

Physical activity in the aetiology and preoperative management of oesophageal adenocarcinoma

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Thesis overview

This thesis is composed of three distinct chapters, all of which aim to improve our understanding of the relationship between physical activity and oesophageal adenocarcinoma.

In the first two chapters, two specific aspects of physical activity are explored:

- Physical activity in the aetiology of oesophageal adenocarcinoma; through its role in the development of pre-malignant Barrett's oesophagus.
- A preoperative physical activity programme (prehabilitation) prior to oesophageal cancer surgery to improve fitness and reduce the incidence of postoperative complications.

In the third chapter, the association between preoperative physical fitness and postoperative outcome after oesophageal cancer surgery is investigated.

The main aims of this thesis are to:

- 1) Consider whether physical activity should be added to the aetiological model of Barrett's oesophagus and oesophageal adenocarcinoma.
 - 2) Inform and justify a future randomised controlled trial of prehabilitation prior to oesophagectomy.
 - 3) To stratify a patient's risk of post-oesophagectomy complications according to their preoperative physical fitness.
-

Declaration

This dissertation and the work presented in it are my own and have been generated by me as the result of my own original research.

I confirm that:

- 1) This work was done wholly or mainly while in candidature for a research degree at this University;
- 2) This work has not been submitted for a degree, diploma or any other qualification at this University or any other institution;
- 3) Where I have consulted the published work of others, this is always clearly attributed;
- 4) Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- 5) I have acknowledged all main sources of help;
- 6) Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- 7) Parts of this work have been published before submission as:

Lam S, Alexandre L, Luben R, Hart AR. The association between physical activity and the risk of symptomatic Barrett's oesophagus: a UK prospective cohort study. Eur J Gastroenterol Hepatol. 2018 Jan;30(1):71-75.

Specific author contributions: Hart AR & Lam S: study concept. Lam S: drafting of the manuscript. All authors contributed to the study design, analysis and interpretation of data and critical revisions. All authors contributed to the final draft of the manuscript.

Lam S, Hart AR. Does physical activity protect against the development of gastroesophageal reflux disease, Barrett's esophagus, and Esophageal adenocarcinoma? A review of the literature with a meta-analysis. Dis Esophagus. 2017 Nov 1;30(11):1-10.

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Specific author contributions as on page 3.

Stephen Lam:



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Abstract

Oesophageal adenocarcinoma has the fastest growing incidence of any solid tumour in the western world. Physical activity affects gastric emptying, intra-gastric pressure, systemic inflammation, and the regulation of body weight and may play an important role in the aetiology of the metaplasia-dysplasia-carcinoma sequence of oesophageal adenocarcinoma. Furthermore, exercise causes physiological adaptations resulting in improved cardiac output and lung ventilation volumes, as well as increased capillary and mitochondrial density in skeletal muscle, all of which improves efficiency in cellular aerobic respiration. As major surgery places large physiological stresses on the human body through; blood loss, catabolic muscle breakdown, systemic inflammatory vasodilation, and disruption of normal lung mechanics, the adaptive changes, achieved through preoperative exercise, may maximise cardiopulmonary and skeletal muscle reserves and reduce the risk of postoperative complications after cancer resection surgery (oesophagectomy).

This research aimed to investigate: 1) associations between both occupational and recreational levels of physical activity and the development of Barrett's oesophagus, the precursor lesion of oesophageal adenocarcinoma; 2) the feasibility of delivering a short-term preoperative exercise programme (prehabilitation) in a feasibility randomised controlled trial; and (3) associations between preoperative aerobic fitness, as measured objectively by cardiopulmonary exercise testing, and postoperative outcomes after oesophagectomy.

Results from a population-based prospective cohort study of 30 445 participants suggested a U-shaped association between occupational levels of physical activity and the risk of Barrett's oesophagus, where moderate levels of activity in standing occupations had an inverse association with disease risk (when compared to sedentary occupations), HR=0.50, 95% CI 0.31-0.82, p=0.006, but heavy manual occupations were associated with an increased risk, HR=1.66, 95% CI 0.91-3.00, p=0.09. No associations were found between recreational activity and the risk of Barrett's oesophagus (HR 1.34, 95% CI 0.72-2.50, p=0.35, highest vs. lowest levels of activity).

A single blinded, parallel group, randomised controlled feasibility trial of prehabilitation in 11 patients with oesophageal adenocarcinoma showed that a hospital-based exercise programme in the time period between completion of neoadjuvant chemotherapy and surgery was safe and acceptable to patients awaiting curative surgery.

A hospital-based cohort study of 254 patients found that there was no association between aerobic fitness (VO_{2peak}) and postoperative complications after oesophagectomy (OR 1.00, 95% CI 0.94-1.07, $p=0.86$). This suggests that the impact of fitness on postoperative outcome, in the context of oesophagectomy, is likely to be insubstantial.

Overall, this thesis suggests that occupational levels of physical activity may play a role in the aetiology of oesophageal adenocarcinoma, but preoperative fitness, even if feasibly modifiable with prehabilitation, may not significantly affect the risk of short-term postoperative morbidity after oesophagectomy.

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Abbreviations

ACSM	American College of Sports Medicine
AF	Atrial fibrillation
AJCC	American Joint Committee on Cancer
ASR	Age standardised incidence rate
AT	Anaerobic threshold
ATP	Adenosine triphosphate
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPEX	Cardiopulmonary exercise
DH	Department of Health
DPAQ	Determinates of Physical Activity Questionnaire
ECCG	Esophageal Complications Consensus Group
ECG	Electrocardiogram
EELV	End expiratory lung volume
EPIC	European Prospective Investigation of Cancer
ERAS	Enhanced recovery after surgery
ExPO	Exercise Prior to Oesophagectomy
FRC	Functional residual capacity
GCS	Glasgow Coma Scale
GORD	Gastroesophageal reflux disease
HGD	High-grade dysplasia
HR	Heart rate
IMT	Inspiratory muscle training
IPAQ	International physical activity questionnaire
ISGPF	International study group for pancreatic fistula
LGD	Low-grade dysplasia
LOS	Lower oesophageal sphincter

Abbreviations

MCAR	Missing completely at random
NNUH	Norfolk and Norwich Hospital
OGD	Oesophagogastroduodenoscopy
OGJ	Oesophagogastric junction
OR	Odds ratio
POMS	Post-Operative Morbidity Survey
P-POSSUM	Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
Q	Cardiac output
QOL	Quality of life
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
RR	Relative risk
SIRS	Systemic inflammatory response syndrome
SV	Stroke volume
TLOSR	Transient lower oesophageal sphincter relaxation
TV	Tidal volume
UICC	Union for International Cancer Control
VC	Vital capacity
VCO ₂	Volume of carbon dioxide
VO ₂	Volume of oxygen consumed
VO _{2max}	Volume of oxygen consumed at maximal exercise
WHR	Waist-to-hip ratio

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Chapter 1: Physical activity in the aetiology of oesophageal adenocarcinoma

An overview

In this chapter, the associations between both occupational and recreational levels of physical activity and the risk of developing oesophageal adenocarcinoma, as well as its precursor diseases, gastroesophageal reflux disease (GORD) and Barrett's oesophagus, are examined.

Firstly, overviews of the definitions, descriptive epidemiology and aetiology, as well as the management of oesophageal adenocarcinoma, are presented.

Secondly, the literature investigating associations between physical activity and the risk of developing GORD, Barrett's oesophagus oesophageal adenocarcinoma is reviewed.

Thirdly, the results of an original prospective cohort study of 30 445 people resident in Norfolk in the United Kingdom (UK) enrolled in The European Prospective Investigation of Cancer (EPIC-Norfolk) examining the associations between both recreational and occupational levels of physical activity and the development of Barrett's oesophagus (the precursor lesion of oesophageal adenocarcinoma) are presented, the first such epidemiological study in this field.

1.1 Introduction

1.1.1 Definition of oesophageal adenocarcinoma

Histological subtypes

The two main histological types of oesophageal cancer are adenocarcinoma and squamous cell carcinoma. These two cancers are very different in their; pathogenesis, epidemiology, clinical management and prognosis. Squamous cell cancer progresses from epithelial dysplasia to carcinoma *in situ* and then invasive oesophageal carcinoma, with tobacco and alcohol use identified as major positive risk factors.¹ Oesophageal adenocarcinoma occurs due to dysplastic change in the mucosa, where chronic reflux of gastric and duodenal contents into the lower oesophagus results in reactive metaplasia of the normal squamous epithelium into a glandular mucosa (Barrett's oesophagus).² Proliferation of this altered mucosa generates biologically unstable cells, with damaged DNA, that are prone to subsequent malignant degeneration.³ Oesophageal adenocarcinoma is the histological subtype which is investigated in this thesis as there is epidemiological evidence that sedentary behaviours⁴ and obesity⁵ are associated with its aetiology. Furthermore, the incidence of oesophageal adenocarcinoma is rapidly rising in the Western world, and now represents the commonest histological subtype of oesophageal cancer in the UK.⁶ Understanding the aetiology of this cancer is therefore important to develop and institute preventative measures.

Oesophageal junctional tumours

Cancer of the oesophagus describes tumours which may involve either the oesophagus in isolation, or the junction between the oesophagus and stomach - so called junctional or oesophagogastric junction (OGJ) tumours. Historically, there has been confusion about the distinction between oesophageal and gastric cancers when they occur at the junction.⁷ Defining which group a cancer belongs to has importance because, as with the differences between the histological subtypes of oesophageal cancers, gastric cancers are also distinct from oesophageal cancer in both their aetiology and clinical management.⁸ The Siewert classification system, proposed in the 1980's, defined junctional tumours as three distinct types based on their anatomic positions relative to the OGJ.⁹ Type I are distal oesophageal tumours which infiltrate the OGJ from above. Type II are those arising

at the OGJ. Type III, are subcardial gastric tumours which invade the OGJ and distal oesophagus from below (figure 1.1). The most recent definition of oesophageal junctional cancers, in the eighth addition of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) staging manual, defines junctional tumours to be oesophageal cancer if the tumour epicentre is located no more than 2cm into the proximal stomach (Siewert types I/II).¹⁰ Tumours with the epicentre located more than 2cm into the proximal stomach are gastric cancers (Siewert type III). Therefore, according to these recent staging definitions, Siewert type I and II tumours are oesophageal cancers, while type III (where the tumour centre is located >2cm in the stomach) are defined as gastric cancers.

Figure 1.1 Schematic of Siewert type I, II and III oesophagogastric cancers showing a dashed 2cm boundary line, which differentiates oesophageal from gastric cancers.

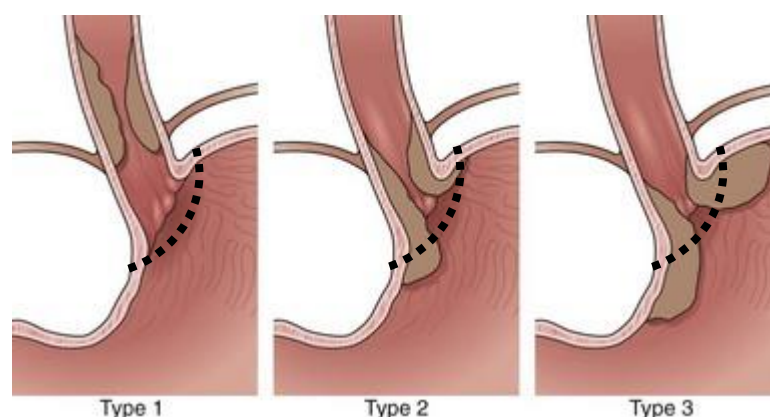


Image from Siewert J, Stein H, Carcinoma of the cardia: Carcinoma of the gastroesophageal junction—classification, pathology and extent of resection. *Dis Esophagus*. 9:173–182.¹¹

1.1.2 Incidence of oesophageal adenocarcinoma

Approximately 52 000 cases of oesophageal adenocarcinoma occurred worldwide in 2012, with an age standardised incidence rate (ASR) of 0.7/100 000 (1.1 in men and 0.3 in women).¹² Of these, 46% occurred in Northern and Western Europe, North America and Oceania (figures 1.2 and 1.3). The regions with the lowest incidences were East/South East Asia and Sub-Saharan Africa (0.3/100 000), although this figure may represent less comprehensive data collected from these regions.¹² The highest ASR for oesophageal adenocarcinoma in the world was in the UK (7.2/100 000 in men and 1.4/100 000 in women).¹² An analysis of population-based cancer registry data in England between 1971 and 2009, estimated a continued increase in incidence of approximately 2-3 cases/ 100 000 person years per decade.¹³

Figure 1.2 A world map showing the distribution of age-standardised incidence rates for oesophageal adenocarcinoma in men.

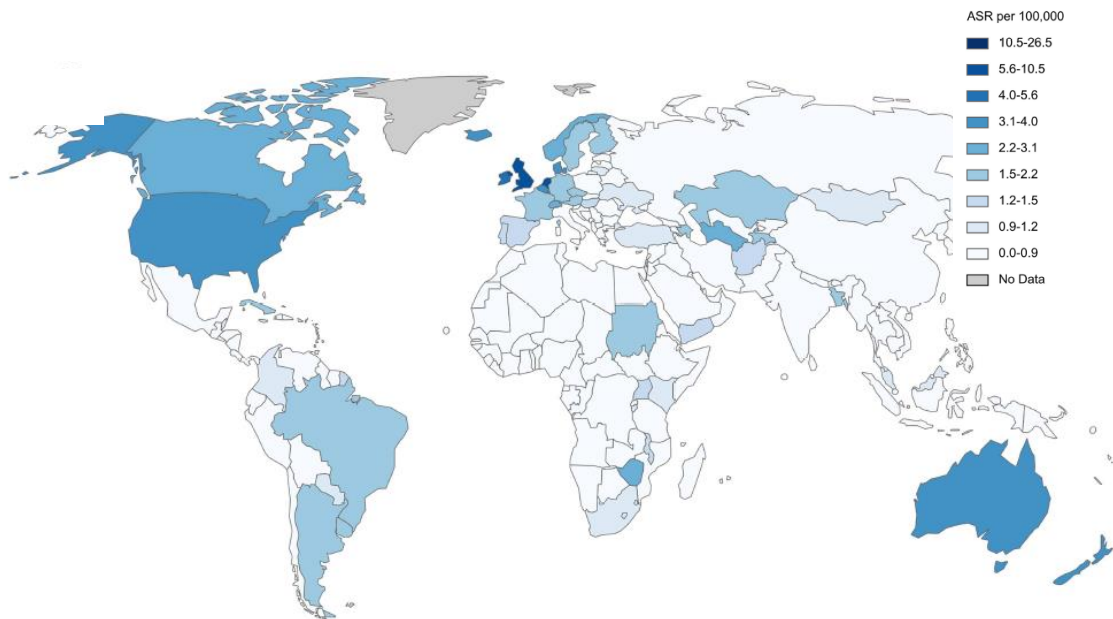
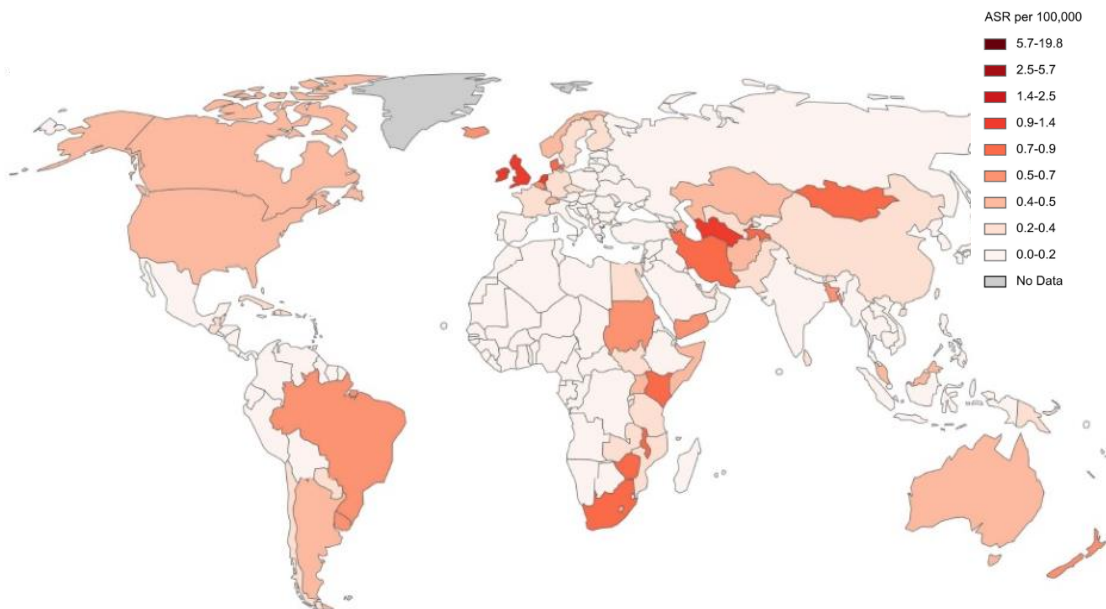


Figure 1.3 A world map showing the distribution of age-standardised incidence rates for oesophageal adenocarcinoma in women.



The highest reported incidence of oesophageal adenocarcinoma in the world was in the UK (7.2/100 000 in men and 1.4/100 000 in women). Images from Arnold M, Soerjomataram I, Ferlay J, *et al.* Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015;64(3):381-7.¹²

1.1.3 Aetiology of oesophageal adenocarcinoma

Histological surveillance studies have demonstrated that oesophageal adenocarcinoma develops through a morphological sequence of inflammation, metaplasia, dysplasia and eventual cancer.¹⁴ Two early distinct diseases mark this progression to cancer: gastroesophageal reflux disease (GORD) and Barrett's oesophagus.

Gastro-oesophageal reflux disease

Whilst occasional reflux of gastric contents into the lower oesophagus is a normal physiological occurrence, prolonged reflux, which causes troublesome symptoms is described as gastro-oesophageal reflux disease (GORD).¹⁵ GORD is the single most important risk factor for oesophageal adenocarcinoma.¹⁶ A systematic review estimated the prevalence of GORD to be 10-20% in the Western world, with a lower prevalence in Asia.¹⁷ The main causative mechanism underlying reflux is thought to be failure of the lower oesophageal sphincter (LOS),¹⁸ either through anatomical disruption of the LOS and diaphragm, or through its inappropriate relaxation.^{19 20}

Anatomical disruption of the LOS occurs in hiatal hernia disease, a condition in which the gastroesophageal junction and stomach are displaced superiorly above the diaphragm and through the oesophageal hiatus into the mediastinum. Hiatus hernias are thought to occur through damage to the phrenoesophageal ligament (responsible for maintaining the normal position of the gastroesophageal junction). Excessive stresses from increased intra-abdominal pressures as in pregnancy, central adiposity and strenuous vigorous exercise are thought to play important roles.²¹ If anatomical displacement of the gastroesophageal junction occurs, then contractions of the crural diaphragm are no longer over and around the LOS, compromising the anti-reflux barrier. Hiatus hernia disease is present in up to 72- 96% of patients with Barrett's oesophagus.²²

Figure 1.4 Schematic of the lower oesophageal sphincter showing the related adjacent structures.

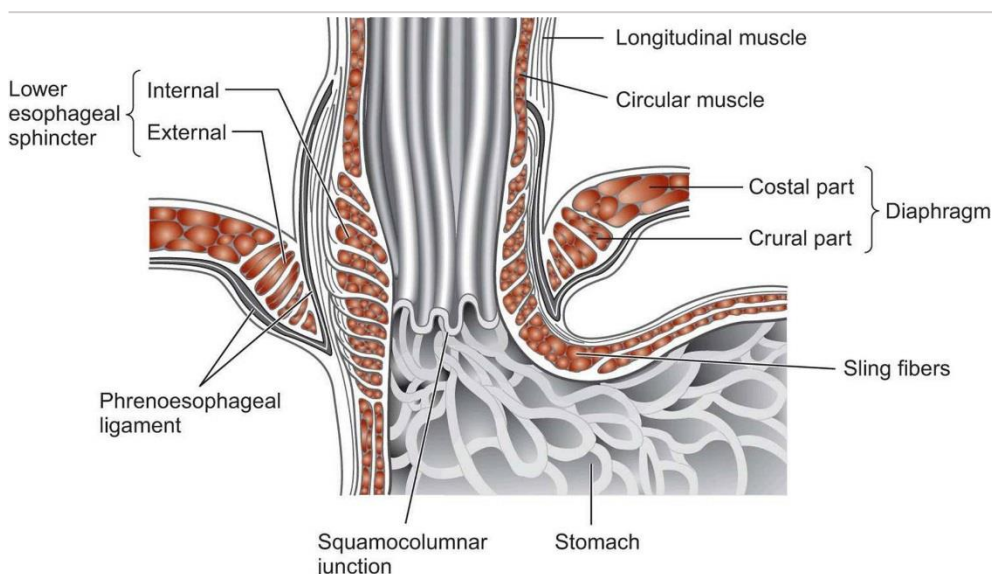


Image taken from Ganong's Review of Medical Physiology.²³

Inappropriate relaxation of the LOS is described as transient lower oesophageal sphincter relaxations (TLOSRS). These are pathological prolonged relaxations of the LOS and crural diaphragm in the absence of swallowing.¹⁸ Distension of the stomach by air or food is thought to activate gastric vagal afferents and/or stretch receptors in the subcardiac region, triggering a TLOSRS.¹⁸ Prolonged GORD as a result of hiatus hernia and TLOSRS lead to endoscopic histological inflammation of the oesophagus (oesophagitis). The clinical symptoms of GORD and oesophagitis typically include dyspepsia and regurgitation.²⁴ Other less common symptoms are epigastric discomfort, nausea, bloating, belching and fullness.²⁴ Rare symptoms are dysphagia, cough, wheeze and laryngitis.²⁴

The constituents of reflux most likely to cause oesophagitis are both gastric (hydrochloric acid and pepsin) and duodenal (bile acids and trypsin). Animal models have demonstrated the injurious effect of various gut secretions on oesophageal mucosa including: high concentrations of acid, lower concentrations of acid in the presence of the enzyme pepsin, and bile acids and the pancreatic proteolytic enzyme trypsin.²⁵ Hydrochloric acid is thought to damage cellular pump mechanisms, notably Na^+/K^+ ATP and amiloride sensitive Na^+ pumps, causing a raised intracellular Na^+ concentration with resultant cell swelling and death.²⁵ Both pepsin and trypsin are proteolytic and cause shedding of the epithelial cell surface, probably by digestion of intercellular structures.²⁶ The pathogenic mechanism of bile acids is less clear, but may be via its detergent properties causing break

down of lipid membranes.²⁷ Alternatively, because of the lipophilic nature of bile, it may cross cell membranes and interfere with cellular functions.²⁸

Barrett's Oesophagus

The injurious effects of acid, bile and enzymes in GORD results in the release of inflammatory cytokines, with an increase in IL-1 β , IL-8 (pro-inflammatory neutrophil chemo attractants) and IFN- γ (Th-1 cytokine).^{29 30} This local inflammatory environment is highly mutagenic,³¹ resulting in the intracellular accumulation of genetic defects. This promotes mutagenesis in columnar cells with a selective proliferative advantage over genetically normal squamous cells, resulting in metaplasia.³² Barrett's oesophagus is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by such metaplastic columnar epithelium.³³

Figure 1.5 Macroscopic view of Barrett's oesophagus obtained at endoscopy.



Barrett's oesophagus can be appreciated macroscopically at endoscopy, where the normal pale-pink squamous mucosa is contrasted with the deep salmon-pink metaplastic mucosa of Barrett's oesophagus. A prominent tongue of Barrett's mucosa can be seen in the 4 o'clock position, with a smaller projection at 8 o'clock.

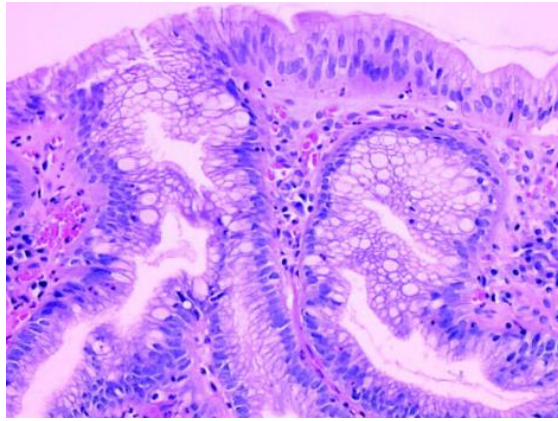
Three subtypes of metaplastic columnar epithelium have been identified and classified in Barrett's oesophagus: junctional-type (containing cardiac mucous glands), atrophic gastric fundic or oxyntocardiac (containing mucous, chief and parietal cells), and specialised/intestinal (with mucous glands, a villiform surface and goblet cells like those in the intestines). Intestinal epithelium is thought to be the most biologically unstable and most prone to malignant degeneration, which occurs in a sequence from metaplasia to dysplasia to malignant infiltration.

Approximately 3-5% of patients with GORD will progress to Barrett's oesophagus.³⁴ However, the precise prevalence of Barrett's oesophagus is unknown as approximately 45% of affected people are asymptomatic and therefore go undiagnosed by endoscopy.¹⁴ Evidence from population based studies, where asymptomatic people had an upper gastrointestinal endoscopy, estimated the prevalence to be 0.5-1.5% in Western populations.¹⁴ The public health importance of Barrett's oesophagus lies in its association with the development of oesophageal adenocarcinoma¹⁶ with an absolute risk of progression of 0.2 to 0.7%, per patient, per year.³⁵

Dysplasia

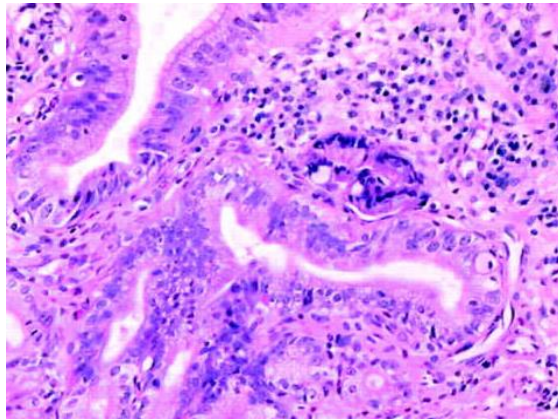
Histologically, progression from Barrett's mucosa to invasive cancer occurs through a sequence of increasing grades of dysplasia.³⁶ Dysplasia is defined as a morphologically changed (neoplastic) epithelium confined within the basement membrane of the gland from which it arises.³⁷ The level of dysplasia can be determined by microscopy of oesophageal tissue biopsies obtained at upper gastrointestinal endoscopy, and described in terms of both the architectural and cytological abnormalities (figures 1.6-1.8). Architectural changes include glandular distortion and crowding, while cytological abnormalities include enlargement of the nucleus and nucleolus, and hyperchromatism.³⁷ Based on the number and degree of abnormalities present, dysplasia is graded from low-grade dysplasia (LGD) to high-grade dysplasia (HGD). Surveillance cohort studies of patients with Barrett's oesophagus have established that those with dysplasia are at an increased risk of oesophageal adenocarcinoma,³⁸ with HGD representing the highest risk of invasive progression.

Figure 1.6 Histology slide of Barrett's oesophagus (haematoxylin–eosin, original magnification x400)



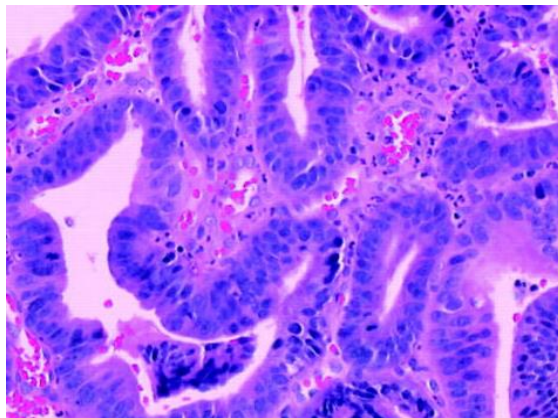
The epithelium is composed of goblet cells interspersed between intermediate mucous cells, both in the surface and glandular epithelium. The nuclei are basally located, small and ovoid. All images on this page are from Flejou, J-F, Barrett's oesophagus: from metaplasia to dysplasia and cancer, Gut 2005;54(Suppl I):i6–i12.³⁶

Figure 1.7 Histology slide of low grade dysplasia (haematoxylin–eosin, original magnification x400)



Low grade architectural and cytological abnormalities are present including some patchy losses of basal orientation of surface nuclei with an increase in nuclear size.

Figure 1.8 Histology slide of high-grade dysplasia (haematoxylin–eosin, original magnification x400)



High grade architectural and cytological abnormalities are present including scant cytoplasm, and enlarged and hyperchromatic nuclei.

As the level of dysplasia is based on the interpretation of morphology, assessment of dysplasia is highly subjective resulting in substantial variations in diagnoses between pathologists.¹⁶ Therefore, the precise conversion rates from LGD to HGD and/or adenocarcinoma are uncertain as there is great variability in estimates between studies. A recent review of 12 studies with 971 patients estimated an annual incidence of progression from LGD to HGD and/or oesophageal adenocarcinoma of between 0.5% and 4% per year.³⁹ However, the difficulties in accurately diagnosing LGD were noted. For LGD, only 37.5% of samples had a consensus on diagnosis after review by two or more expert pathologists. Furthermore, LGD was frequently not detected on follow-up biopsies, suggesting either regression may occur or an incorrect initial diagnosis was made.¹⁶ The above pooled estimate is therefore likely to be affected by misclassification bias. Estimates from different studies for the progression from HGD to adenocarcinoma are also variable, with 5-year cumulative incidences of between 10% and 59%.¹⁶

Other risk factors for oesophageal adenocarcinoma

Why some patients with GORD progress to Barrett's oesophagus and then to adenocarcinoma is poorly understood. The rapidly rising incidence of oesophageal adenocarcinoma in the UK is thought to be related to environmental exposures, including obesity, which, due to changes in diet and decreased levels of physical activity is rapidly increasing.⁴⁰ Body fat, in particular visceral fat, is metabolically active, releasing adipocytokines, resulting in low-grade inflammation, chronic hyperinsulinemia and an increased risk of insulin-like growth factor-mediated carcinogenesis.⁴¹ However, obesity may also increase disease risk through a mass effect, where central adiposity raises intra-gastric pressures, which in turn compromises the LOS, resulting in reflux disease.⁴² Meta-analyses of epidemiological studies have estimated that obesity (BMI > 30 kg/m²), compared to a normal weight (18.5-24.9 kg/m²), is a positive risk factor for GORD (OR = 1.94, 95% CI 1.47-2.57)⁴³, Barrett's oesophagus (OR = 1.70, 95% CI 1.36-2.12)⁴⁴ and oesophageal adenocarcinoma (OR = 2.78, 95% CI 1.85-4.16).⁴³ Currently, it is unclear if fatty foods are an independent risk factor for oesophageal adenocarcinoma, but data from case-control studies suggests that an increased intake of fruit,⁴⁵ plant-based fibre⁴⁶ and vegetables⁴⁸ is inversely associated with disease; although spurious over-estimations of the effect sizes due to recall bias, which are inherent in case-control studies, may explain these findings. Based on a review of population-based case-control studies it is likely that alcohol consumption is not associated with oesophageal

adenocarcinoma risk, although the methodological weaknesses of case-control studies in terms of selection and information biases were noted.⁴⁹ Smoking does appear to be associated with disease risk, with summarised case-control data suggesting it approximately doubles the risk of disease.¹⁶

Unmodifiable risk factors include age, with 56% of cases diagnosed in people aged 70 years and over⁵⁰, and gender,⁴⁰ with a striking disparity between incidence in both sexes; which is as high as 5:1 (men: women) in the UK.¹² The reasons for this higher incidence in men are unknown, but a possible explanation is the difference in distribution of excess adiposity, where men are prone to centripetal storage, while premenopausal women tend to store fat in the buttocks, thighs and hips, but not around the waist.⁵¹ Adiposity in men may therefore predispose to raised intra-gastric pressures and reflux. Premenopausal oestrogens may also be influential, both in terms of determining fat distribution in premenopausal women and via their anti-inflammatory properties, which may also be protective.¹⁴ The role of physical activity in the aetiologies of both Barrett's oesophagus and oesophageal adenocarcinoma is discussed in detail later in this chapter.

1.1.4 Management of oesophageal adenocarcinoma

Screening for oesophageal adenocarcinoma

The British Society of Gastroenterology has published guidelines relating to the use of screening for Barrett's oesophagus by endoscopy.³³ It is recommended that patients with chronic GORD symptoms are not screened unless multiple risk factors are present (>50 years, white, male, obesity, family history). It is further recommended that patients with Barrett's oesophagus (shorter than 3cm with intestinal metaplasia) should receive endoscopic surveillance every 3-5 years, or 2-3 years if ≥ 3 cm, while those with low-grade dysplasia should receive an endoscopy every 6 months.³³ However, a recent review found that up to 90% of patients with Barrett's oesophagus die from causes unrelated to their Barrett's disease and that up 93% of oesophageal adenocarcinomas are not detected by endoscopic screening programmes, but rather present as symptomatic cancers.⁵² This represents both significant over-diagnosis of Barrett's oesophagus and under-diagnosis of oesophageal adenocarcinoma through endoscopic screening.

Future advances in genome technology may present a more accurate screening method to stratify patients with Barrett's oesophagus with the highest risk of cancer progression. Genetic studies have attempted to identify the molecular events which can be used to predict the risk of progression. In a multivariable analysis from a genetic study examining both tumour suppressor genes (including TP53 and CDKN2A) and DNA abnormalities in Barrett's oesophagus: chromosome instability markers, loss of heterozygosity (LOH) and DNA content abnormalities (tetraploidy and aneuploidy) were all independent risk factors for cancer progression.³¹ Future research in this area is required to help make surveillance programmes more effective, both clinically and financially.

Presentation and prognosis of patients with oesophageal adenocarcinoma

Most patients with oesophageal adenocarcinoma tend to present with late symptoms of tumour invasion of the oesophagus (difficulty and pain with swallowing resulting in associated weight loss). The commonest route of diagnosis is via a 'two week wait' referral from a General Practitioner, where subsequent hospital endoscopy obtains tissue diagnosis.⁵³ The chance of survival from oesophageal cancer is bleak, with only 15% of patients alive at 5 years and 12% at 10 years.⁵³ This poor survival is related to both the aggressive nature of the cancer and its late clinical presentation.

Staging and treatment of oesophageal adenocarcinoma

The clinical staging of oesophageal adenocarcinoma is crucial in determining the appropriate treatment. Staging usually always includes endoscopy and computed tomography (CT) of the chest, abdomen and pelvis. If at this stage there is clear evidence of metastatic disease, no further investigations are usually indicated. However, if a patient is being considered for potentially curative treatment, further staging modalities, such as positron-emission (PET) CT (to determine T and M staging), endoscopic ultrasound (EUS) (to determine precise T staging), or laparoscopy (to determine N and M staging) may be used. Management is informed by the depth of tumour invasion (T), lymph node involvement (N) and the presence or absence of distant metastasis (M). A cancer staging system maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) developed the TNM classification based on these three variables. The latest TNM staging system in current clinical use (7th Edition) is based on data from 4 627 patients from three different continents who underwent oesophagectomy without adjuvant therapy.⁵⁴ Generally, superficial tumours (T1a)

without nodal or metastatic spread may be treated by endoscopic mucosal resection, although surgery may also be indicated. T1b tumours may be managed surgically without the need for adjuvant chemotherapy or radiotherapy. For tumours with nodal involvement and up to T4a, oesophagectomy with adjuvant chemotherapy and or radiotherapy is indicated.⁵⁵ Metastatic tumours or those with invasion of structures unamendable to surgery are usually treated palliatively.

Figure 1.9 Schematic of the TNM staging system for oesophageal adenocarcinoma

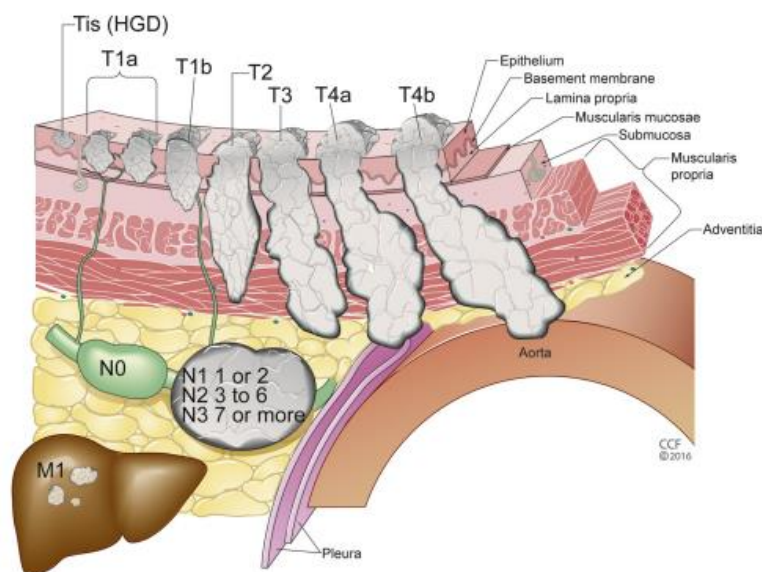


Image from Rice TW, Ishwaran H, Ferguson MK, *et al.* Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. *J Thorac Oncol* 2017;12(1):36-42.¹⁰

The roles of surgery, chemotherapy and radiotherapy in the management of oesophageal adenocarcinoma

Surgery is the only treatment modality to date, which consistently offers a potential cure for oesophageal adenocarcinoma.³⁴ However, surgery as monotherapy, particularly when there is node positive disease, has a poorer survival compared to surgery combined with other therapies such as chemotherapy or radiotherapy.⁵⁵ Whether combination therapy should be bimodal (surgery and chemotherapy) or trimodal (inclusion of radiotherapy) remains unclear. The MAGIC trial reported that induction chemotherapy without radiotherapy provided a survival benefit at 5 years over surgery alone (HR 0.75, 95% CI 0.60-0.93), $p=0.009$ and is the treatment adopted in the United Kingdom for oesophageal

adenocarcinoma. This chemotherapy regimen consists of three preoperative and three postoperative cycles of epirubicin, cisplatin and fluorouracil. The exception to this regime is in patients with T1N0 disease who may undergo surgery alone.³⁴

1.1.5 Plausible biological mechanisms for the effects of physical activity on the development of GORD, Barrett's oesophagus and oesophageal adenocarcinoma

As the incidence of oesophageal adenocarcinoma is rapidly rising and the prognosis is poor, understanding the aetiology of this cancer, including its pre-malignant stages (GORD and Barrett's oesophagus) is important to aid prevention. Physical activity may influence the risk of GORD in opposing ways depending on both its type and intensity. Therefore, consideration of physical activity related to both occupation and recreation may have relevance to its aetiology. There are several plausible mechanisms through which exercise could induce reflux, although the precise details are not fully understood. Intra-abdominal pressure is increased by recreational activities which involve abdominal straining such as weightlifting or cycling (with a bent over posture), which may force gastric contents retrograde, beyond the lower oesophageal sphincter into the oesophagus.⁵⁶ Also, vigorous exercise, that is above 75% of VO_{2max} , has been shown to delay gastric emptying,⁵⁷ likely by decreasing splanchnic blood flow.⁵⁸ These mechanisms may account for the documented positive relationship between reflux episodes and high intensity exercise,⁵⁹ with a high prevalence of GORD in elite athletes (estimated at 60%).⁵⁶ Occupational activity may also increase the risk of GORD, particularly in heavy manual jobs, which involve bending and heavy lifting. Occupational activities are also more likely to occur post-prandially when reflux episodes are common.⁶⁰ Associations between heavy manual occupations and reflux have not been previously studied in the literature, but an increased risk of reflux in occupations which involve intra-abdominal straining, such as in wind instrument players^{61 62} and choir or opera singers^{62 63} are documented.

