



Original research

The preoperative level of physical activity is associated to the postoperative recovery after elective cholecystectomy – A cohort study



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H I G H L I G H T S

- We examined preoperative physical activity and the recovery after cholecystectomy.
- Physically active had fewer long sick leaves and shorter hospital stay.
- Physically active had better mental recovery post-operatively.
- Assessment of preoperative physical activity could give prognostic information.

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A B S T R A C T

Introduction: There is an increasing interest in the role of preoperative physical activity for postoperative recovery. The effect of preoperative physical activity and recovery after cholecystectomy is unknown. The aim of this study was to evaluate the association of self-reported leisure-time preoperative physical activity with postoperative recovery and complications after elective cholecystectomy due to gallstone disease.

Methods: Prospective observational cohort study with 200 patients scheduled to undergo elective cholecystectomy. Level of self-assessed leisure-time physical activity was compared with recovery.

Results: Regular physical activity was associated with a higher degree of return to work within three weeks post-operatively (relative chance (RC) 1.26, $p = 0.040$); with a higher chance of leaving hospital within one day post-op (RC 1.23, $p = 0.001$), as well as with better mental recovery (RC 1.18, $p = 0.049$), compared to physically inactive. No statistically significant association was seen with return to work within one week or with self-assessed physical recovery.

Discussion: In clinical practice, evaluating the patients' level of physical activity is feasible, and may potentially be used to identify patients being more suitable for same-day surgery. Given the study design, the results from this study cannot prove causality.

Conclusion: The present study shows that the preoperative leisure-time physical activity-level, is positively associated with less sick leave, a shorter hospital stay and with better mental recovery, three weeks post-elective cholecystectomy. We recommend assessing the physical activity-level preoperatively for prognostic reasons. If preoperative/postoperative physical training will increase recovery remains to be shown in a randomized controlled study.

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1. Introduction

All surgical procedures are followed by a phase of postoperative recovery, which inevitably includes suffering and resource consumption. Efforts have been made to enhance recovery and limit postoperative complications [1]. In recent years, preoperative lifestyle interventions have been increasingly in focus, with studies of the effects of both preoperative smoking and alcohol intake cessation on postoperative recovery being undertaken and, with such measures also being implemented into clinical practice [2,3]. In attempts to further reduce complications and enhance recovery after surgery, prehabilitation (preoperative physical activity) has been studied with promising results in patients undergoing thoracic surgery [4–7]. However, at present, there is insufficient evidence in support of prehabilitation as effective in reducing complication rates and improving recovery after abdominal surgery [8].

Lack of physical activity is considered to be the fourth most important risk factor for over-all death by the World Health Organization (WHO), due to its effect on cardiovascular disease and other non-communicable diseases [9]. Prospective observational studies have shown that physical activity reduces the risk of developing gallstone disease in both men and women [10,11]. Physical activity has known positive effects on aerobic fitness, muscle power, stress and mental state [12,13], which could potentially influence postoperative recovery positively. However, assessment of physical activity before cholecystectomy, and its association to the recovery process, has not previously been studied.

The aim of this study was to evaluate the association of self-reported leisure-time preoperative physical activity with postoperative recovery and complications after elective cholecystectomy due to gallstone disease. Our primary outcome was return to work. Secondary outcomes were length of hospital stay, self-assessed recovery, re-operations and re-admissions.

2. Material and methods

2.1. Patients

We conducted a prospective observational cohort study on patients scheduled for elective cholecystectomy, due to gallstone disease, between December 2012 and May 2014 at two participating hospitals. After giving informed consent, patients were asked to answer questionnaires preoperatively as well as 3 weeks postoperatively. These questionnaires included questions on the level of physical activity, sick leave, co-morbidity, Quality of Life (QoL), as well as on mental and physical recovery. The questionnaires were developed using well-validated and previously described methods [14–18]. An expert panel consisting of surgeons, cardiologist and physical therapist, statisticians and nurses specialized in surgery developed the questionnaire using validated questions regarding physical and mental recovery. The entire questionnaire was face-to-face validated by patients undergoing gallbladder surgery using validation methods described previously [14,19]. Exclusion criteria were: no informed consent and inability to understand information due to language barriers. A research nurse contacted all patients before sending the postoperative questionnaire three weeks postoperatively. Patients who did not return the questionnaire were reminded by a phone call from the research nurse.

