The role of physical activity for recovery after surgical procedures

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To Anna for patiently listening to my harping about scientific issues and to Rut, Märta, and Sixten for turning my thoughts to more important matters.

The role of physical activity for recovery after surgical procedures

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ABSTRACT

The aim of this thesis was to determine the association between and effect of preoperative physical activity and postoperative recovery after surgery due to gallbladder disease or colorectal cancer.

Paper I examined the association between self-reported level of physical activity before cholecystectomy and postoperative recovery in an observational cohort study. Participants with regular physical activity had lower risk for prolonged sick leave compared to participants who were inactive. Papers II and III determined the association between self-reported level of physical activity before colorectal cancer surgery and recovery in an observational cohort study. Habitual physical activity was not associated with the primary outcome measure, length of hospital stay, but an association was found between higher levels of physical activity and improvements in physical recovery three weeks postoperatively and reduced risk for postoperative complications. Paper IV describes the design of a randomised controlled trial with a pragmatic short-term physical activity intervention before and after colorectal cancer surgery, aimed to improve self-assessed physical recovery four weeks postoperatively as well as several secondary outcome measures of postoperative recovery. Paper V reports the main results from this randomised controlled trial, where the intervention had no effect on any of the primary or secondary short-term outcome measures in the study. The results from the works included in this thesis imply that habitual physical activity is associated with faster postoperative recovery after cholecystectomy and colorectal cancer surgery, but that postoperative recovery cannot be improved by a short-term physical activity intervention.

Keywords: physical activity, surgery, colorectal cancer

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SAMMANFATTNING PÅ SVENSKA

Syftet med denna avhandling var att besvara frågan om vilken roll fysisk aktivitet inför kirurgi spelar för återhämtningen efter kirurgi för gallstenssjukdom eller tjock- och ändtarmscancer. Detta analyserades först i två observationella kohortstudier som genomfördes på dels patienter som var planerade för operation för gallvägssjukdom (n=200) och dels patienter som var planerade att genomgå kirurgi för tjock- eller ändtarmscancer (n=115). I dessa studier fick patienterna inför operation svara på ett antal frågor, bland annat om sin fysiska aktivitetsnivå på fritiden och om ett antal störfaktorer (confounders). Efter operationen fick deltagarna svara på hur pass väl återhämtade de kände sig och om de hade varit sjukskrivna, medan information om vårdtid, reoperationer, återinläggningar samt postoperativa komplikationer (endast tjock- och ändtarmscancer) uthämtades från hälso- och sjukvårdssystem. En randomiserad kontrollerad studie genomfördes sedan där 761 patienter som var planerade för operation för tjock- eller ändtarmscancer lottades till antingen ett program med fysisk aktivitet före och efter operationen eller rutinvård. Patienterna fick efter operationen svara på samma frågor angående återhämtning, och information om postoperativa komplikationer, vårdtid, reoperationer och återinläggningar uthämtades från hälso- och sjukvårdssystem.

Resultaten visade att habituell fysisk aktivitet inför operation för gallvägssjukdom var kopplat till lägre risk för lång sjukskrivning, kortare vårdtid, samt bättre chans att känna sig psykiskt återhämtad 3 veckor efter operationen. Habituell fysisk aktivitet inför operation för tjock- eller ändtarmscancer var inte kopplat till kortare vårdtid, men däremot till bättre chans att känna sig fysiskt återhämtad 3 veckor efter operationen och till en lägre risk för postoperativa komplikationer. En intervention med fysisk aktivitet inför planerad kirurgi för tjock- eller ändtarmscancer hade ingen effekt på upplevd fysisk återhämtning, eller på postoperativa komplikationer, vårdtid, reoperationer eller återinläggningar.

Studierna i denna avhandling visade att fysisk aktivitetsnivå när en individ får veta att han/hon ska genomgå operation för gallvägssjukdom eller tjock- eller ändtarmscancer var kopplat till bättre postoperativ återhämtning. Den randomiserade kontrollerade studien visade dock att detta inte nödvändigtvis gick att översätta till att patienter skall börja träna när de får sin diagnos, utan att det snarare är viktigt att etablera hälsosamma levnadsvanor hos hela befolkningen, av vilka en andel sedermera utvecklar dessa sjukdomar.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Onerup A, Angeras U, Bock D, Borjesson M, Fagevik Olsen M, Gellerstedt M, et al. The preoperative level of physical activity is associated to the postoperative recovery after elective cholecystectomy - A cohort study. International journal of surgery. 2015;19:35-41.

II. Onerup A, Bock D, Borjesson M, Fagevik Olsen M, Gellerstedt M, Haglind E, et al. Is preoperative physical activity related to post-surgery recovery? -a cohort study of colorectal cancer patients. Int J Colorectal Dis. 2016;31(6):1131-40.

III. Onerup A, Angenete E, Bonfre P, Borjesson M, Haglind E, Wessman C, et al. Self-assessed preoperative level of habitual physical activity predicted postoperative complications after colorectal cancer surgery: A prospective observational cohort study. Eur J Surg Oncol. 2019;45(11):2045-51.

IV. Onerup A, Angenete E, Bock D, Borjesson M, Fagevik Olsen M, Gryback Gillheimer E, et al. The effect of pre- and post-operative physical activity on recovery after colorectal cancer surgery (PHYSSURG-C): study protocol for a randomised controlled trial. Trials. 2017;18(1):212.

V. Onerup A, Andersson J, Angenete E, Bock D, Börjesson M, Ehrencrona C, Fagevik Olsén M, Larsson P-A, de la Croix H, Wedin A, Haglind E. Effect of short-term homebased pre- and postoperative exercise on recovery after colorectal cancer surgery (PHYSSURG-C): A randomized clinical trial. Manuscript.

CONTENT

ABBREVIATIONS

CI	Confidence interval
DAG	Directed acyclic graph
ERAS	Enhanced recovery after surgery
IPAQ	International physical activity questionnaire
MET	Metabolic equivalent
OR	Odds ratio
PAP	Physical activity on prescription
RCT	Randomised controlled trial
RR	Relative risk
WHO	World Health Organization

DEFINITIONS IN SHORT

Exercise	A subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective (WHO 2020)
Physical activity	Any bodily movement produced by skeletal muscles that require energy expenditure (WHO 2020)
Physical inactivity	An insufficient physical activity level to meet present physical activity recommendations (WHO 2020)
Postoperative complication	Any deviation from the normal postoperative course (Dindo et al. 2004)

1 INTRODUCTION

1.1 PHYSICAL ACTIVITY AND HEALTH

Physical activity has several positive health effects, and the World Health Organization (WHO) has declared physical inactivity the fourth leading risk factor for global mortality.[1 2] Physical inactivity increases the risk for major non-communicable diseases such as coronary heart disease and type 2 diabetes but also breast and colon cancer, as well as mental health issues.[3] It has been estimated that physical inactivity leads to costs of more than $50 billion for healthcare systems annually.[4] Physical inactivity may refer to both lack of physical activity and sedentary time, which has been proposed as an independent risk factor for unfavourable health outcomes. In this thesis physical inactivity refers to inadequate levels of physical activity.

Due to its known health benefits, it is of priority to increase physical activity in the general population. One way of achieving this is by societal initiatives, for example by establishing well-functioning bicycle lanes and economic subsidies for physical activity. Another way is healthcare-initiated physical activity. In Sweden there is a model for prescribing physical activity, Physical Activity on Prescription (PAP), which is under implementation by several other countries in the European Union. The PAP model is based on three core elements: 1. Patient-centred dialogue. 2. Individually tailored physical activity recommendation with written prescription, and 3. Follow-up.[5] There is moderate scientific evidence that this model increases level of physical activity.[6] The book FYSS presents evidence for preventing[7] and treating common conditions, such as hypertension[8] and diabetes mellitus,[9] with physical activity, and is easily available as a support for prescribers of PAP.

1.2 DISEASES INCLUDED IN THIS THESIS

The papers included in this thesis report results from studies in patients with gallstone disease (paper I) or colorectal cancer (papers II-V). There are similarities between these diseases; Both are treated curatively with abdominal surgery, operations for both diseases are relatively common, and both diseases are more common in physically inactive individuals.[3 10 11] However, there are also some important differences. Gallstone disease is a benign disease, while colorectal cancer is a malign disease. This has implications for both acceptable waiting times from diagnosis to surgery and for concurrent medications. Another difference is in terms of surgical trauma. While elective cholecystectomies may be performed as day surgery, colorectal cancer surgery is a major surgical trauma.

1.2.1 Gallstone disease

Gallstone disease occurs due to the development of gallstones in the gallbladder. Obesity and rapid weight loss are risk factors for gallstone disease, and physical activity has been associated with reduced risk for developing symptomatic gallstone disease in both men and women.[10 11] Surgery due to gallstone disease can be performed both as emergency surgery due to cholecystitis, and as elective surgery due to recurrent pain episodes or previous cholecystitis. In Sweden, ≈14 000 cholecystectomies were performed in 2019, of which ≈8 000 were elective.[12] 97% of these were performed with laparoscopic surgery, which leads to faster recovery.[12] Elective cholecystectomies are often performed in specialised outpatient surgery clinics. The rate of postoperative complications after elective cholecystectomies was <5% in 2019.[12]

1.2.2 Colorectal cancer

Colon cancer is the fourth and rectal cancer the ninth most common cancers in Sweden.[13] Colorectal cancers occur on the basis of a combination of genetic and environmental factors, where some of these may be modifiable. The risk for developing colon cancer has been associated with physical inactivity,[3] and it has been estimated that modifiable risk factors (obesity, diet, physical inactivity, alcohol consumption, and smoking) contribute to ≈70% of colon cancers in middle-aged US men.[14] The curative treatment for colorectal cancer consists of surgery, sometimes with chemotherapy and/or radiotherapy before or after surgery. Approximately 3 100 colon and 1 200 rectal cancer patients underwent elective surgery in Sweden in 2019.[15 16] Colorectal cancer surgery is burdened by a high risk for postoperative complications. The exact rate of postoperative complications depends on how these are defined. According to the Swedish Colorectal Cancer Registry, 26% of patients operated electively for colon and 38% of patients operated electively for rectal cancers suffered from postoperative complications ≤30 days postoperatively.[15 16]

1.3 RECOVERY AFTER SURGERY

Postoperative recovery may be defined and assessed in several ways, depending on the perspective. One perspective is the patient's perspective, where quality of life and activities of daily life are examples of commonly used outcome measures. Another perspective is by healthcare or societal costs, where recovery can be measured by for example length of hospital stay, consumption of intensive care, rate of reoperations, or return to work. All these measures affect each other, for example a patient who suffers an anastomotic leak requiring prolonged hospital stay and several reoperations is likely to have a negatively affected quality of life and is less likely to be able to perform activities of daily life. On the other hand, none of these aspects can represent the full panorama of postoperative recovery on its own. Some measures apply to all participants, such as quality of life, self-assessed recovery, and length of hospital stay, while for example return to work only applies to participants of occupational age. No matter the aspect, patients operated for colorectal cancer suffer a high risk for prolonged recovery, while patients undergoing elective cholecystectomies are of a considerably lesser risk.