Alternatively, moderate levels of recreational physical activity may protect against GORD. Engagement in regular exercise helps maintain a normal body weight,⁶⁴ preventing obesity induced reflux disease.⁶⁵⁻⁶⁸ It has also been postulated that regular exercise strengthens the crural diaphragm,⁶⁹ which is an important component of the anti-reflux barrier of the LOS. Finally, low or moderate intensity (30-60% of VO_{2max}) running or walking

increases, rather than delays, gastric emptying and may therefore decrease reflux episodes.⁵⁷ As the type, duration and intensity of physical activity at both work and leisure may influence reflux in opposing ways, measuring the precise characteristics of recreational and occupational activities is likely to be important in aetiological epidemiological investigations, although to the best of our knowledge this has not been studied previously.

Physical activity may also influence the development of Barrett's oesophagus. As discussed previously, the metaplastic transition from a squamous to columnar oesophageal epithelium is thought to be driven by inflammation,^{29 30} where chronic exposure of oesophageal mucosa to reflux results in the release of pro-inflammatory cytokines and a subsequent reactive metaplastic change.^{29 30} Regular physical activity reduces inflammatory biomarker expression, and may prevent this inflammation-driven process.⁷⁰⁻⁷³ However, further work is required to elucidate the relative importance of the potential anti-inflammatory mediated effect of physical activity.

Finally, physical activity may have direct anticancer effects. Regular physical activity may not only regulate body fat levels, but also lower plasma insulin and insulin resistance over and above the effect of weight loss alone.⁷⁴ Hyperinsulinemia and insulin resistance are both associated with increased cancer risk.⁷⁵ Furthermore, aerobic exercise is thought to reduce oxidative stress and improve DNA repair, which may inhibit carcinogenesis.⁷⁶ Therefore, increased levels of physical activity could have protective pathways which may or may not rely on modification of BMI, although more work is needed to determine the relevance and importance of these mechanisms.

To support the biological mechanisms for how physical activity may influence the risk of oesophageal adenocarcinoma and its precursor diseases (GORD, and Barrett's oesophagus) evidence from epidemiological studies is needed. The next section of this chapter reviews the published epidemiological evidence for associations between physical activity and the risk of all three disease states, which together constitute a metaplasia-dysplasia-carcinoma sequence. The methodological strengths and weaknesses of such work are also discussed.

1.2 Does physical activity influence the development of gastroesophageal reflux disease, Barrett's oesophagus and oesophageal adenocarcinoma? A review of the literature with a meta-analysis

1.2.1 Abstract

Background: Physical activity affects the functioning of the gastrointestinal system through both local and systemic effects and may play an important role in reducing the risk of oesophageal adenocarcinoma. This review assesses the published epidemiological literature for associations between physical activity and the development of oesophageal adenocarcinoma and its precursor diseases; gastroesophageal reflux disease (GORD) and Barrett's oesophagus.

Methods: A search of PubMed, Medline, Embase and CINAHL was conducted from their inception to 25th March 2017 for analytical studies that examined associations between recreational and/or occupational levels of physical activity and the risk of GORD, Barrett's oesophagus and oesophageal adenocarcinoma. Where appropriate, a meta-analysis of effects was undertaken.

Results: Seven studies were included (2 cohort, 5 case-control). For GORD, there were 3 case-control studies with 10 200 cases among 78 034 participants, with a pooled estimated OR of 0.67 (95% CI 0.57-0.78) for high vs. low levels of recreational physical activity. In Barrett's oesophagus, there was a single case-control study, which reported no association between recreational activity and disease risk, OR 1.19 (95% CI 0.81-1.73). Occupational activity was not investigated. For oesophageal adenocarcinoma there were 3 studies (2 prospective cohort, 1 case control) with 666 cases in 910 376 participants. The largest cohort study reported an inverse association for high vs. low levels of recreational physical activity (RR 0.68, 95% CI 0.48-0.96). The remaining 2 studies reported no associations with either occupational or combined recreational and occupational activities. Heterogeneity in the measurement of exposure (recreational, occupational and both) made a pooled estimate for oesophageal adenocarcinoma inappropriate.

Conclusion: Although limited, there is some evidence that higher levels of recreational physical activity may reduce the risk of both GORD and oesophageal adenocarcinoma, but further large cohort studies examining the type, intensity and duration of activities that may be beneficial are needed.

1.2.2 Introduction

As discussed in the previous section there is an ongoing rise in the incidence of oesophageal adenocarcinoma, which is reaching epidemic proportions.^{12 13 77 78} Geographical variations, with higher incidences in more affluent countries, suggests that aspects of lifestyle may be involved in its aetiology.¹² Increasingly sedentary behaviours with reduced levels of both occupational and recreational physical activity may be an important contributing factor.⁷⁹ Histological surveillance studies have demonstrated that oesophageal adenocarcinoma develops through a morphological sequence of inflammation, metaplasia, dysplasia and eventual cancer, with gastroesophageal reflux disease (GORD), Barrett's oesophagus, and oesophageal adenocarcinoma clinically marking the progression. If moderate levels of physical activity have a protective effect, inverse associations in published studies between regular engagement and the development of all three diseases would be anticipated. Similarly, if vigorous exercise, particularly though occupation, is hazardous; then consistent positive associations would be found. Therefore, the aim was to review the reported associations between physical activity and GORD, Barrett's oesophagus and oesophageal adenocarcinoma in the published literature.

1.2.3 Methods

Eligibility criteria

Original investigations with an analytical design and control group (i.e. randomised controlled trials (RCTs), cohort and case-control studies) that examined levels of physical activity (occupational and/or recreational) and the incidence of GORD, Barrett's oesophagus and oesophageal adenocarcinoma were selected. Only studies which described both the method of measuring physical activity (e.g. questionnaire) and its quantification (e.g. ≥ 30 mins of recreational exercise/day) were included. The measurement of the disease outcome needed to be clearly stated (e.g. endoscopic and histological confirmation). Furthermore, only studies which specifically investigated oesophageal adenocarcinoma as a distinct histological subtype were included.

Search strategy

A literature search of PUBMED, EMBASE, MEDLINE and CINAHL (from commencement to 25th March 2017) was conducted using the terms: “exercise”, “activity”, “physical”, “occupational”, “recreational”, “Barrett's”, “oesophagus”, “oesophageal”, “adenocarcinoma”, “cancer”, “carcinoma”, “GORD”, “heartburn”, “reflux”, “acid”, “bile”, “gastro-oesophageal”, “oesophagitis”, “oesophageal inflammation”. An independent search of each disease was undertaken using both English and American (e.g. GERD, esophagus) spellings. The reference lists of all selected articles, as well as reviews, were also searched to identify other relevant papers.

Data synthesis and statistical analysis

A total of 7 studies were included in this review (2 cohort, 5 case-control). No RCTs were identified. Data was extracted from each study (table 1.1). For a meta-analysis of GORD, Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to calculate a summary effect using the inverse variance method, based on the odds ratios (ORs) and upper and lower boundaries of the confidence intervals (CIs) in the included studies. Due to variations in the type, duration and intensity of recreational physical activity between studies, a random effects model was applied to estimate the mean of a distribution of effects. Only a single study in Barrett's oesophagus was identified. For oesophageal adenocarcinoma, there was significant heterogeneity in the measurement of exposures (either recreational⁴ or occupational activity⁸⁰ or a combination of both).⁸¹ Therefore, meta-analyses were not appropriate for these two diseases.

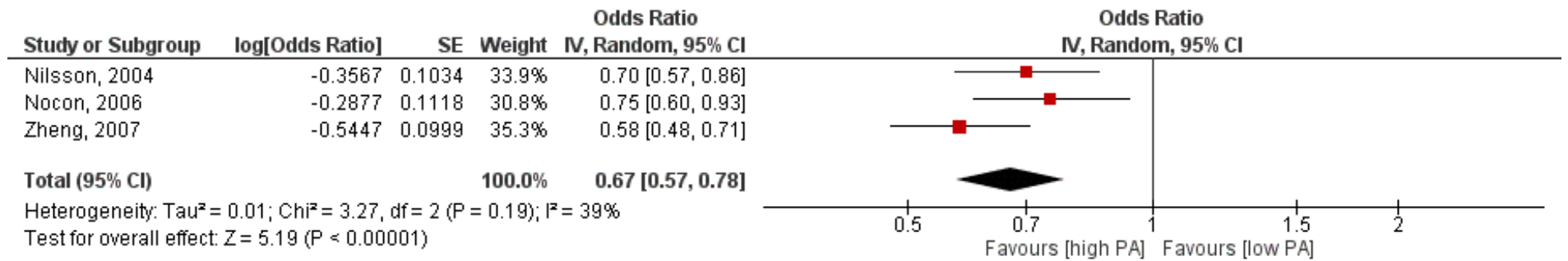
1.2.4 Results

Physical activity and the development of GORD

The search terms identified 1 426 potentially relevant articles, which were screened by title; with inclusion of 66. After removal of duplicates, 6 were included by abstract. Of these, 3 were excluded by full paper review according to the inclusion criteria. One paper was identified from the reference lists, but later excluded after full review. In total, 3 papers were included and the characteristics are shown in table 1.1. All 3 were case-control studies with a total of 10 200 symptomatic cases of GORD identified among 78 034 participants. The largest case-control study was of 43 363 men and women aged

≥20 years from a single county in Norway. In this study, physical activity levels were measured with a questionnaire and divided into 4 categories according to the number of 30 min recreational exercise sessions engaged in per week (none, <1/week, 1-3/week and >3/week). GORD was defined as self-reported 'severe and recurrent heartburn or regurgitation during the previous 12 months'. The authors reported an OR of 0.50 (95% CI 0.40-0.70) for 30mins/week vs none and development of GORD,⁶⁹ but a lesser association with exercise levels above this, OR 0.70 (95% CI 0.60-0.90) for >90mins vs. none. The second largest study was of 27 717 monozygotic twins aged 42-104 years recruited from the Swedish Twin Registry. Both recreational and occupational activities were measured by questionnaire and divided into 4 categories. The highest recreational physical activity category was defined as 'much', the lowest as 'almost no'. GORD symptoms were assessed by questionnaire. The authors reported an OR of 0.60 (95% CI 0.47-0.77) for men (highest vs. lowest levels of recreational physical activity and GORD symptoms) and 0.56 (95% CI 0.41-0.75) for women, with a dose-dependent trend, $p=0.002$ and $p=0.001$, respectively.⁸² No associations were found for high vs. low levels of occupational activity for either men, OR 1.23 (95% CI 0.99-1.53), or women, OR 1.16 (95% CI 0.78-1.72). The smallest study was of 6 954 German men and women aged 18-79 years recruited by national survey. Only sports activities were measured and categorised as: none, ≤2hrs/week and >2hrs/week. GORD was established by self-reported questionnaire on symptoms of heartburn or regurgitation. The authors reported an OR of 0.75 (95% CI 0.60-0.93) for sports activity of >2hrs/week vs. no sports.⁸³ All studies adjusted for known covariates (age, gender), but also for unestablished risk factors (e.g. education, coffee consumption and intake of salt, dietary fibre and bread). All adjusted for BMI, and by doing so they assumed that physical activity has an independent effect that does not rely on a reciprocal change in BMI. None conducted an unadjusted BMI analysis to assess the effect of physical activity via the regulation or reduction of BMI (the BMI mediated effect). In a meta-analysis, the estimated mean effects of the 3 studies produced an OR of 0.67 (95% CI 0.57-0.78) for the highest vs lowest levels of physical activity and the risk of GORD (figure 1.9). Statistical heterogeneity was low ($I^2 = 39\%$).

Figure 1.10 Forest plot of the association between high vs. low levels of recreational physical activity (PA) and the risk of GORD



The findings from this meta-analysis suggests that higher levels of physical activity may reduce the risk of GORD by a third. However, there are several potential sources of bias which should be considered when interpreting the result. None of the three studies used a validated questionnaire to measure physical activity, which may represent a source of measurement error, reducing any associations towards the null. Furthermore, the specific types of physical activities (e.g. cycling, swimming, running) were not analysed in any of the studies. Instead, all were grouped together and categorised according to duration (e.g. 'physical activity of at least 30mins' or 'sports \leq 2hrs/week'). This may suffice to explore the cardiometabolic benefits of physical activity, but in the context of reflux disease; where specific activities or intensities might increase risk, such categorisation may confound associations. Not accounting for occupational activity is a further potential source of error as it is likely to be an important confounder, particularly in the case of heavy manual work, which may involve intra-abdominal straining. However, only one of the studies undertook a separate analysis of both occupational and recreational activities,⁸² where the risk of GORD did appear to be increased in strenuous occupations, OR 1.23 (95% CI 0.99-1.53 - most physically strenuous vs. sedentary), although conventional statistical significance was not demonstrated, $p_{\text{trend}} = 0.055$. Use of a validated questionnaire to measure GORD was used in two studies,^{69 82} but none, by the nature of their retrospective designs, measured exposure prior to disease onset. This may be a significant source of measurement bias (if cases reduced their exercise levels due to reflux symptoms and exercise was measured during their symptomatic period). Finally, the study of monozygotic same sex twins represents a select population, and although participants were specifically chosen to examine the genetic influences of GORD, the generalisability of these findings is limited.

Summary of findings: There is limited observational evidence that engaging in any recreational physical activity may reduce the risk of GORD by up to a third. However, to clarify such associations, a large and well-designed prospective cohort study, where exposure is accurately measured prior to disease onset, is required. The specific effect of occupational physical activities is uncertain as there is only one study, highlighting the need for further investigations.

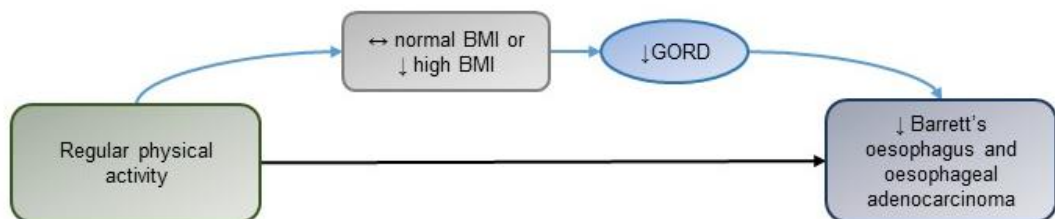
Physical activity and the development of Barrett's oesophagus

Sixty seven potentially relevant articles were screened by title and 10 were suitable for abstract review. After removal of duplicates and screening by abstract, only 1 remained, which was included by full paper review. This was a case-control investigation of 307 cases of Barrett's oesophagus and 1724 controls. The participants were US war veterans (men and women) aged 40-80 years recruited by a screening and surveillance endoscopy programme in Texas, USA. One hundred and six (35%) of the cases were known to have Barrett's oesophagus prior to recruitment. The exposure was measured using the International Physical Activity Questionnaire (IPAQ), which asks about the previous 7 days recreational exercise (occupational exercise was not measured). Cases were confirmed both endoscopically and histologically. The authors reported no association between the highest vs. lowest levels of physical activity and odds of Barrett's oesophagus (OR = 1.19, 95% CI 0.82-1.73).⁸⁴ The statistical model used in the study adjusted for age, sex, race, GORD symptoms, *Helicobacter pylori* infection status (which may reduce risk if positive), BMI and high waist to hip ratio (WHR).

Although IPAQ is a validated physical activity questionnaire, its use in this study population (to measure lifelong physical activity exposure) may introduce significant measurement error. This is because war veterans are likely to have engaged in high levels of physical activity during their military service, which would not be reflected in their previous 7 days post-retirement activities as measured by IPAQ. Measurement bias is also likely to occur in the 106 surveillance cases of Barrett's disease who may have changed their physical activity levels due to symptoms. Therefore, physical activity would have been inappropriately measured during the symptomatic period, or after disease onset. The authors also adjusted for GORD and BMI/WHR which lie along the presumed causal pathway (figure 1.10). If we assume that the protective effect of exercise is largely by regulation of weight and reduction of reflux risk (a reasonable assumption) then controlling on these variables is likely to reduce any association between physical activity and Barrett's oesophagus towards the null. Collinearity between BMI and WHR is also likely to be high, yet the authors adjusted for both in the same model. Finally, the study sample (US war veterans) is unlikely to be representative of the general population. Overall, the findings of this study are difficult to interpret and definitive conclusions about physical activity and Barrett's oesophagus risk are unable to be made based on its results.

Summary of findings: There is insufficient evidence to define the association between physical activity and Barrett’s oesophagus. Evidence from large and well-designed prospective cohort studies are needed, which use an accurate and validated measure of both recreational and occupational physical activity prior to disease onset.

Figure 1.11 A simplified diagram of the proposed causal pathway for physical activity in the aetiology of GORD, Barrett’s oesophagus and oesophageal adenocarcinoma.



The blackline represents a potential independent pathway which does not rely on modification of BMI (e.g. by decreasing inflammation or improving insulin sensitivity).

Physical activity and the development of oesophageal adenocarcinoma

Five hundred and seventy three potentially relevant articles were screened by title with inclusion of 49. After removal of duplicates, 17 were included by abstract. Of these, 14 were excluded by full paper review according to the inclusion criteria. Two papers were included by reference lists but later excluded after full review. In total, 3 papers were included in this review (2 large prospective cohort studies⁴⁸¹ and one case-control study)⁸⁰ and the characteristics are shown in table 1.1. A total of 666 cases of oesophageal adenocarcinoma were identified among 989 046 participants. The largest prospective cohort study investigated men and women aged 50-71 years recruited from the general population by postal questionnaire in the US.³¹ Only recreational physical activity was measured (by questionnaire) and categorised into 5 levels based on the number of sessions lasting ≥ 20 mins/week (0, <1, 1-2, 3-4, ≥ 5). Disease outcome was confirmed using cancer registry data. The authors reported a RR of 0.68 (95% CI 0.48-0.96) for recreational physical activity of ≥ 5 sessions/week vs. none, with a dose-dependent trend ($p=0.007$). There was some attenuation of the effect size when BMI was added to the model; OR=0.75 (95% CI 0.53-1.06). The second largest cohort study identified men and women aged 25-70 years from 9 European countries recruited by postal questionnaire.³³ Exposure

was measured using a questionnaire for both recreational and occupational physical activities, which was combined into a 4-level physical activity index: inactive, moderately inactive, moderately active and active. Confirmation of cases was largely confirmed by a panel of pathologists, but also from cancer registry data. This study reported a HR of 0.98 (95% CI 0.48-2.01) for the highest levels of occupational and recreational physical activity vs the lowest. Finally, the case-control study was of US men and women aged between 30-74 years identified from a cancer surveillance programme.⁸⁰ Only occupational physical activity was measured and based on job title. Case confirmation was by using cancer surveillance data. The authors reported an OR of 0.67 (95% CI 0.38-1.19, $p_{\text{trend}} = 0.07$), for the highest vs lowest physically active occupations. All 3 studies adjusted for known confounders (age, gender, smoking status), but also for unconfirmed potential risk factors (e.g. education, fruit and vegetable intake). All 3 adjusted for BMI, but only one included results of a multivariable model excluding BMI.³¹

Whilst the largest prospective study³¹ (374 cases) measured leisure time activity, the specific types of exercise were not defined. Furthermore, occupational activity was not measured or adjusted for as a potential confounder. Nonetheless, the estimated RR of 0.68 (95% CI 0.48-0.96) (unadjusted for BMI) likely represents the least biased estimate of effect size currently in the literature for recreational physical activity and the risk of oesophageal adenocarcinoma. The second largest study³³ used a validated questionnaire to measure physical activity, but both recreational and occupational activities were combined to produce a physical activity index (ranging from inactive to active) and were not reported separately. Therefore, all groups contained a heterogeneous population in terms of the types of physical activity they engaged in. The reported HR for the active vs. inactive category of 0.98 (95% CI 0.48-2.01) may represent the dilution of any potential protective effect of recreational exercise by the hazardous effect of heavy manual work. The number of cases (n=80) was also relatively small resulting in statistical imprecision of the effect size. The case-control study⁸⁰ measured physical activity identified by job title from which an index was created based on the levels of activity associated with each job (from sedentary to highly active). Jobs with high levels of exertion may involve bending and lifting which could increase the risk of reflux disease, particularly if done post-prandially. This was not accounted for in the study, but rather all high energy expenditure jobs were categorised together without any distinction. Furthermore, recreational exercise was not measured and therefore could not be included in the statistical model.

Summary of findings: There is a limited evidence from a large prospective cohort study that recreational physical activity of at least 100mins every week vs. no activity may reduce the risk of oesophageal adenocarcinoma by up to 32%.

1.2.5 Discussion

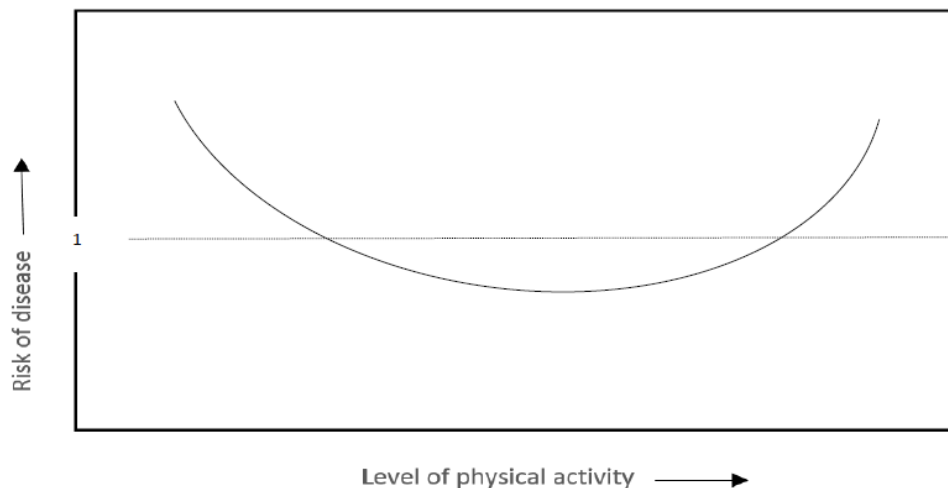
This review shows there is some evidence, although limited, that increasing levels of recreational physical activity may be associated with a reduced risk of GORD and oesophageal cancer. However, the type, duration and intensity of recreational exercise that may be protective is poorly defined. Whilst there are no other reviews on physical activity and risk of GORD and Barrett's oesophagus, there have been several for oesophageal adenocarcinoma.⁸⁵⁻⁸⁸ All estimated a pooled risk reduction for the highest vs. lowest levels of physical activity of between 21-52%.⁸⁵⁻⁸⁸ However, pooling of observational data from different study designs is methodologically questionable,⁸⁹ particularly when some examined different exposures (occupational or recreational activity). Case-control studies, by virtue of their design, also have inherent selection and recall biases which may give erroneous findings. The only review to investigate one type of activity (recreational) and pool data only from prospective cohorts studies reported a HR of 0.58 (95% CI 0.37-0.89) for high vs. low levels of physical activity and the risk of oesophageal adenocarcinoma.⁸⁵ The authors also included a BMI adjusted HR estimate of 0.62 (95% CI 0.40-0.97), suggesting that physical activity has a mostly non-BMI mediated effect as the magnitude of the effect size was not markedly affected. However, pooling of data from different cohort studies, particularly where the measurements of physical activity differ introduces potential error.

An important point to consider when investigating associations between physical activity and the risk of GORD, Barrett's oesophagus and oesophageal adenocarcinoma is the complex interplay which likely occurs between levels of physical activity, diet and BMI. People who engage in higher levels of recreational physical activity would be expected to eat a healthier diet and avoid high levels of alcohol consumption. These factors may therefore confound any associations with physical activity and disease risk. However, although dietary modification is often recommended to control symptoms of GORD,⁹⁰ it is currently unknown from the literature whether specific dietary components are

involved in the aetiology.⁹¹ A comprehensive review of published epidemiological studies (case-series, cross-sectional and case-control studies) did not support a role for diet (including fatty foods, chocolate, fruit and vegetables) in the development of symptoms of GORD.⁹¹ However, in the absence of prospective cohort data, where diet is measured prior to disease onset, results could be subject to recall bias. For Barrett's oesophagus and oesophageal adenocarcinoma, a review has suggested that a diet low in fruit and vegetable intake may represent a modest risk factor for both diseases.¹⁶ This is based on evidence from case-control studies that an increased intake of fruit,⁴⁵ plant-based fibre^{46 47} and vegetables⁴⁸ was inversely associated with disease risk. However, spurious over-estimation of the effect sizes due to recall bias in those with disease may explain these findings, which are derived from retrospective investigations. Alcohol does not seem to have an important role in the aetiology of all three disease states. Large case-control studies found no associations between alcohol intake and the risk of GORD.^{69 82} Consistent with these findings, a review of population-based case-control studies reported no overall effect of alcohol consumption on the development of Barrett's oesophagus or oesophageal adenocarcinoma, although the methodological weaknesses of case-control studies in terms of selection and information biases were noted.⁴⁹ Large prospective cohort studies are now required to examine dietary intake prior to disease onset, which would reduce the effects of reverse causation bias (i.e., patients are more likely to avoid foods which they feel exacerbate their symptoms or eat foods which alleviate them). As there are no consistent associations documented between any specific dietary factors and the risk of GORD, Barrett's oesophagus or oesophageal adenocarcinoma, it is reasonable not to currently include dietary intake in statistical modelling. However, emerging data in the future from prospective studies may show this is required. For BMI, the epidemiological evidence does support a positive correlation between being overweight and disease risk, which was discussed in the previous section (1.1.3). BMI is therefore an established risk factor, which should be measured and analysed when considering physical activity and the risk of all three disease states. An approach to this would be to provide both BMI adjusted and unadjusted values when estimating the effect size of physical activity on disease risk, as this would clarify whether the effect of physical activity is mediated through BMI.

In conclusion, this review is the first to examine the associations between physical activity and the risk of GORD, Barrett's oesophagus and oesophageal adenocarcinoma. All three disease states were included in this review as consistent associations (in a disease which occurs in sequence) would provide supportive evidence for causality. The evidence from biological and epidemiological studies does suggest a potential protective effect of moderate levels of recreational physical activity on the risk of GORD and oesophageal adenocarcinoma, but there is insufficient data for an assessment for Barrett's oesophagus, highlighting an absence in the literature. An inverse association between increased recreational activity with both GORD and oesophageal adenocarcinoma does provide some credibility to a causal association, but the evidence should be interpreted with caution as it is mainly derived from case-control investigations. As discussed in the previous section (1.1.5), the association between physical activity and risk of oesophageal adenocarcinoma is likely to be non-linear, where both low and very high levels of recreational activity may increase risk, but moderate levels decrease risk (figure 1.11).

Figure 1.12 A graph of the proposed U-shaped association between levels of physical activity and the risk of GORD, Barrett's oesophagus and oesophageal adenocarcinoma.



However, the potentially hazardous effect of high intensity recreational exercise, or heavy manual occupations; particularly those that raise intra-gastric pressure, has not been fully investigated in epidemiological studies. In fact, only one of the studies in this review considered a possible differential effect of occupational and recreational activities, which suggested that vigorous work may indeed increase GORD risk.⁸² However, further large prospective studies are required investigating the type, duration and intensity of recreational and occupational physical activity that may be protective or hazardous. If these find consistent inverse associations with the development of GORD, Barrett's oesophagus and oesophageal adenocarcinoma, physical activity could be included in the aetiological model and may offer a public health intervention to reduce the rising epidemic of oesophageal adenocarcinoma.

The absence of prospective data investigating the associations between recreational and occupational physical activity and the risk of Barrett's oesophagus, the precursor lesion of oesophageal adenocarcinoma, is addressed in the next section in a large prospective cohort study (EPIC-Norfolk).

Table 1.1 Characteristics of the included studies (Does physical activity influence the development of GORD, Barrett's oesophagus and oesophageal adenocarcinoma? A review of the literature)

First author and year of publication	Study design	Study sample	Validated exposure measure?	Quantification of physical activity	Outcome measure	Validated outcome measure?	Cases (n)	Adjusted variables in statistical model	Effect size (95% CIs)
GORD									
Nilsson, 2004 ²⁰	Case-control	Men and women aged ≥20 years from a single county in Norway recruited by postal questionnaire (n=43 363)	No	Recreational physical activity of at least 30mins duration. Categorised as: never, <1/week, 1-3/week and >3/week	Self-reported questionnaire of severe and recurrent heartburn or regurgitation during the past 12 months	Yes	3 153	Age, gender, BMI, smoking and intake of coffee, salt, dietary fibre and bread	OR for highest vs lowest level of physical activity =0.70 (0.60-0.90)
Zheng, 2007 ³⁷	Case-control	Monozygotic same sex twins aged between 42-104 years recruited from the Swedish Twin Registry by postal questionnaire (n=27 717)	No	Ordinal scale from 1-4 for both occupational and recreational physical activity separately. Occupational= sedentary, walking, lifting, strenuous. Recreational= almost no, little, medium and much	Questionnaire delivered by telephone interview	Yes	4 083	Age, BMI, smoking, coffee intake and education	OR for highest vs. lowest recreational physical activity in men = 0.60 (0.47-0.77). In women = 0.56 (0.41-0.75). OR for highest vs. lowest occupational physical activity in men = 1.23 (0.99-1.53). In women = 1.16 (0.78-1.72)
Nocon, 2006 ³⁸	Case-control	Men and women aged 18-79 years in Germany recruited by national survey (n=6 954)	No	Recreational sports only. Categorised as none, ≤2hrs/week or >2 hrs/week	Self-reported heartburn or acid regurgitation. Categorised as no, mild, moderate and severe	No	2 964	Age, gender, BMI, smoking, alcohol and 12 nutritional factors	OR for highest vs lowest level of sport =0.75 (0.60-0.93)

Table 1.1 continued

First author and year of publication	Study design	Study sample	Validated exposure measure	Quantification of physical activity	Outcome measure	Validated outcome measure?	Cases (n)	Adjusted variables in statistical model	Effect size (95% CIs)
Barrett's oesophagus									
Hilal, 2015 ³⁹	Case-control	Men and women aged 40-80 years in Texas USA attending a Veteran Affairs Medical Centre for an elective endoscopy (n=2 172)	Yes	Recreational levels of physical activity categorised as low, moderate or high. Moderate is defined as 150mins moderate or <75 mins vigorous exercise/week. Low =<moderate. High=>moderate	Endoscopic and histological appearance consistent with Barrett's oesophagus	Yes	323	Age, gender, race, GORD symptoms, <i>H.pylori</i> infection status, BMI and high WHR	OR for highest vs lowest level of physical activity =1.19 (0.82-1.73)

Table 1.1 continued

First author and year of publication	Study design	Study sample	Validated exposure measure	Quantification of physical activity	Outcome measure	Validated outcome measure?	Cases (n)	Adjusted variables in statistical model	Effect size (95% CIs)
Oesophageal adenocarcinoma									
Leitzmann, 2009 ³⁴	Prospective cohort	US men and women aged between 50-71 years. Recruited from the general population by a postal questionnaire (n=487 732)	No	5 categories according to the number of moderate recreational physical activity sessions lasting ≥20 minutes (0,<1,1-2,3-4,≥5)	Cancer registry	n/a	374	Age, gender, race, smoking, alcohol, education, marital status, family history of cancer, intake of fruit, vegetables and red meat (+/- BMI)	RR for highest vs. lowest physical activity category=0.68 (0.48-0.96) (unadjusted for BMI)
Huerta, 2010 ³⁶	Prospective cohort	Men and women from 9 European countries aged 25-70 years. Recruited from general population by postal questionnaire (n=420 449)	Yes	A validated physical activity index of four ordinal categories combining both occupational and recreational levels of physical activity (inactive, mod inactive, mod active, active)	Confirmed by a panel of pathologists (69%), pathology reports (15%) and cancer registry (16%)	n/a	80	Age, gender, height, weight, education, smoking, alcohol, energy intake, fruit, red meat and processed meat intake	HR for highest vs. lowest category= 0.98 (0.48-2.01)
Vigen, 2005 ³⁵	Case-control	US men and women aged 30-74 years identified by a cancer surveillance programme. Controls were matched based on gender, race, date of birth and residence (n=2 195)	No	A Total Activity Index calculated by multiplying the number of years worked in a sedentary (0), moderate (1) or highly active (2) job over a lifetime	Cancer surveillance programme data	n/a	212	Age, gender, race, smoking status, education, birthplace and BMI	OR for highest vs lowest category= 0.67 (0.38-1.19)

1.3 The association between physical activity and the risk of symptomatic Barrett's oesophagus - a UK prospective cohort study (EPIC-Norfolk)

1.3.1 Abstract

Background: Physical activity affects the functioning of the gastrointestinal system through both local and systemic effects and may play an important role in the aetiology of GORD, Barrett's oesophagus and oesophageal adenocarcinoma; the so called metaplasia-dysplasia-carcinoma sequence. For the first time, in a large prospective cohort study, this study examined associations between recreational and occupational levels of physical activity and the incidence of Barrett's oesophagus, the precursor lesion of oesophageal adenocarcinoma.

Methods: EPIC–Norfolk recruited 30 445 men and women between 1993 and 1997. Occupational and recreational levels of physical activity were measured using a baseline questionnaire. The cohort was followed up until 2015 to identify symptomatic cases of Barrett's oesophagus. Cox proportional hazard regression estimated hazard ratios (HR) for physical activity (occupational and recreational separately) and the risk of developing disease.

Results: Two hundred and three participants developed Barrett's oesophagus (mean age 70.6 years) the majority of whom were male (70.9%). There was an inverse association between standing occupations and disease risk when compared to sedentary jobs (HR 0.50, 95% CI 0.31-0.82, $p=0.006$). Heavy manual occupations were positively associated with disease risk (HR 1.66, 95% CI 0.91-3.00), but conventional statistical significance was not reached ($p=0.09$). No associations were found between recreational activity and the risk of Barrett's oesophagus (HR 1.34, 95% CI 0.72-2.50, $p=0.35$, highest vs. lowest levels of activity).

Conclusion: This study suggests that occupational levels of physical activity may be associated with the risk of Barrett's oesophagus. However, further aetiological work in other populations is required to confirm and describe specific occupations which may be protective or indeed hazardous.

1.3.2 Introduction

Physical activity affects gastric emptying,⁵⁷ intra-gastric pressure,⁵⁶ systemic inflammation,⁷⁰ and the regulation of body weight⁶⁴ and may play an important role in the metaplasia-dysplasia-carcinoma sequence. As described in the previous section of this thesis (1.2), several epidemiological studies have examined associations between physical activity and the risk of both GORD^{69 82 83} and oesophageal adenocarcinoma,^{4 80 81} and reported a potential protective role for recreational physical activity in the risk of both diseases. The evidence for occupational activity from these studies was inconsistent.^{80 82} To date, only one study (case-control) has investigated Barrett's oesophagus and reported no association between recreational exercise and disease risk (occupational activity was not measured).⁸⁴ The aim of this study was to investigate, for the first time in a prospective cohort study, the relationship between both occupational and recreational levels of physical activity and the incidence of Barrett's oesophagus.

1.3.3 Methods

Recruitment and measurement of exposure

The European Prospective Investigation of Cancer (EPIC-Norfolk) study⁹² recruited 30 445 men and women, aged 39 to 79 years, between the years 1993 and 1997, who were identified from 35 general practices across the county of Norfolk in the United Kingdom (EPIC-Norfolk is part of the wider EPIC study, one of the largest cohort studies in the world, with more than half a million (521 000) participants recruited across 10 European countries). At baseline, participants completed a questionnaire documenting their health and lifestyle including both occupational and recreational levels of physical activity. The physical activity component contained questions relating to participants' physical activities over the previous 12 months both at work and at home (appendix 1). For occupational activity, participants were asked to choose one of four categories which best described the physical demands of their job (sedentary, standing occupation, manual work or heavy manual work). In a validation study; this simple four-level occupational classification was strongly associated with objective measures of daytime energy expenditure ($P_{\text{trend}} < 0.001$).⁹³ Recreational activity was measured during both winter and summer months by asking how many hours participants typically spent per week during the last year participating in: walking, cycling, gardening, housework, do-it-yourself (DIY)

and other forms of physical exercise (e.g. aerobics, swimming, jogging). A four category recreational index was derived based on the average number of hours per week that participants engaged in cycling or other recreational physical activity (0, <3.5, <7 and >7 hrs/week). Anthropometric measurements including height and weight were recorded at baseline health-check visits, conducted between 1993 and 1998. The EPIC-Norfolk study was approved by the Norwich District Health Authority Ethics Committee and all participants provided their written consent for involvement.

Figure 1.13 A map showing the boundary line for the county of Norfolk in East Anglia.



Image from www.maps-of-britain.co.uk/map-of-norfolk.html [accessed on 24/10/2017].

Figure 1.14 Photograph of London Street, Norwich in Norfolk. The spire of Norwich Cathedral can be seen in the distance.



Image from <http://www.tournorfolk.co.uk/shopsnorwich.html> [accessed on 24/10/2017].

Follow-up and identification of cases

After recruitment, the cohort was followed up to June 2015 to identify participants subsequently diagnosed with Barrett's oesophagus detected due to reflux symptoms. Cases were identified by linking the EPIC-Norfolk database with the Norfolk and Norwich Hospital histology database, with all potential cases verified by review of their medical notes. To be included, cases had to meet the diagnostic criteria as defined by the British Society of Gastroenterology,³³ i.e., required both endoscopic characteristics of Barrett's oesophagus of ≥ 1 cm and histological confirmation of metaplasia. The medical notes of all potential cases were reviewed to exclude participants with prevalent Barrett's oesophagus at recruitment. To ensure the physical activity levels were more likely to represent pre-symptomatic levels, symptomatic Barrett's oesophagus cases were excluded if diagnosed within 1 year of recruitment into EPIC-Norfolk.

Statistical analysis

Participants were followed up from study entry until the earliest date of: first diagnosis, death, or last data collection date (June 2015). Comparative analyses between cases and

controls were undertaken using Student t-tests for continuous, and X^2 tests for categorical variables. In multivariable analyses, Cox proportional hazard regression models estimated hazards ratios (HRs), with 95% confidence intervals (CI), for associations between both recreational and occupational physical activity. The fully adjusted model contained the covariates: age, gender, smoking category (never, ex-smoker, current smoker) and alcohol intake (units/week). As it is unclear whether body mass index (BMI) lies along the causal pathway between physical activity and Barrett's oesophagus (whether or not the effect of physical activity is by regulation of BMI) both BMI unadjusted and adjusted analyses were presented.