With 150 evaluable patients there would be 80% power to detect improved postoperative recovery as measured by a reduction in average hospitalization of 1 day. This was considered to reflect a general recovery as described by outcomes such as sick leave [20].

Three hundred and eighty five patients planned for elective cholecystectomy were screened for eligibility (Fig. 1). In total 210 patients gave informed consent to participate in the study and answered the preoperative questionnaire. Of these, 10 patients

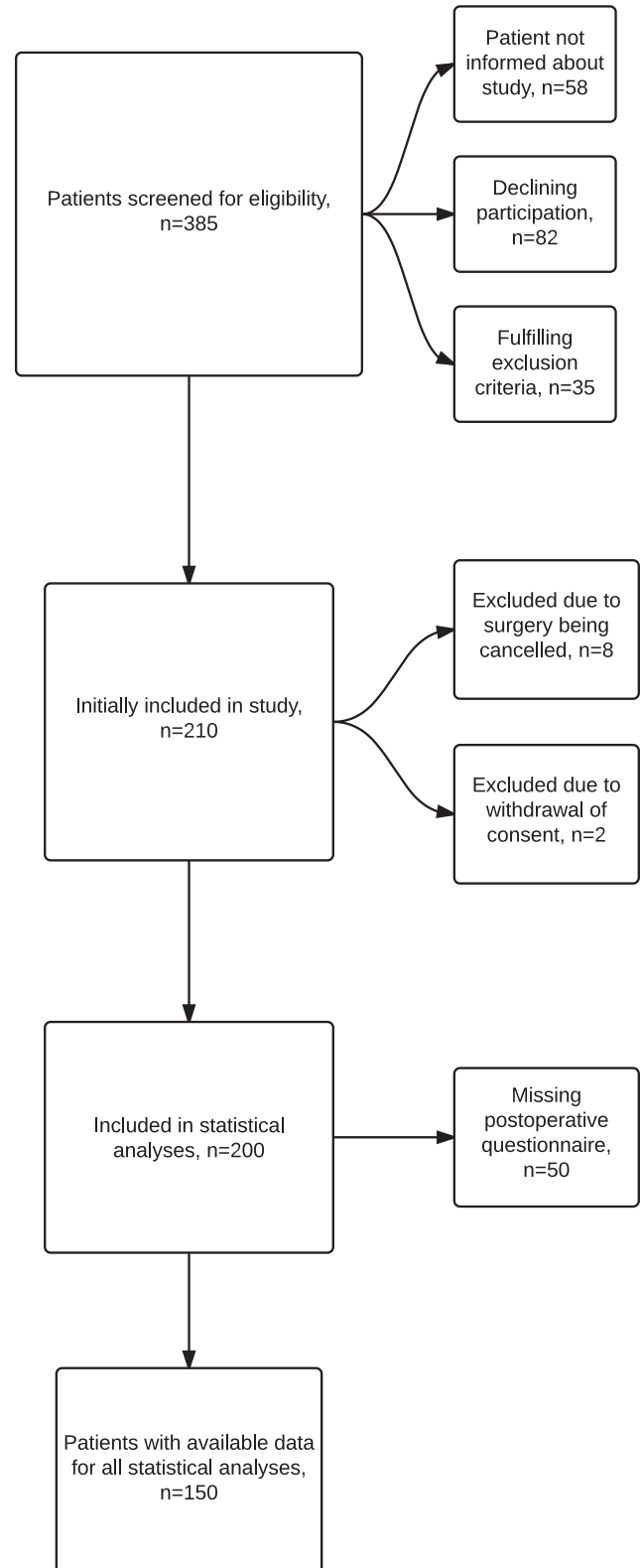


Fig. 1. Flow chart.

were excluded due to cancellation of the operation from various reasons ($n = 8$) and due to withdrawn consent ($n = 2$).

