Preoperative functional optimization for better surgical outcome

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PERIOPERATIVE PROGRAMME PÉRIOPÉRATOIRE

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Learning Objectives

- Address the pathophysiological factors which can influence outcome following surgery and cancer
- Introduce the concept of surgical ***prehabilitation***
- Review the literature of surgical prehabilitation and preliminary results

What if surgery could be done without:

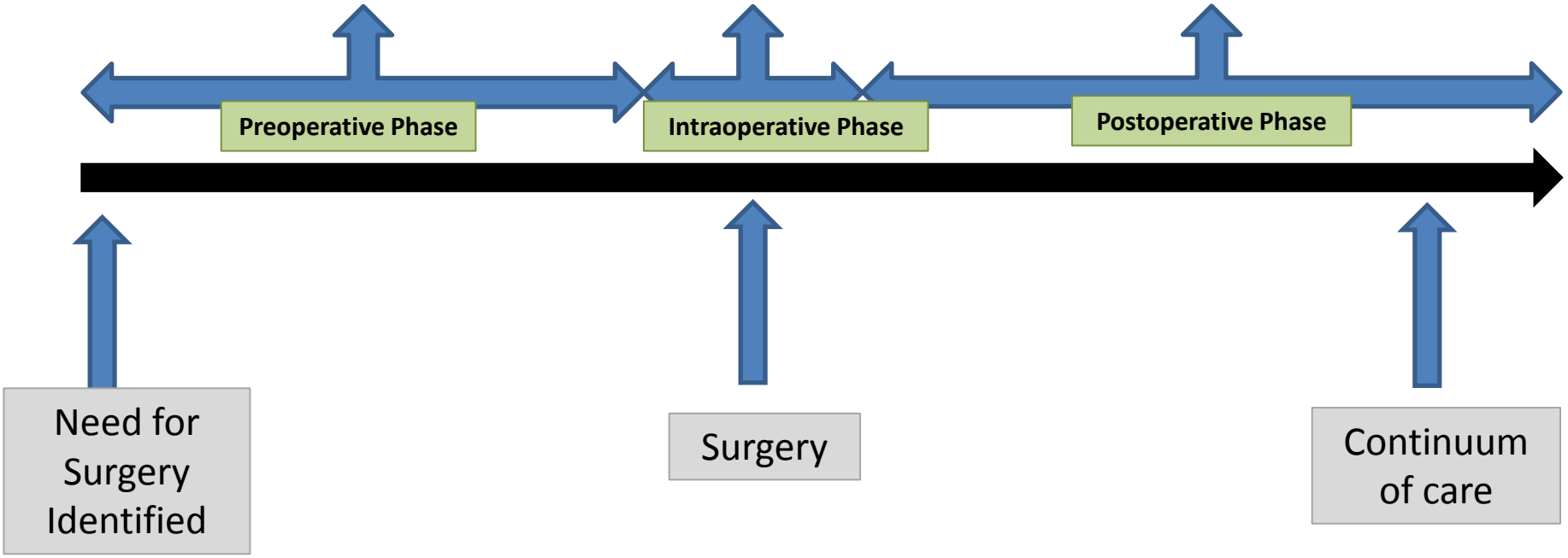
- Stress response
- Pain
- Organ dysfunction
- Complications
- Fatigue

…then recovery will be fast, and then length of stay and costs will decrease too

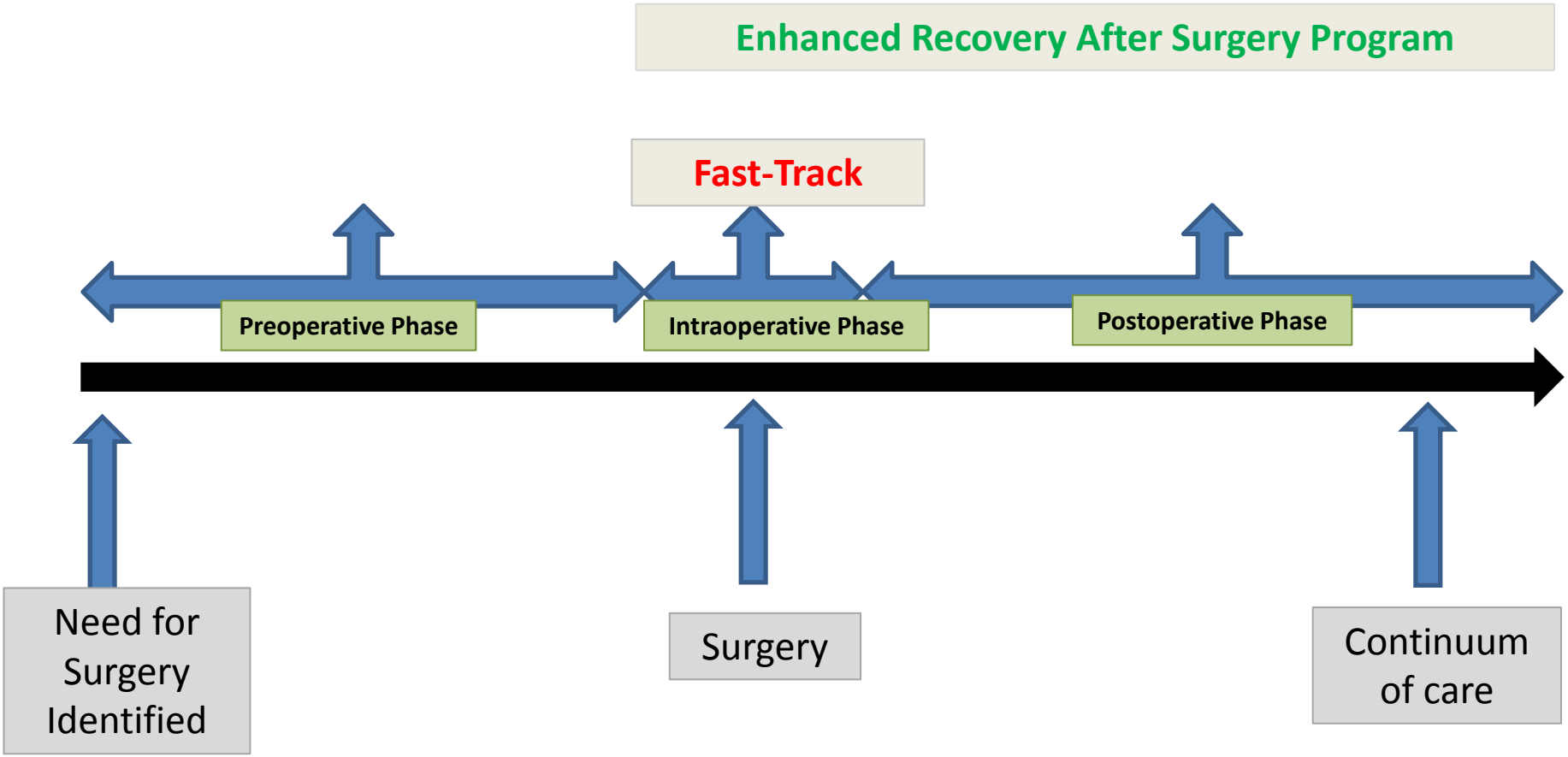
postoperative recovery, 1980

- Loss of body weight, less muscle mass
- Deconditioning
- Increased heart rate with work
- Decrease in muscle strenght

Trajectory of Surgical Care



Trajectory of Surgical Care



fast-track- enhanced recovery 1990

Preoperative Optimization

Modulation of stress response

Pain Control

Nutrition

Activity

Accelerated convalescence and reduced morbidity

High rate of postoperative morbidity after elective abdominal surgery

NSQIP database (2005-2006)

Table 1. Relative Contribution of 36 Procedures to Adverse Events and Excess Length of Stay in General Surgery, American College of Surgeons – National Surgery Quality Improvement Program, 2005–2006

Procedure	Procedures		Adverse event rate, %	Proportion of all adverse events, %	Average excess length of stay for adverse event, d	Proportion of all excess length of stay, %
	n	% of total				
1. Colectomy ± colostomy	12,767	9.9	28.9	24.3	9.8	23.5
2. Small intestine resection	3,576	2.8	32.9	7.7	13.9	10.6
3. Cholecystectomy/inpatient	11,718	9.1	7.5	5.7	8.7	4.9
4. Ventral hernia repair	7,477	5.8	10.1	4.9	6.3	3.1
5. Pancreatectomy	1,927	1.5	34.9	4.4	6.8	3.0
6. Appendectomy	9,016	7.0	7.2	4.3	4.4	1.9
7. Bariatric procedures	6,167	4.8	8.3	3.4	3.7	1.2
8. Proctectomy ± colectomy ± anastomosis	1,402	1.1	31.5	2.9	6.2	1.8
9. Lysis of adhesions	1,323	1.0	23.1	2.0	10.5	2.1
10. Liver resection	1,045	0.8	27.0	1.9	8.8	1.6
11. Mastectomy/simple, radical, or subcutaneous	4,313	3.3	5.6	1.6	0.9	0.1

Schilling et al. JACS 2008

Still high rate of postoperative morbidity after elective abdominal surgery……
……5 years later

- 76,076 resections for esophageal, gastric, pancreatic, hepatobiliary, and colorectal cancers at 316 hospitals from the **2006 to 2011** ACS NSQIP
- 3% esophagectomy, 5% gastrectomy, 16% pancreatectomy, 4% hepatectomy, 63% colectomy, and 9% proctectomy
- **21-45%** of patients experienced a postoperative complication and 1.1-4.4% died. The incidence of patients with any complication **24%**

Lucas DJ, Surgery, 2013

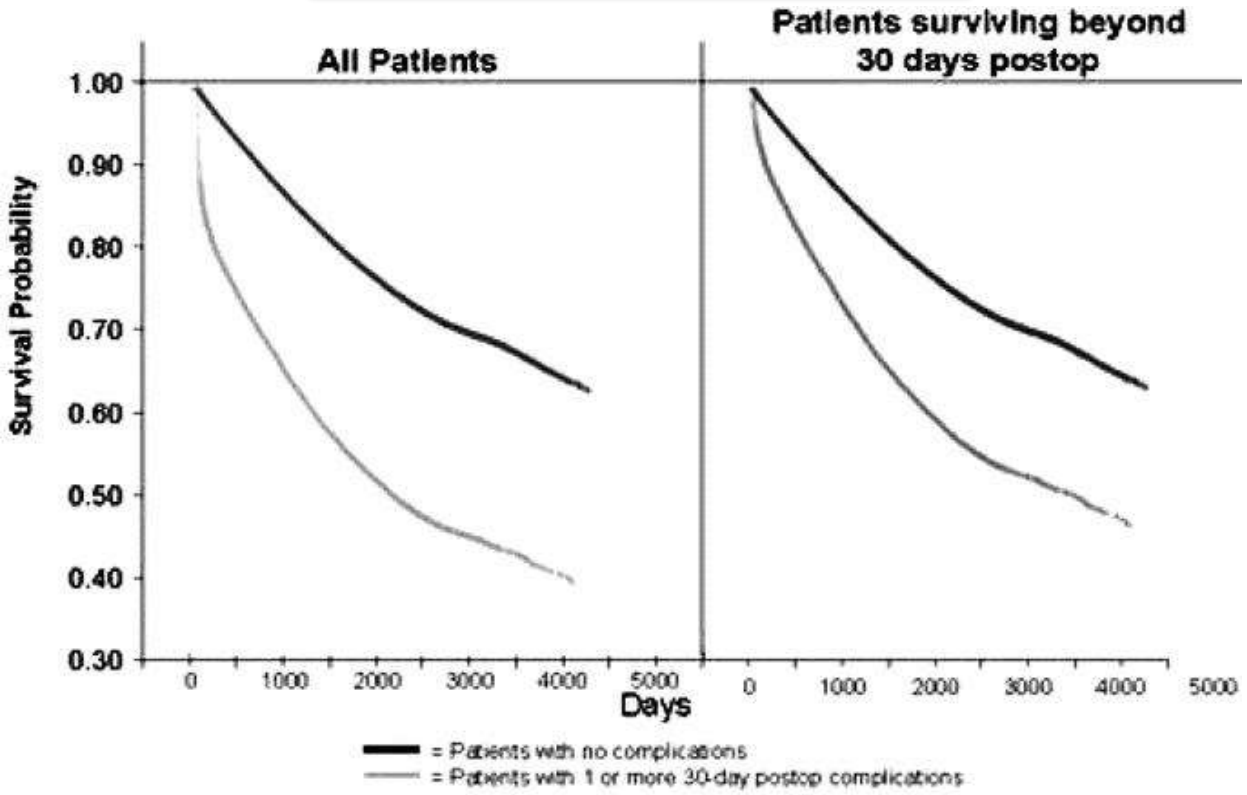
Despite intraoperative interventions & advances in anesthesia and surgical care

Complications are still between 25 and 55%

Postoperative complications are a burden and impact on long term outcomes

Khuri et *al*. Ann Surg 2005;242: 326–343

Reduced survival by **69%** at 8 yr
(from 18.4 yr to 5.6 yr)



Redesigning Surgical Decision Making for High-Risk Patients

Laurent G. Glance, M.D., Turner M. Osler, M.D., and Mark D. Neuman, M.D.

N ENGL J MED 370;15 NEJM.ORG APRIL 10, 2014

Surgical risk stratification
Surgical risk attenuation

ACS risk calculator
15 variables predicting higher risk

Model generated from N=28,863 colorectal procedures at 182 hospitals

Not Modifiable

- ASA III/IV
- Sepsis
- Indication for surgery
- Disseminated cancer
- Extent of surgery
- Emergent
- **Age >65**
- Creatinine
- COPD
- Wound class
- PTT >35

Potentially Modifiable

- Functional health status
- BMI
- Dyspnea
- Albumin ≤35

Cohen *et al.* , Bilimoria, Ko, Hall. JACS 2009

Optimizing Surgical Care of Colon Cancer in the Older Adult Population

Gregory D. Kennedy, MD, PhD, Victoria Rajamanickam, MS†, Erin S. O'Connor, MD*, Noelle K. Loconte, MD‡, Eugene F. Foley, MD*, Glen Leverson, PhD†, and Charles P. Heise, MD**

(*Ann Surg* 2011;253:508–514

- Factors that predict complications:
- Age >75 y
- BMI >25
- COPD
- ETOH
- Duration of surgery

the United States continues to age. Surgeons will have to operatively approach an older group of patients with multiple preoperative co-morbidities. It is clear from these data that preoperative health and functional status as well as operative approach contribute to short-term outcomes.