1.3.4 Results

Of 30 445 individuals aged between 39 and 79 years in EPIC-Norfolk, 24 110 (79.2%) had a record of physical activity, attended a base-line health check, had no previous cancer diagnosis, subsequent diagnosis of oesophageal adenocarcinoma or diagnosis of Barrett's oesophagus within the first year of recruitment (figure 1.15). Follow-up ended a mean of 17.6 years (SD 4.5) after cohort entry, totalling 424 336 person years. During the maximum follow-up of 22 years, 203 of 24 110 individuals (0.84%) developed reflux symptoms which led to referral for gastroscopy and diagnosis of Barrett's oesophagus. The mean age at diagnosis was 70.6 years (\pm SD 9.3), and 70.9% were male. The median time of diagnosis after study enrolment was 12 years (interquartile range (IQR), 8 to 17 years). The subtypes of metaplasia were documented as: intestinal (69.5%, n=141), gastric (9.9%, n=20), mosaic (9.9%, n=20), and non-specified in 10.8% (n=22). Dysplasia was present in 5% of cases. A hiatal hernia was present in 72% of participants. In the descriptive analyses, cases of Barrett's oesophagus, compared to controls, were more likely to be male and older at the time of recruitment (table 1.2). They were also more likely to have formerly smoked and be overweight, with higher levels of alcohol consumption. Finally, a greater percentage of cases had either sedentary or heavy manual occupations.

Figure 1.15 Study flow chart (The association between physical activity and the risk of symptomatic Barrett's oesophagus - a UK prospective cohort study).

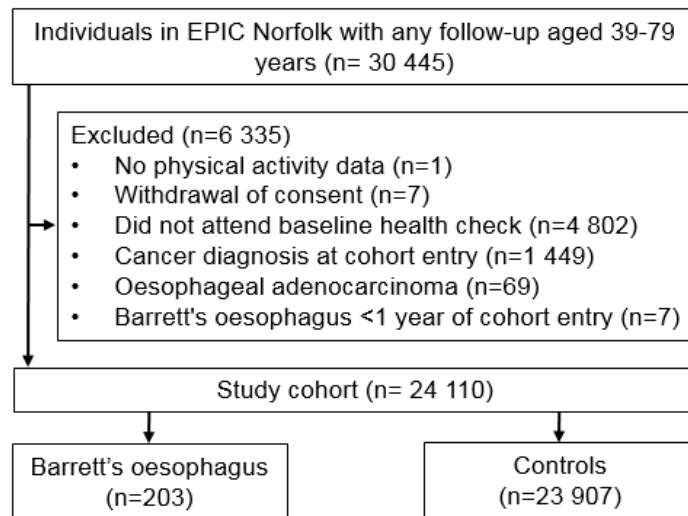


Table 1.2 Comparative characteristics of cases and controls (The association between physical activity and the risk of symptomatic Barrett's oesophagus - a UK prospective cohort study).

Variable	Barrett's oesophagus (n=203)	Controls (n=23 907)	P-value
Age at recruitment			
(mean, years & SD)	60.3 (±8.6)	59.0 (±9.3)	0.05
Gender (male)	144 (70.9)	10 978 (45.9)	<0.001
Cigarette smoking			
Never	66 (32.5)	10 938 (45.8)	<0.001
Former	109 (53.7)	9 985 (41.8)	0.001
Current	26 (12.8)	2 781 (11.6)	0.60
Missing data	2 (1.0)	203 (0.8)	0.83
WHO BMI category (kg/m²)			
Underweight (<18.5)	0	115 (0.5)	0.32
Normal weight (18.5 to <25)	65 (32.3)	9 293 (38.9)	0.05
Overweight (25 to <30)	107 (52.7)	10 826 (45.3)	0.03
Class I obesity (30 to <35)	25 (12.3)	2 935 (12.3)	0.98
Class II obesity (35 to <40)	4 (2.0)	532 (2.2)	0.81
Class III obesity (≥40)	2 (1.0)	206 (0.9)	0.85
Alcohol			
(mean units/week & SD)	9.8 (11.4)	7.2 (9.5)	0.001
Missing data	n=2 (1.0)	n=244 (1.0)	
Occupational activity			
Sedentary	57 (28.1)	6 362 (26.6)	0.64
Standing	24 (11.8)	6 002 (25.1)	<0.001
Manual	39 (19.2)	4 161 (17.4)	0.50
Heavy manual	14 (6.9)	575 (2.4)	<0.001
Unemployed	69 (34.0)	6 807 (28.5)	0.08
Recreational activity			
None	116 (57.1)	12 651(52.9)	0.23
<3.5 hours	49 (24.1)	7 201 (30.1)	0.06
3.5 to <7 hours	22 (10.8)	2 591 (10.8)	1.00
>7 hours	16 (7.9)	1 464 (6.1)	0.30

Data shown are the number of patients and percentage unless otherwise stated.

In the adjusted Cox model for physical activity and the risk of Barrett's oesophagus, there was a suggestion of a U-shaped association between levels of occupational activity and disease risk (table 1.3); with a decreased risk in participants with a standing vs sedentary occupation (HR 0.50, 95% CI 0.31-0.82, $p=0.006$) and an increased risk with heavy manual jobs, although conventional statistical significance was not reached (HR 1.66, 95% CI 0.91-3.00, $p=0.09$). The effect sizes were not attenuated by adjustment for BMI. No associations were found for levels of recreational activity in either models; adjusted, or unadjusted, for BMI. In a sub-analysis of only the cases with intestinal metaplasia ($n=141$) the results remained similar to the findings for all types of metaplasia. In a model adjusted for: age, sex, smoking and levels of recreational activity the results for standing vs. sedentary occupations estimated a HR of 0.55, 95% CI 0.31-0.99, $p=0.046$. For heavy manual vs. sedentary occupations the HR was 1.78, 95% CI 0.87-3.61, $p=0.11$.

Table 1.3 Multivariable Hazard Ratios (HRs) for physical activity and the risk of symptomatic Barrett's oesophagus.

Type of physical activity	HR (95% CI), P-value	
	Not BMI adjusted	BMI adjusted
Occupational^a		
Sedentary	Reference (1.00)	Reference (1.00)
Standing	0.50 (0.31-0.82), p=0.006	0.51 (0.31-0.83), p=0.006
Manual	0.91 (0.61-1.34), p=0.67	0.93 (0.61-1.40), p=0.71
Heavy manual	1.66 (0.91-3.00), p=0.09	1.66 (0.92-3.02), p=0.09
Recreational^b		
None/week	Reference (1.00)	Reference (1.00)
<3.5 hours/week	0.84 (0.56-1.30), p=0.43	0.85 (0.56-1.30), p=0.46
3.5 to <7 hours/week	0.98 (0.56-1.72), p=0.94	0.99 (0.57-1.75), p=0.98
>7 hours/week	1.34 (0.72-2.50), p=0.35	1.36 (0.73-2.51), p=0.33

Multivariable models were adjusted for age, gender, smoking status and alcohol consumption +/- BMI. ^aAdditional adjustment for recreational activity. ^bAdditional adjustment for occupational activity.

1.3.5 Discussion

This is the first prospective cohort study to investigate associations between levels of physical activity and the development of Barrett's oesophagus. Although there were no associations with recreational activity, a possible U-shaped association between levels of occupational activity and disease risk was found. There are biologically plausible mechanisms how such an association could exist which were discussed in detail in the previous section of this thesis (1.1.4). In brief, low to moderate levels of physical activity in standing occupations, which involve frequent walking, may protect against GORD by helping to maintain a normal body weight,⁶⁴ thus preventing obesity induced reflux disease⁶⁵ (central adiposity increasing intra-gastric pressure, creating a gastro-oesophageal reflux gradient and hiatus hernia formation).⁶⁶⁻⁶⁸ Low intensity exercise such as walking also increases gastric emptying and may therefore decrease reflux episodes.⁵⁷ Finally, regular physical activity reduces inflammatory biomarker expression, and thus may prevent the inflammation-driven metaplastic process involved in the aetiology of Barrett's oesophagus.⁷⁰⁻⁷³ Alternatively, heavy manual occupations may involve both bending and heavy lifting, increasing intra-abdominal pressure and forcing gastric contents retrograde, beyond the lower oesophageal sphincter into the oesophagus.⁵⁶ Activity at work is also likely to occur post-prandially, when reflux episodes are most likely.⁶⁰

The finding of no association between recreational physical activity and the risk of Barrett's oesophagus is consistent with the only other epidemiological study (a case-control investigation of 307 cases of Barrett's oesophagus and 1724 controls), where the authors reported no association between the highest vs. lowest levels of physical activity and odds of Barrett's oesophagus (OR = 1.19, 95% CI 0.82-1.73).⁸⁴ Limitations of that study included the potential for both measurement error and bias in their assessment of exposure through the use of a 7-day exercise questionnaire in patients who had already developed the disease of interest. A further potential limitation was adjustment for GORD, BMI and WHR, which lie along the presumed causal pathway and would therefore be likely to reduce any association between physical activity and Barrett's oesophagus towards the null. The findings of their study are difficult to interpret and definitive conclusions about physical activity and Barrett's oesophagus risk are unable to be made based on its evidence.

The strengths of this study include; its prospective design, which minimised both selection and recall biases; adjustment in the analyses for potential confounders; confirmation of all incident cases of Barrett's oesophagus by medical note review; and a long follow-up period of up to 22 years. Follow-up bias was minimised by studying a cohort that was geographically stable, with 94.6% of participants still living in the county of Norfolk 20 years after recruitment. As this is a large population based-study, the findings are also generalisable, with inclusion of both men and women from: rural, suburban and inner city areas. However, exclusion of participants from larger UK urban areas such as London and Manchester may limit the UK-wide generalisability of the findings. Nonetheless, the case numbers are similar to larger UK cohorts. Cohort data derived from primary care databases in the UK reported 12 312 Barrett's oesophagus cases among 6 885 420 people (0.18%) aged ≥ 18 years⁹⁴, compared to the 0.84% found in this study. The higher figure in this study likely reflects an older population (aged 39-79 years). Finally, by measuring both occupational and recreational activity, an estimate of the differential effects of both could be undertaken. A study limitation was the inability to identify participants with asymptomatic Barrett's oesophagus in the cohort. Including only symptomatic disease, diagnosed by oesophagogastroduodenoscopy (OGD), may identify as little as 55% of all cases within a population.⁴⁰ Nevertheless, it would be expected that misclassification of asymptomatic Barrett's oesophagus cases (as non-cases) would be non-differentially distributed between physical activity categories and therefore draw associations to the null. The only way to identify all cases of Barrett's oesophagus within a population would be by screening with gastroscopy, which is unfeasible in large studies. A further potential limitation was the use of a questionnaire measure of physical activity, rather than an objective physiological variable. Questionnaires are a pragmatic necessity of measuring physical activity in large population studies and although measurement error could arise it would again reduce the magnitude of the effect size of any association, rather than inflate it.

In summary, this study was the first to examine the associations between both occupational and recreational levels of physical activity and the risk of Barrett's oesophagus. The findings suggest that whilst differing levels of recreational exercise may not be associated with disease risk, occupational physical activity may be either protective (as in standing occupations), or possibly hazardous (as in heavy manual occupations). The public health importance of Barrett's oesophagus lies in its association with oesophageal

adenocarcinoma.¹⁶ If further work is able to confirm specific occupations which may be hazardous then occupational physical activity would form an important component of the aetiological model for Barrett's oesophagus and oesophageal cancer.

Chapter Two: Prehabilitation to reduce the risk of short-term complications after oesophagectomy

Overview

This thesis will now progress from investigating physical activity in the aetiology of oesophageal adenocarcinoma and explore whether short-term physical activity programmes could be used as a preoperative intervention to reduce the risk of complications after oesophageal adenocarcinoma resection surgery (oesophagectomy).

Firstly, the adaptations of the human body to exercise training are discussed.

Secondly, the pathophysiology of both the intraoperative and early postoperative periods are reviewed.

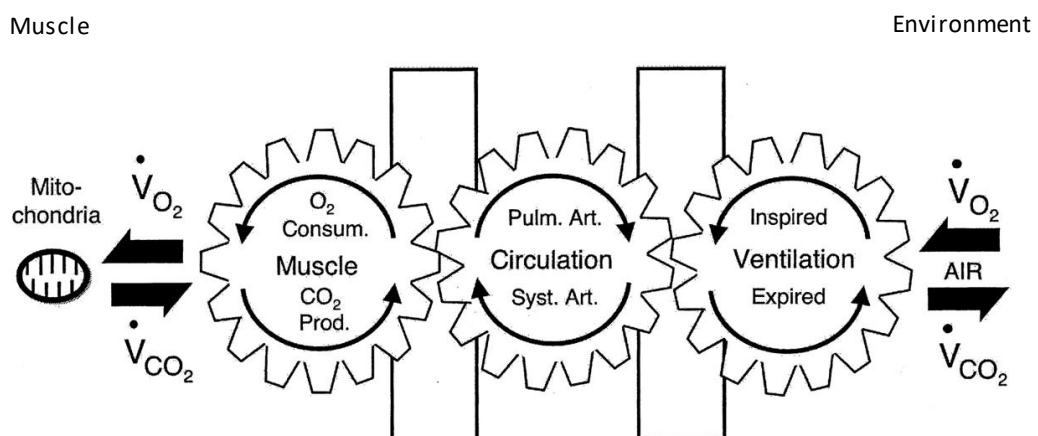
Thirdly, the protective role of physical fitness in reducing post-oesophagectomy complications are discussed.

Finally, the methodology and results of a feasibility single-blinded randomised control trial of prehabilitation prior to oesophagectomy for oesophageal adenocarcinoma are presented. Such a feasibility trial is required to both justify and inform a future multi-centre randomised controlled trial of preoperative supervised hospital exercise to reduce postoperative complications.

2.1 A review of adaptations to physical activity training

Physical activity is defined as “bodily movement produced by skeletal muscles that requires energy expenditure”.⁹⁵ The ability to engage in prolonged physical activity is dependent on a series of integrated physiological events involving the heart, lungs and skeletal muscles, where the predominant goal is to transport oxygen from the environment to working muscle (figure 2.1). Regular physical activity training produces adaptations to both the musculoskeletal and cardiopulmonary systems to improve the body’s efficiency and capacity to utilise oxygen for exercise. For clarity, training is defined as regular physical activity which “exceeds the capacity for endurance in the untrained state, and therefore acts as a stimulus for change in an organism”.⁹⁶

Figure 2.1 Schematic showing the independent organ systems that contribute to the movement of gases to and from the environment to mitochondria.



Adapted from Wasserman, *et al.* Principles of Exercise Testing and Interpretation.⁹⁷

2.1.1 Cardiovascular adaptations to training

During exercise one of the primary functions of the cardiovascular system (the heart, blood vessels and blood) is to provide working muscle with oxygen. As work rate increases, oxygen uptake (VO_2) increases linearly.⁹⁸ Increasing oxygen demand is met by an increased cardiac output (Q), defined as the volume of blood in mls/min pumped from the left ventricle of the heart. Q is the product of (SV) stroke volume (volume of blood pumped per beat) x (HR) heart rate (number of heart beats/min). There is an almost linear response of Q to an increase in oxygen demand, with increasing work rate (figure 2.2).

Figure 2.2 Graph showing the changes in cardiac output with increasing rates of work on a cycle ergometer.

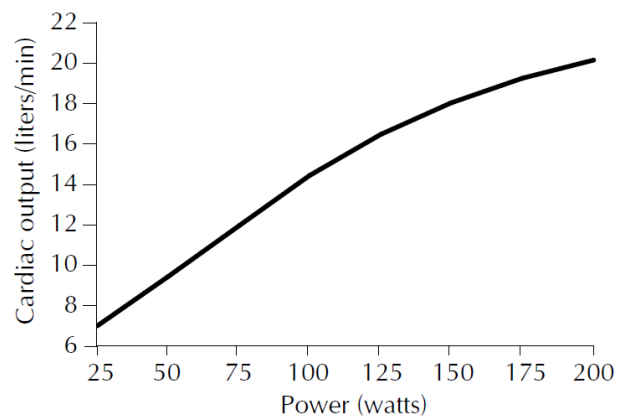


Image from Physical Activity and Health: A Report of the Surgeon General, Centers for Disease Control and Prevention.⁹⁸

In a study of college students, before and after bed rest, followed by a two-month training programme,⁹⁹ there was almost no change in the mean maximal heart rate after training, but an increase in SV and Q (figure 2.3).

Figure 2.3 Cardiovascular and pulmonary functional capacities determined during maximal exercise in college students and Olympic athletes.

	Control	After bedrest	After training	Olympic athletes
Maximal oxygen uptake, liters/min	3.30	2.43	3.91	5.38 ^b
Maximal voluntary ventilation, liters/min	191	201	197	219
Transfer coefficient for O ₂ , (ml/min)/(mmHg)	96	83	86	95
Arterial O ₂ capacity, vol %	21.9	20.5	20.8	22.4
Maximal cardiac output, liters/min	20.0	14.8	22.8	30.4 ^b
Stroke volume, ml	104	74	120	167 ^b
Maximal heart rate, beats/min	192	197	190	182
Systemic arteriovenous O ₂ difference, vol %	16.2	16.5	17.1	18.0

College students (n=5), Olympic athletes (n=6). Mean values are shown. ^bSignificantly different from the college students after training, p<0.05. Adapted from: Blomqvist et al. Cardiovascular adaptations to physical training.⁹⁹

The comparatively lower maximal HR in Olympic athletes (who had significantly higher SV and Q), demonstrates adaptations to intense and longer-term training, where the heart is able to supply the body with much higher volumes of blood at a lower heart rate, which demonstrates greater cardiac efficiency. Laboratory work by Levine, *et al*, using direct invasive techniques, explored how higher SVs are achieved in elite athletes. They demonstrated that myocardial contractility was not markedly different between athletes and non-athletes.⁹⁸ However, the difference in SV between the groups was due to a larger end-diastolic volume in the athlete's hearts: attributed to enhanced cardiac chamber compliance. The Starling mechanism predicts that an increased left ventricle filling pressure (end-diastolic pressure) increases SV.¹⁰⁰ Training appears to result in a more compliant myocardium, capable of generating a greater Q through increased SV, rather than improved cardiac contractility, which is minimally affected by training.¹⁰¹ Other changes due to training include an increase in capillary density of the ventricular myocardium, providing greater blood flow to the heart to support cardiac work and an increase in left ventricle cavity size and wall thickness.⁹⁸

2.1.2 Respiratory adaptations to training

The respiratory system also has the capacity to adapt to increased tissue oxygen demands through training, although in a less dramatic fashion than the heart. There is no marked lung parenchyma or airway differences between athletes and non-trained controls.¹⁰² Rather, respiratory muscles improve in strength and endurance with training, just as other skeletal muscles do, allowing an increased ventilatory effort.⁹⁸

2.1.3 Musculoskeletal adaptations to training

Skeletal muscle mass increases with most types of physical activity, as does capillary density; which increases oxygen flow to working muscle.⁹⁸ Training also produces large increases in both the volumes of mitochondria⁹⁶ and oxidative enzymes in skeletal muscle tissue¹⁰³, which improves adenosine triphosphate (ATP) availability (the energy source required for all muscle action).¹⁰⁴ ATP is produced either in the presence of oxygen via the oxidative pathway or, in its absence, via the glycolytic pathway. Training has little or no effect on enzymes of the glycolytic pathway, but large and rapid effects on oxidative enzymes.¹⁰³ The net result of these changes due to exercise is muscle which is larger in size with a greater blood flow and an increased capacity to produce ATP from oxygen.

2.1.4 Adaptations summary

Exercise training may improve the efficiency of oxygen delivery to active muscle tissue. This is mostly achieved through changes in the cardiovascular, respiratory and musculoskeletal systems. Improvements in cardiac output are achieved through an increase in myocardial compliance, while ventilatory effort is increased through greater respiratory muscle strength. Finally, muscle tissue develops a greater capacity to produce ATP, via an increase in capillary and mitochondrial densities.

2.2 A review of the pathophysiology of the postoperative period

Surgery can be considered as controlled tissue trauma. As with any traumatic injury, of whatever size, a series of processes occur within the body that are evolved to evoke healing and ensure survival.¹⁰⁵ In severe trauma, such as that induced by major surgery, a complex hyper-metabolic and hyper-inflammatory state is initiated, involving the secretion of catabolic hormones, inhibition of anabolic hormone effects and systemic inflammation.¹⁰⁶ These processes are termed the 'surgical stress response', where the net effect is catabolism of stored body fuels including muscle protein; with an associated increase in oxygen consumption to meet metabolic needs - a state which persists for several days after an operation.¹⁰⁷ In the context of modern surgery this 'stress response' may be detrimental to the patient and be an underlying cause of postoperative complications. Anaesthesia and bedrest are also important factors which challenge normal body functions, particularly lung mechanics. The next section will discuss the effect of surgery and the perioperative period on the cardiovascular, respiratory and musculoskeletal systems.

2.2.1 Intraoperative and postoperative changes to the cardiovascular system

Early observations in the 1950's demonstrated that Q increases after surgery dependent on the severity of the operation, which is maximal at day one and returns to baseline levels by days 4-7 (in patients undergoing surgery without complications).¹⁰⁸ The increases in Q reflects higher tissue oxygen demands. Oxygen consumption increases significantly up to 8 hours after surgery and may reach levels 1.5 times above a normal resting state (5ml/kg/min vs. 3ml/kg/min).¹⁰⁹ Postoperative blood loss and systemic inflammatory vasodilation may threaten the ability of the cardiovascular system to maintain adequate pressure to meet this increased oxygen demand. In a volume depleted or hypotensive patient, splanchnic vasoconstriction maintains an adequate circulating volume, but increases the risk of gut ischaemia. As the myocardium has an almost complete dependence on aerobic metabolism it is vulnerable to damage if oxygen supply is not constant.⁹⁸ A decreased end-diastolic volume through systemic inflammatory vasodilation requires an increased HR to maintain Q. This greater myocardial work increases the risk of myocardial ischaemia and infarction, particularly in patients with underlying coronary artery disease.

2.2.2 Intraoperative and postoperative changes to the respiratory system

Functional Residual Capacity (FRC) is the volume of gas that remains in the lungs at the end of expiration, also known as the End Expiratory Lung Volume (EELV). FRC is important in lung mechanics because it prevents collapse of the small airways at the end of expiration, preventing atelectasis (collapse or closure of the lung parenchyma).¹¹⁰ During general anaesthesia, functional residual capacity (FRC) is decreased by approximately 20%.¹¹¹ The factors which contribute to this are firstly; loss of respiratory muscle tone, resulting in chest wall recoil and increased lung recoil, and secondly; increased intra-abdominal pressure, displacing the diaphragm superiorly.¹¹¹ An investigation of perioperative patients by serial CT scans demonstrated lower lobe bilateral compressive atelectasis within 5 mins of induction of anaesthesia, which persisted in 5 out of 10 patients after 24 hours.¹¹² Even more dramatic effects on lung mechanics occur postoperatively, due to incisional pain and reflex diaphragmatic dysfunction, which may result in a reduction of FRC by up to 80%.¹¹¹ Loss of the diaphragmatic contribution to tidal volume (TV, the volume of air moved during normal breathing) results in shallow rapid breathing, propagating compressive atelectasis; causing perfusion ventilation mismatching and inefficient gas exchange. Vital capacity (VC) is the volume of air that can be forced from the lungs after maximal forced inspiration. VC is important in producing a sufficient voluntary cough flow to clear airway secretions. VC is reduced by up to 50% post-surgery, thus reducing a patient's ability to cough effectively.¹¹¹ This is compounded by decreased mucociliary clearance,¹¹¹ promoting the onset of pulmonary infections. On assuming a standing position from supine; FRC is increased by up to 25%; lung compliance by 25%; and airways resistance decreases by 40%.¹¹¹ These collective improvements are thought to occur mostly due to descent of the diaphragm and expansion of alveoli (due to gravity acting on lung parenchyma), reflecting the importance of posture on normal lung mechanics.

2.2.3 Postoperative changes to the musculoskeletal system

After any surgical incision, afferent neural stimuli acting on the hypothalamus cause the release of stress hormones.¹⁰⁶ Cortisol, secreted from the adrenal cortex after trauma is an important catabolic hormone, which promotes gluconeogenesis, with resultant hyperglycaemia providing a rapid fuel source to muscle for "fight or flight". Substrates for

gluconeogenesis are provided by breakdown of skeletal muscle as a source of protein. This muscle loss after major surgery is compounded by further muscle wasting through both bedrest and anorexia. The overall result for the patient is muscle weakness, delaying both early mobilisation and the restoration of normal lung mechanics. Hyperglycaemia also increases the risk of infection and delays wound healing.

2.2.4 Postoperative inflammation

Tissue damage, due to surgical incisions and resections, results in inflammation; with the release of several pro-inflammatory cytokines, leukocytes and acute phase reactants.¹¹³ Whilst this response initiates the healing and repair of damaged tissue; high levels of inflammatory markers lead to capillary leakage.¹⁰⁶ This results in oedema and potential hypotension mediated through a systemic inflammatory response syndrome (SIRS), which in turn may lead to organ hypo-perfusion and failure.¹¹⁴ Furthermore, both local and systemic postoperative inflammation is thought to be a cause of postoperative atrial fibrillation (AF), particularly when there is surgical dissection of or around the pericardium.^{115 116}

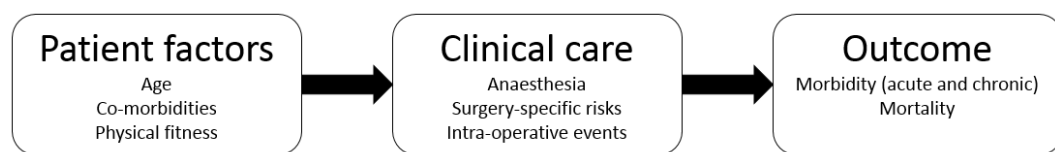
2.2.5 Intraoperative and postoperative changes summary

Both the intraoperative and early postoperative periods after major surgery are physiologically demanding on the human body. There is an increase in oxygen demand at a time when the cardiopulmonary system is challenged by: blood loss, systemic inflammatory vasodilation, and disruption of normal lung mechanics. Catabolic muscle losses further delay patient mobilisation, thus prolonging recovery of normal function. Whilst this section of the thesis has examined the physiological changes common to all major surgeries, the next focuses specifically on the unique physiological challenges related to oesophageal cancer resection surgery (oesophagectomy) and how improvements due to fitness training may attenuate the risk of complications unique to this operation.

2.3 A review of how an increase in physiological fitness hypothetically decreases the risk of postoperative complications after oesophagectomy

The risk of a complication after an oesophagectomy is multifactorial and includes both patient factors and those associated with aspects of clinical care (figure 2.4).

Figure 2.4 Schematic of the factors involved in determining postoperative outcomes.



Adapted from Minto, *et al*, Assessment of the High-Risk Perioperative Patient.¹¹⁷

2.3.1 Patient factors

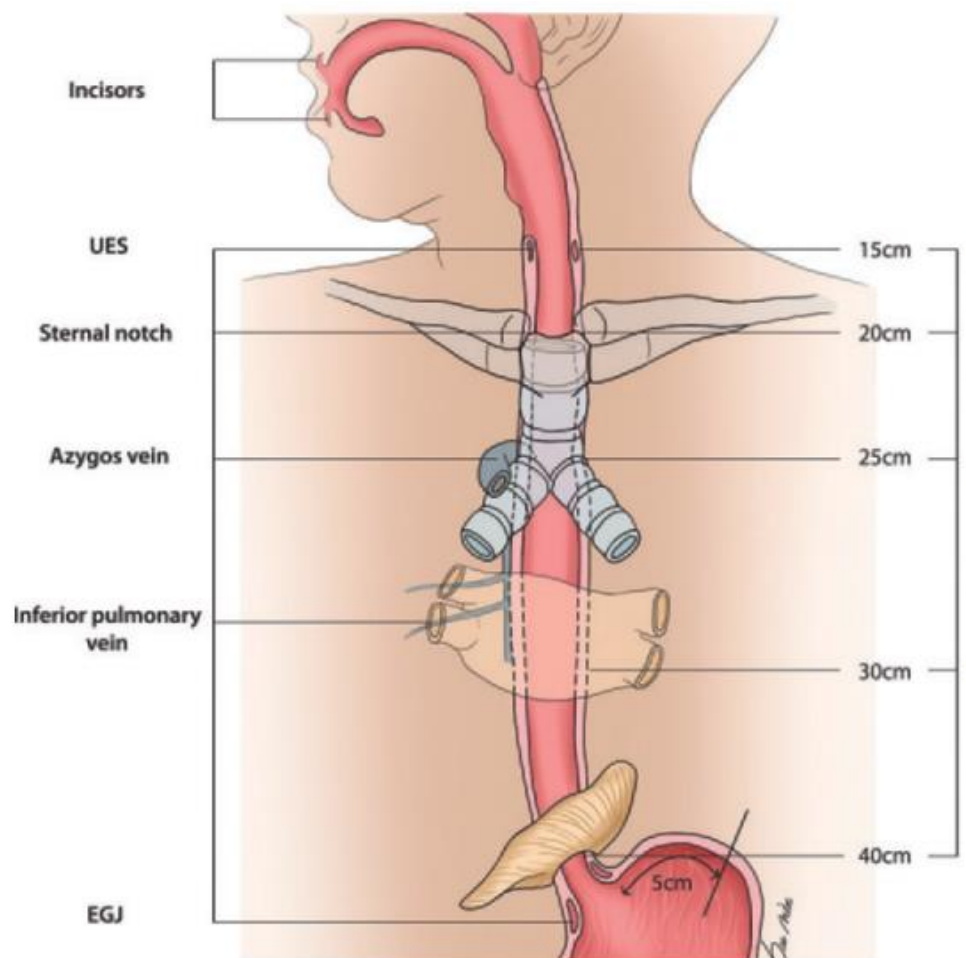
Ageing is associated with a decline in cardiopulmonary fitness, muscle mass, organ function and wound healing,¹¹⁸ as well as an increasing burden of co-morbidities. The Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM) is one of the most accurate risk stratification tools to predict complications after oesophagectomy.¹¹⁹ It is a multivariable model which includes age, cardiac and respiratory disease, preoperative physiological parameters, Glasgow Coma Scale (GCS) score and operative parameters to calculate a risk of morbidity and mortality. The numerous variables included in this scoring system demonstrates the complex interplay between patient factors and clinical care, which may determine postoperative outcome. Patient factors are a part of a casual pathway to an outcome, which may influence but do not necessarily decide it; particularly in surgeries of such great magnitude of physiological insult as an oesophagectomy. Physical fitness needs to be considered in the context of this complex model. The next section describes the operative steps of an oesophagectomy and its anaesthesia.

2.3.2 Clinical care

Surgery for cancer of the oesophagus (oesophagectomy)

To appreciate the potential complications after oesophagectomy, and the possible influence on these of physical activity, the anatomy of the oesophagus and adjacent structures, as well as operative details of an oesophagectomy, including anaesthesia, are described.

Figure 2.5 Schematic of the anatomy of the oesophagus and its related structures.



UES= upper oesophageal sphincter, EGJ= oesophagogastric junction. Image from Hong SJ, Kim TJ, Nam KB, et al. New TNM staging system for esophageal cancer: what chest radiologists need to know. *Radiographics* 2014;34(6):1722-40.¹²⁰

Surgical anatomy

The oesophagus is a muscular tube connecting the pharynx to the proximal stomach, measuring approximately 25cm in length in most adults. It starts at the cricopharyngeal sphincter, transverses the posterior mediastinum, passes from the chest into the abdomen via the oesophageal hiatus within the diaphragm and connects to the cardia of the stomach (figure 2.5). Anatomically, it lies posterior to the pericardium and trachea but anterior to the spine. The left atrium and inferior pulmonary veins lie in contact with the anterior and left wall of the lower third of the oesophagus, while more proximally the arch of the azygous vein lies on the right lateral side, with the aortic arch on the left lateral side. The cervical oesophagus is defined superiorly by the upper oesophageal sphincter and inferiorly by the sternal notch. The upper oesophagus runs from the sternal notch to the level of the bifurcation of the trachea. The middle oesophagus is defined superiorly by the bifurcation of the trachea to the midpoint between this and the oesophagogastric junction. The lower oesophagus is from the lower margin of the middle oesophagus to the oesophagogastric junction.

Operative details of oesophagectomy

Whilst the surgical approach to an oesophagectomy differs depending on both the individual patient and the training and preference of the surgeon, the operative steps are similar.³⁴ The operation begins with abdominal exploration via laparotomy or laparoscopy for evidence of metastatic disease and resectability of the tumour. This is followed by gastric mobilisation from the hiatus and fashioning of the stomach into a conduit (figure 2.6). The oesophagus is then transected and the specimen delivered. An oesophagogastric anastomosis is then formed between the gastric conduit and the remaining oesophagus (figure 2.7)

Figure 2.6 Schematic showing formation of a gastric conduit from the stomach

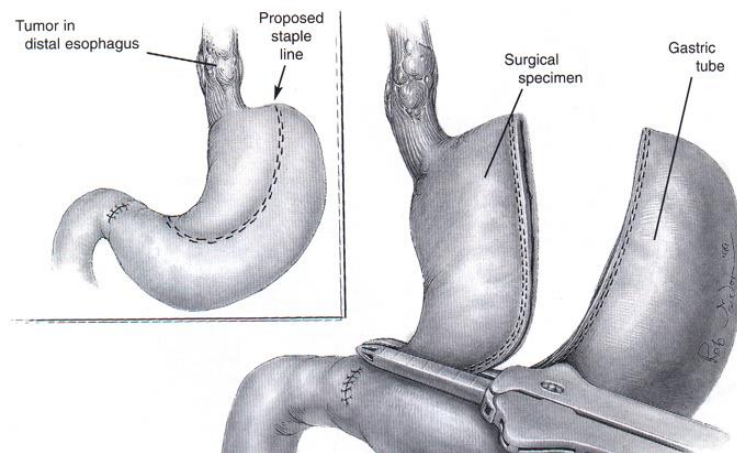


Image from www.ctsnet.org/article/transhiatal-esophagectomy [accessed on 24/10/2017].

Figure 2.7 Schematic showing the anatomical phases of an oesophagectomy

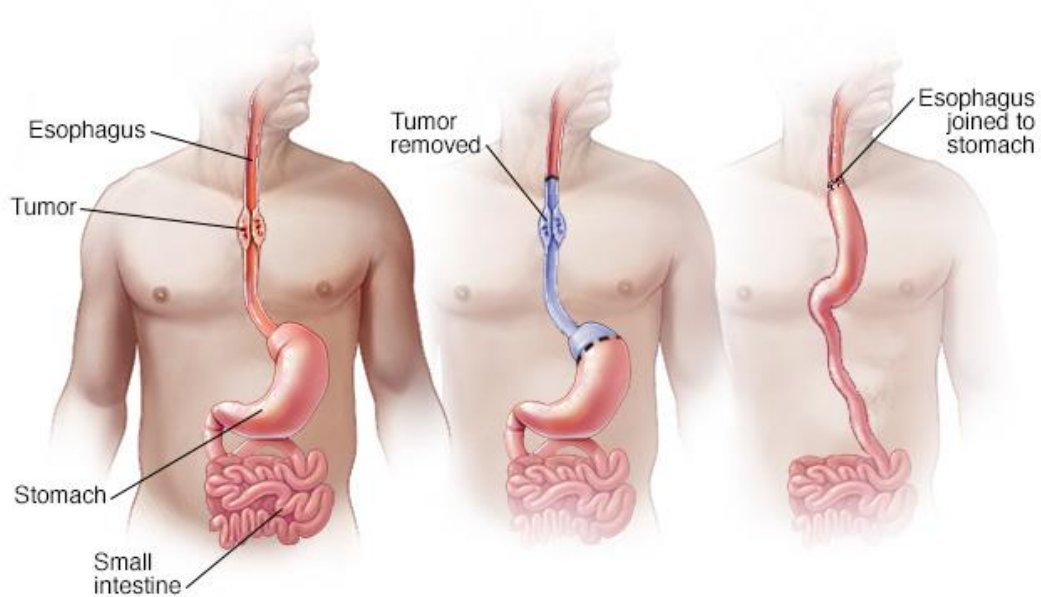


Image from <http://www.mayoclinic.org/diseases-conditions/esophageal-cancer/multimedia/esophageal-cancer-surgery/img-20006034> [accessed on 24/10/2017].

The commonest operative approach at the Norfolk and Norwich Hospital is a two stage oesophagectomy via a right thoracotomy, originally described by Lewis¹²¹ and Tanner¹²² (Ivor Lewis oesophagectomy). A laparotomy or laparoscopic approach is used for the first abdominal phase (figure 2.8), during which the stomach is mobilised and fashioned into a conduit.

Figure 2.8 Port placement for the laparoscopic abdominal phase of Ivor Lewis minimally invasive oesophagectomy.

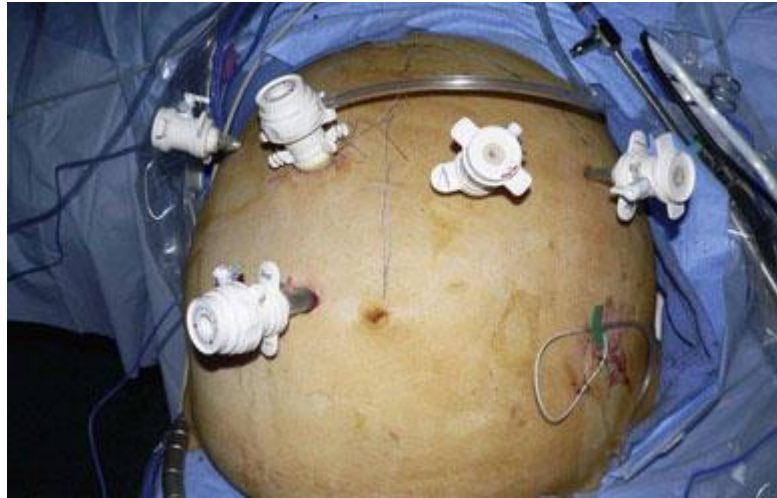


Image from Wizorek JJ, Awais O, Luketich JD: Minimally invasive esophagectomy. In Zwischenberger JB, editor: Atlas of Thoracic Surgical Techniques, 1st edition. Philadelphia, 2010, Saunders, pp 305–319.).

The second thoracic phase involves a thoracotomy usually at the 5th intercostal space or a VATS mini-thoracotomy (figure 2.9) where the stomach is delivered into the chest and the anastomosis formed.

Figure 2.9 Port placement and a low mini-VATS thoracotomy incision for the thoracic stage of a minimally invasive oesophagectomy



Image from Robotic-assisted Ivor Lewis esophagectomy: technique and early outcomes. Nora J, Shridhar R, Meredith K. Robotic Surgery: Research and Reviews. 27 September 2017. Volume 2017:4 Pages 93—100.

This operation can be performed with a laparotomy and thoracotomy (open Ivor Lewis), a laparoscopic abdominal stage and thoracotomy (partially minimally invasive Ivor Lewis) or a laparoscopic abdomen and VATS thoracotomy (minimally invasive Ivor Lewis). Some surgeons prefer to divide the oesophagus in the neck, which allows better access for anastomosis. This requires an additional neck incision phase, or three phase oesophagectomy. The approach was recommended by McKeown on the basis that anastomotic leak at the neck has a lower risk of mortality compared to a thoracic leak.³⁴ Finally a transhiatal oesophagectomy can also be performed without a thoracotomy, with abdominal and cervical stages, similar to a McKeown oesophagectomy. These operations describe the approach for any lesion, which may or may not be a cancer, located in the upper, mid and lower portions of the oesophagus. Lesions located in the hypopharynx and

cervical oesophagus, require a pharyngolaryngo-oesophagectomy, which is beyond the scope of this thesis.

