Care Unit, LOS = Length of Stay
*= No value given for Vo_2 Peak

Pancreatic surgery

Mortality

Three studies exclusively reported on the ability of AT to predict postoperative mortality and concluded that there was no significant relationship. Ausania and colleagues[28] reported similar mortality rates between groups, AT ≤10.1 and >10.1 ml kg^{-1} min^{-1} (P=1.00). Anaerobic threshold was not associated with postoperative mortality (P=0.74).[29] Ausania and colleagues[30] performed Cox regression analysis and reported that AT was not correlated with long-term survival (P=0.5). Their study failed to quantify the length of long-term survival. Junejo and colleagues[31] reported $\dot{V}_E/\dot{V}co_2$ to be a significant predictor of both 30 day (P=0.03) and in-hospital mortality (P=0.02; Table 3).

Preoperative AT is not predictive of postoperative mortality after pancreatic surgery; however, $\dot{V}_E/\dot{V}co_2$ may be able to predict postoperative survival. Further studies are required to determine the validity of $\dot{V}_E/\dot{V}co_2$.

Length of stay

Only two studies examined LOS and CPET variables. Chandrabalan and colleagues[29] reported that an AT <10 ml kg^{-1} min^{-1} was predictive of a median of 6 days longer LOS than those of AT ≥10 ml kg^{-1} min^{-1} (P<0.01). Likewise, Ausania and colleagues[28] reported that an AT value of ≤10.1 ml kg^{-1} min^{-1} resulted in a median LOS of 29.4 days, whereas patients with an AT >10.1 ml kg^{-1} min^{-1} had a median LOS of 17.5 days (P<0.01; Table 4).

An AT of 10–10.1 ml kg^{-1} min^{-1} appears to be predictive of LOS after pancreatic surgery. This may be used in current practice to guide postoperative care. Future studies will be required to validate this CPET result.

Morbidity

Junejo and colleagues[31] reported that no CPET variable was related to postoperative morbidity (P<0.05). Ausania and colleagues[30] reported that patients with a mean AT of 14.1 (range 10.3–16.9) ml kg^{-1} min^{-1} experienced no complications, whereas patients who did develop complications had a mean AT of 11.3 (range 6.2–15.4) ml kg^{-1} min^{-1} (P=0.02). In contrast, Chandrabalan and colleagues[29] reported that an AT <10 ml kg^{-1} min^{-1} was significantly related to postoperative pancreatic fistula (P=0.03) and major intra-abdominal abscesses (P=0.04), but not cardiac (P=0.31) or pulmonary complications (P=0.66). Ausania and colleagues[28] reported that the postoperative complication rate was significantly lower in the group with AT >10.1 ml kg^{-1} min^{-1} (P=0.01).

Renal transplant

Mortality

Ulubay and colleagues[32] were unable to determine whether CPET was predictive of postoperative mortality after renal transplant surgery because there were no deaths in the relatively small sample size (*n*=16; Table 3).

Length of stay

No single study examined whether there was a relationship between CPET variables and LOS after renal transplant. Ting and colleagues[33] reported that mean AT was significantly lower in the CCU admission group *vs* the non-CCU admission group (P<0.01; Table 4).

Morbidity

There was no study that examined the prognostic ability of CPET for postoperative morbidity after renal transplant.

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Table 5: Preoperative Cardiopulmonary Exercise Testing and Morbidity

Cardiopulmonary Exercise Testing and Morbidity								
Author	**Sample Size**	**Morbidity Measure**	**In-hospital**	**7 days**	**30 days**	**90 days**	**>90 Days**	**Not Reported**
Hepatic Resection and Transplant								
Dunne and colleagues[18]	197	Clavien-Dindo	–	–	Heart Rate at AT and Heart Rate at Vo_2 Peak	–	–	–
Junejo and colleagues[12]	94	POMS, Clavien-Dindo	–	–	V_E/Vco_2 at AT	–	–	–
Kaibori and colleagues[15]	61	Clavien-Dindo	–	–	–	–	AT <11.5 ml/kg/min	–
Abdominal Aortic Aneurysm								
Nugent and colleagues[19]	30	Self-Defined		–	–	–	Vo_2 Peak – Not Significant	–
Prentis and colleagues[23]	185	Self-Defined	AT ≤10 ml/kg/min, Vo_2 Peak* and V_E/Vco_2	–	–	–	–	–
Colorectal								
Lee and colleagues[27]	112	Clavien-Dindo	–	–	Vo_2 Peak*	–	–	–
West and colleagues[25]	95	POMS, Clavien-Dindo	–	–	AT <10.1 ml/kg/min and Vo_2 Peak 16.7 ml/kg/min	–	–	–
West and colleagues[26]	136	POMS, Clavien-Dindo	–	–	–	–	Vo_2 Peak <18.6 ml/kg/min and AT <10.6 ml/kg/min	–
Pancreatic								
Ausania and colleagues[28]	124	POMS, ISGPF	–	–	AT ≤10.1 ml/kg/min	–	–	–
Ausania and colleagues[30]	50	POMS	–	–	–	–	–	AT ≥14.1 ml/kg/min
Chandrabalan and colleagues[29]	100	Clavien-Dindo and ISGPF	AT <10 ml/kg/min					
Junejo and colleagues[31]	64	ISGPS for pancreatic complications. Non pancreatic complications were self-defined.	–	–	–	–	No CPET variable was significant	–
Upper Gastrointestinal								
Moyes and colleagues[36]	108	Cardiopulmonary complications defined according to the Common Terminology Criteria for Adverse Events. Non-cardiopulmonary complications were self-defined.	–	–	–	–	–	AT 9.9 (complications) vs. 11.2 (no complications) ml/kg/min

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Nagamatsu and colleagues[35]	91	Self-Defined	–	–	–	–	–	Vo_2 Max/m^2 *
Bariatric								
Hennis and colleagues[38]	106	POMS	AT <11 ml/kg/min	–	–	–	–	–
McCullough and colleagues[37]	109	Self-Defined	–	–	Vo_2 Peak <18.5 ml/kg/min	–	–	–
Intra-Abdominal								
Hightower and colleagues[46]	32		–	Heart Rate at AT, Difference between Heart Rate from rest to AT and Percentage of predicted AT achieved (<75% vs. ≥75%)	–	–	–	–
James and colleagues[47]	83	Major adverse cardiac events and self-defined	–	–	AT <10.6 ml/kg/min and Vo_2 Peak <14.0 ml/min/kg	–	–	–
Prentis and colleagues[44]	69	Clavien-Dindo	AT <12 ml/kg/min	–	–	–	–	–
Snowden and colleagues[48]	116	POMS	AT (POMS ≤1) 11.9 vs. 9.1 ml/kg/min (POMS >1)	–	–	–	–	–
Tolchard and colleagues[45]	105	Clavien-Dindo	–	–	–	AT (complications) 10.6 vs. 11.8 ml/kg/min (no complications), Vo_2 Peak (complications) 14.3 vs. 15.4 ml/kg/min (no complications), V_E/Vco_2 complications 33.3 (complications) vs. 30.3 (no complications)	–	–

AT = Anaerobic Threshold, ISGPF = International Study Group on Pancreatic Fistula, POMS = Postoperative Morbidity Survey
*= No value was given

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Upper gastrointestinal surgery

Mortality

Forshaw and colleagues[34] could not conclude whether CPET was predictive of postoperative mortality because there was only one death after oesophagectomy (Table 3).

Length of stay

Forshaw and colleagues[34] reported that there was no apparent correlation with AT and LOS (P=0.89). Cardiopulmonary exercise testing appears unable to determine LOS after upper GI surgery, but there have been few studies in this area. The present review expresses the need for more high-quality CPET prognostic studies in the area of upper GI surgery.

Morbidity

Nagamatsu and colleagues[35] reported that $\dot{V}_{O_2}$ max m^{-2} was lower in patients with cardiopulmonary complications *vs* patients without complications (P<0.01) after oesophagectomy with lymphadenectomy. In contrast, Moyes and colleagues[36] reported that $\dot{V}_{O_2}$ peak was not associated with cardiopulmonary complications (14 *vs* 16 ml min^{-1} kg^{-1}, P=0.07) but that AT was associated with morbidity (P=0.05).

There have been too few studies to conclude whether CPET is predictive of postoperative morbidity after upper GI surgery, but the results are optimistic. The present review expresses the need for more high-quality CPET prognostic studies in the area of upper GI surgery.

Bariatric surgery

Mortality

McCullough and colleagues[37] (total n=99) reported that $\dot{V}_{O_2}$ peak was predictive of morbidity and mortality (grouped together); however, there was only one death, and the results of this study cannot solely predict postoperative mortality (Table 3).

Length of stay

McCullough and colleagues[37] reported that $\dot{V}_{O_2}$ peak was predictive of LOS (P<0.01). The AT of patients with LOS >3 days was lower than that of patients with LOS ≤3 days after gastric bypass surgery (P=0.02).[38] The literature suggests that CPET is able to identify patients subject to increased LOS, but a consensus on the optimal CPET variable and cut-point is required.

Morbidity

Hennis and colleagues[38] reported that AT was significantly lower in patients with complications compared with those without complications (P<0.05). McCullough and colleagues[37] presented a multivariable model using $\dot{V}_{O_2}$ peak as a continuous variable and included smoking status that was a significant predictor of complications (odd ratio 1.61, 95% CI 1.19–2.18, P<0.01; Table 5).

Cardiopulmonary exercise testing shows potential for determining patients at risk of postoperative complications in the preoperative period, but further studies are required to quantify the optimal CPET variable and cut-off point.

Intra-abdominal surgery

Mortality

Anaerobic threshold has been reported in four of the above-mentioned studies to be a significant predictor of mortality.[39–42] Snowden and colleagues[39] reported an AT of 10.9 ml kg^{-1} min^{-1} to be predictive of postoperative survival; however, their follow-up was limited to in-hospital stay. An AT of 10.9 ml kg^{-1} min^{-1} was reported to be predictive of survival up to 90 days (P=0.03).[40] Two studies presented an AT <11 ml kg^{-1} min^{-1} to be predictive of postoperative mortality.[41 42]

Colson and colleagues[43] concluded that AT was not a statistically significant predictor of mortality. Prentis and colleagues[44] reported only two postoperative deaths, and no statistical analysis was performed. Tolchard and colleagues[45] reported an insufficient sample size (Table 3).

The present review suggests that an AT of 10.9 ml kg^{-1} min^{-1} may have good clinical utility. It may also be beneficial to explore the prognostic ability of other CPET variables. A $\dot{V}_E/\dot{V}_{CO_2}$ of 34 has been reported to be associated with postoperative mortality at 90 days (P=0.02).[40]

Length of stay

Tolchard and colleagues[45] reported that a lower mean oxygen uptake was correlated with ICU admission (14.9 *vs* 16.5 ml kg^{-1} min^{-1}, P<0.05) and $\dot{V}_E/\dot{V}_{CO_2}$ ≥33 correlated with LOS (P<0.01). Wilson and colleagues[40] reported that the overall median LOS was lower in the group with AT ≥11 ml kg^{-1} min^{-1} (8 *vs* 9 days, P<0.01). Snowden and colleagues[39] reported that cardiovascular fitness was a significant independent predictor of hospital and critical care LOS. The prognostic ability of CPET in predicting LOS after intra-abdominal surgery is strong; however, a consensus needs to be reached on the optimal CPET variable.

Morbidity

Hightower and colleagues[46] reported that HR at AT (P<0.01), the difference between HR at rest and at AT (P=0.01), and the percentage AT achieved (P=0.02) to be predictive of postoperative morbidity. Tolchard and colleagues,[45] using Mann–Whitney U-tests, compared patients who experienced complications with those who did not and showed $\dot{V}_{O_2}$ peak (P=0.02) and $\dot{V}_E/\dot{V}_{CO_2}$ (P<0.01) to be predictive of complications. The following AT cut-off values have been reported: 12,[44] 11,[45] 10.6,[46] and 10.1 ml kg^{-1} min^{-1}.[48]

Anaerobic threshold is the strongest predictor of postoperative morbidity in intra-abdominal surgery. Patients with an AT of <10.1 ml kg^{-1} min^{-1} should have appropriate measures adopted to ensure a smooth postoperative outcome. Any patients with an AT between 10.1 and 12 ml kg^{-1} min^{-1} should be considered with caution.

Discussion

There are two main theories on how CPET can predict postoperative outcome. One theory suggests that patients with a higher level of fitness function better with the prolonged increase in oxygen delivery induced by surgery without outpacing their anaerobic physiological parameters. The alternative theory suggests that regular exercise can create a systemic effect similar to ischaemic preconditioning. By increasing a person's ability to extract oxygen and tolerate ischaemic conditions, this lessens the impact of any deficit in oxygen delivery and demand associated with surgery.[8]

Previous reviews concluded that CPET is valuable, but more research is needed to determine its validity in non-cardiopulmonary surgery.[6 8] The area has since grown, and the present review has analysed considerably more studies and is the largest systematic review of preoperative CPET to date. Given that a quantitative synthesis approach was undertaken, definite conclusions cannot be drawn from the present review regarding the ability of CPET to predict postoperative outcome after surgery, but certain areas can be highlighted and suggestions can be made.

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Main findings

This review recommends that CPET is included in the preoperative assessment of liver, pancreatic, and intra-abdominal surgery and AAA repair and that the following cut-points are used.

- Hepatic transplant and resection: 90 day survival, AT 9 ml kg^{-1} min^{-1}; 3 yr survival, AT 11.5 ml kg^{-1} min^{-1}; and ICU/CCU admission, AT <9.9–11 ml kg^{-1} min^{-1}.
- Abdominal aortic aneurysm repair: 90 day survival, $\dot{V}O_2$ peak 15 ml kg^{-1} min^{-1}.
- Pancreatic surgery: LOS and morbidity, AT 10–10.1 ml kg^{-1} min^{-1}.
- Intra-abdominal surgery: mortality, AT of 10.9 ml kg^{-1} min^{-1}; morbidity, AT <10.1 ml kg^{-1} min^{-1}; and patients with an AT 0f 10.1–12 ml kg^{-1} min^{-1} should be treated with caution.

Anaerobic threshold is the optimal predictor of outcome in liver, pancreatic, and intra-abdominal surgery. The reason for the variation in the type and strength of the relationship between CPET variable and outcome in various surgical interventions has been underexplored, but a possible explanation may be that there is variation in the relative importance of different CPET variables predisposing to adverse outcome.[6] Despite this, the results suggest AT to be the superior indicator within certain surgical interventions.

Studies were divided based on surgery type, similar to previous reviews.[6 8 9] The variation in cut-points between surgeries may be because of the possibility that certain surgical procedures require a greater physiological demand, or the pre- and postoperative management varies between surgical procedures.[7] This topic has been underexplored and requires further validation.

There are four main reasons for associations in observational studies between cardiopulmonary fitness and postoperative outcome: bias, confounding, chance, and cause.[49] The level of bias and confounding was assessed using the QUIPS tool.[11] The level of chance of association is summed up by the 95% CIs and *P*-value (Supplementary material, Tables S2–S4). The CPET-derived cut-points are similar between studies; as the level of bias, chance, and confounding have been accounted for, it is possible that a cause of poor postoperative outcome is cardiorespiratory fitness below these cut-points.

Morbidity after pancreatic surgery has produced some conflicting results. One study reported no relationship between AT and morbidity,[31] and two studies produced similar findings,[28 29] whereas one study produced different results. The present review suggests using an AT of 10–10.1 ml kg^{-1} min^{-1} as a cut-point for morbidity after pancreatic surgery[28 29] instead of 14.1 ml kg^{-1} min^{-1} as reported by Ausania and colleagues[30] because we found this study, using the QUIPS tool, to have a relatively high bias in a number of areas.

There is large heterogeneity between studies; therefore, results could not be pooled to produce a meta-analysis. All surgeries were grouped together by surgical intervention (or grouped into the intra-abdominal cohort when no distinctions were made) to improve homogeneity. Despite this, there is considerable variation in areas such as surgical procedure (e.g. laparoscopic *vs* open), the outcome measures used (e.g. postoperative morbidity survey *vs* self-defined morbidity), and accounting for co-morbidities. A number of important variables, such as type of anaesthesia, were not reported in most studies (n=34). The choice of statistical approaches also varied between studies.

The present review included studies that did not have *a priori* power calculation. The sample sizes of the included studies may be underpowered and could potentially influence results. In order for future studies to have sufficient power to determine the ability of an AT <11 ml kg^{-1} min^{-1} to predict mortality at 90 days, we estimate that a sample size of 406 patients above and below AT <11 ml kg min is required, and for 2 yr mortality a sample size of 253 above and below AT <11 ml kg min is required (α=0.05, β=0.80). The calculations were based on data reported by Lai and colleagues.[24]

A robust methodology should also be used[50] consisting of the following: (i) reporting all measured CPET variables (e.g. $\dot{V}O_2$ peak, AT, $\dot{V}E/\dot{V}CO_2$, and HR); (ii) predetermined outcome time points should be used, including 30 day, 90 day, 1, 3, and 5 yr time points for mortality and morbidity, and LOS should include overall hospital stay, ICU/HDU/CCU admission, and length of stay along with readmission; (iii) morbidity should be measured using a combination of the Clavien–Dindo classification scoring system[51] and the Postoperative Morbidity Survey;[52] and (iv) odds ratios should be determined for mortality and morbidity outcomes to allow results to be pooled in a future meta-analysis. Length of stay should be recorded with medians, standard deviations, and CIs.

Many studies conclude separate CPET-defined cut-points that predict postoperative outcome. Perhaps a single cut-point cannot be recommended; instead, subgroups based on fitness could be created to stratify patients before surgery based on the risk of poor surgical outcome.[37] It is also possible that the variation between CPET variables and strength of relationship with outcome between studies is subject to the inconsistent methodology coupled with data analysis and presentation.

Future research

The areas of colorectal, renal transplant, upper GI, and bariatric surgery require further research to draw conclusions concerning the ability of CPET to predict postoperative outcome. In hepatic surgical intervention, the postoperative morbidity has not been well analysed; currently, there is no consensus on the CPET variable and cut-point to use. To predict LOS after hepatic surgery, the ability of AT produces a divided opinion. The $\dot{V}O_2$ peak shows potential, but evidence in its support is weak. It is recommended that future studies examine the possible link between preoperative aerobic fitness and morbidity and LOS.

A number of studies have examined CPET and survival after AAA repair, but time points to survival vary and so future studies will need to use specific time points, such as 1 and 5 yr survival. The present review suggests future research should examine the possible relationship between CPET and LOS and morbidity after AAA repair because research in this area is lacking.

Increased physical fitness is correlated with improved postoperative outcome. Patients with cardiopulmonary fitness below the recommended cut-points are susceptible to postoperative complications and mortality. Preoperative exercise programmes can improve fitness before surgery.[53] The ability of preoperative exercise interventions to improve postoperative outcome requires further validation.

Conclusion

Cardiopulmonary exercise testing provides a good objective measure of a patient's preoperative fitness, which in turn is a strong predictor of postoperative outcome. Cardiopulmonary exercise testing has been well documented in certain surgical interventions (liver, AAA, pancreatic, and intra-abdominal), but it is less well defined in other areas (colorectal, renal transplant,

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upper GI, and bariatric). The CPET variables AT and $\dot{V}_{O_2}$ peak are the most analysed. Anaerobic threshold is a stronger predictor of outcome in hepatic, pancreatic, and intra-abdominal surgery, whereas $\dot{V}_{O_2}$ peak is superior in AAA repair. Variables such as $\dot{V}_E/\dot{V}_{CO_2}$ show emerging significance but continue to be underused. Future studies should use a robust methodology to clarify further the role of CPET in preoperative risk prediction.

Authors' contributions

Conception: J. Moran, F.W., J.H., J. Moriarty
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Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

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Review

The preoperative use of field tests of exercise tolerance to predict postoperative outcome in intra-abdominal surgery: a systematic review☆,☆☆

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Field tests of exercise tolerance;
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Abstract
Study objective: To assess the ability of field tests of exercise tolerance, such as the 6-minute walk test (6MWT) and incremental shuttle walk test (ISWT), to predict postoperative outcome following intra-abdominal surgery.
Design: A systematic review.
Setting: A hospital-affiliated university.
Measurements: The following databases were searched: AMED, CINAHL, EMBASE, PEDro, PubMed/MEDLINE, and The Cochrane Library. Six full-text articles were included. Data extraction included author, population demographics, surgery type, postoperative outcome measure, and field test results. The risk of bias was performed using the Quality in Prognosis Studies tool.
Results: Surgical procedures reviewed were colorectal (n = 3), upper gastrointestinal (n = 1), and intra-abdominal surgery (n = 2). Field tests of exercise tolerance showed little ability to predict postoperative mortality; however, the overall rate of mortality was low. Patients achieving lower distances on the ISWT tended to have longer hospital stays and an increased risk of overall complications. The 6MWT does not appear able to predict postoperative cardiac or pulmonary complications; however, it may be suitable to predict general complications.
Conclusions: Field tests may be able to predict postoperative outcome; however, further validation is needed. The ISWT appears to be the superior field test. The 6MWT and stair climb test require further validation to assess their predictive ability.
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1. Introduction

Physical fitness is predictive of postoperative outcome following intra-abdominal surgery [1-4], and cardiopulmonary exercise testing (CPET) is the criterion standard method of measuring an individual's aerobic capacity. Field tests of exercise tolerance such as the 6-minute walk test (6MWT) and incremental shuttle walk test (ISWT) differ from CPET because they do not directly assess the relationship between pulmonary gas exchange during exercise; however, they provide an objective measure of physical fitness when CPET is not readily available.

Field tests are practical, cheap, and easy to administer. CPET requires specialized equipment, increased safety precautions, and extra staff, which limit wide clinical application [5,6]. Consequently, field tests are often used in the clinical setting because they are do not require previous training by the clinician and require little equipment. Examples of field exercise tests include the 20-m shuttle test [7], self-paced walking test [8], bag and carry test [9], and the 12-minute walk test [10]. The field tests used in the articles included for review in this article were the stair climb test (SCT), the ISWT, and the 6MWT.

The 6MWT was adapted from the 12-minute walk test [11]. The self-paced 6MWT is a submaximal assessment of exercise tolerance. The test does not require any exercise equipment or previous experience for clinicians [12]. Patients are required to walk and cover as much distance as possible over a flat, hard-surfaced 30-m stretch of corridor in 6 minutes. The 6MWT is a dynamic, noninvasive method of assessing the cardiopulmonary system, neuromuscular units, and muscle metabolism. The 6MWT is significantly correlated with V_{O_2} peak as measured by CPET in chronic heart failure patients and middle-aged and older adults [13,14].

In contrast, the externally paced ISWT is a maximal exercise test and is controlled by a series of prerecorded signals [15,16]. Two cones are placed 9 m apart. Participants are required to cover a distance of 10 m (to account for the turns around the cones) in time set to auditory cues. The time between cues progressively decreases, requiring the patient to increase walking speed. The test is stopped when the patient can no longer keep up with the auditory cues. The maximum duration of the test is 6 minutes. The ISWT is also significantly correlated with V_{O_2} peak in chronic heart failure patients [13].

The SCT is a test of an individual's ability to ascend and descend a flight of stairs. The test is timed (in seconds), and the number of stairs will depend on the environment. The SCT has been reported to be predictive of postoperative pulmonary complications (PPCs) in noncardiac thoracic surgery [17]. The SCT demonstrates high correlation with V_{O_2} peak in patients with chronic obstructive pulmonary disease and patients scheduled for spirometry [18,19]. Brunelli et al (2013) [20] advise clinicians that lung cancer patients being considered for resectional surgery should complete the SCT or ISWT. If patients are unable to complete >25 shuttles (400 m) or climb >22 m, then they should be considered for formal CPET testing.

The aim of this review is to assess the prognostic ability of field tests of exercise tolerance in predicting poor postoperative outcome following noncardiopulmonary intra-abdominal surgery. The objectives are to (1) determine the ability of the following field tests of exercise tolerance to predict postoperative outcome following intra-abdominal surgery: 6MWT, SCT, or ISWT, and (2) determine the optimal distance cut point predictive of postoperative outcome.

Postoperative outcome includes all-cause mortality, morbidity, and length of stay (LOS). Morbidity following surgical intervention includes all complications: pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, and hematological. The outcome LOS covered the overall LOS in hospital, intensive care unit, high-dependency unit, and critical care unit admission and LOS.

2. Materials and methods

This review was originally part of a separate article examining the role of cardiopulmonary fitness as a predictor of complications following noncardiopulmonary surgery, as assessed by all measures of cardiopulmonary fitness. CPET is an assessment of the pulmonary gas exchange variables such as oxygen and carbon dioxide while exercising and therefore provides a direct assessment of cardiopulmonary fitness. In contrast, field tests estimate exercise tolerance from distance or time to completion of a defined functional activity and therefore have a different role in the clinical environment. Hence, although the initial search strategy captures all methods of assessing cardiopulmonary fitness, the resultant outcomes of the 2 methods are presented separately.

2.1. Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standardized reporting guidelines were used to homogenize the methods of conducting and reporting this review [21]. The databases AMED, CINAHL, EMBASE, PEDro, PubMed/MEDLINE, and The Cochrane Library were searched up until May 2015. A search strategy was defined with all keywords and subject headings included (Appendix). The abstracts from the annual European Anaesthesiology Congress (2004-2014), the Anesthetic Research Society (2007-2015), the Society of Academic & Research Surgery (2012-2015), the Vascular Society (2005-2012), the International Anesthesia Research Society (2003-2015), the World Federation of Society of Anaesthesiologists (2008-2012), and the American Society of Anesthesiologists (2000-2014) were reviewed for eligibility. Reference lists of the studies of interest were searched to identify extra articles.

The inclusion criteria consisted of:

1. Prognostic studies of intra-abdominal surgery among adult populations
2. The use of a preoperative field exercise test (eg, 6MWT or ISWT)

3. Measurement of postoperative outcome (mortality, morbidity, and/or LOS)
4. Comparison of preoperative exercise test results with postoperative outcome

Studies were excluded if they contained:

1. Cardiopulmonary surgical procedure
2. Pediatric surgery
3. Head and neck surgery
4. Orthopedic surgery
5. Spinal surgery
6. Transfusion procedures, for example, blood or stem cell
7. Preoperative interventions, for example, preoperative exercise programs
8. Systematic reviews, meta-analyses, case studies, letters to the editor, and abstracts with no full text available

If studies had split the analysis of intra-abdominal and cardiopulmonary surgery, then the subgroup containing intra-abdominal surgery was taken, and the cardiopulmonary surgery group was excluded. Procedures involving multiple incisions which included major intra-abdominal surgery were included (eg, esophagectomy).

2.2. Data extraction

Data extraction was performed independently by the lead author (J.Moran). The data were reviewed blind by another author (FW). The data extracted included author, population demographics, study setting, surgery type, postoperative outcome measure, and field exercise test used (Table 1).

A total of 1086 titles were identified using the search strategy on the above-mentioned databases; 1080 studies were excluded (Fig. 1). Five full-text articles were excluded, 3 studies did not compare CPET results with postoperative results, 1 study did not perform CPET, and 1 study combined examined patients who went for surgery and those who did not together. Thirty-seven articles were included in a separate systematic review [4]. One article was featured in both reviews because it featured the use of both CPET and 6MWT [22]. The authors (J.Moran and FW) excluded articles based on titles and abstracts. If any disagreements arose and were not resolved through discussion, an independent third author was asked to intervene (JH). There were no disagreements. Six full-text articles were included in the data extraction and synthesis (Fig. 1). The authors of abstracts and conference posters were contacted for full-text articles. If full texts were not acquired, then abstracts were excluded because of the potential high risk of bias and lack of a detailed methodology.

2.3. Risk of bias assessment

The methodological quality of the studies was assessed using the Quality in Prognosis Studies (QUIPS) tool [23]. The QUIPS tool analyzes the risk of bias in observational prognostic studies in 6 key areas. The areas included study participation, attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each area contained several criteria. If a study failed to address ≤1 criterion within an area, it was deemed to have a low risk of bias. Two authors (JM and FW) independently assessed the risk of bias in each study. An independent third author (JH) was asked to intervene if any disagreements could not be resolved through discussion. The overall risk of bias is presented in Table 2.

2.3.1. Study participation

Three studies were ranked with a low risk of bias, whereas 3 were ranked with a moderate risk of bias. Studies with a moderate risk of bias for study participation failed to report areas such as population characteristics, inclusion and exclusion criteria, and participation by eligible participants.

2.3.2. Study attrition

The goal of this area was to judge the likelihood that relationship between predictive factors and outcomes is different for completing and noncompleting participants. Only 1 study

Table 1 Demographic details of included studies

Author	Surgery	Sample size (n)	Age (y)	Sex	Location	Outcome	CPET type	Variables reported
Arruda et al (2013)	Upper abdominal and thoracic surgery	78	55.6 (14.5)	49 Male, 29 female	Sao Paulo, Brazil	Morbidity	6MWT	Distance
Lee et al (2013)	Colorectal surgery	112	59.9 (15.5)	65 Male, 47 female	Montreal, Canada	Morbidity	Cycle ergometer, 6MWT	Vo_2 peak, distance
Moriello et al (2008)	Colon resection	63	60.4 (12)	33 Male, 30 female	Montreal, Canada	Morbidity	6MWT	Distance
Murray et al (2007)	Esophagogastrectomy	51	64	N/R	Sheffield, UK	Mortality, LOS	ISWT	Distance
Nutt and Russell (2012)	Colorectal surgery	120	72 (6.9)	60 Male, 60 female	Belfast, UK	Mortality, morbidity, LOS	ISWT	Distance
Paisani et al (2012)	Upper abdominal surgery	137	N/R	67 Male, 70 female	Sao Paulo, Brazil	Mortality, morbidity, LOS	6MWT	Distance

N/R = not reported.

