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STUDY PROTOCOL

Effect of tailored, intensive prehabilitation for risky lifestyles before ventral hernia repair on postoperative outcomes, health, and costs – study protocol for a randomised controlled trial (STRONG-Hernia)

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Abstract

Background

A substantial untapped potential for risk reduction may be fulfilled by applying intensive lifestyle interventions targeting the co-existing risky lifestyle factors Smoking, Nutrition (both malnutrition and obesity), risky Alcohol intake, and Physical inactivity (SNAP) before surgery. This trial will compare the effect of combined and individually tailored prehabilitation with standard care on postoperative outcomes, health, and cost-effectiveness in short and long term in participants undergoing ventral hernia repair. An interview study will be nested within the randomised trial.

Methods

The study is a multicenter, parallel-group, superiority randomised clinical trial. A total of 400 adult participants undergoing ventral hernia repair with ≥1 SNAP factor will be allocated to the individually tailored STRONG programme or standard care. The STRONG programme is initiated at least four weeks prior to surgery and consists of six sessions. It is delivered as one session a week, approximately, and includes patient education, motivational, and pharmaceutical supports. The primary outcome is postoperative complications requiring treatment within 30 days. Secondary outcomes address other surgical outcomes, changes in lifestyle, health, and cost-effectiveness. Follow-up takes place after 6 weeks (the end of intervention), at surgery, and 30 days, 90 days, and 6 months after surgery, respectively. Long-term

sensitive patient information (data on health and biometric data), and the Danish Data Protection Agency has not approved the sharing of all data with third parties. However, data can be made available upon reasonable request sent to the corresponding author.

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Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; CCI, Comprehensive Complication Index; CO, carbon monoxide; EQ-5D, European Quality of life 5 Dimensions; GSP, gold standard programmeme; HrQoL, health-related quality of life; ICD-10, International Classification of Diseases 10th revision; IMT, inspiratory muscle training, LoS, length of stay; NRS, nutritional risk score; P-PEth, plasma phosphatidylethanol; RCT, Randomised controlled trial; REDCap, research electronic data capture; SNAP, smoking, nutrition (malnutrition and obesity), alcohol, physical inactivity; U-cotinine, Urine cotinine; U-EtG, urine ethylglucuronide.

data on health and costs will be obtained from nationwide registries after two years. Eligible trial participants will be invited to a semi-structured interview study at baseline. Their reflections on the STRONG programme and the choice of participating in the trial or not will be explored.

Discussion

Many patients have multiple SNAP factors adding to the risk of complications related to surgery. As these are modifiable, prehabilitation may be an area with great potential for risk reduction. Nevertheless, no well-acknowledged and evidence-based strategies exist in the preoperative period. The STRONG programme is tailored specifically to the individual patient's preidentified needs including up to all five common risky SNAP factors and may tap into the large unused potential for risk reduction. Overall, the study will add important new knowledge on the effect of individually tailored prehabilitation on complications and other important outcomes in elective surgery, and also clarify if this intervention will have long-lasting implications.

Trial registration

www.clinicaltrials.gov (NCT06611462).

Introduction

A general problem to be solved

Surgery may be associated with postoperative complications and the common risky lifestyles Smoking, Nutrition (both obesity and malnutrition), risky Alcohol intake, and Physical inactivity (SNAP) are known to contribute to the risk of these in varying degrees. Daily smoking [1] and alcohol intake >2 drinks/day [2] each increases the risk of postoperative complications by around 50% whereas severe malnutrition [3], obesity [4,5] and physical inactivity [6,7] add to the risk in a varying degree.

The surgical pathway has been optimised with the Enhanced Recovery After Surgery (ERAS) [8,9] and improvement of surgical and anaesthesiologic techniques over the years. However, there is still a large untapped potential for risk reduction in the preoperative period where the modifiable SNAP factors can be targeted with preoperative interventions commonly known as prehabilitation. For smoking and alcohol, intensive programmes aiming at complete cessation four to eight weeks before surgery have been shown to reduce postoperative complications by up to 50% [10,11]. Likewise, preoperative nutritional interventions for patients with severe malnutrition have also shown a reduction of postoperative complications by around 50% [12–14]. Weight loss interventions in obese patients have only been sparsely investigated in other areas than bariatric surgery [15]. Preoperative physical training programmes have shown improvement of physical capacity. While most studies have not demonstrated a significant impact on postoperative complications [16,17], one recent study suggests a possible benefit [18]. The majority of the prehabilitation evidence comes

from studies only investigating one SNAP factor at a time [19] despite that up to around half of hospital patients have co-existing SNAP factors adding to their surgical risk [20,21].

The STRONG programme investigated in this trial will be tailored to and offered based on the individual participant's preidentified need for lifestyle-related risk reduction and will include up to all five risky SNAP factors if present. To the best of our knowledge, it will be the first programme to combine all five risky SNAP factors. Furthermore, our recent systematic review on multimodal prehabilitation [22] has shown that close to none of the published studies have had a demand for a pre-identified lifestyle-related need of risk reduction when offering prehabilitation. It also showed that most prehabilitation research has been conducted in cancer and other major surgery. Therefore, this trial will be a pioneer study regarding prehabilitation offered based on a pre-identified need as well as prehabilitation before minor surgery.

Ventral hernia repair and SNAP factors

Ventral hernia repair is one of the most common surgical procedures [23] and its benign nature allows time for preoperative optimisation to reduce postoperative complications [24]. Surgical site infections (SSIs) more than double the risk of ventral hernia recurrence [25], and since obesity and smoking are believed to be risk factors for SSIs, prehabilitation at least addressing these factors should be an obvious focus for research [26]. Nevertheless, limited research exists on SNAP prehabilitation. A recent systematic review on lifestyle prehabilitation before ventral hernia repair shows that the amount of research conducted is sparse [27]. Two randomised controlled trials (RCTs) on preoperative smoking cessation were identified [28,29]. Only the RCT investigating an intensive intervention showed a significant result with halving of complications (mainly wound complications) [28]. One study on combined obesity and physical activity intervention was identified. Short-term results showed a lower seroma rate at 30 days in the prehabilitation group and they were also more likely to be complication- and hernia-free [30] but there was no difference between the two groups at long-term [31]. No studies were identified on nutrition/malnutrition, but five studies were identified on a low-calorie diet's effect on weight loss in obese/morbidly obese patients [32–36]. However, none were RCTs and only one commented on postoperative complications. Finally, alcohol intervention was not evaluated in the review.