Preoperative Risk Assessment

Test	Predicting	Scoring	Evidence level	Recommendation
P possum	Mortality and Morbidity	12 physiological and 6 operative variables	High	Strong
Lees index	Perioperative Cardiac complication	6 preoperative clinical factors	Moderate	Strong
Shuttle Walk Test	Perioperative complications	Aerobic fitness	Moderate	Moderate
Shuttle Walk Test	Screening tool to proceed to CPET / echocardiography etc	Aerobic fitness	Moderate	Strong
Cardiopulmonary Exercise testing (CPET)	Perioperative complications	Aerobic exercise – AT and VO_2 max	Moderate	Strong
Cardiopulmonary Exercise testing (CPET)	Selecting patient's suitability for surgery	Aerobic exercise – AT and VO_2 max	Moderate	Moderate

With permission of Scott MJ. 2015

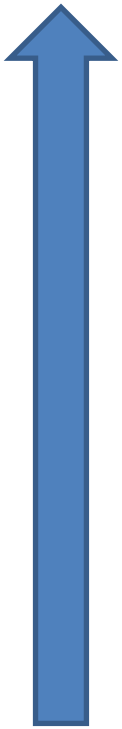
Risk factors for prolonged recovery of Indipendent Activities of Day Living (IADL) after major abdominal surgery in elderly people

	Odds ratio	95% CI	p value
Serious complication	**0.61**	**0.39-0.96**	**0.03**
Physical performance status*	**1.20**	**1.02-1.41**	**0.02**
Geriatric Depression Scale	**0.95**	**0.92-0.98**	**0.003**
Folstein Mini-Mental State	1.04	0.98-1.11	0.22
Creatinine>133 umol/L	0.83	0.47-1.47	0.52
Albumin <30 g/L	0.63	0.15-2.66	0.53
CHF on CXR	0.94	0.46-1.92	0.87
Male	1.25	0.8-1.87	0.29
Age,y	1.0	0.97-1.02	0.80

*score combining Timed Up and Go, Functional Reach, and Hand Grip Strength using Components Analysis

Cox Proportional Hazards Regression
Lawrence et al, JACS, 2009

Poor physical fitness/reserve
is associated with



- all-cause mortality

  Wilson et al, BJA 2010

- postoperative complications

  TN Robinson et all, Am J Surg 2013

- length of hospital stay and discharge destination

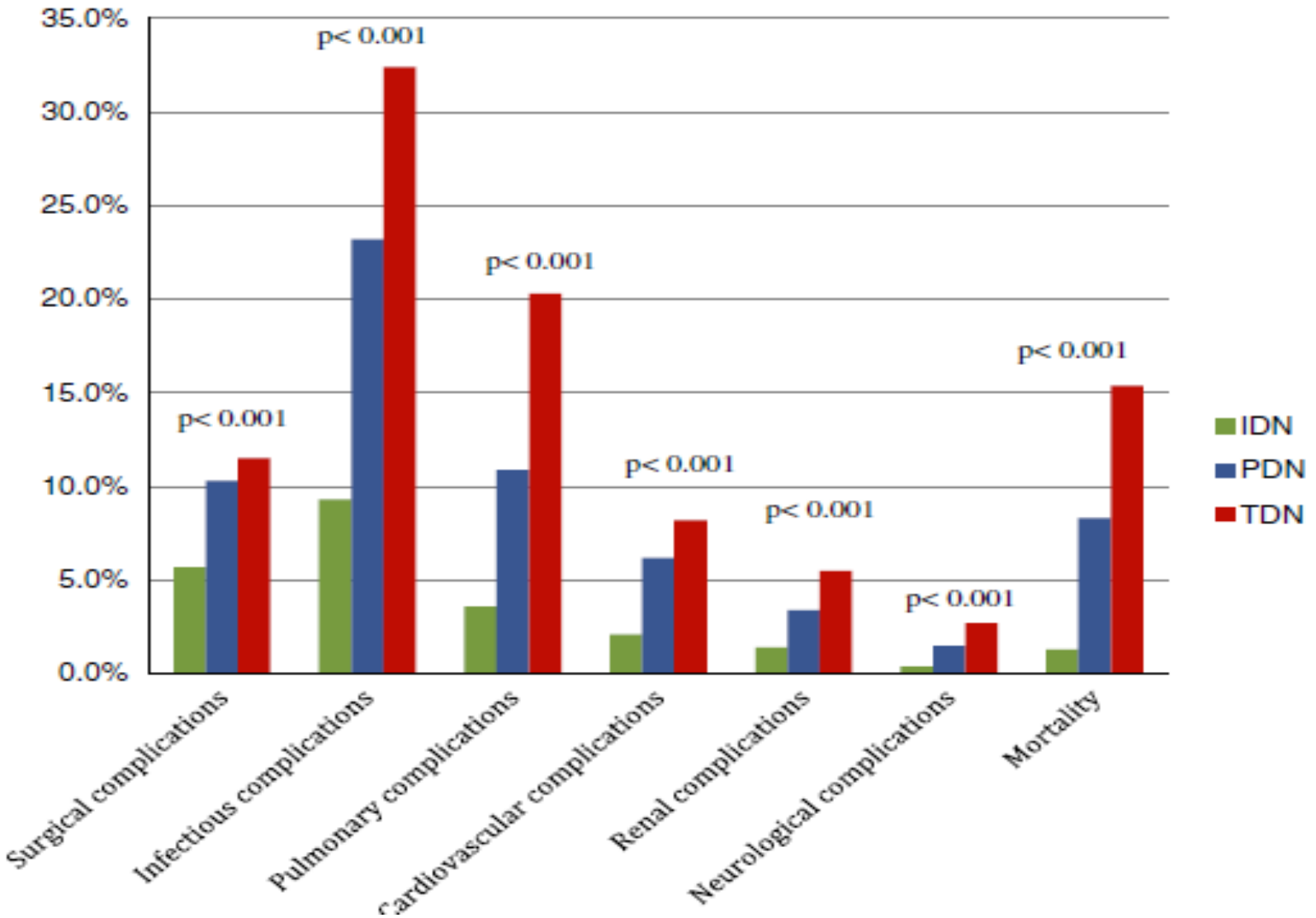
  JJ Dronkers et all, Anaesthesia 2013

- hospital and healthcare costs

TN Robinson et all, Am J Surg 2011

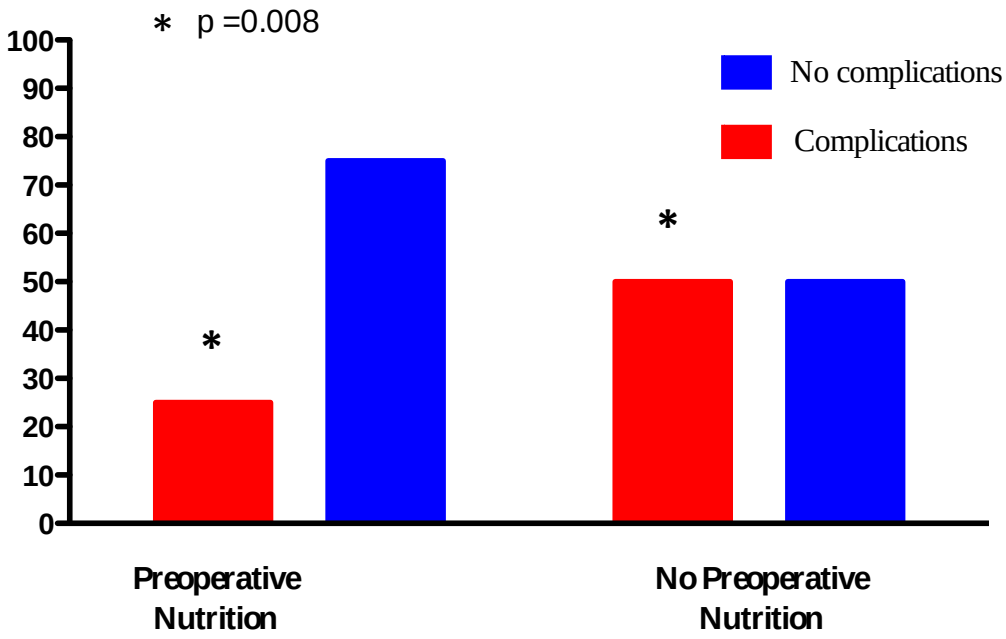
Preoperative functional status and postoperative outcome

Surg Endosc 2015



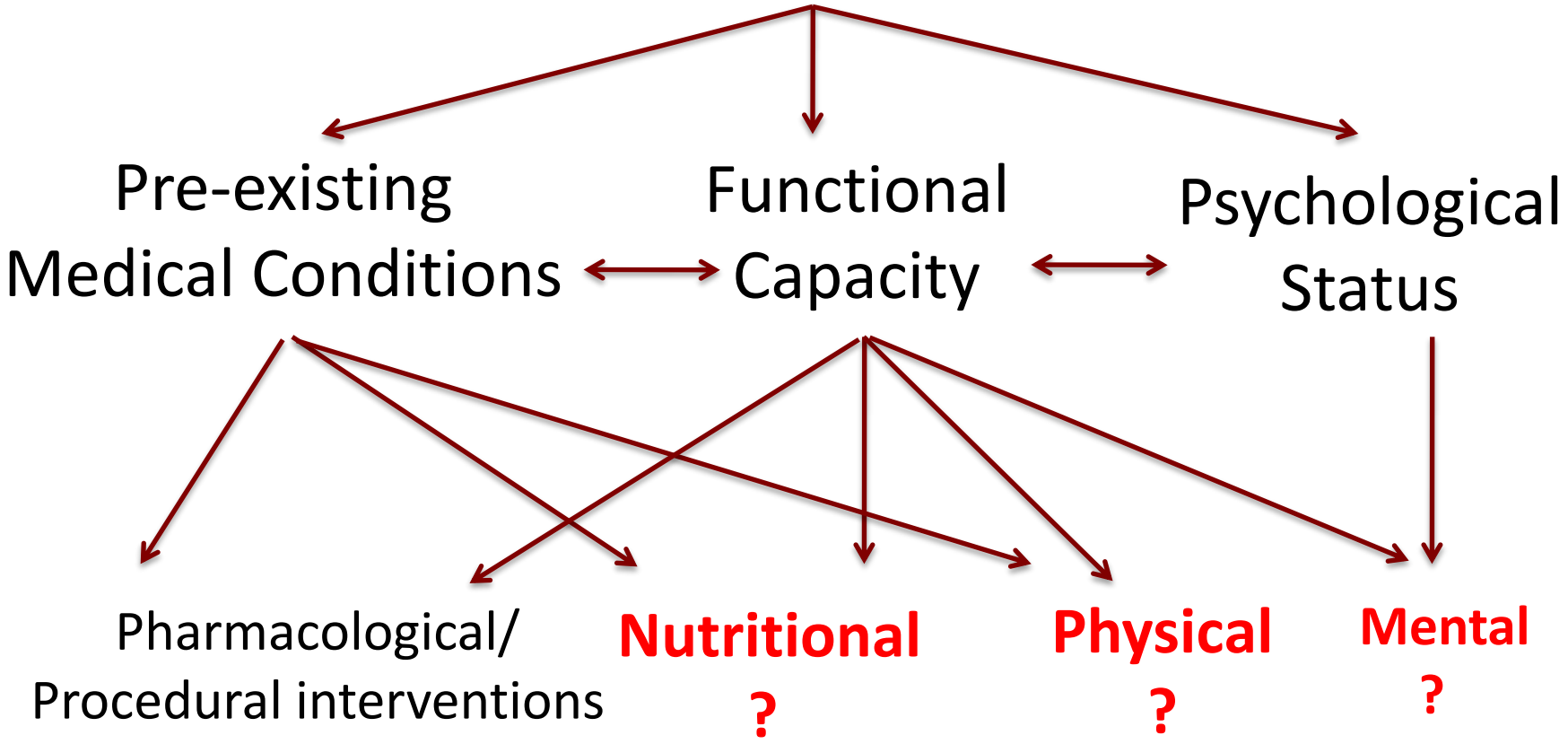
Preoperative nutritional state

elective abdominal surgery, n=1085
Nutritional Risk Screening > 4



Bin J. et al Nutrition 28 (2012) 1022–1027

Optimization in the preop period. What do not we do now?



Current practice is to
predict postoperative complications
and to adjust postoperative resources
(e.g. if AT < 9.8 , postop ICU)

and wait until **after** surgery to intervene to help patients to recover

Rehabilitation

Is the postoperative period the right time to intervene?