Due to the fact that enhanced recovery lies in the interest of both patients and healthcare providers, several aspects of the pre- and perioperative care have been scrutinized in order to find possible improvements. For colorectal cancer surgery, and several other types of surgeries, these interventions have been combined within the Enhanced Recovery After Surgery (ERAS) concept.[17]

1.4 ASSESSING PHYSICAL ACTIVITY

Physical activity may be assessed in several ways, and methods for assessing physical activity should be in line with the intended use of the results. The two main types of assessments are self-reported and sensor-based assessment of physical activity.

Sensor-based assessment of physical activity is more exact and is appropriate when the aim is to define exact levels of physical activity. This was previously done with pedometers where steps taken for defined time period were measured. An advantage with pedometers is that it is usually possible for the individual to see their daily step count, which may serve as motivation. In research on physical activity, pedometers have generally been replaced by more advanced measurements with accelerometers, where physical activity of varying intensity is registered. Measurements with accelerometers are usually performed during several days where for example four days are included in the statistical analysis.[18] While accelerometers are generally affordable, measurements are time consuming. This may be a problem in situations where time is limited.

There are several instruments for self-reported assessments of level of physical activity. The choice of instrument depends on the intended use of the results. If the intention is to make a detailed description of the level of physical activity in a setting where time constraints do not allow for accelerometry, this may be done with instruments where participants report their time spent in different intensity levels of physical activity. One widely used instrument is the international physical activity questionnaire (IPAQ),[19] which is available in both a short and long form. In IPAQ, participants report the time spent in walking, moderate intensity, and vigorous intensity physical activity in a typical week. This allows for calculation of metabolic equivalents (MET) as a continuous score, or for categorization into three levels of physical activity. The intended use of IPAQ is to monitor physical activity in a population, while IPAQ is not recommended for measuring changes in an individual. The number of questions combined with rules for classifying answers also make it hard to use in clinical practice. For use in clinical practice, there have been several instruments with similar design, where individuals are asked to rank their leisure time level of physical activity on a three to five grade scale. One of these is the Saltin-Grimby Physical Activity Level Scale, originally designed in 1968, consisting of a four grade scale.[20] This has been found to predict morbidity and mortality.[21]

1.5 HABITUAL PHYSICAL ACTIVITY AND RECOVERY AFTER SURGERY

Physical activity increases functional capacity, and these two factors are intimately linked. However, poor functional capacity may be explained by for example anaemia caused by colorectal cancer, while a high functional capacity is hard to achieve without performing physical activity. It is therefore of interest to distinguish the difference between studies assessing level of physical activity and functional capacity, and their association to postoperative recovery.

Before we started the observational studies in this thesis, few previous studies had investigated the association between level of physical activity and recovery after colorectal cancer surgery, and there were no reports on the association between level of physical activity and recovery after cholecystectomy. One observational study had determined the association between both self-reported physical activity and functional capacity, measured as both handgrip strength, leg power, and inspiratory muscle strength, and postoperative recovery in 169 major abdominal cancer surgery patients.[22] They reported that self-assessed level of physical activity and inspiratory muscle strength predicted a shorter hospital stay, while factors such as handgrip strength, age and heart disease did not. There were also some reports on the association between prediagnostic levels of physical activity and mortality. One study reported an association between baseline level of physical activity and survival after colorectal cancer in a large cohort study.[23] However, since the time between assessment of physical activity and the colorectal cancer diagnosis was up to 12 years, this information is hard to use in clinical practice. A report from the Nurses' Health Study investigated the association between self-reported level of physical activity before and after a colorectal cancer diagnosis and mortality.[24] Since this study included biennial questionnaires, the median time from assessment of physical activity and colorectal cancer diagnosis was six months. They reported no association between prediagnostic level of physical activity and mortality, but between post treatment level of activity and mortality. The same authors performed a parallel study in a parallel study on a male-only cohort with similar results.[25]

Functional capacity, also referred to as fitness, can be assessed in several ways, both by direct measures, such as cardiopulmonary exercise testing, and by self-reported functional capacity. While direct measures may be more exact for physiologic interpretations of the associations, self-assessments are generally easier and cheaper to perform and allow for use in clinical risk predictions.

There is more evidence for functional capacity than for level of physical activity for predicting postoperative recovery after abdominal surgery. This is true for functional capacity assessed by both direct and self-reported measures. Snowden et al. reported results from a study where they aimed to investigate the relationship between age and fitness, and the association to postoperative mortality and morbidity after major hepatobiliary surgery (n=389).[26] They performed cardiorespiratory exercise testing preoperatively and reported that the increased mortality in patients >75 years old was explained by lower fitness, and that this association disappeared in a multivariate model, where fitness defined as anaerobic threshold was the most significant independent predictor for postoperative mortality. An example of a study using self-reported functional capacity is a study in 600 patients undergoing major noncardiac surgery.[27] Participants were asked to estimate the number of blocks and flights of stairs they could walk without experiencing symptomatic limitation. The results showed that participants classified as having poor exercise tolerance experienced roughly twice as many cardiovascular, neurologic, and total serious complications as participants with good exercise tolerance. For colorectal cancer surgery, preoperative functional capacity has been reported to be associated with both postoperative morbidity[28] and mortality.[29]

1.6 PREOPERATIVE LIFESTYLE INTERVENTIONS

As described above, lifestyle habits have been associated with prolonged postoperative recovery. Thus, a theoretical possibility of improving postoperative recovery is by optimising these lifestyle habits preoperatively. Since lifestyle habits are hard to change, it is important to establish whether a short-term change of a long-term habit improves recovery. This needs to be done in interventional studies before such interventions are implemented in clinical practice.

Certain conditions need to be met for preoperative lifestyle interventions to be feasible. From a physiological perspective the benefits of lifestyle changes cannot happen overnight, and there needs to be a time interval between the start of the lifestyle intervention and the surgery. The exact interval cannot be predicted and can only be established by interventional studies, as it depends on the type of intervention and the patient as well as the surgery characteristics and the organ system to be improved.

Another factor that needs to be considered when developing preoperative lifestyle interventions is the possible benefits. These vary between patients and different types of surgery. Based on the information about postoperative complication rates described above, it would be more rational to direct a preoperative lifestyle intervention to colorectal cancer patients rather than to patients planned for cholecystectomies, since the latter are at less risk for prolonged recovery. Another obvious factor is that these interventions can be expected to be most effective in patients with established unhealthy lifestyle habits. It would for example make little sense to enrol a patient who does not smoke in an extensive smoking cessation program.

1.6.1 Preoperative smoking cessation

The first preoperative lifestyle intervention to be studied, and furthermore implemented in clinical practice, was preoperative smoking cessation. In a systematic Cochrane review it was concluded that an intensive smoking cessation intervention for 4-8 weeks before surgery is effective in achieving smoking cessation and reducing postoperative complications.[30] This conclusion was based on two randomised controlled trials (RCT) with a total of 237 participants planned for either hip or knee joint replacement (n=120) or hernia repair, laparoscopic cholecystectomy, or hip or knee prosthetic surgery (n=117). The results from these two studies have furthermore been extrapolated into recommending this intervention before several other types of surgery, including colorectal cancer surgery.[17]

1.6.2 Preoperative alcohol cessation

The second lifestyle habit to be studied and implemented in clinical practice in some instances was preoperative alcohol cessation. Perioperative alcohol cessation was systematically reviewed in a Cochrane report in 2018.[31] They identified three RCTs evaluating an intensive alcohol cessation intervention in 140 patients with risk drinking planned for colorectal resection (n=42), elective hip arthroplasty (n=28), or acute ankle fracture surgery (n=70). However, only two of these assessed a preoperative intervention since the third study investigated an intervention in the emergency surgery setting. Both RCTs studying a preoperative intervention were performed by the same research group in Denmark, who also participated in the Cochrane review. The conclusion of the review was that intensive alcohol cessation interventions during four to eight weeks preoperatively probably reduced the number of postoperative complications.

1.6.3 Preoperative exercise interventions

While preoperative exercise interventions share characteristics with preoperative smoking and alcohol cessation interventions in that all are preoperative lifestyle interventions, there are also differences. One is the nature of the lifestyle habit. While smoking and alcohol cessation interventions target individuals who have risk habits including dependence, physical activity interventions can be directed to a more general surgical population and is an addition of a healthy habit rather than the cessation of an unhealthy habit. Individuals who perform physical activity at a level where they would not benefit from increased physical activity comprise exceptions in a general population, and this even more true in a population of individuals suffering from surgical diseases. Thus, physical activity interventions may be directed to the general surgical population, while it is reasonable to believe that inactive individuals would benefit most from increased physical activity.

The concept of preoperative optimisation through lifestyle interventions has been referred to as “prehabilitation”. Since this concept has been defined in several ways, and sometimes is considered a synonym to physical activity, and sometimes includes other, for example dietary, psychological, and smoking & alcohol cessation interventions, it is a term which could be confusing.[32] The rationale for prehabilitation is that the time from the treatment decision until surgery, usually spent in waiting, could be used for optimising the patient for surgery. Since the surgical trauma leads to a decline in physical performance to some degree for all participants, an improved starting position could lead to a faster recovery above a critical threshold defining independence.[33]

The first type of surgery where preoperative physical activity interventions were scientifically tested and reported to be effective was thoracic surgery. In 2006, Hulzebos et al. reported effect on postoperative pulmonary complications following inspiratory muscle training in high risk patients planned for coronary bypass surgery.[34] In 2012, a Cochrane review was performed and concluded that evidence suggested that preoperative physical therapy before elective cardiac surgery could reduce postoperative pulmonary complications.[35] In 2018, another systematic review concluded that preoperative physical activity interventions before lung cancer surgery reduced postoperative complications by half and shortened hospital stay.[36] The most studied type of preoperative exercise before both cardiac and lung cancer surgery is inspiratory muscle training, aimed at improving inspiratory muscle strength and reducing postoperative pulmonary complications.

For major abdominal surgery in general, and colorectal surgery in particular, the first reports were published in 2010. Carli et al. from Montréal reported results from an RCT in 112 patients planned for colorectal surgery.[37] This study aimed to achieve a blinding of participants, and participants were therefore randomised to either a structured home-based bicycle and strengthening regime or to a sham intervention. The sham intervention consisted of instructions to walk for ≥30 min daily and to perform deep breathing exercises as well as diaphragmatic breathing, huffing and coughing. The mean intervention duration was 52 days. The primary outcome measure was change in the 6-minute walk test. To their surprise, the authors reported that participants in the control group had a tendency towards increased functional walking capacity during the preoperative period and no difference between baseline and postoperative follow-up. Participants in the intervention group, on the other hand, had a tendency towards reduced functional walking capacity during the preoperative period, and a significant reduction from baseline until the postoperative follow-up. This was later explained by non-adherence to the intervention.[38]

The Montréal-based researchers have subsequently published the majority of reports on preoperative physical activity before colorectal surgery. They have performed several studies designed as pilot studies, or with functional capacity measures as primary outcomes,[39-43] which have subsequently been reanalysed and combined several times.[38 44-47] These studies provide information for choosing the optimal intervention in studies on preoperative exercise interventions. However, they do not add important information regarding the clinical importance of these interventions since they were not designed for such outcomes and the reports for clinically relevant outcomes were results from post hoc analyses and non-systematic combinations of study results.