Overall, there is a call for prehabilitation including more SNAP strategies, and the European Hernia Society strongly recommends conducting high-quality studies of prehabilitation before ventral hernia repair [27].

The frameworks

Two frameworks are integrated in this study:

- Prehabilitation entailing preoperative recovery of dysfunctional organ systems prior to surgery [37,38]
- Lifestyle interventions being introduced by the operational model (based on principles of motivational interviewing, balanced decision-making, and the stages of change model) [39] and delivered as the Gold Standard Programme (GSP) for smoking cessation [40] and adapted versions for the other risky SNAP factors

Objectives

The main objective is to investigate the effect of the STRONG programme – a tailored, intensive SNAP prehabilitation programme – prior to ventral hernia repair for participants with at least one SNAP factor on postoperative complications requiring treatment within 30 days compared with treatment as usual. Secondly, we aim to investigate the effect of the programme on other surgical outcomes, changes in lifestyle, health and cost-effectiveness on short and longer term, as well as participant reflections and preferences.

The main hypothesis is that postoperative complications requiring treatment within one month can be halved by the STRONG programme compared with treatment as usual.

Materials and methods

Trial design and setting

The trial is a multicentre, parallel-group, superiority RCT with an allocation ratio of 1:1, see Fig 1. Furthermore, the project uses other nested relevant study designs to test the hypotheses and answer the research questions including qualitative methods [41], costs, and secondary analyses.

Participants will be recruited from three surgical departments in Denmark: Herlev Hospital, Zealand's University Hospital in Køge, and Zealand's Regional Hospital in Holbæk. More departments may be included if necessary.

The intervention takes place at the hospital from which the participants are included. It is carried out by local project nurses and staff from the participating centres certified by a training course carried out by the STRONG-team. The STRONG-team is anchored at the WHO-CC, Clinical Health Promotion Centre at the Parker Institute, Bispebjerg-Frederiksberg Hospital, part of Copenhagen University Hospital in Denmark.

	STUDY PERIOD												
	Screening	Enrolment & Allocation	Prehabilitation						Surgery	Postoperatively			
TIMEPOINT	$-t_1$	t_0	0w	1w	2w	3w	4w	5w	t_s	30d	90d	6m	2yr
ENROLMENT:													
Eligibility screen	X												
Informed consent		X											
Allocation		X											
INTERVENTIONS:													
Intervention: Prehabilitation		♦	—	—	—	—	—	—	♦				
Control group: Standard care		X							X				
ASSESSMENTS:													
Primary outcome measure										X			
Secondary outcome measures		X						X	X	X	X	X	
Cost-effectiveness data													X

Fig 1. Schedule of enrolment, interventions, and assessments. d : days, m: months, $-t_1$: time point for screening before enrolment, t_0: time of enrolment, t_s: time of surgery, w = week, yr = years.

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The trial is registered at www.clinicaltrials.gov (NCT06611462). Reporting of this study protocol followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline [42].

Eligibility criteria

Inclusion criteria. Participants ≥ 18 years old scheduled for elective ventral hernia repair with a defect < 8 cm and having at least one of the five risky SNAP factors:

- Smoking: daily smoking (defined as ≥1 cigarette or the equivalent of 1 gram of tobacco daily)
- Obesity: BMI ≥ 30 kg/m^2
- Malnutrition: Nutritional Risk Score [43] (NRS) ≥ 3
- Risky alcohol intake: Above 14 units/week during the last month (1 unit is defined as being equivalent to 12 grams of alcohol) [44]
- Physical inactivity: <30 minutes of physical activity per day or < 3.5 hours per week [45]

Upon inclusion, expected time before surgery must allow enough time for at least 4 weeks of prehabilitation.

Exclusion criteria

Exclusion criteria include. Other ventral hernias (para-stomal hernias and giant ventral hernias with defect ≥ 8 cm); pregnancy and/or breastfeeding; allergy or other contradictions to pharmaceutical or nutritional support or exercise in the STRONG programme; not able to give informed consent to the research project (e.g., age < 18 years, severe mental illness, compromised consciousness, language challenges); previous alcohol delirium or seizures; or withdrawal of consent.

Interventions

Intervention group. Participants in the intervention group receive the intensive prehabilitation STRONG programme prior to surgery which is tailored to meet the individual participant's need for lifestyle improvement (Fig 2) and thereby potential risk reduction at surgery. The programme includes a minimum of six sessions distributed over approximately six weeks (i.e., about weekly) including patient education, motivational support, and pharmaceutical support, such as nicotine replacement when indicated, and a hotline where the participants can contact the project staff. The education is directly related to their surgical treatment and includes 1) an introduction to the STRONG programme, level of motivation, ambivalence, pros and cons; 2) symptoms of addiction and/or withdrawal symptoms including their experiences and expectations; 3) relapse description and management; 4) benefits of lifestyle change on short and long term; 5) continued change of lifestyles including handling the risk of relapse; 6) and continued education based on the current conditions at the late stages in the programme.