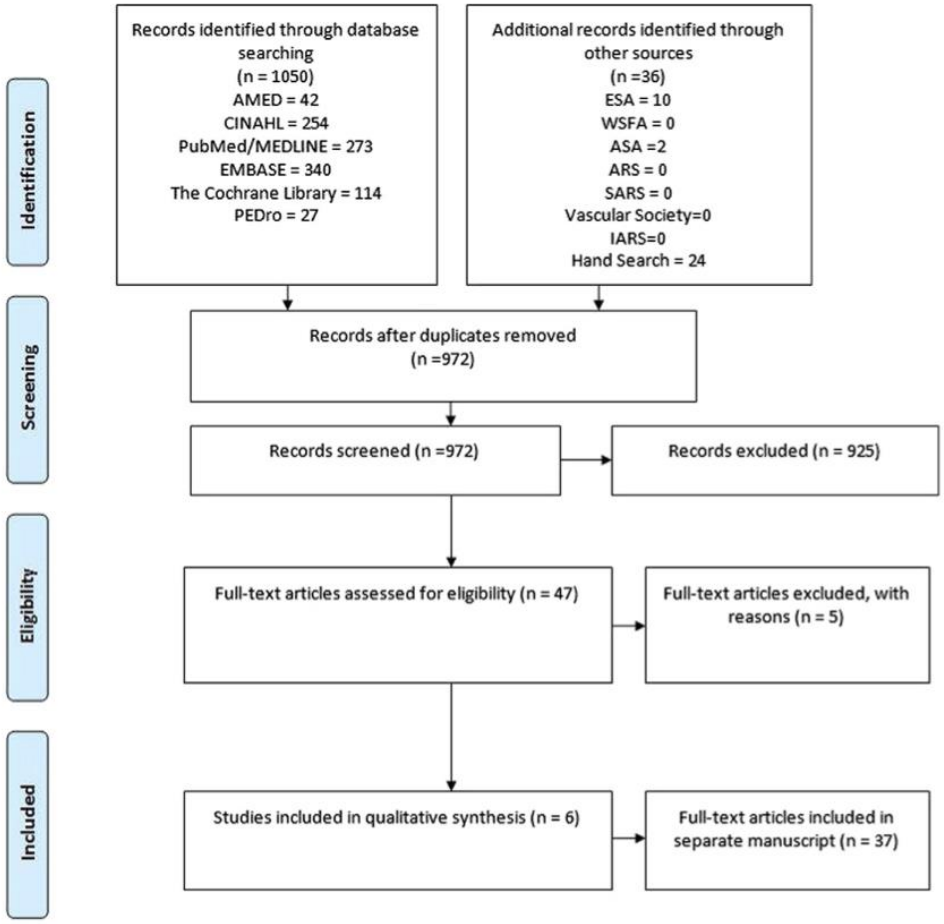


Fig. 1 PRISMA flow diagram.

was rated with a high risk of bias because this study did not report on attempts to collect data from patients who dropped out and these patients are not adequately described [24]. All other studies were rated as low.

2.3.3. Prognostic factor measurement

All studies were rated as low risk of bias because they all used a valid field test of exercise tolerance. Studies used the 6MWT, SCT, or ISWT. One study also used a maximal CPET on a cycle ergometer in conjunction with the 6MWT [22].

2.3.4. Outcome measurement

This section was divided in terms of risk of bias; 3 studies had a low risk and 3 had a moderate risk. Morbidity was often categorized using self-defined criteria [25-27]. Lee et al (2013) [28] and Nutt and Russell (2012) [29] used the

Table 2 Risk of bias assessment

Authors	The QUIPS tool					
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Arruda et al (2013)	Low bias	Low bias	Low bias	Low bias	Moderate bias	Low bias
Lee et al (2013)	Low bias	Low bias	Low bias	Moderate bias	Moderate bias	Low bias
Moriello et al (2008)	Moderate bias	Low bias	Low bias	Low bias	High bias	Low bias
Murray et al (2007)	Low bias	High bias	Low bias	Low bias	High bias	Moderate bias
Nutt and Russell (2012)	Moderate bias	Low bias	Low bias	Low bias	Moderate bias	Low bias
Paisani et al (2012)	Moderate bias	Low bias	Low bias	Moderate bias	Moderate bias	Low bias

Clavien-Dindo classification score, an objective measure of postoperative morbidity. Murray et al (2007) [24] examined postoperative mortality and LOS but did not examine morbidity.

2.3.5. Study confounding

Because of the nature of observational studies, it is difficult to control for all potential confounders. Four studies had a moderate risk of bias. Two studies scored a high risk of bias because the authors found, using the QUIPS tool, that these studies did not account for important and potentially important confounders (eg, comorbidities and smoking status).

2.3.6. Statistical analysis and reporting

Generally, studies had a low risk of bias. Murray et al (2007) [24] did not perform any statistical analysis, and so the authors believe the study to have a moderate risk of bias.

3. Results

3.1. Six-minute walk test

Four studies assessed the ability of the 6MWT to predict postoperative outcome. Moriello et al (2008) [26] reported that 31 of a total of 63 patients developed postoperative complications following colorectal resection and found no statistically significant difference in terms of 6MWT distance between patients with and without complications. The raw data describing preoperative 6MWT distances between groups with and without complications were not reported. Lee et al (2013) [28] noted that the 6MWT correlated with medical (P =.033) and any complication (P = .012) but not surgical complications post colorectal surgery. Medical complications included urinary tract infections, cardiopulmonary complications, upper gastrointestinal bleeding, *Clostridium difficile* infection, and deep vein thrombosis. Surgical complications included surgical site infection, ileus, anastomotic leak, and hematoma requiring transfusion.

Paisani et al (2012) [27] reported that there was no difference in preoperative 6MWT distance in subjects who developed PPCs compared with those without PPCs (P = .57) post upper abdominal surgery. Arruda et al (2013) [25] reported that the 6MWT was unable to predict postoperative cardiopulmonary complications in upper abdominal surgery.

No study examined the ability of the 6MWT to predict postoperative mortality and LOS. Paisani et al (2012) [27] reported that mortality and LOS following upper abdominal surgery were higher in patients who developed PPCs compared with those who did not (P < .01). The authors did not report if preoperative 6MWT distance was predictive of postoperative mortality or LOS (Table 3).

3.2. Incremental shuttle walk test

Two studies required patients to perform the ISWT prior to surgery. The surgical procedures included colorectal resection and esophagogastrectomy. The ability of the ISWT to predict mortality post colorectal surgery is limited because of the low rate of mortality. Nutt and Russell (2012) [29] reported 1 death in their cohort of 120 patients. Murray et al (2007) [24] reported that patients undergoing esophagogastrectomy who walked ≥350 m or more during the ISWT did not die within 30 days of operation; however, there was no statistical analysis performed.

Patients undergoing colorectal surgery with higher preoperative ISWT distances had shorter stays in hospital. Patients with a preoperative ISWT distance <250 m had a LOS of 14 (interquartile range [IQR], 9-24) days compared with patients with a distance >250 m who had a LOS of 8 (IQR, 6-10) days (P < .01). In the study by Murray et al (2007) [24], there was insufficient statistical analysis performed to assess if the ISWT can predict hospital LOS following esophagogastrectomy.

In terms of morbidity, Nutt and Russell (2012) [29] reported that patients undergoing colorectal surgery who developed postoperative complications, as measured by Clavien-Dindo classification score, had a mean preoperative ISWT distances of 256.8 m (SD, 113.8) compared with those without complications who had a mean distance of 382.7 m (SD, 145.3) (Table 3).

3.3. Stair climb test

Only 1 study assessed the ability of the SCT to predict postoperative outcome. Arruda et al (2013) [25] reported the SCT was unable to predict postoperative cardiopulmonary complications post upper abdominal surgery [25].

4. Discussion

There are 2 main theories on how physical fitness can predict postoperative outcome. One theory suggests that consistent exercise can create a systemic effect similar to ischemic preconditioning. By increasing an individual's oxygen extraction and ability to tolerate ischemic conditions, this decreases the impact of any oxygen deficiency and demand associated with surgery [1]. Another theory suggests that subjects with higher levels of aerobic fitness operate better with the continued increase in oxygen delivery induced by surgery without outstripping their aerobic physiological parameters.

4.1. Main findings

This review is unable to conclude if field tests are able to predict postoperative mortality in intra-abdominal surgery because of the low rate of mortality and lack of statistical

analysis. Murray et al (2007) [24] suggests that a cutoff of <350 m may help predict postoperative mortality following esophagogastrectomy. This cutoff requires further validation from future studies, as the authors found this study to have the highest risk of bias of all included studies. Hospital LOS may be predicted post colorectal surgery using the ISWT. A cutoff of 250 m may help predict the postoperative requirements of colorectal surgery patients; however, this result also requires further validation (Table 3). Patients with preoperative ISWT distances greater than 350 m may be subject to an event-free recovery; distances between 250 and 350 m should be interpreted with caution. A distance less than 250 m may be susceptible to poor postoperative outcome and a longer hospital stay.

The ISWT is an externally paced field test during which patients are stressed to a symptom-limited maximal performance and is therefore similar to a maximal CPET. The ISWT generates higher metabolic and ventilatory levels compared with self-paced tests such as the 6MWT [5]. The ISWT has been shown to correlate with V_{O_2} peak among patients with cardiac disease, patients with chronic obstructive pulmonary disease, and patients undergoing lung resectional surgery [30-32]. The ISWT demonstrates stronger correlations with V_{O_2} peak in comparison to the 6MWT [12]. The 6MWT is susceptible to biased results because patients can regulate their physical effort during the test. The ISWT is more demanding than the 6MWT and so may be a superior method of assessing cardiopulmonary fitness, particularly V_{O_2} peak, when CPET is unavailable.

Physical fitness is predictive of postoperative outcome following intra-abdominal surgery [4]. Certain exercise variables provide a superior prediction of postoperative outcome depending on surgical intervention. In abdominal aortic aneurysm surgery, patients with a V_{O_2} peak >15 mL/(kg min) have greater 90-day survival rates than patients below this cutoff [4]. In hepatic surgery, postoperative mortality and morbidity are predicted by Anaerobic Threshold (AT). Anaerobic threshold is the optimal predictor of postoperative outcome [4]. A study by Irisawa et al (2014) [33] reported the ISWT had a higher correlation with AT (r = 0.775) than the 6MWT (r = 0.587) and the SCT (r = 0.592) [34]. The ISWT may be better able to predict postoperative outcome following abdominal surgery because of higher correlations with AT.

Pollock et al (1993) [18] report distance climbed during the SCT to be correlated with V_{O_2} peak (r = 0.72). In comparison, Cataneo and Cataneo (2007) [19] report that the variable in the SCT most associated with V_{O_2} max was time to complete the test. The SCT is able to predict postoperative complications following thorocotomy [17]. The ability of the SCT to predict postoperative complications following thoracic surgery may lie in its correlation with V_{O_2} peak. The ISWT is also used in thoracic surgery because it also demonstrates a high correlation with V_{O_2} peak [20]. The ability of the SCT to predict postoperative outcome in abdominal surgery has only been investigated by 1 study [25]. Arruda et al (2012) [25] reported the SCT was not correlated with postoperative complications; however, this study only assessed PPCs and not all complications, for example, renal and gastrointestinal. A recent review reported anaerobic threshold to be an effective CPET-derived variable predictive of outcome post abdominal surgery [4]. The SCT is better correlated with V_{O_2} peak than AT [18,19,34]. Perhaps, the SCT may be useful in predicting outcome in surgical procedures that use V_{O_2} peak as a predictive variable, for example, thoracic and abdominal aortic aneurysm.

A recent review by Fotheringham et al (2015) [40] reported that the choice between CPET and field tests is often made on a practical basis. In terms of practicality, field tests present an attractive alternative. Tests such as the 6MWT and ISWT require very little equipment and training prior to use. In comparison, CPET requires trained staff and specialized equipment. CPET provides a more in-depth assessment of cardiopulmonary function and gas exchange and has been reported to predict outcome following intra-abdominal surgery [4]. Unfortunately, CPET may not always be readily available, and so field tests may be used in their place; however, there is currently little evidence to justify their use in the preoperative setting.

Metabolic equivalents (METS) are used to classify functional capacity based on the basal metabolic rate, which is assumed to be 3.5 mL/(kg min) [35]. The studies included in this review did not report METS; however, there is conflicting evidence in regard to the ability of METS to predict postoperative outcome, and further research is required. Biccard (2005) [35] reports that the ability to climb 2 flights of stairs (>4 METS) can predict postoperative outcome in thoracic surgery; however, this does not translate to predicting outcome in intra-abdominal surgery. Furthermore, Wiklund and colleagues [36] reported that METS did not predict cardiac complications in 5939 patients undergoing noncardiac surgery. METS may be able to predict outcome in thoracic surgery; however, their use in intra-abdominal surgery may be limited.

This is the first systematic review of the ability of field tests to predict postoperative outcome following intra-abdominal surgery. The strengths of this review include its adherence to the PRISMA guidelines, along with a detailed keyword search combined with a thorough abstract search giving 6 studies with a generally low risk of bias and a grand total of 561 patients.

A risk of bias assessment is important in systematic reviews of prognostic studies. Clinicians rely on prognostic tools to help inform decisions regarding patient care. Bias has the potential to distort results of prognostic studies and impede clinical decision making [23]. The QUIPS tool assesses bias in prognostic studies, allowing reviewers to objectively decide if bias could distort results [23]. Included studies were generally of low bias; many studies were given a moderate or high bias in the study confounding area. This was due to the difficulty of observational studies to control for all potential confounders.

Despite the strong search strategy and large number of patients involved, there was a small amount of studies identified. Included studies demonstrated varying methodology, adding to the heterogeneity between studies. A meta-analysis

Table 3 Field tests and postoperative outcomes

6MWT

Author	Surgery	Mortality	LOS	Morbidity
Arruda et al (2013)	Upper abdominal and thoracic surgery	N/A	N/A	Duration of follow-up: • In-hospital stay Morbidity measure: • Self-defined cardiopulmonary complications No exercise variable presented a significant correlation with complications in upper abdominal surgery. There was a significant correlation between complications in thoracic surgery and the 6MWT distance (P = .0062) and SCT time (P = .0012).
Lee et al (2013)	Colorectal surgery	N/A		Duration of follow-up: • 30 d Morbidity measure: • Clavien-Dindo 6 min vs Vo_2 peak, for each meter increase in distance, Vo_2 peak increased by 0.042 (95% CI = 0.035-0.050) mL/(kg min). Multivariate analysis: 6MWD and any complication; 0.51 (95% CI = 0.30-0.87, P = .012), 6MWD and medical complication; 0.49 (95% CI = 0.25-0.94, P = .033). No statistically significant correlation with surgical complication. Vo_2 peak and medical complication; 0.31 (95% CI = 0.13-0.71, P = .006). No statistically significant correlation with all or surgical complications.
Moriello et al (2008)	Colon resection	N/A	N/A	Duration of follow-up: • 6 wk Morbidity measure: • Self-defined complications No statistically significant difference in terms of 6MWT

				distance between the group with postoperative complications and the group without complications.
Paisani et al (2012)	Upper abdominal surgery	N/A	N/A	Duration of follow-up: • In-hospital stay Morbidity measure: • Self-defined PPCs PPCs group (6MWT distance = 466.0 ± 97.0 m) vs no PPCs group (6MWT distance = 485.3 ± 107.1); $P = .57$
ISWT				
Murray et al (2007)	Esophagogastrectomy	Duration of follow-up: • 30 d No patient who walked 350 m or more died within 30 d. No statistical analysis performed.	There was not a sufficient statistical analysis performed. Destination at 30 d (median): home; 540 m, ward; 445 m, critical care; 370 m	N/A
Nutt and Russell (2012)	Colorectal surgery	Duration of follow-up: • 30 d 1 Postoperative death (0.8%)	ISWT distance <250 m LOS was 14 d (IQR: 9-24) vs >250 m was 8 d (IQR: 6-10) $P < .0001$.	Duration of follow-up: • 30 d Patients suffering major complication mean distance 256.8 m (SD: 113.8) compared with patients without complication, mean distance 382.7 m (145.3). ROC curve analysis, ISWT distance cut point of 250 m, AUC = 0.74, 95% CI = 0.64-0.83, $P < .0001$, 88% specificity and 58% sensitivity
SCT				
Arruda et al (2013)	Upper abdominal and thoracic surgery	N/A	N/A	Duration of follow-up: • In-hospital stay Morbidity measure: • Self-defined cardiopulmonary complication There was no significant difference in time to complete SCT between patients who developed complications and those who did not post upper abdominal surgery ($P = .212$)

6MWD = 6-minute walk distance, CI = confidence interval, N/A = not applicable.

approach would have been unsuitable because of the small number of studies included and the significant heterogeneity between studies.

The studies included varied in their surgical intervention, outcome measure, and type of field test. Studies assessing morbidity used varying definitions of morbidity. Only 2 studies used the Clavien-Dindo classification score, an objective measure of morbidity [22,29,37]. Arruda et al (2013) [25] examined the incidence of self-defined cardiopulmonary complications, whereas Paisani et al (2012) [27] reported exclusively on the occurrence of PPCs. Moriello et al (2008) [26] did not report the method of measuring morbidity. It is difficult to assess the predictive ability of field tests between studies when different outcome measures are used. The use of objective measures such as the Postoperative Morbidity Survey [38] allows easy comparison between studies of the incidence of complications. Studies that use the Clavien-Dindo classification also allow clinicians to grade and compare the severity of postoperative morbidity [37].

4.2. Future research

The ISWT appears to be the superior test of predicting postoperative outcome; however, more studies are needed to define preoperative cut points which may help predict postoperative outcome. More studies are required to conclude on the use of the 6MWT to predict postoperative complications. When using the 6MWT, studies should follow the American Thoracic Society (2002) [12] guidelines to standardize the test and limit the effects of coaching [39]. The SCT requires further evaluation. It is well established in thoracic surgery and demonstrates high clinical utility; however, its use in abdominal surgery is limited perhaps because of its lower correlation with AT than ISWT.

Future studies should use the following points to allow for ease of comparison: (1) Postoperative time points should be similar between studies, such as 30-day, 90-day, and 1-year time points for mortality; LOS should include overall hospital stay, intensive care unit/high-dependency unit/critical care unit admission, and LOS along with readmission. (2) Morbidity should be measured using a combination of the Clavien-Dindo classification scoring system [37] and the Postoperative Morbidity Survey [38] (this allows for the measurement of pulmonary and cardiac complications along with other complications such as renal and infectious complications). If a future meta-analysis were to be performed, odds ratios should be performed for mortality and morbidity outcomes to allow results to be pooled, and LOS should be recorded with medians and standard deviations.

CPET is a superior method of predicting postoperative outcome following intra-abdominal surgery. The evidence behind field tests of exercise tolerance is weaker, and so future research is needed to justify their use. Field tests are cheaper, are easy to administer, and do not require specialist equipment or trained medical staff, unlike formal CPET. This review recommends that, in the absence of CPET, clinicians use the ISWT to predict postoperative outcome. As the ISWT is externally paced, patients are more likely to reach their maximal exercise tolerance as opposed to the 6MWT which is subject to patients regulating their physical activity. The SCT requires further research to justify its use in an abdominal surgery cohort. The 6MWT requires further studies to validate its use at predicting postoperative outcome because of the conflicting results of the studies in this review.

Separate article

Originally, a systematic review of CPET to predict postoperative outcome was performed combining CPET and field tests. Upon completion, it was deemed most appropriate to deal with CPET and field tests separately. The review entitled "Role of cardiopulmonary exercise testing as a risk assessment method in patients scheduled for intra-abdominal surgery: a systematic review" has been published in the *British Journal of Anesthesia*[4] (DOI: 10.1093/bja/aev454).

Author contributions

JM: conception, study design, data acquisition, analysis, drafting article, revision, and final approval. FW: study design, analysis, interpretation of data, drafting article, revision, and final approval. EG: data acquisition, analysis, drafting article, revision, and final approval. PMcC: study design, analysis, drafting article, critical revision of manuscript, and final approval. JH: conception, study design, revision, and final approval. JM: conception, study design, revision, and final approval.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jclinane.2016.09.019.

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The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis

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Background. *Preoperative physical fitness is predictive of postoperative outcome. Patients with lesser aerobic capacity are at greater risk of postoperative complications, longer hospital stays, and mortality. Prehabilitation may improve physical fitness, but it is unknown whether enhanced fitness translates to an improvement in postoperative outcome.*
Methods. *This systematic review and meta-analysis aimed to assess the ability of prehabilitation to influence postoperative outcome after intra-abdominal operations. Randomized controlled trials with at least 1 group undergoing a preoperative exercise intervention/prehabilitation were included. The following databases were searched: AMED, CINAHL, EMBASE, PubMed/Medline, and The Cochrane Library. Data extracted from 9 full-articles included author(s), population demographics, type of operation, postoperative measures of outcome, and type of treatment of the prehabilitation and control groups. Methodologic quality was assessed using GRADEpro, and the Cochrane risk of bias tool was used to measure study bias.*
Results. *Prehabilitation consisting of inspiratory muscle training, aerobic exercise, and/or resistance training can decrease all types of postoperative complications after intra-abdominal operations (odds ratio: 0.59, 95% confidence interval: 0.38–0.91,* P = *.03). It is unclear from our meta-analysis whether prehabilitation can decrease postoperative length of stay, because the number of studies that examined length of stay was small* (n = *4). No postoperative mortality was reported in any study, and conclusions could not be drawn on the ability of exercise to influence operative mortality. The methodologic quality of studies was, however, "very low."*
Conclusion. *Prehabilitation appears to be beneficial in decreasing the incidence of postoperative complications; however, more high-quality studies are needed to validate its use in the preoperative setting. (Surgery 2016;160:1189-201.)*

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Globally, an estimated 230 million operative procedures are performed annually.[1] Operative intervention carries substantial postoperative risk, and the number of patients undergoing elective operations is increasing.[2] After major abdominal operations, the overall, 30-day postoperative mortality averages 3.7% for all patients but varies with the operation.[3] Postoperative complications are more common than mortality with a rate of about 35% after an abdominal operation.[4] Postoperative morbidity is a substantial burden on health systems

and patients and can prolong hospital length of stay (LOS) and may lead to repeated hospital admissions, chronic ill health, and a decrease in functional capacity and quality of life.[5-8]

Physical fitness is an overall term encompassing aerobic capacity, muscular strength and endurance, body composition, and flexibility. Preoperative physical fitness (an individual's level of physical fitness prior to an operation) is predictive of postoperative outcome.[9-14] Optimizing preoperative physical fitness through prehabilitation may improve postoperative outcome and decrease ultimately the associated hospital costs of operative intervention and enhance patient quality of life. Prehabilitation is defined as the course of improving the functional capacity of an individual to withstand a stressful event.[15,16]

A previous review by Pouwels et al[4] concluded that preoperative exercise therapy may improve physical fitness of patients prior to a major abdominal operation. This review, however, concluded that the ability of prehabilitation to improve postoperative outcomes is unclear and that further randomized controlled trials (RCTs) are needed to determine its effect. Since the publication of Pouwels' review, the number of trials has increased; therefore, we not only updated this review, but we also completed a meta-analysis.

The primary objective of our work was to assess the ability of preoperative exercise therapy/prehabilitation to improve postoperative outcome (mortality, morbidity, and LOS). The secondary objectives were to assess the influence of prehabilitation on all postoperative complications compared with no intervention, to assess the ability of prehabilitation to influence postoperative pulmonary complications compared with control treatments, and to assess the ability of prehabilitation to influence preoperative physical fitness measured through aerobic capacity, muscular strength and endurance, and respiratory muscle strength.

METHODS

Patients scheduled for intra-abdominal operations undergoing prehabilitation were included in the study. We included RCTs examining exercise modalities, such as aerobic or strength training, including inspiratory muscle training aimed at increasing musculoskeletal, cardiovascular, or respiratory muscle function. All causes for operative intervention were included (eg, cancerous or inflammatory conditions). Patients undergoing any nonabdominal or orthopedic operations were excluded.

Intervention groups consisted of patients scheduled for major, noncardiopulmonary, intra-abdominal operations who received a preoperative exercise program. Patients scheduled for intra-abdominal operations who received standard treatment and no prehabilitation were considered a control group. Patients prescribed an exercise intervention with a lesser volume/intensity compared with the intervention group were also considered a control group. Incentive spirometry was considered a control treatment, because it has been reported not to influence postoperative outcome;[17] similarly, the exclusive use of breathing exercises and incentive spirometry was not considered an exercise intervention. Interventions prescribing pelvic floor exercises were also excluded. Usual care consisted of no specific prehabilitative treatment[18-21] or breathing exercises, such as diaphragmatic breathing, deep inspirations with incentive spirometry, coughing, and forced expiration techniques.[22]

The primary outcomes included (1) postoperative mortality: all-cause mortality in the postoperative period; (2) LOS: general LOS in hospital and intensive care unit (ICU)/critical care unit/high dependency unit and hospital readmission; and (3) morbidity: all postoperative complications, as defined by study authors (listed in Supplementary Table I, online version only) but preferably measured objectively using the Postoperative Morbidity Survey, Clavien-Dindo Classification Score, or the Comprehensive Classifications Index.

The databases CINAHL, AMED, PEDro, EMBASE, The Cochrane Library, and PubMed/MEDLINE were searched from April 2013 to August 2015. A search strategy was defined with all keywords and subject headings included (Online Appendix), and a search of relevant gray literature was performed. The abstracts from the annual European Anaesthesiology Congress (2004–2014), the Anaesthetic Research Society (2007–2015), the Society of Academic & Research Surgery (2012–2015), the Vascular Society (2005–2012), the International Anesthesia Research Society (2003–2015), the World Federation of Societies of Anaesthesiologists (2008–2012), and the American Society of Anesthesiologists (2000–2014) were reviewed for eligibility. A hand search of reference lists of the studies of interest was conducted to identify extra articles.

Two review authors (J. Moran and FW) selected trials for inclusion independently based on the titles, keywords, and abstracts (generated from the search strategy) to determine eligibility in terms of intervention, participants, and design. The full-text

versions of all relevant trials were retrieved. If a full-text version could not be retrieved, then the study was excluded due to the lack of a detailed methodology and the possibility of a high risk of bias.

Data extraction was performed independently by the lead author (J. Moran). All data were reviewed blindly by another author (FW). Extracted data included details of methods, operative interventions, exercise interventions, control group, and measures of outcome. The data extraction form was piloted on 2, randomly selected studies. After completion, the form was deemed appropriate for data extraction. Any disagreements were discussed; if a conclusion could not be reached after discussion, a third party was asked to intervene (JH).

Two review authors (J. Moran and FW) assessed the risk of bias in included studies independently, using The Cochrane Collaboration's "Risk of bias" tool.[23] Studies were graded for risk of bias in each of the following domains: sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessment), incomplete outcome data, selective outcome reporting, and other source of bias. Any disagreements were discussed; if a conclusion could not be reached, an independent third reviewer was asked to intervene (JH).

Measures of treatment effect. Dichotomous data were reported as odds ratios (ORs) and 95% confidence intervals (CIs). For continuous data, the mean difference and standard deviation with 95% CI were calculated using RevMan software (Version 5.3), (Review Manager (RevMan) Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Dealing with missing data. Authors were contacted via e-mail about missing data. All relevant data were reviewed.

Assessment of heterogeneity. Clinical heterogeneity was based on information from the participants of each study, interventions, and outcome measurements. Statistical heterogeneity was assessed by visual inspection of the overlap of the CI on the Forest plots and consideration of the χ^2 test ($P < .1$ was interpreted as significant heterogeneity) and the I^2 statistic. I^2 results were interpreted as follows: 0–40% might not be important, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity, and 75–100% may represent considerable heterogeneity.[24] The results of comparable groups were pooled using random-effects models.

Assessment of methodologic quality. The GRADEpro software (http://tech.cochrane.org/revman/other-resources/gradepro/download) was used to assess the methodologic quality of included studies (Fig 1). The GRADEpro highlights key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on important outcomes in a summary of findings table.

RESULTS

The database search was completed in August 2015. The search strategy yielded 906 articles including AMED (n = 24), CINAHL (n = 142), The Cochrane Library (n = 153), EMBASE (n = 325), and PubMed/MEDLINE (n = 262). Three additional articles were identified through searching conference abstracts, as well as 6 more articles by searching the reference lists of key studies.

Of these results, 204 duplicates were removed, and 687 articles were excluded based on title and abstract. Fifteen studies were excluded because they did not meet the inclusion criteria: 3 were not RCTs; 4 were excluded because participants had no operative intervention; 2 were excluded because there was no preoperative intervention; 3 abstracts were excluded because there was no full-text version available; 1 study was excluded because there was no postoperative follow-up; 1 study did not include participants undergoing a laparotomy incision of the abdomen; and 1 was a reanalysis of previously included data. Overall, a total of 9 studies met the inclusion criteria (Fig 2).