The first report of an RCT designed for improving clinically relevant outcome measures by preoperative exercise interventions including colorectal cancer patients was published in 2018.[48] High-risk patients planned for major abdominal surgery had been randomised to either intervention or usual care (n=144). Approximately 60% had colorectal surgery and 75% surgery due to cancer. The intervention consisted of three parts: A motivational interview to explore motivation and individualise the intervention, a personalised program to promote daily physical activity by brisk walking, and a supervised high intensity endurance exercise program. The supervised program was planned to take place 1-3 times per week. The minimum duration was four weeks, but the mean duration was six weeks, and twelve supervised sessions. The primary outcome measure was any postoperative complication. The intervention was reported to reduce the number with postoperative complications by 51%. This reduction was mainly explained by reductions in cardiovascular events (2% vs 13%), infections of uncertain source (0% vs 11%), and paralytic ileus (0% vs 16%).

In 2020, the Montréal-based researchers reported results from their first RCT designed for clinically relevant outcome measures.[49] In this study 120 frail patients planned for colorectal cancer surgery were randomised to either multimodal prehabilitation or postoperative rehabilitation. The intervention included the same elements in both the pre- and postoperative treatment arms and consisted of a combined psychological, nutrition, and exercise intervention. The exercise intervention included both supervised moderate intensity aerobic exercise once weekly and home-based moderate intensity walking 30 min daily and resistance training three times weekly. The primary outcome measure was postoperative complications measured with the comprehensive complication index, a measure for grading the postoperative course on a scale between 0 and 100, based on the Clavien-Dindo classification of surgical complications.[50] Secondary outcome measures were length of hospital stay, readmissions, emergency department visits, functional capacity, and patient-reported measures of health-related quality of life, anxiety and depression and energy expenditure. There was no effect on any of these outcomes.

In summary, before we started the studies in this thesis there was a need for further studies defining the association between preoperative level of physical activity and recovery after both cholecystectomy and colorectal cancer surgery. There was also a need for high quality interventional studies defining the effect of added exercise preoperatively on clinically important measures of recovery after colorectal cancer surgery.

2 AIM

The overall aim of this thesis was to investigate the relationship between preoperative physical activity and postoperative recovery after two different types of surgical interventions. The hypotheses tested for the included papers were the following:

- The level of habitual leisure-time physical activity can be used to prognosticate the risk for prolonged recovery after elective cholecystectomy (paper I).
- The level of habitual leisure-time physical activity can be used to prognosticate the risk for prolonged recovery and postoperative complications after elective colorectal cancer surgery (papers II & III).
- A short-term exercise intervention before and after elective colorectal cancer surgery improves postoperative recovery (papers IV & V).

3 PATIENTS AND METHODS

3.1 INCLUDED STUDIES

The papers included in this thesis are based on the results from three separate studies. The methods used will be discussed for all three studies combined. To facilitate reading of these descriptions, the three studies are now summarized:

A. Observational cohort study in 200 patients planned for elective cholecystectomy. Exposure of interest was self-reported habitual level of leisure-time physical activity. Primary outcome was return to work. Secondary outcomes were length of hospital stay, self-assessed physical and mental recovery three weeks postoperatively, and risk for reoperations and readmittances. Results were reported in paper I.[51]
B. Observational cohort study in 115 patients planned for surgery due to colorectal cancer. Exposure of interest was self-reported habitual level of leisure-time physical activity. Primary outcome was length of hospital stay. Secondary outcomes were return to work, self-assessed physical and mental recovery three and six weeks postoperatively, and risk for reoperations and readmittances. Results were reported in paper II.[52] In an additional data collection, postoperative complications were registered retrospectively and results reported in paper III.[53]
C. Randomised controlled study where 761 patients planned for colorectal cancer surgery were recruited. Participants were randomised to either an intervention with preoperative home-based aerobic exercise and inspiratory muscle training and postoperative aerobic exercise, or to usual care. Primary outcome was self-assessed physical recovery four weeks postoperatively. Secondary outcomes included postoperative complications, length of hospital stay, risk for reoperations and readmittances. The full study protocol was reported in paper IV,[54,55] and main results in paper V.

3.2 STUDY DESIGN

The three studies in this thesis were of two principal types; Studies A & B were observational cohort studies while study C was an interventional RCT. These two study designs have their inherent strengths and limitations, and this is even more pronounced in studies of physical activity.

Observational cohort studies are generally easier to perform and require less resource use as well as less commitment from study participants. They work well with identifying risk factors and may be used for creating risk prediction models. In some instances, observational studies may be suitable for drawing conclusions on causality. In the case of physical activity this is hard to do, since physical activity helps prevent the development of health impairments such as obesity, hypertension and diabetes mellitus. It is hard to establish within an observational study whether the relationship between physical activity and the outcome studied is due to a direct effect or due to the association between physical activity and other factors with direct effects on the outcome. This is further discussed in the section ”Statistical analysis” below.

Randomised controlled trials are generally considered more appropriate for causal inference. However, this is only true for well performed studies where the randomisation has been successful. For easier evaluation of study quality there are reporting guidelines including all relevant information needed for evaluation of a study. They were originally developed for RCTs and are called CONSORT.[56] Subsequently guidelines were developed for other study types, e.g. observational studies (STROBE)[57] and systematic reviews (PRISMA)[58].

The possible causal effect of preoperative physical activity on postoperative recovery could be understood in two ways. One is whether physical activity prior to surgery, irrespective of the time period, improves postoperative recovery. Since physical activity usually tracks well throughout adulthood it is likely that individuals who have developed disease due to inadequate levels of physical activity will continue to be insufficiently physically active. Even if this causality could be shown, it would not be possible to draw any conclusions on the effect of increased physical activity during the time period between diagnosis and surgery. In order to conclude anything on this effect, intervention studies, preferably RCTs, have to been performed.

Interventional studies can be of varying character. One division is between pragmatic and explanatory trials, also referred to as efficacy or effectiveness trials.[59] The difference between the two types of studies lies in the aim. While explanatory trials aim to investigate whether an intervention is effective under optimal circumstances, pragmatic trials aim to determine the effect of an intervention under real-life circumstances. Pragmatic trials are needed to determine the effect of implementing an intervention in clinical practice, and explanatory trials of the intervention can be useful when interpreting negative results in pragmatic trials. In order to help in the design of trials a tool has been designed, called PRECIS-2.[60] When we designed study C, the PRECIS-2 tool had not been developed yet, and we were unaware of the preceding PRECIS tool.[59] However, we had an explicit aim of developing a pragmatic trial in order to determine an effect possible to achieve in clinical reality. I have therefore scored study C with the PRECIS-2 tool retrospectively. The tool consists of nine dimensions scored between one (very explanatory) and five (very pragmatic). The scores are illustrated on a radar plot where a larger area represents a more pragmatic design. While the individual scores are not exact, and it is hard for researchers to maintain neutrality towards their own studies, this can help the reader of a study to easily understand the general role of the study results – explanatory or pragmatic?

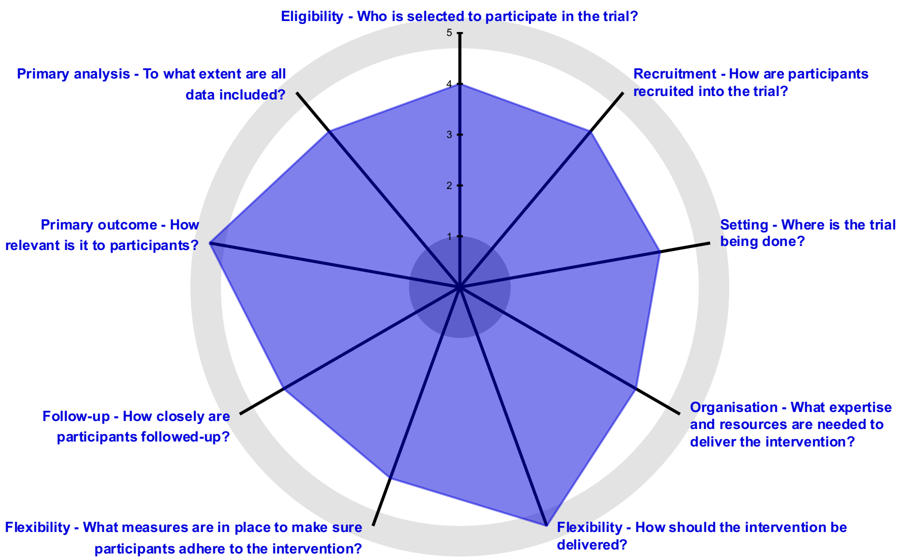

Figure 1. PRECIS-2 wheel illustrating the pragmatic nature of study C.

3.2.1 Setting

All studies included in this thesis recruited participants at several centres including both county and university hospitals. This improves the generalisability of the results, since patients operated at different types of hospitals may differ. In the case of colorectal surgery, patients operated at a university referral hospital often represent a more selected group of patients demanding more complicated surgery. Since surgery of more complicated cases more often leads to prolonged recovery, it is important to include patients with tumours demanding more complicated surgery as well as standard procedures if the aim is pragmatic.

3.2.2 Publication of protocols

According to the Helsinki Declaration, all studies performed involving human subjects must be registered in a publicly accessible database before recruitment of the first participant.[61] In order to further increase transparency in the scientific community, researchers are encouraged to publish their study protocols. Several high impact journals require researchers to publish their full study protocol online for RCTs,[62] and there are now several peer review journals specialised in publishing study protocols.

There are several reasons for this. When it comes to publicly accessible registration of studies, this can reduce selective publication and reporting, and increase transparency. Both registration of studies and publication of full study protocols can improve adherence to the initial study plan. In a study published in 2004, 122 reports from studies performed in Denmark were scrutinised and compared to study protocols.[63] They found that a majority of the planned outcomes were incompletely reported and that almost two thirds of the studies had changed their primary outcomes.

We registered all our studies included in this thesis at *clinicaltrials.gov*, a publicly accessible database. For study C we also published the full study protocol in a peer review journal (paper IV). The full study protocol is also available at the research group's website (www.ssorg.net).

3.3 PARTICIPANTS

3.3.1 Inclusion and exclusion criteria

In line with our pragmatic approach (study C) and ambition to be able to generalise our results we had wide inclusion criteria and few exclusion criteria in all studies. If inclusion and exclusion criteria select patients who are of high risk for the outcome and with high probability of effect from the intervention, the sample size needed to show effect from the intervention is considerably lower. This is due both to higher observed frequency of the outcome as well as to a lower proportion of the population with no effect, otherwise diluting the results. This is a major difference between our study and the two other reported studies designed to evaluate the effect of preoperative exercise interventions in populations of colorectal surgery patients, where physically inactive, frail patients were recruited in the other studies.[48 49] While our general study populations have been a strength, it has also required a large sample size for study C.