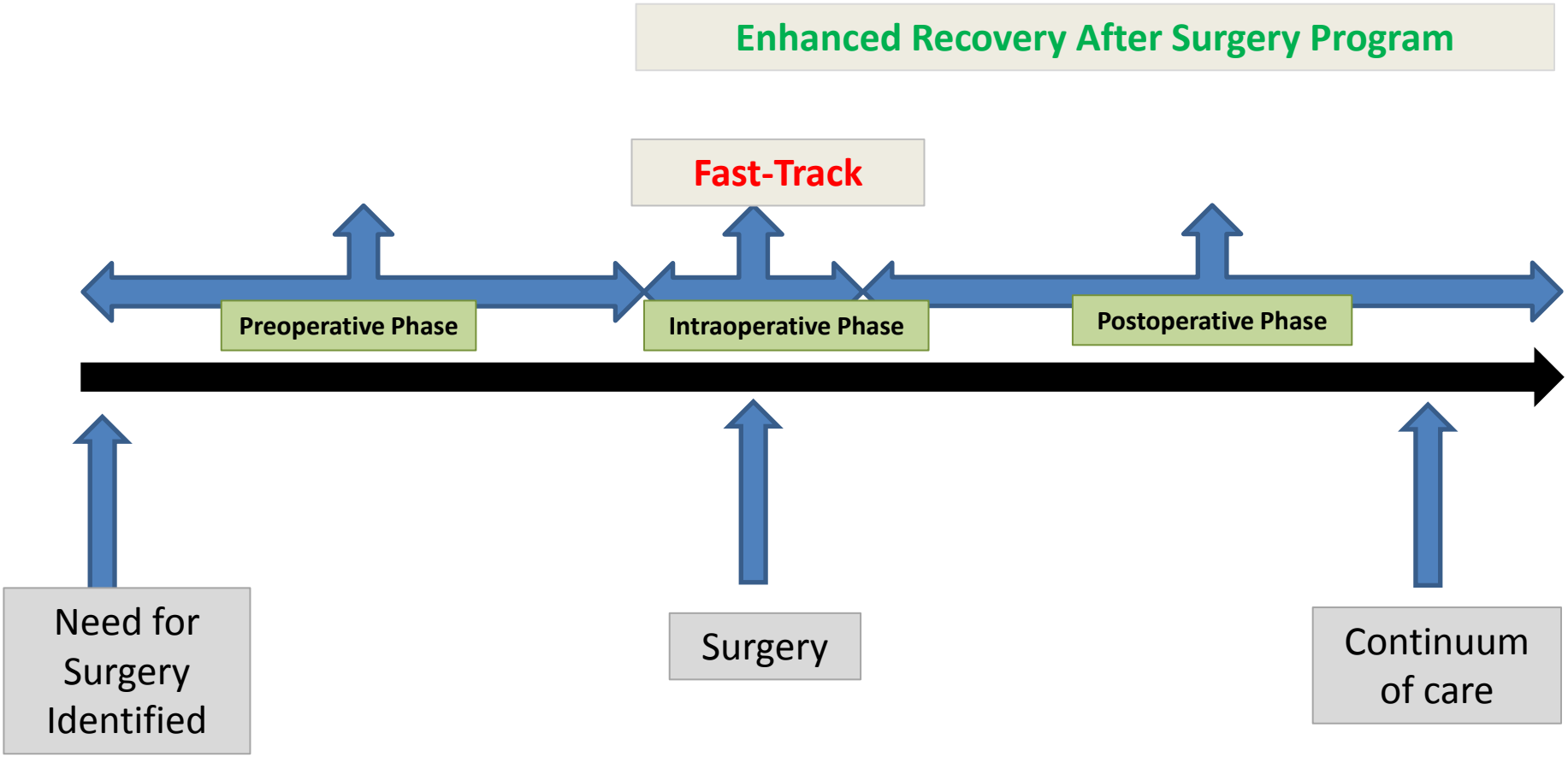
Patients are tired, depressed, weak

What about modify the preoperative risk assessment ?

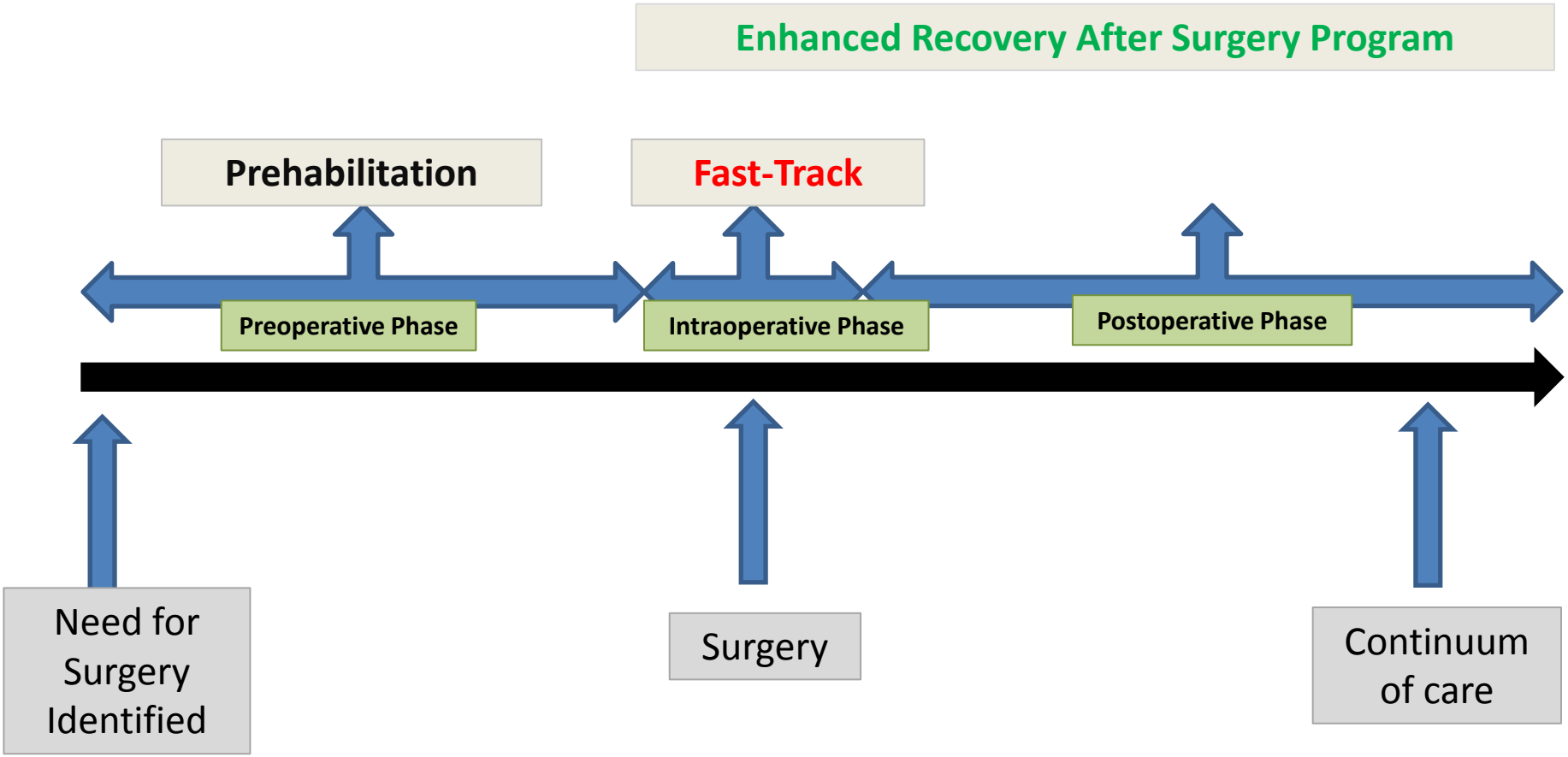
Can we improve patient's fitness before surgery, while waiting ?

Prehabilitation

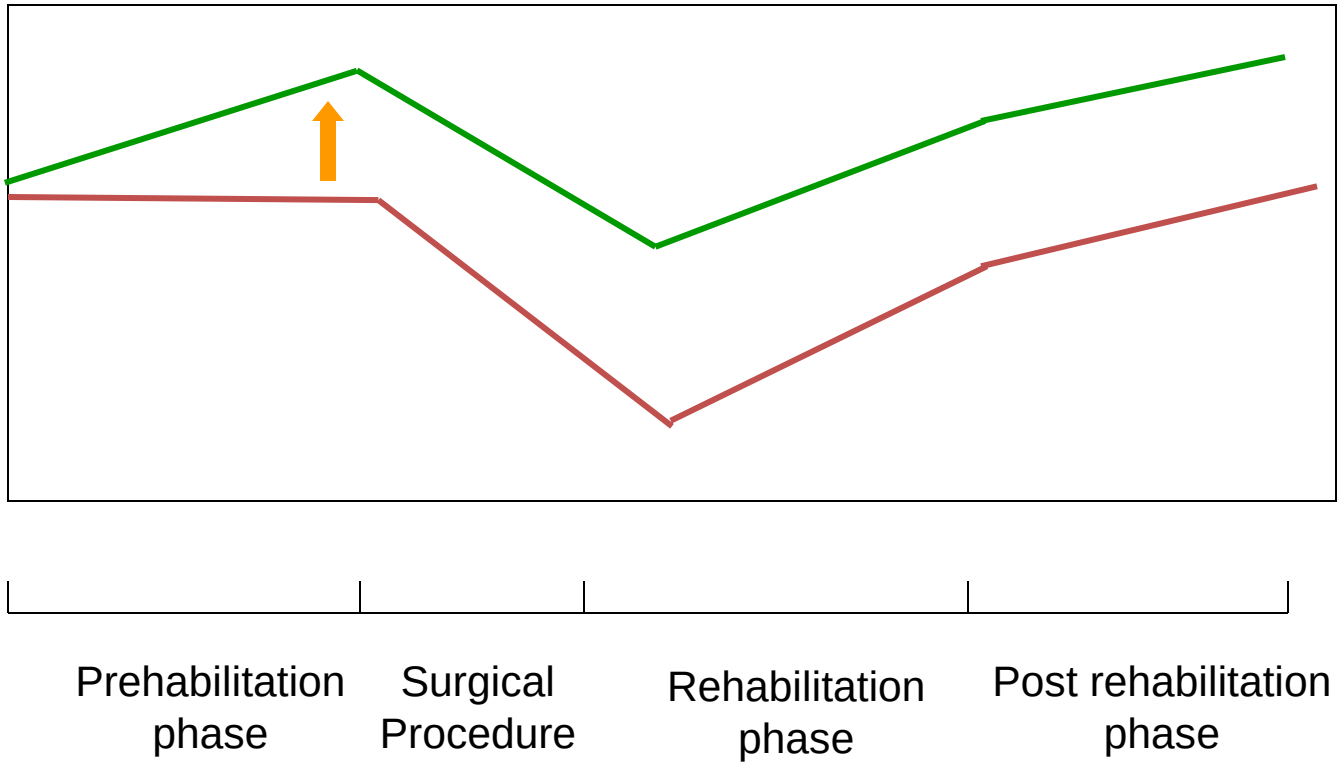
Trajectory of Surgical Care



Trajectory of Surgical Care



Increase physiological reserve to overcome the stress of surgery and accelerate the recovery process



Carli F, Zavorsly G 2005,

Clinical Rehabilitation 2011; **25**: 99–111

The effects of preoperative exercise therapy on postoperative outcome: a systematic review

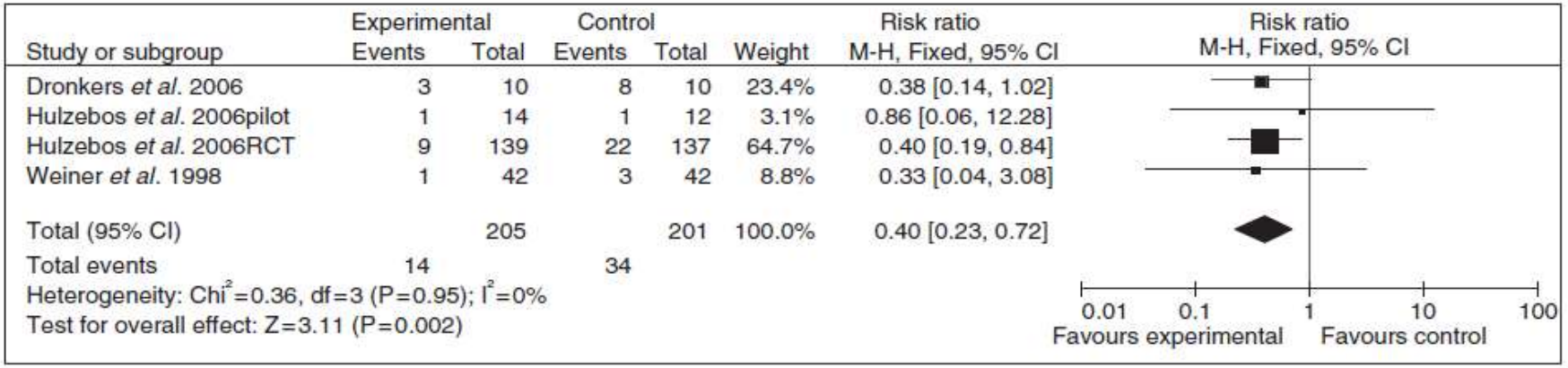


Figure 2 Effect of preoperative inspiratory muscle training on postoperative pulmonary complications after cardiac or abdominal surgery.

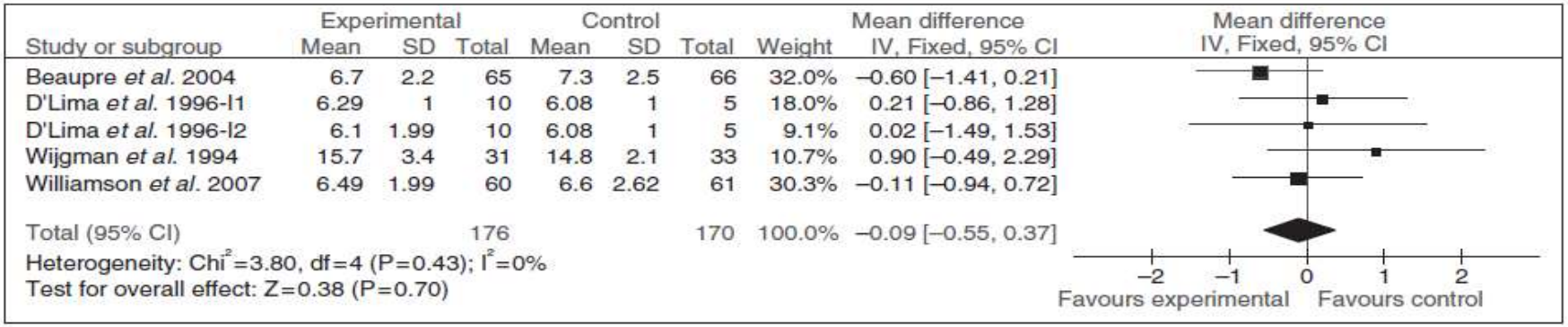


Figure 4 Effect of preoperative exercise therapy on length of hospital stay after joint replacement surgery.