Included studies. *Participants.* A total of 435 operative patients were included. Operations included colorectal,[19,25,26] abdominal,[20-22] upper gastrointestinal,[27] hepatectomy,[28] and open bariatric operations.[18] The mean age of participants between groups ranged from 34.8–71.3 years. One study recruited women only.[18] The remaining 8 studies recruited men and women (Supplementary Table I).

Interventions. Exercise interventions consisted of a variety of methods, such as aerobic training, resistance training, inspiratory muscle training, or a combination of all. The frequency, intensity, time, and type of prehabilitative interventions were recorded (Supplementary Table I). Six studies compared exercise interventions with no treatment or usual care. Here, usual care consists of no treatment[18-21] or preoperative breathing exercises, such as deep breathing exercises, incentive spirometry, and forced expiration techniques.[22] Four studies compared prehabilitation with a lesser impact intervention group considered a control group. The lesser impact interventions consisted of walking,[25,26] endurance-based inspiratory muscle training,[27] and a diet-based intervention.[28]

Preoperative exercise in the prevention of postoperative morbidity

Patient or population: patients with postoperative morbidity
Settings:
Intervention: preoperative exercise

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Preoperative exercise**				
Morbidity	**Study population**		**OR 0.59** (0.38 to 0.91)	435 (9 studies)	⊕⊖⊖⊖ **very low**[1,2,3,4,5]	
	359 per 1000	**249 per 1000** (176 to 338)				
	Moderate					
	400 per 1000	**282 per 1000** (202 to 378)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias (Fig. 2).
[2] I^2=43%, p=0.02
[3] There was a wide variety of surgeries included
[4] Most studies had small sample sizes. Only Barbalho-Moulim et al. (2011) and Carli et al. (2010) performed sample size calculations
[5] Unable to detect publication bias due to small number of studies

Preoperative exercise to reduce postoperative length of stay

Patient or population: patients with to reduce postoperative length of stay

Settings:

Intervention: preoperative exercise

Preoperative exercise to decrease postoperative length of stay

Patient or population: patients with to reduce postoperative length of stay
Settings:
Intervention: preoperative exercise

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Preoperative exercise**				
Length of	The mean length of	The mean length		232	⊕⊖⊖⊖	

Stay Scale from: 0 to 45.	stay ranged across control groups from **2.1-21.6 Days**	of stay in the intervention groups was **1.6 lower** (7.6 lower to 4.3 higher)	(4 studies)	**very low**[1,2,3,4,5]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
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Very low quality: We are very uncertain about the estimate.

[1] Risk of bias (Fig. 2).
[2] I^2=53%, p=0.59
[3] There was a wide variety of surgeries included
[4] Most studies had small sample sizes. Only Barbalho-Moulim et al. (2011) and Carli et al. (2010) performed sample size calculations
[5] Unable to detect publication bias due to small number of studies

Fig 1. GRADEpro assessment of methodologic quality of included studies examining the ability of preoperative exercise interventions to decrease morbidity and length of stay. (Color version of this figure is available online.)

Included studies are described in detail in Supplementary Table I. Four studies prescribed inspiratory muscle training only in the preoperative period.[18,20,22,27] Two studies prescribed a combination of inspiratory muscle training and aerobic exercise.[21,26] Two studies prescribed a combined intervention of aerobic and resistance exercise.[19,25] One study prescribed a walking-based intervention.[28] Six studies delivered a mix of supervised and unsupervised programs.[18,21,22,25,26,28] Unsupervised sessions were expected to be completed at home. In 2 studies, participants were educated about the exercise protocol during the initial session and then completed the remaining sessions unsupervised.[19,20]

Outcomes. The primary outcome measures of the review were mortality, morbidity, and LOS. Only 1 study reported on postoperative mortality.[28] LOS was regarded as time of operation to discharge from hospital, LOS of ICU admission, and hospital readmission rates, and was assessed in 8 studies. Morbidity was assessed using the Clavien-Dindo Classification Score,[29] postoperative pulmonary complications by Kroenke et al,[30] and self-defined complications. Morbidity was measured in 9 studies.

Risk of bias in included studies. Risk of bias was assessed for all studies using the Cochrane "Risk of bias" tool (Fig 3).[23] Due to the nature of exercise interventions, it was difficult for studies to blind participants and personnel, which led to a high risk of bias in 6 studies. It was unclear if blinding was attempted in the remaining studies.

Allocation (selection bias). Allocation concealment was often "unclear," because many studies did not report if the envelopes used were opaque. The randomization process was unclear, because many studies did not report on the method of randomization. Three studies reported the method employed, of which 2 were a sufficient method (computer-generated randomization) deemed low risk. One study reported using an independent research assistant to stratify patients into 2 groups; this was deemed high risk.[22]

Blinding (performance bias and detection bias). Overall performance bias was high, because it is difficult to blind participants and personnel to exercise-based interventions. The risk of detection bias was less than performance bias, with 4 studies scoring a low risk of bias[19,22,26,27]; however, 3 studies scored unclear,[21,25,28] and 2 scored high.[18,20]

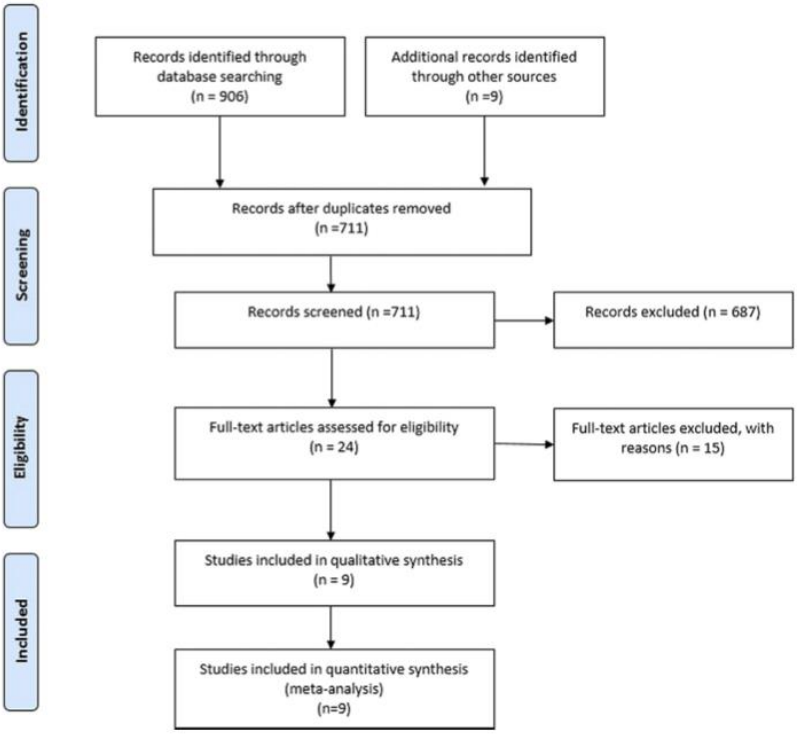


Fig 2. PRISMA flow diagram. (Color version of this figure is available online.)

Incomplete outcome data (attrition bias). Attrition bias was low generally, with 7 studies receiving a low risk of bias.

Selective reporting (reporting bias). Reporting bias was unclear mostly, because many trials did not report the protocols in which to check the original outcomes intended for study. One study scored a high risk of bias, because there were certain outcomes not presented in the articles.[28]

Other potential sources of bias. We were unclear if studies were free of potential sources of bias in 4 cases. Four studies scored a high risk, while only 1 study scored a low risk of bias. Potential sources of bias included significant differences in baseline between intervention and control groups[18,22,26] and walking interventions that were not well monitored.[21,25] One author had a royalty share in the Powerbreathe inspiratory muscle trainer, a device used by the intervention group.[20]

Morbidity. All included studies examined the impact of preoperative interventions on all postoperative complications and were included in the Forest plot (Fig 4). Prehabilitation was associated with a decrease in overall postoperative complications (OR: 0.59, 95% CI: 0.38–0.91, $P = .03$). Interventions consisted of a mixture of inspiratory muscle training, aerobic exercise, and resistance training. Control groups consisted of no treatment, breathing exercises, lower intensity inspiratory muscle training, and walking. Moderate heterogeneity existed between studies ($I^2 = 43\%$), and the level of evidence was very low, as measured using the GRADEpro.

Exercise versus usual care. Five of the 9 studies reviewed compared preoperative interventions to control groups receiving "usual care." Usual care consisted of no treatment[18-21] or standard preoperative breathing exercises, and exercise interventions consisted of inspiratory muscle training, walking, and aerobic and resistance exercise (Supplementary Table I).[22] In contrast, 3 studies included a control group, which received an exercise-based intervention. These exercise interventions prescribed lower intensity activities such as walking for 30 minutes a day and endurance-based, inspiratory muscle training (7 sessions of

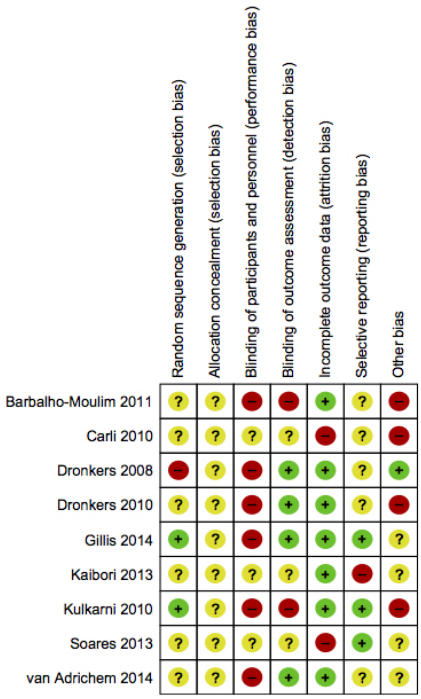


Fig 3. Risk of bias assessment. (Color version of this figure is available online.)

inspiratory muscle training at 30% maximal inspiratory pressure).[25-27] One study compared exercise with preoperative dietary advice.[28] Patients were reported to have a daily energy intake of 25–30 kcal/kg of body weight (BW) with a daily protein intake of 1.0–1.2 g/kg BW and a daily sodium intake of 5–7 g/kg BW. These studies were not considered usual care.

When studies were examined that compared prehabilitation with usual care only, there was a significant decrease in the number of postoperative complications in favor of prehabilitation (Fig 5). There was low heterogeneity between studies (I^2 = 5%). When compared with usual care only, exercise training had a much stronger effect on postoperative complications (OR: 0.35, 95% CI: 0.17–0.71; Fig 5) than when exercise interventions were compared with a mix of usual care and active control groups (OR: 0.59, 95% CI: 0.38–0.91; Fig 4).

Exercise and postoperative pulmonary complications. Six studies examined the effect of exercise training on the incidence of postoperative pulmonary complications only. All interventions were compared with a control group involving lower intensity training or usual care. Of these, 4 studies prescribed preoperative inspiratory muscle training only, while 2 studies prescribed multimodal interventions involving a combination of inspiratory muscle training, aerobic exercise, and resistance training of the lower limbs.[21,26] On meta-analysis, a significant decrease in postoperative pulmonary complications in favor of preoperative training (OR: 0.27, 95% CI: 0.13–0.57) was observed (Fig 6).

Exercise and other complications. Four studies measured all types of complications (eg, anastomotic leak and wound infection) and reported no significant difference between intervention and control groups. Two of these studies assessed complications with the Clavien-Dindo Classification Score,[19,25] while Kaibori et al[28] did not report how complications were measured. Dronkers et al[22] reported no difference between the intervention and control group in terms of self-defined complications (9 vs 8, P = .65).[22]

Gillis et al[19] had a control group who received no treatment, while 2 studies prescribed an exercise program with a lower volume/intensity for the control group as opposed to no treatment or usual care. This approach may have confounded results by increasing the physical fitness of the control group and decreasing the incidence of complications. Another potential reason for these studies not reporting a significant difference in all-cause complications is that the sample size calculations for these studies were not powered effectively. Carli et al[25] and Gillis et al[19] powered their sample sizes to detect differences in postoperative fitness instead of in postoperative complications, while Dronkers et al[26] performed a pilot study and did not provide a sample size calculation.

Length of stay. A total of 8 studies examined the influence of preoperative exercise therapy on general LOS. Of these, 4 studies were pooled for meta-analysis (Fig 7). Prehabilitation consisted of inspiratory muscle training and aerobic exercise and resistance training (Supplementary Table I). It was not possible to estimate the results by Barbalho-Moulim et al[18] due to the standard deviation of zero; therefore, only 3 studies were weighted in the meta-analysis. There were no significant differences in LOS between exercise and control groups (Mean: −1.62, 95% CI: −7.57, 4.33) (Fig 7).

Four studies were unable to be pooled in the meta-analysis, because LOS was non-normally distributed. Van Adrichem et al[27] reported that patients who completed high-intensity inspiratory muscle training (3 sessions a week of inspiratory muscle training at 60–80% maximal inspiratory pressure), as opposed to lower intensity,

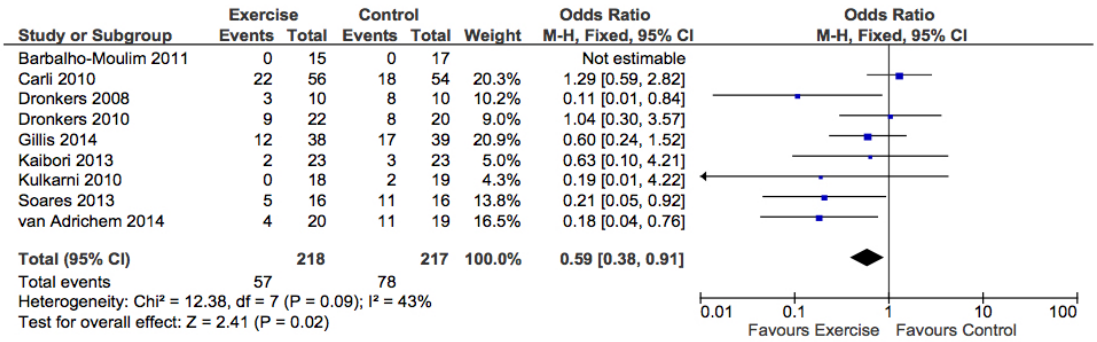


Fig 4. Exercise versus control: Morbidity. (Color version of this figure is available online.)

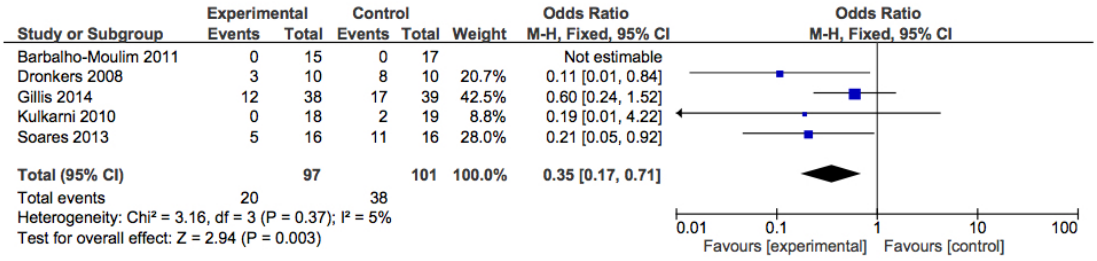


Fig 5. Exercise versus usual care: Morbidity. (Color version of this figure is available online.)

endurance-based inspiratory muscle training (7 sessions a week of inspiratory muscle training at 30% maximal inspiratory pressure), had a shorter LOS (13.5 vs 18 days, $P = .01$). Furthermore, the high-intensity inspiratory muscle training group showed a trend toward a shorter stay in the ICU (0.5 vs 1.5 days, $P = .07$). In contrast, Kulkarni et al,[20] Soares et al,[21] and Gillis et al[19] reported no difference in LOS between intervention and control groups. The exercise interventions prescribed in these 4 studies included inspiratory muscle training and aerobic exercise and resistance training (Supplementary Table I). The GRADEpro lists the methodologic quality of these studies as very low (Fig 1), and the overall risk of bias of these studies is presented in Fig 3. Gillis et al[19] reported there was no difference in readmission rates between the prehabilitation group and the control group (6 [15%] vs 5 [13%], respectively, $P = .780$). No other study reported readmission rates.

Mortality. There was no reported mortality in any of the studies reviewed, and therefore, this analysis was not completed.

Preoperative physical fitness. Due to the heterogeneity of data, a meta-analysis was deemed inappropriate to assess changes in preoperative physical fitness (Supplementary Table II, online version only). Two studies reported conflicting results in improvements in preoperative aerobic capacity as measured by the 6-minute walk test (distance). Gillis et al[19] reported a difference in the improvement of the 6-minute walk test (25.2 ± 50.2 m) in the intervention group compared to the deterioration in the control group (−16.4 ± 46.0 m, $P < .001$). In comparison, Carli et al[25] reported no changes in 6-minute walk test distance in the intervention group preoperatively (494.1 ± 15.5 m preintervention versus 502.8 ± 15.8 m postintervention, $P = .203$); however, there was a difference in VO_2peak (mL/min) measured by cardiopulmonary exercise testing in both the intervention (1,395 ± 76 versus 1,529 ± 88, $P = .003$) and the control groups (1,400 ± 71 versus 1,511 ± 84, $P = .007$) during a mean period of 40 days (SD: 30). Gillis et al[19] prescribed an exercise intervention with a median duration of 24.5 days (interquartile range [IQR]: 20–35); however, the authors did not report if there was an increase in VO_2peak. Dronkers et al[26] reported no differences in physical fitness measured by functional exercise tests, such as the timed up-and-go test and the chair rise time test in either the intervention or control groups.

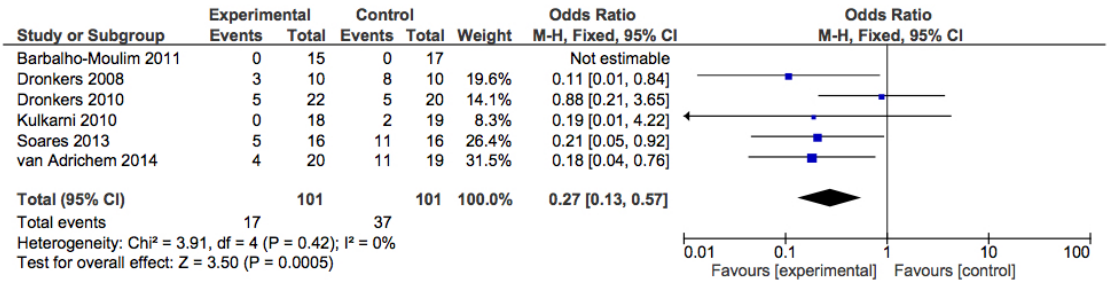


Fig 6. Exercise versus control: Postoperative pulmonary complications. (Color version of this figure is available online.)

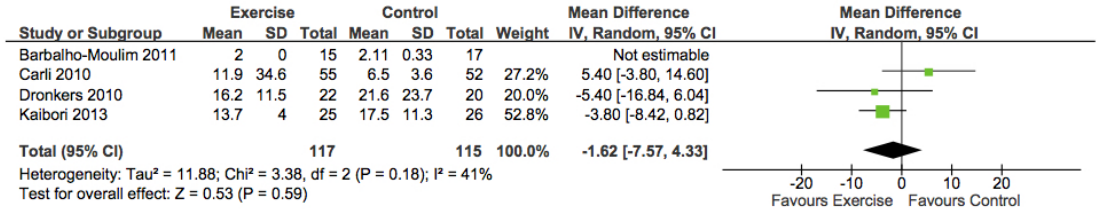


Fig 7. Exercise versus control: Length of stay. (Color version of this figure is available online.)

Dronkers et al[26] used a pedometer to monitor members of the control group who were advised to walk for a minimum of 30 minutes a day. This group reported no significant difference in the number of steps performed by the intervention (4,980 steps per day) and the control groups (5,003 steps per day). The walking intervention performed by Carli et al[25] was monitored poorly; patients were visited once at home and contacted via telephone weekly prior to the operation. In the walking group, VO_2peak increased (1,400–1,511 mL/min, $P = .007$), but there was no significant difference in VO_2peak between the bike/strengthening and walking/breathing group (1,529 mL/min versus 1,511 mL/min, respectively).

Five studies prescribed inspiratory muscle training to increase respiratory muscle strength as assessed by maximal inspiratory pressure. With the exception of Dronkers et al[26] who reported no change in postintervention, maximal inspiratory pressure, all studies reported improvements in maximal inspiratory pressure.[22] Three studies reported a significant difference in maximal inspiratory pressure between baseline and preoperation.[18,20,26] Soares et al[21] reported a nonsignificant improvement in maximal inspiratory pressure during the preoperative period in the intervention group (62 cmH_2O versus 88 cmH_2O $P > .05$); however, there was a difference in postintervention maximal inspiratory pressure between the intervention and the control groups (88 cmH_2O versus 64 cmH_2O, respectively, $P = .049$).

DISCUSSION

Prehabilitation consisting of inspiratory muscle training, aerobic exercise, and resistance training appears to decrease the incidence of all postoperative complications in patients undergoing intra-abdominal operations (OR: 0.59, 95% CI: 0.38–0.91). This effect was strongest when prehabilitation was compared with usual care or breathing exercises only (OR: 0.35, 95% CI: 0.17–0.71). Furthermore, prehabilitation significantly decreased the incidence of postoperative pulmonary complications (OR: 0.27, 95% CI: 0.13–0.57), which were measured as the primary complication of interest in the majority of studies reviewed.

Prehabilitation also significantly improved preoperative physical fitness as measured by inspiratory muscle strength, cardiopulmonary exercise testing, and functional exercise tests (Supplementary Table II). Prehabilitation did not influence postoperative LOS after an intra-abdominal operation; however, the number of studies contributing to the Forest plot was low ($n = 4$). Due to the low readmission rates and no reported mortality, this review cannot conclude if prehabilitation influences these important postoperative outcomes.

This review demonstrates that prehabilitation decreases the risk of postoperative complications;

however, this effect was strongest when examining postoperative pulmonary complications only. Preoperative inspiratory muscle training is an effective form of decreasing postoperative pulmonary complications[31]; however, it remains unclear whether the combination of inspiratory muscle training and aerobic and resistance exercise (n = 3) produces greater decreases in postoperative pulmonary complications compared with inspiratory muscle training alone (n = 3).

Three studies reported no effect of prehabilitation on medical or operative complications.[19,25,26] It is likely that exercise exerts a stronger effect on pulmonary and general medical complications than on operative complications, such as ileus, due to the effect of exercise on the oxygen transport pathway. The oxygen transport pathway is a series of integrated steps, including ventilation of the alveoli and pumping of the oxygenated blood by the heart to metabolically active tissue, designed to deliver oxygen to the necessary metabolic systems. Cardiopulmonary dysfunction arising from impairment of 1 or more steps in this pathway can be caused by intra-abdominal operations. Therefore, it is unlikely that exercise can influence operative complications, such as ileus, which can arise due to mechanical factors.[32]

Greater levels of physical fitness are associated with a decreased risk of postoperative complications, mortality, and increased LOS.[9-14] It is beyond the scope of this review to analyze the theories that contribute to the protective mechanism of increased fitness; however, these mechanisms are discussed comprehensively elsewhere.[9,33]

In 2 of the studies reviewed, control groups performing low intensity walking preoperatively for 30 minutes a day demonstrated greater postoperative outcomes compared with intervention groups consisting of aerobic exercise, resistance training, and/or inspiratory muscle training.[25,26] Walking is often prescribed preoperatively; however, its ability to increase aerobic capacity is not well reported.[34] For example, Englesbe et al[34] prescribed a preoperative walking program to 500 participants scheduled for various operative procedures with the goal of increasing walking distance. Levels of physical activity increased by 85%; however, it is unclear if this improved preoperative aerobic capacity. Walking can increase aerobic capacity,[35] and while the walking interventions in the studies included in this review were designed to serve as control groups; they may have acted as effective preoperative interventions, which may explain why the effect size generated by the Forest plot (Fig 4) decreased when compared with the Forest plot exercise versus usual care (Fig 5). The ability of walking interventions to increase fitness in the preoperative setting is underexplored and warrants further investigation.

The results of this meta-analysis do not suggest that prehabilitation influences LOS after intra-abdominal operations (P = .24). Theoretically, a decrease in overall postoperative complications may translate to a decrease in LOS, and even small decreases in LOS may translate to cost savings. Among the studies reviewed, a mean decrease of 1.6 days was observed (Fig 7). In the United States, the average cost of 1 inpatient day is $2,157,[36] and therefore, a mean decrease of 1.6 days would create a cost savings of $3,451.20 per intra-abdominal operative procedure.

Three studies in this review included patients undergoing neoadjuvant chemo(radio)therapy.[19,25,27] There were no differences in postoperative complication rates between patients who did or did not undergo neoadjuvant chemo(radio) therapy, and no adverse events were reported. Van Adrichem et al[27] delayed commencing prehabilitation by 1–2 weeks to allow for completion of neoadjuvant chemo(radio)therapy, while 2 studies did not report if prehabilitation was performed during or after neoadjuvant chemo(radio) therapy.[19,25]

Neoadjuvant chemo(radio)therapy often leads to some element of cardiopulmonary toxicity and decreases in aerobic capacity.[37] West et al[37] reported a mean decrease in aerobic capacity of 1.4 mL/kg/min (95% CI: −3.1, −1.0) after neoadjuvant chemo(radio)therapy in 25 patients scheduled for operations for rectal cancer, and therefore, the need for prehabilitation in cohorts receiving neoadjuvant therapies may be greater than for those treated with an operation alone. The studies in this review are consistent with current literature, and report that prehabilitation after neoadjuvant chemo(radio)therapy is safe and can increase aerobic capacity.[38]

Current standards in cancer care demand minimal delay between cancer diagnosis and commencement of treatment. As operative intervention/treatment is often the first line intervention in cancer treatment, this intervention poses a challenge to incorporating prehabilitation into the time-restricted clinical pathway. For example, the median time between colorectal diagnosis and an operation is 30 days (IQR: 18–42),[39] and the mean duration of prehabilitaion in the study by Carli et al[25] was 40 days (SD: 30).

The potential for interventions that achieve maximum results over short periods should be

explored. A recent meta-analysis concluded that interval training was more effective than continuous training at increasing both VO_2peak and anaerobic threshold (AT) ($P < .01$ each) and demonstrated a similar safety profile for moderate-intensity training.[40] A preoperative, supervised, high-intensity program of interval training may increase a patient's aerobic capacity prior to an operation within a short time frame. An easier alternative is a walking-based intervention, which can be performed by patients at home; however, this type of moderate-intensity exercise may not create the improvements necessary within a short time frame. The ability of these programs to improve aerobic fitness should be compared in future research.

Prehabilitation and programs of Enhanced Recovery After Surgery (ERAS) aim to minimize operative stress and complications; however, the 2 programs are not often combined.[41] Only 1 study in this review reported administering an ERAS program with prehabilitation, and a recent review found that the literature specific to ERAS and prehabilitation is limited.[19,42] ERAS preoperative management includes counseling, preoperative nutrition, and optimization of blood hemoglobin, and the potential to include exercise prehabilitation as part of ERAS to further decrease postoperative complications should be explored.

This review is unable to recommend a specific type of preoperative exercise therapy intervention that produces the greatest improvement in postoperative outcome; however, any exercise intervention consisting of inspiratory muscle training, aerobic, and/or resistance training is superior when compared with no treatment or breathing exercises (usual care). Further high-quality RCTs such as the PREPARE trial are needed to find the optimal frequency and intensity for these preoperative interventions for a range of operative procedures.[43] Clinicians looking to prescribe prehabilitation can prescribe the interventions included in this meta-analysis (Supplementary Table I).

Several aspects of the included studies may have influenced the results of this review. Two studies prescribed an exercise-based intervention as a control; therefore, the influence of the exercise-based intervention in the "control" groups may have protected against postoperative complications. The fitness of patients prior to intervention may have introduced bias to the results. Two studies reported that participants who consented may have been slightly more fit and healthier compared with the normal population[20,28]; however, Dronkers et al[26] reported participants were 60% less active compared with normative data.

Inconsistencies in the definitions of postoperative complications across the studies reviewed made comparison between studies challenging.[44] We suggest that future studies use a combination of the Clavien-Dindo classification scoring system, the Postoperative Morbidity Survey, and the Comprehensive Complications Index to measure objectively postoperative morbidity.[29,45,46] The methodologic quality of included studies was very low and driven largely by lack of blinding and ambiguity regarding allocation concealment. One of the limitations of exercise-based interventions is the inability to blind participants and personnel to the true intervention; however, sham inspiratory muscle training can be used in future research to blind participants and improve methodologic quality. The results of this meta-analysis should be considered with caution; however the meta-analysis shows that underpowered, pilot RCT's can produce favorable results toward exercise interventions.

In conclusion, prehabilitation can improve postoperative outcome by decreasing all-cause and pulmonary complications. The effect of prehabilitation is strongest when compared with no treatment or breathing exercises. The ability of prehabilitation to decrease postoperative mortality and LOS is inconclusive due to the low rate of mortality and the low number of studies reporting postoperative LOS. Although prehabilitation can decrease postoperative complications, the results of this meta-analysis should be considered with caution due to the relatively low methodologic quality of the included studies. Further RCTs are needed to validate the protective effects of prehabilitation.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2016.05.014.

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Letter to the Editors

Response to: Is prehabilitation limited to preoperative exercise?