The challenges of anaesthesia for oesophagectomy

The anaesthetic challenges of an oesophagectomy are related to: prolonged operating times, one lung ventilation, and providing effective postoperative analgesia.¹²³ Prolonged surgery increases the risk of hypothermia, which; reduces oxygen delivery, increases myocardial work, and propagates the surgical stress response.¹²³ Collapse and re-expansion of the lung on the thoracotomy side (to permit surgical access) may cause acute lung injury via an ischaemic reperfusion mechanism, with resultant increased vascular permeability and oedema.¹²⁴ Furthermore, over-ventilation of the dependent lung can induce acute lung injury through barotrauma.¹²⁴ Both these factors, accompanied by widespread systemic inflammation due to the surgical stress response, may propagate an acute respiratory distress syndrome (ARDS) with impaired pulmonary gas exchange from alveolar inflammation (loss of endothelial integrity with extravasation of fluid, protein and inflammatory cells).^{123 124} Postoperative reductions in FRC and VC are largely attributed to incisional pain and reflex diaphragmatic dysfunction as described previously.¹¹¹

2.3.3 Short-term postoperative complications after oesophagectomy

Oesophagectomy is a high-risk and complex surgical procedure associated with significant postoperative morbidity and mortality. This is related to both the long duration of surgery and the magnitude of surgical resection and reconstruction. UK national audit figures reported 33% of patients suffered a complication after oesophagectomy, most of which (74%) were cardiopulmonary (52% respiratory and 22% cardiac).¹²⁵ Other common non-cardiopulmonary complications included anastomotic leak and chyle leak (due to intra-operative thoracic duct damage).

Pneumonia

During surgery, both lungs are subjected to compressive forces. One lung is collapsed to allow surgical access, while the other dependent lung is compressed due to patient positioning (the weight of the mediastinum and abdominal contents, compounded by diaphragm paralysis)³⁴ Furthermore, postoperative pain inhibits both deep breathing to fully expand the lungs and an effective cough to clear secretions. Both mechanisms are

important in reducing the risk of atelectasis and pneumonia. Clinical measures to reduce such risks include adequate postoperative pain control. Epidural analgesia with opiates and or local anaesthetic agents provide optimal postoperative pain management. This is reflected in a reduction of respiratory complications when used in patients undergoing oesophagectomy.¹²⁶

Atrial Fibrillation

The precise cause of postoperative atrial fibrillation (AF) after oesophagectomy is unknown, but this dysrhythmia constitutes a common complication after thoracic surgery; reflecting the pro-arrhythmogenic impact of surgical resection close to the heart.¹²⁷ During an oesophagectomy, the lower oesophagus is dissected from the pericardium which is likely to induce local pericardial inflammation resulting in dysrhythmias.¹²⁸ Other potential causes include: an altered sympathovagal balance, systemic inflammation and premature atrial complexes associated with sympathetic stimulation due to pain.¹²⁷ Furthermore, AF can be a heralding event of an anastomotic leak, likely due to the local inflammatory effects on the pericardium of extravasated gastric contents. Indeed, the experience from the upper gastrointestinal surgery department at the NNUH in patients with early post-oesophagectomy AF, is that 30% will have subsequent evidence of an anastomotic leak.

Anastomotic leak

Early anastomotic leak (within 72 hours) is thought to be a result of technical error.³⁴ Such technical factors may include 1) tension on the anastomosis, 2) poor approximation or suturing inadequacy and 3) lack of adequate blood supply.³⁴ Other, non-technical aspects may include hypoperfusion of the anastomosis due to hypotension and splanchnic vasoconstriction.

Other complications

Other complications such as chylothorax, recurrent laryngeal nerve damage, and anastomotic stricture may also be attributed to intra-operative technique.³⁴

Mortality

National UK postoperative mortality rates reported between 2012 and 2015, at postoperative days 30 and 90 were, 2.2% (95% CI 1.7-2.8) and 4.3% (95% CI 3.6-5.1), respectively.¹²⁹ These figures demonstrate a slight decrease in mortality since a 2010 report, where 30 and 90 day mortalities were 3.8 and 5.7%, respectively.¹²⁹

How improved aerobic fitness may attenuate early postoperative complications following oesophagectomy

There are several plausible mechanisms for how an increased aerobic fitness may reduce the number of complications after oesophagectomy. Physical activity training results in improved oxygen delivery to metabolising tissue by: increasing cardiac output (Q), lung ventilation, and the mitochondrial and capillary densities of skeletal muscle. Such gains are likely to attenuate the surgical consequences of anaesthesia, tissue trauma, and bed-rest. A more efficient Q is likely to reduce the risk of myocardial and gut hypo-perfusion reducing the incidence of myocardial and anastomosis ischaemia. Improved respiratory muscle strength may attenuate losses in FRC and VC, reducing the risk of atelectatic infection. Greater skeletal muscle bulk, particularly of the major legs muscles, will allow increased reserves for catabolic losses - retaining strength for early mobilisation to enhance lung mechanics. How physical activity training may reduce the incidence of atrial fibrillation is unclear, as its occurrence is likely to be related to postoperative inflammatory changes, either local or systemic.¹¹⁶ However, tachycardia on the first day postoperatively has been shown to be a risk factor for AF post-oesophagectomy,¹³⁰ and exercise training results in a lower resting HR. Furthermore, distention of atrial muscle fibres is associated with an increased risk of AF, while a more compliant myocardium (through exercise training) may also better tolerate acute atrial stretch due to over-administration of perioperative intravenous fluids.

Randomised controlled trials are required to investigate whether improved physical fitness, through a preoperative exercise intervention, results in a reduced risk of complications after oesophagectomy. The next section of this thesis presents the methodology and results of a feasibility randomised controlled trial of short-term exercise therapy versus standard care prior to surgery to reduce the risk of postoperative cardiopulmonary complications. Such feasibility trials are important before a full RCT to both justify and inform its conduct. Important questions to answer are 1) whether

patients are willing to be recruited into such trials, and 2) if the exercise programme offered is safe and adhered to. This feasibility trial was designed and commenced at the beginning of my research time and was based on my interpretation of the available published observational studies showing that fitness, as measured objectively by cardiopulmonary exercise testing, was associated with a decreased risk of cardiopulmonary complications after oesophagectomy. Later during my research training, with a deeper understanding of study methodology and medical statistics, I subsequently re-analysed in more detail and breadth the existing evidence for the association between preoperative fitness and postoperative complications before major cancer resection and found the limitations in such work, including in oesophagectomy, which are detailed and addressed in chapter 3.

2.4 Prehabilitation to improve physical fitness and reduce postoperative cardiopulmonary complications after oesophagectomy in patients with oesophageal adenocarcinoma – a feasibility randomised controlled trial. The ExPO Trial (Exercise Prior to Oesophagectomy)



2.4.1 Abstract

Background: Increasing physical fitness prior to oesophagectomy has the potential to decrease postoperative complication risk, but to date, no trials have investigated this hypothesis. The aim of the EXPO feasibility trial was to use the preoperative period (during and after neoadjuvant chemotherapy, but before surgery) to improve a patient's physical fitness through exercise. Such data are required to justify and inform a future randomised controlled trial (RCT), which would investigate if exercise before surgery (prehabilitation) can reduce the incidence of postoperative cardiopulmonary complications.

Methods: ExPO was a single centre, parallel group, single-blinded, RCT investigating a specifically designed multi-modal personalised exercise programme (prehabilitation) versus standard care in adults with oesophageal adenocarcinoma due to undergo neoadjuvant chemotherapy and oesophagectomy. The prehabilitation intervention consisted of: i) home inspiratory muscle training (IMT), ii) standard care home exercise advice, and iii) a 4 week hospital-supervised aerobic and muscle strengthening exercise programme. Standard care was home exercise advice only. Cardiopulmonary exercise testing (CPEX) before and after the interventions documented any objective changes in physiological fitness. Quality of life (QOL) as well as baseline levels of physical activity and reasons for non-participation were also measured. Cardiopulmonary complications were measured at post-operative day 30 by blinded assessors.

Results: Between October 2016 and June 2017 (9 months), a total of 20 patients were screened, 11 (55%) provided consent for participation and were randomised (5 to the prehabilitation group and 6 to the control group). Of the 11 recruited participants there was 100% retention in the trial. In the prehabilitation arm there was full attendance to all of the sessions offered (median of 5 sessions per participant). There were no adverse reactions reported in either arm to exercise. Overall, adherence to home exercise sessions was low (25% to 49%) mostly due to side effects of chemotherapy. The mean change in VO_{2peak} was +2.0ml/kg/min in the intervention group and +0.3ml/kg/min in the control group ($p=0.61$). AT increased by +1.5ml/kg/min in the prehabilitation group but decreased by -1.2ml/kg/ml in the control group ($p=0.26$). Quality of life did not differ significantly between groups. The 30-day postoperative cardiopulmonary complication rates were also similar in both arms.

Discussion: The ExPO trial provides 'proof of concept' for prehabilitation prior to oesophagectomy in patients with oesophageal adenocarcinoma undergoing chemotherapy. That is, there was a reasonable recruitment rate and the exercise regime was safe, acceptable and well adhered to. The study lacked statistical power to detect whether the improvement in fitness over standard care was statistically significant. This work informs the design of a larger feasibility study in this patient population to investigate whether the fitness of oesophagectomy patients can be improved in the short time between neoadjuvant chemotherapy and surgery.

2.4.2 Introduction

Background

Increasing physical fitness prior to oesophagectomy has the potential to decrease postoperative complications. Such reductions may also have an impact on other important outcomes including: mortality, chronic morbidity, length of hospital stay (LOS), hospital readmission and financial costs, whilst increasing quality of life (QOL).⁹ The current accepted clinical standard in the UK is to allow 5-6 weeks after completion of neoadjuvant chemotherapy before oesophagectomy in patients with operable oesophageal adenocarcinoma.¹⁰ This recovery period may be used to improve patient postoperative outcomes with a preoperative exercise programme (prehabilitation).

The association between aerobic fitness and postoperative outcome

Cardiopulmonary exercise (CPEX) testing is the current gold standard test to measure aerobic fitness, offering an objective, quantitative and composite measure of a person's ability to deliver oxygen to tissues during exercise. Two specific CPEX variables; VO_{2peak} (the maximal oxygen consumed at peak exercise) and VO_2 at estimated anaerobic threshold (AT) have shown promise in observational studies for predicting both morbidity and mortality.¹³¹⁻¹³⁹ In an observational study of 187 elderly patients undergoing major abdominal surgery, a preoperative AT cut-off of $<11\text{ml/kg/min}$ had a sensitivity of 91% and specificity of 74% for predicting short-term mortality.¹³¹ In two large multi-centre studies in lung cancer patients undergoing resection via thoracotomy, with a combined sample size of 2 030 patients, a VO_{2peak} of $<15\text{ml/kg/min}$ was associated with a 2-fold increased risk of early major respiratory complications¹³⁸ and death.^{138 139} There are 3 relatively small observational studies of CPEX testing prior to oesophagectomy ($n=78$,¹³⁶ $n=91$,¹³⁴ $n=103$ patients¹³⁵), two of which reported an inverse association between VO_{2peak} and cardiopulmonary complications ($p=0.001^4$ and $p=0.04^{136}$). The remaining study reported no association for VO_{2peak} ($p=0.07$), but a significant inverse association between AT and cardiopulmonary complications ($p=0.05$).¹³⁵ Whilst this observational work suggests that increased fitness may be beneficial, the findings are likely subject to biases associated with observational work, such as detection and selective reporting bias, which can be addressed in RCTs. To date, no RCT has demonstrated that increased physical fitness improves clinical outcomes after oesophagectomy.

The safety and fitness improvements of prehabilitation

Both the safety of prehabilitation and its improvements in fitness have been investigated in several RCTs¹⁴⁰⁻¹⁴² (although not in oesophageal cancer surgery) and observational studies.¹⁴³⁻¹⁴⁴ In these investigations, exercise sessions were delivered as 4 to 8 week programmes, usually consisting of an aerobic component (either walking or cycling) and muscle strengthening. A systematic review¹³³ of 4 randomised trials and 6 observational studies, totalling 524 patients, reported that exercise training prior to cardiac, lung and colorectal surgeries was: safe, feasible and well tolerated, with only 2 exercise-related adverse events (transient hypotension) reported. Such exercise therapy was also found to be effective in improving objective measures of physical fitness, including VO_{2peak} which was increased by to 2.4 to 2.8ml/kg/min.¹⁴⁵⁻¹⁴⁶ To the best of my knowledge, no interventional studies of aerobic exercise prior to oesophagectomy have been published.

Reduction in postoperative complications due to prehabilitation

Although there is trial evidence reporting that physical fitness can be improved in the limited time between diagnosis and surgery, at the time of writing, there have been only two adequately powered randomised controlled trials reporting on prehabilitation to reduce postoperative complications (neither of which were in oesophageal cancer surgery).^{147,148} The first was a recently published RCT of a preoperative exercise intervention in lung cancer patients.¹⁴⁸ This Swiss trial of 151 patients, compared a high intensity aerobic exercise programme (20 min sprint interval training on a static exercise bike and muscle strengthening) with standard care and found that whilst VO_{2peak} was significantly increased in the intervention group, this did not translate into a significant reduction in postoperative complications (35% of prehabilitation patients suffered a complication vs. 50.6% in the usual care group, $p=0.08$).¹⁴⁸ However, the authors commented that a larger sample size may have detected a smaller effect. A second UK trial in 124 participants investigated a 6-week supervised exercise programme prior to open or endovascular aortic aneurysm repair.¹⁴⁷ The exercise sessions consisted predominantly of muscle strengthening with minimal aerobic exercise (2 mins of cycling on an exercise bike). The authors documented a reduction in the number of both cardiac (8.1% vs. 22.6%, $p=0.025$) and pulmonary (11.3% vs. 21.0%, $p=0.143$) complications in the exercise group compared to the non-exercise group. Unfortunately, a standardised primary outcome measure was not used to report complications, which may have resulted in selective reporting bias and an over estimation of the effect size. The findings

from both of these trials are unlikely to be comparable to oesophageal surgery due to differences in both the preoperative management and the nature of the surgeries. Unlike lung and vascular surgery, most oesophagectomy patients are exposed to 3 cycles of preoperative neoadjuvant chemotherapy lasting approximately 9-10 weeks, which in itself decreases aerobic fitness.¹⁴⁹ Oesophagectomy is also unique in that there is breach of two anatomical cavities, namely the thorax and abdomen. Therefore, the postoperative complication profile consists of both cardiopulmonary and abdominal complications. As such, inferences from trials in lung or vascular surgery applied to oesophagectomy, or indeed any other surgical specialties, cannot be reliably made, highlighting the need for exercise trials in oesophageal cancer patients.

The role of both endurance and high intensity inspiratory muscle training (IMT) in prehabilitation

A further component of prehabilitation to increase physical fitness is inspiratory muscle training (IMT). This consists of a course of breathing exercises using a hand-held resistance device to increase the strength of respiratory muscles. Whilst IMT is normally used by athletes or patients with asthma and COPD, it has been investigated prior to cardiac and abdominal surgeries to reduce pulmonary complications. It is proposed that strengthening of respiratory muscles may attenuate their decline and dysfunction following major surgery. To support this hypothesis, there is evidence from systematic reviews that a 2-4 week programme of preoperative IMT is safe and effective at reducing pulmonary complications after major elective cardiac^{42,43} and abdominal surgeries⁴³ (oesophageal surgery was not included). A 2012 Cochrane Review of 8 RCTs in 856 participants⁴² reported that IMT in patients undergoing cardiac surgery was safe and reduced the risk of atelectasis (RR=0.52, 95% CI=0.32-0.87) and pneumonia (RR=0.45, 95% CI=0.24-0.83) compared to no IMT. However, some trials were small (4 had less than 50 patients) and there were differences in the interventions (2 trials incorporated aerobic exercise as well as IMT). In a later 2015 Cochrane Review⁴³ of 12 trials with 695 participants awaiting cardiac (5 trials) and major abdominal (7 trials) surgery (oesophageal surgery was not included), IMT was without adverse events and also reduced atelectasis (RR=0.53, 95% CI=0.34-0.82) and pneumonia (RR=0.45, 95% CI=0.26-0.77) compared to no IMT. However, the review commented on possible over-estimation of treatment effects due to inadequate blinding and publication bias. These trials investigated endurance IMT (IMT-E) which starts at 15-40% of a patient's maximal inspiratory pressure

(P_{i-max}) and increases progressively up to 60%. IMT that starts at 60-80% of P_{i-max} , and increases progressively upwards (from this higher starting point) is called high intensity IMT (IMT-HI). This type of IMT has been investigated in patients with COPD¹⁵⁰ and heart failure¹⁵¹ and may be superior to IMT-E at increasing a patient's P_{i-max} . There is only a single published investigation of perioperative IMT in oesophagectomy patients.¹⁵² This Dutch randomised pilot study of 39 participants, planned for neoadjuvant chemo-radiotherapy and oesophagectomy for oesophageal cancer, assigned participants to a 3 week preoperative programme of either IMT-HI or IMT-E (with no control group). Intervention adherence was high in both groups (98% and 99%, respectively) with only one adverse event (tension headache). The authors reported no significant difference in the mean increase in P_{i-max} between groups (35% in the IMT-E group vs. 12% in the IMT-HI group, $p=0.316$). Nonetheless, they stated that the frequency of higher grade postoperative pulmonary complications (e.g. pleural effusion, pneumonia, ventilator assistance) was almost three times lower in the IMT-HI group (20% vs. 58%; $p=0.015$). Although, as a seemingly contradictory finding, the IMT-HI group had almost double the number of lower severity pulmonary complications (e.g. atelectasis, hypoxaemia, hypercarbia) compared to the IMT-E group (80% vs. 42%; $p=0.015$). The authors also reported suboptimal IMT training in 6 of the 19 participants assigned to IMT-E (due to equipment issues). In summary, the small sample size, lack of significant difference in P_{i-max} between groups, conflicting findings and equipment issues raises concerns over both the validity and reliability of their findings. As such, it is unclear whether IMT-HI has any benefit over other forms of IMT in oesophagectomy patients.

The optimal components of a prehabilitation intervention

There is no current and accepted prehabilitation programme routinely offered to patients prior to oesophagectomy. Indeed, there is no consensus on the most effective prehabilitation programme prior to any type of surgery to reduce complications. It is unknown whether an exercise programme should consist exclusively of aerobic exercise, muscle strengthening or IMT (either endurance or high intensity) or a combination of some or all. Only IMT, but no other components of prehabilitation have been assessed in any RCT in patients awaiting oesophagectomy, with unclear benefit.¹⁵² However, all components have some trial evidence of efficacy in other surgery types.^{147 153} Perhaps most importantly, the content of an exercise programme should be determined by the specific complication profile of the surgery with a plausible biological reason why the

exercise programme could prevent such complications. In oesophagectomy patients, where the complications are mostly cardiopulmonary, there are physiological reasons why all exercise modalities (aerobic exercise, IMT and muscle strengthening) are likely to be beneficial (as explained in the previous section). As such, all may reduce the risk of complications after surgery, and warrant investigation in clinical trials.

The need for a feasibility trial of prehabilitation prior to oesophagectomy

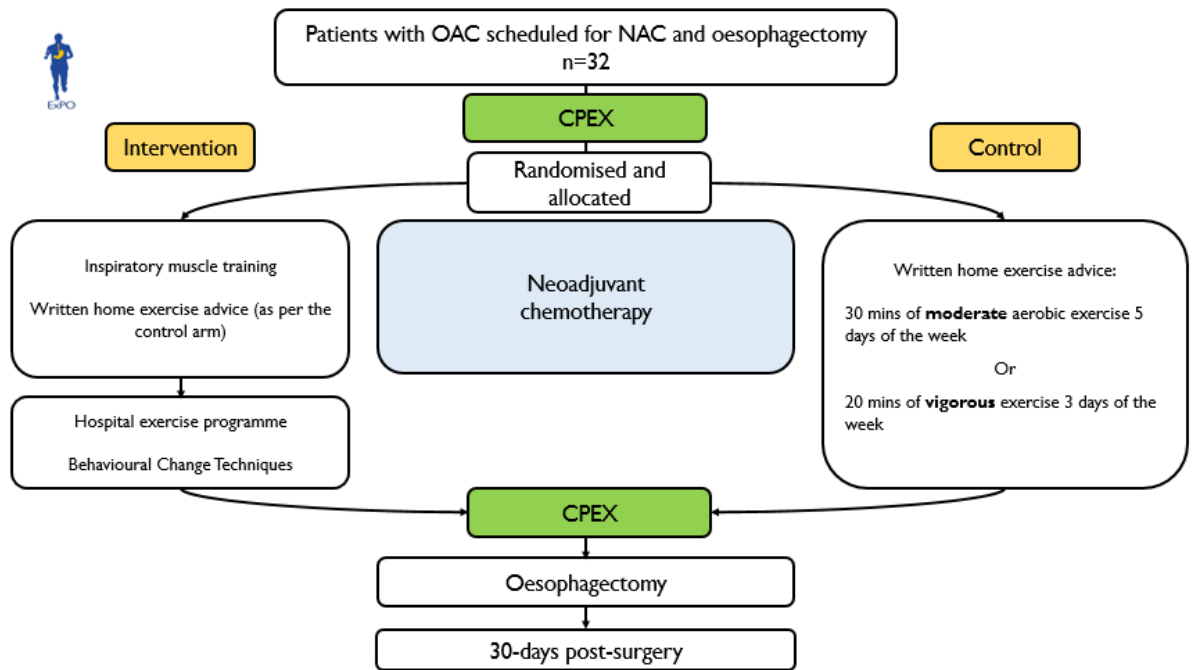
To date, no trial has reported on preoperative exercise in patients undergoing oesophagectomy. However, before a full RCT to assess the potential efficacy of prehabilitation prior to oesophagectomy to reduce complications can be conducted, important feasibility criteria need to be fulfilled to both justify and inform its conduct. These include demonstrating that a short period of exercise prior to oesophagectomy is safe and that sufficient participants are suitable, can be recruited and retained in such a programme. If a future RCT could demonstrate benefits to patients this would support the use of exercise prior to oesophagectomy as standard care across the NHS to reduce the current high number of postoperative cardiopulmonary complications. The purpose of the ExPO feasibility trial was therefore to provide evidence to guide both the design and conduct of a future definitive trial.

2.4.3 Methods

Study design

The ExPO study was a prospective, parallel group, feasibility randomised controlled trial with a recruitment target of 32 participants (16 per arm) The work was registered at the National Institutes of Health ClinicalTrials.gov (NCT02962219) and conducted in the department of Upper Gastrointestinal (UGI) Surgery at the Norfolk and Norwich University Hospitals (NNUH) Foundation Trust, Norwich, United Kingdom. The NNUH is a 1,000 bed teaching hospital, which provides care to a population of approximately 825,000 residents in Norfolk and its adjacent counties. Approximately 45 oesophagectomies are performed at this unit each year. The NNUH takes referrals from its neighbouring hospitals: the James Paget University Hospital (JPUH) in Great Yarmouth and the Queen Elizabeth Hospital (QEH) in King's Lynn. Both these neighbouring hospitals acted as patient identification centres (PICs) for the ExPO trial. The full detailed trial protocol is shown in appendix 3.

Figure 2.10 The ExPO trial CONSORT flow diagram



OAC = oesophageal adenocarcinoma, NAC = neoadjuvant chemotherapy, CPEX = cardiopulmonary exercise testing,

Figure 2.11 Arial photo of The Norfolk and Norwich University Hospital



Image taken from <http://www.panoramio.com/photo/82330913> [accessed 24/10/2017].

Patients

After written approval from the Leicester-South research ethics committee (ref: 16/EM/0317) on behalf of the Health Research Authority (IRAS ID: 206608) patients were identified at weekly NNUH oesophagogastric cancer specialist multidisciplinary team meetings between October 2016 to June 2017. Written informed consent was obtained from all eligible adult patients with histology proven oesophageal adenocarcinoma planned for both neoadjuvant chemotherapy and oesophagectomy. Patients were excluded if there were contraindications to performing exercise training (e.g. severe musculoskeletal disease or uncontrolled cardiac disease). Patients with other histological types of oesophageal cancer (e.g. squamous cell carcinoma) or those proceeding to surgery without chemotherapy were also excluded, as their clinical timelines differed, often with insufficient time for an exercise programme.

Randomisation

Using a CPEX VO_{2peak} cut-off of 15ml/kg/min derived from observational work in thoracic surgery patients^{138 139}, consenting participants were stratified into 'high' and 'low' fitness score groups. This stratification was to help equally distribute those with a 'low' level of

fitness between trial arms, reducing the risk of selection bias, which can occur with relatively small numbers of patients. Randomisation was done by a statistician on a 1:1 basis into prehabilitation and usual care arms using random block sizes (known only to the statistician) generated by computerised randomisation (www.randomization.com). Allocations were placed in opaque envelopes by a secretary independent of the ExPO trial.

Interventions

Both the prehabilitation arm and the usual care arm received usual standard care advice (in written form) to exercise at home both during and after neoadjuvant chemotherapy and up to the time of surgery (a period of approximately 14-16 weeks). The recommended activities were 30 mins of moderate intensity aerobic exercise (e.g. fast walking, cycling) on at least 5 days of the week, or 20 mins of vigorous activity (e.g. jogging) on 3 days of the week in line with general recommendations by the UK Department of Health (DH)¹⁵⁴ and the American College of Sports Medicine (ACSM).¹⁵⁵ In addition to this, those in the prehabilitation arm were asked to complete home exercise diaries and were offered two further exercise interventions:

- 1) Prehabilitation arm participants were asked to engage in home inspiratory muscle training (IMT) for 20 mins every day both during and after neoadjuvant chemotherapy. The IMT programme was as per Hulzebos, *et al*¹⁵³ where maximal inspiratory pressure (P_{i-max}) was measured at baseline, after which participants were given an inspiratory threshold loading device (POWERBreathe Medic). Resistance was set on their device at 30% of their P_{i-max} and participants were instructed to perform IMT for 20 mins 7 days a week and to incrementally increase the resistance on the device by 5% if their rate of perceived exertion was less than 5 as scored on the New Category (0-10) Borg RPE Scale¹⁵⁶ (figure 2.13) Participants were also given an exercise diary to record their use and any adverse events.

Figure 2.12 An inspiratory muscle trainer (IMT) device (The POWEBREATHE Medic)



Image from www.powerbreathe.com/powerbreathe-medic [accessed on 24/10/2017].

Figure 2.13 The new category Borg rating of perceived exertion (RPE) scale.

RPE (UNIT)	Patients Perceived Exertion	Alternative perceived exertion
0	Nothing at all	
0.5	Very, very weak	Just noticeable
1	Very weak	
2	Weak	light
3	Moderate	
4	Somewhat strong	
5	Strong	heavy
6		
7	Very strong	
8		
9		
10	Very, very strong	Almost max

Adapted from Borg, G. Psychophysical bases of perceived exertion, Med Sci Sports Exerc 1982;14 (5):377-81.¹⁵⁶

2) Prehabilitation arm participants were also offered an inpatient Hospital exercise programme in the clinical trials unit at the NNUH consisting of both aerobic exercise on a static exercise bike (Monarch Energy 915) and muscle strengthening. This programme was designed in co-operation with experienced physical therapists specialised in rehabilitation and utilised the standard care period between the end of neoadjuvant chemotherapy and surgery, which is approximately 6 weeks. The aim was to achieve a maximum of 8 sessions, with 2 sessions per week for 4 weeks, each lasting 60 mins. For the aerobic component, participants were invited to begin with 4 mins of warm up by cycling to a perceived exercise intensity of 'light' on the Borg scale (score 9-11) (Figure 2.14).¹⁵⁶ After warm up, remaining on the bike, the participants were invited to engage in aerobic interval training aiming to achieve up to 30 mins of *moderate intensity* (Borg scale rate of perceived exertion (RPE) of 12-13) aerobic exercise. The pedal resistance of the static bike was adjusted to achieve this. Progression was achieved at the discretion of the doctor supervising the programme by increasing exercise intensity on the BORG scale and decreasing the duration and rest periods. After the aerobic component, participants attempted the following sets of muscle strengthening exercises, each for 2 minutes (as per the programme of Barakat, *et al* ¹⁴⁷): heel-raises, knee extensions, knee bends, step-up lunges and biceps curls. This was followed by warm-down stretching.

Figure 2.14 The 15-grade scale for rating of perceived exertion, the Borg's 6-20 RPE scale

RPE (UNIT)	Patients Perceived Exertion	Alternative perceived exertion
6		
7	Very, very light	
8		
9	Very light	
10		
11	Fairly light	
12		Moderate
13	Somewhat hard	Moderate
14		Vigorous
15	Hard	Vigorous
16		Vigorous
17	Very hard	Vigorous
18		
19	Very very hard	
20		

Adapted from Borg, G. Psychophysical bases of perceived exertion, Med Sci Sports Exerc 1982;14 (5):377-81.¹⁵⁶

Figure 2.15 The Monarch 915E static exercise bike, which was used in the ExPO trial.



Image from www.monarkexercise.se [accessed 24/10/2017].

Safety measures

Many measures were incorporated into the programme to ensure its safety. The home and hospital aerobic and muscle strengthening programmes closely followed guidance from the UK DH and ACSM for exercise in older adults. The supervised in-hospital exercise programme in the ExPO trial was also developed in collaboration with a senior clinical physiotherapist experienced in the rehabilitation of patients following oesophagectomy to ensure it was both safe and realistic for this patient group. Additionally, the exercise regime was discussed with two patient groups, the Oesophageal Patients' Association (OPA) and Norfolk Together Against Cancer (TAC), who agreed that the regime would likely be acceptable to participants. The exercise programme was also similar to exercise regimes used in RCTs of different surgical patient populations, which were shown to be safe and achievable.⁸ The following trial procedures were also followed to ensure safety in the ExPO trial.

- i. only recruiting patients who were deemed fit for both neoadjuvant chemotherapy and surgery by consultant clinicians.
- ii. including a baseline health screening assessment (to ensure there were no co-existing diseases which would be exacerbated by exercise).
- iii. use of a baseline CPEX test, to measure fitness and allow personalisation of the hospital exercise programme.
- iv. tailoring exercise to each participants perceived exertion level (through the use of the Borg scale), which was frequently re-assessed so that the participant could rest or stop exercise if they felt that they were over-exerting themselves.
- v. oral consent to exercise was obtained prior to each exercise session to ensure ongoing approval for continuation in the programme.
- vi. a short medical history was re-taken at each exercise visit, to ensure the patient was suitable for exercise at each session.
- vii. a medically qualified doctor was present during all hospital exercise sessions trained in life support with resuscitation equipment available.
- viii. the participant's underwent baseline observations (HR, BP, RR, temperature and oxygen saturations) before each exercise session to ensure they were within acceptable limits.
- ix. the participants were informed that they may cease any or all components of exercise at any stage at their choice without prejudicing future clinical care.

It was anticipated that any adverse reactions to exercise would be both transient and mild including: an exacerbation of existing medical conditions (e.g. angina), delayed onset muscle soreness, soft tissue strains, nausea and transient hypotension. Nonetheless, an ExPO safety management plan was developed prior to patient recruitment and a trial safety committee (TSC) assembled to regularly review any adverse events which occurred during the trial. Full details of the definitions of adverse events, adverse reactions and causality of these events are detailed in the ExPO Safety Management Plan (appendix 4). As an additional measure to ensure the safety of trial participants, an ExPO trial management group (TMG) and an independent trial steering committee (TSC) were assembled. These groups reviewed the progress of the trial and reported to the TSC regarding adverse events.

Surgery

Surgery occurred approximately 6 weeks after completion of chemotherapy and 1 week after completion of the hospital exercise programme. At surgery, patients underwent either: a partially laparoscopic assisted (hybrid), or a fully laparoscopic (minimally invasive) Ivor Lewis oesophagectomy. All patients were admitted to a high dependency unit (HDU) for the first night following surgery. Step down to ward care was decided by the HDU consultant. All patients were managed as per the local enhanced recovery after surgery programme (ERAS).

Measurements and outcomes

In order to determine any changes in levels of physical activity, quality of life and fitness before and after the interventions, measurements were taken both prior to commencement of neoadjuvant chemotherapy and one week prior to surgery. At these times, all participants were asked to complete; the International Physical Activity Questionnaire (IPAQ) which consists of 4 questions, each relating to physical activity performed in the last 7 days; and two quality of life (QOL) questionnaires (EORTC QLQ-C30 and disease specific Oesophago-Gastric QLQ-OGC25). Participants were additionally asked to undergo both a cardiopulmonary exercise test and inspiratory pressure test. Both of these tests were undertaken in a respiratory laboratory at the NNUH by blinded laboratory staff not involved in any other aspect of the trial. CPEX testing was done on an electromagnetically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Lindenstrasse 5, D-72475, Bitz, Germany). Testing consisted of a 3 minute rest period, 3 minutes of free pedalling and an incremental ramped phase, usually lasting 8-12 minutes, until volitional termination. Gas exchange was measured using a metabolic cart (Jaeger Oxycon Pro, CareFusion, Germany 234 GmbH, Leibnizstrasse 7, 97204, Hoechberg). AT was estimated using the V-slope method (change in the linear relationships between VCO_2 and VO_2) and VO_{2peak} was averaged over 30 seconds during peak exercise. P_{i-max} was measured using a respiratory pressure meter (MicroMedical MicroRPM 01), where the average of 3 tests, each within 5cmH₂O of each other were used.

At recruitment, patients in the intervention arm were additionally asked to complete a Determinants of Physical Activity Questionnaire (DPAQ), which contained 34 questions relating participants' knowledge about exercise, social influences, levels of motivation and emotional responses to physical activity. These measures provided information about

factors that may have represented personal barriers or facilitators to participating in an exercise programme. These could then be addressed or encouraged during hospital exercise sessions.

In order to allow comparison of clinical and demographic data between patients both willing and not willing to join the trial, the following variables were obtained for all eligible patients: age, gender, smoking status (never, former, current), comorbidities and TNM staging. After oesophagectomy 30-day postoperative morbidity was measured for all randomised patients by hand review of the medical notes. This outcome assessment was by two blinded consultant anaesthetists not involved in the patients' care, in strict accordance with Esophageal Complications Consensus Group (ECCG) definitions.¹⁵⁷ Each complication was then graded by the assessors in accordance with the Clavien-Dindo classification.¹⁵⁸ In brief; grade 1 complications do not require pharmacological intervention above usual postoperative care, while grade 2 complications do. Grade 3a complications require a surgical intervention without general anaesthesia; grade 3b require a return to theatre; and grade 4 require organ support on ITU.

The primary outcome was to assess the feasibility of prehabilitation in this patient population. Therefore, the primary measures were the number of eligible patients that could be recruited and retained in the trial and both the adherence to and the safety of prehabilitation. Secondary measures to inform future work were: reasons for non-participation in the study and baseline levels of physical activity as well as differences in; quality of life; fitness (VO_{2peak} and P_{i-max}); 30-day postoperative complications; and 30-day mortality between arms before and after the interventions.

Sample size

As this was a feasibility trial, a formal sample size calculation was not required to determine the statistical significance of the effect size of the intervention on the number of cardiopulmonary complications between groups. However, this trial was powered to detect a statistically significant change in VO_{peak} of 3.6ml/kg/min between the two groups after the intervention. The sample size calculation was based on data from previous observational studies^{145 146} and a randomised controlled trial¹⁴² investigating preoperative exercise therapy of similar durations to the ExPO trial. These studies suggested that an in-hospital exercise regime may increase baseline VO_{2max} by 2.6ml/kg/min. This was

calculated from two observational studies, where VO_{2max} was increased by 2.8 and 2.4ml/kg/min after 4-6 week out-patient exercise programmes.^{145 146} To estimate the effect size in the baseline standard care arm, information was taken from a randomised controlled trial of 35 subjects, demonstrating that standard advice to exercise at home may cause a worsening of VO_{2max} of at least -1ml/kg/min.¹⁴² Therefore, assuming a mean difference of VO_{2max} of 3.6ml/kg/min and a standard deviation of 3.0,^{142 145 146} then using a two sample t-test the trial would require 11 individuals per group for the trial to have 80% power at the 5% level of significance to detect a statistically significant difference in VO_{2peak} between treatment arms. Accounting for a participant drop-out rate of 27%,^{142 146} at least 30 subjects were needed to be recruited to achieve 11 individuals per group for a per-protocol analysis. Based on the above information the aim was to recruit 32 patients in total.

Statistical analysis

The baseline participant demographic and clinical characteristics and trial outcomes for participants in each of the 2 arms were reported. For categorical variables, the numbers and percentages were presented and for continuous variables the means (and standard deviations) or medians (and interquartile ranges) depending on their distributions. Mean differences between groups were compared using Student-t tests.

2.4.4 Results

Between October 2016 and June 2017, a total of 20 patients were screened, 11 (55%) provided consent for participation and were randomised. Of these, 5 were randomised to the prehabilitation group and 6 to the control group (table 2.1). There was a smaller than anticipated number of eligible patients over the 9 month recruitment period (at least 35 patients were expected in line with figures from the previous 6 years at the NNUH).

Table 2.1 Baseline characteristics of the two allocation arms in the ExPO trial

Variable	Control (n=6)	Intervention (n=5)
Male gender	6 (100)	4 (80)
Mean age at operation (years + SD)	65.4 (9.1)	66.3 (9.4)
Hypertension	1 (17)	1 (20)
Coronary artery disease	0	1 (20)
Diabetes	1 (17)	2 (40)
T staging		
T3	5 (83)	5 (100)
T4	1 (17)	0
N staging		
N0	1 (17)	3 (60)
N1	2 (33)	1 (20)
N2	3 (50)	1 (20)
Smoking status		
Never	1 (17)	3 (60)
Former	3 (50)	1 (20)
Current	2 (33)	1 (20)
BMI (mean in kg/m² + SD)	27.0 (4.4)	27.1 (4.4)
IPAQ category of recreational physical activity		
Low	2 (33)	4 (80)
Moderate	1 (17)	0
High	3 (50)	1 (20)
Quality of life summary scores (mean +SD)		
C30	75 (13.0)	78.2 (14.0)
OG25	34.9 (13.8)	34.4 (14.9)
CPEX variables (mean in ml/kg/min + SD)		
VO _{2peak}	22.6 (6.4)	21.4 (6.4)
AT	13.3 (1.6)	12.8 (1.7)

Data shown are the number of patients and percentage unless otherwise stated.

Primary outcomes

Of the 20 patients approached all were deemed eligible to participate in the ExPO trial. The recruitment rate was 55%, with 9 patients not recruited: 7 did not want to participate (3 were unwilling to travel, 2 felt that they did not require any additional support to engage in exercise, 1 felt that exercise was too much work, and 1 expressed a dislike for exercise) and 2 patients who were willing to participate were excluded as CPEX testing was unable to be arranged due to no availability at the laboratory. The demographics and clinical characteristics of both willing and non-willing patients were similar (table 2.2).

Table 2.2 Comparison of the demographic and clinical characteristics of patients that were willing (n=13) and not willing (n=7) to join the ExPO trial.