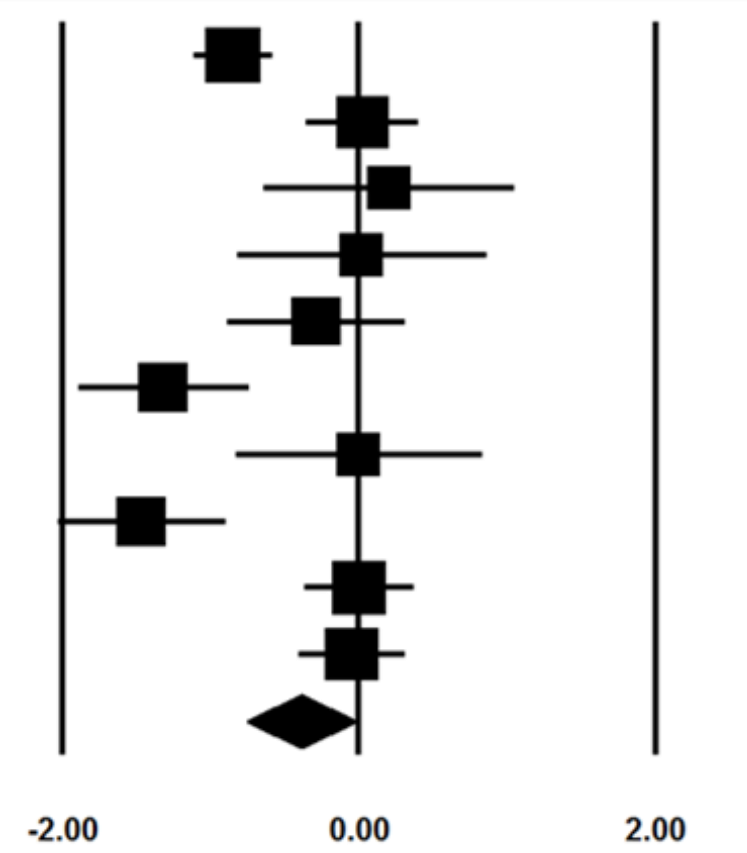
Systematic Review & Meta-Analysis of Systemic Prehabilitation

Inclusion criteria:

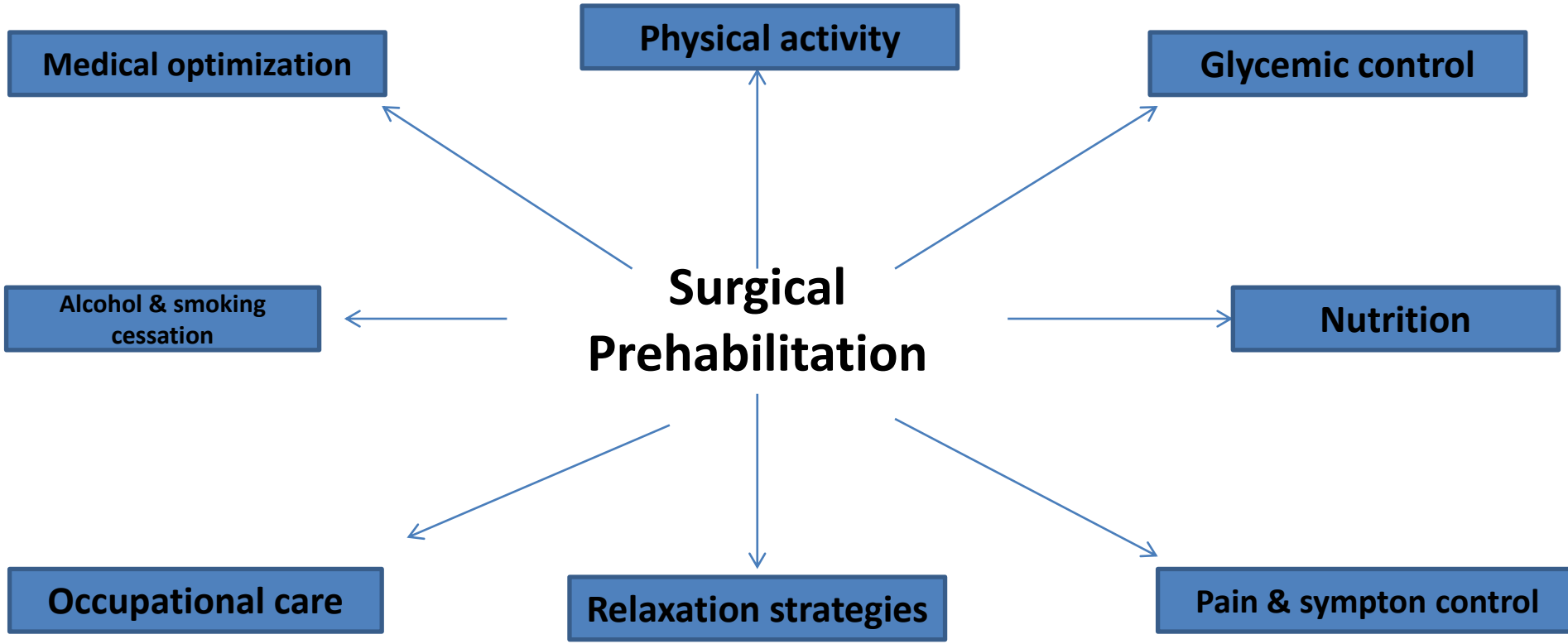
- Total body MSK ± aerobic exercise & postop outcomes

Results:

- 1996-2011
- K=21 (17 RCTs); median sample n=54
  - 13 orthopaedic, 1 abdominal, 3 cardiac
- Moderate-poor methodological quality
- Majority found improved postop:
  - Pain, LOS, physical function
- Equivocal benefits to:
  - Aerobic fitness, complications & QOL
- Adverse event in 2/669 prehab patients



(Santa Mina et al, 2014, Physiotherapy)


Surgical Prehabilitation
Physical activity
Medical optimization
Glycemic control
Alcohol & smoking cessation
Nutrition
Occupational care
Relaxation strategies
Pain & sympton control

Prehabilitation to enhance postoperative recovery for an octogenarian following robotic-assisted hysterectomy with endometrial cancer

Carli F, Brown R, Kennephol S. CJA 2012; 59: 779-84

Age	88 y
Past Medical History	CAD, Stent x2, CABG x3, AS, HTN, periods of CHF, postoperative delirium x2, UTI, Mild MCI
Weight loss	30 lbs in 1 year
Education	MA Theology at the age of 60 years!

Sedentary, Depressed, Frustrated and Malnourished

Time of assessment	SF36		6 Minute Walk Test	RBANS* Total Score
	Physical Component	Mental Component		
Initial Assessment	33.7 (-0.7)	47.2 (-0.8)	91.2m	58 (<1)
4 Weeks before Surgery	39.6 (-0.1)	45.4 (-1.0)	136.8m	75 (5)
8 Weeks after Surgery	65.3 (1.2)	65.3 (1.2)	144.8m	81 (10)

* Repeatable Battery or the Assessment Neuropsychological Status

4 Major Scientific Studies on Surgical Multimodal Prehabilitation : Proof of Concept

Intense exercise vs. walking & breathing

2010

Preop: ~1/3 of patients *deteriorated* & program compliance was 16%
Postop: change in preop function predicted trajectory of recovery!

Pilot prehabilitation vs. standard of care

2012

Preop: prehab increased 6MWT by 42 ± 41 m.
Postop: greater proportion (81% vs 40%, p<0.01) of prehab patients had recovered by 8 weeks.

Prehabilitation vs. rehabilitation

2014

Preop: prehab improved 6MWT by 25.2 ± 50.2 m, while rehab declined by 16.4 ± 46.0 m.
Postop: greater proportion (84% vs 62%, p=0.011) of prehab patients recovered by 8 weeks.

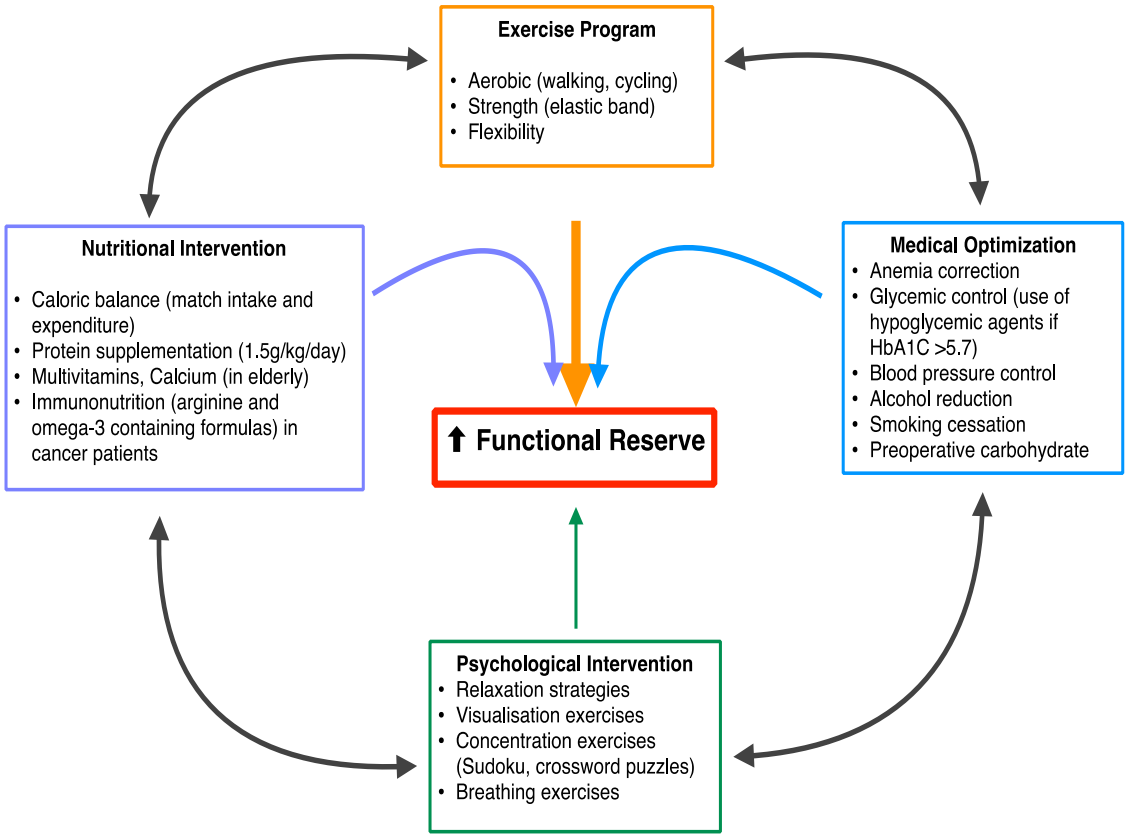
Nutrition Prehab vs. Placebo

2014

Preop: Nutrition prehab improved 20.8 ± 42.6 m, while placebo improved by 1.2 (65.5).
Postop: Four weeks after surgery, recovery rates
were similar between groups.

Carli, F et al.*BJS*.2010; Li et al. *Surg Endosc*. 2012; Gillis C et al. *Anesthesiology*.2014

Multimodal Prehabilitation : The McGill Experience



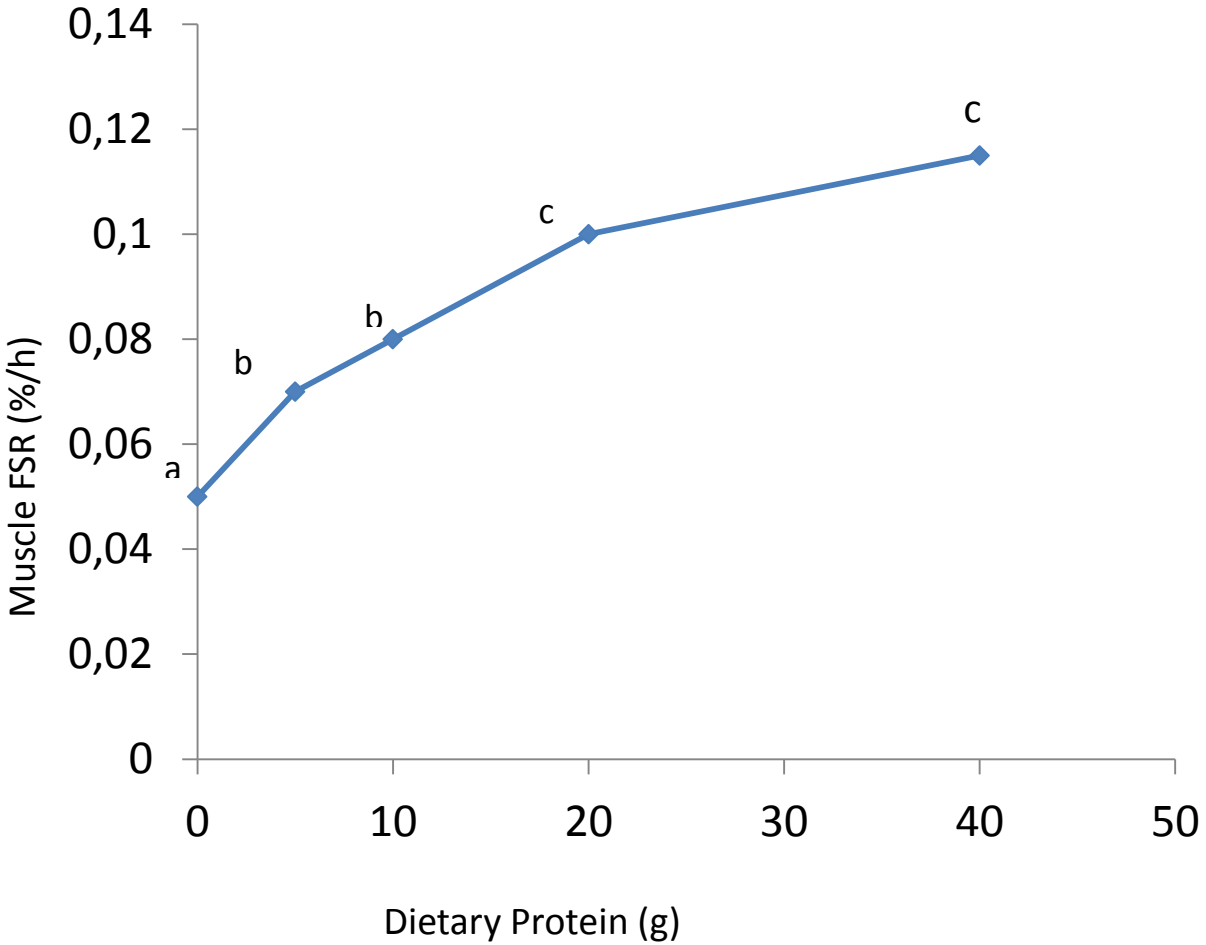
Multimodal Prehabilitation to Increase Functional Reserve

- Up to 1/3 of patients are at nutrition risk → Whey Protein Supplementation

Aerobic and resistance exercise

- 20% of patients may have mood changes like anxiety / depression while waiting for surgery → Anxiety Reduction Strategies

Increase in muscle protein synthesis following exercise with whey proteins (Anabolic Window)