To the Editors:

We thank Le Roy and Slim[1] for their letter and insightful comments suggesting that prehabilitation should not be limited to exercise and advocating that prehabilitation should encompass a multimodal treatment pathway, including preoperative nutrition and psychosocial support. We agree with Le Roy and Slim[1] that prehabilitation should be multimodal. Surgery is a complex intervention with substantial postoperative risk. Postoperative morbidity, mortality, and duration of stay vary depending on the operation, health status of the patient, and a number of other factors.[2]

To combat the multifactorial nature of poor postoperative outcome, preoperative interventions should be multimodal and targeted toward specific patient needs; however, prior to introducing a multimodal program, it is necessary to validate the impact of individual programs in an effort to optimize prehabilitation.

Le Roy and Slim[1] suggest that nutritional interventions should be included in prehabilitation, because malnutrition is present in up to 40% of patients with cancer and optimizing preoperative nutritional status may combat preoperative cachexia.[3] Despite the reported benefits of preoperative nutrition, numerous reviews have reported the evidence in support of the concept that nutritional intervention is lacking.[4,5]

Furthermore, in our meta-analysis, we included 9, randomized, controlled trials examining prehabilitation, and of those, only 1 study included preoperative nutrition.[6] Excluding this study from the analysis of the impact of prehabilitation on postoperative morbidity changed the results from (OR 0.49, 95% CI 0.26–0.94, $P = .03$) to (OR 0.44, 95% CI 0.20–1.00, $P = .05$). The combination of exercise and nutrition has an effect on postoperative outcome, however it is difficult to quantify the individual contributions within mutlimodal programs. Psychosocial interventions may also be implemented in the preoperative period, because they can improve certain psychologic outcomes (eg, depression) and quality of life; however, these interventions did not influence improving morbidity, mortality, or duration of stay.[7]

In comparison to nutrition and psychosocial interventions, considerable evidence support exercise as a key component of prehabilitation. Improved physical fitness is protective against poor postoperative outcome; however, the exact mechanisms for this interaction are not fully understood. It is likely that operative intervention increases oxygen demand, and those with greater levels of cardiorespiratory fitness are better able to meet this demand. Therefore, aerobic exercise interventions aimed at improving cardiorespiratory fitness are ideal.

Le Roy and Slim[1] also state that there is no formal consensus regarding the duration of prehabilitation and advocate a period of 6 to 8 weeks because compliance is poor in programs >3 months, and 2 to 4 weeks is insufficient. A period of 6 to 8 weeks would be unsuitable for the National Health Service (United Kingdom) because it aims to treat patients within 31 days from decision to treat.[8]

Prehabilitation presents clinicians with a difficult decision to delay operative intervention and allow for prehabilitation, which increases risk of cancer spread, or not performing prehabilitation and increasing the risk of a poor postoperative outcome. We consider that in the event that time is restricted, intensity may be increased to compensate. For example, high-intensity interval training may be used to address the cardiorespiratory component of prehabilitation, because it produces superior improvements in physical fitness compared to moderate intensity exercise.[9] Furthermore, a recent review reported that preoperative interventions lasting 2 to 4 weeks are fitting.[10]

In conclusion, although nutritional and psychosocial support are reported to be effective preoperative interventions, there is currently a lack of evidence to support this contention. Currently, the majority of the literature supports exercise as a key component of prehabilitation. A number of factors influence postoperative outcome, and prehabilitation should be aimed at addressing these specific needs; however, the effectiveness and optimal duration of unimodal interventions, such as exercise and nutrition, should first be validated prior to introducing multimodal interventions.

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B. Ethics approval

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Ph: 4142199 email: Ursula.Ryan1@amnch.ie

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Jonathan Moran
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29th July 2014

RE: Preoperative Physical Fitness in the Prevention of Post-operative Complications following Colorectal Surgery

REC Reference: 2014/04/Chairman (2) / 2014-07-List 27 (13)
(Please quote reference on all correspondence)

Dear Jonathan,

Thank you for your recent correspondence in which you sent in response to the Committee's request for clarifications in relation to the above referenced study.

The Chairman of the Committee has reviewed your response and has given ethical approval on behalf of the Committee.

The following documents was reviewed:

- Patient Information Leaflet & Consent Form

Full ethical approval is now in place for this study.

Yours sincerely

Ms. Ursula Ryan
Secretary, SJH/AMNCH Research Ethics Committee

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

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Mr. Jonathan Moran
School of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8.

4th February 2016

RE: High Intensity Interval Training in Patients Scheduled for Colorectal and Thoracic Surgery: A Feasibility Study

REC Reference: 2015/11/04/ 2016 List 7 (2)
(Please quote reference on all correspondence)

Dear Mr. Moran,

Thank you for your recent correspondence in which you responded to the conditions as requested by SJH/AMNCH Research Ethics Committee.

The Chairman of the Committee has reviewed this correspondence, is satisfied with the response and advises that full ethical approval is in place for this study.

The following documents were reviewed and approved:

- Cover Letter
- Standard Application Form
- Patient Information and Consent Form

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

NSV Code: WPA 00486

8.1 C. Participant information leaflets & consent forms

Participant Information Leaflet

Preoperative Physical Fitness in the Prevention of Post-operative Complications following Colorectal Surgery

What is the study about?

Following many types of surgeries, patients are at risk of developing post-operative complications which can lead to a delay in recovery and a longer hospital stay. Emerging research suggests that patients with a higher level of physical fitness are less likely to develop complications post-operatively. This study aims to assess a patient's level of physical fitness through a variety of measures prior to operation and monitor the development of post-operative complications after surgery.

Who is being asked to participate?

Men and women, over 18 years of age, diagnosed with colorectal cancer and scheduled for colorectal surgery are being offered the opportunity to participate in this study. Your surgeon is happy for the research team to contact you and has provided medical approval for you to complete the assessments involved in this study. All assessments are free of charge.

Who is not allowed to participate?

I understand that I am not eligible to participate if I have any of the following:

- Unable to give informed consent
- Recent myocardial infarction (within two days)
- Uncontrolled cardiac arrhythmias causing symptoms of hemodynamic instability
- Uncontrolled symptomatic heart failure
- Symptomatic severe aortic stenosis
- Suspected or known dissecting aneurysm
- Acute myocarditis or pericarditis
- Acute pulmonary embolus or pulmonary infarction
- Acute systemic infection, accompanied by fever, body aches or swollen lymph glands
- Unable to walk independently
- Emergency surgery

What do I have to do?

You would be required to attend the Welcome Trust – HRB Clinical Research Facility at St. James's Hospital in advance of the admission date for the planned surgery, for one appointment during which

your assessment will take place. The preoperative assessment will last approximately two hours thirty minutes. The postoperative assessment will last approximately fifteen minutes.

What assessments are involved?

Body Composition:

You will be asked to stand on a machine called a body composition analyzer. This machine will calculate your body mass index, which is an equation used to estimate the ideal weight for your height. In addition, the machine will provide details on your percentage body fat, your muscle mass and your total body water. The machine is painless and takes 30 seconds to complete the measurements.

In addition, we will measure your waist circumference and wait to hip ratio. This will measure the amount of weight you store on your stomach which is a factor to be considered in the development of post-operative complications.

Physical Activity:

We will measure physical activity in two ways. Firstly, the researcher will go through a questionnaire with you during your appointment. The questionnaire, called the Yale Physical Activity Survey, will ask you about your physical activity patterns in the past week.

You will be given an activity monitor to wear when you leave the centre, called the Actigraph GT3X. It is worn on the band of your trousers and you will be asked to wear it for one week. You will be provided with a stamped addressed envelope to post the monitor back to the study investigator.

Aerobic Capacity:

Your aerobic fitness will be tested by undertaking an exercise treadmill test. You will be given time to get familiar with walking on the treadmill before the test starts. The test will last 10-15 minutes. Your heart rate and blood pressure will be measured before the test starts and will be monitored throughout. You are free to stop the test at any time and the study investigator will be beside the treadmill for the duration of the test. The test will require you to initially walk at a slow pace and then every three minutes the gradient and then after the initial few stages the speed will increase.

The six minute walk test is a simple functional test. You will be asked to walk for a total of six minutes between two points on a 30 meter corridor. You will be required to cover as much distance within six minutes as possible. You are free to stop, sit down and rest and continue until the six minutes are up and you are able to stop and not continue during the test at any time. You will be asked to do this test in the preoperative session before surgery and once after surgery prior to discharge.

Lung Function Tests:

You will be asked to undertake a spiromtery test. A simple test which requires you to exhale forcefully into a machine three times to assess your lung function. You will be given proper instruction and time for questions before the test.

Inspiratory muscle strength will also be assessed by inhaling forcefully. A small device will be able to assess the strength of your diaphragm and inspiratory muscles by measuring your maximal inspiratory pressure. You will be asked to inhale maximally three times.

Grip Strength:

You will be asked to squeeze a hand-held dynamometer (pictured) three times, performing one hand at a time. The average result will be recorded. This is an effective method of measuring upper limb and overall strength.

What are the benefits to me?

You will receive feedback regarding all the assessments completed during the study from a chartered physiotherapist with a particular interest in cancer research. In addition, you will be invited to ask any questions you may have regarding physical activity and exercise guidelines.

What are the risks?

We do not anticipate adverse effects during the assessments. Occasionally, people can feel dizzy or breathless when doing an exercise test. However, because the exercise test is carefully graded, the risks of this happening are minimal. You will be required to complete a medical screening questionnaire prior to participation to assess suitability. The assessment will be conducted by a qualified physiotherapist with experience in all of the assessments outlined above. If any concerns are expressed, you will have the opportunity to be followed up by referral to the Physiotherapy Department or appropriate medical team for review. The practitioners involved in this study have current medical indemnity cover.



Will my information be confidential?

Your identity and data will remain confidential. Your name will not be published and will not be disclosed to anyone outside of the hospital. The medical team performing the study may need access to your patient records as part of this study, however all information will again remain confidential.

Compensation

The postgraduate research student who is conducting the assessment is a chartered physiotherapist and is covered by the Trinity College Dublin insurance scheme. Nothing in this document restricts or curtails your rights.

What if I change my mind?

If you volunteer to participate in this study, you may stop at any time. If you decide not to participate, or if you stop, you will not be penalised and will not give up any benefits which you had before entering the study.

Stopping the study

Your doctor or the investigator in this study may stop your participation at any time without your consent.

Compensation

Your doctors are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

Permission

This study has received Hospital Research Ethics committee approval.

I have more questions who will I ask?

Jonathan Moran, Lead Investigator

PhD Candidate,

Trinity Centre for Health Sciences

St. James's Hospital

Dublin 8

E-mail Address: moranj2@tcd.ie

Mobile Number: 0863063050

Consent Form

Preoperative Physical Fitness in the Prevention of Post-operative Complications following Colorectal Surgery:

This study and this consent form have been explained to me. The investigator has answered all my questions to my satisfaction.

I understand that I am to participate in this research study. I understand that I am to attend a testing session in the HRB – Welcome Trust Clinical Research Facility at St. James's Hospital in advance of the admission date for the planned surgery and a follow up session on day six after surgery or prior to discharge. I am aware that the first testing session will consist of a treadmill based exercise test, a body composition analysis, a physical activity questionnaire, a six minute walk test, a test of lung function and muscle strength; the second testing session will consist of a six minute walk test. I am happy to take home an activity monitor which I will wear for one week. I will post these items back to the study investigator in the stamped addressed envelope provided to me. I accept that the study will be following me up after my surgery. I agree to allow the investigator to track my progress post-operatively until either day 30 after the operation or discharge from hospital.

I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care being affected. I understand that access to my patient records may be required as part of the study and I grant permission to access my patient records if required. I agree to allow the investigator in this study to access my medical chart in order to record information that might be relevant to the study. I consent to the publication of data from this study and understand that my identity will remain confidential. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights

PARTICIPANT'S NAME:_____

PARTICIPANT'S SIGNATURE:_____

Date:_____

Date on which the participant was first furnished with this form:_____

Statement of investigator's responsibility

I have explained the nature, purpose, procedures, benefits, risks of or alternatives to this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's Signature:_____

Date:_____

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Patient Information Leaflet

Study Title: Preoperative High Intensity Interval Training in Patients Scheduled for Colorectal and Thoracic Surgery: The PHITT Trial

Study doctor:	Dr. Jeanne Moriarty
Site Address:	St. James's Hospital
Phone Number:	01 416 2516/8

This is a clinical study, a type of research study. Your study doctor and her research team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

1. Why is this study being done?

According to current research, physical fitness before surgery is protective against outcome after surgery. People with a certain level of aerobic fitness have a shorter stay in hospital less chance of complications and reduced risk of death. We are aiming to determine if a short term high intensity exercise programme can increase aerobic fitness in the two weeks leading to surgery. Current exercise programmes cannot improve fitness in the two weeks between diagnosis and surgery.

High intensity interval training has been shown to be as safe to perform as continuous moderate intensity exercise, however it produces greater improvements in fitness in smaller time frames. This study aims to assess the feasibility of such an exercise intervention prior to colorectal (surgery of the bowel) and thoracic (surgery of the lungs) surgery.

2. Why am I being asked to take part?

You are being asked to take part in this study because you have been scheduled for colorectal or thoracic surgery. Men and women, over 18 years of age and scheduled for surgery are being offered the opportunity to participate in this study.

3. Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time. You will be asked why you are withdrawing consent, however you are not required to give a reason. If you decide to leave the study, your future treatment and care will not be affected. Any information collected before you withdraw will be included in the study analysis.

4. How many people will take part in the study?

Approximately 20 people will take part in this study, in one study site, The Wellcome-Trust Clinical Research Facility, St. James's Hospital in Ireland.

The study will last approximately 5-6 months and your participation will last 2.5 weeks

5. What will happen to me if I take part?

You would be required to attend the Wellcome Trust – HRB Clinical Research Facility at St. James's Hospital in advance of the admission date for the planned surgery, for a number of sessions. Participants included in this study will attend 12 sessions.

The first session (1st):

Your first session will be to assess your baseline characteristics and fitness and introduce you to the exercise programme.

The intervention sessions (2nd-11th):

There will be a total of ten sessions. The intervention will of high intensity interval training on an exercise bike. Each session will consist of a warm-up, high intensity exercise and a cool-down. Sessions will last about 1 hour in duration.

The final session (12th):

The final session will be performed prior to surgery and will be a repeat of the first session.

Screening	*First Session*	*Exercise Sessions (2-11)*	*Last Session*	*Post-Surgery Assessment*
Explain the study	Explain testing procedure	Resting vitals, heart rate monitor set-up, warm-up	Reminder of testing procedure	Review of medical chart
Time for questions	Measurement of height, weight, body composition, waist and hip circumference	High intensity interval training	Measurement of height, weight, body composition, waist and hip circumference	Questions related to your recovery
Screen to see if you are eligible to take part	Spirometry and inspiratory muscle strength assessment	Cool down and resting vitals	Spirometry and inspiratory muscle strength assessment	
24 hours to give consent	Resting vitals, ECG and maximal exercise test		Resting vitals, ECG and maximal exercise test	

6. What will I have to do?

<u>Before you begin the study:</u>

You will be required to perform the following prior to the first and last session.

1. Avoid food **2** hours beforehand
2. Avoid caffeine **2** hours beforehand
3. Avoid smoking **8** hours beforehand
4. Avoid vigorous intensity exercise **24** hours beforehand
5. Wear comfortable shoes and clothes to exercise in

For the exercise sessions, (number 2-11) you will be required to:

1. Wear comfortable shoes and clothes to exercise in

<u>During the study:</u>

You will need to attend the clinical for all 12 of the study visits which will last between 45 minutes and 2 hours each. You will be required to complete the following assessments at two time points, the start and the end of the exercise intervention. All testing and interventions will be performed before surgery. In the post-op stage you will not be required to perform any exercise related tasks. One member of the research team will perform a follow-up on your recovery, this will include a review of your chart and questions related to your postoperative recovery.

Maximal Cardiopulmonary Exercise Test:

A maximal cardiopulmonary exercise test will assess how well the heart, lungs and muscles work both individually and together. The test requires participants to exercise on a stationary bike until exhaustion. You will be required to wear a face mask and have a pin prick blood test taken during the test. You will have your heart rate, breathing and blood pressure measured throughout the test. You will be monitored by a physiotherapist and doctor. The test will last approximately 6-10 minutes.



Lung Function Tests:

You will be asked to undertake a spirometry test, a simple test which requires you to exhale forcefully into a machine to assess your lung function. You will be given proper instruction and time for questions before the test.

Inspiratory muscle strength will also be assessed by inhaling forcefully. A small device (pictured) will be able to assess the strength of your diaphragm and inspiratory muscles by measuring your maximal inspiratory pressure.



Body Composition:

You will be asked to stand on a machine called a body composition analyzer. This machine (pictured) will calculate your body mass index, which is an equation used to estimate the ideal weight for your height. In addition, the machine will provide details on your percentage body fat, your muscle mass and your total body water. The machine is painless and takes 30 seconds to complete the measurements.



In addition, we will measure your waist circumference and wait to hip ratio using a measurement tape. This will measure the amount of weight you store on your stomach. You will also have your height, weight, and vital signs (heart rate, blood pressure, oxygen saturation) measured.

Exercise Sessions:

Following the first testing session you will be required to attend ten exercise sessions. The sessions will be performed 5 days a week, Monday to Friday for 2 weeks. Each session will consist of having your heart rate, blood pressure and oxygen saturation levels measured. You will then perform a warm-up by cycling on a stationary bike. Following the warm-up you will do a high-intensity exercise programme on the bike. You will perform maximal exercise for 15 seconds and then rest for 15 seconds. This pattern will repeat for up to 30 minutes or until you are tired. Each session should last 45 minutes to 1 hour.

If for any reason your surgery is delayed you will continue with the exercise programme. If surgery is delayed by one week or less you will continue with performing 5 sessions a week until the scheduled surgery date. In the unlikely event surgery is delayed by 1-2 weeks you will perform three sessions a week. In the extremely unlikely event surgery is delayed by more than 2 weeks you will perform 2 sessions a week.

Final Session:

The last session will be a repeat of the first session. You will perform a maximal cardiopulmonary exercise test, lung function tests and body composition analysis.

At the end of/After the study*:*

You will proceed to surgery. Following surgery a member of the research team will follow you up. This member of the team will take notes on your recovery including number of complications and length of stay. You will not be required to perform any measures following surgery. Upon completion of testing, a member of the research team will send you your results.

7. What are the benefits of taking part?

You will receive feedback regarding all the assessments completed during the study from a chartered physiotherapist with a particular interest in cancer research. In addition, you will be invited to ask any questions you may have regarding physical activity and exercise guidelines.

It is anticipated that this study will inform a much larger study aiming to help reduce postoperative complications and improve surgical participant's outcome.

8. What are the risks of taking part?

We do not anticipate adverse effects during the assessments or exercise sessions. You will have your blood lactate assessed via a pin prick assessment. This may cause slight pain but there will be no lasting harm and will only take a moment. This blood sample is minimal and will not be stored.

Occasionally, people can feel dizzy or breathless when doing an exercise test. However, because the exercise test is carefully graded and monitored by a physiotherapist and doctor, the risks of this happening are minimal. You will be cleared by your consultant to participate in this programme. The assessment will be conducted by a qualified physiotherapist and doctor with experience in all of the assessments outlined above. If any concerns are expressed, you will have the opportunity to be followed up by referral to the Physiotherapy Department or appropriate medical team for review. The practitioners involved in this study have current medical indemnity cover.

9. Do I have other treatment choices?

Your doctor will discuss other treatment options with you and will explain the advantages and disadvantages of the different treatments.

10. Will I receive payment for being part of this study?

We will reimburse you for the cost of travelling to your study visits. You may receive up to €5 per visit for travel.

11. What happens if I get hurt taking part in this study?

The Clinical Research Facility where all sessions will be performed have trained medical professionals on site. In the case of an emergency during an exercise assessment or class the hospital emergency response crash team will be contacted. In the event of a participant becoming unwell during an exercise assessment or class they will be evaluated by a doctor and treated appropriately.

All participants and professional working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact Jonathan Moran. Contact details are listed at the end of this document.

12. Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with Trinity College Dublin. Any information that identifies you (such as your name and address) will not be shared with Trinity College Dublin. Your study data will be identified with a code number, which will not include your name or other information that directly identifies you.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine if this exercise intervention can be used prior to surgery to help improve outcome. This can include reducing the amount of complications, hospital length of stay and the risk of mortality.

Your information will be kept on file for up to 5 years and will be destroyed securely after that time.

The results of the study may be used in presentations or published in scientific reports. You will not be identified in any presentation or publication.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin, external auditors or

inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

13. What happens if new information becomes available during the study?

Sometimes, during the course of a study, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it, and discuss with you whether you want to continue in the study.

If you decide to stop taking part in the study, your doctor will advise on the most suitable treatment for you.

If you decide to continue in the study, you will be asked to sign a new consent form.

On receiving new information, your study document might consider it best to take you out of the study. He or she will explain the reasons to you and arrange for your care to continue.

If the study is stopped for any reason, you will be told why and your continued care will be arranged.

14. Who should I contact if I have any questions?

If you have any more questions about this study, at any time, you can contact the lead investigator, Jonathan Moran, Monday – Friday 9:00 am to 5:00 pm.

Telephone: 01-8963613

Email: moranj2@tcd.ie

15. Has this study been approved?

Yes, this study has been reviewed and approved by the Tallaght Hospital/St James's Hospital Joint Research Ethics Committee ethics committee.

ST. JAMES'S HOSPITAL
Ospidéal Naomh Séamas, Sráid Shéamais, Baile Átha Cliath 8.
St. James's Hospital, James's Street, Dublin 8.
+ 353 1 410 3000 www.stjames.ie

Consent Form

Study Title: Preoperative High Intensity Interval Training in Patients Scheduled for Colorectal and Thoracic Surgery: The PHITT Trial

Study doctor:	Dr. Jeanne Moriarty
Site Address:	St. James's Hospital
Phone Number:	01 416 2516/8
Subject Number:	

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

1. I have read and understood the Patient Information Leaflet, Version 01, dated 24/11/2015. I have had time to consider it and the opportunity to ask questions.	☐
2. I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise.	☐
3. I understand that my medical records may be looked at by authorised personnel from Trinity College Dublin, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study.	☐
4. I understand what will happen to my blood/tissue samples.	☐
5. I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name.	☐
6. I agree to take part in this study	☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*

Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

9

D. PHIIT feedback questionnaire

Feedback Questionnaire

Study Title: High Intensity Interval Training in Patients Scheduled for Colorectal and Thoracic Surgery: A Feasibility Study

1. How would you rate the programme? Please tick the appropriate circle

Poor	Fair	Good	Great	Excellent
○	○	○	○	○

2. How many sessions do you think is appropriate? Please tick the appropriate circle

5 or less	6-9	10	11-14	15 or more
○	○	○	○	○

3. Was it convenient to attend the scheduled sessions? Please tick the appropriate circle

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

4. Would you change anything about the programme? Please specify

5. What did you enjoy about the programme?

6. What did you not enjoy about the programme?

7. Was the information clearly presented before starting the intervention? Please tick the appropriate circle

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

8. Were the investigators helpful? Please tick the appropriate circle

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

9. Did the intervention help prepare you for surgery? Please tick the appropriate circle

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

10. Did you feel safe throughout the intervention? Please tick the appropriate circle

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

11. Was there anything you wanted/required during the study that we should provide to people in future?

12. Do you have any other comments?

Thank you for taking part in the study and completing the questionnaire

E. Registered study protocols

PROSPERO Records

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Role of cardiopulmonary exercise testing as a risk assessment method in intra-abdominal surgery: a systematic review

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
19/05/2014

4 Anticipated completion date
Give the date by which the review is expected to be completed.
12/01/2015

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Jonathan Moran

7 Named contact email
Enter the electronic mail address of the named contact.
moranj2@tcd.ie

8 Named contact address
Enter the full postal address for the named contact.
School of Physiotherapy, Trinity Center for Health Sciences, Dublin 8, Co. Dublin, Ireland

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
353863063050

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Trinity College Dublin

Website address:
www.tcd.ie

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mr	Jonathan	Moran	Trinity College Dublin
Dr	Juliette	Hussey	Trinity College Dublin
Dr	Fiona	Wilson	Trinity College Dublin

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
All management and financial aspects of this review will be supported by the School of Physiotherapy, Trinity College Dublin.

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
To assess the value of cardiopulmonary exercise testing in predicting the perioperative morbidity and mortality associated with non-cardiopulmonary thoraco-abdominal surgery.

To review and contrast cardiopulmonary measurements, such as Anaerobic Threshold, VO2 max and VO2/work rate slope, to find the most accurate measure of aerobic fitness in calculating perioperative risk prior to non-cardiopulmonary thoraco-abdominal surgery.

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
The databases CINAHL, AMED, PEDro, EMBASE, The Cochrane Library and PubMed. A search strategy has been defined with all keywords and subject headings included.. All articles are to be in the English language and must assess the value of cardiopulmonary exercise testing as a preoperative risk assessment tool in non-cardiopulmonary thoraco-abdominal surgery. The articles must measure preoperative aerobic fitness through cardiopulmonary exercise testing and compare those levels with postoperative mortality and defined morbidity. Articles will be excluded if surgery is non-thoraco abdominal surgery e.g. orthopaedic or cardiopulmonary surgery.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Patients undergoing non-cardiopulmonary thoraco-abdominal surgery will be assessed. All causes for surgical intervention will be included.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Patients undergoing non-cardiopulmonary thoraco-abdominal surgery will be assessed. All causes for surgical intervention will be included e.g. tumour resection and inflammatory disease. Participants of all ages above 18 years.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Articles reviewed must involve human patients scheduled for major non-cardiopulmonary thoraco-abdominal surgery undergoing a preoperative cardiopulmonary exercise test and use an objective measure such as VO2, distance or anaerobic threshold. Following surgery all peri- and post-operative morbidity and mortality must be recorded using an objective measure such as the Clavien Dindo Classification or Postoperative Morbidity Index. . Any articles containing patients undergoing non thoraco-abdominal surgery will be excluded.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Aerobic fitness as measured by cardiopulmonary exercise testing (using measures such as, Anaerobic Threshold, VO2, or distance etc.) to assess its value in predictive postoperative morbidity and mortality

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Included studies will be observational. Systematic reviews, meta-analyses, case studies and letters to the editor will be excluded. Articles including a preoperative cardiopulmonary exercise performed by patients scheduled for non-cardiopulmonary thoraco-abdominal surgery will be included. These studies must also measure peri- and postoperative mortality and morbidity. Any articles containing non thoraco-abdominal surgery will be excluded.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)

Give the most important outcomes.

Morbidity (as measured by the Clavien-Dindo Classification of Surgical Complications or Postoperative Morbidity Index and mortality in the postoperative period. Aerobic fitness as measured by an objective cardiopulmonary exercise test using suitable measures such as Anaerobic Threshold, VO2 or distance

Give information on timing and effect measures, as appropriate.

Morbidity and mortality must be measured in the postoperative period until time to discharge or beyond.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

None

Give information on timing and effect measures, as appropriate.

26 Data extraction (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

To determine the risk of bias two investigators will use the RTI item bank and the Newcastle-Ottawa scale on all included articles. If any disagreements arise between the review authors a third review author will be asked to resolve the situation.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
We will provide a narrative (descriptive) synthesis of the findings from the included studies, structured around the type of surgery, the year undertaken, country of origin, cardiopulmonary exercise test design, total number of recruited patients, aerobic fitness measurement, outcome measures, study results and findings. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes).

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned.

Review general information

30 Type and method of review
Select the type of review and the review method from the drop down list.
Prognostic, Systematic review

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Ireland

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.
Not applicable.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)

Preoperative

Cardiopulmonary

Exercise

Testing

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
The role of preoperative exercise therapy in intra-abdominal surgery: a systematic review

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
20/05/2015

4 Anticipated completion date
Give the date by which the review is expected to be completed.
30/09/2015

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started √

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Mr Moran

7 Named contact email
Enter the electronic mail address of the named contact.
moranj2@tcd.ie

8 Named contact address
Enter the full postal address for the named contact.
Department of Physiotherapy, School of Medicine, Trinity Centre for Health Sciences, St. James's Hospital, Dublin 8, Co. Dublin

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
353863063050

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Trinity College Dublin

Website address:
www.tcd.ie

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mr	Jonathan	Moran	Trinity College Dublin
Dr	Fiona	Wilson	Trinity College Dublin
Dr	Juliette	Hussey	Trinity College Dublin
Dr	Emer	Guinan	Trinity College Dublin
Dr	Paul	McCormick	St. James's Hospital
Dr	Jeanne	Moriarty	St. James's Hospital

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

All management and financial aspects of this review will be supported by the School of Physiotherapy, Trinity College Dublin.

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

Assess the ability of preoperative exercise therapy to improve postoperative outcome (mortality, morbidity and length of stay)

Find the preoperative exercise therapy intervention that produces the greatest improvement in postoperative outcome

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The databases CINAHL, AMED, PEDro, EMBASE, The Cochrane Library and PubMed. A search strategy has been defined with all keywords and subject headings included. All articles are to be in the English language. Included articles must be randomised controlled trials comparing a preoperative exercise intervention to a control treatment. All studies should be performed on an abdominal surgical cohort and measure postoperative mortality, morbidity or length of stay. Any non-randomised controlled trial will be excluded along with any cardiopulmonary, paediatric, head and neck, orthopaedic, spinal surgery or transfusion procedure.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Patients undergoing non-cardiopulmonary intra-abdominal surgery will be assessed. All causes for surgical intervention will be included.