3.3.2 Recruitment and informed consent

Participants in all studies included in this thesis were recruited during visits at the hospital. Since neither of the studies relied on treatment decided by physicians, participants were recruited by a research nurse. This probably facilitated the logistics, since the preoperative appointments with physicians are generally filled with information on diagnosis, treatment and possible side effects. During the course of study C, it was decided that participants at the recruiting university hospital should be offered an appointment for preoperative information on patient-performed measures, for example preoperative smoking and alcohol cessation and preoperative skin preparation. This was performed in group consultations at the clinic, and patients were also informed about ongoing studies including study C and recruited in individual appointments following these group consultations. Patients not attending these group consultations were informed in association with their preoperative visits.

All participants in the studies included in this thesis gave signed informed consent to participation in the studies. In study C, a subpopulation of participants had levels of circulating growth factors (IGF-1 & IGFBP-3) determined in blood.[64] Since these blood samples had to be collected in association with preoperative blood samples collected for usual care according to the ethical permission, and these blood samples were collected directly before the appointment where participants gave written informed consent, participants in this subpopulation were contacted by telephone prior to their visit at the hospital and gave a preliminary oral consent in order to collect the blood samples, and subsequently gave a written informed consent.

3.4 EXPOSURE AND MASKING

The exposure of interest in this thesis was physical activity. Physical activity is tightly connected to functional capacity, also referred to as fitness. However, these are separate entities and should not be used as synonyms. Physical activity precedes functional capacity in the causal chain between physical activity and improved health outcomes, but there are also other factors influencing functional capacity. In cancer patients this may be anaemia and weight loss leading to a decreased functional capacity in spite of preserved levels of physical activity.

3.4.1 Methods used for assessing physical activity

We chose to include self-reported physical activity using the Saltin-Grimby Physical Activity Level Scale in all studies in this thesis. In the observational studies this was chosen since it is a feasible tool for grading physical activity in clinical practice. In study C we also included IPAQ. We considered including sensor-based assessments of physical activity in study C, but with the coming implementation of programmes for shorter lead times it was doubtful if there would be time for preoperative baseline accelerometer assessments. This consideration proved to be correct, and a preoperative accelerometer assessment would have obstructed the possibility for a preoperative exercise intervention. When we reported the results from study C it became apparent that baseline level of physical activity measured with two different self-reported instruments was redundant. Since the rate of missing data was considerably higher for IPAQ, only information from the Saltin-Grimby Physical Activity Level Scale was reported. The four levels in Saltin-Grimby Physical Activity Level Scale are “Sedentary”, “Some physical activity”, “Regular physical activity and training”, and “Regular hard physical training for competition sports”.[21] In papers I-III we labelled these “Inactive”, “Light activity”, and “Regular activity”, while we labelled them according to their official English translation in paper V. As described, the Saltin-Grimby Physical Activity Level Scale has been slightly modified in several studies where it has been used.[21] We used one of the previously used versions.

3.4.2 Randomisation

We chose to randomise using an electronic online system designed for this purpose. The benefits of this are that no one had to create the allocation sequence, and that block numbers could be kept secret from randomising staff. This made it practically impossible to predict whether an individual would be randomised to intervention or control.

Since there were some factors which we knew to be strongly associated with postoperative recovery, we chose to stratify randomisation for these. These factors were colon or rectal cancer, neoadjuvant radiotherapy, and open or laparoscopic surgery. This stratification was performed to prevent an unbalanced randomisation regarding these factors from affecting results. We planned to include recruiting hospital as a stratification factor, and this was stated in paper IV. However, when the results were analysed, we realised that this had never been included in the electronic randomisation system. We have therefore published a correction for paper IV.[55]

3.4.3 Masking

The case of masking is a general problem in studies of exercise interventions. Since the intervention is performed by the participant, it is impossible to perform a strict masking of the participant. Since the intervention needs to be delivered by someone who can motivate towards behavioural change, this person is also hard to mask. However, it is possible to achieve at least partial masking of participants regarding allocation. This can be achieved by informing participants that the intervention will consist of an exercise intervention, and then delivering different types of exercise interventions to different treatment groups. One example of a study where this was done, which also illustrates a problem with this approach, was one of the first RCTs for exercise before colorectal surgery.[37] In this study, the control group received a sham intervention with walking and deep breathing. However, this group conserved their functional capacity while the intervention group did not. Hence, it is hard to achieve masking while still determining the additive effect compared to usual care, which is an important part of a pragmatic study. Another issue with this is how to achieve sufficient information to participants for ethical permissions, while still allowing for masking. After discussing this, we decided that it would be too hard to achieve a credible masking without risking contamination of the control group and decided not to mask participants.

However, we did mask investigators registering outcomes. This was of importance, since investigators hoping for results in line with the hypothesis would risk introducing measurement bias if not blinded. For postoperative complications, there are several grey zone cases where unconscious bias could otherwise have affected the results. We also kept the information to a minimum for participants in the control group regarding type and dose of physical activity in order to reduce the risk for contamination of the group.

3.5 CONTROL GROUPS

While the studies in this thesis are of both observational and interventional characters, all studies were controlled. This is important in order to be able to differentiate a treatment effect/association from a natural course, especially in the perioperative period where lots of changes occur to all patients. In interventional studies it is obvious which group is intervention and which group is control, and the decision is what the control group should receive. In our pragmatic approach we chose that the control group in study C should receive usual care. In the observational studies we had to decide whether the exposure should be low physical activity or regular physical activity. While this wouldn't make any difference in terms of statistical significance, it would send a signal on whether the important message was to refrain from low physical activity or to adhere to regular physical activity. Since we wanted to promote a positive message, we decided to use physical inactivity as control group and increased physical activity as exposure in paper I & II. In paper III we changed perspective and reported risk increases for low physical activity instead, since this was considered a more conventional way of reporting results.

3.6 PROCEDURES

Physical activity is a complex behaviour with several components, including both motivational aspects, types of activity and dose of activity. When developing study C, we wanted to investigate an intervention which would be feasible to implement in clinical practice if shown effective. The method we chose for achieving increased physical activity was designed in accordance with the Swedish model for physical activity on prescription (see 1.1), including both a patient-centred approach, an individually adapted physical activity recommendation with written instructions, and a structured follow-up.

Regarding the duration of the intervention, we originally planned on a strict preoperative intervention. However, during the design of the study it became apparent that the time frame available from decision to treat until surgery would shorten during the study period. We were aware that Sweden would adopt standardised lead times for colorectal cancer surgery during the course of study C. These stated that decision to treat should not be more than two weeks after a colorectal cancer diagnosis, and that treatment should start no more than two weeks after decision to treat.[65] This was adopted in order to standardise care, but without evidence of better outcomes after fast-track surgery, and in contrast with recommendations for duration of preoperative smoking and alcohol cessation programs. Since we considered it impossible to start prehabilitation before patients had been informed about their diagnosis and planned surgery, we considered two weeks to be a feasible intervention duration preoperatively. We further assumed that two weeks could be too short to achieve meaningful effects on functional capacity and subsequent improvements in postoperative recovery and decided to add a postoperative intervention period after discharge from hospital. The postoperative intervention was also considered to be motivated since postoperative complications after colorectal cancer surgery may also occur after discharge and not only during hospitalisation.

Regarding the dose of physical activity, we decided to design the aerobic intervention in line with the general recommendations on physical activity. At the time, these recommended all individuals to perform activity of at least moderate intensity for at least 30 minutes daily. Based on the assumption that most participants would not meet these recommendations at baseline, but to allow for an intervention also for those already meeting these guidelines, we decided to recommend that all individuals should *add* 30 minutes of moderately intense aerobic physical activity to their normal daily routine.

For types of physical activity, we chose both a general intervention with aerobic activity and a directed pulmonary intervention with inspiratory muscle training. The rationale for this was that short-term inspiratory muscle training had been shown effective in preventing postoperative pulmonary complications after thoracic surgery,[34] with postoperative pulmonary complications being relatively frequent after colorectal cancer surgery and that we assumed that the short time frame would make it less probable for an isolated aerobic preoperative intervention to affect postoperative recovery.

There were no study-related visits, in line with the pragmatic approach of the study. However, there were postoperative questionnaires four weeks and twelve months postoperatively. In order to reduce loss to follow-up, these were preceded with a phone call from a research nurse and followed-up with a letter of appreciation after receiving the questionnaire or a reminder if the questionnaire had not been submitted. To increase validity and reduce loss to follow-up, all postoperative questionnaires were dispatched from the central study secretariat together with prepaid return envelopes, rather than being distributed by healthcare personnel associated to the care of participants.

3.7 OUTCOMES

When designing clinical research studies, choosing primary outcomes are critical decisions in need of careful consideration. On one hand there is no need to perform a study if there is no chance of detecting a difference for the desired outcome. On the other hand, showing a difference in an outcome of no importance is not meaningful. The choice of outcome measures differs between pragmatic and explanatory studies. While the former often focus on outcomes of importance to the participant, the latter tend to choose surrogate measures of high probability to be affected by the intervention.[60] In our ambition of performing a pragmatic trial, we chose to include outcome measures strictly relevant to participants in study C. This may have impeded some aspects of the interpretation of the results (see 3.7.2).

3.7.1 Patient-reported outcome measures

The primary outcome measure in study C and several secondary outcome measures in all studies in this thesis were patient-reported. Patient-reported outcome measures have gained importance, not least with health-related quality of life attaining a central position in health economic analyses, and they are currently being introduced in routine health care.[66]

We have used both general instruments, for example instruments for health-related quality of life, as well as instruments developed for these studies. Before the start of the observational studies, we developed two single item instruments for measuring physical and mental recovery. These were face validated with patient representatives, together with the full questionnaires. The main purpose of face validation was to ensure that participants understood the questions in the same way that we did, but also to ensure that they were able to answer them to reduce the rate of missing data. The question was formulated "To what extent do you feel fully physically recovered after surgery?", with pre-specified answering alternatives of "Not applicable, I do not feel recovered at all", "I feel physically recovered to 25%", "I feel physically recovered to 50%", "I feel physically recovered to 75%", or "I feel completely physically recovered after surgery, which I did already ___ weeks after surgery". A second question was formulated in the same way with "physically" changed to "mentally". These two questions were used in all studies in this thesis. It could be objected that the questions include a tautology, since it is hard to see how someone can be *fully* recovered to for example 50%. However, participants seemed to be able to answer the questions, and participants were well distributed between the categories. When we chose to use the question regarding physical recovery as primary outcome measure in study C, we chose not to alter the wording.

3.7.2 Functional capacity

In our determination not to design study C for measuring proxy measures, we excluded all forms of functional capacity measures. During the course of the study, it became apparent that some sort of functional capacity measure at baseline, at time of surgery and possibly at the postoperative routine visit around four weeks postoperatively could have aided interpretation of the results. This might have been performed as a sub-maximal cardiopulmonary exercise test or a 6-minute walk test. This could also have been combined with measurement of maximal inspiratory pressure. While these tests do not measure level of physical activity, they could have been used as an objectively measured proxy for adherence to the intervention rather than an outcome measure. They have an important advantage compared to objective physical activity measures in that they only require less than one hour to perform, and thus measurement at baseline and at surgery would have been feasible within the tight time constraints. Results from these tests could also have facilitated interpretation of the null results – did the intervention not have any effect due to no improvement in functional capacity, or was it due to the fact that improved functional capacity is not enough to reduce the risk for prolonged postoperative recovery? However, inclusion of these tests would have decreased the pragmatic design of the study and resulted in considerably higher resource use and demand for logistics in order to perform these repeated tests for more than 700 participants at six hospitals.