Variable	Willing to join (n=13)	Not willing to join (n=7)
Male gender	12 (92)	7 (100)
Mean age at operation (years + SD)	66.9 (9.7)	67.0 (6.8)
Hypertension	3 (23)	4 (57)
Coronary artery disease	1 (8)	2 (29)
Diabetes	3 (23)	1 (14)
Smoking status		
Never	5 (39)	3 (43)
Former	5 (39)	3 (43)
Current	3 (23)	1 (14)
T staging		
T3	12 (92)	7 (100)
T4	1 (8)	0
N staging		
N0	6 (46)	5 (71)
N1	3 (23)	0
N2	4 (31)	2 (29)

Data shown are the number of patients and percentage unless otherwise stated.

Of the 11 recruited patients none dropped-out during the trial period, representing 100% retention. The median number of in-hospital exercise sessions attended was 5 (interquartile range of 4-5 sessions). There was 100% attendance of all of the sessions offered with complete adherence to the aerobic and muscle strengthening exercises. It was not feasible to offer the maximum 8 sessions to any of the patients, due to the earlier than anticipated scheduling of either surgery or second CPEX test. There were no adverse reactions to any of the in hospital exercise sessions. Adherence to home exercise sessions was variable in the intervention arm ranging from low to good (table 2.3). Reasons for low adherence included side effects of chemotherapy, during which time the patients felt unable to engage in exercise. No adverse reactions to exercise were documented in the exercise diaries. Similarly, adherence to IMT was variable. Diaries showed gaps in IMT use due to side-effects of chemotherapy such as “dry mouth”, “mouth ulcers” and “cold sores”, which made using the device uncomfortable.

Table 2.3 Adherence to prehabilitation in the ExPO trial

Patient number	No. of hospital exercise sessions attended	Adherence to home exercise	Adherence to IMT
1	5	Low	Low
2	7	Good	Good
3	5	Moderate	Low
4	3	Moderate	Good
5	2	Very low	Very low

Categories of adherence are based on the percentage of suggested exercises that the patients documented as completed in their exercise diaries, where non-adherence=0%, very low=1-24%, low=25-49%, moderate=50-74%, good=75-99%, and complete adherence=100%.

Secondary outcome results

Of the 5 patients that completed the exercise sessions, all of whom had comparative CPEX data, the differences in mean VO_{2peak} and AT before and after the intervention were +2.0ml/kg/ml and +1.5ml/kg/min, respectively (Table 2.4). Of the 6 patients in the control group, only 4 had comparative CPEX test data (2 standard care CPEX tests were not arranged), which showed a small mean change in VO_{2peak} (+0.3ml/kg/min) and a decrease in mean AT of -1.2ml/kg/min. The mean differences between arms were not statistically significant. Due to equipment issues, comparative P_{i-max} testing of inspiratory mouth pressure could not be done. Because 2 patients in the control arm did not attend a second CPEX test, physical activity and QOL data were also missing for these participants, which would have been measured, per protocol, at this time. Physical activity levels as measured by IPAQ increased in the prehabilitation arm, but remained the same in the control arm. Quality of life did not differ significantly between groups. The 30-day postoperative cardiopulmonary complication rates were also similar between arms (table 2.5). No deaths occurred at 30 days.

Table 2.4 Changes in mean variables before and after standard care or prehabilitation in the ExPO trial

ΔVariable mean	Standard care (n=4)	Prehabilitation (n=5)	p-value
VO_{2peak} ml/kg/min	+0.3 (SD 3.2)	+2.0 (SD 1.4)	0.61
AT ml/kg/min	-1.2 (SD 2.3)	+1.5 (SD 1.1)	0.26
MET-mins/week	-432 (SD 315)	+883 (SD 1893)	0.12
QOL (C30 summary score, max score = 100)	-3 (SD 2.9)	+ 2 (SD 1.5)	0.18
QOL (OG25 summary score, max score = 100)	13 (SD 7.4)	5 (SD 15.0)	0.46

Table 2.5 Complications after oesophagectomy in the ExPO trial

Outcomes	Standard care (n=6)	Prehabilitation (n=5)
30-day morbidity		
Cardiopulmonary complications	4 (67)	3 (60)
Non-cardiopulmonary complications	4 (67)	3 (60)
30-day mortality	0	0

Data shown are the number of patients and percentage.

2.4.5 Discussion

This work represents the first feasibility trial of prehabilitation prior to oesophagectomy. The findings demonstrate proof of concept for a future trial in that: all patients referred for neoadjuvant chemotherapy and oesophagectomy were eligible for exercise, could be recruited in reasonable numbers and engaged in the aerobic and muscle strengthening exercises offered; which were safe and well tolerated, with no significant adverse effects or decrease in their quality of life. However, whilst there was an improvement in fitness in the intervention arm, this study was unable to demonstrate a statistical difference, as measured objectively by CPEX testing, over standard care. More participants would be needed to see if there was a difference. This study measured complication data to assess the safety of prehabilitation rather than its efficacy and no serious adverse reactions were reported. Much larger patient numbers would be required in a definitive RCT to investigate the effect of prehabilitation on postoperative complications.

Strengths of this study included the design of a unique personalised exercise regime with input from physiotherapists, clinicians, patients and patient groups, which was well tolerated by patients. A weakness of the study was the small sample size, which was due to both a much lower than anticipated number of oesophagectomies at the NNUH over the recruitment period and logistical problems with arranging baseline CPEX testing for potential participants who wanted to join the trial. As such, I demonstrated proof of concept for a future trial with this feasibility information. This was also a single-centre study, and patients from Norwich may not be representative of those in other areas of the UK, including those from more urban areas, limiting the generalisability. However, I was able to demonstrate that patients that declined to participate were similar in demographics to recruited patients.

Additional measures to improve recruitment in future work could include the capacity to offer supervised exercise sessions closer to patient's homes as a long travel distance was the commonest reason for non-participation. As 18% of participants in this study did not receive a second comparative CPEX test (as part of their usual clinical care) and I was unable to arrange a baseline CPEX for two potential participants (due to unavailability of the CPEX laboratory), it is questionable whether CPEX testing would be feasible in a larger future trial to demonstrate the efficacy of an exercise programme. Other tests of fitness such as a 6-minute walk test, which does not require any specialist equipment, may be more a more feasible measure of fitness improvement in future work.

In summary, the ExPO trial demonstrates that prehabilitation prior to oesophagectomy in patients with oesophageal adenocarcinoma undergoing chemotherapy is safe, acceptable and well adhered to, but was not able to demonstrate a statistically significant improvement in fitness due to small patient numbers (the referral rate for oesophagectomy was less than expected). Therefore, this work informs the design and planning of a larger feasibility study in this patient population to investigate whether the fitness of oesophagectomy patients can be improved in the short time between neoadjuvant chemotherapy and surgery by an intervention. Such feasibility data is required prior to a full RCT investigating whether prehabilitation can reduce the incidence of postoperative complications.

2.4.6 An introduction to the next chapter

During the ExPO trial it became clear to me that not all patients would require a supervised exercise intervention as some were already engaging in very high levels of physical activity (above that offered by the ExPO trial). One of the patients who declined to join the study was a keen amateur triathlon competitor, another participant in the control arm had a VO_{2peak} of 35.4ml/kg/min - the highest CPEX value recorded for any oesophagectomy patient at the NNUH since CPEX testing was introduced 6 years previously. Due to this observation, I commenced an observational study while recruiting into the ExPO trial, which analysed all oesophagectomy postoperative outcomes at the NNUH where preoperative CPEX testing was used. The aim was to determine a threshold value for either VO_{2peak} or AT at which patients were at an increased risk of postoperative complications. Such a cut-off could then be used to identify a sub-population of relatively 'unfit' oesophagectomy patients that may benefit from exercise prehabilitation. These 'unfit' patients could then be randomised in a future trial, whereas those that were objectively deemed 'fit' would not be offered prehabilitation as they would be unlikely to benefit. The results of this observational work, which was the largest of its kind, were surprising in that they were contrary to previously published studies in oesophagectomy patients¹³⁴⁻¹³⁶. All studies reported that a lower fitness predicted poor outcomes, and thus justified the conduct of the ExPO trial. This new observational work reported that, in this specific patient population, there was no association between preoperative fitness, as measured by CPEX testing, and postoperative complications of any type or severity. Therefore, the evidence base for fitness as an interventional target to reduce complications was now inconsistent. As such, after discussion with the chief investigator, recruitment into the ExPO trial was paused. This decision was then reviewed by the trial management group and trial steering committee. The final decision was to end recruitment 6 weeks earlier than originally intended. The basis of this decision was that previous retrospective work had methodological flaws, which were addressed in this new work. Therefore, further well conducted observational studies were now needed to justify a future interventional trial. A review of the available observational evidence and the new observational study is presented in the next chapter.

Chapter Three: Preoperative aerobic fitness and short-term complications after oesophagectomy – a review of the literature and an observational study.

Overview

In this chapter, the association between cardiopulmonary fitness, as measured objectively using cardiopulmonary exercise (CPEX) testing, and short term morbidity after oesophagectomy are examined in an observational study. A purpose of this work was to help stratify patients who may benefit from a future preoperative exercise programme.

Firstly, the laboratory method of CPEX testing and details about its derived variables is described.

Secondly, the current literature is reviewed to examine whether there is an association between fitness, as measured using CPEX, and short term outcomes after major cancer resection surgery, including oesophagectomy.

Thirdly, the results of an original retrospective observational study examining the associations between CPEX variables and postoperative outcome in patients who underwent an oesophagectomy at the Norfolk and Norwich University Hospital between September 2011 and February 2017 is presented. In the discussion, the impact of this research and whether future trials in exercise interventions should be progressed is considered.

3.1 Cardiopulmonary exercise testing (CPEX) an objective measure of fitness

3.1.1 CPEX overview

Cardiopulmonary exercise testing is a clinical exercise “stress test”, which assesses exercise limitation. CPEX provides an objective and quantitative assessment of the integrated responses of the cardiopulmonary and skeletal muscle systems to increasing exercise intensities¹⁵⁹, and is considered the gold standard measurement of aerobic fitness.¹⁶⁰ As a reasonably inexpensive and non-invasive investigation, it is increasingly being used for a wide range of clinical applications including: to investigate breathlessness, to detect cardiac ischaemia, to monitor patients with cardiac disease including heart failure, and provide an assessment of functional cardiopulmonary reserve in patients prior to undergoing major surgery.¹⁶¹

3.1.2 CPEX exercise protocol

There are many different protocols used for exercise testing, but most are similar. The test protocol used at the Norfolk and Norwich Hospital is described here. Prior to the test, the patient is connected to an electrocardiogram (ECG) monitor as well as a pulse oximeter and sphygmomanometer (figure 3.1). A facemask is then fitted tightly to ensure there is no air leak and the patient is seated on a static exercise bike with the seat and handlebar height adjusted for both comfort and optimal cycling performance (a treadmill can be used, but an exercise bike has the advantages of allowing accurate quantification of work rate and is more inclusive of patients with limited mobility). A predicted number of watts of power that the patient should be able to achieve is calculated by the CPEX testing software using the patient variables: age, height and weight. A 10 minute exercise protocol is then selected, which incrementally increases pedal resistance over 10 mins to achieve their predicted watts. The patient is instructed to pedal at 60 revolutions per minute and to exercise to their limit. The test contains 4 different phases. The first is a *Rest Phase*, typically lasting 3 mins, where the patient sits still on the bike. This allows the

patient's heart rate and respiratory rate to 'settle', particularly if they are feeling anxious by their surroundings and equipment. The second phase is *Unloaded Cycling* lasting 3 mins, which allows assessment of oxygen consumption without a load applied to the pedals, and the effect of hyperventilation usually resolves during this phase. The *Ramp Phase*, describes the incremental loading or breaking of the bike as though the patient were cycling up a hill, which is gaining in steepness. The test is stopped by the clinician if the patient develops ischaemic ST segment changes on the ECG, or by the patient if they have symptoms such as: pre-syncope, severe breathlessness or leg pain, which prevents further exercise. The final fourth phase is a further *Rest Phase* lasting 3-5mins, with monitoring of heart rate and ECG.

Figure 3.1. A cardiopulmonary exercise test being performed on a static exercise bike (cycle ergometer) at the CPEX laboratory at Norfolk and Norwich University Hospital.



1=ECG monitor, 2=Gas exchange monitor, 3=saturation probe, 4=face mask. Image from Parasuraman et al. Healthcare professional's guide to cardiopulmonary exercise testing. Br J Cardiol 2015(2015;22:156).¹⁶¹

3.1.3 CPEX variables

VO₂

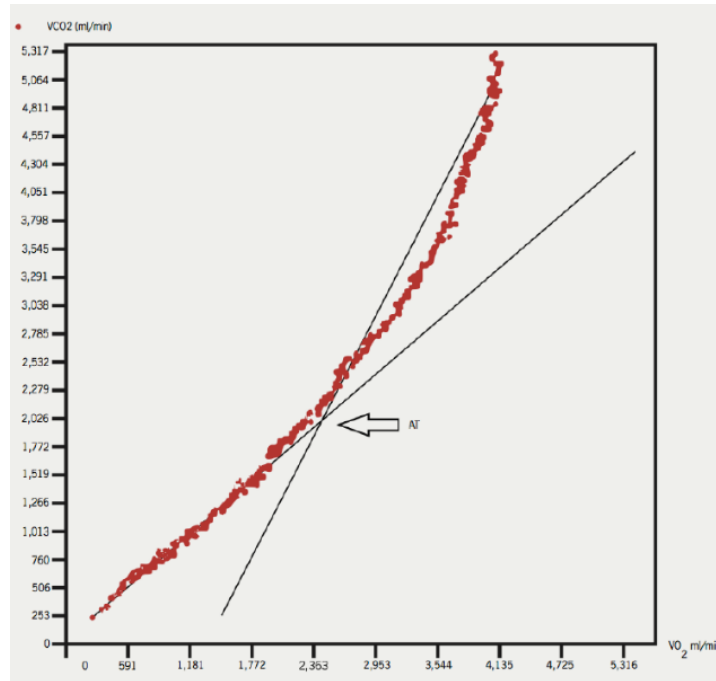
The data obtained during a CPEX test includes heart rate, respiratory rate, the volume of oxygen inhaled per minute (VO₂) and the volume of carbon dioxide exhaled per minute (VCO₂). Arguably, the most informative value is the volume of oxygen inhaled (VO₂), which is expressed in millilitres per minute (ml/min) and then divided by the patient's bodyweight in kilograms, to give the unit: VO₂ml/kg/min. VO₂ provides information on the oxygen transport system, which involves the heart, lungs and muscle tissues, where O₂ is transferred from the environment to muscle mitochondria. This volume at maximal exercise intensity is called VO_{2max} and is the gold standard measure of a patient's aerobic fitness.¹⁶⁰ In reality, most elderly patients are unable to achieve their true VO_{2max} as they may be limited by co-morbidities (such as knee arthritis). Therefore, VO_{2peak} is used instead, which refers to the volume of oxygen consumed when the patient exercises to their peak, which may not necessarily reflect their potential VO_{2max}. Despite the differences between VO_{2max} and VO_{2peak}, both variables are often used interchangeably, which may not necessarily be correct.

Anaerobic threshold

The VO₂ at anaerobic threshold (AT) is another important variable. Broadly this represents the onset of lactate-related anaerobic metabolism, where the glycolytic pathway supplements the oxidative pathway in ATP production. In reality, there is likely to be a degree of anaerobic metabolism at all work rates.¹⁶² However, AT can be thought of as the estimated point at which there is a rapid increase in the concentration of blood lactate. This point can be measured non-invasively using VCO₂; as an increase in lactate is accompanied by an almost equal reduction of bicarbonate concentration, with a resultant increase in CO₂ output (independent of O₂ uptake).¹⁶² The VO₂ at AT can be estimated using the V-slope method, which describes the point at which VCO₂ relative to VO₂ increases (in the absence of hyperventilation).¹⁵⁹ This is a distinct point because at exercise intensity below AT, both VO₂ and VCO₂ increase linearly.¹⁶² As opposed to VO₂, which is volitional (an unmotivated patient may not wish to exercise to their peak, a patient with knee pain may be prohibited from doing so), AT is not. Therefore, AT may be a more reliable measure of aerobic fitness, particularly in patients with co-morbidities.¹⁶³

However, because AT is often estimated using the V-slope method there is an element of inter and intra-observer variability in its visual detection.¹⁵⁹ This is not the case for VO₂.

Figure 3.2 A graph demonstrating the V-slope method for detecting anaerobic threshold in CPEX testing.



The arrow indicates the approximate point of anaerobic threshold. Image from Parasuraman, *et al.* Healthcare professional's guide to cardiopulmonary exercise testing. Br J Cardiol 2015(2015;22:156).¹⁶¹

Figure 3.3 The CPEX reference values for VO_{2peak} and AT for healthy volunteers according to recreational exercise behaviour (active or sedentary) and age group (55-64 and 65-74).

		Age range: 55-64 years	Age range: 65-74 years
Active men	VO _{2peak}	35.3 ± 6.2 ml/kg/min	30.0 ± 6.1 ml/kg/min
	AT	23.3 ± 5.2 ml/kg/min	19.9 ± 4.8 ml/kg/min
Active women	VO _{2peak}	28.6 ± 6.1 ml/kg/min	25.1 ± 4.4 ml/kg/min
	AT	18.9 ± 4.4 ml/kg/min	17.4 ± 3.1 ml/kg/min
Sedentary men	VO _{2peak}	30.0 ± 6.3 ml/kg/min	23.1 ± 6.3 ml/kg/min
	AT	19.1 ± 4.0 ml/kg/min	15.9 ± 6.3 ml/kg/min
Sedentary women	VO _{2peak}	23.9 ± 4.2 ml/kg/min	21.2 ± 3.4 ml/kg/min
	AT	16.1 ± 2.8 ml/kg/min	14.9 ± 2.9 ml/kg/min

Adapted from Herdy *et al.* Reference values for cardiopulmonary exercise testing for sedentary and active men and women. Arq Bras Cardiol 2011;**96**(1):54-9.¹⁶⁴

VE/VCO₂

A final important variable is VE/VCO₂ at AT. This is a ratio of the volume of air exhaled per minute (VE) to VCO₂. Patients with lung disease, such as chronic obstructive pulmonary disease (COPD) may require a greater volume of ventilation to eliminate CO₂. Therefore, patients with a high VE/VCO₂ at AT have an inefficiency of CO₂ excretion, or a ventilatory inefficiency.¹⁶⁵

3.2 The association between preoperative CPEX variables and outcome after major cancer resection surgery: a review of the literature

3.2.1 Abstract

Background: Postoperative complications after major surgery are thought to be associated with reduced fitness. Surgical cancer patients are often malnourished, cachexic and receive neoadjuvant chemotherapy resulting in low preoperative fitness levels. This literature review examined the associations between aerobic fitness, as determined objectively by preoperative cardiopulmonary exercise testing (CPEX), and short-term morbidity after cancer surgery.

Methods: A literature search was undertaken using PubMed, Medline, Embase, CINAHL and the Cochrane Library for studies that examined associations between preoperative CPEX variables and postoperative complications following surgery for the ten commonest cancers.

Results: A total of 21 observational studies were identified with 4 957 patients that underwent CPEX testing prior to: lung, colorectal, liver, oesophagogastric, bladder and pancreas resections. The median sample size was 105 patients (range 64 – 1 684). No studies were found for breast or brain cancers or lymphomas. In lung cancer patients undergoing thoracotomy, a $VO_{2peak} \leq 15 \text{ ml/kg/min}$ was associated with an increased risk of respiratory complications and death. None of the studies in other cancer types had adequate sample sizes to report on mortality. CPEX testing had poor to average discriminatory accuracy to predict postoperative morbidity in other cancer resection surgeries. Findings across the studies were inconsistent, and detection and selective reporting biases were likely to be significant.

Conclusions: The utility of CPEX testing prior to cancer surgery is questionable and currently should not be used as a single discriminatory tool, except perhaps in patients undergoing lung cancer resection by thoracotomy. Larger studies with more robust methodologies are currently required to determine the utility of CPEX.

3.2.2 Introduction

The surgical stress response following major surgery results in muscle wasting and systemic inflammation, with a large increase in tissue oxygen demand and consumption;¹⁰⁹ increasing the risk of ischaemic events.¹⁰⁵ Furthermore, postoperative bed-rest and incisional pain inhibits normal lung mechanics, promoting shallow breathing, atelectasis and infective lung consolidation.¹¹¹ These physiological challenges are in part met by a patient's cardiopulmonary reserves, or their ability to increase cardiac output and ventilation to meet increased demand. Such reserves are greater in physiologically 'fitter' patients. Cancer patients represent a specific population, more likely to have underlying malnutrition and cachexia than non-cancer patients, with depleted fitness levels.^{149 166} Neoadjuvant chemotherapy has also been shown to independently reduce aerobic fitness.⁵ By measuring a patient's preoperative cardiopulmonary reserve, or functional capacity, we may hypothetically be able to discriminate patients that may or may not tolerate the physiological insult associated with surgery. Therefore, measurement of preoperative fitness may serve as a preoperative risk prediction tool for the development of complications prior to major cancer resection.

CPEX testing represents the gold standard test of aerobic fitness. VO_{2peak} (the maximal oxygen consumed at the peak of exercise) and VO_2 at estimated anaerobic threshold (AT), (a measure of sustainable aerobic activity) are two CPEX variables which have shown promise in observational studies to predict both morbidity and mortality after major elective surgery.¹⁶⁷ In a seminal study from 1993, of 187 elderly patients undergoing major abdominal surgery, a preoperative AT cut-off of 11ml/kg/min had a sensitivity of 91% and specificity of 74% for predicting postoperative mortality after major abdominal surgery.¹³¹ Since then, multiple, often small, observational studies have been published in various cancer surgery specialities. However, the results from these are inconsistent, possibly explained by biases inherent in the methodology such as performance and detection biases (due to unblinded clinical teams and outcome assessors, respectively) as well as selective reporting bias, which is likely to be substantial.¹⁶⁸ Although 3 reviews of CPEX testing and major surgeries have been published,^{167 169 170} all included non-cancer patients and excluded common cancers such as lung and bladder. Furthermore, important sources of bias do not appear to have been adequately considered previously. The aim of this review was to assess the association between CPEX testing and short-term postoperative

morbidity and mortality after common major cancer resection surgery; with due and full consideration of potential biases both in terms of their magnitude and direction. If a convincing inverse association exists, it may not only support the preoperative use of CPEX to determine operability and postoperative monitoring and management, but also identify fitness as a modifiable risk factor for investigation in randomised controlled trials of surgical cancer patients.

3.2.3 Methods

The preferred reporting items for systematic reviews (PRISMA) guidelines were used to standardise the methods of conducting and reporting this review.¹⁷¹ The ten commonest causes of cancer deaths in the UK in 2014⁵⁰ were identified (lung, bowel, breast, prostate, pancreas, oesophagus, bladder, brain, liver and lymphoma) and a literature search was conducted using PubMed, Medline, Embase, CINAHL and the Cochrane library (from commencement to 5th July 2017) for studies that examined associations between preoperative CPEX and postoperative complications following cancer resection surgery. The search terms used were: CPEX, CPET, exercise testing, anaerobic threshold, VCO_2 , ventilatory inefficiency, oxygen consumption, VO_2 , preoperative exercise, aerobic exercise. For each cancer, additional specific search terms were added (appendix 2).

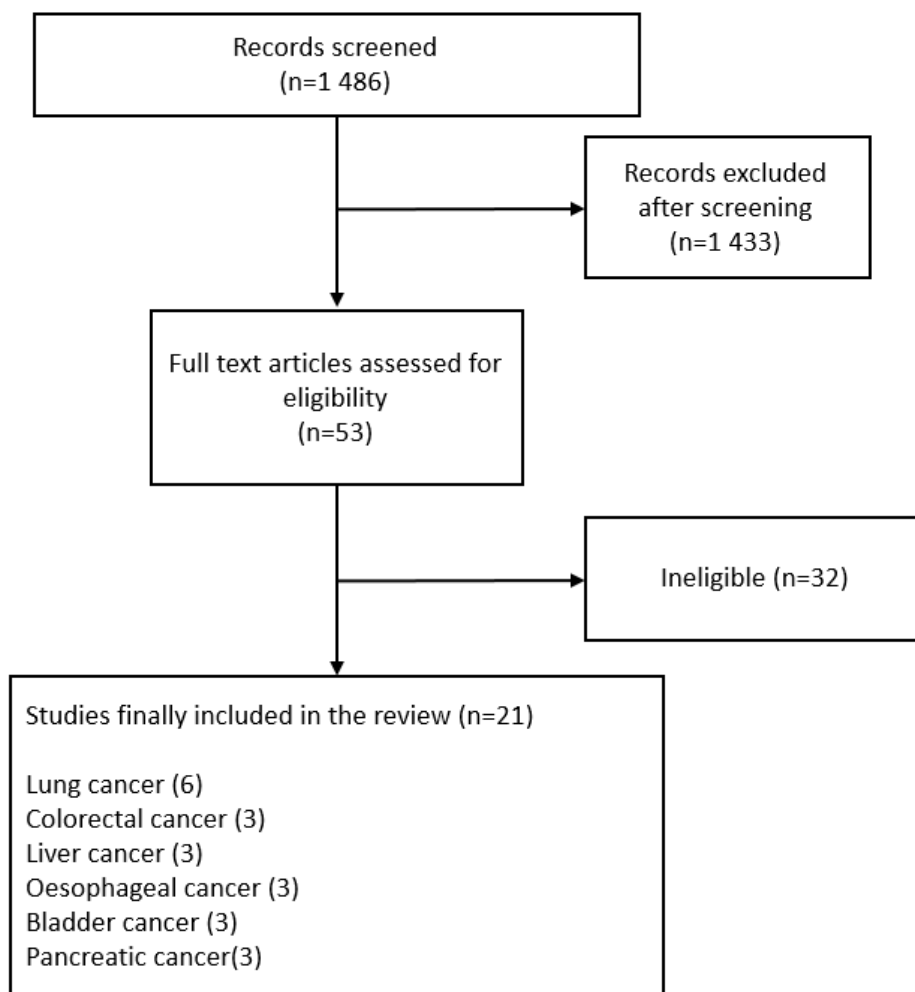
Inclusion/exclusion criteria

Analytical studies (cohort, case-control, randomised controlled trials) that investigated the association between preoperative CPEX variables and short-term (up to 90 days) morbidity and mortality were included. Due to the large number of initial studies identified across all surgical specialities, studies were excluded with sample sizes <100 patients, unless there were <2 studies in that surgical population in which case the total sample size needed to be at least 60 patients, which was considered the minimum size to determine associations with a moderate event rate.¹⁷² In order to select studies which examined only cancer populations, studies with a large proportion ($\geq 25\%$) of non-cancer patients were also excluded (unless cancer patients were analysed separately) as were investigations that combined multiple surgical patient populations (e.g. colorectal, urological and upper gastrointestinal cancer patients), unless these groups were sub-analysed.

3.2.4 Results

A total of 21 hospital-based cohort studies (12 prospective, 9 retrospective) were included in this review consisting of 4 957 patients that underwent CPEX testing prior to: lung, ¹³⁸ ¹³⁹ ¹⁷³⁻¹⁷⁶ colorectal, ¹⁷⁷⁻¹⁷⁹ liver, ¹⁸⁰⁻¹⁸² oesophagogastric, ¹³⁴⁻¹³⁶ bladder ¹⁸³⁻¹⁸⁵ and pancreas resections ¹⁸⁶⁻¹⁸⁸ (figure 3.4). No studies were found in breast, brain or lymphoma cancers. No randomised controlled trials of any cancer site were identified. Data was extracted from each study (including study design, sample size, outcome measurement and effect sizes) and tabulated (table 3.1).

Figure 3.4 PRISMA diagram



Lung cancer

Four hundred and three studies were identified, with 63 potentially relevant papers by title. A review of these abstracts identified 23 potentially relevant papers. Six studies¹³⁸⁻¹³⁹ met the inclusion criteria and were included in this review. All were observational cohort studies (2 prospective, 4 retrospective), with a total of 2 814 patients from hospitals within Europe and the USA. The largest study was a retrospective analysis of 1 684 patients who had lung cancer surgery identified from the European Society of Thoracic Surgeons (ESTS) database,¹³⁹ which is voluntarily contributed to by clinicians from 235 sites across Europe. The authors reported no association between VO_{2peak} and all cause morbidity (for either video assisted thoracoscopic surgery (VATS) or thoracotomy resections), but a significant association with mortality in patients undergoing thoracotomy resection with a $VO_{peak} < 15 \text{ ml/kg/min}$ (χ^2 test, $p=0.008$). Whilst this study had several strengths including, a large sample size and use of propensity matching to reduce selection bias, it had significant limitations, which were acknowledged by the authors. The largest of these was the potential for measurement error for complications through the use of a voluntary multi-institutional database, where the accuracy of the data entry has not been validated.¹³⁹ Inaccurate recording of outcome would lead to an attenuation of any associations between CPEX variables and outcome.

The second largest study was a multi-centre (9 centres) prospective observational investigation of 346 patients from the USA who underwent thoracotomy and lung cancer resection surgery.¹³⁸ In contrast to the results of the previous study, the authors reported that VO_{2peak} was significantly lower in the group with complications (15.2ml/kg/min) compared to those without (16.7ml/kg/min) although the mean difference was small: -1.47ml/kg/min (95% CI 0.55-2.4), $p=0.002$. The authors also undertook a further sub-analysis in patients with the outcomes of respiratory failure ($n=33$) and death ($n=15$). Both events were associated with a lower mean VO_{2peak} (14.7ml/kg/min), $p=0.041$ compared to those without complications (mean difference 2ml/kg/min), although the small number of events is noted. Whilst the large sample size, prospective design and multi-centre participation increases power, reduces bias and enables generalisability, respectively, there were limitations. A pre-defined criteria for what constituted each complication was not established, nor were the postoperative outcomes measured in a blinded fashion, both of which could contribute to detection bias resulting in spurious over-estimation of the associations found. Furthermore, the authors defined

postoperative morbidity as a composite outcome, which included complications lacking a clear plausible mechanistic relationship with aerobic fitness; such as red blood cell transfusions (n=38). Such an event is more likely to be associated with intra-operative blood loss (perhaps due to longer operating times in patients with underlying lung disease), suggesting that residual confounding may explain some of the associations found.

The other 4 studies in lung cancer patients were all hospital-based cohort studies, which reported inconsistent findings.¹⁷³⁻¹⁷⁶ Two of the investigations were conducted by the same research group,^{174 176} which reported an inverse association between VO_{2peak} and respiratory complications ($p=0.015$) in one of their studies,¹⁷⁴ but were unable to subsequently replicate this finding ($p=0.50$) in the other¹⁷⁶ - despite similar methodologies and patient populations. Detection bias due to non-blinded assessment of outcomes may have contributed to the variability in the findings. The two other studies reported an inverse association between higher VO_{2peak} and cardiopulmonary complications, OR 0.05 (95% CI 0.01-0.58), $p=0.02$ ¹⁷⁵ and OR 0.79, 95% CI 0.71-0.88, $p<0.0001$.¹⁷³ However, the large variation in the effect size estimates and wide confidence intervals reflects the imprecision of their findings. Again, outcome assessment was not blinded, which may have spuriously inflated the reported effect sizes if the CPEX scores were known to the assessor.

Summary of findings: Observational studies have reported that VO_{2peak} is associated with complications after lung cancer resection surgery. More specifically, the two largest studies reported that a $VO_{2peak} < 15 \text{ ml/kg/min}$ was associated with an increased risk of respiratory failure¹³ and death following lung cancer resection by thoracotomy.^{138 139} This association is plausible given the nature of the surgery. However, only one study in lung cancer surgery examined outcomes after VATS and found no association between VO_{2peak} and morbidity or mortality.¹³⁹ As VATS is increasingly becoming used for lung cancer resection, the utility of CPEX testing needs to be updated to determine if it is of value in less invasive surgeries for lung cancer resection.

Colorectal cancer

The literature search identified 431 studies, of which 30 were considered relevant based on their title. These were reduced to 13 after reading the abstracts, of which 3 met the

inclusion and exclusion criteria and were included in this review.¹⁷⁷⁻¹⁷⁹ The main reason for excluding other investigations was their inclusion of >25% of non-cancer patients. All 3 were observational studies from the same UK group. The largest was a retrospective multi-centre (6 sites) UK investigation¹⁷⁹ of 703 patients, most of which had malignant disease (87%). In contrast to the studies in lung cancer surgery, all cause morbidity was measured using a validated PostOperative Morbidity Survey (POMS)¹⁸⁹ at postoperative day 5.¹⁵⁸ The severity of complications were graded using the system devised by Clavien and Dindo.¹⁵⁸ This grading system is based upon the level of intervention required to treat a complication; from normal postoperative adjuncts such as supplementary oxygen, analgesia and anti-emetics (grade 1), to additional medicines above usual standard care, including antibiotics (grade 2). Grade 3 is a complication requiring operative intervention and grade 4 complications require organ support in critical care. The authors reported a significant difference in both median VO_{2peak} and AT in patients with and without all cause morbidity of any Clavien-Dindo grade ($p=0.031$ and $p=0.002$, respectively). Receiver Operator Characteristic (ROC) Curve analyses were also undertaken to show how sensitivity and specificity varied with changing thresholds, which was expressed as an area under the ROC curve (AUC). The AUC takes into consideration the accuracy of a diagnostic test (in terms of sensitivity and specificity) across a range of threshold values.¹⁹⁰ In the context of CPEX testing, where the association may be inverse, the AUC is equal to the probability that if a pair of patients (one with a complication and one without) are selected at random, the patient with a complication will have a lower CPEX value than the complication-free patient.¹⁹⁰ An AUC of 1.0 indicates a perfect test, and 0.5 a completely uninformative one, i.e., a result occurring by chance. An AUC of <0.7 would be indicative of a poor predictive test, 0.7-0.8 average accuracy and >0.8 good accuracy as a diagnostic test across a range of thresholds.¹⁹⁰ In this study, AT had average discrimination (i.e. 0.70-0.80) with an AUC of 0.79, 95% CI 0.76-0.83 with an optimal cut-point at 11.1ml/kg/min (78% sensitivity and 71% specificity). The AUC for VO_{2peak} was 0.77, 95% CI 0.71-0.82 with an optimal cut-point of 18.2ml/kg/min (70% sensitivity and 72% specificity). However, similar to the previous studies in lung cancer, the outcome assessors were not blinded to CPEX data, so detection bias could explain the associations found. Indeed, there were significant variations ($p<0.001$) in AUC values across recruited hospital sites (supplementary material), where the largest recruiting centre (239 patients) had more modest values for VO_{2peak} (AUC 0.73) and AT (AUC 0.68) compared to the above pooled values. Complications without a clear plausible biological relationship with aerobic fitness

were associated with CPEX values including; postoperative pain and gastrointestinal symptoms (such as ileus). Therefore, residual confounding may explain some inverse associations found. The same group previously published a prospective blinded observational study in 136 patients undergoing colonic surgery, most of whom (89%) had malignant disease.¹⁷⁸ With detection bias removed, the predictive performance of CPEX for day 5 morbidity was poor (AUC < 0.70). For AT the AUC was 0.63, 95% CI 0.54-0.73, with a lower optimal cut-point at 10.1ml/kg/min (68% sensitivity and 58% specificity). The AUC for VO_{2peak} was 0.63, 95% CI 0.53-0.73 with an optimal cut-point of 16.7ml/kg/min (55% sensitivity and 69% specificity). Furthermore, 14% of their sample who underwent CPEX testing and surgery were excluded as they “lacked complete data”. It is unclear whether these data were missing at random, and may therefore represent a source of selection bias.

The final study by the same group investigated 95 rectal cancer patients undergoing resection surgery, 68 of whom received neoadjuvant treatment.¹⁷⁷ Morbidity and mortality were measured blinded, using the same methods reported in their other work.^{178 179} Both VO_{2peak} and AT were associated with total morbidity at day postoperative day 5. For AT, the AUC showed good accuracy at 0.87 (95% CI 0.79-0.95) with an optimal cut-point of 10.6ml/kg/min (84% sensitivity and 92% specificity). VO_{2peak} had an AUC of 0.85 (95% CI 0.77-0.93) and cut-point of 18.6ml/kg/min (82% sensitivity and 80% specificity). However, the small sample size increased the risk of a chance finding.

Summary of findings: Overall the association between preoperative CPEX and postoperative outcome following colorectal cancer surgery is derived from observational studies from the same research group. There were inverse associations between VO_{2peak} and AT and all cause morbidity at day 5 post surgery. However, detection bias and residual confounding could not be excluded. Furthermore, 5 day POMS morbidity measured complications of a low severity (Clavien-Dindo ≤2) in the majority of patients, which makes the clinical usefulness of these findings questionable. POMS has also not been validated as an index of overall morbidity.¹⁸⁹ The decision of whether or not to undergo surgery is unlikely to be meaningfully informed by this work. Larger multicentre studies are required to address whether improved fitness prior to colorectal surgery reduces the risk of major postoperative outcomes including death for which there are plausible biological mechanisms, with morbidity measured by assessors blinded to CPEX data.

Liver Cancer

One hundred and eight studies were identified using the search terms, of which 7 were considered relevant based on their title. These were reduced to 4 after reading the abstracts and 3 met the inclusion criteria and were included in this review.¹⁸⁰⁻¹⁸² All 3 were UK hospital-based cohort investigations (2 prospective and 1 retrospective) of patients that underwent both major and minor hepatectomies.¹⁸⁰⁻¹⁸² The largest, a retrospective study of 197 patients, found no associations between in-hospital morbidity and VO_{2peak} or AT.¹⁸¹ The study did not measure complications using a validated outcome measure or blind its assessors to CPEX values. However, the result of such bias may inflate, rather than reduce, the effect size reported. The second largest study, a UK prospective cohort of 104 patients, did report an association between both VO_{2peak} , AT and complications.¹⁸² This used a validated outcome measure (POMS) with assessors blinded to the CPEX scores. However, the authors chose to report complications at postoperative day 3, which is not a conventional time at which to report outcomes. This timeframe was not defended in the study, and in the absence of a pre-defined protocol, selective reporting bias cannot be ruled out, which may have produced a false positive result. Furthermore, the high complication rate (70%) likely reflects routine, less severe, postoperative interventions (analgesia, urinary catheter, oxygen supplementation), which are likely to be clinically insignificant and rare beyond day 3.¹⁸⁹ When the authors graded the severity of complications according to Clavien-Dindo they found no associations between CPEX variables and complications of grade 3 (needing surgical intervention) or above. The final study was a UK prospective cohort investigation of 92 patients, which reported no associations between VO_{2peak} or AT and 30 day morbidity (as measured by POMS).¹⁸⁰ The authors did document that VE/VCO_2 (a CPEX measure of ventilatory efficiency) was associated with complications, but its predictive value was poor; where a value of 34.5 provided a sensitivity of only 47% for complications.

Summary of findings: Currently, there is insufficient data demonstrating an association between CPEX and outcome following hepatic resection. A large well designed multicentre study, with 30-day complication data measured blinded to CPEX data, is needed to assess CPEX in liver surgeries.