The final study population thus consisted of 200 patients. All patients were analysed regarding length of hospital stay, re-operations and re-admissions. Out of the 200 patients, 150 (75%) answered the postoperative questionnaire and were included in the statistical analyses regarding self-reported postoperative outcomes (length of sick leave, mental recovery and physical recovery). A dropout analysis was performed for the 50 patients who did not answer the postoperative questionnaire and showed no statistically significant differences except for age, with dropouts being slightly younger than patients who answered both questionnaires.

2.2. Self-assessment of physical activity

In the preoperative questionnaires, patients were asked to estimate their level of physical activity, according to the self-reported 4-level Saltin-Grimby Physical Activity Level Scale [18]. “How much do you move and exert yourself physically during leisure time? If your activity varies greatly try to estimate an average.” The answering categories were:

1. Physically inactive: Being almost completely inactive, reading, watching television, watching movies, using computers or doing other sedentary activities, during leisure-time.
2. Some light physical activity: Being physically active for at least 4 h/week as riding a bicycle or walking to work, walking with the family, gardening, fishing, table tennis, bowling etc.
3. Regular physical activity and training: Spending time on heavy gardening, running, swimming, playing tennis, badminton, calisthenics and similar activities, for at least 2–3 h/week.
4. Regular hard physical training for competition sports: Spending time in running, orienteering, skiing, swimming, soccer, European handball etc. several times per week.

The Saltin-Grimby Physical Activity Level Scale has been shown to have a high validity and reliability, being associated to cardiovascular risk factors [21,22], morbidity [23,24] and mortality [25]. The questionnaire referred to the last week before the patient answered. In our cohort only three patients considered their activity to be regular hard physical training and therefore group 3 and 4 were merged into one in the analyses, as previously has been described [24].

2.3. Basal characteristics

Factors that may affect postoperative rehabilitation were retrieved from the preoperative questionnaire; age, BMI, marital status, co-morbidity (hypertension, diabetes, hyperlipidaemia), depression, anxiety, preoperative pain, general quality of life (QoL), smoking and alcohol consumption. Type of surgery, laparoscopic or open surgery, was retrieved from the Hospital Administrative system.

Depression was evaluated with one single question with the answering options “yes”, “no” and “I don’t know”. This question has been found to correlate well to established depression scales [15]. Anxiety and preoperative pain were assessed with single questions according to Steineck et al. [14]. QoL was measured using the validated instrument EQ5D Visual Analogue Scale (0–100) [26,27]. General QoL, physical health and mental well-being were assessed in an ordinal seven-point Likert-type response format [28]. The patients indicated one of seven numbers on a line anchored by, for example, “no mental well-being” and “the best possible mental well-being”. Smoking was measured with one single question, with the answer alternatives: never-smoker, ex-smoker (age at cessation), yes

(less than once per week), yes (packs of cigarettes/pipe tobacco per week). Alcohol consumption was measured with a modified AUDIT-C scale adopted from Steineck et al. [14,19]. The cut-off for defined alcohol consumption in the statistical analysis was set at alcohol consumption at least once per week.

2.4. Outcomes

2.4.1. Return to work

Return to work/sick leave was assessed using two questions., “Have you been on sick leave after your operation?” (Yes/no) and “If yes, for how long time were you on sick leave?” (length of sick leave as well as degree in percent). In Sweden, the population is covered by public health insurance. The National Board of Health and Welfare issues guidelines including a recommendation of appropriate length of sick leave for different diagnoses and surgical procedures. For laparoscopic and minimally invasive cholecystectomies, the recommendation is up to one week except for patients with a very high physical load at work, for whom up to two weeks off work might be needed. For patients operated with open surgery, the recommended length of sick leave is up to two weeks for patients with no physical strain in their work, and up to three weeks for patients with a high physical load in their work. The vast majority of our patients were operated with a laparoscopic technique. To cover both the short and long sick leave recommendation we conducted two analyses for sick leave where sick leave was dichotomized as yes/no with a cut-off set at sick leave for more than one week and three weeks, respectively. Sick leave was analysed for patients at age 66 or younger, which corresponds to the retirement age in Sweden.

2.4.2. Length of hospital stay

Length of hospital stay was retrieved from the Hospital administrative systems and was measured as number of nights spent in hospital from the day of surgery until discharge. It was dichotomized with a cut-off set at a hospital stay of at least two nights.