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Patients undergoing non-cardiopulmonary intra-abdominal surgery will be assessed. All causes for surgical intervention will be included e.g. tumour resection and inflammatory disease. Participants of all ages above 18 years.

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Articles reviewed must involve human patients scheduled for major non-cardiopulmonary intra-abdominal surgery who receive a preoperative exercise programme will be the intervention group. Exercise intervention may consist of a variety of methods such as aerobic, resistance or a combination. Breathing exercises only will not be considered an intervention.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Patients going for non-cardiopulmonary intra-abdominal surgery who do not receive a preoperative exercise intervention and receive standard treatment. Breathing exercises only will be considered a control.

22 Types of study to be included
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Only Randomised Controlled Trials (RCT's) with one group receiving a preoperative exercise intervention will be included. All other study types will be excluded from analysis.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)
Give the most important outcomes.
At least one of the following outcomes will be required for inclusion: Postoperative Mortality (all cause), postoperative morbidity (complications) postoperative length of stay (overall length of stay, ICU/CCU/HDU admission and length of stay and hospital readmission).

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
None

Give information on timing and effect measures, as appropriate.

26 Data extraction (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Two reviewers (JM and FW) will review all articles using a standardised data extraction form. Data extracted will include: author, population demographics, study setting, surgery type, postoperative outcome measure and preoperative exercise intervention. Any differences will be resolved through discussion. If a conclusion cannot be reached, a third independent reviewer will be asked to intervene (JH).

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
The risk of bias will be assessed using the Cochrane Risk of Bias tool and PEDro scale. Two reviewers (JM and FW) will independently assess each study using the aforementioned tools. If any disagreements cannot be resolved through discussion a third reviewer will be asked to intervene (JH).

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
We will provide a quantitative synthesis of the findings from the included studies, structured around the type of surgery, the year undertaken, country of origin, preoperative exercise intervention, total number of recruited patients, aerobic fitness measurement, outcome measures, study results and findings. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes).

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
Sub-groups will be divided based on the type of surgical intervention based on site e.g. hepatic and colorectal.

Review general information

30 Type and method of review
Select the type of review and the review method from the drop down list.
Intervention, Prevention, Systematic review

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Ireland

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.
Not applicable

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
The manuscript will be written and published in a suitable journal. The abstract will be submitted to a conference.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
Preoperative

exercise

postoperative

outcome

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

ClinicalTrials.gov Registration

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: May 17, 2017

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Study Identification

Unique Protocol ID:	CRFSJ0086
Brief Title:	Preoperative High Intensity Interval Training: The PHIIT Trial
Official Title:	Preoperative High Intensity Interval Training in Patients Scheduled for Colorectal and Thoracic Surgery: The PHIIT Trial
Secondary IDs:	

Study Status

Record Verification:	May 2017
Overall Status:	Completed
Study Start:	February 2016 []
Primary Completion:	December 2016 [Actual]
Study Completion:	December 2016 [Actual]

Sponsor/Collaborators

Sponsor:	University of Dublin, Trinity College
Responsible Party:	Principal Investigator Investigator: Jonathan Moran [jmoran] Official Title: Mr Affiliation: University of Dublin, Trinity College
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 2015/11/04 2016 List 7 (2) Board Name: AMNCH/St. James's Hospital Joint Research Ethics Committee Board Affiliation: AMNCH/St. James's Hospital Phone: 14142199 Email: claire.hartin@amnch.ie Address: Research and Ethics Dept.

	Tallaght Hospital Tallaght Dublin 24
Data Monitoring:	
Plan to Share IPD:	
FDA Regulated Intervention:	No

Study Description

Brief Summary:	Colorectal and thoracic surgical patients are susceptible to poor postoperative outcome including complications, mortality and increased length of stay. Preoperative physical fitness is protective against poor postoperative outcome in intra-abdominal and thoracic surgery. The current colorectal/thoracic pathway from diagnosis to surgery is about 2 weeks and therefore interventions of longer duration are not feasible. Clinicians may be presented with a difficult choice in delaying surgery to perform prehab or cancel the pre-op intervention. To create greater improvements in aerobic fitness, participants are required to exercise at high levels of VO2peak (e.g. ≥80% VO2peak). High intensity interval training (HIIT) requires participants to exercise at high levels of VO2peak (≥80% VO2peak) for short periods (e.g. 15 seconds) followed by a recovery (active or passive) and typically continue this pattern for 30 minutes or until exhaustion. HIIT programmes are safe and a recent meta-analysis noted that HIIT produced a more pronounced incremental gain in participants' mean VO2peak when compared with continuous moderate intensity exercise (+1.78mL/kg/min, 95% CI: 0.45-3.11). HITT has not been investigated as a preoperative intervention to either optimize fitness prior to surgery or reduce post-surgical complications. Preoperative HIIT is an intense intervention which will require significant participant adherence. The safety, cost and clinical application of such a programme needs to be performed. This feasibility study aims to assess the ability of HIIT to improve aerobic fitness two weeks prior to surgery and determine its feasibility.
Detailed Description:	Colorectal and thoracic surgical patients are susceptible to poor postoperative outcome. In colorectal surgery the rate of post-op complications is between 15-20% and the rate of 30 day mortality is 2.3%. Thoracic surgery also carries significant risk, 30 day mortality is 2.2% while the rate of post-op complications is 29.3%. Poor postoperative outcome significantly affects the patients recovery and increases hospital costs. Reducing postoperative risk therefore conveys significant benefit to the patient and the hospital. Preoperative physical fitness is predictive of postoperative outcome in intra-abdominal and thoracic surgery. In a systematic review of 6 studies preoperative exercise interventions improved pre-op physical fitness in patients undergoing abdominal surgery, however it is unclear if this translates into an improvement in postoperative outcome. An updated systematic review and meta-analysis was performed on the effects of pre-habilitation on postoperative outcome. While the results demonstrated that preoperative exercise interventions of 4-6 week duration reduced post-op complications a significant amount of work is still to be performed in this area. The current colorectal/thoracic pathway from diagnosis to surgery is about 2 weeks and therefore interventions of longer duration are not feasible. Clinicians may be presented with a difficult choice in delaying surgery to perform prehab or cancel the pre-op intervention.

To create greater improvements in aerobic fitness, participants are required to exercise at high levels of VO2peak (e.g. ≥80% VO2peak). High intensity interval training (HIIT) requires participants to exercise at high levels of VO2peak (≥80% VO2peak). Participants exercise for short periods (15 seconds) followed by 15 seconds of rest and typically continue this pattern for 30 minutes or until exhaustion.

A recent review reported HIIT programmes to be safe in individuals with coronary artery disease and stable heart failure. In agreement with this paper a recent meta-analysis noted that HIIT produced a more pronounced incremental gain in participants' mean VO2peak when compared with continuous moderate intensity exercise There are a number of factors to take into account when designing a HIIT programme e.g. duration and intensity of exercise phase and type of recovery period (active vs. passive). Two papers compared a selection of HIIT protocols for safety and time at a high percentage of VO2peak (≥ 80% VO2peak). Protocols with rest periods (passive recovery) allowed patients to exercise for longer and had lower perceived difficulties. In one study of 20 patients with CAD, HITT was prescribed with 15s exercise and passive recovery intervals at 100% Peak Power Output (PPO) or Maximal Aerobic Power (MAP) with no adverse events. PPO or MAP is the power of the last completed stage during a maximal exercise test (watts). This intervention had the highest duration above 80% VO2peak (819s) and a high completion rate of 63%. This protocol was chosen for this study.

HITT has not been investigated as a preoperative intervention to either optimize fitness prior to surgery or reduce postsurgical complications. Preoperative HIIT is an intense intervention which will require significant participant adherence. The safety, cost and clinical application of such a programme needs to be performed. This feasibility study aims to assess the ability of HIIT to improve aerobic fitness two weeks prior to surgery and determine its feasibility.

Conditions

Conditions:	Colorectal Neoplasms Lung Neoplasms
Keywords:	Exercise Preoperative High Intensity Interval Training Colorectal Thoracic Postoperative

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	N/A
Interventional Study Model:	Single Group Assignment
Number of Arms:	1
Masking:	No masking
Allocation:	N/A
Enrollment:	20 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Intervention Patients within this arm will perform two weeks of high intensity interval training prior to colorectal/thoracic surgery. Exercise intensity will be 100% of the peak power output (PPO) during maximal cardiopulmonary exercise testing. Patients will exercise for 15 seconds at 100% PPO and rest for 15 seconds (passive) for 30 minutes or until exhaustion. This will be performed 5 days a week for 2 weeks.	High Intensity Interval Training Exercise programme High intensity interval training (HIIT) requires participants to exercise at high levels of VO2peak (≥80% VO2peak). Participants exercise for short periods (e.g. 15-30 seconds) followed by periods of rest (active or passive) and typically continue this pattern for a set time period or until exhaustion. Other Names: • HIIT

Outcome Measures

Primary Outcome Measure:

1. Cost
   The cost of the programme will be recorded. Expected costs include, parking, room rental charges, equipment rates, employee rates.

   [Time Frame: 6 months]

2. Adherence/Compliance
   The adherence rates will be measured by recording the number of appointments each participant attends.

   The number of missed sessions per participant and the reasons for missing sessions will be recorded and reported. If a participant misses an exercise sessions they will be contacted by the research team to determine the reason and to reschedule the class for later that day if possible. If a participant misses more than 50% of total exercise sessions in the absence of a defined reason (acute illness or scheduled holiday), it will be recorded as a protocol violation.

   [Time Frame: 6 months]

3. Incidence of Adverse Events
   Adverse events will be assessed at every clinic visit and the following details recorded: type, incidence, severity, timing, seriousness, and relatedness to a) disease and b) the intervention.

   [Time Frame: 6 months]

4. Satisfaction/Acceptability
   Self-administered questionnaire on completion of programme will be administered. Participants will also be asked to highlight what they liked and didn't like about the programme and any suggestions for change.

   [Time Frame: 6 months]

5. Withdrawal of participants
   Participants are free to withdraw from the trial at any stage without providing a reason and without consequence. This information will be stated in the participant information leaflet. Participants can inform the research team at their local site of their decision to withdraw. If a participant withdraws from the study, any data collected on them up to that point in the study will go forward for study analysis. This information will be stated in the participant information leaflet. If a participant withdraws from the intervention, but provides consent to complete subsequent follow-up measurements they will continue to attend study assessments and data will be used for intention-to-treat analysis. Participants will be asked for their reason to withdrawing consent, participants are not required to give a reason. Reasons for stopping the intervention will be recorded and reported

   [Time Frame: 6 months]

6. Protocol deviations/Adaptations
   The following deviations will be recorded and reported.

   • Changes to exercise protocol (e.g. reduction in number of sessions, change in % PPO performed during exercise session)

   [Time Frame: 6 months]

7. Compliance
   Compliance will be measured in the percentage of exercise sessions attended and successfully completed.

   [Time Frame: 6 months]

Secondary Outcome Measure:

8. Postoperative mortality
   Postoperative mortality will be recorded until day 30 post-op.

   [Time Frame: Up to day 30 post-op]

9. Changes in Aerobic Capacity
   Participants will perform a maximal CPET prior to beginning of intervention to establish baseline aerobic fitness. Upon completion of the intervention, prior to surgery, participants will repeat the maximal CPET.

   [Time Frame: 6 months]

10. Length of stay
    Length of stay will include general hospital stay from time of operation to discharge, ICU/HDU admission rates and length of stay as well as readmission rates.

    [Time Frame: 6 months]

11. Postoperative complications assessed using the Postoperative Morbidity Survey
    Postoperative morbidity will be assessed using the postoperative morbidity survey (POMS) (type and number of complications on a specific day). POMS will be performed on Day 3, 5, 6 and 7.

    [Time Frame: Up to 7 days post-op]

12. Readmission rates
    The amount of readmission's to hospital due to surgery related reasons.

    [Time Frame: 6 months]

13. ICU/HDU admission rates
    The amount of admissions to the Intensive Care Unit/High Dependency Unit due to surgery related reasons

    [Time Frame: 6 months]

14. ICU/HDU length of stay
    The amount of time (recorded in days) a patient spends in ICU/HDU due to surgery

    [Time Frame: 6 months]

15. Clavien-Dindo Classification Sore
    The most severe complication experienced by a patient will be assessed and recorded using the Clavien-Dindo Classification Score

    [Time Frame: 6 months]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria:

1. Patients scheduled for colorectal or thoracic surgery
2. Able to give informed consent
3. Ability to understand English

Exclusion Criteria:

- Acute myocardial infarction
- Unstable angina
- Uncontrolled arrhythmias causing symptoms or hemodynamic compromise
- Syncope
- Active endocarditis
- Symptomatic severe aortic stenosis
- Uncontrolled heart failure
- Acute pulmonary embolous or pulmonary infarction
- Thrombosis of lower extremities
- Suspected dissecting aneurysm
- Uncontrolled asthma
- Pulmonary edema
- Room air desaturation at rest ≤85%
- Respiratory failure
- Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)
- Cognitive impairment leading to inability to cooperate
- Left main coronary stenosis or equivalent
- Moderate stenotic valvular heart disease
- Severe untreated arterial hypertension at rest (>200 mmHg systolic, >120 mmHg diastolic)
- Tachyarrhythmias or bradyarrhythmias
- High-degree atrioventricular block
- Hypertrophic cardiomyopathy
- Significant pulmonary hypertension
- Pregnancy
- Electrolyte abnormalities
- Orthopaedic impairment that compromises exercise performance
- Individuals with pacemakers or defibrillators
- Epilepsy
- Past history or MRI evidence of brain damage, including significant trauma, stroke, transient ischaemic attack (TIA), hydrocephalus, mental retardation, or serious neurological disorder
- Non resectable disease
- Emergency surgery

Contacts/Locations

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Study Officials:

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St. James's Hospital
Dublin, Ireland
Contact: Jonathan Moran 18963613 Ext. +353 moranj2@tcd.ie

References

Citations:

Links:	
Study Data/Documents:	

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

F. Systematic review search strategies

Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review

PUBMED:

((((((((((exercise test[tiab] OR exercise capacity[tiab] OR cardiopulmonary exercise[tiab] OR CPET[tiab] OR CPEX[tiab] OR cpx [tiab] OR vo2[tiab] OR anaerobic threshold[tiab] OR aerobic capacity[tiab] OR peak oxygen[tiab]OR preoperative exercise [tiab] OR pre operative exercise[tiab] OR cardiopulmonary exercise test*[tiab] OR cardiopulmonary exercise capacity[tiab] OR aerobic fitness[tiab] OR oxygen consumption[tiab] OR cardiopulmonary reserve[tiab])) OR ((((((("Exercise Test"[Mesh]) OR "Oxygen Consumption"[Mesh]) OR "Physical Fitness "[Mesh]) OR "Anaerobic Threshold "[Mesh])))))) AND ((((((preoperative[tiab] OR pre-operative[tiab] OR pre-surgery[tiab])))) OR ((((("Preoperative Care"[Mesh]) OR "Risk Assessment"[Mesh]) OR "Survival Analysis"[Mesh])))))) AND ((((((postoperative[tiab] OR length of stay[tiab] OR discharge[tiab] OR survival[tiab] OR risk[tiab] OR mortality[tiab] OR predictive value[tiab] OR risk factor[tiab] OR prognosis[tiab] OR preoperative period[tiab])))) OR (((((("Postoperative Complications/etiology"[Mesh] OR "Postoperative Complications/physiopathology"[Mesh])) OR "Treatment Outcome"[Mesh]) OR "Patient Discharge"[Mesh]) OR "Length of Stay"[Mesh]) OR "Postoperative Complications/mortality"[Mesh])))))) NOT (("Pulmonary Surgical Procedures"[Mesh]) OR "Cardiac Surgical Procedures"[Mesh]))) AND (((((((abdominal[tiab] OR gastric[tiab] OR gastrointestinal[tiab] OR colorectal[tiab] OR colon[tiab] OR rectum[tiab] OR liver surgery[tiab] OR pancreaticoduodenectomy[tiab] OR abdominal aortic aneurysm[tiab] OR major colonic surgery[tiab] OR kidney transplant*[tiab] OR renal transplant*[tiab] OR urological[tiab] OR hepatectomy[tiab] OR cystectomy[tiab] OR oesophageal[tiab] OR esophageal[tiab] OR esophagectomy[tiab] OR oesophagectomy[tiab] OR pancreatic surgery[tiab] OR liver transplant[tiab] OR gastric bypass[tiab] OR hepatic resection[tiab] OR intra-abdominal surgery[tiab])) OR ((((((("Abdomen/surgery"[Mesh]) OR "Abdominal Wall/surgery"[Mesh]) OR "Abdominal Cavity/surgery"[Mesh]) OR "Colon/surgery"[Mesh]) OR "Rectum/surgery"[Mesh])))) OR (("Thoracic Surgery"[Mesh]) OR "Thoracic Surgical Procedures"[Mesh]))

EMBASE:

(('exercise test'/exp OR 'cardiopulmonary exercise test'/exp OR 'oxygen consumption'/exp OR 'fitness'/exp OR 'aerobic capacity'/exp) OR ('exercise near/2':ab,ti AND (test:ab,ti OR capacity:ab,ti) OR 'cardiopulmonary near/4':ab,ti AND (exercise:ab,ti AND test:ab,ti OR exercise:ab,ti AND capacity:ab,ti OR reserve:ab,ti) OR 'aerobic near/2':ab,ti AND (capacity:ab,ti OR fitness:ab,ti) OR cpet:ab,ti OR cpex:ab,ti OR cpx:ab,ti OR vo2:ab,ti OR anaerobic:ab,ti AND threshold:ab,ti OR peak:ab,ti AND oxygen:ab,ti OR preoperative:ab,ti AND exercise:ab,ti OR 'pre operative':ab,ti AND exercise:ab,ti OR oxygen:ab,ti AND consumption:ab,ti)) AND ((preoperative:ab,ti OR 'pre operative':ab,ti OR 'pre surgery':ab,ti) OR ('preoperative period'/exp OR 'risk assessment'/exp OR 'survival'/exp)) AND ((postoperative:ab,ti OR length:ab,ti AND of:ab,ti AND stay:ab,ti OR discharge:ab,ti OR survival:ab,ti OR risk:ab,ti OR mortality:ab,ti OR predictive:ab,ti AND value:ab,ti OR risk:ab,ti AND factor:ab,ti OR prognosis:ab,ti OR preoperative:ab,ti AND period:ab,ti) OR ('postoperative complication'/exp OR 'treatment outcome'/exp OR 'hospital discharge'/exp OR 'length of stay'/exp)) AND (((abdominal NEAR/2 (aortic OR aneurysm)):ab,ti OR gastric:ab,ti OR gastrointestinal:ab,ti OR colorectal:ab,ti OR colon:ab,ti OR rectum:ab,ti OR (surgery NEAR/4 (liver OR major OR colonic OR 'intra abdominal' OR pancreatic)):ab,ti OR 'pancreaticoduodenectomy':ab,ti OR kidney:ab,ti AND (transplant* NEAR/3 (kidney OR renal OR liver)):ab,ti OR urological:ab,ti OR hepatectomy:ab,ti OR cystectomy:ab,ti OR oesophageal:ab,ti OR esophageal:ab,ti OR esophagectomy:ab,ti OR oesophagectomy:ab,ti OR (gastric NEAR/1 bypass):ab,ti OR (hepatic NEAR/1 resection):ab,ti) OR ('abdominal surgery'/exp OR 'colon surgery'/exp OR 'colorectal surgery'/exp OR 'rectum surgery'/exp OR 'thorax surgery'/exp NOT 'heart surgery'/exp NOT 'lung surgery'/exp NOT 'pleurectomy'/exp))

CINAHL:

TI ((‘exercise N2' AND (test OR capacity) OR 'cardiopulmonary N4 AND (exercise AND test OR exercise AND capacity OR reserve) OR 'aerobic near/2' AND (capacity OR fitness) OR cpet OR cpex OR cpx OR vo2 OR anaerobic AND threshold OR peak AND oxygen OR preoperative AND exercise OR 'pre operative' AND exercise OR oxygen AND consumption)) OR AB ((‘exercise N2' AND (test OR capacity) OR 'cardiopulmonary N4 AND (exercise AND test OR exercise AND capacity OR reserve) OR 'aerobic near/2' AND (capacity OR fitness) OR cpet OR cpex OR cpx OR vo2 OR anaerobic AND threshold OR peak AND oxygen OR preoperative AND exercise OR 'pre operative' AND exercise OR oxygen AND consumption) OR (MH "Exercise Test") OR (MH

"Exercise Test, Cardiopulmonary") OR (MH "Oxygen Consumption") OR (MH "Physical Fitness/PH") OR (MH "Anaerobic Threshold/PH") OR TI (pre-operative' OR Preoperative OR presurgery OR 'pre surgery') OR AB (pre-operative' OR Preoperative OR presurgery OR 'pre surgery') OR (MH "Preoperative Care") OR (MH "Preoperative Education") OR (MH "Risk Assessment") OR (MH "Survival Analysis") OR TI (postoperative OR length of stay OR discharge OR survival OR risk OR mortality OR predictive value OR risk factor OR prognosis OR preoperative period) OR AB (postoperative OR length of stay OR discharge OR survival OR risk OR mortality OR predictive value OR risk factor OR prognosis OR preoperative period) OR (MH "Postoperative Complications/ET/PP") OR (MH "Treatment Outcomes") OR (MH "Patient Discharge") OR (MH "Transfer, Discharge") OR (MH "Length of Stay") OR TI ((((abdominal N2 (aortic OR aneurysm)) OR gastric OR gastrointestinal OR colorectal OR colon OR rectum OR (surgery N4 (liver OR major OR colonic OR 'intra abdominal' OR pancreatic)) OR 'pancreaticoduodenectomy' OR kidney AND (transplant* N3 (kidney OR renal OR liver)) OR urological OR hepatectomy OR cystectomy OR oesophageal OR esophageal OR esophagectomy OR oesophagectomy OR (gastric N1 bypass) OR (hepatic N1 resection))) OR AB ((((abdominal N2 (aortic OR aneurysm)) OR gastric OR gastrointestinal OR colorectal OR colon OR rectum OR (surgery N4 (liver OR major OR colonic OR 'intra abdominal' OR pancreatic)) OR 'pancreaticoduodenectomy' OR kidney AND (transplant* N3 (kidney OR renal OR liver)) OR urological OR hepatectomy OR cystectomy OR oesophageal OR esophageal OR esophagectomy OR oesophagectomy OR (gastric N1 bypass) OR (hepatic N1 resection))) OR (MH "Surgery, Digestive System") OR (MH "Surgery, Elective") OR (MH "Surgery, Ob-Gyn") OR (MH "Surgery, Urogenital") OR (MH "Surgery, Laparoscopic") NOT (MH "Surgery, Cardiovascular")

COCHRANE:

exercise test or exercise capacity or cardiopulmonary exercise or CPET or CPEX or cpx or vo2 or anaerobic threshold or aerobic capacity or peak oxygen or preoperative exercise or pre operative exercise or cardiopulmonary exercise test* or cardiopulmonary exercise capacity or aerobic fitness or oxygen consumption or cardiopulmonary reserve:ti,ab,kw OR [Exercise Test] OR [Oxygen Consumption] OR [Physical Fitness] OR [Anaerobic Threshold]

AND

preoperative or pre-operative or pre-surgery:ti,ab,kw OR [Preoperative Care] OR [Risk Assessment] OR [Survival Analysis]

AND

postoperative or length of stay or discharge or survival or risk or mortality or predictive value or risk factor or prognosis or preoperative period:ti,ab,kw OR [Postoperative Complications] OR [Treatment Outcome] OR [Patient Discharge] OR [Length of Stay]

AND

abdominal or gastric or gastrointestinal or colorectal or colon or rectum or liver surgery or pancreaticoduodenectomy or abdominal aortic aneurysm or major colonic surgery or kidney transplant* or renal transplant* or urological or hepatectomy or cystectomy or oesophageal or esophageal or esophagectomy or oesophagectomy or pancreatic surgery or liver transplant or gastric bypass or hepatic resection or intra-abdominal surgery:ti,ab,kw OR [Colorectal Surgery] OR [Gynecology] OR [Urology]

AMED:

TI ((‘exercise N2' AND (test OR capacity) OR 'cardiopulmonary N4 AND (exercise AND test OR exercise AND capacity OR reserve) OR 'aerobic near/2' AND (capacity OR fitness) OR cpet OR cpex OR cpx OR vo2 OR anaerobic AND threshold OR peak AND oxygen OR preoperative AND exercise OR 'pre operative' AND exercise OR oxygen AND consumption)) OR AB ((‘exercise N2' AND (test OR capacity) OR 'cardiopulmonary N4 AND (exercise AND test OR exercise AND capacity OR reserve) OR 'aerobic near/2' AND (capacity OR fitness) OR cpet OR cpex OR cpx OR vo2 OR anaerobic AND threshold OR peak AND oxygen OR preoperative AND exercise OR 'pre operative' AND exercise OR oxygen AND consumption) OR “EXERCISE TESTING” OR OXYGEN CONSUMPTION” OR “PHYSICAL FITNESS”

AND

TI (pre-operative’ OR Preoperative OR presurgery OR ‘pre surgery’) OR AB (pre-operative’ OR Preoperative OR presurgery OR ‘pre surgery’) OR “PREOPERATIVE CARE” OR “RISK FACTORS” OR “SURVIVORS”

AND

TI (postoperative OR length of stay OR discharge OR survival OR risk OR mortality OR predictive value OR risk factor OR prognosis OR preoperative period) OR AB (postoperative OR length of stay OR discharge OR survival OR risk OR mortality OR predictive value OR risk factor OR prognosis OR preoperative period) OR “POSTOPERATIVE COMPLICATIONS” OR “POSTOPERATIVE PERIOD” OR “TREATMENT OUTCOME” OR “PATIENT DISCHARGE” OR “PATIENT DISCHARGE, LENGTH OF STAY” OR “LENGTH OF STAY”

AND

TI (abdominal N2 (aortic OR aneurysm)) OR gastric OR gastrointestinal OR colorectal OR colon OR rectum OR (surgery N4 (liver OR major OR colonic OR 'intra abdominal' OR pancreatic)) OR 'pancreaticoduodenectomy' OR kidney AND (transplant* N3 (kidney OR renal OR liver)) OR urological OR hepatectomy OR cystectomy OR oesophageal OR esophageal OR esophagectomy OR oesophagectomy OR (gastric N1 bypass) OR (hepatic N1 resection) OR AB (abdominal N2 (aortic OR aneurysm)) OR gastric OR gastrointestinal OR colorectal OR colon OR rectum OR (surgery N4 (liver OR major OR colonic OR 'intra abdominal' OR pancreatic)) OR 'pancreaticoduodenectomy' OR kidney AND (transplant* N3 (kidney OR renal OR liver)) OR urological OR hepatectomy OR cystectomy OR oesophageal OR esophageal OR esophagectomy OR oesophagectomy OR (gastric N1 bypass) OR (hepatic N1 resection) OR “SURGERY” OR “SURGERY OPERATIVE”

PEDRO:

Preoperative exercise test*

The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis

EMBASE:

1 'abdominal surgery'/exp OR 'cancer surgery'/exp OR 'elective surgery'/exp OR 'general surgery'/exp OR 'geriatric surgery'/exp OR 'major surgery'/exp OR 'minimally invasive surgery'/exp OR 'esophagus surgery'/exp OR 'aneurysm surgery'/exp OR 'transplantation'/exp OR 'urologic surgery'/exp OR 'colon surgery'/exp OR 'colorectal surgery'/exp OR 'rectum surgery'/exp OR 'thorax surgery'/exp

2 (abdominal NEAR/3 (aortic OR aneurysm)):ab,ti

3 (‘gastric bypass’ OR ‘hepatic resection’ OR ‘stomach resection’ OR 'colonic resection' OR ‘colon resection’ OR ‘gastric resection’ OR gastroresection OR pancreaticoduodenectomy OR cystectomy OR oesophagectomy OR esophagectomy OR hepatectomy OR gastrectomy):ab,ti

4 (surgery NEAR/4 (liver OR abdominal OR abdomen OR 'intra abdominal' OR intraabdominal OR intra-abdominal OR pancreatic OR kidney OR oesophageal OR esophageal OR urolog* OR gastric OR gastrointestinal OR colorectal OR colon* OR rect*)):ab,ti

5 (transplant* NEAR/3 (kidney OR renal OR liver OR gastric)):ab,ti

6 1 OR 2 OR 3 OR 4 OR 5

7 'heart surgery'/exp OR 'lung surgery'/exp OR 'pleurectomy'/exp OR 'cardiovascular surgery'/exp OR 'ear nose throat surgery'/exp OR 'emergency surgery'/exp

8 #6 NOT #7

9 (‘pre operative’ OR pre-operative OR preoperati* OR presurg* OR ‘pre surgery’ OR pre-surgery OR ‘pre surgical’):ti,ab

10 prior NEAR/2 Surg*

11 'preoperative period'/exp

12 9 OR 10 OR 11

13 'exercise'/exp OR 'kinesiotherapy'/exp OR 'physical activity, capacity and performance'/exp OR 'physiotherapy'/exp OR 'sport'/exp

14 (Exercis* OR ‘physical activity’ OR endurance OR physiotherap* OR prehab* OR ‘physical functioning’ OR ‘physical fitness’ OR ‘aerobic capacity’ OR ‘anaerobic threshold’ OR ‘resistance training’ OR ‘muscle strengthening’ OR ‘oxygen consumption’

OR ‘aerobic fitness’ OR ‘cardiorespiratory fitness’ OR ‘cardiopulmonary fitness’ OR ‘inspiratory muscle’ OR ‘breathing exercise’):ti,ab

15 (Exercis* NEAR/3 (therap* OR protocol* OR intervention* OR test OR exam OR capacity OR cardiopulmonary OR performance)):ti,ab

16 13 OR 14 OR 15

17 8 AND 12 AND 16

18 EBM: Cochrane, Control, Randomised, Meta, Systematic

PUBMED:

1 ((((("Colon/surgery"[Mesh]) OR "Rectum/surgery"[Mesh]) OR (("Abdomen/surgery"[Mesh]) OR "Abdominal Wall/surgery"[Mesh]) OR "Abdominal Cavity/surgery"[Mesh]) OR "Bariatric Surgery"[Mesh]) OR "Thoracic Surgery"[Mesh]) OR "Colorectal Surgery"[Mesh]) OR "Urologic Surgical Procedures, Male"[Mesh]) OR "Gynecologic Surgical Procedures"[Mesh]) OR "Minimally Invasive Surgical Procedures"[Mesh]) OR (("Kidney Transplantation"[Mesh]) OR "Liver Transplantation"[Mesh]) OR "Pancreas Transplantation"[Mesh]

2 (abdominal surger*[tiab] OR abdomen surger*[tiab] OR gastric surger*[tiab] OR gastrointestinal surger*[tiab] OR colorectal surger*[tiab] OR colon surger*[tiab] OR colonic surger* [tiab] OR rectal surger*[tiab] OR rectum surger*[tiab] OR liver surger*[tiab] OR hepatic surger*[tiab] OR pancreaticoduodenectomy[tiab] OR abdominal aortic aneurysm surger*[tiab] OR major colonic surgery[tiab] OR kidney surger*[tiab] OR urolog* surger*[tiab] OR hepatectomy[tiab] OR cystectomy[tiab] OR oesophageal surger*[tiab] OR esophageal surger*[tiab] OR esophagectomy[tiab] OR oesophagectomy[tiab] OR pancreatic surger*[tiab] OR gastric bypass surger*[tiab] OR hepatic resection[tiab] OR intra-abdominal surger*[tiab] OR intraabdominal surger*[tiab] OR intra abdominal surger*[tiab] OR major abdominal surger*[tiab])

3 (kidney transplant*[tiab] OR renal transplant*[tiab] OR liver transplant*[tiab] OR gastric transplant*[tiab])

4 1 OR 2 OR 3

5 ((("Cardiac Surgical Procedures"[Mesh]) OR "Pulmonary Surgical Procedures"[Mesh]) OR "Cardiovascular Surgical Procedures"[Mesh]) OR "Otologic Surgical Procedures"[Mesh]

6 4 NOT 5

7 (preoperative[tiab] OR preop*[tiab] OR presurg* [tiab] OR pre-operative[tiab] OR pre surgery[tiab] OR presurgical[tiab] OR prior to surger*[tiab])

8 "Preoperative Period"[Mesh] OR "Preoperative Care"[Mesh]

9 7 OR 8

10 (exercise*[tiab] OR exercise therap*[tiab] OR exercise protocol*[tiab] OR exercise intervention*[tiab] OR exercise capacity[tiab] OR exercise performance[tiab] OR (prehab*[tiab] OR physical activit*[tiab] OR endurance[tiab] OR physiotherapy*[tiab] OR physical functioning[tiab] OR physical fitness[tiab] OR aerobic capacity[tiab] OR anaerobic threshold[tiab] OR resistance training[tiab] OR muscle strengthening[tiab] OR oxygen consumption[tiab] OR aerobic fitness[tiab] OR cardiorespiratory fitness[tiab] OR cardiopulmonary fitness[tiab] OR inspiratory muscle[tiab] OR breathing exercise[tiab])

12 "Exercise"[Mesh] OR "Physical Therapy Modalities"[Mesh]

13 10 OR 11 OR 12

14 4 OR 9 OR 13

Clinical, Controlled Clinical, Randomised...