3.7.3 Postoperative complications

Postoperative complications are generally defined as any deviation from the normal postoperative course. While this may sound simple in theory, defining the normal postoperative course can be challenging. There are several established ways of reporting postoperative complications. The most widely accepted instrument in surgery is Clavien-Dindo classification of postoperative complications.[67] This is a system where all deviations from the normal postoperative course are graded in a seven-grade scale, according to the intervention needed to treat the complication. Grades I-II represent complications treated with different types of medications, IIIa/b complications treated with surgical/radiological/endoscopical interventions without (a) or with (b) general anaesthesia, IVa/b complications treated in intensive care units due to single (a) or multi organ (b) failure, and V postoperative mortality. While this system is stringent, it may be objected that it is not very patient-oriented. A patient who suffers from a postoperative myocardial infarction leading to lifelong congestive heart failure is for example classified as II, while a patient suffering from a mild gastric ulceration cured endoscopically is classified as IIIa. Until recently, complications according to Clavien-Dindo were reported with the highest grade suffered for each individual. To better reflect the total burden for a patient, the comprehensive complication index was developed.[50] This index combines all registered postoperative complications according to Clavien-Dindo within a given time frame, resulting in a score between 0 and 100, where 0 represents no postoperative complication and 100 reflects postoperative mortality. This facilitates statistical analysis of postoperative complications and increases sensitivity, while still being based on the same instrument with the same limitations in terms of patient-orientation.

When we planned for data collection of this outcome measure, we also had to decide on the time frame of follow-up. The general recommendation is to analyse postoperative complications within 90 days postoperatively. However, for the colorectal cancer population, this would further increase the problem of determining the normal postoperative course since a subgroup within this population receives postoperative chemotherapy, starting approximately 4-8 weeks postoperatively. If common chemotherapy side-effects such as neutropenia and nausea would be registered as postoperative complications, a possible increase in patients receiving postoperative chemotherapy would be seen as an increase in postoperative complications in the statistical analysis. Since other studies evaluated exercise during adjuvant chemotherapy with the aim to increase the number of patients who can tolerate adjuvant chemotherapy after colorectal cancer surgery, this seemed irrational. We therefore changed to evaluating postoperative complications both 30 and 90 days postoperatively, where complications registered 31-90 days postoperatively did not include common chemotherapy-related complications.

Postoperative complications were not included as an outcome measure when the observational studies were performed. Since the interest in this outcome grew, an additional data collection was performed in 2017, after supplementary ethical permission was granted. This data collection resulted in paper III. The data collection was performed by a medical student as his master thesis. Information on postoperative complications was collected from medical charts, from the physicians' discharge note, with special attention to documentation on postoperative pain and nausea. The data collector was not explicitly masked regarding exposure, which is a limitation. Most of the data collection was performed by the medical student but some was missing and thus I performed a part of the data collection. In order to increase validity of the data collected, this was performed strictly according to the criteria defined for the first data collection.

For study C, postoperative complications were included as a secondary outcome measure at the start of the study. However, it became apparent during the course of the study that postoperative complications should have been considered for primary outcome. We originally planned for data on postoperative complications to be reported by physicians at each hospital. Since we theoretically considered that the exercise intervention would have the best chance of reducing the rates of non-surgical complications, such as cardiovascular, pulmonary, and infectious complications, all data on postoperative complications was therefore instead collected by me. This was done according to a document defining postoperative complications, where less focus was spent on nausea and pain, and more focus was directed towards respiratory and cardiovascular complications. This document was defined before collection of postoperative complications.

3.7.4 Other outcome measures

All studies in this thesis have included several other outcome measures, in addition to patient-reported outcome measures and postoperative complications. These consist of length of hospital stay, re-operations, re-admittances and return to work. For all studies, each of these variables has been defined before data collection to ensure that for example a re-admittance for a seemingly unrelated event is registered in the same way for all participants in order to increase validity.

3.8 STATISTICAL ANALYSIS

The statistical analysis of a study is an equally important step to design. Since a statistician has been involved in all stages of the studies in this thesis, and not only in data analysis, we have been able to prepare for statistical interpretation of the results early in the processes.

3.8.1 Sample size

Determining the sample size needed to achieve sufficient statistical power for the primary outcome measure is an important step in designing a study. An underpowered study will not be able to determine whether a null result was due to no real effect or to insufficient power. On the other hand, an overpowered study will perform research on more individuals than necessary, which is unethical. To perform a sample size calculation, there are some parameters which have to be known: a point estimate and variance of the underlying event rate in the population, an expected effect size, an acceptable level of significance, and a desired power to detect a difference. Several of these variables are up to subjective decisions. To prevent this, standard levels are often chosen. Level of significance is often set at 5%, power at 80%, and levels for minimally important difference have been developed for several outcome measures. However, the reliability of the sample size calculation also depends on whether the type of analysis performed is to be the same as the primary analysis in the final report. If sample size calculation for example was performed with an unadjusted analysis of a dichotomised variable, and the primary analysis is performed using the full scale in an adjusted analysis, the final analysis will yield higher power than the analysis performed for sample size calculation.

All studies in this thesis were preceded by sample size calculations. However, all of these sample size calculations had flaws. In study A, the primary outcome measure was return to work, but sample size calculation was performed for a reduction in length of hospital stay. When sample size calculations for both studies A and B were performed there was no data on distribution of habitual level of physical activity for these populations, and it was assumed that 30% would achieve levels three or four regarding physical activity assessed with Saltin-Grimby physical activity level scale. However, only 19% of cholecystectomy patients and 15% of colorectal cancer patients reported these levels of physical activity, reducing statistical power considerably. For study B, sample size was calculated for our primary outcome measure, recovery, but the study was closed before reaching the sample size due to the start of study C.

Study C was originally designed with two primary outcome measures – self-assessed physical recovery and return to work. Since study C was designed and started before any results from study B were analysed, we had no reliable data on underlying event rate or variance of either our newly developed instrument for self-assessment of physical recovery or for length of sick leave. We therefore started the study with a roughly estimated sample size of 370 individuals and with a plan for a sample size re-estimation by an external committee after 100 evaluable participants had been recruited. The sample size re-estimation for return to work revealed that we could not achieve sufficient power for sick leave with a reasonable sample size since a majority of the participants were retired from work due to high age. With return to work not being an applicable measure of recovery for a majority of the population, it was changed into a secondary outcome measure, possible to include in a health economic analysis. For self-assessed physical recovery, the sample size calculation was performed with the variable dichotomised as in the reports from studies A & B. Instead of determining a minimally important difference for this outcome, the point estimate seen after 100 recruited participants was considered to be the expected effect size. In the published protocol for study C (paper IV), we stated that the significance level would be set to 2.5% due to second look. However, we soon realised that this was unnecessarily strict since no statistical testing had been performed in the interim analysis and thus no second look would be performed. In the final statistical analysis of the study, we analysed the full scale for the primary outcome measure in an adjusted model as our primary analysis, which increases power compared to the analysis performed for the sample size calculation.

There are also instances of sample size calculations based on assumptions that were not met in other studies. In fact, most clinical studies not sponsored by pharmaceutical industry seem to suffer from this to some degree. As an example, this was also the case for the two other studies reporting results on clinically relevant outcomes for preoperative exercise before colorectal surgery. The first study anticipated an underlying complication rate of 30%, while the observed complication rate in the control group was 60%.[48] This does not necessarily decrease statistical power, but may raise concern if there could have been a measurement bias, since the assumed underlying complication rate was observed in the intervention group, and they do not explicitly state that investigators registering were masked regarding allocation. The other study assumed a mean comprehensive complication index of 10.45 and set the expected effect size at a 10-point difference, reflecting a mean decrease by one grade I complication per participant.[49] There are several aspects of these assumptions that could be questioned. One is that the comprehensive complication index is the result of a squared root function. This means that removing a grade I complication does not result in the same comprehensive complication index decrease for individuals with different number of complications. For example, an individual with one reoperation (IIIb), one antibiotic treatment (II), and one pain episode (I) will go from comprehensive complication index 40.6 to 39.7 if the grade I complication is removed. On the other hand, a patient who only suffers from postoperative pain (I) goes from comprehensive complication index 8.7 to 0 if the pain episode is removed. Hence, a 10-point decrease never reflects a reduction by a grade I complication. Furthermore, it is hard to understand how they could assume a reduction from comprehensive complication index 10.45 to 0.45 when they designed their study, as commented by others.[68] It should have been apparent that such a treatment effect would be unreasonable and that they should have decreased their assumed treatment effect and increased their sample size. This illustrates how easy it is to find less than perfect sample size calculations.

3.8.2 Statistical significance

Traditionally, statistical analyses have been interpreted in terms of statistical significance, where $p<0.05$ is considered interesting and “null results” ($p\geq0.05$) uninteresting. This way of dichotomising results into statistically significant or insignificant has been questioned. In an article in Nature,[69] the authors raised several concerns regarding this dichotomisation. One was the conceived controversy between studies reporting “significant” or “null” results, where the observed point estimates were the same, only differing regarding statistical power. Another concern was the misunderstanding of interpreting null results as similarity between the interventions. One area of research associated with preoperative lifestyle interventions is investigations of the safety of postponing cancer surgery, since it is possible that this is needed in order to achieve proper preoperative optimisation. Several studies have been reported lately where this conclusion has been made,[70 71] instead of performing non-inferiority analyses.[72] The authors in Nature also proposed that researchers should consider the point estimate to be most probable true effect, and allow for interpretations of this regardless of the p-value. This demands that both researchers and readers of the articles are familiar with research methodology and interpretation of results. While this is somewhat utopic, it should at least allow for discussing explanations for observed (statistically significant) effects in terms of mediating effects not reaching statistical significance.

3.8.3 Statistical analysis plan

One way of preventing excessive testing in order to find statistically significant effects is to write statistical analysis plans before data analysis is commenced. This way, researchers are forced into stating exactly how analyses will be performed, how outcomes are categorised etc. We have worked with statistical analysis plans in papers III and V, but not in papers I and II. This makes a real difference, in the same way as being masked when registering postoperative complications did. While one may have the best of intentions, it is hard to discard a statistically significant analysis once it has been discovered. In the studies where we have formulated statistical analysis plans, this has felt like the right thing to do, while risking that we would miss interesting results.