It is introduced with the surgical recommendations in "Engage in the process of change" with the operational model [39]. It combines three behavioural change theories (Fig 3): motivational interviewing (the line tool) [46], decisional balance (the box tool) [47], and the transtheoretical model of change (the circles) [48]. The line tool: Participants will be presented with three lines with numbers each ranging from 0–10. Each is introduced with a statement setting the scene and then a related question making the participants reflect and rank their motivation (line 1), priority (line 2), and self-believe (3) in changing their lifestyle before the surgery. The box tool: Consists of a box divided into four sections asking the participants to fill out pros and cons for changing their current lifestyle or continuing it, respectively. The circles: A model describing how changing addictive behaviours occurs in stages and how recycling through the stages of change several times is a natural part of the progress towards quitting an addictive behaviour. The combination of the three

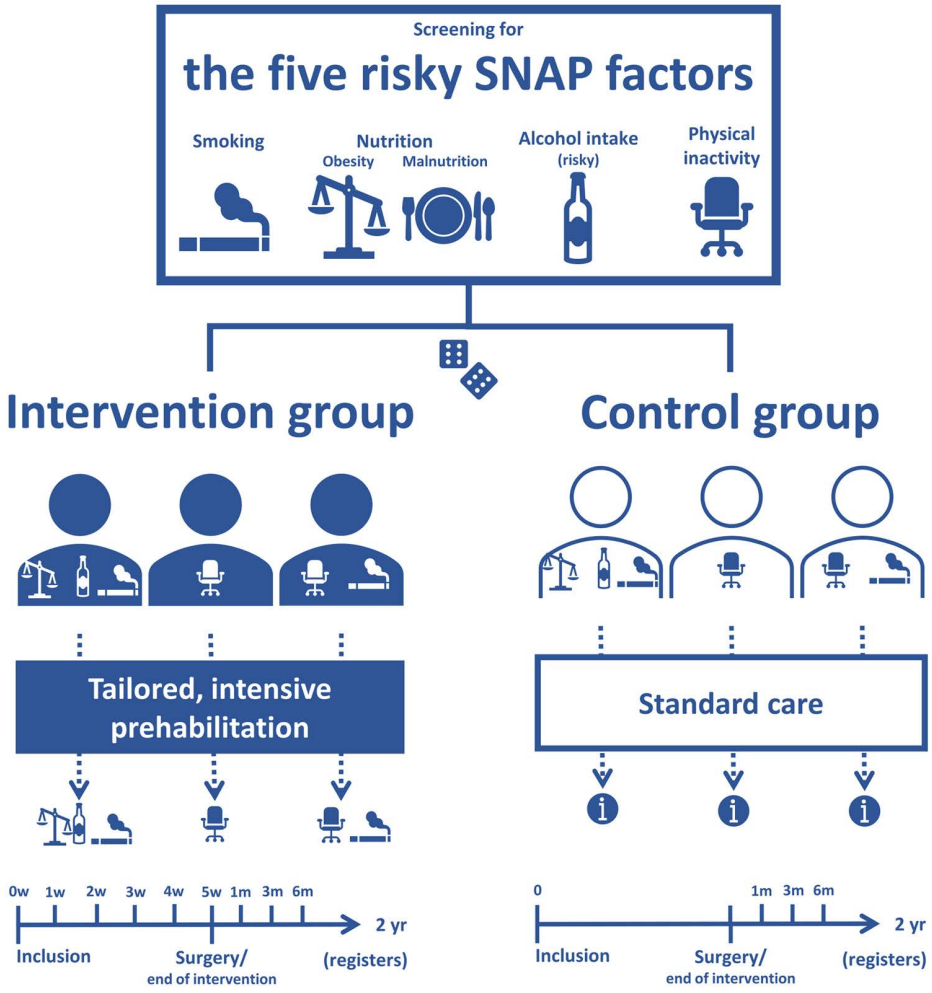

Fig 2. An overview of the STRONG-Hernia trial conduct. The figure illustrates the screening for the five risky SNAP factors (Smoking, Nutrition (obesity and malnutrition), risky Alcohol intake, Physical inactivity), the randomisation into the intervention and the control group, and how the intervention group (blue persons) receives a tailored, intensive prehabilitation intervention on exactly the risky SNAP factor that they present with whereas the control group (white persons) receives standard care. At the bottom of the figure is a timeline for scheduled visits and follow-ups in each group, respectively. i = information and demands for each hospital is: Herlev Hospital, generalized preoperative optimization including smoking and BMI (no cut-off); Zealand University Hospital, information on weight loss and smoking cessation with telephonic follow-up by nurses (aim of BMI < 35 and smoking cessation is mandatory); Zealand Regional Hospital, aim of BMI < 35 and no demand or help regarding smoking cessation. m: months, w: week, yr: years.

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theories facilitates a successful lifestyle change by facilitating the dialogue about lifestyle change, making the participant reflect on their ambivalence with pros and cons of changing/not changing their current risky lifestyle, inducing a feeling of empowerment to reach a decision, and achieving a better understanding overall of the process of change.

The smoking cessation intervention follows the Gold Standard Programme GSP [40] whose principles and structure have been used for creating the nutritional intervention, the alcohol cessation intervention used in previous RCTs [49,50], and the physical activity intervention. The focus of the STRONG programme generally lies on healthy days, i.e., days without smoking or alcohol intake, eating according to the nutritional plan and being physically active according to the plan. The number of SNAP factors involved is according to the individual participant's profile of risky lifestyles. For smoking, personalised nicotine replacement therapy based on the internationally acknowledged Fagerström test [51] for