CINAHL:

1 (MH "Preoperative Period+") OR (MH "Preoperative Care+")

2 TI (‘pre operative’ OR preoperati* OR pre-operati* OR presurg* OR ‘pre surgery’ OR ‘pre surgical’) OR AB (‘pre operative’ OR preoperati* OR presurg* OR ‘pre surgery’ OR ‘pre surgical’)

3 TI prior N2 Surg* OR AB prior N2 Surg*

4 S1 OR S2 OR S3

5 TI (surger* N4 (liver OR abdominal OR abdomen OR 'intra abdominal' OR intraabdominal OR pancreatic OR kidney OR oesophageal OR esophageal OR urolog* OR gastric OR gastrointestinal OR colorectal OR colon* OR rect*)) OR AB (surger* N4 (liver OR abdominal OR abdomen OR 'intra abdominal' OR intraabdominal OR pancreatic OR kidney OR oesophageal OR esophageal OR urolog* OR gastric OR gastrointestinal OR colorectal OR colon* OR rect*))

6 TI (‘gastric bypass’ OR ‘hepatic resection’ OR ‘stomach resection’ OR 'colonic resection' OR ‘colon resection’ OR ‘gastric resection’ OR gastroresection OR pancreaticoduodenectomy OR cystectomy OR oesophagectomy OR esophagectomy OR hepatectomy OR gastrectomy) OR AB (‘gastric bypass’ OR ‘hepatic resection’ OR ‘stomach resection’ OR 'colonic resection' OR ‘colon resection’ OR ‘gastric resection’

OR gastroresection OR pancreaticoduodenectomy OR cystectomy OR oesophagectomy OR esophagectomy OR hepatectomy OR gastrectomy)

7 (MH "Surgery, Digestive System+") OR (MH "Biliary Tract Surgical Procedures+") OR (MH "Colectomy+") OR (MH "Enterostomy+") OR (MH "Gastroenterostomy+") OR (MH "Pancreas Transplantation+") OR (MH "Surgery, Elective+") OR (MH "Surgery, Laparoscopic+") OR (MH "Surgery, Ob-Gyn+") OR (MH "Surgery, Urogenital+") OR (MH "Thoracic Surgery+") OR (MH "Kidney Transplantation+") OR (MH "Surgery, Urologic, Male+") OR (MH "Liver Transplantation")

8 TI (transplant* N3 (kidney OR renal OR liver OR gastric)) OR AB (transplant* N3 (kidney OR renal OR liver OR gastric))

9 S5 OR S6 OR S7 OR S8

10 (MH "Surgery, Cardiovascular") OR (MH "Surgery, Endocrine") OR (MH "Heart Surgery+") OR (MH "Surgery, Lung+") OR (MH "Cell Transplantation") OR (MH "Bone Transplantation") OR (MH "Facial Transplantation") OR (MH "Heart Transplantation") OR (MH "Lung Transplantation")

11 S9 NOT S10

12 (MH "Exercise+") OR (MH "Physical Fitness+") OR (MH "Therapeutic Exercise+") OR (MH "Physical Therapy")

13 TI (Exercis* OR ‘physical activity’ OR endurance OR physiotherap* OR prehab* OR ‘physical functioning’ OR ‘physical fitness’ OR ‘aerobic capacity’ OR ‘anaerobic threshold’ OR ‘resistance training’ OR ‘muscle strengthening’ OR ‘oxygen consumption’ OR ‘aerobic fitness’ OR ‘cardiorespiratory fitness’ OR ‘cardiopulmonary fitness’ OR ‘inspiratory muscle’ OR ‘breathing exercise’) OR AB (Exercis* OR ‘physical activity’ OR endurance OR physiotherap* OR prehab* OR ‘physical functioning’ OR ‘physical fitness’ OR ‘aerobic capacity’ OR ‘anaerobic threshold’ OR ‘resistance training’ OR ‘muscle strengthening’ OR ‘oxygen consumption’ OR ‘aerobic fitness’ OR ‘cardiorespiratory fitness’ OR ‘cardiopulmonary fitness’ OR ‘inspiratory muscle’ OR ‘breathing exercise’)

14 S12 OR S13

15 S4 AND S11 AND S14

AMED:

1 DE "PREOPERATIVE CARE"

2 TI (‘pre operative’ OR preoperati* OR presurg* OR ‘pre surgery’ OR ‘pre surgical’) OR AB (‘pre operative’ OR preoperati* OR presurg* OR ‘pre surgery’ OR ‘pre surgical’)

3 TI prior N2 Surg* OR AB prior N2 Surg*

4 S1 OR S2 OR S3

5 TI (surger* N4 (liver OR abdominal OR abdomen OR 'intra abdominal' OR intraabdominal OR pancreatic OR kidney OR oesophageal OR esophageal OR urolog* OR gastric OR gastrointestinal OR colorectal OR colon* OR rect*) OR AB (surger* N4 (liver OR abdominal OR abdomen OR 'intra abdominal' OR intraabdominal OR pancreatic OR kidney OR oesophageal OR esophageal OR urolog* OR gastric OR gastrointestinal OR colorectal OR colon* OR rect*)

6 TI (‘gastric bypass’ OR ‘hepatic resection’ OR ‘stomach resection’ OR 'colonic resection' OR ‘colon resection’ OR ‘gastric resection’ OR gastroresection OR pancreaticoduodenectomy OR cystectomy OR oesophagectomy OR esophagectomy OR hepatectomy OR gastrectomy) OR AB (‘gastric bypass’ OR ‘hepatic resection’ OR ‘stomach resection’ OR 'colonic resection' OR ‘colon resection’ OR ‘gastric resection’ OR gastroresection OR pancreaticoduodenectomy OR cystectomy OR oesophagectomy OR esophagectomy OR hepatectomy OR gastrectomy)

7 (DE "SURGERY") OR (DE "SURGERY OPERATIVE")

8 S5 OR S6 OR S7

9 (DE "EXERCISE") OR (DE "EXERCISE MOVEMENT TECHNIQUES") OR (DE "EXERCISE THERAPY")

10 (DE "PHYSICAL ENDURANCE") OR (DE "PHYSICAL FITNESS") OR (DE "PHYSICAL THERAPY MODALITIES") OR (DE "PHYSICAL THERAPY TECHNIQUES")

11 TI (Exercis* OR ‘physical activity’ OR endurance OR physiotherap* OR prehab* OR ‘physical functioning’ OR ‘physical fitness’ OR ‘aerobic capacity’ OR ‘anaerobic threshold’ OR ‘resistance training’ OR ‘muscle strengthening’ OR ‘oxygen consumption’ OR ‘aerobic fitness’ OR ‘cardiorespiratory fitness’ OR ‘cardiopulmonary fitness’ OR ‘inspiratory muscle’ OR ‘breathing exercise’) OR AB (Exercis* OR ‘physical activity’ OR endurance OR physiotherap* OR prehab* OR ‘physical functioning’ OR ‘physical fitness’ OR ‘aerobic capacity’ OR ‘anaerobic threshold’ OR ‘resistance training’ OR ‘muscle strengthening’ OR ‘oxygen consumption’ OR ‘aerobic fitness’ OR ‘cardiorespiratory fitness’ OR ‘cardiopulmonary fitness’ OR ‘inspiratory muscle’ OR ‘breathing exercise’)

11 S9 OR S10 OR S11

12 S4 AND S8 AND S12

COCHRANE:

1 Preoperative or pre operative or pre-operative or pre-surg*:ti,ab,kw

2 [mh "Preoperative Period"] or [mh "Preoperative Care"]

3 #1 or #2

4 [mh Colon/surgery] or [mh Rectum/surgery] or [mh "Thoracic Surgical Procedures"] or [mh Abdomen/surgery] or [mh "Abdominal Wall/surgery"] or [mh "Abdominal Cavity/surgery"] or [mh "General Surgery"] or [mh "Bariatric Surgery"] or [mh "Thoracic Surgery"] or [mh "Colorectal Surgery"] or [mh "Urologic Surgical Procedures, Male"] or [mh "Gynecologic Surgical Procedures"] or [mh "Elective Surgical Procedures"] or [mh "Minimally Invasive Surgical Procedures"] or [mh Transplantation]

5 "abdominal surger*" or "abdomen surger*" or "gastric surger*" or "gastrointestinal surger*" or "colorectal surger*" or "colon surger*" or "rectum surger*" or "liver surger*" or "hepatic surger*" or pancreaticoduodenectomy or "abdominal aortic aneurysm" or "major colonic surgery" or "kidney surger*" or "urolog* surger" or hepatectomy or cystectomy or "oesophageal surger*" or "esophageal surger*" or esophagectomy or oesophagectomy or pancreatic or "gastric bypass" or "hepatic resection" or "intra-abdominal surger*" or "intraabdominal surger*" or "intra abdominal surger*" or "major abdominal surger*":ti,ab,kw

6 kidney transplant* or renal transplant* or liver transplant* or gastric transplant*:ti,ab,kw

7 #4 or #5 or #6

8 [mh "Cardiac Surgical Procedures"] or [mh "Pulmonary Surgical Procedures"] or [mh "Cardiovascular Surgical Procedures"] or [mh "Otologic Surgical Procedures"]

9 #7 not #8

10 [mh "Exercise Therapy"] or [mh "Exercise"]

11 exercise* or prehab* or "physical activit*" or endurance or physiotherapy* or "physical function*" or "physical fitness" or "aerobic capacity" or "anaerobic threshold" or "resistance training" or "muscle strengthening" or "oxygen consumption" or "aerobic fitness" or "cardiorespiratory fitness" or "cardiopulmonary fitness" or "inspiratory muscle" or "breathing exercise"

12 #10 or #11

13 #3 and #9 and #12

G. Systematic review supplementary tables

Preoperative Cardiopulmonary Exercise Testing and Mortality

Author	Surgery	Duration of Follow-Up	CPET Variable	Summary Findings
Ausania et al. (2012a)	Pancreaticoduodenectomy	30 Day post-op	AT	Death was similar between groups with AT <10.1 or >10.1 ml/kg/min p=1.00
Ausania et al. (2012b)	Pancreatic (Palliative Double Bypass) Surgery	N/R	AT	Cox Regression Analysis: AT was not associated with overall long term survival, p<0.05
Bernal et al. (2014)	Liver Transplant	1 Year	AT	Non-survivors AT 9.8 ml/kg/min (8.1-12) [median (IQR)] vs. non-survivors AT 11.7 ml/kg/min (9.3-14.3), p=0.04. Non-survivors VO_{2peak} ml/kg/min 17.1 (13.3-19.7) vs. survivors 15.9 (13.4-19.2), p=0.85. Univariate Analysis: HR=0.87, 95% CI=0.75-1.01, p=0.08. Multivariable Analysis: AT. HR=0.88, 95% C.I=0.69-0.98 p <0.05
Carlisle and Swart (2007)	Abdominal Aortic Aneurysm Repair	Median 35 Months	V_E/VCO_2, V_E/VO_2, VO_{2peak}, AT	Univariable Analysis: V_E/VCO_2; HR=1.14, 95% C.I=1.08-1.20 p=<0.01, V_E/VO_2; HR=1.12, 95% C.I=1.07-1.18, p=<0.01, AT; HR=0.74, 95% C.I=0.63-0.87, p=<0.01, VO_{2peak}; HR=0.83, 95% C.I=0.74-0.94, p<0.01. Multivariable Analysis: V_E/VCO_2; HR=1.13, 95% C.I=1.07-1.19, p=<0.01, AT; HR=0.84, 95% C.I=0.72-0.98, p=0.03.

Chandrabalan et al. (2013)	Pancreatic Surgery	In-hospital stay	AT	Postoperative mortality was not associated with AT (HR=0.77, 95% C.I=0.16-3.61, p=0.74)
Colson et al. (2012)	Major Thoraco-Abdominal Surgery	30 Day, 1 year and 5 year	AT	BMA Analysis: AT-PeO_2 [P(B≠0)=70%], AT- VO_2/HR [P(B≠0)=65%], AT-RER [P(B≠0)=57%], AT- VO_2/Kg [P(B≠0)=54%]
Epstein et al. (2004)	Liver Transplant	100 days	VO_2peak, VO_2@AT, O2 Pulse	Survivors vs. Non-survivors: Peak VO_2 <60% predicted (number of patients), p=0.04, VO_2-AT <50% predicted peak VO_2 (number of patients), p=0.03, VO_2peak <60% predicted and VO_2-AT <50% predicted VO_2peak (number of patients), p=<0.01
Forshaw et al. (2008)	Oesophagectomy	In-hospital stay	N/R	Only one death (1.3%)
Grant et al. (2015)	Abdominal Aortic Aneurysm Repair	Median 26 Months	VE/VCO_2, VO_2peak, AT	Univariable Analysis: VE/VCO_2 @ AT <42; p=0.005, VO_2peak <15 ml/kg/min; p<0.01, AT <10.2 ml/kg/min; p<0.01. Multivariable Analysis: VE/VCO_2 > 42 @ AT, HR=1.628, 95% C.I=1.009-2.627, p<0.05. VO_2peak <15 ml/kg/min, HR=1.676, 95% C.I=1.002-2.803, p<0.05. AT was not included in multivariate analysis due to missing values and strong linear relationship between VO_2 and AT
Hartley et al. (2012)	Abdominal Aortic Aneurysm Repair	30 Days, 90 Days	VE/VCO_2, VO_2peak, AT	Univariable Analysis: 30 Day Mortality: AT <10.2 ml/kg/min; OR=4.50, 95% C.I=1.24-16.38, p=0.01, VO_2peak <15 ml/kg/min; OR=5.51, 95% C.I=1.22-24.94, p=0.03. 90 Day Mortality: AT <10.2 ml/kg/min;

				OR=3.46, 95% C.I=1.22-9.80, p=0.01, VO_{2peak} <15 ml/kg/min; OR=3.06, 95% C.I=1.19-7.87, p=0.02. Multivariable Analysis: 30 Day: AT <10.2 ml/kg/min, OR 6.35, 95% C.I=1.84-29.80, p<0.01. 90 Day: VO_{2peak} <15 ml/kg/min, OR 8.59, 95% C.I=2.33-55.75, p=<0.01. V_E/VCO_2 significant in the univariable analysis, 30 day; p=0.032, 90 day; p<0.05
Junejo et al. (2012)	Hepatic Resection	30 days post-op	AT	In-hospital mortality: AT of 9.9 ml/kg/min, OR=0.48, 95% C.I=0.25-0.94, p=0.03, 100% sensitivity and 76% specificity. No CPET variable associated with 30-day post-op mortality.
Junejo et al. (2014)	Pancreaticoduodenectomy Cancer Surgery	Median - 1,057 days (424-1,596)	V_E/VCO_2	Simple Logistic Regression Analyses: 30 Day Mortality, V_E/VCO_2; OR=1.35, 95% C.I=1.03-1.77, p=0.030. ROC, V_E/VCO_2, AUC=0.95, 95% C.I=0.89-1.02, p=0.03, 100% sensitivity and 92% specificity. In-Hospital Mortality, V_E/VCO_2, AUC=0.84, 95% C.I=0.63-1.07, p=0.02, 75% sensitivity and 93% specificity
Kaibori et al. (2013)	Hepatectomy	Median 24 months (12-36)	VO_{2peak}, AT VO2	AT ≥11.5 ml/kg/min, survivors vs. non-survivors, p=0.03. VO_{2peak} ≥16.5 ml/kg/min, survivors vs. non-survivors, p=0.03. Multivariate Analysis: AT (≥11.5 vs. <11.5 ml/kg/min) Coeff=1.004, SE=0.412, RR=2.730, p<0.05
Lai et al. (2013)	Colorectal Surgery	2 years	AT	Patients stratified into Fit (AT ≥11.0 ml/kg/min), Unfit (AT <11.0 ml/kg/min) or Unable (failed to pedal or demonstrate an AT). Binary Logistic Regression, Unable vs. Fit, mortality at 2 years, OR=3.98, 95%

				C.I=1.32-11.97, p=0.01. Mortality between groups Fit vs. Unfit. Vs. Unable @ 30 day, 90 day and 2 year was significant, p <0.01, <0.01, <0.01, respectively
McCullough et al. (2006)	Bariatric Surgery	30 Days Post Discharge	VO_2peak	One death. A composite primary outcome including; myocardial infarction, unstable angina, deep venous thrombosis, pulmonary embolisum, renal failure, stroke and death: VO_2peak mean = 13.7 ml/kg/min (6.8-15.8) vs. mean 17.1 ml/kg/min (15.9-18.4) and mean 21.2 ml/kg/min (18.5-27.7), p=0.03
Neviere et al. (2014)	Liver Transplant	1 year	VO_2peak, O_2 Pulse	VO_2peak; Survivors (18.6 ml/kg/min {2.8}) vs. Non-survivors (17.1 ml/kg/min {3.3}), p=0.02. O2 Pulse; Survivors (11.3 ml/beat {2.7}) vs. Non-survivors (10.0 ml/beat {2.8}), p=0.04
Nugent et al. (1998)	Abdominal Aortic Aneurysm Repair	1 year	VO_2peak	Two groups. Group 1 (perioperative complications or died within the first year) vs. Group 2 (no complications or mortality within the first year), no significant difference in VO_2peak
Older et al. (1993)	Major Abdominal	N/R	AT	AT=8-10.9 ml/kg/min 8/51 patients died vs. AT=11-13.9 ml/kg/min, 1/86 patients died, p <0.01
Older et al. (1999)	Major Abdominal Surgery	N/R (Longest follow-up 40 days)	AT	21/548 patients died. 9 patients died of cardiovascular causes, 7/9 patients had an AT <11 ml/kg/min. 5 patients died of surgical complications, 3/5 patients had an AT <11 ml/kg/min. 19 of the 21

				patients who died were triaged to the ICU or HDU; 14 of these 19 patients had an AT of <11 ml/kg/min
Prentis et al. (2012a)	Liver Transplant	90 Days	AT	Survivors mean AT 12.0 (2.4) ml/kg/min vs. non-survivors mean AT 8.4 (1.3) ml/kg/min, p<0.01. Multivariable Analysis: AT of 9.0 ml/kg/min. ROC analysis, AUC=0.92, 95% C.I=0.82-0.97, p<0.01, 90.7% sensitivity and 83.3% specificity.
Prentis et al. (2013)	Radical Cystectomy	In-hospital stay	AT	Only two deaths (2.6%)
Snowden et al. (2013)	Non-Laproscopic Hepatobiliary Surgery	In-hospital stay	AT	Multivariable analysis: AT. p=0.003, OR=0.52, B= -0.657, ROC, AT cut-point 10 ml/kg/min, AUC=0.75, 95% C.I=0.65-0.85, p<0.01
Tolchard et al. (2015)	Radical Cystectomy	90 Days	AT, VO_{2peak}, VE/VCO_2	The sample size (n=105) was not great enough to produce meaningful results with regards to CPET parameters and mortality
Ulubay et al. (2010)	Renal Transplant	1 month post-op	N/R	No mortality in renal transplant cohort (n=16)
West et al. (2014)	Major Colonic Surgery	30 Days Post Discharge	N/R	Only two deaths (1.5%)
West et al. (2013)	Rectal Cancer Surgery	1 year	VO_2 @ AT	Non-survivors (n=7), all had VO_2 @ AT <10.6 ml/kg/min

Wilson et al. (2010)	Colorectal Resection, Radical Nephrectomy or Cystectomy	90 Days	AT, V_E/VCO_2	Hospital Mortality: ROC Analysis. AT of 10.9 ml/kg/min: AUC=0.68, 95% C.I=0.59-0.76, 88% sensitivity and 47% specificity. V_E/VCO_2 of 34, AUC=0.69, 95% C.I=0.55-0.82, 88% sensitivity and 47% specificity. 90 Day Survival: AT of 10.9 ml/kg/min, p=0.034, AUC=0.60, 95% C.I=0.52-0.68, 71% sensitivity and 47% specificity. V_E/VCO_2 of 34, p=0.02, AUC=0.64, 95% C.I=0.54-0.73, 68% sensitivity and 53% specificity

This table provides a more detailed overview of the predictive ability of CPET in regards to mortality presented in Chapter 3.

AT = Anaerobic Threshold, AUC = Area under the Curve, BMA = Bayesian Model Averaging, CI = Confidence Interval, HDU = High Dependency Unit, HR = Hazard Ratio, ICU = Intensive Care Unit, N/R = Not Reported, OR = Odds Ratios, ROC = Receiver Operating Characteristic, VO_2 @ AT = Anaerobic Threshold

Preoperative Cardiopulmonary Exercise Testing and Length of Stay

Author	Surgery	CPET Variable	Summary Findings
Ausania et al. (2012a)	Pancreaticoduodenectomy	AT	AT >10.1 ml/kg/min, median LOS=17.5 (8-99) days vs. AT ≤10.1 ml/kg/min, median LOS =29.4 (12-54) days (p<0.01)
Bernal et al. (2014)	Liver Transplant	AT, VO_{2peak}	AT <9.2 ml/kg/min; LOS 21 days (IQR: 14-30) vs. AT ≥9.2 ml/kg/min; 15 days (13-23), p <0.03. VO_{2peak} <13.4 ml/kg/min longer ICU stays, 4 days (3-8) vs. 3 days (2-5) (VO_{2peak} ≥13.4 ml/kg/min), p<0.01
Chandrabalan et al. (2013)	Pancreatic surgery	AT	Low AT (<10 ml/kg/min); median of 6 days longer in hospital, Mann-Whitney U-test, p<0.01. Multivariate Cox regression analysis; AT <10 ml/kg/min, HR= 1.74,

			95% C.I=1.14-2.65, p=0.01. Univariate Analysis; AT <10 ml/kg/min, HR=1.74, 95% CI=1.14-2.64, p=0.01. Univariate Analysis; AT <11, HR=1.44, 95% CI=0.94-2.22, p<0.01
Dunne et al. (2014)	Liver Surgery	VO_2 @ AT, VO_{2peak} (L/min)	VO_2 @ AT (L/min): HR=2.15, 95% C.I=1.18-3.90, p = 0.01. VO_{2peak} (L/min): HR=1.41, 95% C.I=1.03-1.94, p=0.03. Multivariable Model, VO2 @ AT (L/min): HR=2.16, 95% C.I=1.18-3.96, p=0.01
Forshaw et al. (2008)	Oesophagectomy	AT	AT <11 ml/kg/min (n=12); LOS 19 (9) vs. AT >11 ml/kg/min (n=63); LOS 19 (23), p=0.89. No apparent correlation with AT and length of stay
Hennis et al. (2012)	Gastric Bypass Surgery	AT	AT of patients with LOS >3 days was lower than patients with LOS ≤3 days, p=0.02. ROC Curve Analysis; AUC= 0.640 (0.524-0.756), p=0.03. Cut-point point; 11.4 ml/kg/min, 76% sensitivity and 53% specificity
Junejo et al. (2012)	Hepatic Resection	AT	A significant negative correlation between AT and ICU stay (rs=-0.26, p=0.01) but not overall length of stay. AT below 9.9 ml/kg/min was associated with increased unplanned ICU stay (1.2 vs. 0.3 days; p<0.01)
Lai et al. (2013)	Major Colorectal Surgery	AT	Total Length of Hospital Stay: AT ≥11 ml/kg/min; LOS 7.1 (4.9-10.8) days vs. AT < 11 ml/kg/min; 9.9 (5.5-15.0) days vs. Unable to generate AT; 14.0 (10.5-23.8) days, p <0.01
McCullough et al. (2006)	Bariatric Surgery	VO_{2peak}	VO_{2peak} and Length of Stay, p<0.01.