3.8.4 Categorising variables before analysis

Some variables are naturally dichotomised, with mortality as the extreme example. Several other variables are ordinals or continuous variables. When analysing such variables, one has to decide on whether to use the full information or to dichotomise. The choice between the two is often the choice between keeping statistical power and achieving intuitive understanding of the results. This is most obvious for continuous variables of exposure. If, for example, functional capacity measured with the 6-minute walk test is the exposure, this could either be analysed as a continuous variable with the number of meters walked or as a dichotomised variable of “good functional capacity” and “bad functional capacity”. The dichotomisation would discard all information on dose-response relationships, as well as risking to dichotomise at a level not representing the real threshold level, if such a level exists. The benefit would be that the result could be expressed in terms of one group having a reduced risk compared to the other group, and that the point estimate could be understood, for example as a relative risk. When effect measures are presented for continuous exposures, these are usually expressed as the change in outcome per change in exposure, which is harder to intuitively understand. This is not the case when the continuous variable is an outcome rather than an exposure, since a ratio for the outcome can then be presented between the groups of exposures. As shown in paper II for length of hospital stay, there are also instances where dichotomisations result in statistically significant results while analysis as a continuous scale does not.

There are several details of the analyses performed in studies A & B which could be changed in retrospect. The exposure of interest in these studies is categorised in four categories, where category four was combined with category three due to few participants. This is reasonable, but it might have been better not to dichotomise length of hospital stay, return to work, self-assessed physical or mental recovery or postoperative complications (CCI). When we, much more recently, planned the analyses for study C, we decided to keep more of the variables in their original format rather than dichotomising.

3.8.5 Covariates in observational studies

When analysing relationships between an exposure and an outcome, there is a risk for interpreting associations between the two variables as a causal effect when the association is actually explained by a third variable, known as a confounder. A confounder has to fulfil three conditions:

1. To be associated with the exposure.
2. To be associated with the outcome.
3. Not be part of the causal chain between the exposure and the outcome.

All three conditions have to apply in order for confounding to occur. In randomised controlled trials, confounding is handled by randomisation where known and unknown confounders are evenly distributed between the treatment groups, if randomisation is performed correctly, thus eliminating the first criterion. In observational studies, confounding is a major obstacle that needs to be handled. A common way of handling this is to perform adjusted statistical analyses, where known confounders are included in a multivariable statistical model. Adjusting for known variables will never eliminate the risk for confounding from unknown variables, but if well performed it should reduce confounding.

For studies A and B, we had to handle another problem with confounding. The problem was that we wanted to investigate the association between level of physical activity assessed at diagnosis and postoperative recovery. However, level of physical activity at the time of diagnosis can be assumed to be similar to level of physical activity several years prior to diagnosis for a majority of participants, since level of physical activity usually is stable. Since physical activity reduces development of cardiovascular disease, diabetes mellitus, and overweight, inactive individuals would probably be overrepresented regarding comorbidity and overweight, which are factors associated with prolonged recovery. Therefore, we had to choose between adjusting for comorbidity and overweight, or not adjusting for these variables, accepting the fact that we could not conclude causality between the level of physical activity at time of diagnosis and postoperative recovery. To aid our decision, we drew a directed acyclic graph (DAG). This is a tool for exploring variables and making decisions on what variables to include as covariates in statistical modelling. Since a DAG quickly gets hard to interpret due to too many arrows and boxes, a simplified version is included here as illustration.

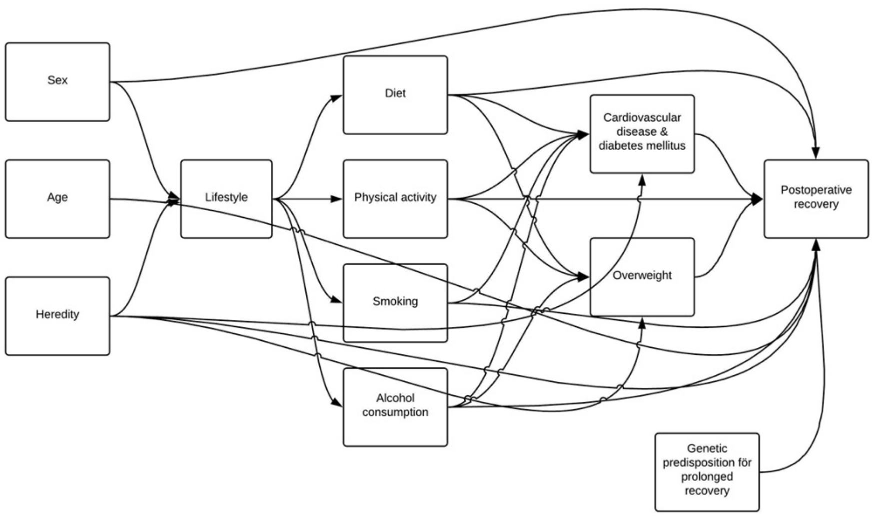

Figure 2. Directed acyclic graph showing selected factors involved in recovery after surgical procedures.

Our conclusion was that comorbidity and overweight should not be included as covariates since these were parts of the causal chain between physical activity and postoperative recovery. This conclusion also highlighted the need for performing interventional studies to determine the effect of preoperative exercise on postoperative recovery rather than investigating this in observational studies, since the associations might be explained by factors not reversible within the preoperative period such as cardiovascular disease and overweight.

3.8.6 Multivariable modelling in observational studies

There are several types of statistical models for performing multivariable analyses. These are generally based on assumptions which have to be met in order for the model to be appropriate. Parametric distributions are required in some models, while others work also for non-parametric data distributions. In some instances, analysing data on the logarithmic scale can turn non-parametric distributions into parametric distributions, allowing for parametric models to be used. The nature of the exposure and outcome variables (dichotomised, categorical, or continuous) are also important when deciding on suitable statistical models. Since distribution of data cannot always be predicted, statistical analysis plans often need to be expressed with a primary option and a secondary option, for example if a parametric assumption is not met.

All analyses performed in the studies in this thesis were planned together with an experienced statistician, who proposed models and performed the models decided on. While this has offered a wider palette of options available, it has sometimes led to choosing less well-known models, resulting in reviewers and fellow researchers questioning the methods used. In study A, dichotomised variables were analysed using a modified Poisson regression model. Another more frequently used choice for these analyses would have been log binomial regression, also modelling results as relative risks rather than odds ratios. The modified Poisson regression was chosen since this model has less problems with convergence than log binomial regression. This was illustrated in study B where a log binomial model had to be abandoned in favour of the modified Poisson regression model due to problems with convergence, while a log binomial model could be used in study C. This is just one example of choices between different models in instances where several models are available.

3.8.7 To adjust or not to adjust in RCTs

As described previously, the main strength of a randomised controlled design is that confounding is handled by randomisation, and that this should be true for both known and unknown confounders. This makes multivariable modelling less necessary within randomised trials. However, there are instances where statistically adjusting analyses are motivated. One is in the case of stratifying for variables in randomisation. This is performed in order to distribute participants with such variables evenly between the treatment groups, but also has as effect that these characteristics are not distributed at random. While it may feel counter-intuitive to adjust for variables already stratified for, stratification factors should therefore be included in a multivariable analysis. Other covariates than stratification factors may be included as covariates in the analysis to help narrowing confidence intervals. An argument against further adjusting is that it should not be needed if the randomisation has been effective and the groups are balanced. When this isn't the case and groups are unbalanced, adjusting is necessary. However, this effectively takes away the randomised design and caution should be applied when interpreting and communicating the results. Fortunately, the groups were well balanced in study C. We could therefore perform analyses adjusted for stratification factors as well as study site, as stated in the statistical analysis plan. Study site was included since it was planned to be a stratification factor, as explained in 3.4.2.

3.8.8 Intention to treat vs per protocol analyses

In the analysis of RCTs, one has to decide on who to include in the analysis. This is another decision which should be based on whether the aim is to perform a pragmatic or an explanatory study. The pragmatic study performs the analysis on all participants, as randomised, and this type of analysis is referred to as intention to treat analysis. The explanatory study focuses more on whether the participants actually performed the intervention, and this type of analysis is called per protocol. It is considered standard procedure that intention to treat analyses are used for primary analyses when reporting results from an RCT, and that per protocol analyses are used as supportive analyses, which we also did for study C.

3.8.9 Multiple analyses, and the family-wise error rate

In the quest to find $p<0.05$ traditionally undertaken in order to be able to publish results, one effective measure is to perform multiple analyses. Since p reflects the probability that the results would occur at random, there is generally a 5% chance at finding $p<0.05$ for a comparison between two groups where there is no true difference. When 20 tests are performed, the chance of finding at least one $p<0.05$ is approximately 65% ($1 – (1 – 0.05)^{20} = 0.65$). This is referred to as the family-wise error rate, or alpha inflation, and needs to be handled if results are not to be interpreted as strictly exploratory. There are several ways of handling the family-wise error rate. One simple way is with a single step Bonferroni correction, where alpha (the significance level) is divided by the number of tests performed, and each test is then interpreted against this alpha. If performing five tests and the overlying alpha is 5%, the significance level for each test is 1%. There are also several types of sequential adjustments for handling of the family-wise error rate. In study C, we chose a sequential model where the planned tests were ordered according to level of interest. Alpha was first divided in two tests of equal interest (primary outcome and comprehensive complication index 90 days postoperatively), and subsequent tests in each branch would only be interpreted if the null hypothesis could be rejected for the test preceding in each branch, see figure 3. In studies A and B, the results were performed with an exploratory approach. This was stated as a limitation in paper I and II, and the general exploratory nature of the additional analyses was stressed in paper III. However, there is always a risk of readers only finding $p<0.05$ and concluding a shown effect, with readers of scientific reports having varying degrees of scientific knowledge.

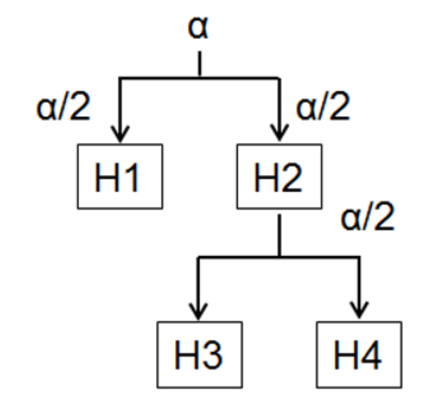

Figure 3. Handling of the family-wise error rate in study C.

3.9 ETHICAL PERMISSIONS

The WMA Declaration of Helsinki states that for all studies on human subjects *"The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins".* While this general principle goes without saying, it also poses an obstacle needed to pass before a study can commence. As described above, one implication for research on exercise interventions is that the need for fully informed participants collides with the scientific demand for masked participants. This is generally no problem for pharmaceutical interventions where detailed information can be provided for all possible treatment arms without risking masking, while this is impossible for exercise interventions since the participants can then easily understand if they receive active treatment or a sham intervention.

4 RESULTS

4.1 SUMMARY OF THE RESULTS

The detailed results for the studies in this thesis are provided in the included papers, and are only summarised here.

In study A, participants with regular physical activity had a higher chance for returning to work within three weeks (relative risk (RR) 1.26, 95% confidence interval (CI) 1.03-1.55), but not for returning to work within one week (RR 1.28, 95% CI 0.88-1.86), compared to participants who were sedentary. They also had a higher chance for leaving hospital within one day postoperatively (RR 1.23, 95% CI 1.05-1.43) and for feeling highly mentally recovered three weeks postoperatively (RR 1.18, 95% CI 1.00-1.40), but not for feeling highly physically recovered three weeks postoperatively (RR 1.12, 95% CI 0.84-1.49). All these results were adjusted for age, sex, type of surgery, smoking, alcohol risk consumption, and marital status. There were no associations for any of these outcome measures when participants with some physical activity (level 2/4) were compared to sedentary participants.