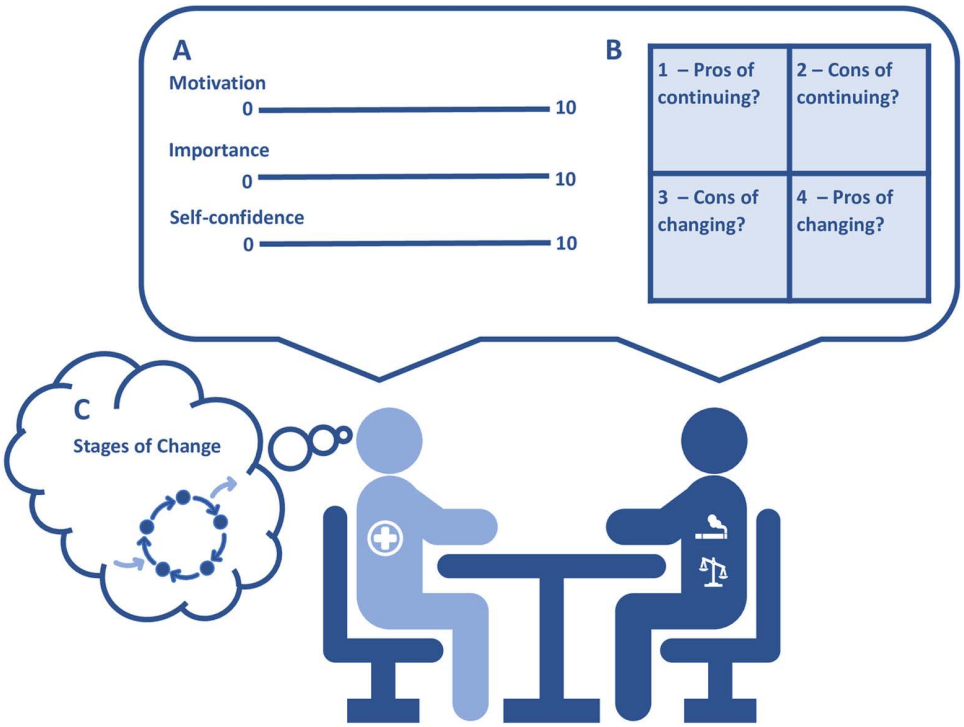

Fig 3. Behavioural change theories. Health care professional introduces behavioural change to a participant with risky lifestyles using A) the line tool through motivational interviewing and B) the box tool to make the participant reflect on changing lifestyle. Meanwhile, the health professional uses C) the circles in the stages of change model to evaluate where in the process of changing lifestyle the participant is.

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nicotine dependency and participant preferences is offered. The nutrition programme includes an individual assessment of the nutritional needs of the participant resulting in a nutritional plan targeting malnutrition and/or obesity. Participants with a risky alcohol intake are offered pharmaceutical support including thiamine (300 mg daily) and combined B vitamins, alcohol withdrawal prophylaxis and treatment (chlordiazepoxide 10 mg) and a low dose of disulfiram (200 mg × 2 weekly, administered only if the participant has a negative alcohol breath test). The pharmaceutical support for smoking and alcohol cessation interventions follows the national recommendations. All pharmaceutical support is an offer and not a requirement for participating in the intervention. It will be offered for free during the intervention period. The physical activity intervention consists of five minutes of inspiratory muscle training (IMT) and 25 minutes of other physical activities, adding up to 30 minutes per day. The IMT needs to be trained every day for the participants to be compliant, but the other physical activities can differ in time between days as long as the total amount of IMT and other physical activities add up to a total of minimum 3.5 hours per week. Furthermore, all participants in the intervention group will receive oral immunonutrition supplements in the five days up to surgery which both provide nutrition and boost the immune system [52]. The entire programme is adapted to the individual participant including guidance on supportive medicine. The STRONG prehabilitation will be considered completed if the participant has attended at least 75% of the six meetings.

At each meeting, we look at the current status and follow up using logbooks with self-reported information by the participants on the intervention since the last meeting as well as provide the motivational support and the patient education session. Participants are asked if they have experienced harms related to the pharmacological support. All potentially unknown harms will be reported and if serious they may lead to the trial being terminated early. The control group receives the project information as well as standard care of the involved departments, see Fig 2 (e.g., smokers may be offered a Very Brief Advice and referral to a municipal clinic). They also all have telephone access to the research nurse during the

project. All receive routine procedures on general patient information, thromboembolic prophylaxis and antibiotics, anaesthesia, surgical intervention, and postoperative care as used at the centres.

Control group. Comparators will be equal to the participants in the intervention group, i.e., having one to five risky SNAP lifestyles and undergoing elective ventral hernia repair, but receiving standard treatment in the preoperative period according to local routines instead of the intensive STRONG intervention (Fig 2). The control group will receive brief advice regarding the SNAP factors as part of the current standard protocol for surgical patients in the respective departments participating in the study.

The control group will receive the same project information about the study as the intervention group. Furthermore, they will receive the same routine procedures on general patient information, thromboembolic prophylaxis, antibiotics, anaesthesia, surgical intervention, and postoperative care used at the centres as the intervention group. Standard treatment regarding the SNAP factors for the involved hospitals is very brief information on weight loss and/or smoking cessation (Fig 2).

All participants in both groups are allowed to seek and use any support available outside the project, e.g., free municipal guidance on lifestyle change.

Criteria for discontinuing or modifying allocated interventions. Participant withdrawal from the study is an option at any point and for any reason without impacting any future investigations and/or treatments at the site. The investigator may discontinue any participant's participation for any reason, e.g., an adverse event, safety concerns, or failure to comply with the protocol. The study may be terminated by the principal investigator at any time. Reasons include but are not restricted to unsatisfactory fulfilment of the design, enrolment of participants, keeping the time schedule, or administrative agreements.

Strategies to improve adherence to interventions. Adherence to the intervention is measured as meeting adherence registered during the intervention and follow-ups. The motivation work conducted at each meeting and the 24/7 hotline should help keep up meeting adherence and improve the number of healthy days the participants have between the meetings. Participants will fill out logbooks at home regarding their risky lifestyles, and the lifestyle changes will then be monitored by interviews at the meetings and validated by objective measures as well as blood and urine markers. The general interest among participants regarding their personal results of measurements and monitoring may further improve adherence to intervention.

Outcomes

No core outcome set exists for trials on prehabilitation before elective surgery or ventral hernia trials, but a new scoping review gives an overview of the different outcomes reported in randomised trials of surgical prehabilitation [53]. Many of the outcomes reported in this trial will be consistent with some of the most commonly reported outcomes in other prehabilitation RCTs across different kinds of surgery. Four clusters of outcomes will be evaluated: surgical outcomes, changes in lifestyles, health, and cost (Fig 4). All outcomes will be evaluated within the intervention and control group separately, if not stated otherwise.