2.4.3. Physical and mental recovery

Physical and mental recovery was self-assessed by the study subjects, using the single question: “To what extent do you feel fully physically recovered?” Answering categories were:

1. Not applicable, I don’t feel recovered at all.
2. I feel recovered up to 25%.
3. I feel recovered up to 50%.
4. I feel recovered up to 75%.
5. I feel completely recovered.

The question regarding mental recovery was constructed in exactly the same way. The answers were dichotomized into highly recovered (75–100%) and incompletely recovered (0–50%) for physical and mental recovery, respectively.

2.4.4. Re-operations and re-admissions

Re-operations and re-admissions were retrieved from the hospital administrative systems. All surgical procedures performed within 6 weeks after index surgery at the same hospital were considered as re-operations. Re-admissions were all admissions to a surgical ward within 6 weeks of index surgery at the same hospital.

2.5. Statistics

All data was collected in a database and statistical analysis was performed using SAS v.9.3 software (SAS Institute). Patient characteristics were summarized descriptively. To assess the objective of

the study a Poisson regression model with a robust error variance and with physical activity as a fixed effect was used [29]. Variables prespecified as possibly influencing postoperative recovery were age, type of surgery, smoking status, alcohol consumption and marital status. For length of hospital stay the hospital performing surgery was also included in the model as differences in routines regarding hospital stay can occur. The influence of these variables was adjusted for in the model by including them as additional factors and covariates in a multivariate model. To emphasize the positive possibilities from physical activity results were reported as relative chance, with 95% confidence intervals and p-values.

2.6. Ethical considerations

The study is approved by the Regional Ethical Board in Göteborg, dnr 180-12. The protocol was registered at clinicaltrials.gov, NCT01707121.

3. Results

3.1. Basal characteristics

Patient characteristics are seen in Table 1. More than half of the patients regarded themselves as lightly physically active (answering category 2) in leisure-time, preoperatively. Patients being regularly

active (answering category 3 or 4), suffered significantly less from overweight, diabetes, dyslipidaemia, pain, anxiety and depression. They also reported a higher QoL (total, mental and physical QoL) preoperatively, were more often married and they were also younger than their inactive peers. The highest rate of alcohol consumption (more than once per week) was seen in the regularly active patients, and the highest rate of smokers was found in the lightly active patients. All of these differences were statistically significant (p-value < 0.05).

3.2. Sick leave

Results of all adjusted analyses are seen in Table 2. For our primary outcome, length of sick leave, there was no statistically significant association between the degree of leisure-time physical activity and the subsequent postoperative chance of returning to work within one week. Men had a 39% higher relative chance of returning to work within one week compared to women (p = 0.004). Patients drinking alcohol less frequently than once per week, had a 51% higher relative chance returning to work within one week, than patients drinking alcohol more often (p = 0.037). Patients operated with a laparoscopic technique had more than a threefold higher relative chance of returning to work within one week, compared to patients operated with laparotomy (p = 0.029). In total 68% of the patients in working age returned to work within one week.

Table 1
Baseline characteristics of patients divided into level of physical activity.