Oesophageal Cancer

Four hundred and seventy eight studies were identified of which 11 were considered relevant based on their title, and reduced to 5 after reading the abstracts. Of these, 3 met the inclusion criteria and were included in this review.¹³⁴⁻¹³⁶ All 3 were retrospective hospital-based cohort studies with small sample sizes from single institutions. The largest was a Japanese analysis of 91 patients who underwent McKeown oesophagectomy for squamous cell carcinoma.¹³⁴ Only cardiopulmonary complications were measured and occurred in 19% of patients. The mean VO_{2peak} was lower in patients with, vs. those without cardiopulmonary complications (789ml/min/m² vs. 966ml/min/m², *t-test* $p < 0.001$). These values approximate to 20.9ml/kg/min vs. 25.6ml/kg/min [conversion using the average height and weight of a Japanese male].¹⁹¹ No association was found between AT and complications (*t-test*, $p = 0.12$). The second largest study was a UK investigation of 78 patients, predominantly with adenocarcinoma (74%), undergoing oesophagectomy (64% receiving neoadjuvant chemotherapy).¹³⁶ Cardiopulmonary outcomes occurred in 42% of patients ($n = 33$) and non-cardiopulmonary in 24% ($n = 19$). Similar to the Japanese study, a low mean VO_{2peak} was associated with cardiopulmonary complications although the mean difference was small (19.2ml/kg/min in those with complications vs. 21.4ml/kg/min in those without, *t-test* $p = 0.04$). AT was also not associated with complications (13.2ml/kg/min in those with complications vs. 14.4ml/kg/min in those without, *t-test* $p = 0.07$). ROC curve analysis estimated the predictive value of both VO_{2peak} and AT to be poor (i.e., < 70), AUC 0.63 (95% CI 0.50-0.76, $p = 0.02$) and 0.62 (95% CI 0.49-0.75, $p = 0.03$), respectively. The same group subsequently published a further study of 103 patients with both oesophageal and gastric cancers that underwent CPEX testing prior to oesophagectomy (62%) and gastrectomy.¹³⁵ The findings were the reverse of their previous work, in that, this time; a lower AT was associated with cardiopulmonary complications (9.9ml/kg/min in those with complications vs. 11.2ml/kg/min in those without, $p = 0.05$), while VO_{2peak} was not (16.6ml/kg/min in those with complications vs. 14.6ml/kg/min in those without, $p = 0.07$). ROC analysis again reported both AT and VO_{2peak} to be poorly predictive of complications (AUC 0.62 (95% CI 0.50-0.74, $p = 0.06$) and 0.60 (95% CI 0.48-0.72, $p = 0.08$, respectively). The most significant limitation of all three studies, apart from their small sample sizes and single institution design was the potential for detection bias for complications due to unblinded outcome assessments, particularly for complications which can be subjectively diagnosed (e.g. pneumonia). This bias could lead to an over-estimate of the association between CPEX

variables and outcomes. Such methodological error may explain why the same group were unable to replicate their previous findings.^{135 136}

Summary of findings: Associations between CPEX variables and outcome after oesophagectomy are from small retrospective observational studies that did not use a validated measure of postoperative outcomes, or capture complications with blinding to CPEX values. The absence of blinding could result in an inflation of the association between CPEX values and postoperative outcomes. Further large studies where complications are strictly defined and measured by assessors blinded to CPEX values are needed.

Bladder Cancer

Thirty five studies were identified, with 9 potentially relevant papers identified by their title. A review of these 9 abstracts identified 5 potentially relevant papers, but only 3 met the inclusion criteria. All were prospective hospital-based cohort studies, with a total of 256 patients from hospitals in the UK.¹⁸³⁻¹⁸⁵ The largest was of 105 patients who underwent preoperative CPEX testing prior to either robot assisted (n=38) or open (n=67) cystectomy.¹⁸⁴ Complications were measured at day 90 by blinded assessors and were associated with a significantly lower median AT (10.6 vs 11.8, *U*-test *p*=0.007) and VO_{2peak} (14.3 vs 15.4, *U*-test *p*=0.02) compared to patients without complications. Additionally $VE/VECO_2$ was higher in the complication group than in those without (33.3 vs 30.3, *U*-test *p*=0.007). Whilst these findings are convincing in that there is consistency of associations across 3 CPEX values, the small study sample from a single institution presents a significant limitation to a more generalised interpretation of their results. The second largest study was of 82 patients who underwent CPEX prior to intracorporeal robotic assisted radical cystectomy.¹⁸⁵ There were no associations between any CPEX variables and outcome. However, both the small sample size and low number of complications (n=14) results in a lack of statistical power to detect clinically meaningful associations with CPEX. The smallest prospective cohort study was of 69 patients who underwent radical cystectomy. Again, no CPEX values were predictive of complications when the patients were divided into two groups, composed of those with and without a complication. However, sub-analysis according to the presence of a Clavien-Dindo grade ≥ 3 complication (n=13 vs n=56) found an inverse association between AT and major complication risk, OR 0.74 (95% CI 0.57-0.97). Again, the results of this single institution

study with a small sample size are difficult to interpret, particularly when no *post-hoc* analyses according to different complication severities were undertaken, which increases the risk of a chance finding in a small sub-group.

Summary of findings: The evidence of an association between CPEX and post-cystectomy outcomes is from small single institution studies, which reported conflicting findings. Therefore, larger studies which limit sources of bias are required to clarify whether an association exists.

Pancreatic Cancer

Thirty one studies were identified, with 8 potentially relevant papers by title. A review of these 8 abstracts identified 3 potentially relevant papers and all 3 met the inclusion criteria.¹⁸⁶⁻¹⁸⁸ These were UK hospital based-cohort studies (2 retrospective, 1 prospective) with a total of 288 patients. None of the studies used blinded outcome assessments. The largest was a retrospective study of 124 patients who had CPEX testing prior to pancreaticoduodenectomy.¹⁸⁶ Complications occurred in 44% of patients and were defined using POMS¹⁸⁹ and the International Study Group definition of Pancreatic Fistula (ISGPF).¹⁹² There was no association between VO_{2peak} and complications, including pancreatic leak. AT was dichotomised using a cut-point of 10.1ml/kg/min (a value derived from their previous work),¹⁹³ and included in a multivariable logistic regression model, which estimated that $AT < 10.1 \text{ ml/kg/min}$ greatly increased the odds of a pancreatic leak, $OR = 5.79$ (95% CI 1.62-20.63). The imprecision of this estimate likely reflects both the dichotomisation of a continuous variable and the small pancreatic leak events in the total sample ($n = 29$). The second largest study was a retrospective analyses of 100 patients that underwent preoperative CPEX and major pancreatic surgery (98% pancreaticoduodenectomy).¹⁸⁷ Again, AT was dichotomised, rather than treated as a continuous variable. The chosen point of dichotomisation (10ml/kg/min) was not justified in the report and it was unclear if chosen *a priori*. The results showed a greater frequency of pancreatic leak (occurring in 25 patients), when AT was $< 10 \text{ ml/kg/min}$ (35.4% vs. 16%, $p = 0.028$). However, statistical significance was lost when leaks were graded according to the ISGPS classification ($p = 0.091$). Selective reporting bias cannot be excluded, particularly when a seemingly arbitrary threshold was used to dichotomise a continuous variable. Furthermore, dichotomisation during analysis, results in a loss of statistical power and increases the risk of a false positive result.¹⁹⁴ The final investigation was a

prospective cohort study of 64 patients who underwent pancreaticoduodenectomy, which included a per-protocol statistical analysis.¹⁸⁸ The authors reported no associations between AT or VO_{2peak} and all complications, OR 1.07 (95% CI 0.83-1.39) and OR 1.00 (95% CI 0.86-1.18), respectively.

Summary of findings: The studies in pancreatic cancer surgery have small patient numbers and potential sources of detection and selective reporting biases which makes interpretation of their findings difficult. Similar to other cancer resection surgeries, large well-designed studies are needed to clarify whether there is an association between fitness, as determined by CPEX testing, and outcome.

3.2.5 Discussion

Overall, the evidence for associations between preoperative CPEX values and postoperative outcome after cancer resection surgeries is mostly derived from small observational studies. Many were underpowered to report on the risk of mortality, which was usually a secondary outcome measure. However, in the largest study of its kind, a low VO_{2peak} was associated with increased mortality after lung cancer resection by thoracotomy.¹³⁹ However, minimal access lung cancer surgery (VATS) is now becoming increasingly common, with 40% of all lobectomies for lung cancer in 2016 performed via this approach (vs. 30% in 2014).¹⁹⁵ Therefore, the evidence base for CPEX needs to be updated to reflect changes in operative practice. For morbidity, preoperative CPEX testing has at best, poor^{135 136 178} to average¹⁷⁹ discriminatory accuracy to predict postoperative outcomes after cancer resection surgery, so has limited utility as an isolated preoperative screening tool. Furthermore, investigations often used composite outcomes and included low Clavien-Dindo graded complications,^{178 179 182} which reduces the clinical meaningfulness of associations found.¹⁹⁶ Much research in CPEX testing has been a continuation of the seminal work of Older *et al*, in a paper published in 1993; reporting that AT may predict postoperative cardiac related death after major surgery.¹³¹ However, subsequently there seems to have been incorrect interpretations of this original plausible hypothesis. Cardiac related death has a relationship with aerobic fitness; mortality events are a reflection of how patients respond once complications have occurred.¹⁶³ Patients that die as a result of such complications are likely to lack the necessary cardiopulmonary and musculoskeletal reserves, which are required when there are ongoing physiological

stresses and prolonged ITU bed-rest.¹⁶³ These outcomes are very different to those measured in some of the CPEX studies in this review, which include surgical wound infection on postoperative day 3¹⁸² or increased analgesia need due to postoperative pain¹⁷⁹ (as measured by POMS¹⁸⁹). Ideally, observational studies investigating cardiac death are now required, but pragmatically may be difficult due to the small number of such events. However, to justify preoperative use of CPEX in cancer surgery, it should be shown that CPEX can accurately identify patients at risk of significant postoperative complications which have a substantial impact on clinical care.

Early evidence from randomised controlled trials (RCTs) suggests that cardiopulmonary fitness may not be an interventional target to reduce complications after surgery. A double-blinded RCT sought to improve cardiac output in unfit patients using intraoperative stroke volume optimisation with intravenous fluids in 220 patients having either rectal resections (n=208) or cystectomy (n=12).¹⁹⁷ However, the authors reported no significant difference between the intervention and standard care groups in postoperative complication rates (p=0.72), or length of stay (p=0.091). Complication rates, including major events such as anastomotic leak and re-operation, were no more frequent in patients with an AT <11ml/kg/min than those above this threshold. The first RCT of a preoperative exercise intervention in lung cancer patients was recently published. This Swiss trial of 151 lung cancer patients, compared a high intensity exercise programme with standard care and found that whilst VO_{2peak} was significantly increased in the intervention group, this did not translate into a significant reduction in postoperative complications (X^2 p=0.08).¹⁴⁸ Although the authors noted that a larger sample size may have detected a smaller effect size. To date, there are no published exercise intervention RCTs in oesophageal surgery.

In conclusion, it is plausible that physiological changes in the cardiopulmonary and skeletal muscle systems through exercise training could reduce some postoperative complications and deaths following major cancer resection surgery. However, the evidence from observational studies suggests that the effect size, if present at all, is likely to be small. This unintuitive finding may be explained by the size of the physiological insult associated with major cancer resection surgery. Taking oesophagectomy as an example; resection and reconstruction of the upper gastrointestinal tract results in a complication profile reflective of the operative field rather than fitness, where the cardiopulmonary

system is directly affected. However, cardiorespiratory and musculoskeletal reserves may be critical in the ability of a patient to respond once a complication has occurred.¹⁶³ To assess the relationship between CPEX variables and mortality requires a large multi-centre observational study to acquire an adequate sample size. Until this evidence is available, CPEX testing in isolation is unlikely to meaningfully inform cancer surgery practice, and RCTs of fitness interventions to improve short term outcomes after cancer surgery are not currently justified.

Table 3.1 Characteristics of studies investigating the association between preoperative CPEX and postoperative complications following major cancer resection surgery

Author, year	Study design	Sample size (n=)	Postoperative complications measured (rate of occurrence)	Diagnostic criteria for complications?	Complication severity classified?	Blinded complication assessment?	Association between VO _{2peak} and measured complications (effect size)	Association between AT and measured complications (effect size)
Lung cancer								
Begum, 2015 ¹²	Retrospective case-matched multi-centre cohort study	1 684	In-hospital cardiopulmonary complications (30%)	✗	✗	✗	No association	Not measured
Brunelli, 2012 ¹⁷	Retrospective hospital-based cohort study	225	30-day cardiopulmonary complications (23%)	✓	✗	✗	No association	Not measured
Licker, 2011 ¹⁴	Retrospective hospital-based cohort study	210	In-hospital cardiopulmonary complications (22%)	✓	✗	✗	OR = 0.79, 95% CI 0.71-0.88, p=<0.0001	Not measured
Torchio, 2010 ¹⁶	Retrospective hospital-based cohort study	145	30-day cardiopulmonary complications (15%)	✓	✗	✗	OR 0.05, 95% CI 0.01-0.58, p=0.017	Not measured
Brunelli, 2009 ¹⁵	Prospective hospital-based cohort study	204	In-hospital cardiopulmonary complications (23%)	✓	✗	✗	No association	No association
Loewen, 2007 ¹³	Prospective hospital-based multi-centre cohort study	346	30-day cardiopulmonary complications (40%)	✗	✗	✗	Yes, but no RR/OR/HR reported	Not measured

Table 3.1 (continued)

Author, year	Study design	Sample size (n=)	Postoperative complications measured (rate of occurrence)	Diagnostic criteria for complications stated?	Complication severity classified?	Blinded complication assessment?	Association between VO _{2peak} and measured complications (effect size)	Association between AT and measured complications (effect size)
Colorectal cancer								
West, 2016 ²⁰	Retrospective multi-centre cohort study	703	All cause morbidity at postoperative day 5 (36.7%)	POMS	Clavien-Dindo	✘	≤18.2ml/kg/min, OR 2.15, 95% CI 1.01-4.59, p=0.05	≤11.1ml/kg/min, OR 7.56, 95% CI 4.44-12.86, p=<0.001)
West, 2014 ¹⁸	Retrospective hospital-based cohort study	95	All cause morbidity at postoperative day 5 (48%)	POMS	Clavien-Dindo	✓	≥18.8ml/kg/min, OR 0.07, 95% CI 0.03-0.19, p=<0.001	≥11.2ml/kg/min, OR 0.07, 95% CI 0.03-0.19, p=<0.001)
West, 2014 ¹⁹	Prospective hospital-based cohort study	136	All cause morbidity at postoperative day 5 (48%)	POMS	Clavien-Dindo	✓	No RR/OR/HR reported)	OR 0.77, 95% CI 0.66-0.89, p=0.0005)
Liver cancer								
Kasisvisvanathan, 2015 ²³	Prospective hospital-based cohort study	108	3-day all cause morbidity (70%)	POMS	Clavien-Dindo	✓	Uninterpretable from data provided	Uninterpretable from data provided
Dunne, 2014 ²²	Retrospective hospital-based cohort study	197	All cause in-hospital morbidity (44%)	✘	Clavien-Dindo	✘	No association	No association
Junejo, 2012 ²¹	Prospective hospital-based cohort study	92	All cause in-hospital morbidity (51%)	POMS	None	✘	No association	No association

POMS=Postoperative Morbidity Survey (a validated measure of postoperative complication outcomes). Clavien-Dindo is a standardised therapy orientated grading system for the severity of postoperative complications in surgical practice.

Table 3.1 (continued)

Author, year	Study design	Sample size (n=)	Postoperative complications measured (rate of occurrence)	Diagnostic criteria for complications stated?	Complication severity classified?	Blinded complication assessment?	Association between VO _{2peak} and measured complications (effect size)	Association between AT and measured complications (effect size)
Oesophageal cancer								
Moyes, 2013 ²⁵	Retrospective hospital-based cohort study	103	All cause in-hospital morbidity (55%)	CTCAE	✗	✗	No association	Yes, but no RR/OR/HR reported
Forshaw, 2008 ²⁴	Retrospective hospital-based cohort study	78	All cause in-hospital morbidity (not stated)	CTCAE	✗	✗	Yes, but no RR/OR/HR reported	No association
Nagamoto, 2001 ²⁶	Retrospective hospital-based cohort study	91	In-hospital cardiopulmonary complications (19%)	✗	✗	✗	Yes, but no RR/OR/HR reported	No association
Bladder cancer								
Lamb, 2016 ²⁹	Prospective hospital-based cohort study	82	30-day Clavien-Dindo grade ≥3 all cause morbidity (12.6%)	✗	Clavien-Dindo (grade ≥3 only)	✗	No association	No association
Tolchard, 2014 ²⁸	Prospective hospital-based cohort study	105	90-day all cause morbidity (31%)	✗	Clavien-Dindo	✓	Yes, but no RR/OR/HR reported	AT ≥11.0ml/kg/min, OR 0.72, 95% CI 0.58-0.91)
Prentis, 2013 ²⁷	Prospective hospital-based cohort study	69	In-hospital all cause morbidity (56%)	✗	Clavien-Dindo	✓	No association	No association

CTCAE=Common Terminology for Adverse Events (a descriptive terminology used in Adverse Event (AE) reporting, usually in clinical drug trials)

Table 3.1 (continued)

Author, year	Study design	Sample size (n=)	Postoperative complications measured (rate of occurrence)	Diagnostic criteria for complications stated?	Complication severity classified?	Blinded complication assessment?	Association between VO _{2peak} and measured complications (effect size)	Association between AT and measured complications (effect size)
Pancreatic cancer								
Chandraban, 2013 ³¹	Retrospective hospital-based cohort study	100	Not stated	ISGPF	Clavien-Dindo	✘	Not stated	No association
Junejo, 2013 ³²	Prospective hospital-based cohort study	64	In-hospital all cause morbidity (64%)	ISGPF	Fistula by ISGPF	✘	No association	No association
Ausania, 2012 ³⁰	Retrospective hospital-based cohort study	124	In-hospital all cause morbidity (44%)	ISGPF & POMS	Fistula by ISGPF	✘	No association	AT ≤10.1ml/kg/min, OR 5.79, 95% CI 1.62-20.63)

ISGPF=International study group on Pancreatic Fistula (a definition derived by an international panel of pancreatic surgeons)

3.3 The association between preoperative cardiopulmonary exercise test variables and short-term morbidity following oesophagectomy: a hospital-based cohort study.

3.3.1 Abstract

Background: Postoperative complications after oesophagectomy are thought to be associated with reduced fitness. This observational study explored the associations between aerobic fitness, as determined objectively by preoperative cardiopulmonary exercise testing (CPEX), and 30-day morbidity after oesophagectomy.

Methods: Two hundred and fifty four consecutive patients that underwent oesophagectomy at a single academic teaching hospital between September 2011 and March 2017 were retrospectively identified. Postoperative complication data were measured using the Esophageal Complications Consensus Group definitions and graded using the Clavien-Dindo classification system of severity (blinded to CPEX values). Associations between preoperative CPEX variables and postoperative outcomes were estimated using logistic regression.

Results: Two hundred and six patients (77% male) were included in the analyses, with a mean age of 67 years (SD 9). The mean values for VO_{2peak} and AT were 21.1ml/kg/min (SD 4.5) and 12.4ml/kg/min (SD 2.8), respectively. The vast majority of patients (98.5%) had malignant disease; predominantly adenocarcinoma (84.5%), for which most received neoadjuvant chemotherapy (79%) and underwent minimally invasive Ivor Lewis oesophagectomy (53%). Complications at postoperative day 30 occurred in 111 patients (54%), the majority of which were cardiopulmonary (72%). No associations were found between preoperative CPEX variables and morbidity for either VO_{2peak} (OR 1.00, 95% CI 0.94-1.07) or AT (OR 0.98, 95% CI 0.89-1.09).

Conclusions: Preoperative CPEX variables were not associated with 30-day complications following oesophagectomy. This suggests that the effect of aerobic fitness on postoperative outcome, is at best likely to be small. The findings do not support the use of CPEX as an isolated preoperative screening tool to predict short-term morbidity after oesophagectomy. However, replication of these findings in other representative populations is now required before definitive conclusions can be drawn.

3.3.2 Background

Oesophageal resection and reconstruction (oesophagectomy) is the only consistent treatment modality that offers a potential cure for oesophageal cancer,¹⁹⁸ but carries a high risk of postoperative complications. UK national audit figures report that 33% of patients suffer a complication after oesophagectomy, most of which (74%) affect the cardiopulmonary system (52% respiratory and 22% cardiac).¹²⁵ Increased preoperative physical fitness may reduce the number of postoperative complications. Exercise results in a greater cardiac output, improved respiratory muscle strength and skeletal muscle adaptations (improved transport and metabolism of oxygen to produce adenosine triphosphate (ATP)).⁹⁸ These adaptations may attenuate the physiological insults of oesophagectomy which include; disruption of normal lung mechanics through incisional pain and diaphragmatic dysfunction;¹¹¹ blood loss and sympathetic activation, resulting in splanchnic vasoconstriction - which jeopardises any newly formed gastroesophageal anastomosis; and a surgical stress response, resulting in catabolism of skeletal muscle protein¹⁰⁶ and increased oxygen demand and consumption.¹⁰⁹ Accurate measurement of preoperative cardiopulmonary fitness may identify patients at higher risk of complications due to low cardiopulmonary reserves. This could allow better perioperative management to improve outcomes, including modification of fitness with an exercise programme.

CPEX is an objective, quantitative and composite measure of a person's overall aerobic fitness. There have only been 3 relatively small observational studies of CPEX testing prior to oesophagectomy (n=78,¹³⁶ n=91,¹³⁴ n=103¹³⁵) and its association with complications. Whilst two of these studies reported an inverse association between VO_{2peak} and cardiopulmonary complications^{134 136}, one did not.¹³⁵ Similar conflicting findings were found for AT, with only one study reporting a significant association.¹³⁵ Differences in the measurement of outcomes by non-blinded assessors is likely to have introduced significant methodological error, which may explain the variation in findings. As such, the utility of CPEX prior to oesophagectomy has not been determined. This study aimed to clarify the associations between CPEX variables, specifically VO_{2peak} and AT, and 30-day morbidity after oesophagectomy through the use of a larger sample size and measurement of outcomes using a standardised assessment tool, blinded to CPEX data.

3.3.3 Methods

Study setting and patient population

This hospital-based cohort study was conducted in the Department of Upper Gastrointestinal (UGI) Surgery at the Norfolk and Norwich University Hospitals (NNUH) Foundation Trust, Norwich, United Kingdom. The NNUH is a 1,000 bed teaching hospital, which provides care to a population of approximately 825,000 residents in Norfolk and adjacent counties. Approximately 45 oesophagectomies are performed at this unit each year. I retrospectively identified all patients that underwent an oesophagectomy at the NNUH between 1st September 2011 (the date of the first CPEX test prior to oesophagectomy) and 9th March 2017 (the latest date that would allow 30-day outcome assessment). Data was pseudo-anonymised and entered onto a database using Microsoft Access (2013). Patients were excluded if they had emergency or palliative surgery, a pharyngolaryngo-oesophagectomy, oesophagectomy and gastrectomy or did not undergo CPEX testing. The study protocol (appendix 5) was registered on ClinicalTrials.Gov (NCT03216694) and formal ethical approval was granted by the North West - Liverpool Central Research Ethics Committee after proportionate review (17/NW/0435, IRAS Project ID: 222793).

Cardiopulmonary exercise testing

CPEX testing was undertaken as per the protocol in section 2.4.3. The median time between CPEX testing and surgery was 11 days (interquartile range (IQR) = 7-19 days). At surgery, patients underwent either: McKeown, partially laparoscopic assisted (hybrid), or fully laparoscopic (minimally invasive) Ivor Lewis oesophagectomy. All patients were admitted to a high dependency unit (HDU) for the first night following surgery. Step down to ward care was decided by the HDU consultant.

Measurement of variables

The following patient data were obtained by review of medical notes: age, gender, smoking status (never, former, current), body mass index (BMI), comorbidities (classified according to the Charlson comorbidity index), TNM staging, chemotherapy regimen, type of surgery received and histology. To reduce the risk of selective reporting bias, CPEX variables of interest (VO_{2peak} and AT) were decided *a priori* under a registered protocol. CPEX data was obtained by an investigator who was not involved in the collection of

outcome data. Similarly, the outcome assessor was blinded to preoperative CPEX values and not involved in the collection of CPEX data. In order to reduce complication measurement error, short-term morbidity was measured by review of the medical notes, in strict accordance with Esophageal Complications Consensus Group (ECCG) definitions.¹⁵⁷ Each complication was then graded in accordance with the Clavien-Dindo classification.¹⁵⁸ The primary aim was to establish the association between the preoperative CPEX variables VO_{2peak} and AT and 30-day morbidity (all cause, cardiopulmonary and non-cardiopulmonary) as defined by ECCG of Clavien-Dindo grade 2 or above (complications of significant clinical importance). Secondary aims were to measure associations between CPEX variables and specific common complications and 30 and 90 day mortality.

Statistical methods

Continuous variables were reported as the mean and standard deviation or the median and IQR depending on their distributions. Categorical variables were presented as frequency (%) to assess differences between groups. P-values were obtained using Student-t tests, X^2 or Fisher's exact tests. For the comparative analyses in table 2, statistical significance was taken at $p=0.0008$ after Bonferroni correction for multiple statistical testing. A multivariable logistic regression model was constructed based on variables with both a plausible and univariable association with outcome, with CPEX values treated as a continuous variable. All statistical analyses were done using Stata (version 12.1).

3.3.4 Results

Between 1st September 2011 and 9th March 2017 (5 ½ years) 254 patients underwent an oesophagectomy at the NNUH. Of these patients, 48 (18.9%) were excluded: 40 did not undergo CPEX testing, 4 had emergency surgery and 4 had extended and palliative oesophagectomies. Therefore, 206 patients (77% male) were included in the analyses, with a mean age of 67 years (SD 9) at the time of surgery (table 3.2). In the whole cohort, the mean values for VO_{2peak} and AT were 21.1ml/kg/min (SD 4.5) and 12.4 ml/kg/min (SD 2.8), respectively. The vast majority of patients (98.5%) had malignant disease; predominantly adenocarcinoma (84.5%), for which most received neoadjuvant chemotherapy (79%) and underwent minimally invasive Ivor Lewis oesophagectomy (53%). Thirty day complications occurred in 111 patients (54%), the majority of which were cardiopulmonary (72%). The 40 patients that underwent oesophagectomy without preoperative CPEX were similar in their demographics and outcomes compared to those with CPEX data (supplementary table 3.1). The reasons for absence of CPEX testing was not documented in the notes, and were most were likely due to logistical issues associated with arranging these tests. The assumption was that these data were missing completely at random (MCAR). There was no documented evidence that any of these patients were selected not to undergo CPEX testing. The median length of hospital stay was 9 days (IQR 7-14 days). No deaths occurred at postoperative day 30, but 7 patients died at day 90 (3.4%); 2 due to malignant progression, 2 due to cardiopulmonary complications (VO_{2peak} 16.2 and 21.1ml/kg/min and AT 10.1 and 9.5ml/kg/min), and 3 due to non-cardiopulmonary complications (VO_{2peak} 14.5, 15.6 and 20.8ml/kg/min and AT 8.7, 8.8 and 10.6ml/kg/min).

Table 3.2 Patient characteristics

Variable	Study cohort (n=206) Number and percentage (unless otherwise stated)
Gender (male)	158 (76.7)
Age at operation in years (mean + SD)	66.9 (9.2)
Charlson co-morbidity index	
0	128 (62.1)
1	48 (23.3)
2	19 (9.2)
3 or above	11 (5.4)
WHO BMI category (kg/m²)	
Underweight (<18.5)	5 (2.4)
Normal weight (18.5-24.9)	56 (27.2)
Overweight (25-29.9)	89 (43.2)
Class I obesity (30-34.9)	42 (20.4)
Class II obesity (35-39.9)	10 (4.9)
Class III obesity (≥40)	4 (1.9)
Smoking status	
Never	65 (31.6)
Former	120 (58.3)
Current	12 (5.8)
Missing	9 (4.4)
T staging (TNM)	
T1	14 (6.8)
T2	25 (12.1)
T3	156 (75.7)
T4	6 (2.9)
Unable to be staged	5 (2.4)
N staging (TNM)	
N0	93 (45.1)
N1	66 (32.1)
N2	45 (21.8)
Unable to be staged	2 (1.0)
Histology	
Adenocarcinoma	174 (84.5)
Squamous cell	29 (14.1)
Other (leiomyoma, high-grade dysplasia)	3 (1.5)
Received neoadjuvant chemotherapy	162 (78.6)
Type of oesophagectomy	
Open McKeown	14 (6.8)
Open or partially laparoscopic assisted Ivor Lewis	83 (40.3)
Fully laparoscopic (minimally invasive) Ivor Lewis	109 (52.9)

Table 3.3 shows patients grouped by whether or not they suffered; any complication; a cardiopulmonary; or a non-cardiopulmonary complication. These groups differed in ASA grade I, type of operation, duration of surgery and length of stay. However, only length of stay met statistical significance after adjustment for multiple statistical testing (Bonferroni correction, $p=0.0008$). Neither VO_{2peak} or AT were associated with complications of any type or severity (table 3.4). Patients were further grouped by whether or not they suffered one of the commonest complications, namely pneumonia, atrial fibrillation or anastomotic leak (supplementary table 3.2). Length of hospital stay in patients that suffered an anastomotic leak was significantly increased compared to those without this event (8 vs. 22 days, $p<0.00001$), but no other variables were significantly different between groups after correction for multiple testing.

Finally, univariable logistic regression analyses were undertaken using variables with a plausible association with outcome (age, gender, Charlson comorbidity index, smoking status, BMI, and type of operation) and estimated ORs, in turn, for; any complication; cardiopulmonary; and non-cardiopulmonary complications. Only age and operation type showed associations ($p=0.10$) and were included in a multivariable regression model as shown in table 3.5 (values are from the model excluding CPEX variables). The CPEX variables VO_{2peak} and AT were then added individually (due to collinearity) to the model to derive their ORs. No associations were found between preoperative CPEX variables and morbidity for either VO_{2peak} (OR 1.00, 95% CI 0.94-1.07) or AT (OR 0.98, 95% CI 0.89-1.09) and any type of complication. Similar null associations were found for cardiopulmonary and non-cardiopulmonary complications.

Table 3.3 Comparisons between variables of interest according to postoperative complications after oesophagectomy

Variable	Any complication		Cardiopulmonary complication		Non-cardiopulmonary complication	
	Yes (n=111)	No (n=95)	Yes (n=80)	No (n=126)	Yes (n=59)	No (n=147)
Gender (male)	82 (74%)	76 (80%)	62 (78%)	96 (76%)	42 (71%)	116 (79%)
Mean age at operation (years + SD)	66.0 (9.4)	67.9 (9.0)	66.2 (10.0)	67.3 (8.7)	65.0 (8.5)	67.6 (9.4)
Charlson co-morbidity index						
0	73 (65.8)	55 (57.9)	48 (60.0)	80 (63.5)	37 (62.7)	91 (61.9)
1	22 (19.8)	26 (27.4)	17 (21.3)	31 (24.6)	12 (20.3)	36 (24.5)
2	10 (9.0)	9 (9.5)	10 (12.5)	9 (7.1)	6 (10.2)	13 (8.8)
3 or above	6 (5.4)	5 (5.3)	5 (6.3)	6 (4.8)	4 (6.8)	7 (4.8)
BMI (mean in kg/m² + SD)	27.5 (5.7)	27.0 (4.7)	27.5 (5.2)	27.1 (5.3)	27.3 (6.0)	27.3 (4.9)
Smoking status						
Never	35 (31.5)	30 (31.6)	25 (31.3)	40 (31.7)	17 (28.8)	48 (32.7)
Former	65 (58.6)	55 (57.9)	45 (56.3)	75 (59.5)	36 (61.0)	84 (57.1)
Current	7 (6.3)	5 (5.3)	7 (8.8)	5 (4.0)	5 (8.5)	7 (4.8)
Missing	4 (3.6)	5 (5.3)	3 (3.8)	6 (4.8)	1 (1.7)	8 (5.4)
T staging						
T1	9 (8.1)	5 (5.3)	7 (8.8)	7 (5.6)	6 (10.2)	8 (5.4)
T2	15 (13.5)	10 (10.5)	14 (17.5)	11 (8.7)	7 (11.9)	18 (12.2)
T3	80 (72.1)	76 (80.0)	52 (65.0)	104 (82.5)	43 (72.9)	113 (76.9)
T4	4 (3.6)	2 (2.1)	4 (5.0)	2 (1.6)	1 (1.7)	5 (3.4)
Unable to be staged	3 (2.7)	2 (2.1)	3 (3.8)	2 (1.6)	2 (3.4)	3 (2.0)
N staging						
N0	53 (47.7)	40 (42.1)	40 (50)	53 (42.1)	31 (52.5)	62 (42.2)
N1	35 (31.5)	31 (32.6)	23 (28.8)	43 (34.1)	18 (30.5)	48 (32.7)
N2	22 (19.8)	23 (24.2)	16 (20.0)	29 (23.0)	10 (16.9)	35 (23.8)
Unable to be staged	1 (0.9)	1 (1.1)	1 (1.3)	1 (0.8)	0	2 (1.4)
Histology						
Adenocarcinoma	91 (82.0)	83 (87.4)	64 (80.0)	110 (87.3)	51 (86.4)	123 (83.7)
Squamous cell	18 (16.2)	11 (11.6)	14 (17.5)	15 (11.9)	8 (13.6)	21 (14.3)
Other (leiomyoma, HGD)	2 (1.8)	1 (1.1)	2 (2.5)	1 (0.8)	0	3 (2.0)
Received neoadjuvant chemotherapy	85 (76.6)	77 (81.1)	59 (73.8)	103 (81.7)	46 (78.0)	116 (78.9)
Type of oesophagectomy						
Open McKeown	10 (9.0)	4 (4.2)	5 (6.3)	9 (7.1)	8 (13.6)	6 (4.1) ^d
Open or partially laparoscopic assisted Ivor Lewis	48 (43.2)	35 (36.8)	32 (40.0)	51 (40.5)	32 (54.2)	51 (34.7) ^c
Fully laparoscopic (minimally invasive) Ivor Lewis	53 (47.7)	56 (58.9)	43 (53.8)	66 (52.4)	19 (32.2)	90 (61.2) ^b
Duration of surgery in mins (median, 25th-75th percentile)	464 (365-542)	455 (381-525)	478 (391-556)	443 (369-519) ^f	424 (334-509)	465 (385-541) ^e
Length of stay in days (median, 25th-75th percentile)	12 (8-20)	7 (6-9) ^a	11.5 (8-18.5)	8 (6-11) ^a	17 (12-29)	8 (7-10) ^a

Data shown are the number of patients and percentage unless otherwise stated. For categorical variable, X² tests were used, but only when total cell counts were >50, otherwise Fisher's exact tests were applied. For continuous variables with a normal distribution, Student's-t tests were used, where distribution was non-normal, Mann-Whitney U tests were used. All percentages represent the proportion of patients with/without a complications (yes/no). P-values reaching conventional statistical significance (p=0.05) are shown in superscript. Bonferroni adjusted significance is p=0.0008, in which case the superscript is shown in bold. ^aP<0.00001, ^bP=0.001, ^cP=0.01, ^dP=0.02, ^eP=0.04, ^fP=0.05.

Table 3.4 Comparisons between mean cardiopulmonary exercise testing variables according to postoperative complication outcomes.

CPEX variable	Type of complication		P-value
	Any complication (n=111)	No complication (n=95)	
VO _{2peak} (ml/kg/min)	21.3 (4.7)	20.9 (4.2)	0.54
AT (ml/kg/min)	12.4 (2.9)	12.4 (2.8)	0.95
	Any complication of C-D grade 3 (n=39)	No complication (n=95)	
VO _{2peak} (ml/kg/min)	20.4 (4.4)	20.9 (4.2)	0.52
AT (ml/kg/min)	12.2 (3.1)	12.4 (2.8)	0.73
	Any complication of C-D grade 4 (n=16)	No complication (n=95)	
VO _{2peak} (ml/kg/min)	21.0 (3.3)	20.9 (4.2)	0.94
AT (ml/kg/min)	13.0 (3.1)	12.4 (2.8)	0.42
	Cardiopulmonary complication (n=80)	No cardiopulmonary complication (n=126)	
VO _{2peak} (ml/kg/min)	21.7 (5.0)	20.8 (4.1)	0.14
AT (ml/kg/min)	12.5 (2.9)	12.3 (2.8)	0.59
	Non-cardiopulmonary complication (n=59)	No non-cardiopulmonary complication (n=143)	
VO _{2peak} (ml/kg/min)	20.8 (4.1)	21.2 (4.6)	0.56
AT (ml/kg/min)	12.4 (2.9)	12.3 (2.8)	0.91

Data shown are the means and standard deviations. C-D= Clavien-Dindo severity classification (grade 3 = surgical, endoscopic or radiological intervention required and grade 4 = life-threatening complication requiring intensive care unit management). All P-values obtained using Student-t tests.

Table 3.5. Multivariable logistic regression modelling of the association between CPEX variables and postoperative complications after oesophagectomy.

CPEX variable	Any complication	Cardiopulmonary complication	Non-cardiopulmonary complication
	Odds ratio , 95% CI and P-value	Odds ratio , 95% CI and P-value	Odds ratio , 95% CI and P-value
VO _{2peak} (ml/kg/min)	1.00 (0.94-1.07), p=0.862	1.04 (0.98-1.12), p=0.204	0.98 (0.88-1.03), p=0.191
AT (ml/kg/min)	0.98 (0.89-1.09), p=0.769	1.02 (0.92-1.13), p=0.675	0.98 (0.88-1.11), p=0.792

Adjustments are for age and type of operation by category (minimally invasive, open or hybrid Ivor Lewis, McKeown oesophagectomy).

3.3.5 Discussion

This study investigated the association between preoperative CPEX values and 30-day morbidity in 206 patients undergoing oesophagectomy. No associations were found between preoperative cardiopulmonary fitness, as measured by CPEX testing and short-term postoperative morbidity. This finding is surprising in that it contradicts a seemingly intuitive inverse association. CPEX testing is a measure of how efficiently patients are able to deliver oxygen from the environment to cellular mitochondria and we would therefore expect patients with large volumes of VO_{2peak} to have a lower risk of complications in the early postoperative period, when the demand for oxygen is increased up to 1.5 times the normal resting state.¹⁰⁹ However, oesophagectomy is a complex operation which delivers a large physiological insult, with complications related to the operative field (anastomotic leak, pneumonia and atrial fibrillation). Therefore, the effect of improved aerobic fitness, if present, is likely to have a small effect on complications directly related to the surgery. However, cardiorespiratory and musculoskeletal reserves may be critical in the ability of a patient to respond once a complication has occurred.¹⁶³ This study was unable to analyse this association as mortality was a rare event ($n=7$).