Surgical outcomes. The primary outcome is the number and proportion of participants with ≥1 postoperative complication requiring treatment within 30 days after surgery. This will also be evaluated at three and six months postoperatively as secondary outcomes. The complications will also be categorised according to the Clavien-Dindo classification [54].

Secondary outcomes also include the Comprehensive Complication Index (CCI) [55] at 30 days, three, and six months postoperatively. The CCI is calculated from the Clavien-Dindo classification [54] of the postoperative complications. Hernia-specific complications such as hernia recurrence will also be reported with number and proportion at 30 days, 90 days, and six months. Participants will undergo a physical examination at all postoperative follow-ups in addition to questions about complications.

Fig 4. Overview of the four clusters of outcomes in STRONG-Hernia. HrQoL: health-related quality of life.

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Other pre-specified outcomes include postoperative length of stay (LoS) defined as the total time spend in-hospital from the end of surgery and within the first 30 postoperative days, number and proportion of participants with readmission within 90 days, and the time back to work/usual activities asked at 30 days, three months and six months follow-up. Both LoS and time back to work/usual activities will be presented as median and/or mean. The number and proportion of participants with any visits to primary care at 30 days postoperatively will be calculated based on self-reported data from the 30-day follow-up.

Changes in lifestyles. The outcomes include the number and proportion of participants who eliminated all pre-operative risky lifestyles and those who showed any improvement compared to baseline. Both outcomes will be evaluated at the end of intervention, surgery, 30 days, three months, and six months postoperatively. For the separate SNAP factors, quitting a risky lifestyle is defined by:

- Successful smoking cessation defined as no use of any tobacco products at any time, validated by carbon monoxide (CO) in the breath test and urine-cotinine (u-cotinine)
- Malnutrition: not at risk of malnutrition defined by NRS < 3 [43]
- Obesity: BMI < 30 or 5–10% loss of body mass compared to baseline [56] without developing malnutrition (due to loss of fat-free mass) [3] at end of intervention/surgery and below 1% gain of body mass (as fat mass) at postoperative follow-ups

- Successful alcohol cessation defined as zero alcohol intake at 6 weeks of intervention/end of intervention and surgery and below risky limits (<14 units per week) at 30 days, 3 months, and 6 months postoperatively. Validation by blood phosphatidylethanol (B-Peth) and urine ethylglucuronide (U-EtG)
- Physical activity: at least 3.5 hours every week [45] throughout the study period

Any improvement is defined as a reduction of smoking or alcohol intake, any loss of body fat mass, any improvement in risk of malnutrition (including NRS score or albumin level [3]) or physical activity. Quit rates for the separate lifestyles will be descriptively reported.

In the intervention group, the association between motivation, priority, and self-efficacy, respectively, and the actual change in lifestyles 6 months postoperative will be examined. The participants' self-estimated motivation, priority and self-efficacy, respectively, for lifestyle changes are collected prior to the intervention. The information is measured on a scale from 0–10 (10 being the highest level) for each participant in each of the three areas using the line tool (line 1: importance of avoiding complications; line 2: importance of changing lifestyle now; line 3: self-efficacy of actually changing lifestyle), Fig 3. Another outcome is themes in participants' reflections on advantages and disadvantages of the intervention. In the intervention group, the participants will use the box tool to describe their reflections on the advantages and disadvantages of the lifestyle intervention prior to beginning the intervention. Themes will be derived through qualitative analysis. Finally, associations between meeting adherence and change in risky lifestyle in the intervention group will be explored. Meeting adherence is defined as attendance at meetings and measured as a proportion. Completion is defined as attending ≥75% of meetings.

Other pre-specified and descriptively reported outcomes are the number and proportion of participants with an improvement in ASA score level compared with baseline and related to an improvement of one or more risky lifestyles, and the number and proportion of participants with improvement in frailty score compared to baseline. Both outcomes will be evaluated at the end of intervention, at surgery, after 30 days, three months, and six months of follow-up. Frailty is measured by Fried's Modified Frailty Score [57]. This frailty scale is chosen as it is associated with the development of complications [57].

Health. Health-related quality of life (HrQoL) will be measured by the European Quality of life 5 Dimensions (EQ-5D) instrument [58] in a Danish translated validated version [59], a generic and well-used instrument in many clinical studies. It includes the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and each is divided into five levels of perceived difficulties. The higher the level, the more challenges are perceived by the participant. The overall health will be evaluated with a visual analog scale going from 0 to 100 with a higher score representing better health. Health-related quality of life will be assessed at baseline and then again at end of intervention, at surgery, and at follow-up 30 days, three months, and six months after surgery. Outcomes will be calculated as the number and proportion of participants with improvement of HrQoL compared with baseline at the different time points.

Morbidity after two years is measured as grouped diagnoses groups via the International Classification of Diseases 10th revision (ICD-10) Danish version [60] based on data from the Danish National Patient Registry [61] and will be descriptively reported.

Through qualitative analysis of transcribed semi-structured interviews, themes related to the participants' reflections on the STRONG programme, their health status, changing lifestyle, and participating in the STRONG-Hernia-trial will be derived and reported.

Costs. Costs will be reported after 30 days, six months, and two years postoperatively as a comparison between intervention and control group. Costs will be measured as individual direct and indirect healthcare costs per participant based on perioperative costs, time back to work or reuptake of previous activities, total stay, and visits/contacts to hospital and primary healthcare (from the national registries).

Cost-effectiveness based on data up to two years after surgery will also be reported. In addition to the costs mentioned above, data includes the EQ-5D as previously described, morbidity after two years measured as described above, visits and stay at hospital (via the Danish National Patient Registry [61]), visits in primary care (via the primary care registry, Danish National Health Service Registry [62]), prescribed medicine (via the Medicine Rregistry [63]), and mortality after two years (via the Danish Civil Registration System [64]).

Participant timeline

Participants will be enrolled, randomised to the intervention or control group, and begin the trial around the same time (preferably on the same day if possible). The intervention group will meet with project staff once a week, approximately, for a total of six meetings, Figs 1 and 2. Both groups will have a follow-up meeting at the time of surgery and after one, three, and six months. If more than eight weeks pass between inclusion and surgery, the control group will have an extra meeting after six weeks corresponding to the end of intervention meeting (the sixth meeting) in the intervention group.