	Level of physical activity				Total
	1	2	3–4	Not reported	
Patients % (n)	26.5 (53)	54 (108)	18.5 (37)	1 (2)	(200)
Age, mean years (SD) ^a	51.8 (12.7)	54.1 (14.9)	45.5 (15.3)	58.3 (–)	51.9 (14.7)
Sex:					
Female % (n)	73.6 (39)	67.6 (73)	56.8 (21)	50 (1)	67 (134)
Marital status ^a					
Married/Cohabiting %, (n)	66.0 (35)	69.4 (75)	70.3 (26)	50 (1)	68.5 (137)
BMI mean(SD) ^a	29.8 (6.1)	28.2 (4.8)	26.8 (4.9)		28.3 (5.2)
Obese (BMI > 30) % (n)	37.7 (20)	27.8 (30)	18.9 (7)		28.5 (57)
Co-morbidity ^{b,a}					
Yes, % (n)	34.0 (18)	33.3 (36)	10.8 (4)		29.0 (58)
Smoking ^a					
Yes ^c % (n)	11.3 (6)	14.8 (16)	10.8 (4)		13.0 (26)
Alcohol ^d					
Risk consumption % (n) ^d	18.9 (10)	18.5 (20)	27.0 (10)	50 (1)	20.5 (41)
Preoperative pain: ^a					
Moderate–severe % (n)	75.5 (40)	66.7 (72)	59.5 (22)	50 (1)	67.5 (135)
Anxiety: ^a					
Moderate–severe % (n)	39.6 (21)	32.4 (35)	24.3 (9)		32.5 (65)
Depression: ^a					
Don't know % (n)	5.7 (3)	10.2 (11)	10.8 (4)		9 (18)
Yes % (n)	17.0 (9)	8.3 (9)	0 (0)		9 (18)
Type of surgery:					
Laparoscopy % (n)	90.6 (48)	85.2 (92)	97.3 (36)	100 (2)	89.0 (178)
Laparotomy % (n)	9.4 (5)	14.8 (16)	2.7 (1)		11.0 (22)
Total QoL score ^{e,a}					
0–2% (n)	26.4 (14)	12.0 (13)	8.1 (3)		15.0 (30)
3–6% (n)	71.7 (38)	88.0 (95)	91.9 (34)	50 (1)	84.0 (168)
Mental QoL score ^{f,a}					
0–2% (n)	32.1 (17)	22.2 (24)	10.8 (4)	50 (1)	23.0 (46)
3–6% (n)	67.9 (36)	77.8 (84)	89.2 (33)		76.5 (153)
Physical QoL score ^{g,a}					
0–2% (n)	15.1 (8)	8.3 (9)	2.7 (1)		9.0 (18)
3–6% (n)	84.9 (45)	91.7 (99)	97.3 (36)	50 (1)	90.5 (181)
Eq5d5 (0–100), mean (SD)	63 (22.3)	71.9 (18.7)	78.2 (13.4)		70.8 (19.5)

^a p-value < 0.05 from Chi-square tests and ANOVA for categorical and continuous variables, respectively.

^b Defined as diagnosed with diabetes mellitus, hypertension and/or hyperlipidaemia.

^c Defined as all forms of current smoking.

^d Defined as alcohol consumption at least once per week.

^e “How would you describe your quality of life last month?” (0–6).

^f “How would you describe your mental well-being last month?” (0–6).

^g “How would you describe your physical well-being last month?” (0–6).

Table 2
Results from analyses for each endpoint variable in separate analyses.