In study B, habitual physical activity was not associated with the primary outcome measure, length of hospital stay, when participants with regular physical activity (RR 0.81, 95% CI 0.60-1.10) or some physical activity (RR 0.83, 95% CI 0.66-1.06) were compared to sedentary participants. However, participants with regular physical activity had a higher chance of feeling highly physically recovered three weeks postoperatively (RR 3.28, 95% CI 1.07-10.1) than sedentary participants. Regularly active individuals also had higher chances of feeling highly physically recovered six weeks postoperatively (RR 1.91, 95% CI 0.89-4.10), and of feeling highly mentally recovered three (RR 1.54, 95% CI 0.86-2.75) and six weeks postoperatively (RR 1.46, 95% CI 0.87-2.44) than their sedentary peers, with none of these associations reaching $p<0.05$. For postoperative complications, sedentary participants had a comprehensive complication index 12 points (95% CI 4.3-19.1) higher than individuals with some activity and 17 points (95% CI 7.8-26.8) higher than regularly active participants. For the risk of having a comprehensive complication index ≥20, roughly equal to a single grade II complication, this was 4.4 times higher (95% CI 2.05-9.36) for sedentary participants and 2.7 times higher (95% CI 1.30-5.39) for individuals with some activity, compared to participants with regular activity.

The results from study C showed no effect from the short-term exercise intervention on self-assessed recovery (odds ratio (OR) 0.84, 95% CI 0.62-1.15), postoperative complications within 30 (OR 1.04, 95% CI 0.36-2.96) or 90 days (OR 1.17, 95% CI 0.40-3.47), length of index hospital stay (OR 1.91, 95% CI 0.42-8.62), or rate of readmissions (RR 1.06, 95% CI 0.77-1.46) or reoperations (RR 1.45, 95% CI 1.01-2.07).

4.2 BASELINE DEMOGRAPHICS

The first table in reports from clinical studies is usually a table of baseline participant demographics. While this is the same for both observational and randomised studies, the use of the table differs to some degree. One common application for both types of studies is for assessing generalisability to the general population, that is whether the population studied is similar to the general population where the results are intended to be used. For observational studies, this table also provides information on important possible confounders, and differences between the groups for such factors should be taken into account and should possibly be included in statistical modelling. For study A, this table showed that both obesity and comorbidity was overrepresented in sedentary participants, while these factors weren't included in the statistical model (reasons described previously). For study B, the two reports (papers II and III) illustrate the differences between different levels of detail for information. In paper II, it appears that participants were relatively comparable in terms of comorbidity, while paper III reveals relatively large differences when comorbidity was reported separately for diabetes mellitus, hypertension, and hyperlipidaemia.

For randomised studies, the primary use of table 1, in addition to assessing generalisability, is to show whether randomisation succeeded, and groups were balanced. If groups are balanced for a selection of important variables, it is assumed that this balance also applies for unknown confounders. If groups are unbalanced in table 1 randomisation has failed, and this needs to be handled in some way. Fortunately, the groups were very balanced in study C.

It is tempting to perform statistical testing of demographic variables. However, this is generally not recommended. In RCTs, such differences should have occurred by chance and hence p-values should not be reported according to CONSORT. For observational studies, statistical testing is often requested by reviewers, while recommended not to be reported by the STROBE guidelines.[57] We performed no testing for study C, while reporting $p<0.05$ for studies A and B.

4.3 LOSS TO FOLLOW-UP

Loss to follow-up poses a significant problem in clinical studies. The reason for this is that it is usually impossible to know whether this loss to follow-up occurred at random, that is independently of exposure and outcome, or if loss to follow-up was associated with any of these variables. If loss to follow-up is completely at random, it is not a big problem except for a reduced statistical power due to smaller sample size available for statistical analyses. However, since it is often hard to claim that loss to follow-up occurred at random, loss to follow-up usually constitutes a threat to the validity of the results and increases risk for bias. In the extreme form, participants who receive the intervention and who also experience negative outcomes withdraw from the study. If the study outcome is relatively rare, even small numbers lost to follow-up may have considerable impact on the study results.

The most important way of handling loss to follow-up is to try to prevent it from occurring. This may be done in several ways. For participant-reported outcome measures, it can be through collecting these in a way this is easy for the participant population studied (for example electronically if the population is assumed to be comfortable with that), by focusing on important instruments at important time points to reduce the risk for questionnaire fatigue, to supply pre-paid, pre-addressed envelopes in case of paper questionnaires, to remind participants, and to show participants that their contribution counts by thanking them for their participation. We caried out all of these measures in the studies included in this thesis. Had the studies been designed today, it is possible that an option to participate through electronic questionnaires could have further reduced missing data. However, with a majority of participants in studies B and C being >68 years old, it is reasonable to believe that most of the participants were more comfortable with printed than electronic questionnaires. Furthermore, collecting data from different sources increases demands on data logistics and resource use. Another measure for reducing loss to follow-up is to make sure that all questions make sense. This was included in the face validation of the questionnaires where we tried to enhance the instruments to prevent loss to follow-up of individual questions.

Another way of handling the problem of loss to follow-up is to use outcome measures where loss to follow-up can be controlled. Examples of such measures are length of hospital stay and postoperative complications where information can be obtained from hospital records as long as participants do not withdraw their consent. Our experience was that it was more common that participants did not want/have the strength to continue to actively contribute to the studies than that they wished to withdraw their consent. We chose to include both patient-reported outcome measures and information from hospital records in order to use the full palette of information relevant for both participants and healthcare providers.

There are also ways of handling loss to follow up when analysing study results. One is sensitivity analyses, where a commonly used strategy is to assess the maximal change in outcome in case the participants lost to follow-up had had different outcomes. This can be useful in studies with small numbers lost to follow-up and high rates of positive outcomes, while it is not useful in studies where this type of sensitivity analysis makes conflicting results possible.[73] Another way is to perform imputation techniques, preferably multiple imputation. While it may feel counter-intuitive to perform imputation for outcome measures, this has been recommended.[74] We have used the complete case method, that is only analysing participants with available data for all variables included in the statistical models, for all studies included in this thesis. This was feasible since the covariates included in the adjusted analyses showed low rates of missing data. Had these rates been higher, this approach would have resulted in a higher than acceptable loss of participants finally analysed. For the studies where statistical analysis plans were formulated, a paragraph on this was included stating that multiple imputation would be performed for covariates in the case of higher rates of missing data than acceptable.

4.4 TABLES

In addition to table 1, the results of the study are generally provided in one or more tables. Paper I included only one result table, while papers II, III, and V present both crude results and results from statistical models in separate tables. It is generally recommended to present results in terms of absolute numbers instead of just relative results, since this adds important information on the absolute effect.[57 75] In the case of rare outcomes, a small absolute effect can result in large relative effects. Thus, paper I should have been supplemented with an additional table showing crude numbers for the outcomes reported.

4.5 FIGURES

In addition to reporting results in tables, results may also be presented with figures. This could be bar charts, charts showing change over time, or radar plots for composite outcome measures. While figures generally help intuitive understanding of results, we have generally refrained from using figures in the articles in this thesis and instead used figures in conference presentations or lectures where instant understanding is of higher importance. However, in paper V we included a figure presenting the results for the main outcome measure. It helped illustrate the similarity between the groups in a way that at least I could not see just by looking at the numbers in the table and highlighted the use of well-chosen figures in articles.

4.6 REPORTING OF SCIENTIFIC RESULTS

The main output for scientific results is through peer review journals. However, this channel can be complemented by other means of communicating results, such as international conferences, national professional media, common media channels, and relevant patient associations. Since discoveries within the field of physical activity often result in recommendations directed to the general public or general practitioners, results often benefit from a wider dissemination. All results in this thesis have been published in or submitted to (paper V) peer review journals. We also plan on using other channels described above.

5 DISCUSSION

The combined results from the studies in this thesis imply that habitual leisure-time physical activity before cholecystectomy and colorectal cancer surgery is associated with better postoperative recovery, but that this association cannot easily be translated into a recommendation for pre- and postoperative physical activity for patients newly diagnosed with colorectal cancer.

Only one of the studies, study A, rejected the null hypothesis for the primary outcome measure. This was for one of the two parts of the primary outcome measure, where the null hypothesis for the more relevant outcome measure of return to work within one week could not be rejected. However, it could be argued that only one of the three studies to report "null results" on an overall level. Both studies A and B highlighted important associations between habitual leisure-time physical activity and recovery after cholecystectomy and colorectal cancer surgery, albeit that these results should be considered exploratory. The first results from study B (paper II) might reflect a lack of power, with a risk for type II errors, with several associations not reaching the 5% significance level. Study C on the other hand was designed to determine the effect of pre- and postoperative exercise on various aspects of postoperative recovery. The intervention resulted in no positive effect on any of the outcomes reported, and the null hypothesis should be considered true for the specific intervention tested in this study and the outcomes reported.

5.1 HABITUAL PHYSICAL ACTIVITY AND RECOVERY AFTER CHOLECYSTECTOMY

As described in the introduction, there are several studies reporting an association between physical activity and the risk for developing gallstone disease requiring cholecystectomy.[10 11] To my knowledge there are no other reports on the association between physical activity and recovery after cholecystectomy. There are a few reports where level of physical activity has been used as a way of measuring postoperative recovery, but where preoperative level of physical activity has not been compared to postoperative recovery.[76 77] Hence, the results presented in paper I add important new knowledge to this field. While these results are in line with what could be anticipated, it is important to show that a simple instrument for assessing leisure time habitual physical activity can help predict postoperative recovery.