Sample size

A total of 400 participants will be included. The power calculation is based on the literature presented in the introduction section showing that postoperative complications, in general, can be halved after intensive programmes for smoking, alcohol, and malnutrition [10–14]. The impact of physical activity is lower, and obesity is sparsely investigated but targeting co-existing SNAP factors like the STRONG programme should increase the effect due to positive interactions. Therefore, the main hypothesis is clinically relevant.

Postoperative complication rates after ventral hernia repair and the definitions vary (e.g., surgical site infections or respiratory complications, exclusively), and often different ventral hernias and different surgical techniques are mixed as one population in the literature (e.g., primary and secondary repairs, umbilical and incisional hernias, and mesh and non-mesh repairs). An RCT and a register-based study on primary ventral hernia repairs with mesh found similar complication rates (broad definition) of around 25% [65,66]. A cohort study has shown that reoperation rates underestimate the overall risk of recurrence by four- to fivefold and reported a combined reoperation and hernia recurrence rate of around 15% [67]. Furthermore, surgical site occurrences are common after both incisional and primary ventral hernia repairs [68,69]. In this trial, we include all complications requiring any treatment (including complications handled outside the hospitals such as medical pain prescriptions for prolonged pain and antibiotics by general practitioners), hence, a higher complication rate could be expected. Finally, postoperative complications are more common in patients with risky lifestyles such as smoking, alcohol use disorder, and obesity [4,68,70], so we expect higher complication rates in the trial population than in the general ventral hernia repair population, which consists of a mixture of patients with and without risky lifestyles. For ventral hernia in participants with risky lifestyles, STRONG would expectantly reduce by half the overall rate of complications requiring treatment from conservatively 20% to 10%. When using 80% power and $2 \times \text{alpha} = 0.05$, the number of participants needed is 2×199 participants.

Recruitment

The participant flow at the three included departments should be high enough to achieve the target sample size for which the primary outcome is powered. If necessary, more departments – including in the private sector – may be included after approval from the Ethical Scientific Committee and the Danish Data Protection Agency.

Recruitment takes place in connection with outpatient visits where participants are already in the hospital. Intervention and follow-ups are planned together with participants to accommodate their wishes within the framework of the study.

Assignment of interventions

Allocation. The allocation sequence will be generated with computer-generated random numbers. The randomisation is stratified by centre, number of risky SNAP factors, and hernia type. Participants are allocated in a 1:1 ratio in varying

block sizes from 2–6. The participants are randomised and allocated directly after giving informed consent by the project personnel enrolling them. They use a computerised randomisation system in research electronic data capture (REDCap) with the randomisation scheme hidden from all project personnel. The system is always accessible, and the use is logged. The allocation sequence as described above will be generated and uploaded to REDCap by a person not otherwise involved in the trial.

Blinding. Blinding intensive lifestyle intervention is rarely achievable. Allocation of the participants is not registered in the medical record system, but there is no assurance that participants will not disclose their intervention group allocation to clinicians and outcome assessors. However, all biomarker analyses for validation and all statistical analyses will be conducted blinded.

Data collection and management. Plans for assessment and collection of outcomes, baseline, and other trial data are illustrated in Table 1. At baseline, participants will be asked an elaborate set of questions regarding their risky SNAP factors identified at screening. Smokers will be asked questions to establish their smoking pattern, nicotine dependency, Fagerström's test for nicotine dependency [51], and previous experiences with smoking cessation [71]. For participants who are obese and/or at risk of malnutrition data will be collected regarding their nutritional intake [72], NRS score [43], and use of weight loss medication. Waist measurement and bioimpendance measurements will also be collected. The bioimpedance measurements at baseline include weight in kg, BMI, muscle mass, body fat mass, and total body water. Collected data for risky drinkers include the number of drinks per week (using the timeline follow-back method), AUDIT-C score [73], DSM5 score [74], and if the participant experiences withdrawal symptoms then also a CIWA-AR score [75]. The level of physical activity will be explored qualitatively equal to the screening. Most of the data items collected for risky drinkers, participants who are obese/at risk of malnutrition, and participants who are physically inactive at baseline will also be collected again at different meetings in the intervention group, and for all at the time point of the end of intervention/surgery, after 30 days, 90 days and six months postoperatively, see Table 1.

At each meeting during the intervention, participants in the intervention group are interviewed about healthy days, i.e., days without smoking or alcohol intake, eating according to the nutritional plan and being physically active according to the plan as well as use of any prescribed support medication.

Plans to promote participant retention and complete follow-up. All meetings are planned with the participants to accommodate their wishes best possible within the framework of the study. The Ethical Scientific Committee has approved that drop-out participants are asked for consent to follow them in the medical record system and a telephone interview. It is our experience from previous studies that 90% of drop-out participants accept this. Therefore, the primary outcome, complications requiring treatment, will be available for close to all randomised participants.

Data management and confidentiality. REDCap is used for safe storage of the gathered data. It is a secure platform approved by the Danish Data Protection Agency, Capital Region of Denmark. Only the project group has access and all access is logged. Throughout the trial, the conduction follows the Danish Data Protection Agency guidelines. After the study period has ended, all personal information will be destroyed and the other data will be stored at the Danish National Data Archive in line with the Danish and European guidelines for data management and protection.

Biological specimens for genetic or molecular analysis in this trial/future use. All participants have blood and urine tests sampled at baseline and the four scheduled follow-ups (surgery, 30 days, 90 days, and six months) for the identification of alcohol- and tobacco biomarkers (B-PetH, U-EtG and U-cotinine), for routine nutrition profile analyses (plasma-albumin), and routine analyses on blood-hemoglobin, plasma aspartate transaminase, and plasma-bilirubin as well as for measurement of possible new markers developed during the project period. In total, approximately 30 ml blood and 10 ml urine are collected at inclusion, end of intervention (only if it is more than a week before surgery), surgery, and at the three follow-ups (one, three, and six months). The intervention group will also have blood and urine colleced at the third intervention meeting. If additional informed consent is given, half of the samples are kept for analyses of new biomarkers possibly developed during the project period (see below).