Modelled	Model	Variable	Comparison	Relative chance*	95% confidence interval	P-value**	
Chance of return to work within one week	Unadjusted	Physical activity	Regular/Inactive	1.280 (0.80/0.63)	0.889–1.847	0.187	
			Light/Inactive	1.076 (0.67/0.63)	0.751–1.544	0.689	
	Adjusted	Physical activity	Regular/Inactive	1.278	0.879–1.858	0.199	
			Light/Inactive	1.047	0.739–1.483	0.796	
		Age				0.320	
		Sex	Male/Female	1.388	1.108–1.738	0.004	
		Type of surgery	Laparoscopy/Laparotomy	3.115	1.124–8.632	0.029	
		Smoking	No/Yes	1.315	0.770–2.246	0.315	
		Alcohol	Modest/Much	1.513	1.025–2.234	0.037	
		Marital status	Married/Alone	1.035	0.771–1.388	0.821	
	Chance of return to work within three weeks	Unadjusted	Physical activity	Regular-hard/Inactive	1.263 (1.00/0.79)	1.029–1.551	0.026
				Light/Inactive	1.148 (0.91/0.79)	0.920–1.433	0.221
		Adjusted	Physical activity	Regular/Inactive	1.263	1.011–1.579	0.040
				Light/Inactive	1.187	0.934–1.508	0.161
Age						0.631	
Sex			Male/Female	1.109	0.988–1.245	0.080	
Type of surgery			Laparoscopy/Laparotomy	2.475	1.044–5.870	0.040	
Smoking			No/Yes	1.125	0.908–1.396	0.282	
Alcohol			Modest/Much	1.121	0.944–1.332	0.193	
Marital status			Married/Alone	1.020	0.905–1.148	0.751	
Chance of hospital stay one day or less		Unadjusted	Physical activity	Regular/Inactive	1.265 (0.97/0.77)	1.080–1.482	0.003
				Light/Inactive	1.023 (0.79/0.77)	0.856–1.223	0.801
		Adjusted	Physical activity	Regular/Inactive	1.227	1.051–1.432	0.001
				Light/Inactive	1.085	0.921–1.277	0.329
	Age					0.930	
	Sex		Male/Female	0.930	0.812–1.066	0.298	
	Type of surgery		Laparoscopy/Laparotomy	3.581	1.654–7.753	0.001	
	Smoking		No/Yes	1.061	0.903–1.246	0.475	
	Alcohol		Modest/Much	0.965	0.857–1.096	0.621	
	Marital status		Married/Alone	1.006	0.879–1.151	0.932	
	Chance of feeling highly physically recovered at 3 weeks	Unadjusted	Physical activity	Regular/Inactive	1.161 (0.86/0.74)	0.910–1.480	0.231
				Light/Inactive	1.005 (0.75/0.74)	0.796–1.270	0.964
		Adjusted	Physical activity	Regular/Inactive	1.121	0.842–1.492	0.434
				Light/Inactive	1.084	0.839–1.399	0.539
Age						0.276	
Sex			Male/Female	0.968	0.856–1.248	0.734	
Type of surgery			Laparoscopy/Laparotomy	2.698	1.268–5.742	0.010	
Smoking			No/Yes	1.043	0.740–1.471	0.809	
Alcohol			Modest/Much	1.083	0.855–1.371	0.510	
Marital status			Married/Alone	0.946	0.767–1.167	0.604	
Chance of feeling highly mentally recovered at 3 weeks		Unadjusted	Physical activity	Regular/Inactive	1.200 (1.00/0.83)	1.037–1.389	0.014
				Light/Inactive	1.048 (0.87/0.83)	0.886–1.240	0.585
		Adjusted	Physical activity	Regular/Inactive	1.183	1.001–1.398	0.049
				Light/Inactive	1.068	0.885–1.240	0.492
	Age					0.600	
	Sex		Male/Female	1.020	0.920–1.130	0.708	
	Type of surgery		Laparoscopy/Laparotomy	1.220	0.924–1.611	0.160	
	Smoking		No/Yes	1.140	0.886–1.467	0.307	
	Alcohol		Modest/Much	1.162	0.969–1.395	0.106	
	Marital status		Married/Alone	1.037	0.895–1.202	0.625	
		Married/Live-apart	1.068	0.808–1.411	0.645		

*Numbers within brackets represent predicted absolute chance of outcome per level of PA.

** Numbers in bold show p-values <0.05.

When return to work within three weeks was analysed, patients with regular physical activity had a 26% higher relative chance of being back to work within three weeks than their inactive peers ($p = 0.040$). There was still an association related to the type of surgery and sick leave for more than three weeks, but not for sex or alcohol consumption. In total 91% of all patients in working age returned to work within three weeks postoperatively.

3.3. Length of hospital stay

There was a strong association between the self-assessed level of physical activity and the length of hospital stay ($p = 0.001$).

Patients with regular physical activity had a 23% higher relative chance of leaving hospital within one day after surgery. There was also a strong association between type of surgery and length of hospital stay, with patients operated with laparoscopic technique having 3.6 times higher chance of leaving the hospital within one day after surgery, compared with patients operated with laparotomy ($p = 0.001$). In total 82% of all patients were discharged within one day after index surgery.

3.4. Self-assessed recovery

In our analysis of self-assessed *physical recovery*, there was no

association between physical activity at baseline and feeling highly physically recovered, three weeks postoperatively. There was, however an association between the type of surgery and physical recovery, patients operated with a laparoscopic techniques had a 2.7 times higher chance of feeling recovered than patients operated with open surgery ($p = 0.010$). In total 77% of all patients felt highly physically recovered three weeks postoperatively.