Prentis et al. (2012a)	Liver Transplant	AT	No significant predictors of the hospital length of stay. AT was a significant predictor of the critical care length of stay. AT <11 ml/kg/min, Critical care LOS 8.1 (10.1) days vs. AT ≥11 ml/kg/min 2.8 (2.9) days, p <0.01
Prentis et al. (2012b)	Abdominal Aortic Aneurysm Repair	AT, VO_{2peak}, VE/VCO_2	Open Repair: AT cut-point 10 ml/kg/min, Critical Care LOS in unfit patients (median; 4.1 [95% CI=1.6-6.5] mean; 6.4 days) vs. fit patients (median; 1.2 [95% CI=1.0-1.4] mean 2.4 days) (p<0.01). Total Hospital LOS in unfit (median; 16 [95% CI=8.5-23.5] mean; 23.1 days) vs. fit (median; 8 [95% CI=7.5-8.9], mean 11.0) (p <0.01). EVAR; Cox Regression of AT: A significant predictor of hospital LOS (HR=1.13, 95% CI=1.04-1.23, p<0.01), not a significant predictor of critical care LOS (HR=1.08, 95% CI=0.99-1.17, p=0.64)
Prentis et al. (2013)	Radical Cystectomy	N/R	Patients who had a postoperative complication had a significantly increased length of stay compared with those patients who had no complication (median 21 vs. 15 days, p <0.01; HR=3.66, 95% C.I=1.98-6.76)
Snowden et al. (2010)	Major Surgery	AT, VO_{2peak}	Patients with a POMS Day 7 score ≤1 median LOS 10 days (IQR: 8-12) compared with a POMS Day 7 >1 median 26 days (21-31), p<0.01. Mean AT in patients with POMS Day 7 ≤1 was 11.9 (2.4) vs. POMS Day 7 >1 AT=9.1 (1.7), p<0.01.
Snowden et al. (2013)	Non-Laproscopic Hepatobiliary Surgery	AT	Cox Regression; cardiovascular fitness was a significant independent predictor of hospital and critical care length of stay (p <0.01). AT <10 ml/kg/min spent longer in hospital (median) 16 days (95% C.I=12.7-19.3) vs. AT ≥10 ml/kg/min, LOS=12

			days (p <0.01). Critical Care: AT <10 ml/kg/min, LOS=2.6 vs. AT ≥10 ml/kg/min, LOS=0.9 days (p <0.01)
Ting et al. (2013)	Kidney Transplant	VO2 @ AT	Measure of VO_2 @ AT was strongly correlated with VO_2 Peak (r=0.77, 95% C.I=0.65-0.85), O_2 Pulse (r=0.54, 95% C.I=0.35-0.69) and maximum work rate (r=0.55, 95% C.I=0.36-0.69). Mean VO_2 @ AT was significantly lower in CCU admission group vs. Non-CCU Admission group (p <0.01). VO_2 @ AT, OR=0.43, 95% C.I=0.27-0.68, p <0.01
Tolchard et al. (2015)	Radical Cystectomy	VO_2peak, VE/VCO_2, AT	Lower VO_2peak correlated with admittance to ICU (14.9 vs. 16.5 ml/kg/min, p<0.05). Spearman's rank correlation coefficient showed that LOS was negatively correlated with AT (r=-0.206, p<0.05) and positively correlated with VE/VCO_2 (r=0.324, p<0.01) but not with peak VO_2 (r=-0.181, p<0.05). VE/VCO_2 was the most significant predictor. Mann Whitney U-test and Kaplan-Meier analysis which showed a significantly greater LOS in patients with a VE/VCO_2 ≥33 (p<0.01)
West et al. (2014)	Major Colonic Surgery	AT, VO_2 Peak, VE/VCO_2	Evidence to suggest, independent of other predictive variables, patients with VO_2 @ AT (p<0.01) or VO_2peak, (p<0.01) above the cut-point and VE/VCO_2 @ AT (p <0.01) below the cut-point have a significantly reduced LOS.
Wilson et al. (2010)	Major Intra-Abdominal Surgery	AT	Overall median length of hospital stay was lower in the group with AT 11 or greater (8 vs. 9 days, p <0.01). Significantly more patients in the low AT (<11 ml/kg/min) being electively admitted after surgery (p <0.01)

This table provides a more detailed overview of the predictive ability of CPET in regards to LOS presented in Chapter 3.

AT = Anaerobic Threshold, CCU = Critical Care Unit, CI = Confidence Intervals, ICU = Intensive Care Unit, LOS = Length of Stay, N/R = Not Reported, POMS = Postoperative Morbidity Survey, VO_2 @ AT = Anaerobic Threshold

Preoperative Cardiopulmonary Exercise Testing and Morbidity

Author	Surgery	Duration of Follow-Up	Method of Morbidity Measure:	CPET Variable	Summary Findings
Ausania et al. (2012a)	Pancreaticoduodenectomy	30 Day post-op	POMS, ISGPF	AT	Postoperative complication rate was significantly lower (median; 38.5 vs. 70%, p<0.01) in the group with AT >10.1 ml/kg/min. Multivariable analysis, AT ≤10.1 ml/kg/min significantly associated with pancreatic leak (p<0.01)
Ausania et al. (2012b)	Pancreatic (Palliative Double Bypass) Surgery	N/R	POMS	AT	AT (ml/kg/min): Participants with no complications = 14.1 (10.3-16.9) vs participants with complications = 11.3 (6.2-15.4): p<0.05
Chandrabalan et al. (2013)	Pancreatic Surgery	In-hospital stay	Clavien-Dindo and ISGPF	AT	AT <10 ml/kg/min significantly greater incidence of post-op pancreatic fistula (35.4% vs. 16%, p<0.05) and major intra-abdominal

					abscesses (CD Grade 3-4, 22.4% versus 7.8%, p<0.05. AT showed no association with cardio or pulmonary complications (p=0.308, p=0.657 respectively).
Dunne et al. (2014)	Liver Surgery	30 Day post-op	Clavien-Dindo	HR @ AT	Only CPET variables predictive of all complications, HR @ AT; OR=1.02, 95% C.I=1.02, 95% C.I=1.01-1.04, p=0.01, HR @ VO_{2peak}; OR=1.02, 95% C.I=1.00-1.03, p=0.03. HR @ AT and major (grade 3 and 4) complications; OR=1.03, 95% C.I=1.01-1.04, p<0.01, HR @ VO_{2peak} and major complications; OR=1.02, 95% C.I=1.01-1.04, p<0.01. Multivariable Model combining HR @ AT and hepatectomy type for all complications (OR=1.02, 95% C.I= 1.00-1.04, p=0.02) and grade 3 and 4 complications (OR=1.02, 95% C.I=1.00-1.04, p=0.01)
Forshaw et al. (2008)	Oesophagectomy	In-hospital stay	Cardiopulmonary complications defined according to the Common	VO_{2peak} and AT	VO_{2peak} was significantly lower in patients with cardiopulmonary complications compared to those without (p=0.04), there was a trend towards significance for AT (p =

			Terminology Criteria for Adverse Events. Non-cardiopulmonary complications were self-defined.		0.07). ROC Curve Analysis; VO_{2peak}, AUC=0.63, 95% C.I=0.50-0.76, p=0.02. AT; AUC=0.62, 95% C.I=0.49-0.75; p=0.03
Hennis et al. (2012)	Gastric Bypass Surgery	In-hospital stay	POMS	AT	AT, significantly lower in patients with complications vs. those without complications ($p<0.05$). ROC Curve Analysis; AUC=0.693, 95% CI=0.51-0.88, p=0.06. Cut-point point; 11 ml/kg/min, 78% sensitivity and 54% specificity
Hightower et al. (2010)	Major Abdominal Surgery	7 days post-op	Self-Defined	Heart Rate @ AT, Diff. Between Heart Rate @ AT and Heart Rate at Rest, Percentage of predicted AT achieved (<75% vs. ≥75%, dichotomised), Multivariate	HR @ AT: AUC=0.734, 95% C.I=1.01-1.13, p=0.025, 56% sensitivity and 94% specificity. Diff. Between Heart Rate from rest to AT: AUC=0.799, 95% C.I=0.65-0.95, p=0.01, 81% sensitivity and 63% specificity. Percentage AT Achieved: AUC=0.72, 95% C.I=0.57-0.87, p=0.02, 88% sensitivity and 56% specificity. Multivariable Model combining diff. between heart rate from rest to AT and percentage AT

				Model combining Resting Heart Rate and Percentage Predicted AT Achieved.	achieved: AUC=0.83, 95% C.I=0.68-0.97, p=0.02, 81% sensitivity and 69% specificity
James et al. (2013)	Intra-Abdominal	28 Days post-op	Major adverse cardiac events and self-defined	AT and VO_{2peak}	The predictive value of CPET derived variables was greater than that of scoring systems and plasma biomarkers. Both AT (sensitivity 75%, specificity 85% for an optimal threshold value of 10.6 ml/min/kg) and VO_{2peak} (sensitivity 88%, specificity 69% for an optimal threshold value of 14.0 ml/min/kg) were good predictors of MACE and poor predictors of all complications.
Junejo et al. (2012)	Hepatic Resection	30 days post-op	POMS, Clavien-Dindo	VE/VCO_2 @ AT	Simple logistic regression showed cardiopulmonary morbidity was associated with age and VE/VCO_2 at AT (data not shown). VE/VCO_2; AUC=0.65, 95% C.I=0.53-0.77, p=0.02. In a multivariable predictive regression model both age (OR=1.07, 95%

					C.I=1.01-1.14, p=0.03) and a V_E/VCO_2 value of 34.5 at AT (OR=3.45, 95% C.I=1.31-1.94, p=0.01). ROC Curve Analysis for any postoperative complication; V_E/VCO_2 at AT of 34.5, 47% sensitivity and 84% specificity
Junejo et al. (2014)	Pancreaticoduodenectomy	Median - 1,057 days (424-1,596)	ISGPS for pancreatic complications. Non pancreatic complications were self-defined.	AT, V_E/VCO_2, VO_{2peak}	No CPET variable was a significant predictor ($p < 0.05$) of postoperative complications.
Kaibori et al. (2013)	Hepatectomy	Median 24 months (12-36)	Clavien-Dindo	N/R	Morbidity grouped into Mortality (event-free survival)
Lee et al. (2013)	Colorectal Surgery	30 days post-op	Clavien-Dindo	VO_{2peak}	VO_{2peak} and Medical Complication; 0.31 (95% C.I=0.13-0.71, $p<0.01$). No statistically significant correlation with All or Surgical Complications.
McCullough et al. (2006)	Bariatric Surgery	30 Days Post Discharge	Self-Defined	VO_{2peak}	Multivariate analysis found the first tertile of VO_{2peak}, OR=12.89, 95% C.I=1.14-146.21, p=0.04. The second multivariate model used

					VO_{2peak} as a continuous variable and included smoking status, OR=1.61, 95% C.I=1.19-2.18, p<0.01, was a significant predictor of complications. VO_{2peak}; AUC=0.77, Cut-point of 15.8 ml/kg/min, 75% sensitivity and 73.3% specificity. Cut-point of 18.5 ml/kg/min, 87.5% sensitivity and 34.7% specificity for overall postoperative complications
Moyes et al. (2013)	Oesophagogastric Cancer Surgery	N/R	Cardiopulmonary complications defined according to the Common Terminology Criteria for Adverse Events. Non-cardiopulmonary complications were self-defined.	AT and VO_{2peak}	Mean AT in those with cardiopulmonary complications was 9.9 ml/min/kg compared with a mean of 11.2 ml/min/kg in patients with no cardiopulmonary complications (p=0.05). Majority of cardiopulmonary complications occurred in those with a low AT (p=0.04). A low VO_2 Peak was not associated with an increased risk of cardiopulmonary complications (14 vs. 16 ml/min/kg, p=0.07). ROC Curve: AUC VO_{2peak}; 0.62 (95% CI=0.50-0.74, p=0.06). AUC AT; 0.60 (95% CI=0.48-0.72, p=0.08).

Nagamatsu et al. (2001)	Oesophagectomy and Lymphadenectomy	N/R	Self-Defined	VO_2max/m^2	VO_2max was lower in patients with cardiopulmonary complications vs. patients without complications ($p < 0.01$)
Nugent et al. (1998)	Abdominal Aortic Aneurysm Repair	12 months	Self-Defined	VO_2peak	No statistically significant difference between group with complications and group without complications in terms of VO_2 Peak
Prentis et al. (2012a)	Abdominal Aortic Aneurysm Repair	In-hospital stay	Self-Defined	AT, VE/VCO_2, VO_2peak	Open Repair: ROC Curve Analysis, AT 10 ml/kg/min, AUC=0.75, 95% CI=0.63-0.83; $p<0.01$. Univariate Analysis of AT, OR=0.71, 95% CI=0.67-0.88, $p<0.01$. VO_2peak, OR=0.83, 95% CI=0.71-0.96, $p<0.01$. VE/VCO_2, OR=1.02, 95% CI=0.95-1.10, p=0.54. EVAR: No independent variables were significantly predictive of major postoperative complications on univariate analysis. No multivariate analysis was performed.
Prentis et al. (2012b)	Radical Cysectomy	In-hospital stay	Clavien-Dindo	AT	Multivariate Logistic Regression showed AT was the only significant independent predictor for postoperative major morbidity (Clavien ≥3) when compared with those with no or minor

					(Clavien <3) complications; OR=0.74, 95% C.I=0.57-0.97, p=0.03. ROC Curve Analysis; AUC=0.72, 95% C.I=0.60-0.82, p<0.01, Cut-point=12.0 ml/kg/min, 77% sensitivity and 63% specificity
Snowden et al. (2010)	Major Surgery	In-hospital stay	POMS (Day 7)	AT	The mean AT in patients with a POMS ≤1 was 11.9 (2.4) vs. POMS >1 was 9.1 (1.7) ml/kg/min (p<0.01). ROC Curve Analysis; AT cut-point 10.1 ml/kg/min, AUC=0.85, 95% C.I=0.78-0.91, p <0.01, 88% sensitivity and 79% specificity.
Tolchard et al. (2015)	Radical Cysectomy	90 Days	Clavien-Dindo	AT, V_E/VCO_2, VO_{2peak}	Mann Whitney test shows patients with complications had a significantly lower median AT; 10.6 ml/kg/min (range 6.1-15.1) vs. 11.8 ml/kg/min (range 5.8-22), p=0.02, VO_{2peak}; 14.3 ml/kg/min vs. 15.4 ml/kg/min, p=0.02. Higher median V_E/VCO_2 were observed in patients that suffered complications 33.3 (range 25-47.2) vs. 30.3 (range 21-43.2), p<0.01. Multivariable Binary Logistic Regression, AT (OR=0.724, 95% C.I=0.577-

					0.907, p<0.01), V_E/VCO_2 (OR=1.162, 95% C.I=1.041-1.297, p<0.01). ROC curve analysis AT, V_E/VCO_2 and hypertension; AUC=0.78, 95% C.I=0.69-0.87, p<0.01,
West et al. (2014)	Major Colonic Surgery	30 Days Post Discharge	POMS, Clavien-Dindo	VO_{2peak}, VO_2 @ AT, V_E/VCO_2	Independently, VO_{2peak}, VO_2 @ AT and V_E/VCO_2 were associated with day 5 morbidity (p=0.01, p <0.01, p <0.01). VO_2 @ AT; AUC=0.63, 95% C.I=0.54-0.73, Cut-point 10.1 ml/kg/min, 68% sensitivity and 58% sensitivity. VO_{2peak}; AUC=0.63, 95% C.I=0.53-0.73. Cut-point 16.7 ml/kg/min, 55% sensitivity and 69% specificity. Multivariable logistic regression model; VO_2 @ AT and gender, AUC=0.71, 95% C.I=0.62-0.80, p <0.01. For complications, a 1 ml/kg/min increase in VO_2 @ AT; OR=0.77, 95% C.I=0.66-0.89, p<0.01.
West et al. (2013)	Rectal Cancer Surgery	1 Year	POMS, Clavien-Dindo	VO_{2peak} and VO_2 @ AT	VO_2 @ AT; ROC; AUC=0.87, 95% C.I=0.78-0.95, Cut-point 10.6 ml/kg/min, 84% sensitivity, 92% specificity. VO_{2peak}; ROC; AUC=0.85, 95% C.I=0.77-0.93, Cut-point 18.6 ml/kg/min, 82%

					sensitivity, 80% specificity. VO_2 @ AT and VO_{2peak} were dichotomised, two identical models, the odds of POMS at day 5 surgical morbidity were reduced by 93% for patients above the median versus those below (OR=0.07, 95% C.I=0.03-0.19, p <0.01). Median values were 11.2 and 18.8 ml/kg/min

This table provides a more detailed overview of the predictive ability of CPET in regards to morbidity presented in Chapter 3. AT = Anaerobic Threshold, AUC = Area under the Curve, CD = Clavien-Dindo, CI = Confidence Interval, Diff. = Difference, HR = Hazard Ratio, HR @ AT = Heart Rate at Anaerobic Threshold, ISGPF = International Study Group on Pancreatic Fistula, N/R = Not Reported, OR = Odds Ratios, POMS = Postoperative Morbidity Survey, VO_2 @ AT = Anaerobic Threshold

Appendix 1. Quality in Prognostic Studies (QUIPS) tool

Domains	Prompting items for Consideration	Ratings
Study Participation	a. Adequate participation in the study by eligible persons b. Description of the source population or population of interest c. Description of the baseline study sample d. Adequate description of the sampling frame and recruitment e. Adequate description of the period and place of recruitment f. Adequate description of inclusion and exclusion criteria	**High bias:** The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants **Moderate bias**: The relationship between the PF and outcome may be different for participants and eligible nonparticipants **Low bias**: The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants
Study Attrition	a. Adequate response rate for study participants b. Description of attempts to collect information on participants who dropped out c. Reasons for loss to follow-up are provided d. Adequate description of participants lost to follow-up e. There are no important differences between participants who completed the study and those who did not	**High bias**: The relationship between the PF and outcome is very likely to be different for completing and non-completing participants **Moderate bias**: The relationship between the PF and outcome may be different for completing and non-completing participants **Low bias**: The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants
Prognostic Factor Measurement	a. A clear definition or description of the PF is provided b. Method of PF measurement is adequately valid and reliable c. Continuous variables are reported or appropriate cut points are used d. The method and setting of measurement of PF is the same for all study participants e. Adequate proportion of the study sample has complete data for the PF f. Appropriate methods of imputation are used	**High bias**: The measurement of the PF is very likely to be different for different levels of the outcome of interest **Moderate bias**: The measurement of the PF may be different for different levels of the outcome of interest **Low bias**: The measurement of the PF is unlikely to be different for different levels of the outcome of interest

	for missing PF data	
Outcome Measurement	a. A clear definition of the outcome is provided b. Method of outcome measurement used is adequately valid and reliable c. The method and setting of outcome measurement is the same for all study participants	**High bias**: The measurement of the outcome is very likely to be different related to the baseline level of the PF **Moderate bias**: The measurement of the outcome may be different related to the baseline level of the PF **Low bias**: The measurement of the outcome is unlikely to be different related to the baseline level of the PF
Study Confounding	a. All important confounders are measured b. Clear definitions of the important confounders measured are provided c. Measurement of all important confounders is adequately valid and reliable d. The method and setting of confounding measurement are the same for all study participants e. Appropriate methods are used if imputation is used for missing confounder data f. Important potential confounders are accounted for in the study design g. Important potential confounders are accounted for in the analysis	**High bias:** The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome **Moderate bias:** The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome **Low bias:** The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome
Statistical Analysis and Reporting	a. Sufficient presentation of data to assess the adequacy of the analytic strategy b. Strategy for model building is appropriate and is based on a conceptual framework or model c. The selected statistical model is adequate for the design of the study d. There is no selective reporting of results	**High bias**: The reported results are very likely to be spurious or biased related to analysis or reporting **Moderate bias**: The reported results may be spurious or biased related to analysis or reporting **Low bias**: The reported results are unlikely to be spurious or biased related to analysis or

		reporting

Source: Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6

Abbreviation: PF prognostic factor

The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Possible approach for *summary assessments* outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

Criteria for judging risk of bias in the 'Risk of bias' assessment tool

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: ▪ Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: ▪ Sequence generated by odd or even date of birth; ▪ Sequence generated by some rule based on date (or day) of admission; ▪ Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: ▪ Allocation by judgement of the clinician; ▪ Allocation by preference of the participant; ▪ Allocation based on the results of a laboratory test or a series of tests; ▪ Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: ▪ Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); ▪ Sequentially numbered drug containers of identical appearance; ▪ Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: ▪ Using an open random allocation schedule (e.g. a list of random numbers); ▪ Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); ▪ Alternation or rotation; ▪ Date of birth; ▪ Case record number; ▪ Any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; ▪ Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; ▪ Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient information to permit judgement of 'Yes' or 'No'; ▪ The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No missing outcome data; ▪ Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); ▪ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; ▪ Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ▪ 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; ▪ Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); ▪ The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any of the following: ▪ The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; ▪ The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Not all of the study's pre-specified primary outcomes have been reported; ▪ One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; ▪ One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); ▪ One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; ▪ The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: ▪ Had a potential source of bias related to the specific study design used; or ▪ Stopped early due to some data-dependent process (including a formal-stopping rule); or ▪ Had extreme baseline imbalance; or ▪ Has been claimed to have been fraudulent; or ▪ Had some other problem.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: ▪ Insufficient information to assess whether an important risk of bias exists; or ▪ Insufficient rationale or evidence that an identified problem will introduce bias.

I. BORG RPE scale



1 - 10 Borg Rating of Perceived Exertion Scale	
0	Rest
1	Really Easy
2	Easy
3	Moderate
4	Sort of Hard
5	Hard
6	
7	Really Hard
8	
9	Really, Really, Hard
10	Maximal: Just like my hardest race

J. Additional information about abdominal surgery procedures and cancer staging

This section contains additional information about the various abdominal surgical procedures featured in the systematic review entitled 'Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review' in Chapter 3.

Hepatic surgery

Hepatic (liver) resection, or hepatectomy, involves the full or partial surgical incision of the liver. The aim is to resect the liver with minimal bleeding and maintain liver function, avoiding postoperative hepatic insufficiency (Aragon and Solomon, 2012). The liver is divided into eight functional segments, these segments are based are based on the blood supply, the venous drainage, and the biliary drainage of the organ (Aragon and Solomon, 2012). To perform a safe resection of the liver, the internal structure and vascular structures must be fully understood.

The liver can be divided into the right and left anatomical lobes, and further divided into segments (I-VIII) (Aragon and Solomon, 2012). Surgical terminology is dictated by the area of resection (Aragon and Solomon, 2012). Right hepatectomy (or hemihepatectomy) involves resection of segments V-VIII, while resection of segments II-IV is referred to as left hepatectomy.

Liver related complications post-hepatic resection include bile leak (1.5%) and transient liver failure (1.0%), surgical related complications include incisional bleed, wound infection, and intra-abdominal bleeding. General complications consist of pleural effusion, pneumonia, and urinary tract infection (Nguyen et al., 2009).

Laparoscopic and open hepatic resection related morbidity rates have been reported at 18.31% and 29.77%, respectively. Laparoscopic procedures also have decreased blood loss and length of stay compared to open resection. Mortality rates are reported at 0.4% and do not differ between laparoscopic and open resection (Ciria et al., 2016).

Liver transplant

Liver transplant is the main treatment for patients with end-stage liver disease and hepatocellular carcinoma. Survival rates post liver transplant have improved due to improvements in surgical and anaesthetic techniques, and immunosuppressive drugs. Despite this, the one year mortality rates post liver transplant remain high (7.6%-18%) (Burroughs et al., Neviere et al., 2014).

Oesophageal surgery

Oesophageal cancer is the eight most common cancer worldwide (Ferlay et al., 2015). In Ireland, oesophageal cancer is the 11th most common cancer among males and females (12th males, and 14th females), with around 389 cancers diagnosed annually (Ireland, 2016a). Oesophageal cancer is more common in men than women (Ireland, 2016a). The two main histopathological subtypes are squamous cell carcinoma (SCC) and adenocarcinoma. Although SCC is the most common cancer overall, the incidence of adenocarcinoma is higher in western countries such as United States of America, the United Kingdom and Australia (Napier et al., 2014).

The 5-year survival rate between 2008-2012 in Ireland is reported as 18.1% (95% C.I: 16.0-20.2%) (Ireland, 2016a). Adenocarcinoma account for 80% of stomach cancers, while adenocarcinoma's account for 43% of oesophageal cancer, and SCC accounts for 41%. The incidence rates for SCC have fallen for females (0.9%) and males (1.4%), while adenocarcinoma rates increased for both genders (2.2% for females, and 3% for men) (Deady S and H., 2011). This increase in adenocarcinoma is noted in countries such as Australia, the United States of America, and the United Kingdom (Deady S and H., 2011). Smoking and chronic alcohol consumption are linked to SCC incidence, while adenocarcinoma is commonly associated with gastroesophageal reflux disease (GORD), Barret's oesophagus, and obesity (Cameron and Romero, 2000).

Treatment for oesophageal cancer consists of a multimodal approach including surgery, chemotherapy, and radiotherapy. In Ireland, 26% of patients with oesophageal cancer received surgical intervention, 31% underwent chemotherapy, and 43% had radiotherapy (Deady S and H., 2011). In all patients with resectable carcinoma of the oesophagus, surgery remains the mainstay of treatment in conjunction with neoadjuvant chemoradiotherapy (Luketich, 2014). Oesophageal and gastric surgery, or oesophagogastrectomy is associated with considerable morbidity and mortality. The mortality rate post oesophagectomy is approximately 5% (Barbour et al., 2008, Feeney et al., 2011).

Types of oesophageal resection

The two main types of resection are the transhiatial oesophagogastrectomy (THE) and the transthoracic (Ivor-Lewis) oesophagectomy (TTE). Hulscher et al. (2001) performed a meta-analysis and reported that although there is a significant difference in PPC's, there is no difference in mortality rates between TTE and THE surgical procedures and the choice of procedures depends on tumour location (Hulscher et al., 2001).

Transthoracic (Ivor-Lewis) oesophagogastrectomy

The TTE or Ivor-Lewis procedure is performed via a laparotomy, a right thoracotomy and intrathoracic anastomosis (D'Amico, 2007). This procedure begins with a mid-line laparotomy incision to allow access to the stomach. The stomach is disconnected from its vascular attachments. A muscle sparing right lateral thoracotomy is performed through the fifth intercostal space and the stomach is transposed to the thoracic cavity. Finally, an oesophagogastric anastomosis is performed. This particular approach is used for tumours of the distal oesophagus (D'Amico, 2007).

Transhiatial oesophagogastrectomy

Transhiatial oesophagectomy consists of an abdominal and left cervical incision (D'Amico, 2007). The mobilisation of the stomach for use as the conduit is similar to the above mentioned TTE procedure. The cervical oesophagus is mobilised through a cervical incision and is transected at the thoracic inlet. Finally, a laparotomy incision is performed and the gastric conduit is drawn through the mediastinum and exteriorised in the cervical incision for the oesophagogastric anastomosis. This particular procedure can be used for oesophageal tumours at any level, however large tumours located adjacent to the trachea can be difficult to perform (D'Amico, 2007).

McKeown (Three Incision) oesophagogastrectomy

The McKeown approach is similar to the above mentioned TTE procedure (D'Amico, 2007). It is an alternative three-incision procedure. The first stage is a right thoracotomy, to allow for mobilisation of the oesophagus and complete thoracic lymph node dissection, followed by repositioning of the patient in the supine position for abdominal and left cervical incision. This allows for a cervical oesophagogastric anastomosis. This surgical procedure may be used for mid oesophageal tumours that require extensive dissection (D'Amico, 2007).

Left thoracoabdominal oesophagogastrectomy

Left thoracoabdominal oesophagogastrectomy (LTE) involves a laparotomy and left thoracic incision through the eight intercostal space (D'Amico, 2007). Mobilisation of the stomach is performed as above and oesophagectomy is accomplished via the left thoracotomy. This surgical procedure may be used for lesions in the distal oesophagus (D'Amico, 2007).

Minimally invasive oesophagectomy

Minimally invasive oesophagectomy (MIE) are strategies that combine laparoscopic mobilisation of the stomach with complete laparoscopic oesophageal mobilisation and cervical anastomosis, or with a thoracoscopy for a thoracic anastomosis. A review by Biere et al. (2009) compared MIE and open oesophageal surgery in terms of surgical outcome (Biere et al., 2009). There were no reported differences in major morbidity between MIE TTE and open TTE (OR: 0.88, 95% C.I: 0.36-2.14, p=0.78),

and MIE THE and open THE (72% vs. 70% rates of morbidity) (Biere et al., 2009). However, there were significantly lower rates of anastomotic leakage between MIE TTE and open TTE (OR: 0.51, 95% C.I: 0.28-0.95, p=0.03) (Biere et al., 2009). In terms of mortality there were no significant differences between MIE and open procedures, however there were few included studies. There seems to be a shorter LOS in patients undergoing MIE THE compared to open THE, again however, there were few included studies.

Oesophagectomy postoperative complications

Overall morbidity post oesophagectomy is 22.9-50% (Connors et al., 2007, Rutegard et al., 2012), and complications can be subdivided into wound, infectious, pulmonary gastrointestinal, and cardiovascular complications.

Postoperative Oesophagectomy Complications	
Wound	Haematoma
	Disruption of wound
	Fistula
Infectious	Skin/wound infection
	Systemic infection
	Abscess
Cardiovascular	Cardiac related
	DVT/PE
	Stroke
	Phlebitis/thrombophelebitis
Pulmonary	Atelectasis/Pneumonia
	ARDS
	Pneumothorax
	Pulmonary oedema
	Respiratory failure
Gastrointestinal	Ileus/bowel obstruction
	Nausea/vomiting
	Pancreatitis
	Anastomosis

Table 17: Based on complications recorded by Connors et al. (2007)(Connors et al., 2007)

Postoperative pulmonary complications

Postoperative pulmonary complications (PPC's) occur in 15-30% of patients post oesophagectomy and are the main cause of morbidity and mortality (Feeney et al., 2011). PPC's include, atelectasis, pneumonia, and acute respiratory distress syndrome. The aetiology is multifactorial, however surgery contributes to the pathophysiological changes that develop into PPC's (Feeney et al., 2011).

The development of PPC's are associated with a 4.5-fold increase in mortality (Avendano et al., 2002, Ferguson and Durkin, 2002), and are responsible for 45.5%-55% of deaths (Law et al., 2004, Whooley et al., 2001). Risk factors for PPC's include increasing age (≥80 years), severe chronic obstructive pulmonary disease (COPD), preoperative shock, advanced ASA classification, smoking status, and physical activity levels (Feeney et al., 2011, Yang et al., 2015).