Table 1. Overview of collected data items with time points.

Data variable	Definition & instrument	Inclusion	Intervention group only							Surgery	Postoperatively			
			0w	1w	2w	3w	4w	5w	5w		1m	3m	6m	2y
Screening														
Smoking daily	≥1 gram (y/n)	X							X	X	X	X	X	
Obesity	BMI > 30 kg/m² (y/n)	X							X	X	X	X	X	
Risk of malnutrition	NRS ≥ 3 (y/n) [43]	X							X	X	X	X	X	
Alcohol use	>14 units/w (y/n)	X							X	X	X	X	X	
Physical inactivity	<3.5 hours/w (y/n)	X							X	X	X	X	X	
Demographics														
Age	In years	X												
Sex	Men/women	X												
Housing	Living alone & type	X												
Education level	8 categories	X												
Socioeconomics	16 categories	X												
Charlson Comorbidity Score	Medical records [76]	X												
Surgical data														
Complications	Medical records + interview + clinical examination										X	X	X	
Clavien-Dindo	Medical records + interview [77]										X	X	X	
CCI	Medical records + interview [55]										X	X	X	
Hernia recurrence	Clinical examination										X	X	X	
Reop. for hernia recurrence	Medical records										X	X	X	
Length of stay	Medical records										X			
Readmission	Medical records											X		
Return to work/usual activities	Interview										X	X	X	
Primary care visits	Interview										X			
Intraoperative data	Medical records									X				
Lifestyle data														
Smoking history	Interview [71]	X												
Smoking status	Interview ± CO test	X		X	X	X	X		X	X	X	X	X	
Nutritional intake	Interview	X												
Nutrition status	Interview + measurements	X			X				X	X	X	X	X	
Alcohol intake	TLFB	X		X	X	X	X		X	X	X	X	X	
Alcohol misuse/dependency	DSM5-score [74], AUDIT-C [73]	X			X				X	X	X	X	X	
Alcohol withdrawal symptoms	CIWA-AR [75]	X		X	X	X	X		X	X	X	X	X	
Alcohol validation	Breath test	X		X	X	X	X		X	X	X	X	X	
Physical activity	Interview			X	X	X	X		X	X	X	X	X	
ASA score	Medical records + interview [78]	X			X				X	X	X	X	X	
Frailty score	Measurements + interview [57]	X			X				X	X	X	X	X	
Health data														
HrQoL	ED-5Q [58]	X			X				X	X	X	X	X	
Morbidity	Register-based [61]													X
Patient reflections	Semi-structured interview	X												
Cost data														
Healthcare costs	Register-based [61–64]										X		X	X
Intervention specific data														
Participant expectations	The line tool [46]		X											
Participant reflections	The box tool [47]		X											

(Continued)

Table 1. (Continued)

Data variable	Definition & instrument	Inclusion	Intervention group only						Surgery	Postoperatively			
			0w	1w	2w	3w	4w	5w	5w		1m	3m	6m	2y
Healthy SNAP days	Logbook + interview ± measurements			X	X	X	X	X						
Harms	Interview + medical records			X	X	X	X	X						
Compliance	Interview			X	X	X	X	X		X				
Laboratory tests														
Routine blood tests	Hgb, albumin, ASAT, bilirubin	X			X				X	X	X	X	X	
Smoking validation	Urine cotinine	X			X				X	X	X	X	X	
Alcohol validation	B-Peth, U-EtG	X			X				X	X	X	X	X	

Semi-structured interviews are conducted according to a semi-structured interview-guide. Interviews are structured questions orally discussed with the participants.

ASAT: aspartate aminotransferase, BMI: body mass index, B-PEth: blood phosphatidyl-ethanol, CCI: Comprehensive Complication Index, hgb: hemoglobin, m: month(s), n: no, NRS: nutritional risk score, reop: reoperation, U-Etg: urine ethyl glucuronide, w: week, y: yes.

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The routine analyses are performed at the local centres. The analyses of the established biomarkers on tobacco and alcohol are performed together for one factor at a time, mainly after collection of all samples with the aim of validating the self-reported data on lifestyle outcomes. During the project and until analysed, they will be stored in a biobank at the Parker laboratory at Bispebjerg-Frederiksberg Hospital.

New markers may be developed during the project period, and we will therefore (if additional informed consent is given) keep half of the samples in a pseudo-anonymised form stored for further analyses related to measurement of new markers for risk reduction at surgery developed during the study period (until December 31 2033). The samples can be used in future research only after approval from the Scientific Ethical Committee and the Danish Data Protection Agency.

Statistical methods

Analyses are conducted as Intention-to-Treat. They are done blinded, thus only the statistician will have access to the final dataset and not the investigators. We will use Fisher's exact test or Chi square test for frequencies (depending on the expected values), Mann-Whitney (non-parametric) for continuous unpaired variables, and $p < 0.05$ is chosen for statistical significance. To benefit future meta-analyses, we will also give the parametric results. This would also meet the tradition that costs are usually reported with means and standard error (SE), mean difference (MD), and 95% confidence interval (CI). Bootstrapping procedures are used to calculate the cost-effectiveness plane and the acceptability curve by repeatedly resampling the data (1,000 incremental cost and effect pairs). Descriptive outcome data will be reported with numbers, proportions (%), and 95% CI.

Sensitivity analyses will be performed for differences in local standards for the control groups among the surgical centres. Analyses as per-protocol, dose-response, prediction, sensitivity, and the other secondary analyses are done by logistic regression models including control for confounders and effect-modifiers and reported as odds ratios with 95% CIs which are considered significant if they do not involve 1.00.