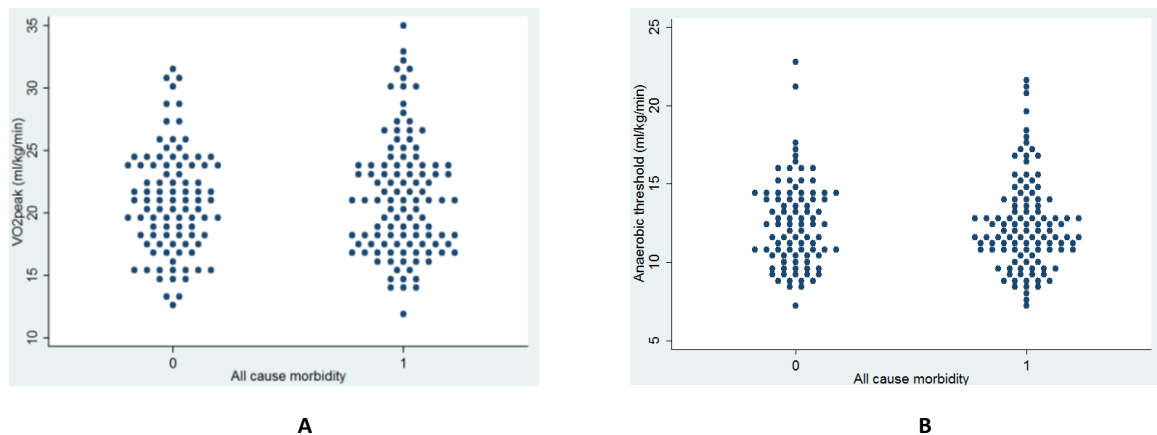
Three similar, but smaller, studies on CPEX prior to oesophagectomy have been published to date¹³⁴⁻¹³⁶ and are described in detail in section 3.2.4 of this thesis. Whilst all 3 studies reported inverse associations between complications and either VO_{2peak} ^{134 136} or AT¹³⁵ there were potential sources of bias. The most significant in all three studies, apart from their small sample sizes and single institution design, was the potential for detection bias due to unblinded outcome assessment, particularly for complications which can be subjectively diagnosed. This would lead to an inflation of the association between CPEX variables and outcomes.

The strengths of this present study included the use of a defined diagnostic criteria for complications, which would reduce measurement error of outcomes. Outcome assessment was also blinded, which would limit detection bias. Furthermore, this work is the largest study of its kind, with a sufficiently high event rate to detect associations. A *post-hoc* power calculation estimated that this sample size ($n=206$) could identify a mean difference in VO_{2peak} , (between groups with and without a complication of any cause) of 1.75ml/kg/min and 1.1ml/kg/min for AT, with 80% power and alpha level at 0.05. This

suggests that this study had adequate power to detect a small difference in CPEX variables between groups if it were indeed present.

However, there are limitations associated with the study methodology. As with all observational work, residual confounding cannot be excluded. However, as the aim was to determine associations between fitness and complications it is difficult to understand how confounding could operate. CPEX data were also missing in 16% of the patient population who otherwise met the inclusion criteria. However, data was likely to be missing completely at random (MCAR) and this group was comparable to the included group in demography and outcome (supplementary table 1), which reduced the risk of selection bias. Finally, this study sample represents a select population of patients whom were deemed fit for both neoadjuvant chemotherapy and major surgery. However, this selected population had a large range of CPEX values (figure 3.4). I am therefore satisfied that patients with 'low' scores were included in the analyses, with 35% of patients (n=72) having an AT of ≤ 11 ml/kg/min. Finally, as death was a rare event, I was unable to examine the associations between fitness and mortality.

Figure 3.5 Dot plots showing the distribution of VO_{2peak} (A) and AT (B) for patients with and without any complications



n=206, 0=absence of a complication, 1=presence of a complication. For VO_{2peak} the median value for the whole cohort was 20.8ml/kg/min (range 11.6 to 34.9). For AT the median value for the whole cohort was 12.1ml/kg/min (range 7.1 to 22.8)

3.3.6 Conclusions

CPEX testing provides an objective measure of fitness in patient's undergoing oesophagectomy. However, this work has shown, that in this specific population, aerobic fitness was not associated with 30-day morbidity. I postulated that aerobic fitness was likely to have an effect on complication rates, as there are plausible biological mechanisms to support this hypothesis. However, any effect size, if present, in the context of the magnitude of an oesophagectomy, is likely to be small (explaining why it could not be measured in the present modestly sized study). The findings from this study, as well as from previous observational work, challenges the utility of CPEX testing as a preoperative screening tool prior to oesophagectomy, which is poorly discriminatory at best.^{135 136} But also, and perhaps more importantly, the results question whether fitness modification is a worthwhile target in interventional studies as such a small effect size would require a large population of patients to demonstrate any benefit. However, these findings are derived from retrospective observational work and further investigations, ideally blinded prospective cohort studies, are required to clarify the relationship between preoperative cardiopulmonary fitness and postoperative outcome. Such work would justify whether RCTs should be instigated in the future.

Supplementary table 3.1 Comparison of cohorts with and without CPEX data by complications (The association between preoperative cardiopulmonary exercise test variables and short-term morbidity following oesophagectomy: a hospital-based cohort study).

Variable	Any complication of included cohort (n=206)		Any complication of excluded cohort (n=40)	
	Yes (n=111)	No (n=95)	Yes (n=19)	No (n=21)
Gender (male)	82 (74)	76 (80)	13 (68.4)	17 (81.0)
Mean age at operation (years + SD)	66.0 (9.4)	67.9 (9.0)	66.7 (9.8)	63.8 (9.1)
Charlson co-morbidity index				
0	73 (65.8)	55 (57.9)	15 (78.9)	16 (76.2)
1	22 (19.8)	26 (27.4)	4 (21.1)	4 (19.0)
2	10 (9.0)	9 (9.5)	0	1 (4.8)
3 or above	6 (5.4)	5 (5.3)	0	0
Smoking status				
Never	35 (31.5)	30 (31.6)	4 (21.1)	9 (42.9)
Former	65 (58.6)	55 (57.9)	10 (52.6)	11 (52.4)
Current	7 (6.3)	5 (5.3)	4 (21.1)	0
Missing	4 (3.6)	5 (5.3)	1 (5.3)	1 (4.8)
T staging				
T1	9 (8.1)	5 (5.3)	3 (15.8)	2 (9.5)
T2	15 (13.5)	10 (10.5)	3 (15.8)	3 (14.3)
T3	80 (72.1)	76 (80.0)	13 (68.4)	16 (76.2)
T4	4 (3.6)	2 (2.1)	0	0
Unable to be staged	3 (2.7)	2 (2.1)	0	0
N staging				
N0	53 (47.7)	40 (42.1)	8 (42.1)	13 (61.9)
N1	35 (31.5)	31 (32.6)	5 (26.3)	6 (28.6)
N2	22 (19.8)	23 (24.2)	5 (26.3)	2 (9.5)
Unable to be staged	1 (0.9)	1 (1.1)	1 (5.3)	0
Histology				
Adenocarcinoma	91 (82.0)	83 (87.4)	14 (73.7)	18 (85.7)
Squamous cell	18 (16.2)	11 (11.6)	5 (26.3)	3 (14.3)
Other (leiomyoma, HGD)	2 (1.8)	1 (1.1)	0	0
Received neoadjuvant chemotherapy	85 (76.6)	77 (81.1)	15 (78.9)	18 (85.7)
Type of oesophagectomy				
Open McKeown	10 (9.0)	4 (4.2)	3 (15.8)	1 (4.8)
Open or partially laparoscopic assisted Ivor Lewis	48 (43.2)	35 (36.8)	8 (42.1)	12 (57.1)
Fully laparoscopic (minimally invasive) Ivor Lewis	53 (47.7)	56 (58.9)	8 (42.1)	8 (38.1)
Length of stay in days (median, 25th-75th percentile)	12 (8–20)	7 (6-9)	11 (10-22)	7 (6-7)
Duration of surgery in mins (median, 25th- 75th percentile)	464 (365-542)	455 (381-525)	421 (337-519)	416 (345-480)

Data shown are the number of patients and percentage unless otherwise stated.

Supplementary table 3.2 Comparisons between variables of interest according to common postoperative complications (The association between preoperative cardiopulmonary exercise test variables and short-term morbidity following oesophagectomy: a hospital-based cohort study).

Variable	Pneumonia		Atrial fibrillation		Anastomotic leak	
	Yes (n=42)	No (n=164)	Yes (n=36)	No (n=170)	Yes (n=39)	No (n=167)
Gender (male)	35 (83.3)	123 (75.0)	26 (72.2)	132 (77.6)	31 (79.5)	127 (76.0)
Mean age at operation (years + SD)	68.1 (9.1)	66.6 (9.3)	68.3 (8.9)	66.6 (9.3)	64.1 (8.5)	67.5 (9.3) ^f
COPD diagnosis	8 (19.0)	18 (11.0)	9 (25.0) ^d	17 (10.0)	8 (20.5)	18 (10.8)
Previous MI	6 (14.3)	12 (7.3)	3 (8.3)	15 (8.8)	5 (12.8)	13 (7.8)
BMI (mean in kg/m² + SD)	27.7 (5.2)	27.2 (5.2)	27.6 (5.2)	27.2 (5.3)	28.0 (6.6)	27.1 (4.9)
Smoking status						
Never	14 (33.3)	51 (31.1)	11 (30.6)	54 (31.8)	9 (23.1)	56 (33.5)
Former	23 (54.8)	97 (59.1)	24 (66.7)	96 (56.5)	24 (61.5)	96 (57.5)
Current	3 (7.1)	9 (5.5)	1 (2.8)	11 (6.5)	4 (10.3)	8 (4.8)
Missing	2 (4.8)	7 (4.3)	0	9 (5.3)	2 (5.1)	7 (4.2)
Had neoadjuvant chemotherapy	27 (64.3)	135 (82.3) ^d	29 (80.6)	133 (78.2)	32 (82.1)	130 (77.8)
Type of oesophagectomy						
Open McKeown	2 (4.8)	12 (7.3)	2 (5.6)	12 (7.1)	6 (15.4)	8 (4.8) ^e
Open or partially laparoscopic assisted Ivor Lewis	19 (45.2)	64 (39.0)	11 (30.6)	72 (42.4)	20 (51.3)	63 (37.7)
Fully laparoscopic (minimally invasive) Ivor Lewis	21 (50)	88 (53.7)	23 (63.9)	86 (50.6)	13 (33.3)	96 (57.5) ^c
Duration of surgery (mins)	475 (344-545)	455 (370-526)	489 (427-556)	451 (365-526) ^f	406 (334-490)	462 (381-536) ^f
Length of stay in days (median, 25th to 75th percentile)	10 (8-15)	8.5 (7-13)	13 (8-19.5)	8 (7-12) ^b	22 (15-35)	8 (7-10) ^a
CPEX (mean + SD)						
VO ₂ peak (ml/kg/min)	20.8 (5.0)	21.2 (4.3)	21.2 (5.2)	21.1 (4.3)	20.7 (3.7)	21.2 (4.6)
AT (ml/kg/min)	12.0 (2.6)	12.5 (2.9)	12.5 (3.2)	12.3 (2.8)	12.7 (2.9)	12.3 (2.8)

Data shown are the number of patients and percentage unless otherwise stated. For categorical variable, X² tests were used, but only when total cell counts were >50, otherwise Fisher's exact tests were applied. For continuous variables with a normal distribution, Student's t tests were used, where distribution was non-normal, Mann-Whitney U tests were used. All percentages represent the proportion of patients with or without a complications (yes/no). P-values reaching conventional statistical significance (p<0.05) are shown in superscript. Bonferroni adjusted significance is p=0.0008, in which case the superscript is shown in bold. ^aP<0.00001, ^bP=0.0008, ^cP=0.007, ^dP=0.01, ^eP=0.02, ^fP=0.04.

Chapter Four: A summary of the thesis findings

1) Occupational activity may influence the development of Barrett's oesophagus and oesophageal adenocarcinoma

New evidence from this thesis suggests that occupational activity may be associated with the development of Barrett's oesophagus in a U-shaped manner, where moderate levels of activity in standing occupations may be protective over sedentary jobs, but heavy manual occupations may be hazardous. Further epidemiological work to investigate whether these associations exist for oesophageal adenocarcinoma is worth pursuing in order to determine if physical activity should be added to the aetiological model of this increasingly common cancer.

2) Prehabilitation prior to oesophagectomy is possible

I have shown for the first time 'proof of concept' for a randomised controlled trial of prehabilitation prior to oesophagectomy. Elderly patients were willing and able to engage in aerobic and muscle strengthening exercises during and after neoadjuvant chemotherapy. Such exercise in this patient population was also safe and adhered to. Further feasibility work is required to determine if prehabilitation can produce statistically significant improvements in fitness. This would then inform a full RCT to determine whether improvement in fitness results in reduced complications after oesophagectomy. However, further observational work is firstly required to determine whether increased fitness is indeed inversely associated with post-oesophagectomy outcome to justify prehabilitation interventions.

2) The effect of preoperative aerobic fitness on post-oesophagectomy outcome needs to be clarified.

This thesis includes the largest observational study to examine the associations between preoperative fitness, as determined objectively by CPEX testing, and postoperative complications after oesophagectomy. The findings contradict the seemingly intuitive positive association between fitness and improved clinical outcomes. This observational work highlights the need for a further large cohort study examining the associations

between preoperative CPEX and outcomes after oesophagectomy to look for consistency in my findings. Future research worth pursuing is a national multi-centre retrospective observational study examining whether there is an association between preoperative CPEX variables and mortality after oesophagectomy. If an inverse association does exist, then future prehabilitation interventional studies may be justified, which the trial work in this thesis demonstrates are possible. However, if it is indeed shown that there is no association, this would challenge a long-standing presumption that poor aerobic fitness is associated with a high risk of post-operative complications. Such a finding would be equally valuable in that it could justify curative surgery for oesophageal cancer patients who would previously have been deemed too 'unfit'.

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Appendix 1. Physical activity questionnaire (The association between physical activity and the risk of symptomatic Barrett’s oesophagus – a UK prospective cohort study)

1. We would like to know the type and amount of physical activity involved in your work. Please tick what best corresponds to your present activities from the following four possibilities

- Sedentary occupation _____

You spend most of your time sitting (such as in an office)

- or Standing occupation _____

You spend most of your time standing or walking. However, your work does not require intense physical effort (e.g. shop assistant, hairdresser, guard, etc.)

- or Physical work _____

This involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, cleaner, nurse, sports instructor, electrician, carpenter, etc.)

- or Heavy manual work _____

This involves very vigorous physical activity including handling of very heavy objects (e.g. docker, miner, bricklayer, construction worker, etc.)

2. In a typical week during the past 12 months, how many hours did you spend on each of the following activities? (Put '0' if none).

- Walking, including walking to work, shopping and leisure

In summer _____ hours per week

In winter _____ hours per week

- Cycling, including cycling to work and during leisure time

In summer _____ hours per week

In winter _____ hours per week

- Gardening

In summer _____ hours per week

In winter _____ hours per week

- Housework such as cleaning, washing, cooking and childcare

_____ hours per week

- Do-it-yourself

_____ hours per week

- Other physical exercise such as keep fit, aerobics, swimming, jogging

In summer _____ hours per week

In winter _____ hours per week

3. In a typical week during the past year did you practice any of these activities vigorously enough to cause sweating or faster heartbeat?

Yes _____ No _____ Don't know _____

If yes, for how many hours per week in total did you practise such vigorous physical activity? (Put '0' if none)

_____ hours per week

4. In a typical day during the last 12 months, how many floors of stairs did you climb up? (Put '0' if none)

_____ floors per day

Appendix 2. Search strategy (The association between preoperative CPEX variables and outcome after major cancer resection surgery: a review of the literature)

Search terms for cardiopulmonary exercise testing:

"cardiopulmonary exercise", "CPEX", "CPET", "exercise testing", "anaerobic threshold", "VCO₂", "ventilatory inefficiency", "oxygen consumption", "VO₂", "preoperative exercise", "aerobic exercise".

Search terms for outcomes:

"morbidity", "mortality", "outcome", "complication".

Additional search terms for lung cancer:

"lung cancer surgery", "lung resection", "lobectomy", "pneumonectomy"

Additional search terms for colorectal cancer:

"colorectal", "colon", "colectomy", "rectal", "rectum", surgery", "resection"

Additional search terms for colorectal cancer:

"hepatic", "hepatectomy", "liver surgery"

Additional search terms for oesophageal cancer:

"oesophagectomy", "oesophagogastrectomy"

Additional search terms for bladder cancer:

"bladder cancer", "cystectomy"

Additional search terms for pancreatic cancer:

"pancreatic surgery", "pancreatic resection", "pancreaticoduodenectomy"

An example for the whole search string for colorectal cancer:

"(((cardiopulmonary exercise).ti,ab OR (cpex).ti,ab OR (cpet).ti,ab OR (exercise testing).ti,ab OR (anaerobic threshold).ti,ab OR (VCO₂).ti,ab OR (ventilatory inefficiency).ti,ab OR (oxygen consumption).ti,ab OR (VO₂).ti,ab OR (preoperative exercise).ti,ab OR (aerobic exercise).ti,ab) AND (((colorectal).ti,ab OR (colon).ti,ab OR (colectomy).ti,ab OR (rectal).ti,ab OR (rectum).ti,ab) AND ((surgery).ti,ab OR (resection).ti,ab))) AND ((complications).ti,ab OR (outcome).ti,ab OR (morbidity).ti,ab OR (mortality).ti,ab))"

ti=title, ab=abstract

Appendix 3. Study protocol for (Prehabilitation to improve physical fitness and reduce postoperative cardiopulmonary complications after oesophagectomy in patients with oesophageal adenocarcinoma – a feasibility randomised controlled trial. The ExPO Trial (Exercise Prior to Oesophagectomy))



Norfolk and Norwich 
University Hospitals
NHS Foundation Trust

Protocol: Version 1.0, dated 24th May 2016

**The ExPO trial (Exercise Prior to Oesophagectomy).
Prehabilitation to reduce cardiopulmonary complications
after oesophagectomy in patients with oesophageal
adenocarcinoma – a feasibility randomised controlled trial.**



IRAS Project ID: 206608

Protocol registration: ClinicalTrials.gov (NCT02962219)

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ExPO TRIAL SUMMARY

Trial Title	A pre-operative personalised exercise programme (my-PEP) to improve fitness and reduce post-operative cardiopulmonary complications after oesophagectomy in patients with oesophageal adenocarcinoma – a feasibility randomised controlled trial.	
Short title	The ExPO Trial (Exercise Prior to Oesophagectomy).	
Trial Design	Single centre, parallel group, single blinded, randomised controlled trial.	
Study Setting	Norfolk and Norwich University Hospitals NHS Foundation Trust.	
Trial Participants	Adults with oesophageal adenocarcinoma due to undergo neoadjuvant chemotherapy and subsequent oesophagectomy.	
Planned Sample Size	32 participants (16 per arm).	
Intervention arm	A pre-operative personalised exercise programme (my-PEP) consisting of: 1) a advice to promote exercise, using behavioural change techniques (BCTs), 2) home inspiratory muscle training (IMT), 3) a home exercise programme (HEP) - which is also current standard care, 4) a 4 week hospital-supervised aerobic and muscle strengthening programme (Hos-PEP).	
Control arm	Standard care home exercise programme (HEP) of written advice to attempt ≥ 150 mins of moderate or ≥ 75 mins of vigorous aerobic exercise per week (identical to the HEP in the intervention arm).	
Treatment duration	Approximately 16 weeks pre-oesophagectomy.	
Follow up duration	90 days post-oesophagectomy for cardiopulmonary complications.	
Planned Trial Period	24 months.	
Feasibility Objectives	Feasibility Outcome Measures	
To measure: eligibility, recruitment and retention of participants in my-PEP .	The eligibility, recruitment and retention proportions of patients in my-PEP (patients with oesophageal adenocarcinoma referred for oesophagectomy).	
To document and address reasons for non-participation in the ExPO trial.	The number of patients that decline to participate in the trial and assessment of their reasons for non-participation.	
To compare the demographics and clinical characteristics of participants and non-participants to assess generalisability of the results.	Comparison of the demographic and clinical information of those that do and do not participate in the trial.	
To measure baseline physical activity levels in the whole group.	The level of physical activity prior to participation in the trial measured by the International Physical Activity Questionnaire (IPAQ).	
To assess facilitators and barriers to engaging with my-PEP .	The factors which promote or inhibit engagement with my-PEP , measured using the Determinants of Physical Activity Questionnaire (DPAQ).	
To assess adherence with my-PEP .	The number of my-PEP exercise sessions (at home and in hospital) engaged in.	
To assess the safety of my-PEP .	The number of adverse events related to my-PEP compared to standard care (HEP) as defined by CTCAE.	
To assess if my-PEP results in a greater improvement in VO_{2max} than the physical activity of standard care (HEP).	The difference in change of mean VO_{2max} as measured by CPEX between the intervention and control arm.	
To assess if my-PEP results in a greater improvement in P_{i-max} than the physical activity of standard care (HEP).	The difference in change of mean P_{i-max} (as measured by an inspiratory mouth pressure test) between the intervention and control arm.	
To give an estimate of the mean difference and SD in the number of post-operative cardiopulmonary complications (CPCs) per patient between arms.	The mean number of CPCs per patient in both arms, determined by review of the medical notes (when discharged from hospital and at days 30 and 90).	
To estimate the mean difference and SD per patient in the number of post-operative non-cardiopulmonary complications, length of hospital stay (LOS) and mortality between arms.	The mean number of all non-cardiopulmonary complications per patient, LOS and mortality in each group determined by review of the medical notes (when discharged from hospital and at days 30 and 90 after surgery).	
To compare quality of life (QOL) between arms.	The difference in change in QOL between the two arms measured by EORTC QLQ-C30 and QLQ-OGC25 questionnaires.	
To assess overall experience with my-PEP .	Expectations, evaluation, and satisfaction with my-PEP recorded via qualitative interview.	

Background

In the western world, the incidence of oesophageal adenocarcinoma (OAC) has increased by at least 6-fold in the last 30 years.¹ Surgery is the only consistent treatment modality that offers a potential cure.² However, oesophageal cancer resection and reconstruction (oesophagectomy) carries a high risk of serious post-operative complications. Recent UK national audit figures reported 33% of patients suffered a complication after oesophagectomy, most of which (74%) were cardiopulmonary (22% cardiac and 52% respiratory).³ Interventions to reduce the high rate of CPCs are required.

In the first few days after major surgery, the patient enters a catabolic phase, with increased oxygen consumption and breakdown of skeletal muscle reserves for energy.⁴ Lack of mobility and post-surgical pain inhibits normal respiratory function.⁵ Aerobic exercise and inspiratory muscle training improves heart and lung function, while resistance training of all major muscle groups builds muscle bulk. Therefore, pre-operative exercise, or prehabilitation, may increase such reserves, allowing patients to better withstand a surgical insult. Observational data reports that enhanced physical fitness prior to oesophagectomy is associated with fewer post-operative complications.⁶⁻¹² A UK study of 78 consecutive oesophagectomy patients reported a significantly lower pre-operative VO_{2max} for patients with CPCs compared to those without (mean difference of 2.3ml/kg/min ($p=0.04$) between groups).¹¹ A systematic review of 4 randomised trials and 6 observational studies, totalling 524 patients, reported that exercise training prior to: cardiac, lung and colorectal surgery was effective in improving physical fitness and was safe, feasible and well tolerated, but did not report postoperative complication outcomes.¹³ There is evidence from systematic reviews that a 2-4 week programme of pre-operative endurance inspiratory muscle training is safe and effective at reducing pulmonary complications after major cardiac¹⁴ ¹⁵ and non-oesophageal abdominal surgery.¹⁵

To the best of our knowledge, no trial has investigated a multimodal exercise intervention in patients undergoing oesophagectomy combining both aerobic exercise, resistance training and inspiratory muscle training. However, before a full RCT is started to assess such an exercise intervention, important feasibility criteria need to be fulfilled to both justify and inform its conduct. These are demonstrating that a short period of exercise prior to oesophagectomy is safe and that sufficient participants are suitable, can be recruited and retained, with evidence that a pre-operative personalised exercise programme (*my*-PEP) is superior to standard care in improving physiological measures of physical fitness. The feasibility trial would also give an imprecise estimate of the mean number of complications and SD of adverse events in each arm of the trial and allow calculation of the sample size of a subsequent definitive trial. If a future RCT could demonstrate benefits to patients this would support the use of *my*-PEP prior to oesophagectomy as standard care across the NHS to reduce the current high number of post-operative CPCs and improve patient outcomes and quality of life.

Methods/Design

Trial design summary

The ExPO trial is a single centre, single-blinded, parallel group feasibility RCT in patients with OAC to justify and inform a future full RCT investigating a personalised exercise programme (*my*-PEP) vs standard care (written advice to exercise at home), prior to oesophagectomy, to reduce the incidence of 30-day and 90-day post-operative CPCs.

Participants referred for neoadjuvant chemotherapy and scheduled for oesophagectomy will be randomised to receive either a multimodal exercise intervention (*my*-PEP) or standard care advice. Both cardiopulmonary fitness and respiratory muscle strength will be assessed in both arms of the trial before and after the intervention, using CPEX and maximal inspiratory mouth pressure, respectively. After completion of the intervention participants undergo oesophagectomy and are followed up until 90 days after surgery to record post-operative cardiopulmonary complications. Participants must give their written informed consent to participate in the trial. The protocol has been approved by the East Midlands Leicester South Research Ethics Committee (ref: 16/EM/0317) and the Health Research Authority, UK (IRAS ID: 206608).

Trial setting

This single centre clinical trial will be conducted in the Norfolk and Norwich University Hospitals' (NNUH) Oesophagogastric Cancer Centre. The NNUH takes referrals from its neighbouring hospitals, namely the James Paget University Hospital (JPUH) and Queen Elizabeth Hospital (QEH). Approximately 80 oesophagogastric cancer resections are performed at the centre each year.

Trial Population

Patients with OAC who are scheduled for neoadjuvant chemotherapy and subsequent oesophagectomy.

Inclusion Criteria

- i. Male and female
- ii. Aged 18 years or above
- iii. Histological evidence of OAC
- iv. Capable of giving informed consent and complying with trial procedures.

Exclusion Criteria

- i. Patients with oesophageal squamous cell carcinoma.
- ii. Patients with concomitant illness or disability that makes them unsuitable for an exercise programme, as assessed by a clinician (e.g. severe musculoskeletal or neurological disease, unstable angina, severe aortic stenosis, uncontrolled dysrhythmias and uncompensated heart failure).
- iii. WHO performance status 3 (capable of only limited self-care, confined to a bed or chair more than 50% of waking hours) or greater.
- iv. Grade 5 on MRC dyspnoea scale (too breathless to leave the house, or breathless when undressing).

Recruitment

Participants will be identified at the NNUH Oesophagogastric cancer specialist MDT (SMDT). Recruitment will take place over 11 months (September 2016 –August 2017). Patients attending post-SMDT surgical clinics are provided with an information sheet by their surgeon. Those that express a wish to participate will be contacted by the trial team to arrange a research meeting at which time written informed consent will be obtained to participant in the trial.

Randomisation

Using a CPEX VO_{2max} of 15ml/kg/min, participants will be stratified into 'high' and 'low' score groups. Stratification will help to equally distribute those with a 'low' level of fitness between trial arms, reducing the risk of selection bias, which can occur with relatively small numbers of patients. The 32 participants will be randomised into suitable blocks, using random block sizes generated by computerised randomisation (www.randomization.com) by the trial statistician. Allocations will be placed in opaque envelopes by a secretary independent of the trial. The patient pathway following randomisation consists of 3 months of NAC followed 5-6 weeks of recovery before oesophagectomy.

The Intervention arm

my-PEP consists of 4 main components.

1) Inspiratory muscle training/IMT (during and after chemotherapy)

IMT using should be done for a total of 20 mins every day at home during and after NAC (a period of approximately 4 months). The IMT programme is as per Hulzebos, *et al*¹⁶ and is detailed below:

- Maximal inspiratory pressure (P_{i-max}) will be measured at baseline.
- Participants will be given an inspiratory threshold-loading device and shown how to use it.
- Participants start breathing exercise with resistance set on the device equal to 30% of P_{i-max} and instructed to perform IMT for 20 mins 7 days a week.
- The resistance of the inspiratory threshold-loading device is increased incrementally, based on the rate of perceived exertion scored on the New Category (0-10) Borg RPE Scale, where 0 is "nothing at all" and 10 is "very, very strong".¹⁷ If the rate of perceived exertion is less than 5, with 5 being "strong", the resistance of the inspiratory threshold trainer is increased incrementally by 5%.
- Participants are instructed to record daily IMT exercises in a diary.

2) Home exercise programme (HEP) (during and after chemotherapy)

The home aerobic exercise, which is the same as in the standard care arm, is based upon UK Department of Health (DH)¹⁸ and American College of Sports Medicine (ACSM) guidelines¹⁹, summarised below:

- Patients will be asked to engage in cardiorespiratory exercise training for ≥ 30 min/day (in continuous bouts of at least 10mins) on ≥ 5 days/week to achieve a total of ≥ 150 min/week of *moderate* intensity exercise (perceived exertion should be to 12-13 on the 6-20 Borg Scale, or "somewhat hard").
- Alternatively, patients may engage in cardiorespiratory exercise training ≥ 20 min/day on ≥ 3 days/week to achieve a total of ≥ 75 min/week of *vigorous* intensity exercise (perceived exertion should be to 14-17 on the 6-20 Borg Scale, "somewhat hard" to "hard").
- Additionally, a combination of *moderate* and *vigorous* intensity exercise may be engaged in to achieve approximately the same energy expenditure (≥ 500 -1000 MET/min/week) as a moderate or vigorous regime.

- Patients in the *my*-PEP arm are instructed to record the amount and intensity of daily exercise, complaints, and any adverse events in a diary.

3) Hospital personalised exercise programme (*Hos-PEP*)

There are approximately 6 weeks between completion of NAC and oesophagectomy to allow patients to recover prior to surgery. Around 1 week after NAC has finished, the participant will be invited to attend a 4-week out-patient *Hos-PEP*. This hospital supervised exercise component of *my*-PEP is based upon UK DH and ACSM guidelines. The muscle strengthening regime is as per Barakat, *et al.*²⁰ Participants will be invited to attend 8 supervised out-patient hospital exercise sessions over 4 weeks (2 sessions per week), with each lasting approximately 60-90 minutes. The timing of the hospital exercise programme is to allow participation in exercise in the routine time between the completion of chemotherapy and surgery (currently a minimum of 5-6 weeks). During this time participants will also be encouraged to continue their home exercise sessions. The *Hos-PEP* has aerobic and a muscle strengthening components as detailed below:

Aerobic component of *Hos-PEP*

The participant will be invited to begin each session with 5 mins of warm up by cycling on a static exercise bike to their perceived exercise intensity of 'light' on the Borg scale (score 9-11). After the warm up and remaining on the bike, the participant will be invited to engage in aerobic interval training aiming to achieve up to 30 mins of *moderate intensity* (Borg scale rate of perceived exertion (RPE) of 12-13) aerobic exercise. The pedal resistance of the static bike will be adjusted to achieve this.

At subsequent *Hos-PEP* sessions, participants who feel they may progress above the *moderate* level, and have demonstrated that this may be possible from previous sessions, will be encouraged to do so. Progression will be by increasing intensity whilst decreasing the duration and rest period.

Muscle strengthening component of *Hos-PEP*

Before or after the aerobic component (based upon participant preference), the participant will be invited to attempt the following sets of muscle strengthening exercises:

- Heel-raises for 2 minutes (rise up and down to 'tip toes' in a standing position).
- Knee extensions against resistance for 2 minutes (extend the knee with attached ankle weights in a seated position; each leg exercised separately).
- Dumbbells' biceps curls for 2 minutes (flex both arms while holding dumbbells in a standing position).
- Step-up lunges for 2 minutes (step up and down from an exercise step).
- Knee bends against resistance for 2 minutes (flex the knee with attached ankle weights in a standing position; each leg exercised separately).

4) Behavioural Change Techniques (BCTs)

An important component of *my*-PEP is identifying participant's exercise-related needs and the use of tailored strategies to promote adherence. Behavioural change techniques (BCTs) will be employed to improve participant adherence to *my*-PEP.²¹ The use of BCTs will be individualised to each participant. To identify participants' actual and perceived barriers to exercise a specific validated and reliable questionnaire, the Determinants of Physical Activity Questionnaire (DPAQ), will be used.²² All patients randomised to the *my*-PEP arm will be offered a one-to-one discussion with the trial team to discuss the results

and implications of their DPAQ results and, based on these, the trial team can deliver the required tailored BCTs. For example, if the participant scores low in the domain “knowledge” then information about the recommended levels of physical activity could be provided.

Standard Care

Participants randomly allocated to standard care will be given written advice on a home exercise programme. This explains the level of physical activity recommended by the UK DH¹⁸ and the ACSM¹⁹, namely to engage in ≥ 150 mins of *moderate* or ≥ 75 mins of *vigorous* aerobic exercise each week. Aerobic exercise may be in any form that the participant chooses including: on a bicycle, a static exercise bike, walking, power-walking, jogging or swimming.

Questionnaires

1) The International Physical Activity Questionnaire (IPAQ) (all participants)

At the initial research visit, all participants will be asked to complete the IPAQ, which consists of 4 questions. Each is related to physical activity performed in the last 7 days. Exercise levels will then be compared before and after the *my-PEP* intervention or standard care.

2) Quality of life (all participants)

All participants will be asked to complete both the quality of life (QOL) questionnaires EORTC QLQ-C30 and disease specific Oesophago-Gastric QLQ-OGC25 at the beginning and end of the trial to assess the impact of both *my-PEP* and standard care (HEP) on QOL.

3) The Determinants of Physical Activity Questionnaire (DPAQ)

Only participants in the *my-PEP* arm will be invited to complete the Determinants of Physical Activity Questionnaire (DPAQ). This contains 34 questions relating to 11 domains (adapted from a theoretical domains framework (TDF)) including participants’ knowledge about exercise, social influences, levels of motivation and emotional responses to physical activity. These theoretically underpinned measures of determinants of physical activity will provide information about factors that may represent personal barriers or facilitators to participating in an exercise programme. These can then be addressed or encouraged both before and during *Hos-PEP* by applying pre-selected BCTs.

Feasibility objectives and outcome measures

The purpose of the ExPO trial is to provide the following feasibility information to both justify and inform a future RCT:

To justify:

- i. To measure the: eligibility, recruitment and retention rates of patients to *my-PEP* who have OAC and are referred for NAC and oesophagectomy.
- ii. To assess the generalisability of trial participants, compared to patients that decline to participate in terms of demographics and clinical characteristics.

- iii. To measure the level of baseline exercise prior to participation determined by the *International Physical Activity Questionnaire/IPAQ*.
- iv. To measure QOL reported in both arms using the *European Organisation for Research and Treatment (EORTC) quality of life questionnaire, EORTC QLQ-C30* and disease specific *Oesophago-Gastric QLQ-OGC25* module to determine the effect of the intervention on QOL.
- v. To measure the adherence to *my-PEP*.
- vi. To define the safety profile of *my-PEP*.
- vii. To investigate if *my-PEP* provides a greater increase in VO_{2max} and P_{i-max} than standard care (HEP).

To inform:

- i. To record reasons for non-participation, which may be addressed in a future trial.
- ii. To assess participants' facilitators and barriers to engaging with *my-PEP*.
- iii. To record the mean number + SD of 30 and 90 day post-operative cardiopulmonary complications per patient, defined according to the '*Complications Basic Platform*' of the Esophagectomy Complications Consensus Group/ECCG⁹. The severity of complications will be graded according to the Clavien-Dindo Classification. With the number of participants in the trial (n=32), we will be able to provide an estimate of the difference in the mean number of complications per patient to allow calculation of the sample size required for a future trial, where the number of CPCs would be the primary outcome measure.
- iv. To record the number of 30 and 90 day post-operative non-cardiopulmonary complications per patient (defined according to the ECCG), the length of in-hospital stay following oesophagectomy, and the number of 30-day and 90-day post-operative deaths.
- v. To assess the overall participant experience (expectations, evaluation, satisfaction and suggestions) with *my-PEP* (recorded in a qualitative interview).

Complication data

Following surgery, participants will be followed up for CPCs. Post-operative complication data will be assessed by consultant clinicians who are blinded to the intervention and have no role in any other part of the trial or in the patient's routine clinical care. The 30-day and 90-day CPCs will be defined according to the '*Complications Basic Platform*' defined by the Esophagectomy Complications Consensus Group (ECCG).²³ The severity of the complication will be classified according to the Clavien-Dindo grading system from 1 to 5. For the purpose of this trial, only grade 2 complications and above will be included in the analysis. The 30-day and 90-day non-CPCs will also be defined according to the '*Complications Basic Platform*' agreed by the ECCG and graded as per Clavien-Dindo. Length of stay and mortality data will also be collected.

Statistical analysis

The baseline participant demographic and clinical characteristics and trial outcomes for participants in each of the 2 arms (*my*-PEP and HEP) of the trial will be reported. For categorical variables, the numbers and percentages will be presented and for continuous variables the means (and standard deviations) or medians (and interquartile ranges) depending on their distributions. Differences between the groups will be compared using the most appropriate statistical test.

Sample Size calculation

As this is a feasibility trial, a formal sample size calculation is not required to determine the statistical significance of the effect size of the intervention on the number of CPCs. However, this trial is powered to detect a statistically significant change in VO_{2max} of 3.6ml/kg/min between the two groups after the intervention. The sample size calculation was based on data from previous observational studies^{24 25} and a randomised controlled trial²⁶ investigating pre-operative exercise therapy of similar durations to that in our proposed trial. These studies suggest that an in-hospital exercise regime may increase baseline VO_{2max} by 2.6ml/kg/min. This was calculated from two observational studies, where VO_{2max} was increased by 2.8 and 2.4ml/kg/min after 4-6 week out-patient exercise programmes.^{24 25} To estimate the effect size in the baseline standard care arm we used information from a randomised controlled trial of 35 subjects, demonstrating that standard advice to exercise at home may cause a worsening of VO_{2max} of at least -1ml/kg/min.²⁶ Therefore, assuming a mean difference of VO_{2max} of 3.6ml/kg/min and a standard deviation of 3.0,²⁴⁻²⁶ then using a two sample t-test the trial would require 11 individuals per group for the trial to have 80% power at the 5% level of significance to detect a statistically significant difference in VO_{2max} between treatment arms. Accounting for a participant drop-out rate of 27%,^{25 26} at least 30 subjects would be needed to be recruited to achieve 11 individuals per group for a per-protocol analysis. Based on the above information we aim to recruit 32 patients in total.

Discussion/Conclusion

The ExPO feasibility trial aims to determine whether a multimodal exercise intervention (*my*-PEP) is justified, feasible and superior to standard care in improving physiological fitness prior to oesophagectomy. If *my*-PEP is suitable for this patient population, as well as safe, with good participant adherence, and also improves physical fitness, this will inform and justify a future large definitive RCT to determine whether the multi-modal exercise package can decrease the frequency of post-oesophagectomy CPCs. If so, this would lead to an established peri-operative exercise programme prior to esophageal resection surgery to improve patient outcomes in patients with this aggressive cancer.