Burke LM. *Med Sci Sports Exerc*. 2012;44(10):1968-77

Outcome measure of recovery: functional walking capacity

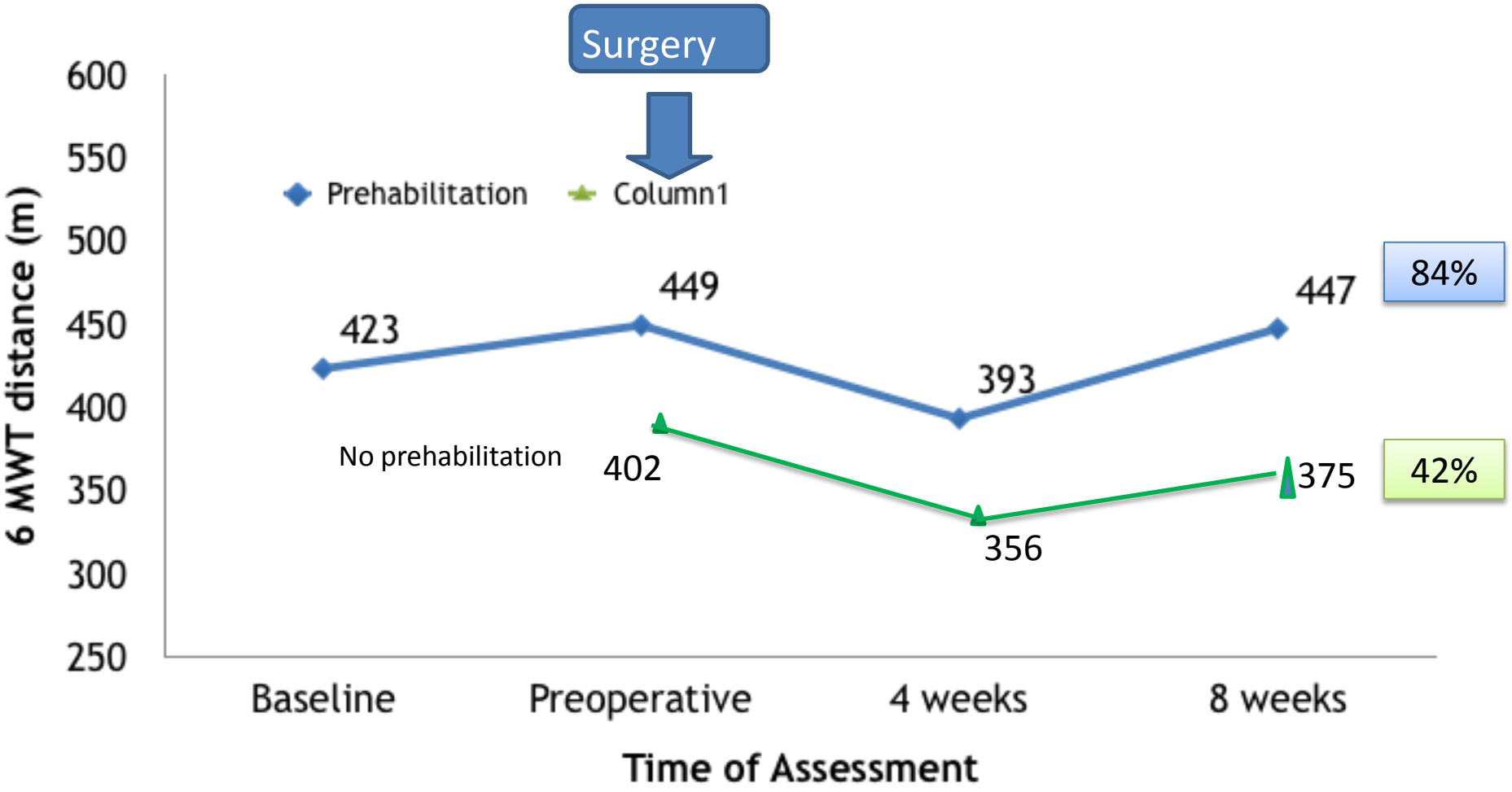
Six-Minute Walk Test

- Objective,Reproducible
- Essential to everyday activities
- Integrates balance, force, speed, endurance
- Cheap, no equipment needed
- Validated measure of surgical recovery (Moriello, 2008, Pecorelli 2015)

Minimal important difference = 20 meters
the smallest change in an outcome measure perceived as beneficial by patients undergoing colorectal surgery

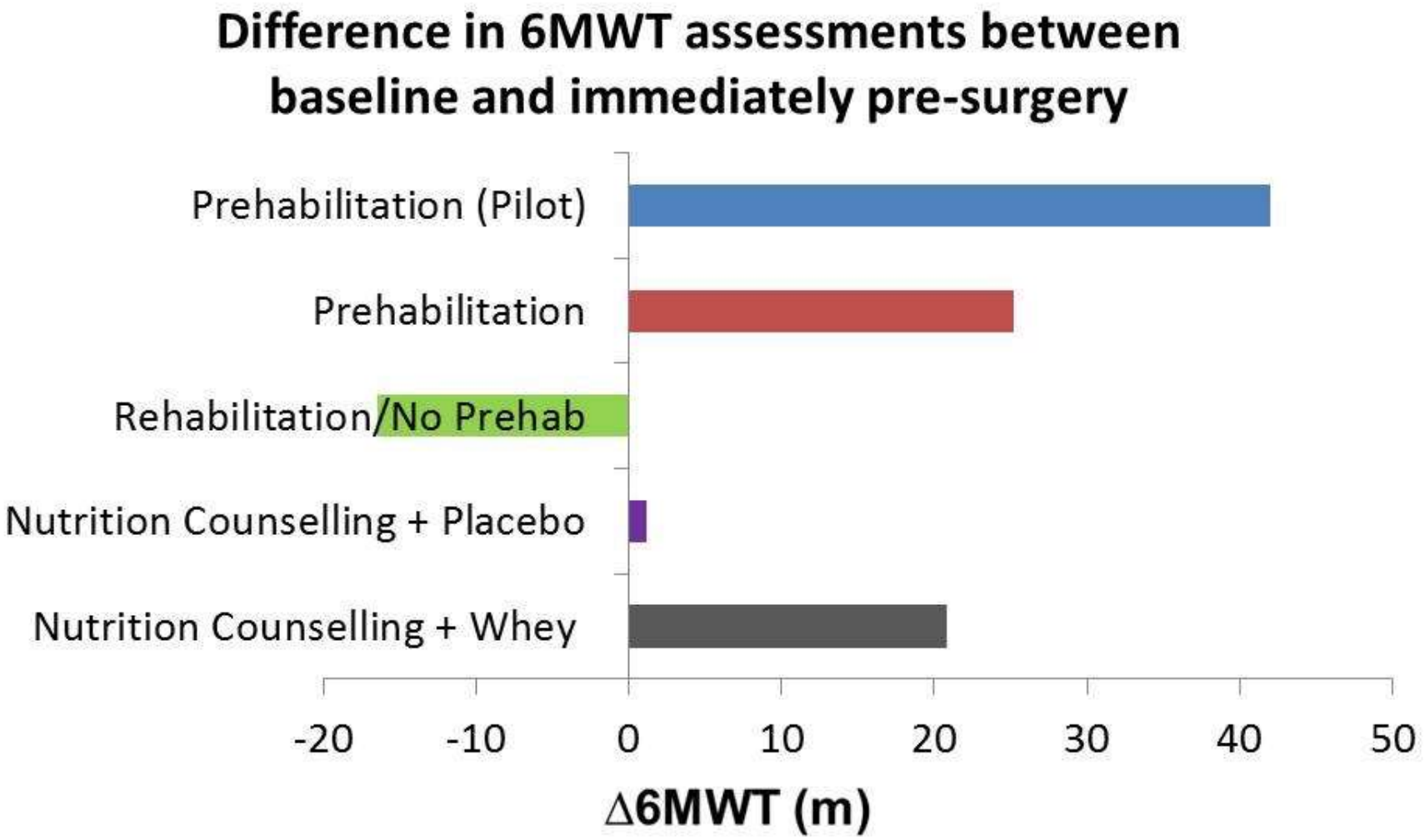
Predicted 6MWT = 868 – (age x 2.9) – (female x 74.7)

Patients with multimodal prehabilitation are stronger before and after surgery for colorectal cancer



Gillis C et al. *Anesthesiology.*2014

Previous Trial Comparisons: Preoperative Period



Randomized clinical trial of prehabilitation before planned liver resection

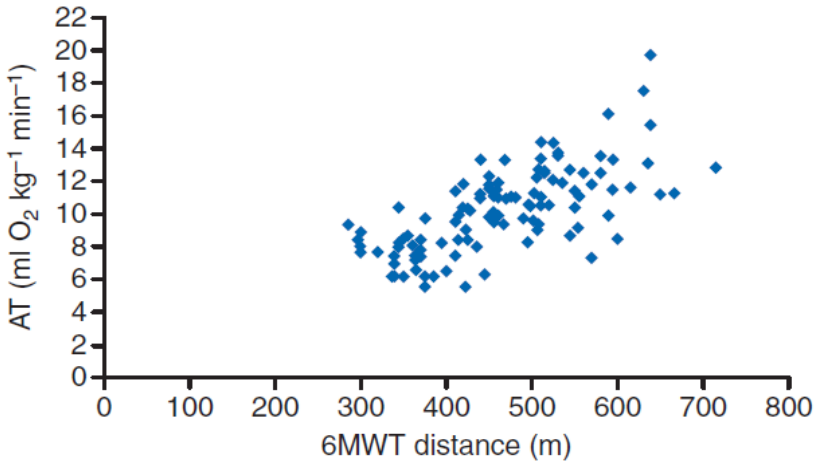
Br J Surg 2016

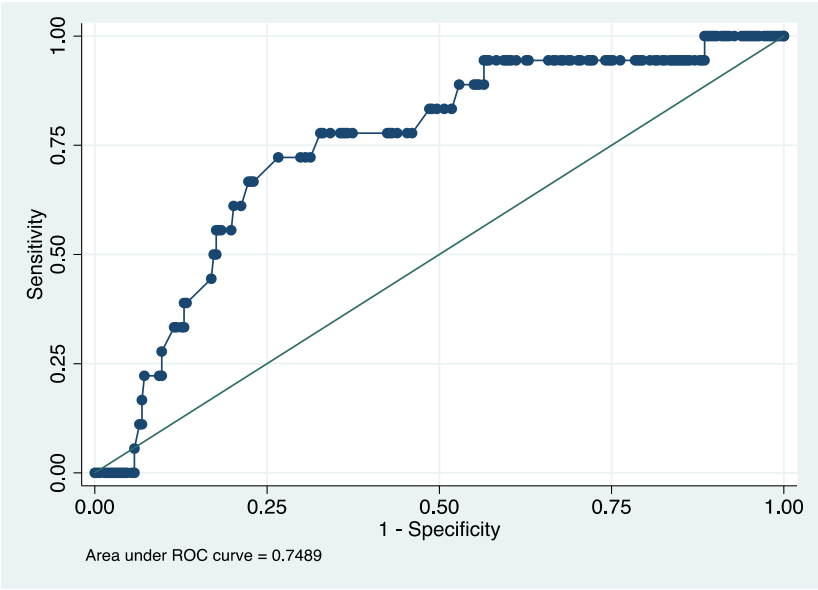
	Prehabilitation				Standard care				Study arm comparison	
	Baseline*	Post*	Change†	*P*‡	Baseline*	Post*	Change†	*P*‡	Exercise *versus* standard†	*P*§
Vo_2 at AT (ml per kg per min)	10·0(0·9)	11·9(2·2)	1·9 (0·1, 3·6)	0·037	9·8(1·1)	9·4(1·1)	−0·4 (−1·4, 0·6)	0·379	2·3 (0·3, 4·2)	0·029
Vo_2 at peak (ml per kg per min)	16·1(2·2)	18·9(4·7)	2·8 (−0·4, 5·9)	0·075	15·7(2·2)	16·0(3·5)	0·3 (−2·0, 2·6)	0·760	2·5 (−1·3, 6·2)	0·157
Oxygen pulse at AT (ml/beat)	8·1(1·9)	9·3(2·2)	1·2 (0·1, 2·3)	0·035	7·3(1·7)	7·3(1·7)	0·0 (−0·5, 0·6)	0·907	1·2 (−0·1, 2·4)	0·062
Oxygen pulse at peak (ml/beat)	9·9(1·9)	11·3(2·2)	1·3 (−0·1, 2·9)	0·068	8·9(2·1)	9·5(2·0)	0·5 (−0·2, 1·3)	0·132	0·8 (−0·9, 2·6)	0·308
Peak work rate (W)	117(20)	130(34)	13 (0, 27)	0·052	118(27)	117(28)	−1 (−9, 7)	0·738	14 (−1, 30)	0·066
Heart rate reserve (beats/min)	54(18)	58(23)	4 (−4, 13)	0·278	59(21)	55(22)	−3 (−7, 1)	0·113	7 (−2, 17)	0·074
SF-36® scores										
Overall physical health	53(27)	66(27)	13 (2, 24)	0·027	53(21)	56(15)	1 (−8, 14)	0·536	10 (−5, 24)	0·151
Overall mental health	63(25)	75(24)	12 (1, 23)	0·038	61(20)	61(25)	0 (−21, 22)	0·963	11 (−9, 31)	0·247
Overall QoL	59(25)	73(23)	14 (1, 27)	0·039	59(21)	59(21)	0 (−14, 15)	0·945	13 (−5, 30)	0·140

Values are *mean(s.d.) and †mean (95 per cent c.i.). Vo_2, oxygen uptake; AT, anaerobic threshold; QoL, quality of life. ‡Paired *t* test; §independent *t* test.

Do patients with poor functional capacity benefit the most from prehabilitation ?