Absolute risk reduction (ARR) is calculated as the events in the control group minus the events in the intervention group, and the relative risk reduction as the ARR divided by the events in the control group. The number needed to treat was calculated by 1/ARR. We will present the mortality as Kaplan-Meier plots and test by the log rank test. In case of missing health data, the lifestyle at baseline will be imputed as the results in order not to overestimate the results of changing lifestyle. This would expectantly impact the results to a similar degree in both groups.

Although the assumptions for the sample size calculation are conservative, they are associated with uncertainties. Furthermore, as this is the first RCT to be conducted with this intensive and broad prehabilitation intervention in minor surgery, a blinded interim data assessment will be conducted to assess whether the assumptions hold.

The qualitative analyses are done using Kirsti Malterud's approach of systematic text condensation [79]. After import into NVivo® qualitative data analysis software version 11, the systematic text condensation in the four steps takes place: 1) Total impression of all answers and identifying preliminary themes, 2) coding by identifying and sorting meaning units, 3) condensation into code groups, and 4) synthesising the condensates into a story grounded in the empirical data.

A more detailed statistical analysis plan (SAP) will be prepared and locked before any data analyses are started.

Oversight and monitoring

The project is managed daily and coordinated through close collaboration between the STRONG team and the involved departments of surgery. Participant panel meetings take place twice a year. The trial steering committee, which includes the principal investigator and local project leaders who oversee the funding, meets two to four times annually. The project management group holds monthly meetings. Additional meetings are arranged as needed.

Daily data monitoring is conducted by the STRONG team while an external independent researcher reviews it biannually. Data regarding any adverse events or other unintended effects related to the intervention are gathered during each meeting. In addition, the participants report on the hotline (telephone and mail). If such events occur, they will be reported to the Danish Medicines Agency. Furthermore, participants have the option to contact the staff through the provided hotline.

Ethics and dissemination

The trial is approved by the Danish Scientific Ethical Committee (protocol version 5, latest approval date 21th of May 2024, H-23028872) and the Danish Data Protection Agency (P-2023–14284). Minor changes were made between the different versions of the protocol including clarifications of included type of ventral hernias and addition of a planned sub-study estimating prevalence of SNAP factors in the potential study population. If any further important protocol modifications are made, they will be communicated to the involved parties, the Danish Scientific Ethical Committee, and the Danish Data Protection Agency. We will also update the trial registry at clinicaltrials.gov as soon as possible.

Consent. Participants will be approached by project personnel in person or by telephone in connection with the outpatient meeting and initial planning of surgery. Here, they will be screened for eligibility and eligible participants will be invited to participate in the trial. A project person will give oral and written information and answer questions. Written, informed consent for participating in the trial will be collected face-to-face for all participants upon inclusion and in time to allow enough time for prehabilitation (Fig 1).

Since new biomarkers may be developed during the trial period, participants will be asked for additional written, informed consent for keeping half of the blood and urine samples stored in a biobank for future research for potential further analyses related to measurements of potential new markers for risk reduction at surgery during the study period.

To investigate if eligible participants who decline to participate in the trial differ from those enrolled, we will ask for permission to follow them per- and postoperatively via the medical records (up to 6 months postoperatively) and for 2 years in the health registries. Those who accept are asked to provide informed consent.

Provisions for post-trial care. Participants in Danish investigator-initiated trials will be protected by the Danish Act on the Right to Complain and Receive Compensation within the Danish Health Service (Patientforsikringsloven). This act specifically applies to patients receiving treatment in Danish public hospitals and is a standard practice for such trials in Denmark.

Dissemination plans. We plan to publish all results when the trial is finalised. Both positive, negative, and inconclusive results will be sought to be published in scientific journals. Additionally, results will be communicated to the public through lectures as well as clinical, research, and public networks.

Trial status

Recruitment began March 4, 2024, and is ongoing. Participant recruitment is expected to be completed in 2.5 years. Data collection will be completed 6 months after last participant has been recruited, i.e., around March 2027. Results are expected to be analyzed within six months after last participant follow-up, thus September 2027. Current trial status will be updated continuously on clinicaltrials.gov.

Discussion

This RCT investigates the effect of intensive combined interventions for up to five risky lifestyles (smoking, malnutrition, obesity, risky alcohol intake, and physical inactivity) before the minor surgical procedure of ventral hernia repair. For smoking, the relatively small effect on public health of brief and even very brief lifestyle interventions are cost-effective at a population level and therefore important for society at longer term [80]. However, in surgical settings, the small improvements after brief interventions have not been shown to affect postoperative complications [10]. The GSP [40] has proven very effective with quit rates of around 50% for smoking and alcohol on short-term following the intensive interventions and a similar reduction in postoperative complications when intensive interventions are used prior to surgery [10,11]. Therefore, the STRONG programme is based on the GSP programme and uses intensive rather than brief interventions [81].

The combined programme is designed for individual delivery by one trained nurse as a part of the surgical pathway. This approach is based on previous experiences showing feasibility problems of several separate interventions delivered by separate personnel, increased administrative resources, and participant preferences toward one integrated programme. A pilot programme combining interventions for alcohol/drug addiction participants found that integrating multiple interventions into one session and delivered by one person was more feasible and aligned with participant perspectives [82]. This combined approach has been well-received in a recent intervention trial on perioperative smoking and alcohol cessation [83]. If the STRONG programme proves effective, it will be easier to implement into practice than a fragmented programme involving different personnel.

An intensive combined programme may be time-consuming for the participant. As ventral hernia repair may not be as life-altering as getting a cancer diagnosis and undergoing chemotherapy while awaiting major surgery (as in the STRONG-Cancer trial [84]), it may be more difficult and important to motivate participants and make them see the advantage of participating in this trial. Therefore, we expect a learning curve in inclusion rates.

This study will bring more knowledge on the effect of prehabilitation. Until now, most prehabilitation research is related to major/cancer surgery. If this trial shows positive results in participants undergoing minor surgery, it will expand the area of use and interest for prehabilitation significantly.

Supporting information

S1 File. SPIRIT 2013 checklist.
(PDF)

S2 File. Protocol approved by ethics committee.
(PDF)

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