Pancreatic surgery

Adenocarcinoma of the pancreas is the most common histological subtype of cancer in the pancreas, accounting for nearly 90% of cancers, and it is also associated with the lowest survival rates of any gastrointestinal malignancy (Fesinmeyer et al., 2005, Ho et al., 2005). Pancreatic cancer is the 7th most common cancer in Ireland (9th in males, and 11th in females), and makes up 2.4% of all invasive cancers (Ireland, 2016b). The 5-year survival rates in Ireland between 2008-2012 for pancreatic cancer is a low 8.7% (95% C.I: 7.2-10.1%) (Ireland, 2016b).

Surgical resection is the only curative treatment for pancreatic cancer, because this particular form of cancer is reportedly resistant to non-surgical treatment of cancer including chemotherapy, radiotherapy and immunotherapy (Ho et al., 2005). Due to the late presentation of this particular malignancy, only 15-20% of patients are suitable for surgical resection (Fernandez-del Castillo et al., 2016). Surgical resection of the pancreas consists of either the standard pancreaticoduodenectomy (PD), Whipple procedure, the pylorus-preserving pancreaticoduodenectomy (PP), the duodenum-preserving pancreatic head resection (DPPHR), the distal pancreatectomy, and the total pancreatectomy.

The pancreaticoduodenectomy is the standard method of treating tumours confined to the head of the pancreas. This procedure has high morbidity rates, but can be undertaken with low mortality rates (Junejo et al., 2014). The distal pancreatectomy is performed for tumours in the body and tail of the pancreas, however this operation is rarely performed as the tumour is usually irresectable due to direct involvement of the middle colic vessels or metastases (Garden, 2005). Currently, postoperative

mortality is reported at <5% (Bradley, 2002), and postoperative morbidity rates are 18-64% (Buchler et al., 2003, Junejo et al., 2014). Postoperative complications include pancreatic leak, postpancreatectomy haemorrhage, and wound infection.

Radical cystectomy

Radial cystectomy (RC) with pelvic lymph node dissection and ileal conduit or orthotopic bladder reconstruction is the gold standard treatment for urinary bladder cancer (UBC) and is indicated for bladder cancer invading beyond the muscolaris propria (Bassi and Pagano, 2007, Prentis et al., 2013). Currently, urinary bladder cancer is the ninth most common form of cancer worldwide and in Ireland (Ploeg et al., 2009). In men it is the eight most common and the fifteenth most common in females, with an incidence of 2.2% in Ireland. Patients with non-invasive bladder cancers may experience very little pain, however patients with more advanced, muscle-invasive bladder cancers may have narrow windows of opportunity which require aggressive treatment and management (Gore et al., 2010). The 5-year net survival rate between 2008-2012 in Ireland is 61.9% (95% C.I: 59.4-64.4%).

Radical cystectomy consists of removal of the bladder through surgical incision, and the associated anterior pelvic organs; the prostate and seminal vesicle in men, and the uterus, urethra, cervix, fallopian tubes, ovaries and the anterior wall of the vagina in females. A lymphadenectomy is performed to remove the surrounding lymph nodes (Bassi and Pagano, 2007).

Radical cystectomy is associated with high postoperative morbidity (19-64%) and mortality rates (6-11%), however there is considerable variability in these results (Prentis et al., 2013). Major complications include, ileus, wound infection, pneumonia, and urinary tract infection (Bassi and Pagano, 2007). Risk factors for complications post-RC may include age, smoking history, and American Society of Anaesthesiologists score (Bassi and Pagano, 2007), however advancing age is not a definitive risk factor, rather the combination of major surgery, age and co-morbidities is an important risk factor (Stein and Skinner, 2006, Clark et al., 2005). Prentis et al. (2013) reports current preoperative risk assessment tools do not have adequate sensitivity and specificity, and more specific preoperative assessments such as echocardiography are designed to measure the risk for a particular type of complication e.g. cardiac (Prentis et al., 2013). Tools to assess the risk for general complications are lacking, and so cardiopulmonary exercise testing may be a viable method of assessing preoperative risk in radical cystectomy.

Radical nephrectomy

Nephrectomy is the surgical removal of the kidney and is widely performed to treat renal tumours, which can be classified as renal cell carcinoma (RCC) or transitional cell carcinoma (TCCA); RCC's constitute 85-90% of renal tumours (Al-Qudah et al., 2007). In Ireland, Kidney cancer is the 5th most common cancer overall, in men it is the 6th most common (373 new cases per year), and the 10th most common in females (197 new cases per year) (Ireland, 2016a). The net five-year survival rate between 2008-2012 in Ireland is 57.4% (95% C.I: 54.8-59.9%), and kidney cancer is ranks as the 12th most common invasive cancer death (Ireland, 2016a).

Radical nephrectomy is the complete removal of the kidney within Gerota's fascia including peri-renal fat and the adrenal gland. It also includes the removal of tumour thrombus, which is composed of the tumour and thrombotic components and can invade the renal vein and extend to the right atrium (Reynard et al., 2008). Radical nephrectomies should be performed if there is extensive local involvement, tumour thrombosus of the renal vein of inferior vena cava, or regional lymphadenopathy (Reynard et al., 2008).

Partial nephrectomy

Partial nephrectomy may be recommended in situations where it is possible to preserve ipsilateral renal tissue without compromising adequate renal tumour excision (Reynard et al., 2008). Consideration of partial nephrectomy is required in the event that a radical nephrectomy could lead to renal insufficiency, dialysis or renal transplantation. Partial nephrectomy can be performed on benign or malignant tumours depending on its size and location (Reynard et al., 2008).

Radical nephrectomy postoperative outcome

In a large systematic review for management of renal masses, non-surgical management was associated with a two-fold inferior overall survival and cancer specific survival compared to surgical management (radical and partial nephrectomy) (Pierorazio et al., 2016). The overall and cancer specific survival between partial and radical nephrectomy was similar, however it should be noted that the strength of evidence was low and moderate, respectively.

Radical nephrectomy postoperative complications

A meta-analysis compared minor and major Clavien-Dindo postoperative complications in partial nephrectomy and radical nephrectomy. There was no significant difference in the incidence of minor

complications (Clavien Grade 1-2) between radical and partial nephrectomy (Pierorazio et al., 2016). A meta-analysis of seven studies comparing major complications (Clavien Grade 3-4) reported a median complication rate of 2.8% of patients post radical nephrectomy, compared to 5.9% of patients post partial nephrectomy, however this was not statistically significant (RR: 0.71, 95% C.I: 0.49-1.05) (Pierorazio et al., 2016). The types of complications include; acute renal failure, wound infection, urinary tract infection, small bowel obstruction, arrhythmia, and pneumonia.

Renal transplant

Kidney or renal transplantation is regarded as the optimal treatment for many patients with end-stage renal failure (Torpey et al., 2010). There are numerous advantages kidney transplantation compared to dialysis treatment, including improved patient QOL, and reduction in costs, however the most notable benefit is improved survival rates (Torpey et al., 2010). Patients who received kidney transplantation have significantly increased 5 year survival rates compared to patients undergoing dialysis treatment (87% vs. 30%) (Torpey et al., 2010). Dialysis is associated with a 17 fold increase in mortality compared to age-matched controls, and it is an expensive procedure (transplantation is cheaper than dialysis) (Torpey et al., 2010).

Renal transplant postoperative complications

Renal transplant, like all surgical operations is subject to a certain amount of postoperative morbidity and mortality. These postoperative complications include; postoperative bleeding, wound infection, graft thrombosis, and urine leak. Postoperative bleeding typically occurs within 24-48 hours of operation, and life-threatening bleeding is rare, however obese patients with impair coagulation are at risk (Torpey et al., 2010). Treatment includes fluid replacement, blood transfusion if haemoglobin (Hb) levels are <8.0 g/dL, and possible surgical exploration (Torpey et al., 2010). The overall incidence of wound complications (wound dehiscence and infection) is about 7%, and reported risk factors are obesity, age, and diabetes (Torpey et al., 2010).

Vascular complications account for 1/3rd of all surgical complications and are mainly due to surgical technique (Torpey et al., 2010). Vascular complications post renal transplant include graft thrombosis, which typically occurs within the first week. Venous thrombosis is more common (4-6%) than renal thrombosis (Torpey et al., 2010). It is reported that vascular thrombosis is the main cause of early graft loss and contributes to significant morbidity in recipients (Torpey et al., 2010). Unfortunately it is very rare to salvage a graft, because usually by the time the diagnosis is made irreversible damage has

occurred. Prevention of graft thrombosis is of paramount importance, this can be performed through excellent surgical technique and appropriate anti-coagulant management (Torpey et al., 2010).

Arterial stenosis is a more frequent vascular complication than graft thrombosis, it typically occurs about 6 months post transplant (Torpey et al., 2010). Surgical correction is rarely required, and most stenosis can be successfully managed by percutaneous transluminal balloon angioplasty (Torpey et al., 2010). Major urological complications of renal transplant include urine leak and ureteric obstruction. Urinary leaks are an early postoperative complication that occur in 1.2-8.9% of cases (Duty et al., 2013). The primary treatment for urinary leak is reinsertion of the urinary catheter, if the leak continues, surgical treatments likely (Sabnis et al., 2016).

Gastric bypass surgery

Obesity can be treated surgically by increasing weight loss, these surgical operations can be divided into restrictive and malabsorptive procedures. The aim of these operations is to reduce calorie intake by modifying the gastrointestinal tract (Montravers et al., 2015).

Restrictive procedures

Restrictive surgical procedures reduce calorie intake by dividing the stomach and creating a smaller 'gastric pouch'. Techniques include adjustable gastric banding, and vertical restrictive (sleeve) gastrectomy. Adjustable gastric banding constitutes placing a silicone ring around the stomach to create a gastric pouch. The 'sleeve' gastrectomy removes about two thirds of the stomach along the greater curvature, and is more commonly used now instead of adjustable gastric banding, because it has superior weight loss results (Arapis et al., 2012).

Malabsorptive operations

Malabsorptive surgical procedures bypass portions of the small intestine and reduce jejunal absorption. The Roux-en-Y gastric bypass procedure combines restrictive and malabsorptive procedures, and is considered the gold standard of weight loss surgery because of its excellent efficacy and safety (Montravers et al., 2015).

In a Roux-en-Y gastric bypass the upper portion of the stomach is divided and stapled to create a gastric pouch of 20-30 mm and the small intestine at the mid-jejunum level. The distal portion of the intestine (or Roux limb) is anastomosed to the newly created gastric pouch (Elder and Wolfe, 2007, Montravers

et al., 2015). Laparoscopic approaches account for 90% of gastric bypass procedures, because there are a number of advantages including reduced postoperative pain, decreased impairment due to pulmonary complications, quicker recovery, and reduction in wound infection rates (Elder and Wolfe, 2007).

Gastric bypass postoperative outcome

The main aim of gastric bypass surgery is weight loss, 80% of patients experience a 60-80% excess weight loss within the first year post-surgery. A meta-analysis reported that there is a mean excess weight loss of 61.2% (95% C.I: 58.1%-64.4%) within 2 years after surgery (Buchwald et al., 2004).

Gastric bypass postoperative complications

Gastric bypass procedures may lead to nutritional deficits because of inadequate calorie intake or loss of nutrients due to frequent vomiting. Gastrointestinal complications following gastric bypass are also of serious concern, and include anastomotic leak, postoperative haemorrhage, and small bowel obstruction. Postoperative complications occur in roughly 11% of patients undergoing bariatric surgery (Hennis et al., 2012, McCullough et al., 2006).

Anastomotic leaks have a reported incidence of 1.5-5.2% (Marshall et al., 2003, Fernandez et al., 2004, Bellorin et al., 2011). These leaks have a mortality rate of nearly 50% (Ballesta et al., 2008, Papasavas et al., 2003), and are one of the strongest independent risk factors for postoperative mortality (Fernandez et al., 2004). Early recognition and operative management is vital for successful surgical repair of anastomotic leak (Griffith et al., 2012). Postoperative haemorrhage occurs in 3.9% of patients (Bellorin et al., 2011), and occurs more frequently in laparoscopic bypass compared to open bypass surgery (Podnos et al., 2003). There are two types of postoperative haemorrhage; bleeding into the abdominal cavity, and intraluminal bleeding at the gastrojejunostomy, the gastric pouch, and the jejunojejunostomy. Small bowel obstruction occurs commonly due to internal hernias with an incidence of 1-9% (Higa et al., 2003, Schneider et al., 2011, Carmody et al., 2005, Steele et al., 2008). It is reported that small bowel obstructions/internal hernias are difficult to diagnose and can pose life-threatening risk to patients, however they can be treated laparoscopically (Griffith et al., 2012).

Postoperative medical complications, particularly pulmonary complications, in bariatric surgery include, pulmonary embolism, respiratory failure, pleural effusions, pneumonia, cardiovascular failure, and cerebral ischemia. Thromboembolic complications account for 13-38.2% of postoperative deaths (Goldfeder et al., 2006, Morino et al., 2007), and pulmonary embolism and deep venous thrombosis have a combined incidence of 12.5% post Roux-en-Y bypass surgery (Carucci et al., 2006). Respiratory

failure occurs in 10-29% of cases, and pleural effusions occur in 5-23% (Carucci et al., 2006, Gonzalez et al., 2007). Atelectasis is reported in 6-92% of patients (Carucci et al., 2006, Ballesta et al., 2008), and pneumonia in 2-3% (Gonzalez et al., 2007, Thodiyil et al., 2008). Cardiovascular failure and cerebral ischaemia are also major causes of postoperative mortality accounting for 17.6% and 2.9% of deaths, respectively (Morino et al., 2007).

Abdominal aortic aneurysm

An abdominal aortic aneurysm (AAA) is a localised enlargement of the abdominal aorta exceeding the normal vessel diameter by 50% or greater than 3 cm (Kent, 2014). The condition is generally asymptomatic, until the point of rupture. Mortality is reported to be 85-90% post rupture (Kent, 2014). The speed of expansion varies between individuals, and the best predictor of rupture is aneurysm size (Kent, 2014).

The pathophysiology of AAA can be divided into 4 categories; (i) lymphocytes and macrophages penetrate the artery wall, (ii) destruction of elastin and collagen, (iii) loss of non-striated (smooth muscle) cells, and (iv) neovascularisation (Kent, 2014). Neovascularisation is the formation of new blood vessels in abnormal areas and differs from angiogenesis, which is the formation of new blood vessels from existing vessels.

Risk factors for AAA can be classified as modifiable and non-modifiable. Non-modifiable risk factors include age (>50 years for men, >60 years for women), gender and family history of AAA. Risk factors that can be treated include hypertension, hyperlipidaemia, obesity, atherosclerotic occlusive disease. The strongest modifiable risk factor is smoking, both the prevalence and size of AAA's are associated with the duration and amount of smoking (Kent, 2014).

Treatment of AAA can be performed through a combination of risk-factor modification, medical therapy and surgical intervention. Risk factor medication consists of smoking cessation, which is associated with a reduced rate of aneurysm growth, and reducing HTN and hyperlipidaemia through appropriate medication, however the evidence for this treatment approach is limited (Kent, 2014, Kent et al., 2010, Bengtsson et al., 1992, Forsdahl et al., 2009).

Surgical intervention can be performed to prevent rupture, however it must be decided if the benefits outweigh the surgery associated risks. Rupture rates significantly increase above 5.5 cm, however AAA below 5.5 cm is ≤1%, consequently surgery on aneuryms <5.5 cm is not recommended (Kent, 2014, Powell et al., 2007, Lederle et al., 2002b, Lederle et al., 2002a).

There are two surgical approaches for treating AAA; open repair and endovascular repair (EVAR). Open repair consists of an abdominal incision, and the vessels above and below the aneurysm are controlled. The aneurysm sac is opened and the synthetic graft is sutured both proximally and distally to the aorta. In comparison, EVAR is a less invasive approach. A covered stent is introduced through the femoral and iliac arteries, without opening the abdomen. The stent passes through the aneurysm sac, it anchors to the above and below the aneurysm to the normal aorta proximally and the iliac arteries distally to the aneurysm. EVAR has surpassed open repair as the more common surgical approach for AAA repair (Sethi et al., 2013). EVAR has a lower rate of 30 day mortality compared to open repair (Thomas et al., 2014), however in regards to long term survival (8-10 years), the results are comparable (Greenhalgh et al., 2010, De Bruin et al., 2010).

Colorectal Surgical Procedures

Surgery	Definition:
Segmental colectomy	Segmental colonic resection consists of removing a non-anatomical section of the diseased colon. This type of procedure is typically only performed when a lesser resection is indicated (e.g. polyp) (Rodriguez-Bigas, 2016).
Ileocolectomy	Ileocecectomy is a resection of the distal portion of the ileum or cecum (Rodriguez-Bigas, 2016)
Right hemicolectomy	A right hemicolectomy is a resection of the ascending colon, a portion of the distal ileum, the cecum, and the transverse colon to the right of the middle colic artery (Rodriguez-Bigas, 2016). Tumours of the ascending and proximal transverse colon can be treated by right hemicolectomy (Fig 2). An extended right or left hemicolectomy can be used to remove tumours of the transverse colon and splenic flexure (MacKay G et al., 2010).
Transverse colectomy	Transverse colectomy is the surgical resection of the transverse colon. Tumours of the transverse colon are uncommon, and so a transverse colectomy is typically not performed (Rodriguez-Bigas, 2016).
Left hemicolectomy	A left colectomy is the surgical removal of the transverse colon to the left of the middle colic artery, descending colon, and the sigmoid colon to the level of the rectum (Rodriguez-Bigas, 2016). Tumours of the descending or sigmoid colectomy can be removed via a left hemicolectomy or sigmoid colectomy depending on the exact positioning of the tumour (MacKay G et al., 2010).
Sigmoidectomy	Surgical removal of the sigmoid colon (Rodriguez-Bigas, 2016)
(Sub)Total colectomy	A total colectomy includes the surgical removal of the intraperitenal colon to the rectum (distal ileum, cecum ascending, transverse, descending, and sigmoid colon). A subtotal colectomy is a large resection of the colon without complete resection (Oakley et al., 1985). A subtotal colectomy may be performed for synchronous lesions, polyposis syndromes or in obstructed cases (MacKay G et al., 2010).

Table J1. Colorectal surgical procedures.

Cancer Staging Criteria

Colorectal Tumour (T)	Colorectal Criteria	Lung Tumour (T)	Lung Criteria
TX	Primary tumour cannot be assessed	**TX**	Primary tumor cannot be assessed, or the tumor is proven by the presence of malignant cells in sputum or bronchial washing but is not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour	**T0**	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria	**Tis**	Carcinoma in situ
T1	Tumour invades submucosa	**T1**	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion more proximal than the lobar bronchus (not in the main bronchus); Superficial spreading of tumor in the central airways (confined to the bronchial wall)
		T1a	Tumor ≤2 cm in the greatest dimension
		T1b	Tumor >2 cm but ≤3 cm in the greatest dimension
T2	Tumour invades muscularis propria	**T2**	Tumor >3 cm but ≤7 cm or tumor with any of the following: Invades visceral pleura; Involves the main bronchus ≥2 cm distal to the carina; Associated with atelectasis/obstructive pneumonitis extending to hilar region but not involving the entire lung
		T2a	Tumor >3 cm but ≤5 cm in the greatest dimension
		T2b	Tumor >5 cm but ≤7 cm in the greatest dimension
T3	Tumour invades through the muscularis propria into pericolorectal tissues	**T3**	Tumor >7 cm or one that directly invades any of the following: Chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium; Or tumor in the main bronchus <2 cm distal to the carina but without involvement of the

			carina; Or associated atelectasis/obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4a	Tumour penetrates to the surface of the visceral peritoneum	**T4**	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, or carina; or separate tumor nodule(s) in a different ipsilateral lobe
T4b	Tumour directly invades or is adherent to other organs or structures		

Table J2: Primary colorectal and lung tumour classification scores reported by the AJCC (7th edition)

Lymph Nodes (N)	Criteria	Lymph Nodes (N)	Lung Criteria
NX	Regional lymph nodes cannot be assessed	**NX**	Regional lymph nodes cannot be assessed
N0	No regional lymph node metatstasis	**N0**	No regional lymph node metatstasis
N1	Metastasis in 1-3 regional lymph nodes	**N1**	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement
N1a	Metastasis in one regional lymph node		
N1b	Metastasis in 2-3 lymph nodes		
N1c	Tumour deposit(s) in the suberosa, mesentery, or nonperitonealised pericolic or perirectal tissues without regional nodal metastasis		
N2	Metastasis in 4 or more regional lymph nodes	**N2**	Metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s)
N2a	Metastasis in 4-6 regional lymph nodes		
N2b	Metastasis in 7 or more regional lymph nodes		
N/a	N/a	**N3**	Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

Table J3: Regional lymph node cancer classification scores for colorectal and lung cancer staging reported by the AJCC (7th edition). N/a; Not applicable

Metastasis (M)	Criteria	Lung Metastasis (M)	Criteria
N/a	N/a	**MX**	Distant metastasis cannot be assessed
M0	No distant metastasis	**M0**	No distant metastasis
M1	Distant metastasis	**M1**	Distant metastasis
M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, non-regional node)	**M1a**	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion
M1b	Metastases in more than one organ/site or the peritoneum	**M1b**	Distant metastasis

Table J4: Metastases cancer classification scores for colorectal and lung cancer staging reported by the AJCC (7th edition). N/a; Not applicable

Stage	T	N	M	Dukes	MAC
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

Table J5: Colorectal cancer staging based on AJCC (7th edition), Dukes and Modified Astler-Coller (MAC) classification (Cancer, 2010)

Stage	T	N	M
1a	T1a	N0	M0
	T1b	N0	M0
1b	T2a	N0	M0
2a	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
2b	T2b	N1	M0
	T3	N0	M0
3a	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
3b	T4	N2	M0
	T1	N3	M0
	T2	N3	M0
	T3	N3	M0
	T4	N3	M0
4a	T Any	N Any	M1a or M1b

Table J6: Lung cancer staging according to the AJCC (7th edition) (Cancer, 2010)

H. Common colorectal and thoracic surgery complications

Anastomotic leak

An anastomotic leak is one of the most significant complications post-colorectal surgery, and occurs in 2-7% of cases (Whitlow et al., 2010, Slieker et al., 2012, Kingham and Pachter, 2009, Hyman et al., 2007, Park et al., 2013). The incidence of anastomotic leaks is higher in distal (colo-anal) anastomoses (10-20%) than proximal (ileocolic) anastomoses (1-3%) (Steele et al., 2006). The United Kingdom Surgical Infection Study Group (1991) defined an anastomotic leak as a "leak of luminal contents from a surgical join between two hollow viscera" (Peel and Taylor, 1991). Most anastomotic leaks occur within 5-8 days postoperatively, and diagnosis is typically suspected by clinical signs and symptoms and confirmed based on radiological, and intraoperative findings (Boushey and Williams, 2016). Immediate management of anastomotic leak includes intravenous fluid replacement, and broad spectrum antibiotics (Boushey and Williams, 2016). Further management depends on the specific scenario, typical treatments include observation, bowel rest, percutaneous drainage, colonic stenting, diversion, drainage, and potentially surgery to correct the anastomotic leak (Boushey and Williams, 2016).

Anastomotic bleeding

Anastomotic bleeding can be minor or major. Minor bleeding does not require a blood transfusion or endoscopic, angiographic, or surgical intervention. In comparison, major anastomotic bleeding is defined by requiring any one of the above mentioned treatments. Major bleeding reportedly occurs in 0.5-4.2% of patients with ileocolic anastomosis (Boushey and Williams, 2016, Cirocco and Golub, 1995, Malik et al., 2008, Martinez-Serrano et al., 2009, Lustosa et al., 2001).

Anastomotic strictures

The incidence of anastomotic strictures (narrowing of the anastomosis) ranges from 0-30% (Schlegel et al., 2001, Shimada et al., 1996, Bannura et al., 2004). Management of strictures depends on the aetiology and anatomical location, however most patients with strictures do not require any intervention (Boushey and Williams, 2016).

Anastomotic fistulas

A fistula is an abnormal anastomosis, and can occur in approximately 1-10% of patients post colorectal surgery. Fistulas may develop between the anastomosis and the skin, vagina, genitourinary system, and presacral space (Boushey and Williams, 2016). Fistulas that develop between the colorectal anastomosis and the skin are usually late developments of untreated anastomotic leaks (Boushey and Williams, 2016). Treatment for fistulas are dictated by addressing the sites involved, and options include conservative management, diverting colostomy, or endoanal/vaginal advancement flap reconstruction (Boushey and Williams, 2016).

Wound infection

Surgical site infection (SSI) is the term given to an infection of the surgical wound. An SSI may be superficial (skin/subcutaneous), deep incisional (fascial/muscle layers) or organ or space infection (MacKay G et al., 2010). Infection rates post colorectal surgery and thoracic surgery are 17.9% and 1.5%, respectively (Hubner et al., 2011, MacKay G et al., 2010, Yoshida et al., 2006). Treatment of SSI typically only requires adequate drainage which may be facilitated by removal of sutures/skin clips (MacKay G et al., 2010).

Wound dehiscence

Wound dehiscence is defined as a separation of the layers of a surgical wound (partial or complete) with fascia disruption within thirty days of surgery, and is a common complication post abdominal surgery (MacKay G et al., 2010, Moghadamyeghaneh et al., 2015). Patients who experienced wound dehiscence post abdominoperineal resection for low rectal cancer had a 1.7 increase in risk of mortality (Hawkins et al., 2014). Management of wound dehiscence depends on clinical findings but may include IV antibiotics and return to theatre (MacKay G et al., 2010, Boushey et al., 2016).

Postoperative ileus

Postoperative ileus is a severe constipation and intolerance of oral intake due to non-mechanical factors that disrupt the normal activity of the gastrointestinal tract. It takes time postoperatively for the GI tract to regain its coordinated muscular activity to facilitate digestion (Kalff et al., 2016). Postoperative ileus is generally resolved without serious complications, it is reported that some degree of ileus is deemed normal postoperatively, however ileus over 3 days long can be referred to as prolonged/paralytic ileus, and leads to patient discomfort, dissatisfaction, and prolonged hospitalisation (MacKay G et al., 2010, Kalff et al., 2016). Treatments and preventative measures may

include opioid sparing analgesia, employment of ERAS protocol, intravenous fluid, and electrolyte therapy. Patients who are able, should be commenced on an oral diet (MacKay G et al., 2010), while those unable will require total parental nutrition (Kalff et al., 2016).

Deep venous thrombosis and pulmonary embolism

Surgical patients are vulnerable to deep venous thromboembolism (DVT) (McNally and Burns, 2009). Venous thromboembolism can occur in approximately 30% of patients post colorectal surgery without prophylactic measures (Alizadeh and Hyman, 2005, MacKay G et al., 2010). Pulmonary embolism (PE) is the most serious complication and can occur in approximately 3% of patients post colorectal surgery (MacKay G et al., 2010). The rates of venous thromboembolism and pulmonary embolism vary considerably in thoracic surgery with reported rates between 0.4%-51% and 1%-5%, respectively (Di Nisio et al., 2015). DVT's and pulmonary embolism can lead to serious consequences such as mortality, and long term disability (McNally and Burns, 2009). Up to 40% of patients with a DVT can develop post-thrombotic limb syndrome, which includes chronic pain and swelling, within 3 years (MacKay G et al., 2010). Preventative measures for DVT and PE include pharmacological prophylaxis and mechanical prophylaxis (e.g. compression stockings) (MacKay G et al., 2010).

Urinary tract infection

Urinary tract infections (UTIs) are common complications post colorectal surgery, and are closely linked to the route and duration of catheterisation, with an approximate increase of risk of UTI by 3-10% per day of catheter in situ (MacKay G et al., 2010). Symptoms of a UTI include dysuria (pain or discomfort when urinating), urgency, and sensation of incomplete emptying of bladder. Treatment is usually through antibiotic management (MacKay G et al., 2010).

Atrial fibrillation

Atrial fibrillation is the most common arrhythmia following pulmonary resection. There is a reported incidence of 10-40% post pulmonary resections, and 33% post lobectomy (Roselli et al., 2005). Risk factors for development of postoperative arrhythmia are: age (>70 years old), amount of lung resected (right pneumonectomy carries a greater risk), and past-history of congestive heart failure or arrhythmia (Ziarnik and Grogan, 2015).

Haemothorax

Major haemorrhage into the thoracic cavity following lung resection usually occurs due to inadequate haemostasis of a bronchial artery or systemic vessels in the chest wall (Rotman et al., 2015). Initial treatment for thoracic haemothorax in haemodynamically unstable patients includes chest tube drainage and surgery. For haemodynamically stable patients, treatment consists of chest tube drainage of blood from the pleural cavity with or without intrapleural fibrinolytic therapy (Boersma et al., 2010).

Bronchopleural fistula

An acute bronchopleural fistula connecting the pleural cavity and the bronchial tree most commonly occurs 8-12 days after surgery, however it can occur at any time during the postoperative period (Rotman et al., 2015). Bronchopleural fistula occurs in approximately 0.5-4% of patients post lung surgery and treatment includes suturing and omentopexy (Liang et al., 2013, Allen et al., 2006).

Empyema

Empyema occurs in approximately 1.1% of patients after lung cancer resection (Allen et al., 2006). Bronchopleural fistula is the main cause of postoperative empyema, however empyema can also be attributed to residual pleural infection and/or intraoperative contamination (Rotman et al., 2015). Treatment options include intravenous antibiotics and chest tube drainage. If chest tube drainage fails, surgery should be considered (Davies et al., 2010)

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