5.2 HABITUAL PHYSICAL ACTIVITY AND RECOVERY AFTER COLORECTAL CANCER SURGERY

For the association between habitual physical activity and postoperative recovery after colorectal cancer surgery, a systematic review and meta-analysis was published in 2019,[78] where one relevant study was identified as reporting results on this association,[22] in addition to paper II (paper III was not published when their search was performed).[78] The other studies reporting results for colorectal cancer patients included in the systematic review were either interventional,[79] reporting results only for composite frailty measures,[80] or reporting associations between mostly functional capacity measures and postoperative recovery.[81] Performing this type of systematic review and combining results for all types of cancer surgery does not account for the differences in surgical trauma between for example breast cancer surgery and colorectal cancer surgery, which makes the overall results from the meta-analysis hard to interpret. The other study reporting associations between preoperative level of physical activity and postoperative recovery after colorectal cancer surgery assessed level of physical activity with the LASA physical activity questionnaire in addition to using several measures of physical fitness.[22] They reported that level of physical activity was associated with improved levels of in-hospital mortality, discharge destination, and length of hospital stay, and that inclusion of level of physical activity better predicted these outcomes than models with other known risk factors. Since this study was performed with another instrument for assessing level of physical activity than study B, and level of physical activity was dichotomised, it is hard to compare effect sizes between the two studies. It is interesting to see that they reported an association with short-term mortality, the most undeniable of all outcome measures. However, this could probably not be seen in a Swedish population since in-hospital mortality is rare. Our results from study B showed a 1% 30-day mortality while study C showed a 0.6% 90-day mortality, with no in-hospital mortality. With such low rates of mortality, a very large sample size would be required in order to have sufficient power to detect a difference. Another interesting thing with this study was the use of prediction modelling. When studies A and B were analysed, I was not aware of these types of analyses. However, given the limitations in observational studies of physical activity discussed previously, analyses with prediction models would possibly have been more appropriate for the intended use. Given the lack of studies reporting on this association, and the lack of effect from the intervention in study C, we have decided to use the data from study C to analyse prediction models including level of physical activity for the postoperative recovery measures reported in paper V. For the study in the systematic review published after paper II, this focused on functional capacity measures.[81] However, they also included the LASA physical activity questionnaires. Unfortunately, the association between level of physical activity and postoperative recovery was only reported for time to recovery of physical functioning, where the odds ratio was 0.994, p=0.054. Irrespective of whether this should be reported as statistically significant or not (se previous discussion regarding statistical significance), it is hard to consider an odds ratio of 0.994 to be clinically relevant. In addition to the studies identified in the systematic review published in 2019, another observational study was recently reported of more than 4 600 patients with colorectal cancer in Taiwan.[82] The study suffered from not reporting how level of physical activity was assessed, limiting the implication of the results. However, they reported an association between preoperative level of physical activity and overall postoperative complications and postoperative mortality, while this was not reflected in differences for any specific type of complications despite the large sample size.

5.3 PREOPERATIVE EXERCISE INTERVENTIONS AND RECOVERY AFTER COLORECTAL CANCER SURGERY

As described in the introduction, there are several RCTs with preoperative exercise interventions in colorectal cancer patients, in addition to non-randomised trials. While several of these may aid in developing interventions that are feasible and effective for improving functional capacity, I have only identified two prior RCTs including colorectal cancer patients, that were designed to determine the effect on clinically relevant outcome measures after preoperative exercise interventions.[48 49] Both of these studies aimed for a minimum of four weeks preoperative exercise, but resulted in approximately six weeks of mean preoperative exercise, compared to a median of 15 days for study C. Another difference between the two previous studies is that the two other studies had preoperative exercise interventions which were a combination of supervised (once weekly in one study, and 1-3 times weekly in the other study) and home-based exercise interventions, while the intervention in study C was exclusively unsupervised. Interestingly, one of the two previous studies showed a 50% reduction in postoperative complications as well as other relevant outcome measures,[48] while both the other previous study and study C showed no effect on similar outcome measures.[49] There were two main differences between the study reporting effect after preoperative exercise and the two studies reporting no effect. One was that the study reporting effect included major abdominal surgery for both benign and malignant diseases, while the two other studies were restricted to colorectal cancer patients. The other main difference was that the aerobic exercise intervention in the study reporting effect included high intensity training (85% of peak work rate), while the two other studies only included moderate-intensity aerobic activity. If the results from the study reporting effect could be repeated for a colorectal cancer population, this would be highly interesting. It is also reasonable to believe that it would be cost effective, while the report analysing health economics from that study was not very convincing regarding cost-effectiveness.[83]

While the other RCTs and non-randomised studies designed as pilot or feasibility studies, or to compare different types of interventions, have little bearing on whether prehabilitation should be implemented or not, there are some aspects from these studies that could be discussed. One is the discussion between supervised and unsupervised exercise. Several authors have proposed that supervised exercise is more effective, and this has been reported in a recent re-analysis[84] of two previous RCTs.[40 41] The authors of the first report from an RCT evaluating the additive effect of supervised sessions once weekly concluded that the addition of supervised sessions did not further enhance postoperative walking capacity,[41] but the post hoc analysis of the same study concluded that supervised sessions improved functional capacity postoperatively.[84] While this is not obvious from the results of this specific study, it is possible that supervised sessions are more effective than unsupervised exercise, based on the condition that participants attend the sessions. However, getting participants to attend supervised sessions have been an obstacle reported from several studies. Carli et al. reported an adherence of 68% to supervised sessions.[49] There are also studies reporting problems recruiting participants to supervised interventions if the participants live too far from the hospital. One example is a study by Dunne et al. where 1/3 of eligible participants were not recruited due to this reason.[85] However, another RCT offered home-based supervised sessions and had similar recruitment issues, with lack of time for planned exercise being the most common reason.[86] Home-based exercise interventions have also been reported to be appreciated by colorectal cancer patients.[87] The intervention in study C was both home-based and unsupervised, which limited these obstacles, while this may possibly have lowered adherence to the intervention. In the study by Dunne et al. only one third of eligible participants were recruited. The last third could not be recruited due to too short time preoperatively. The time to surgery varies greatly between countries, but in some time periods, time to surgery was a reason for many eligible participants not being recruited to study C as well.

Another aspect of the intervention is high intensity vs moderate intensity aerobic activity. As discussed previously, this is one difference between the study by Barberan-Garcia et al. on one hand and Carli et al. and study C on the other hand. However, this can be further problematised. In a recent report by the Montréal-based research group, preoperative interventions with high intensity interval training was compared to moderate intensity activity.[43] They reported that functional capacity increased similarly in the two groups preoperatively. There have also been reports of studies aimed at high intensity training where colorectal cancer participants have not been able to reach this intensity.[86]

There are some previous reports of studies where the interventions have been similar to the intervention in study C. A small RCT from 2014 determined the effect of a pre- and postoperative multimodal intervention to an isolated postoperative intervention in 77 patients with colorectal cancer.[40] The exercise component was home-based and unsupervised, and instructed to be of moderate intensity during 150 min weekly, divided into three 50-minute sessions. They reported an increase in functional capacity preoperatively for the prehabilitation group with similar trajectories postoperatively, but with a higher starting point, similar to the theoretical idea of prehabilitation. This implies that an intervention similar to the intervention in study C could improve functional capacity. Another non-randomised study with historical control reported effect on delirium but not on any of the other clinically relevant outcome measures in 627 major abdominal surgery patients (predominantly colorectal cancer) following an intervention similar to ours.[88]

Several systematic review articles have included a wide range of both surgical procedures and preoperative interventions (preoperative dietary, psychological as well as various forms of exercise interventions). While these serve well for identifying studies with prehabilitation before specific types of surgery, the meta-analyses performed often make little sense. A conclusion regarding the effect of any prehabilitation before cancer surgery is not easier to translate into clinical practice than a conclusion regarding the general effect of medication for cancer, or the general need for surgery in case of abdominal pain. This field of research deserves the same amount of specificity as other fields of medicine. When an intervention has been shown effective for one type of surgical patients, it's tempting to extrapolate these results to other surgical populations. However, the results from study C is one example where this wasn't successful, with short-term inspiratory muscle training previously reported to be highly effective in thoracic surgery populations. This underlines the need for scientific evaluation before interventions are translated to different surgical populations. Unfortunately, preoperative smoking cessation was implemented with weak underlying evidence for several types of surgery, as described in the introduction. Demanding more specific scientific evidence for preoperative exercise interventions creates a double standard for assessing the scientific evidence for preoperative lifestyle interventions. Nonetheless, increasing the underlying evidence for preoperative smoking cessation should be preferred over implementing preoperative exercise interventions without underlying sound scientific evidence.

5.4 IMPLICATIONS OF THE RESULTS

As described in the introduction, it's important to separate results from associations between preoperative level of habitual physical activity and preoperative exercise interventions. If this is not done correctly, the wrong conclusions may be drawn from observational studies. Our hypothesis was that the associations reported from study B could be translated into effect from an intervention tested in study C. However, the intervention tested was not effective for improving postoperative recovery. This should lead to two conclusions. The first is that we have even more compelling evidence of the positive health benefits from regular physical activity for the general population. The second is that we do not have enough scientific evidence for general recommendations on preoperative exercise interventions for colorectal cancer patients. With this said, it is still possible that preoperative exercise interventions could improve recovery after colorectal cancer surgery. However, it is likely that this requires high intensity aerobic exercise, which demands measures to assure adherence to the intervention. It is also possible that it needs a longer duration than current standardised lead times allow for, which underlines the need for studies on the safety of delaying treatment for colorectal cancer surgery. Effective interventions need to be established within high quality scientific studies.

However, recommendations for preoperative exercise interventions are already in place.[17] Broad recommendations for prehabilitation before cancer treatment have been critisised.[89] Recommending an individual recently diagnosed with cancer to rapidly change lifestyle habits he or she probably already knows are unhealthy, and which possibly have contributed to developing cancer, requires that this recommendation is probably going to be effective. While promotion of healthy lifestyle habits is cost-effective and should be given to everyone who needs them, the time of a cancer diagnosis is a life-determining event. When designing study C, we hypothesised that it could be a moment when an individual is easier to motivate into improving lifestyle habits, and to possibly maintain these, after being given a second chance to life after surviving cancer. However, this should not be used if there is no direct benefit for the individual at that time, since the time of a cancer diagnosis is also a time of information overload and stress. Another argument for not recommending an intervention not shown effective is that patients may blame themselves for not being able to prevent postoperative complications experienced. However, it is possible that preoperative exercise interventions could improve other aspects of postoperative recovery than those reported in paper V, such as mental recovery and quality of life in short and long term. These aspects will be analysed in a future report from study C. Another aspect of preoperative physical activity is that patients who enjoy being physically active should be recommended to continue to be active also after a colorectal cancer diagnosis. The discussion regarding whether to recommend preoperative exercise or not applies more to patients who are reluctant about being physically active. If effective interventions will be established, future recommendations will need to specify details on the type, intensity and duration of the exercise for each type of surgery, since it has now been shown that not all types of preoperative exercise interventions are effective for all patients.

6 CONCLUSION

The first conclusion from this thesis is that leisure-time habitual physical activity was associated with better recovery in some aspects after both cholecystectomy and colorectal cancer surgery. The second conclusion is that a short-term homebased exercise intervention before and after colorectal cancer surgery did not improve postoperative recovery in terms of self-assessed physical recovery, postoperative complications, length of hospital stay, or risk for reoperations or readmittances.

7 FUTURE PERSPECTIVES

The reported associations between level of physical activity and postoperative recovery should serve as yet an argument for recommending physical activity for the general population. In light of the paucity in previous research in this field and the relatively low sample size in study B, we will perform additional analyses of study C to describe the association between habitual leisure-time physical activity preoperatively and postoperative recovery.

Combined with another recently reported study, the lack of effect for the tested preoperative exercise intervention should lead to restrictive recommendations for preoperative exercise interventions until effective interventions have been reported.

Since existing studies may favour longer preoperative exercise interventions than possible within existing standardised referral pathways, and the effect of prolonged time to start of treatment for colorectal cancer is uncertain, we plan to determine this in a registry-based study where we will explore the association between time to treatment and mortality with a non-inferiority analysis. If we could show that start of treatment can be safely postponed, this would facilitate the delivery of future studies with longer preoperative exercise interventions for colorectal cancer patients, preferably including high intensity aerobic activity.

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