< 400 m walk distance: indicator of poor functional capacity





1) 400-meter walk test
→ related to frailty and major mobility disability in older adults

2) < 409 m
= VO2peak < 15 ml/Kg/min

3) < 406 m
→ cardio-resp complications after CR surg

Pahor M et al, JAMA 2014
Sinclair RCF et al, BJA 2012
Lee L, Msc Thesis, 2012

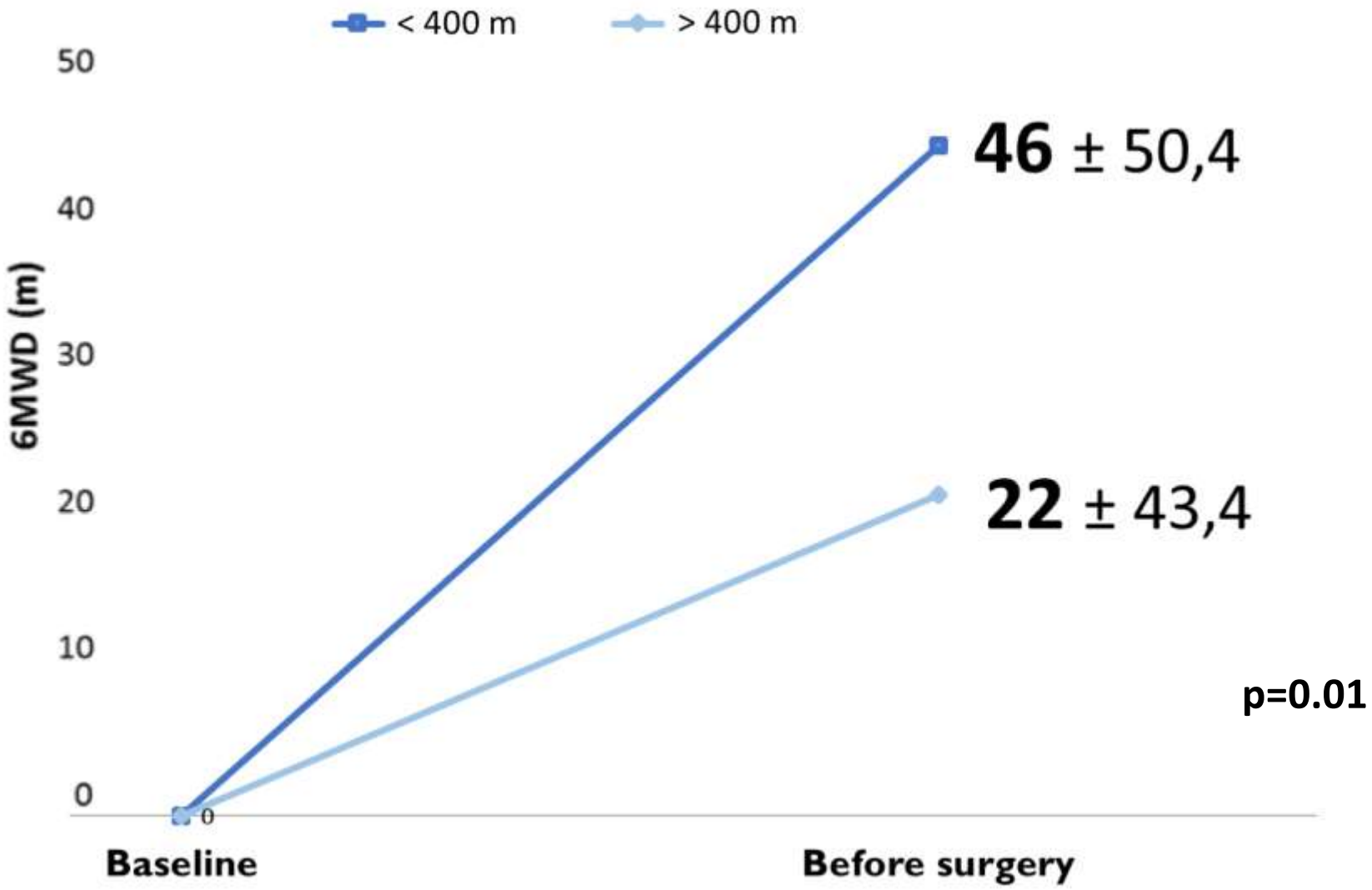
Baseline Patients Characteristics

	> 400 m (n=70)	< 400 m (n=36)
6MWD, *m*	**485 (61)***	**308 (76)**
Age, *years*	**65 (10)***	**75 (13)**
Male gender	46 (66%)	17 (47%)
BMI, kg/m^2	27.6 (4.6)	27.2 (4.3)
Lean body mass, *kg*	54,5 (10,8)	52,5 (10,7)
ASA class		
I-II	56 (80%)	23 (64%)
III-IV	**14 (20%)***	**13 (36%)**
Colon surgery	30 (43%)	22 (61%)
Laparoscopic surgery	65 (93%)	33 (92%)

Data presented as mean (SD) or n(%).
ASA: American Society of Anesthesiologists Classification, BMI: Body Mass Index

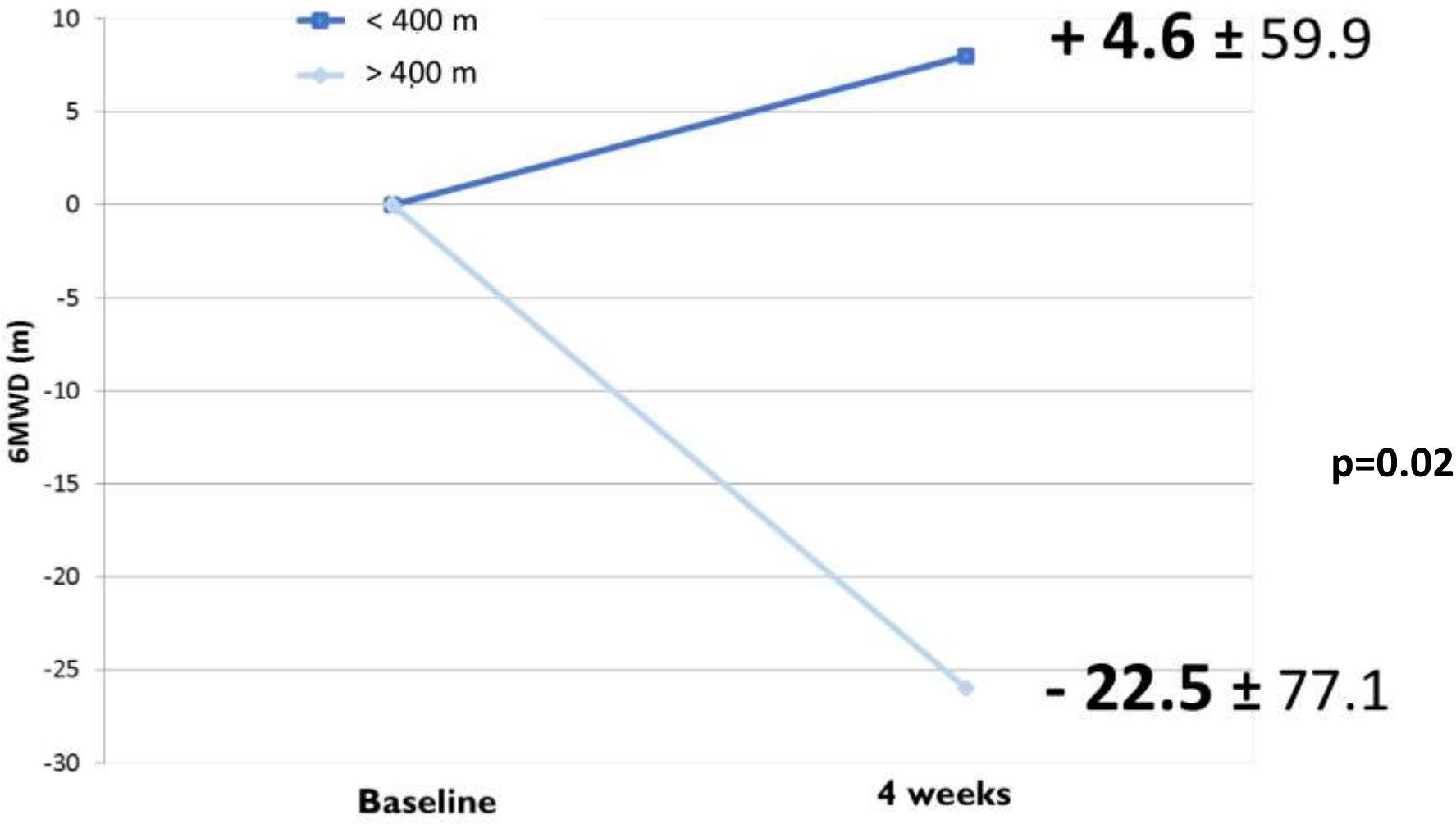
***P < 0.05**

In the preoperative period, less fit patients had a greater improvement in walking capacity



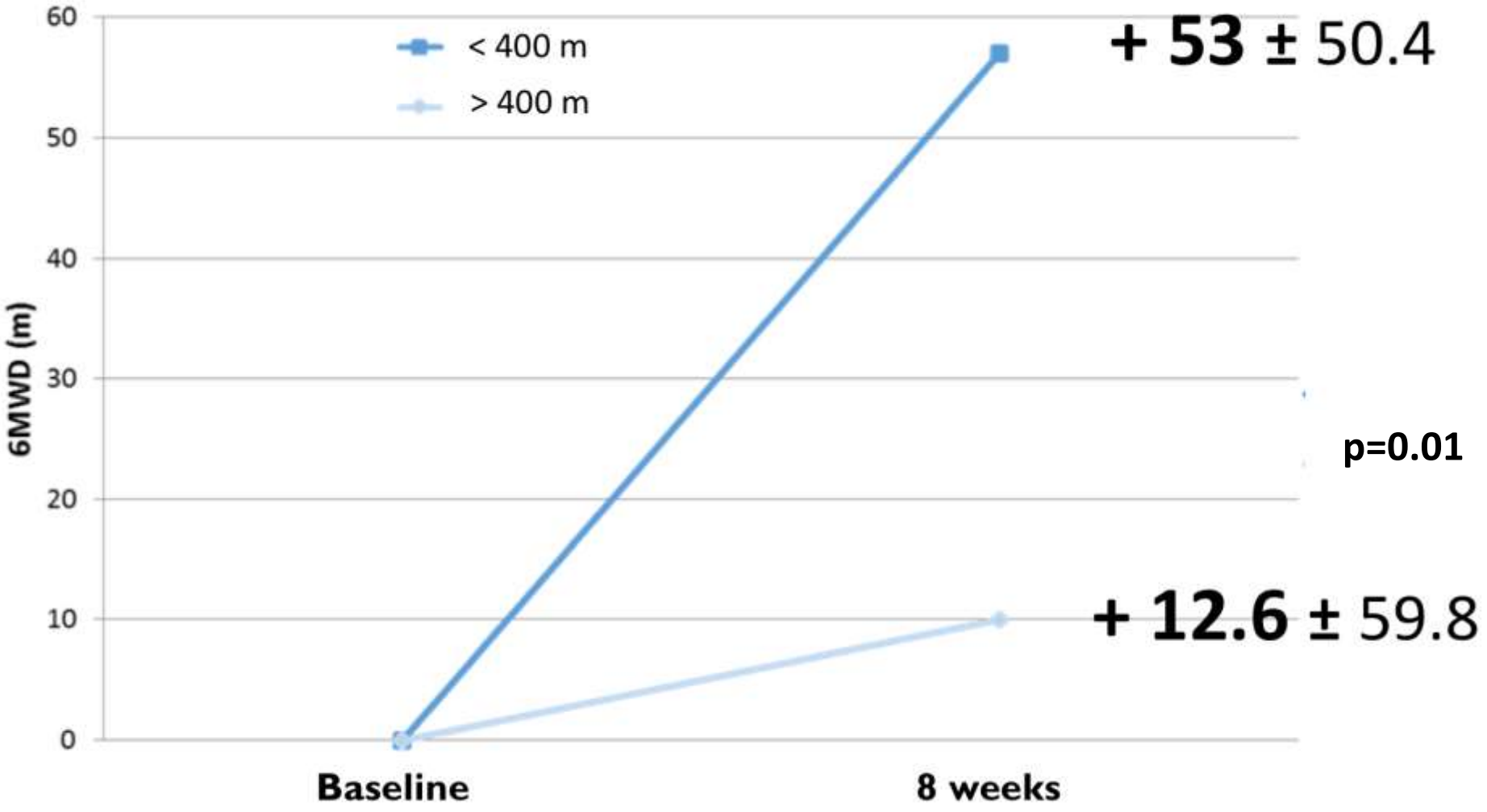
Minnella E Surgery, 2016

At 4 weeks after surgery, less fit patients had a greater improvement in walking capacity



Minnella E Surgery, 2016

At 8 weeks after surgery, low fit patients had a greater improvement in walking capacity



Minnella E Surgery, 2016

Prehab enhances postoperative functional capacity in patients with low reserve

Prehabilitation 58 m

3.5 Lanes of Traffic

395m; 1.1m/s

Rehabilitation 22 m

2 Lanes of Traffic

332m; 0.8m/s

- A 6MWD of > 400 meters is needed to cross 4 lanes of traffic. (1.2 m/s) Criterion for independency and mobility

What is the impact of prehabilitation on clinical outcome?