Abbreviations: **ACSM:** American College of Sports Medicine, **AT:** Anaerobic Threshold (CPEX Parameter), **BCT:** Behavioural Change Techniques, **CPC:** Cardiopulmonary Complication, **CPEX:** Cardiopulmonary Exercise Test, **DPAQ:** Determinates of Physical Activity Questionnaire, **ECCG:** Eosophagectomy Complications Consensus Group, **ExPO:** Exercise Prior to Oesophagectomy, **HEP:** Home Exercise Programme, **Hos-PEP:** Hospital Personalised Exercise Programme, **IMT:** Inspiratory Muscle Training **IPAQ:** International Physical Activity Questionnaire, **LOS:** Length of Stay **MDT:** Multi-disciplinary Team, **MET:** Metabolic Equivalent for Task, **MRC:** Medical Research Council, **my-PEP:** My-Personalised Exercise Programme, **NAC:** Neoadjuvant Chemotherapy, **NNUH:** Norfolk and Norwich University Hospital, **Non-CPC:** Non-

Cardiopulmonary Complication, **OAC**: Oesophageal Adenocarcinoma, **PA**: Physical Activity, **Pi-max**: Maximal inspiratory Pressure, **QEH**: Queen Elizabeth Hospital, **QLQ**: Quality of Life Questionnaire, **QOL**: Quality of Life, **RCT**: Randomised Controlled Trial, **REC**: Research Ethics Committee, **RPE**: Rating of Perceived Exertion, **SMDP**: Specialist Multi-disciplinary Team, **TDF**: Theoretical Domains Framework, **VO2**: Volume of Oxygen Used (CPEX Parameter), **VO2max**: Maximum Volume of Oxygen Used (CPEX Parameter)

Human ethics and consent: Participants must give their written informed consent to participate in the trial. The protocol including the consent form has been approved by the East Midlands Leicester South Research Ethics Committee (ref: 16/EM/0317) and the Health Research Authority, UK (IRAS ID: 206608).

Consent for publication: Not applicable as all individual identifiable data will be removed.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analysed during the time of submission. When data are generated it will be available on reasonable request to the author.

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Chief investigator: Professor Andrew Hart

Trial sponsor: The University of East Anglia.

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ExPO Safety Management Plan (SMP)

A pre-operative personalised exercise programme (*my-PEP*) to improve physical fitness and reduce post-operative cardiopulmonary complications after oesophagectomy in patients with oesophageal adenocarcinoma – a feasibility randomised controlled trial.

Protocol version 1.0, 24th May 2016.

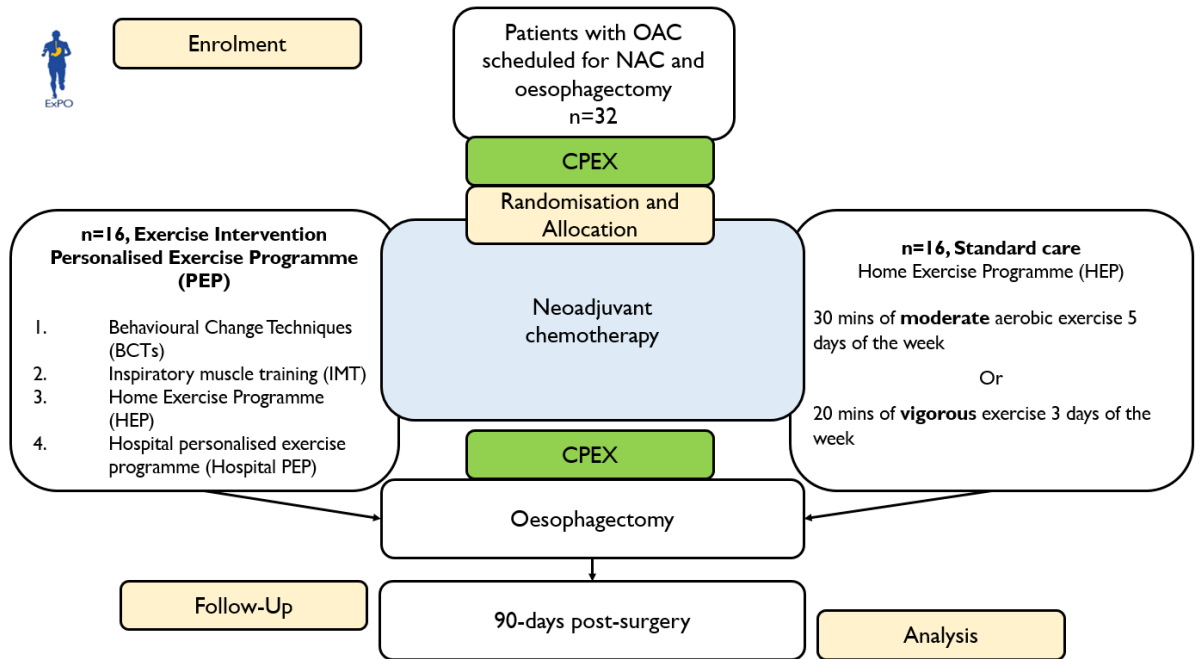
SMP version 1.0, 23rd August 2016

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Trial Flow Diagram



1 PURPOSE

The purpose of the EXPO Safety Management Plan (SMP) is to describe the safety measures and management procedures for the feasibility trial. This includes the definition of the roles and responsibilities for relevant parties for managing Serious Adverse Events (SAEs) and the compilation of safety reports. This document also describes procedures for handling data relating to pregnancies in trial participants, although this is highly unlikely in this patient group. The SMP will be reviewed and approved by the Trial Management Group (TMG) and sponsor.

2 EXPO SAFETY MEASURES

2.1 Possible Expected Adverse Events with Exercise

Based on results from previous trials, significant adverse events related to exercise in ExPO are expected to be rare. Those that do occur are likely to be both transient and mild. Adverse events due to exercise in the post-operative period (at least one week after the last exercise session) are particularly unlikely. A systematic review of 4 randomised trials

and 6 observational studies totalling 524 patients awaiting: cardiac, lung and colorectal surgery reported exercise therapy, similar to the duration and intensity in this trial, to be safe with only 2 mild exercise-related adverse events (transient hypotension) reported across all studies.

Adverse events may include:

- i. exacerbation of an existing medical condition (e.g. coronary artery disease).
- ii. delayed onset muscle soreness (DOMS)
- iii. soft tissue strains/sprains
- iv. nausea and light-headedness
- v. transient hypotension

Procedures to help participants avoid these symptoms are:

- Participants are asked prior to starting exercise if they feel well enough to participate
- Participants will be advised to wear loose clothing and well-fitting sports shoes.
- All exercise equipment will be tailored to the participant including an appropriately adjusted cycle seat height, and appropriate weights sizes.
- A warm up period precedes the exercise programme to prevent soft tissue sprains/strains and DOMS.
- A cool down period is incorporated into the exercise programme to prevent soft tissue sprains/strains and DOMS.
- Muscle stretches after the exercise programme as a warm down to prevent soft tissue sprains/strains and DOMS.
- Regular rest periods throughout the exercise programme have been incorporated to prevent: nausea, light-headedness, soft tissue sprains/strains and DOMS.
- Hydration fluids (water and isotonic drinks) will be available throughout the exercise programme to prevent dehydration resulting in nausea, light-headedness and hypotension.
- Participants may cease exercising at any time of their choice.

2.2 Additional Safety Measures

The *my-PEP* (personalised exercise programme) of the ExPO trial has been designed in accordance with UK Department of Health guidelines which recommends that all adults, including those older than 65 years, should aim to complete ≥ 150 minutes of *moderate* physical activity (e.g. brisk walking), or ≥ 75 mins of *vigorous* activity, (e.g. running) each week, or a combination of both. Nonetheless, adverse events due to exercise are possible. Therefore, the following measures are included to ensure safety in the ExPO trial.

- Recruiting patients referred for major surgery, who will have been deemed medically fit for an operation by consultant clinicians.
- Initial participant health screening assessment (to ensure there are no co-existing diseases which may be exacerbated by exercise) will be obtained prior to exercise. This includes review of the medical notes and direct interview of the participant.
- Baseline cardiopulmonary exercise testing (CPEX), which is also a diagnostic tool to identify any cardiopulmonary deficiency which may be exacerbated by exercise. This measure will be taken into account when personalising each

participants exercise plan. Any CPEX values of concern will be discussed with the clinical team.

- Exercise is tailored to each participant's perceived exertion level, which is frequently re-assessed so that they may rest or stop exercise if they feel they are over-exerting themselves.
- Oral consent to commence exercise will be obtained from the participant prior to each exercise session to ensure ongoing approval for continuation in the programme. The trial team will also re-enforce that the participant may stop exercising at any time during the exercise session should they wish.
- A short medical history will be re-taken at each exercise visit, to ensure the patient is suitable for exercise.
- A medically qualified doctor, nurse or physiotherapist will be present during all [Hos-PEP](#) sessions trained in life support with resuscitation equipment available.
- The participants will undergo baseline observations of heart rate (HR), blood pressure (BP), respiratory rate (RR), temperature and oxygen saturation monitoring before the start of the exercise session and HR and saturation during exercise to ensure that they are within acceptable limits. Exercise will be stopped should any of the observations cause concern to the health professional supervising the programme.
- The participants are informed that they may cease any or all components of exercise at any stage at their choice without prejudicing their future care.

3 DEFINITIONS

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A 'Clinical Safety Data Management: Definitions and Standards for Expedited Reporting', ICH GCP E6 and 'CT-3' (v 2011/C 172/01), to have standard definitions that are relevant to all studies (CTIMP and non-CTIMP).

3.1 Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical research participant who has been administered any research procedure, which does not necessarily have a causal relationship with the treatment or procedure. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with taking part in research procedures, whether or not related to a research procedure.

3.2 Adverse Reaction (AR)

An AR is any untoward and unintended response to a research procedure (in this trial – exercise) at least *possibly* causally related to that procedure. A causal relationship between a research procedure and an AE is at least *possibly* related, i.e. a relationship cannot be definitively ruled out.

3.3 Causality definitions

A causality assessment between the event and the research procedure will take into account the following factors:

- The existence of a temporal relationship between the event and procedure.
- The established risks of the research intervention as outlined in the protocol.

- Factors which, according to medical assessment, are responsible for the event other than the trial intervention, such as prescription of concomitant medication, natural history of oesophageal adenocarcinoma, study procedures, etc.

Causality assessment	Description	Event type
None	There is no evidence of any causal relationship.	Unrelated AE
Unlikely	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).	Unrelated AE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure and/or it follows a clinically reasonable response on withdrawal). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition).	AR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	AR
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. Re-challenge information, where applicable, demonstrates reappearance of similar reactions.	AR

3.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

For the purposes of the EXPO trial, SAEs and SARs include the following:

- I. results in death
- II. results in hospitalisation or prolonged hospital admission
- III. is life threatening ('life threatening' refers to an event in which the patient is at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- IV. results in persistent or significant disability or incapacity
- V. a congenital anomaly or birth defect or spontaneous abortion

- VI. one that is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above).

All SAEs should be reported to the sponsor within 24 hours of the CI becoming aware (during working hours) of the event. SAEs which do not require reporting include admissions or death secondary to known complications of adjuvant chemotherapy (e.g. neutropenic sepsis, symptomatic anaemia, venous thromboembolism, cardiotoxicity and diarrhoea) or due to index cancer (e.g. dysphagia or gastro-intestinal bleeding due to local tumour recurrence, ascites, metastatic disease, deep vein thrombosis or pulmonary embolism) or surgery (pneumonia, empyema, acute respiratory distress syndrome, pulmonary embolism, pleural effusion, surgical conduit dysfunction, anastomotic leak, wound infection, wound dehiscence, oesophageal stricture or pain over the surgical scar). This is not an exhaustive list, there may be other unlisted AEs related to the cancer or its treatment as judged by clinicians. These will be recorded in both the CRF and clinical notes. All SAEs that develop between randomisation to 90 days following surgery will be recorded.

3.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a SAR, the nature or severity of which is **inconsistent** with the known expected events associated with the intervention. The event is categorised as having either: *none, unlikely, possible, probable* or *definite* relationship to a trial intervention **and** is unexpected for that trial. The expectedness of an event is assessed by CI or their delegate.

4 Additional AE guidance

AEs will be reviewed during the trial and recorded in the medical notes, CRF, and if classed as serious on the SAE form and SAE database.

An adverse event is one occurring after randomisation and would include, but is not limited to:

- A change, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition.
- Any unfavourable and unintended sign, symptom, or disease temporally associated with engagement with the research procedures.
- Injury or accidents: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate medical events (e.g. for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately).
- Any deterioration in measurements of a laboratory value or other clinical test (e.g. electrocardiogram (ECG) or X-ray that is associated with least one of the following:
 - Is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.
 - Requires intervention or any other therapeutic intervention.

- Results in discontinuation of exercise or withdrawal of the participant from the trial.
- Requires additional diagnostic evaluation.

An adverse event **does not** include:

- Elective medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition was known prior to signing consent for study participation. In the latter case, the condition should be reported as part of the participant's medical history.
- Pre-existing diseases or conditions present or detected after randomisation that do not worsen.
- Situations where an untoward medical event has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions).

4.1 Notable events

Notable events are significant events that are identified by the: CI, TT or investigators based on knowledge of the characteristics of the intervention.

5 RESPONSIBILITY FOR SAFETY OF PARTICIPANTS

5.1 Trial Team (TT)

The TT is responsible for processing all SAEs and pregnancy reports in line with this Working Practice Document. The TT ensures that all safety data is dealt with appropriately and that the responsibilities of the Sponsor as set out and applicable regulations are adhered to. The CI in collaboration with the TT and TMG, will ensure appropriate safety recording and reporting procedures and subsequently during the trial where necessary. They will check that all trial documentation has the appropriate safety reporting information and guidance i.e. protocols, case report forms (CRFs) which record AEs and trial specific Working Practices, including the SAE reporting form. CRFs will be reviewed by the CI or delegate, which may identify trends in AEs. All SAEs will be reviewed by the CI or delegate, which are documented in the CRF and TMF.

5.2 Trial Management Group (TMG)

The CI takes ultimate responsibility for all safety aspects of the trial. Other members of the Trial Team (TT) will be delegated responsibility for the processing of recording and reporting (where appropriate) SAEs and AEs. These include Research Ethics Committee (REC) reports, Safety Committee (SC) and Trial Steering Committee (TSC) updates. The CI in collaboration with the TT and TMG will review procedures in order to support standardisation and consistency in SAE reporting and will ensure that safety is monitored according to Quality Control (QC) processes described in the trial specific QMMP.

5.3 Safety Committee (SC) & Trial Steering Committee (TSC)

The SC safeguards the interests of trial participants. The committee consists of two independent members who have experience with patients undergoing neoadjuvant chemotherapy and oesophagectomy. Every six months (or more frequently if required) they review all AEs, and comment on whether these are events are either: of no concern, possible concern or cause for concern. Based on the emerging safety data, they judge whether the trial should either continue or be suspended (temporarily or permanently). The SC report their findings to the TSC, CI, sponsor and TT. The TSC consists of independent members and includes clinicians in the relevant specialties, lay members and a representative of the sponsor and site R&D department. The TSC, which meets every 6 months safeguards the interests of trial participants and monitors the main safety measures, overall trial conduct and progress. The EXPOSC and TSC charters document the responsibilities and membership of these two committees. Both have open sessions with members of the TMG and closed sessions.

6 PROCEDURES FOR SAFETY RECORDING AND REPORTING

As per the approved study protocol, AEs will be recorded, and if required reported, from randomisation (start of trial procedures) until 90 days after surgery. AEs are recorded in the clinical notes, CRF and for SAEs an SAE reporting form, 'Report or Serious Adverse Event (SAE)' (see appendix 1). The information on adverse events are: description, severity, causality, seriousness and category.

6.1 SAE Reporting and clinical review

As soon as possible, and within 24 hours following notification of an SAE (during working hours), the CI or delegate is required to:

- a) Complete the 'Report or Serious Adverse Event (SAE)' form as provided in the TMF and in doing so provide sufficient information on: how the event met the regulatory definition of an SAE and details of the event.
- b) Sign and send the SAE form to the sponsor by fax or email.

The CI is required to send the SAE form even if the information is incomplete or it is obvious that more data will be needed for a complete assessment.

As this is a randomised trial, the evaluation of causality must be performed assuming that the patient is in the intervention arm. Expectedness is assessed against the expected adverse events for exercise as listed in the protocol. An event may be considered unexpected if the severity or duration of the event is not consistent with that documented in the protocol. The CI or delegate is required to send any applicable supporting documents in a timely fashion to the sponsor to ensure accurate follow-up in each case. The supporting documents may include, but are not limited to:

- a) Copies of concomitant medication/medical history,
- b) Admission/discharge summary,
- c) Clinical laboratory reports,

d) Death certificates.

Such documents will be anonymised by the CI or delegate in terms of patient information and will be coded with the SAE number, initials, and date of birth, gender and site.

Documents can be scanned and sent electronically.

If a member of the TT has a question regarding safety reporting they should contact the EXPO Trial Team co-ordinator by telephone (0757 830 1811) or by e-mail (expo@nnuh.nhs.uk), or the CI by telephone 01603 593611, email (a.hart@uea.ac.uk), or fax 01603 593752. For SAEs, the patient must be followed up until clinical recovery is complete and laboratory results have normalised, or clinical agreement is reached to close the event.

6.2 Immediate clinical review

SUSARs will require immediate clinical review by the CI or suitable delegate. If an investigator reports a SUSAR and the CI or delegate is unavailable to perform the immediate review within the required timeline for reporting, the TT should request senior support from a member of the TMG and report the SUSAR to the Research Ethics Committee (REC), R+D departments and sponsor. The trial specific clinical review should take place as soon as possible and any necessary follow-up submitted.

6.3 Follow-up of SAEs

The CI or delegate is responsible for ensuring all reportable SAEs are followed until resolution. SAEs will be considered medically closed when the SAE has resolved or stabilised, all fields on the SAE report are appropriately completed, and relevant anonymised supporting documentation (hospital discharge summary, death certificate, autopsy report, etc) are obtained. Where the CI or delegate is certain there will be no more information available on an SAE, the sponsor should be informed and the event closed on the SAE log, following CI/TMG approval. If the CI and/or TMG agree to close an unresolved SAE, the reasons should be clearly documented on the log and in the minutes of the meeting where the event was discussed.

6.4 Causality assessment

The causality assessment should be initially performed by the CI or their clinical delegate. If there is no delegated clinician available to sign the form, the event should be reported and signed by another member of the site TT, but procedures must be in place for review by a delegated clinician as soon as possible. The clinician's assessment, and any follow-up information, should be faxed or e-mailed to CI (fax number: 01603 593752, email: a.hart@uea.ac.uk). There should be documented evidence that the event has been assessed by a medical doctor with a counter signature of the SAE form. The assessment at the time cannot be subsequently overruled by the CI. In the case of disagreement between the person reporting the incident and CI, both opinions will be provided in reports to the REC. Documentation of relevant discussions should be made and filed. If a difference in opinion on causality results in the need for an expedited report (i.e. the event is deemed a SUSAR by one of the clinical reviewers), the clinical reviewer's comments should be included on the cover sheet and it should be sent to all parties who need to receive the SUSAR report. The timelines for expedited reporting begin from the date the clinical reviewer identified the event as a SUSAR. The TT or delegate should ensure that

only medically qualified staff are delegated for causality assessment on the trial's delegation of responsibilities log.

6.5 Expectedness

The events against which expectedness is judged is stated in the EXPO protocol (see section 7.7). The CI must confirm the expectedness as part of the SAE processing procedure trial. Appropriate documentation of discussions and decisions should be made and filed. Where decisions are made that result in modifications on the SAE form, these should be initialled and dated. Where agreement is reached that a SSAR should be reclassified as a SUSAR, the event should be reported to the appropriate REC within the expedited timelines. The timelines for expedited reporting begin from the date the event is first classified as a SUSAR.

6.6 SAE report sign off

The TT will record the SAE form has been reviewed by the CI or his delegate.

6.7 Safety data entry

Data from paper SAE reports will be entered (including severity, causality and type) on the e-CRF database and also in the trial specific SAE log and stored in the TMF.

6.8 Reporting of SUSARS to the REC within 15 days

The CI has responsibility for the reporting of SUSARs to the REC within 15 days of becoming aware of the event using the 'Report of Serious Adverse Event (SAE)' form for non-CTIMPs as published on the HRA website (appendix 1). The intervention allocation will be unblinded and if allocation reveals active intervention the SUSAR will be reported. The same form will also be used for reporting to the sponsor, TSC and SC.

Documentation of submission/ receipt of SUSAR submissions should be filed in the TMF.

6.9 Other expedited reporting

Any finding considered significant and reportable by the SC or TSC should also be evaluated for reporting to appropriate REC and sponsor.

6.10 Follow-up SUSAR reports

If additional information is received after the initial SUSAR report has been submitted, a follow-up SUSAR report must be submitted to all those in receipt of the initial report.

6.11 Unblinding of intervention for SUSAR reporting

Local clinicians may make a request for unblinding to the CI or member of the TT. During working hours all requests for unblinding should be discussed with the CI or their delegate. Unblinding, including out of hours can be performed by the trial co-ordinator, who is unblinded and has access to the allocation data. Alternatively, in the event an SAE reported to CI is subsequently determined to be a SUSAR and where unblinding has not already been performed, the CI can perform unblinding. In the event of a SUSAR the CI must ensure that all exercise activities have stopped. Wherever possible, members of the TT (including the CI) and clinical team will be kept blinded to the status of the participant.

All SUSARs will be unblinded before expedited reporting. Participants carry an ExPO trial card, which gives the phone number that clinicians may contact the CI or TT on.

6.18 Internal safety reporting and review

6.18.1 Trial Team and Trial Management Group reporting and review

SAEs, SSARs and SUSARs arising will be reviewed and documented at the TMG, SC and TSC meetings. The TT and TMG will monitor safety data for any events considered to be caused by trial related procedures. In the event that any trial procedures appear to be resulting in adverse events, the CI/TMG must be contacted immediately for their opinion on whether it is necessary to implement any urgent safety measures and whether the conduct of the trial should be reviewed.

The TT & TMG will monitor safety data for an increase in the incidence or severity of AEs with direct consideration of the frequency of AEs considered rare or very rare. Should this be detected, a report compiled by the TMG and CI detailing the findings must be submitted to the REC and sponsor. The CI and TMG must agree the content of the report before submission.

6.18.2 SC reporting and review

The SC meetings will be held every 6 months during the trial, but more frequently if required. Their purpose and the reporting procedures are described in the EXPO safety committee charter. The SC report is submitted to the TSC & TMG.

6.18.3 Coding of events

Events that are reported in a trial will be recorded in the eCRF which will automatically assign an AE number.

6.18.4 Other considerations

The Quality Management and Monitoring Plan (QMMP) documents that safety is monitored through TT real time review of data. A monitoring report is also produced and reviewed every 3 months. This information is: completion of all inclusion & exclusion criteria, respiratory laboratory results as entered in the eCRF, exercise progression and review of submitted SAE forms. All AE data is reviewed by the CI with safety reports compiled and presented to the SC and TSC every 6 months. On-site monitoring will not be routinely performed, however, if there are concerns regarding safety this can be instituted.

6.19 Pregnancies

Oesophageal adenocarcinoma is uncommon in women of child-bearing age. In the extremely unlikely event of a participant becoming pregnant during the trial this will be recorded and reported to the sponsor within 24 hours. The participant will be eligible to continue in the trial should they so wish, but she will be monitored more closely. Pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and will be followed as such. A spontaneous abortion is always considered to be an SAE.

If the outcome of the pregnancy involves any of the following, an SAE report should be submitted and causality and expectedness assessed as for other SAEs:

- Congenital anomaly(ies) or birth defect in the fetus/neonate
- Fetal death or spontaneous abortion
- Any SAE occurring in the neonate.

6.20 Urgent safety measures

At any time throughout the duration of the trial, it may be decided by the CI/TMG/TT/SC or TSC to apply appropriate urgent safety measures in order to protect trial participants against any immediate hazard to their health and safety.

6.21 Serious Breaches

A serious breach is defined as a breach of the conditions and principles of good clinical practice, or the trial protocol, that is likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial.

6.22 NHS incident reporting systems

Regardless of sponsorship, adverse events affecting NHS trust patients must also be reported to the Trust's clinical risk systems. The CI will take responsibility for this.

6.23 Out of hours cover

Patients will be provided with the PIL and a trial card which contain the contact details for members of the TT. Participants may alternatively ring the hospital switchboards and ask to speak to a member of the ExPO trial team. The TT has the contact number of the CI or his delegate. Participants are also informed of other sources of medical information including their general practitioner, specialist and the accident and emergency department.

6.24 References and sources of information

WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, available from: <http://www.wma.net/en/30publications/10policies/b3/>, accessed 17th August 2016.

Safety Report Form (Non-CTIMPs), available from: www.hra.nhs.uk/documents/2015/02/safety-report-form-non-ctimp.docx, accessed 17th August 2016.

Safety and Progress Reports Table (non-CTIMPs) for UK health departments' RES version 2.1 05.06.2015, available from: <http://www.hra.nhs.uk/documents/2015/06/safety-progress-reports-procedural-table-non-ctimps.pdf>, accessed 17th August 2016.

Standard Operating Procedures (SOPs) for Research Ethics Committees Version 6.1, available from: <http://www.hra.nhs.uk/resources/research-legislation-and-governance/standard-operating-procedures/#sthash.KNjc7JfA.dpuf>, accessed on 17th August 2016.

Appendix 5. Study protocol (The association between preoperative cardiopulmonary exercise test variables and short-term morbidity following oesophagectomy: a hospital-based cohort study)



The association between pre-operative cardiopulmonary exercise test variables and short-term post-operative morbidity following oesophagectomy. A hospital-based cohort study

PROTOCOL VERSION NUMBER AND DATE

Version 1.0 28th June 2017

IRAS Project ID: 222793

Protocol registration: ClinicalTrials.gov (NCT03216694)

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Gastroenterology Research Fund.

Study Summary

Study Title	The association between pre-operative cardiopulmonary exercise test variables and short-term post-operative morbidity following oesophagectomy. A hospital-based cohort study.	
Short title	CPEX prior to oesophagectomy to predict complications	
Trial Design	Single centre, retrospective cohort study	
Study Setting	Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH).	
Study Participants	All patients who underwent both oesophagectomy and pre-operative CPEX testing between the dates September 2011 to February 2017 at the NNUH.	
Planned Sample Size	254	
Aims		Primary Outcome Measures
To determine if the pre-operative CPEX testing variables (VO_{2peak} and AT) can predict the risk of early post-operative complications following oesophagectomy.		30 day complications as defined by ECCG and graded as per Clavien-Dindo.
		Secondary Outcome Measures
To determine if the pre-operative CPEX testing variables (VO_{2peak} and AT) can predict the risk of early post-operative mortality following oesophagectomy.		Post-operative mortality rates at 30 and 90 days.

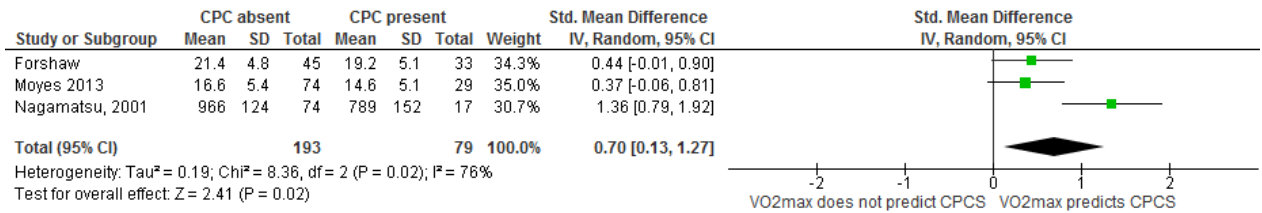
Background Rationale

In the western world, the incidence of oesophageal adenocarcinoma (OAC) has increased by at least 6-fold in the last 30 years¹ with surgery as the only consistent treatment modality that offers a potential cure.² However, oesophageal cancer resection and reconstruction (oesophagectomy) carries a high risk of post-operative complications. Recent UK national audit figures reported that 33% of patients suffered a complication after oesophagectomy, most of which (74%) were cardiopulmonary (52% respiratory and 22% cardiac).³ An accurate and objective clinical risk tool to predict patients at higher risk of CPCs post-oesophagectomy could allow better perioperative management to improve outcomes.

The surgical stress response in the early post-operative period results in metabolic catabolism, with a large increase in oxygen consumption.⁴ Early post-operative bed-rest and incisional pain inhibits normal respiratory function, promoting shallow breathing, atelectasis and infective consolidation.⁵ These physiological challenges are in part met by a patients' cardiopulmonary reserves, or their ability to increase cardiac output and ventilation to meet increased demand. Such reserves are likely to be greater in physiologically 'fitter' patients. By measuring a patient's cardiopulmonary reserve, or functional capacity, we may theoretically be able to discriminate those that may or may not best tolerate the physiological insult associated with oesophagectomy.

CPEX is a fitness 'stress test', whereby a patient exercises, usually on a static bicycle, in laboratory conditions, allowing an objective, qualitative and composite measure of their overall physiological fitness. Pedal resistance or workload is systematically increased until the patient can no longer continue, ideally, due to exhaustion. Two important CPEX variables are captured by analysis of gas exchange at the mouth, VO_{2max} (the maximal oxygen consumed at the peak of exercise) and VO_2 at estimated anaerobic threshold (AT). Both parameters have shown great promise in observational studies to predict both morbidity and mortality.⁶⁻¹² In a study of 187 elderly patients undergoing major abdominal surgery, a pre-operative AT cut-off of 11ml/kg/min had a sensitivity of 91% and specificity of 74% for predicting mortality.⁶ In a multi-centre study of 346 patients undergoing thoracotomy a VO_{2max} cut-off of 16ml/kg/min predicted patients more likely to suffer a complication ($p=0.0001$).¹³ Unfortunately, no such threshold values have been reported specifically for oesophagectomy surgery. To the best of our knowledge, there have been 3 relatively small observational studies, which although reported inverse associations between VO_{2max} , AT and CPCs, were unable to estimate clinically useful cut-off values to predict morbidity or mortality.⁹⁻¹¹ Differences in both the definition of outcome variables and patient populations makes pooling of the data from these individual studies problematic due to such inconsistencies. This is reflected in the statistical heterogeneity of any such attempted meta-analysis as in figure 1 below (chi-squared test, $p=0.02$, $I^2 = 76\%$).

Figure 1.0. Forest plot comparing the mean VO_{2max} of patients with and without cardiopulmonary complications.



The aim of this study is to examine the correlations between pre-operative CPEX variables and post-operative complications in a sample large enough to allow (should significant associations exist) calculation of a threshold value. Such a cut-off value may have important clinical application in risk stratification of patients prior to oesophagectomy to inform perioperative care.

Study Design

A single centre, retrospective cohort study.

Study Setting

This study will be conducted in the Department of Upper Gastrointestinal (UGI) Surgery at the Norfolk and Norwich University Hospitals (NNUH) Foundation Trust. The NNUH is a 1,000 bed teaching hospital, which provides care to a population of approximately 825,000 residents in Norfolk and the adjacent counties. Approximately 45 oesophagectomies are performed in this unit each year.

Eligibility Criteria

Inclusion criteria

- v. Male and female
- vi. Underwent an oesophagectomy
- vii. Completed a pre-operative CPEX test

Exclusion Criteria

- v. Patients that were unable to complete a full CPEX test

Patient Identification

This study will identify patients using the Operating Room Scheduling Office System (ORSOS) database at the NNUH. ORSOS is a surgical scheduling system, which allows contemporaneous data capture before, during and after an operation. ORSOS can be used to generate a list of all oesophagectomies undertaken at the NNUH over a defined time period, namely 1st September 2011 to present. The start date is when CPEX testing was introduced prior to oesophagectomy at the NNUH. ORSOS data includes patient details (name, hospital number, date of birth, sex) as well as an aesthetic data (ASA, type of anaesthesia) and details of the surgery (the operating surgeon and assistants, duration of procedure, number of procedures). This study will also obtain data from 1) CPEX laboratory software for each patient that underwent a CPEX at the NNUH and 2) co-

morbidity and post-operative complication data, obtained by a hand review of the hospital notes (blinded to CPEX data).

Outcome Measures

30-day complications

Post-operative complications (CPCs) will be defined, according to the '*Complications Basic Platform*' defined by the Oesophagectomy Complications Consensus Group (ECCG).¹⁴ The ECCG is comprised of 21 oesophageal surgeons working in high patient volume units from 14 countries, supported by all the major thoracic and UGI societies, who agreed on a standardised list for reporting oesophagectomy complications to improve the generalisability of outcome reporting in clinical studies. The potential post-oesophagectomy CPCs are listed below:

Pulmonary

- Pneumonia (Definition: American Thoracic Society and Infectious Diseases Society of America)^{15 16}
- Pleural effusion requiring additional drainage procedure
- Pneumothorax requiring treatment
- Atelectasis mucous plugging requiring bronchoscopy
- Respiratory failure requiring reintubation
- Acute respiratory distress syndrome (Berlin Definition)¹⁷
- Acute aspiration
- Tracheobronchial injury
- Chest tube maintenance for air leak for >10 days postoperatively

Cardiac

- Cardiac arrest requiring CPR
- Myocardial infarction (Definition: World Health Organization)¹⁸
- Dysrhythmia (atrial) requiring treatment
- Dysrhythmia (ventricular) requiring treatment
- Congestive heart failure requiring treatment
- Pericarditis requiring treatment

Gastrointestinal

- Esophagoenteric leak from anastomosis, staple line, or localized conduit necrosis.
- Conduit necrosis/failure
- Ileus defined as small bowel dysfunction preventing or delaying enteral feeding
- Small bowel obstruction
- Feeding J-tube complication
- Pyloromyotomy/pyloroplasty complication
- Clostridium difficile Infection
- Gastrointestinal bleeding requiring intervention or transfusion
- Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7 d postoperatively
- Pancreatitis
- Liver dysfunction

Urological

- Acute renal insufficiency (defined as doubling of baseline creatinine)
- Acute renal failure requiring dialysis
- Urinary tract infection
- Urinary retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter

Thromboembolic

- Deep venous thrombosis
- Pulmonary embolus
- Stroke (CVA)
- Peripheral thrombophlebitis
- Neurologic/psychiatric
- Recurrent nerve injury.
- Other neurologic injury
- Acute delirium (Definition: Diagnostic and Statistical Manual of Mental Disorders, 5th ed) ¹⁹
- Delirium tremens

Infection

- Wound infection requiring opening wound or antibiotics
- Central IV line infection requiring removal or antibiotics
- Intrathoracic/intra-abdominal abscess
- Generalized sepsis (Definition: CDC) ²⁰
- Other infections requiring antibiotics

Wound/diaphragm

- Thoracic wound dehiscence
- Acute abdominal wall dehiscence/hernia
- Acute diaphragmatic hernia

Other

- Chyle leak.
- Reoperation for reasons other than bleeding, anastomotic leak, or conduit necrosis
- Multiple organ dysfunction syndrome (Definition: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee)²¹

The severity of the complication will be classified according to the Clavien-Dindo grading system from 1 to 5 (table 1). For the purpose of this study only grade 2 complications and above will be recorded and included in the analysis. CPCs will be analysed as the number of participants with a complication. The most serious event will be counted as a complication in each case.

Mortality

Death from any cause within 30 and 90 days of surgery.

Length of Stay

Number of days in hospital after the date of surgery, with the day of surgery counted as day zero.

Table 1. Clavien-Dindo Classification of Surgical Complications

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Surgical, endoscopic, or radiological intervention that is not under general anesthesia
Grade IIIb	Surgical, endoscopic, or radiological intervention that is under general anesthesia
Grade IVa	Life-threatening complication requiring intermediate care or intensive care unit management, single organ dysfunction (including dialysis, brain hemorrhage, ischemic stroke, and subarachnoidal bleeding)
Grade IVb	Life-threatening complication requiring intermediate care or intensive care unit management, multi-organ dysfunction (including dialysis)
Grade V	Death of a patient

DATA ANALYSIS

The following variables will be captured for each patient.

- Age (continuous variable)
- Gender (binary variable)
- BMI (continuous variable)
- ASA grade (categorical variable as per the grading system)
- Smoking status (categorical variable: never, former, current)
- Co-morbidities (categorical variable according to the Charleston comorbidity weighted index)
- TNM (categorical variable as per the classification system)
- Histology (categorical variable)
- Surgical approach (categorical variable as per the operation, e.g. 3 stage McKeown, 2 stage Ivor Lewis, Minimally invasive 2 stage Ivor Lewis.
- Duration of surgery (continuous variable)
- Use of neoadjuvant chemotherapy (binary variable)

- VO_{2max} (continuous variable)
- AT (continuous variable)
- Post-operative complications (binary variable)
- Length of stay (continuous variable)
- Post-operative mortality (binary variable)

Data analysis may require categorisation of a continuous variable to provide clinically useful thresholds.

Patients with and without surgical complications will be grouped. For categorical variables, the numbers and percentages will be presented and for continuous variables the means (and standard deviation) or medians (and interquartile range) depending on their distributions. Differences between the groups will be compared using the most appropriate statistical test. Categorical data will be compared using chi-squared tests. Continuous data will be compared using the students' t-test and the Mann-Whitney U test will be used as appropriate. In the main analysis postoperative complications will be treated as a binary variable, logistical regression models will estimate associations between both VO_{2max} and AT and CPCs and non-CPCs within each Clavien-Dindo category, with confidence intervals and p values of significance at $p < 0.05$. Length of hospital stay will be treated as a continuous variable and correlation coefficients will be calculated for association with CPEX variables.

Derivation and Validation

Depending on the strength of the associations the dataset may be divided into two parts to construct a derivation cohort, which will consist of the first 2/3 of consecutive patients (based on date); and a validation cohort, which will consist of the later 1/3 of consecutive patients. Discrimination performance of VO_{2max} , VO_{2max} percentage predicted and AT may then be assessed using the area under the receiver operating curve (AUC) or C-index. A C-index below 0.70 would indicate poor discrimination, 0.70 to 0.80 average discrimination and values above 0.80 good discrimination. The Hosmer-Lemeshow goodness-of-fit-model will be used to test calibration, or the degree of agreement between the observed and expected values with a p value < 0.05 indicating lack of fit.

The Number of Participants

The study will include 254 patients, a sample which is inclusive of all oesophagectomies undertaken at the NNUH where pre-operative CPEX testing was used.

DATA MANAGEMENT

Data Recording and Record Keeping

A study Microsoft Access database will be designed for the purpose of this study. This database will be password protected and stored on a computer drive which is access restricted and stored on an NHS computer, which is itself password protected. Pseudo-anonymised data will be transferred to this database and each patient will be assigned a study number.

ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki (seventh revision October 2013).

Regulations

The investigators will ensure that this study is conducted in full conformity with GCP guidelines, the Sponsor's SOPs, and other regulatory requirements.

Approvals

The protocol will be submitted to an appropriate Research Ethics Committee (REC), and relevant R&D department for written approval. The investigators will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Reporting

The investigators shall submit on request a report to the REC, host organisation and Sponsor.

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a study number on an electronic database. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Conflict of interest

The investigators declare no conflict of interest

FINANCE AND INSURANCE

Funding

Partial funding for the study is from charitable funds (Oesophageal Cancer Research Fund, NNUH and a Norfolk and Norwich University Hospital Medical Gastroenterology Research Fund).

Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees.

PUBLICATION POLICY

The results of the study will be reported at relevant conferences and published in peer-reviewed medical journals. Acknowledgement will be given to all participants. Ownership of the data arising from the study resides with the study team.

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