For the analysis of self-assessed *mental recovery*, there was a statistically significant association between the preoperative physical activity level, and feeling highly mentally recovered three weeks postoperatively ($p = 0.049$). Patients with regular physical activity had an 18% higher chance of feeling mentally recovered, compared to those being inactive. None of the other analysed factors were associated with mental recovery. In total 88% of all patients felt highly mentally recovered three weeks postoperatively.

3.5. Re-operations and re-admissions within the first 6 postoperative weeks after primary surgery

Since there were so few re-operations and re-admissions (17 and 14, respectively) for included patients, only univariate analyses with Chi-square tests were performed (not included in table). There were no significant associations between physical activity and re-operations or re-admissions.

4. Discussion

The main findings of this study are that the preoperative leisure-time physical activity level of the patient, is positively associated with a shorter post-operative sick leave, and with a shorter hospital stay as well as with a faster psychological (mental) recovery, after elective cholecystectomy.

To our knowledge, the only earlier study regarding preoperative physical activity prior to cholecystectomy was conducted with breathing exercises. This study was a relatively small randomized controlled trial (RCT), comparing preoperative and postoperative incentive spirometry in patients undergoing cholecystectomy, showing effect on lung function but not analysing complications or other areas of recovery [30].

As far as we are aware this is the first study reporting on return to work/sick leave after abdominal surgery, in relation to preoperative level of physical activity. In Sweden, where all inhabitants are covered by the same national health insurance, sick leave is a relevant way of measuring actual recovery. Simultaneously, it is a factor that is of economic importance for the individual, the employer and the society.

Length of hospital stay in relation to prehabilitation has previously been studied in randomised controlled trials (RCT:s) in orthopaedic and thoracic surgery [31]. In a prospective observational study on patients undergoing colorectal surgery, the self-reported level of physical activity was associated with reduced length of hospital stay, and was the most robust predictor of postoperative recovery [32].

The association between increased chances for feeling mentally recovered postoperatively with a higher level of physical activity preoperatively, has not been reported previously in abdominal surgery. Mental recovery could be harder to link to direct economic benefits, but we suggest that it could be of social importance.

In clinical practice, evaluating the patients' level of physical activity using the Saltin-Grimby Physical Activity Level Scale is feasible, and can potentially be used for example to identify patients more suitable for outpatient surgery. Since leisure-time physical activity is generally not associated with high costs or serious side effects, and has well-established positive effects on numerous other forms of morbidity, a recommendation to all

patients planned for cholecystectomy to increase their physical activity seems reasonable. However, before routinely recommending organized preoperative physical exercise in the health-care setting, randomized controlled trials establishing the positive effects, are needed to justify the increased costs.

There are some limitations to this observational study. In the multivariate analyses we have adjusted for factors that are not directly affected by physical activity, although there may be associations. It is known that there are reciprocal interactions between physical activity and for example mental status, preoperative pain, BMI, co-morbidity or QoL. Since these variables may act as both barriers to physical activity and (positive) effects of physical activity these factors were not adjusted for, but reported as baseline characteristics. Hence, being an observational study, with no control-group or randomization, we cannot claim causality and the impact of other factors on postoperative outcomes cannot be separated from that of physical activity. Consequently, the observed effects in this study should be interpreted with caution and RCT:s are needed to prove causality. No correction for multiple testing was made and results should therefore be regarded as interesting findings rather than conclusive evidence. Another limitation of this study is that not all eligible patients were included or completed the study, reducing the external validity. However, the 50 patients who entered the study but did not answer the postoperative questionnaire did not differ significantly from patients who answered both questionnaires, with regard to patients' characteristics.

There are also strengths to our study; one is the use of the previously well-validated and easy-to-use Saltin-Grimby Physical Activity Level Scale, making it possible to implement the results directly into clinical practice. The study was also performed both in a university hospital and a district hospital, which adds to the external validity.

5. Conclusions

The preoperative leisure-time physical activity level was positively associated with fewer sick leaves, a shorter hospital stay and with better mental recovery after elective cholecystectomy. We suggest that the physical activity-level could be measured preoperatively for prognostic and logistic reasons. The effects of preoperative and postoperative training on recovery should be further studied.

Conflict of interest statement

No conflicts of interest reported. This study was financed through funds created by the Swedish Research Council and Region Västra Götaland, Sahlgrenska University Hospital.

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