Preoperative Supervised Exercise Improves Outcomes After Elective Abdominal Aortic Aneurysm Repair

A Randomized Controlled Trial

Complications	Total	Exercise Group	Control Group	*P*
Cardiac*	19 (15.3%)	5 (8.1%)	14 (22.6%)	0.025†
	5: myocardial infarction (2 fatal)	EVAR: 1 (4.3%)	EVAR: 3 (13.0%)	0.608
	5: prolonged inotropic support	OAR: 4 (10.3%)	OAR: 11 (28.2%)	0.044
	5: new-onset arrhythmia (without evidence of myocardial damage or ischemia)			
	3: new-onset arrhythmia with elevated troponin T levels			
	1 – Unstable angina with Troponin level of 0.05			
Pulmonary*	20 (16.1%)	7 (11.3%)	13 (21.0%)	0.143†
	14: postoperative pneumonia	EVAR: 0 (0.0%)	EVAR: 4 (17.4%)	0.109
	3: severe postoperative pneumonia resulting in reintubation or respiratory support	OAR: 7 (17.9%)	OAR: 9 (23.1%)	0.575
	1: postoperative pneumonia and an exacerbation of COPD			
	1: unplanned reintubation			
	1: reintubation and aspiration pneumonia (fatal)			
Renal*	17 (13.7%)	4 (6.5%)	13 (21.0%)	0.019†
	15: more than 20% decrease in creatinine clearance	EVAR: 1 (4.3%)	EVAR: 1 (4.3%)	1.000
	2: renal insufficiency postoperatively requiring hemodialysis/hemofiltration	OAR: 3 (7.7%)	OAR: 12 (30.8%)	0.033
Endpoints (composite outcome measure)	40 (32.3%)	14 (22.6%)	26 (41.9%)	0.021

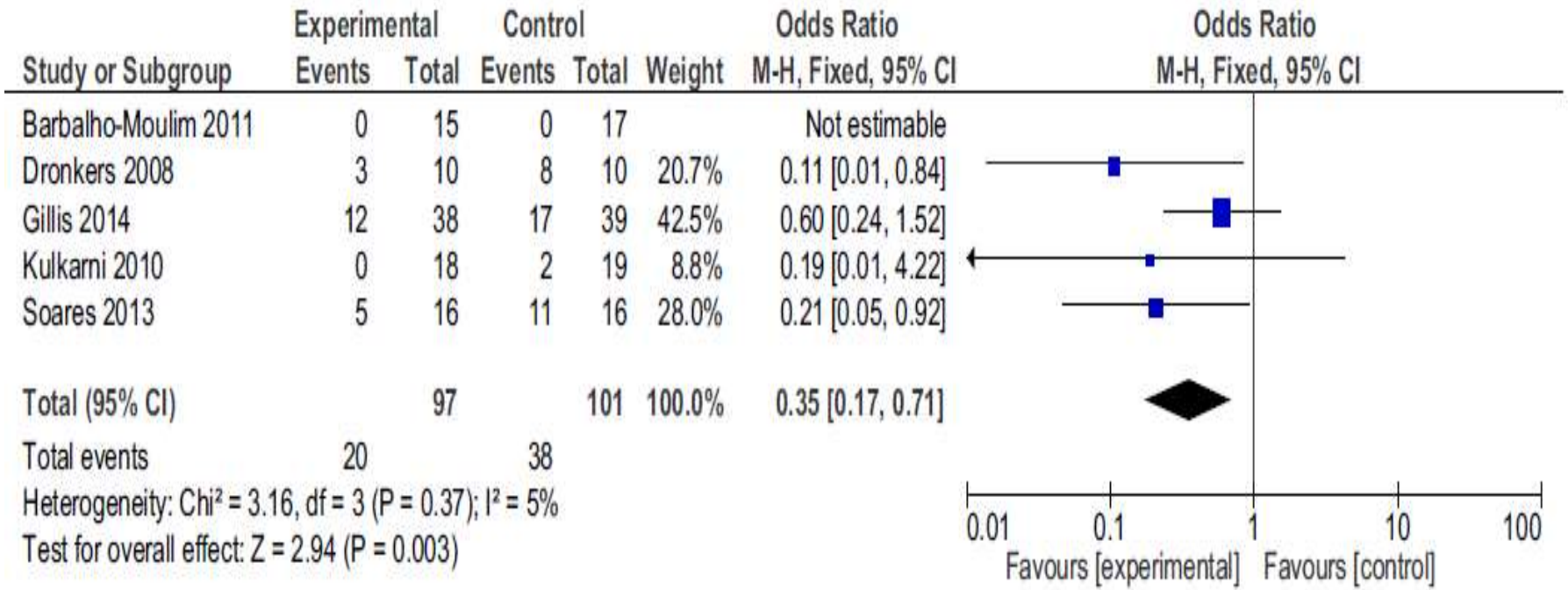
*n (%).

†Chi-square test.

EVAR indicates endovascular aneurysm repair; OAR, open aneurysm repair.

Ann Surg, 2016

The ability of prehabilitation to influence postoperative outcome. Systematic review and meta analysis



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

Heterogeneity: $Chi^2 = 3.16$, $df = 3$ ($P = 0.37$); $I^2 = 5\%$

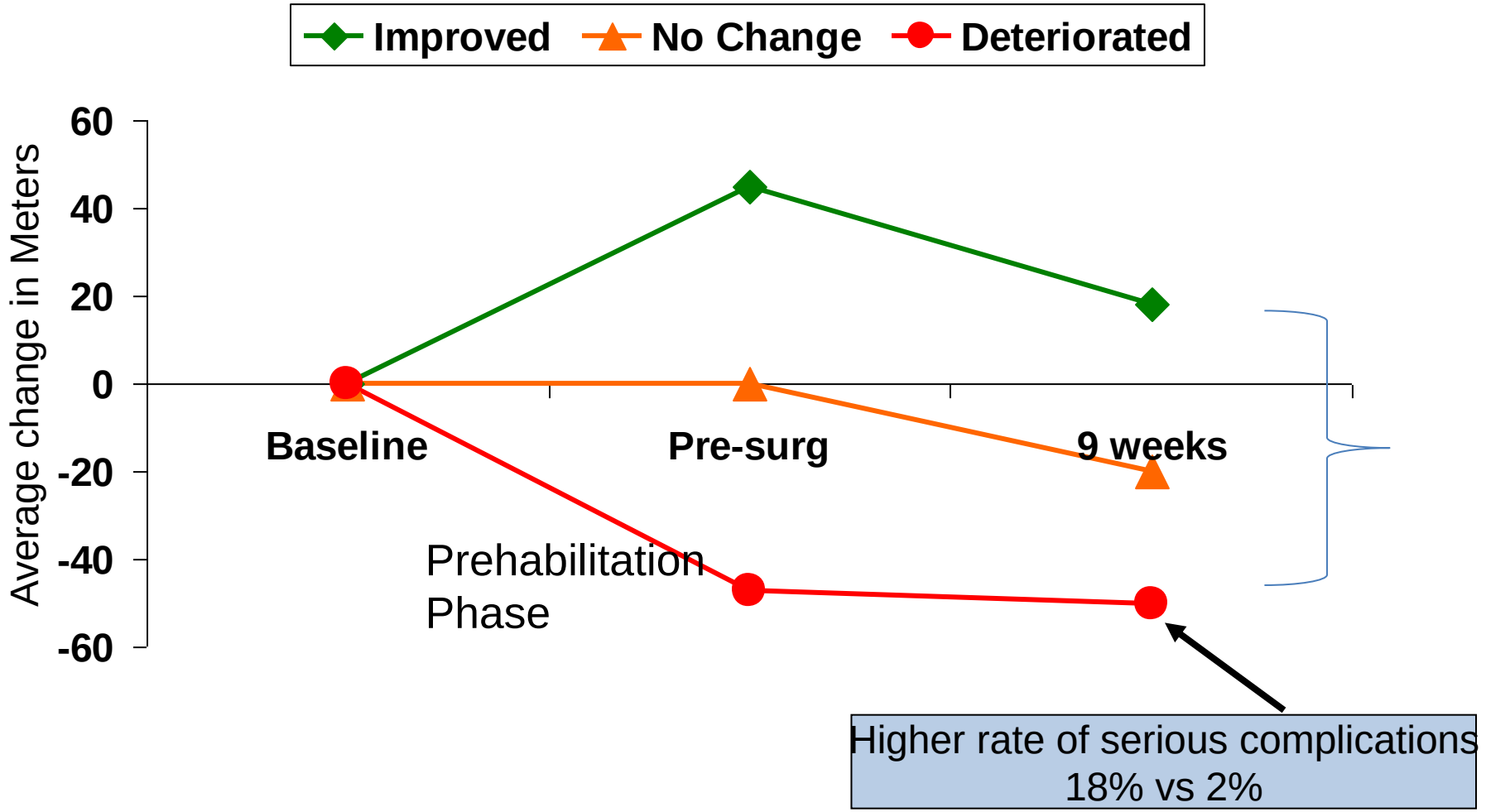
Test for overall effect: $Z = 2.94$ ($P = 0.003$)

Prehabilitation vs usual care: morbidity

Surgery, 2016

Impact of Pre-operative Change in Physical Function on Surgical Recovery after Colorectal Surgery, n=156

Mayo N, Feldman L, Carli F, Surgery, 2011



IMPROVING PREOPERATIVE FUNCTIONAL CAPACITY DESCREASES COMPLICATION AND ED VISTIS

	6MWD change ≥ 20 m		p
	NO n = 99	YES n = 80	
30-day COMPLICATION (CCI), median [IQR]	8.7 [0-22.6]	0 [0-8.7]	0.022
Participants with at least 1 complication within 30 days, n (%)	50 (50)	30 (38)	0.097
Length of primary hospital stay (days), median [IQR]	4 [3-6]	3 [3-5]	0.236
30-day ED visit, n (%)	25 (25)	10 (13)	0.038
30-day hospital readmissions, n (%)	14 (14)	5 (6)	0.142

Minnella E , unpublished

Prehabilitation in colorectal cancer and postoperative clinical outcome

International multicenter study, 2016 (Registered Clinical Trials, NTR 5947)

The Netherlands
Canada
Danemark
France

Take Home Message

- Prehabilitation requires a multidisciplinary approach
- Customize the program to each patient/surgery
- Proof of concept: increases functional capacity
- Can improve postoperative outcome (more data needed)
- Can impact on continuum of cancer care (more data needed)
- Challenges: Compliance? Recording adherence
  Costs? Caregiver, Societal,
  Resources?

Conference

Prehabilitation for the Surgical Patient

June 15-17 2017

Montreal, Quebec, Canada

Contact for more information:
victoria.greco@mail.mcgill.ca

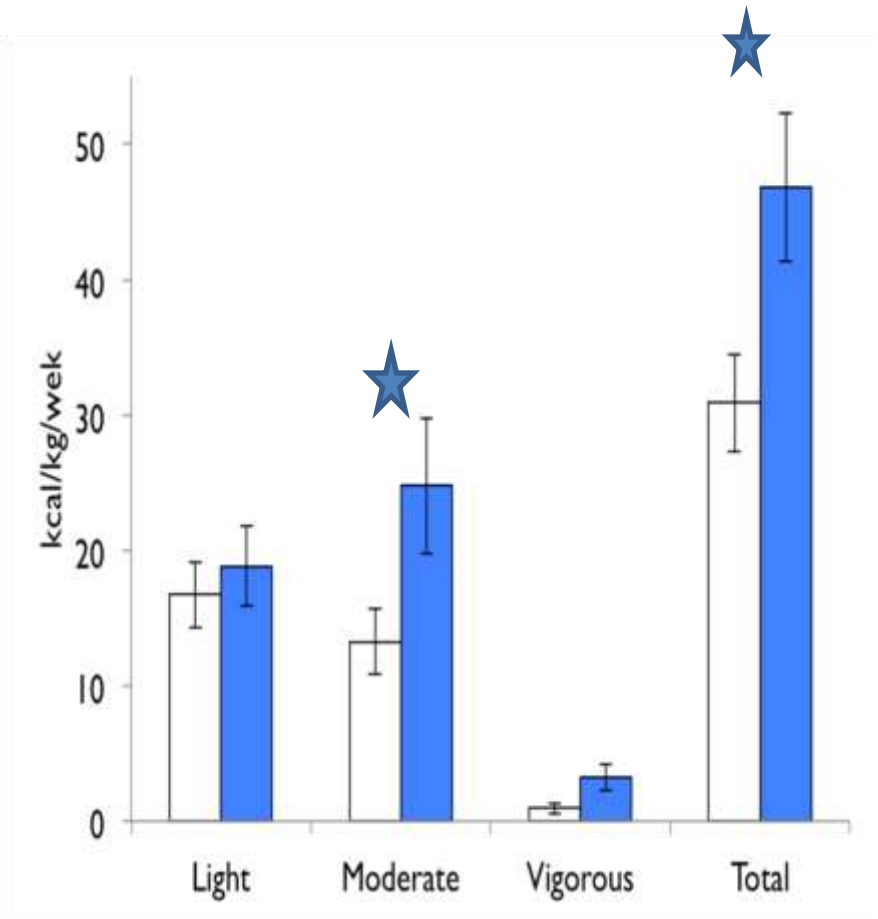
McGill UNIVERSITY

PERI OPERATIVE PROGRAMME PÉRI-OPÉRATOIRE

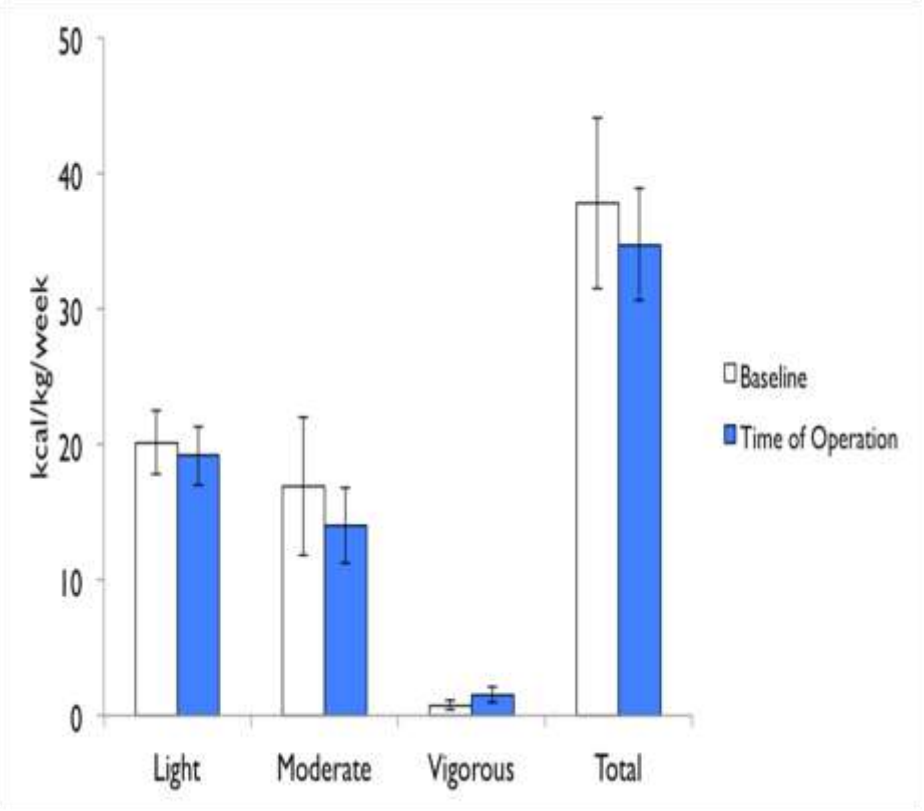
Physical activity increases in the prehab group during the 4 weeks before surgery

(CHAMPS,)

Chen B et al, 2016

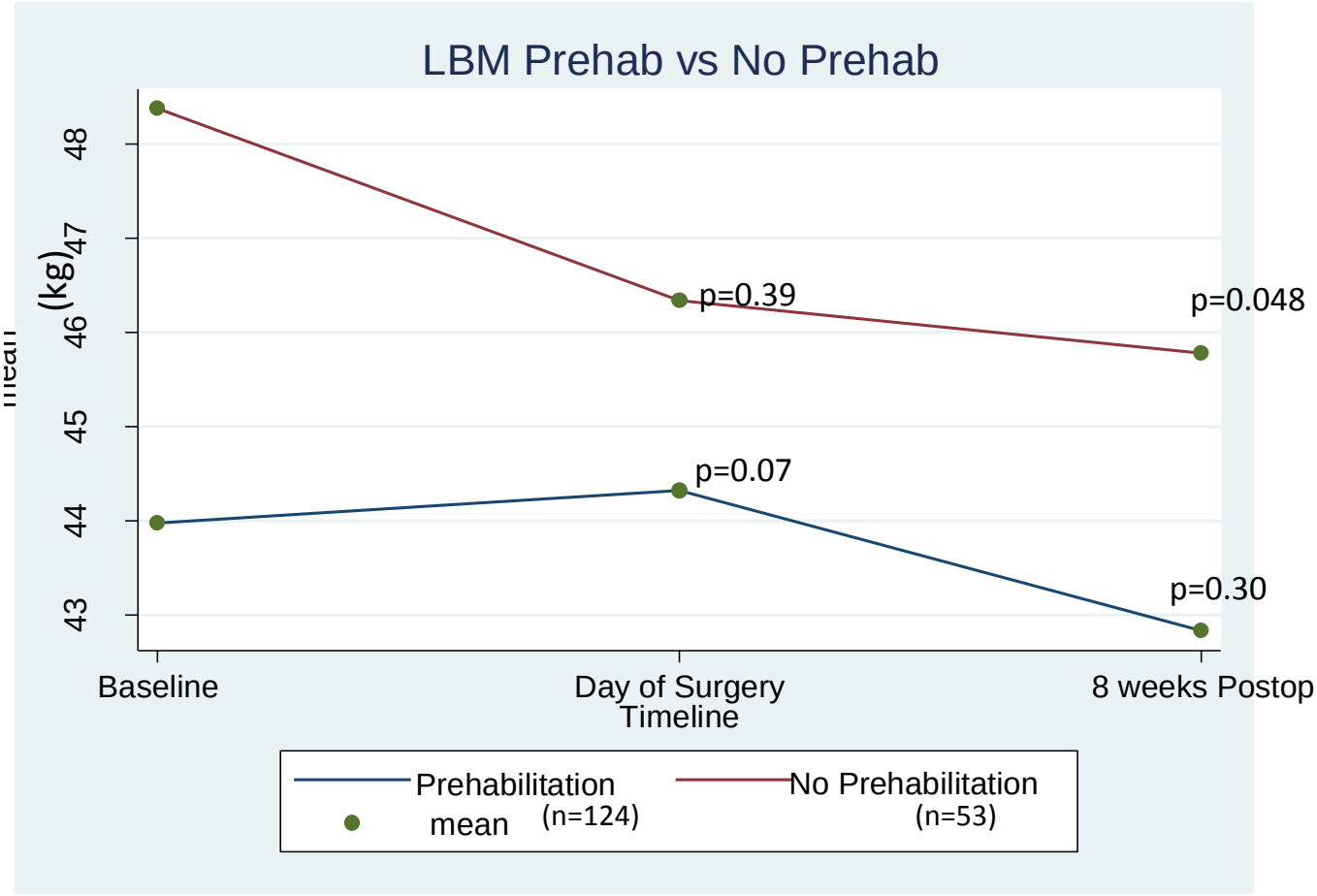


Prehab group



Rehab/control group

BIA within group comparisons Prehabilitation vs. No intervention within an ERAS setting



Gillis C, unpublished

Study Design

n=179 pts
1 cohort + 2 RCTs

Baseline assessment

↓

Preoperative assessment

↓

SURGERY

↓

4 weeks post assessment

↓

8 weeks post assessment

PREOPERATIVE WALKING DISTANCE IMPROVEMENT

≥ 20 m

< 20 m

**Li C et al, Surg Endosc, 2013*
Gillis C et al, Anesthesiology 2014,
Carli F et al (unpublished)

Type of postoperative complications

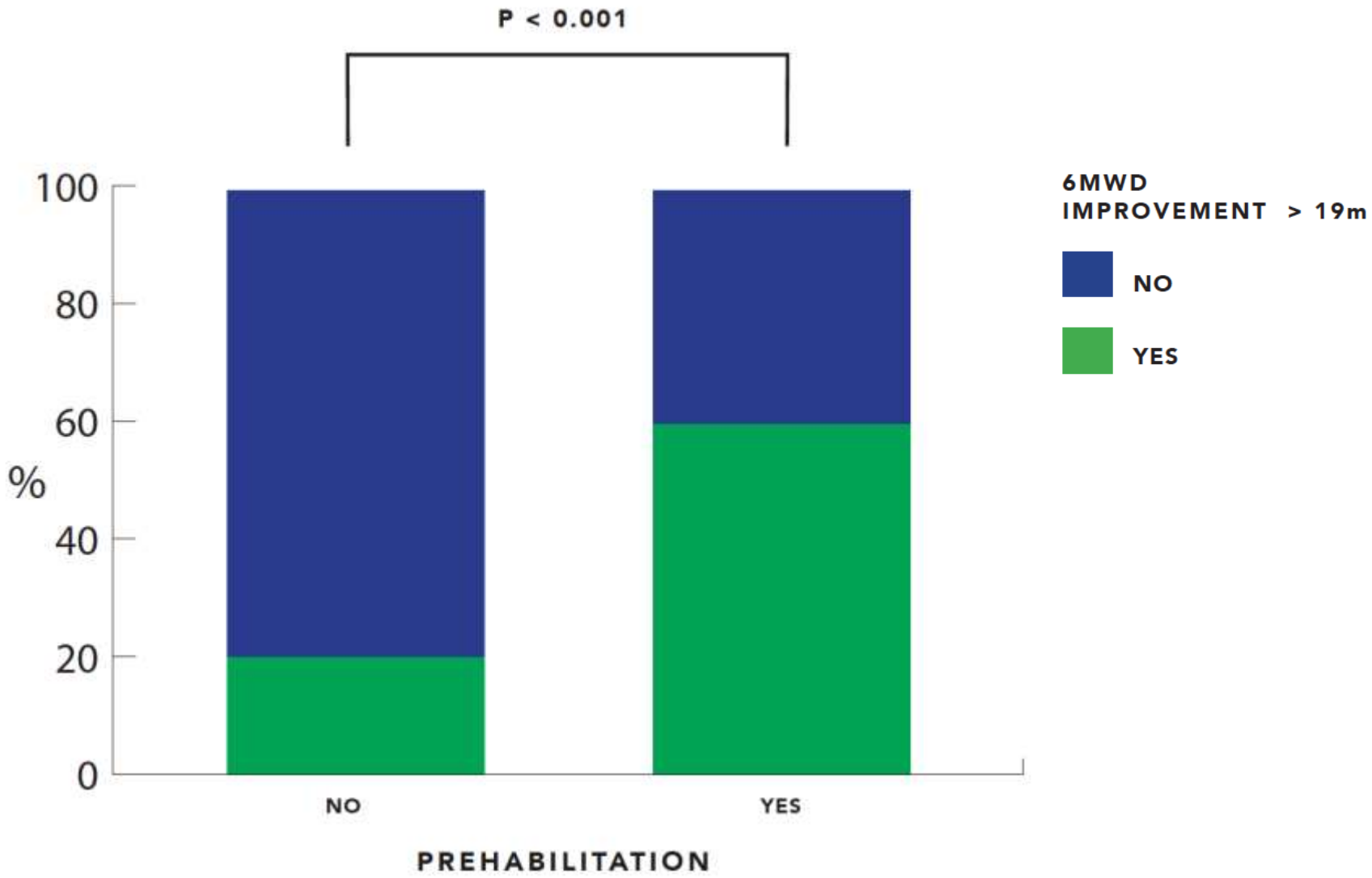
	6MWD change ≥ 20 m	
	NO n = 99	YES n = 80
Medical Complication, n (%)	24 (24%)	15 (19%)
Cardiovascular	6 (6%)	1 (1%)
Respiratory	5 (5%)	2 (3%)
Infectious	5 (5%)	6 (8%)
Other medical	16 (16%)	9 (11%)
Surgical complication, n(%)	24 (24%)	14 (18%)
Anastomotic leak	3 (3%)	0 (0%)
Perforation	1 (1%)	1 (1%)
Ileus	20 (20%)	11 (14%)
Wound dehiscence	1 (1%)	0 (0%)
Bleeding	3 (3%)	2 (3%)
other	1 (1%)	1 (1%)

IMPROVING PREOPERATIVE FUNCTIONAL CAPACITY DESCREASES SEVERITY COMPLICATION

	Severe Complication *CCI ≥ upper quartile*		
	OR	95% CI	p
6MWD change ≥ 20 m	0.28	0.11-0.74	0.01

Multivariate logistic regression analysis testing adjusted for age, gender, BMI, ASA, Charlson Comorbidities Index, cancer stage, surgical approach and surgical site

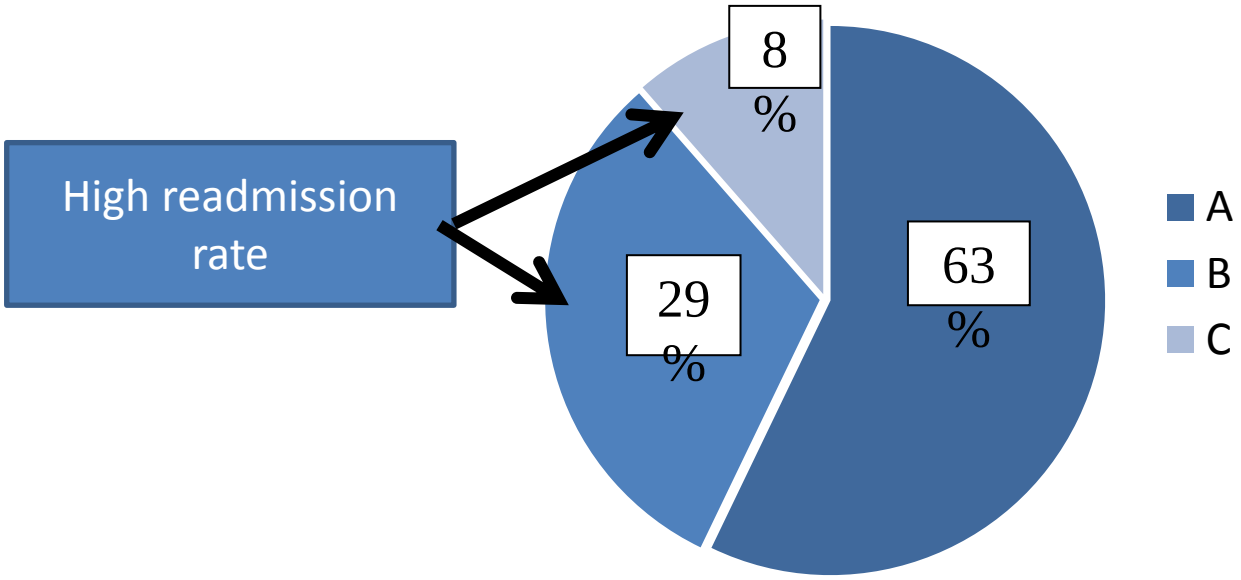
Greater proportion of prehabilitation patients improved



Undernutrition Before Surgery: Our Experience.

Gillis C et al. Nut Clin Pract 2015

The incidence of undernutrition in *all* patients attending preoperative clinic at Montreal General Hospital for *elective colorectal surgery*



Global Assessment (n=70) score A refers to adequately nourished; B moderate or suspected undernutrition; C severely undernourished

Future directions for exercise–oncology research on cancer progression.

Epidemiological studies

- A greater number of large-scale studies assessing both self-reported and/or objective measures of exercise exposure with long-term follow-up and adequate event rates.
- Delineate the association no how changes in exercise behavior, functional capacity/cardiorespiratory fitness measures are associated with clinical outcome across all solid tumors.
- More studies determining the differential association between exercise and prognosis as a function of tumor phenotype/gene expression.
- More studies determining the differential association between exercise and prognosis as a function of host-related circulating factors postulated to mediate the exercise–prognosis relationship.

Clinical biomarker intervention studies

- Delineate the differential effects of differences in exercise prescription dose (e.g., frequency, intensity, duration, modality) on changes in salient biomarkers in randomized trials.
- Determine effects of exercise across different tumor types across the cancer continuum (i.e., from diagnosis to palliation) to expand current efforts as well as extend to other solid tumors where exercise has not been rigorously evaluated.
- Elucidate the most salient biomarkers of interest that mediate the exercise–cancer prognosis relationship to develop a standardized 'exercise–oncology' biomarker panel that is reproducible and can be evaluated/compared across studies.
- Determine the effects of exercise on circulating biomarkers in conjunction with procurement of tumor tissue and/or imaging biomarkers whenever possible.

Preclinical studies

- Orthotopic implantation of syngeneic tumor cell lines or induction of orthotopic tumors via transgenic or chemical methods in immune competent animals to enable investigation of effects on primary tumor growth and metastasis.
- Elucidate the optimal exercise frequency, intensity, duration, and progression, as appropriate. Confirmation of 'training' effect via muscle fiber or mitochondrial function analysis.
- Determine effects on systemic mechanisms (metabolic and sex hormones, inflammation, immunity, and products of oxidation) in conjunction with examination of intratumoral/tumor microenvironmental molecular mechanisms (e.g., cell signaling pathways, angiogenesis, metabolism, migration).

Potential translational (cross-cutting/transdisciplinary) studies

- Elucidation of the optimal dose of exercise to inhibit tumor progression/metastasis in mouse models of solid tumors to guide the dose of exercise to be tested in phase II randomized trials.
- Elucidation of the effects of exercise on both circulating and intratumoral mechanisms associated with tumor growth in mouse models to guide systemic (plasma) biomarker testing in completed and ongoing clinical exercise trials in cancer patients. For further mechanistic investigations, plasma/serum from patients exposed to exercise vs. control conditions can be applied to human cancer cells in vitro to investigate effects on markers of the neoplastic phenotype.
- In epidemiological studies, identify genes or histological sub-types that may mediate the association between exercise and prognosis. Next, in preclinical studies, confirm mechanism of action by examining the effects of exercise in clinically relevant mouse models where the identified gene/pathway/histological sub-type is over-expressed or ablated. For clinical translational, plasma/serum from patients (with the identified histological sub-type or over expression of a specific pathway) exposed to exercise vs. control conditions can be applied to human cancer cells in vitro for further mechanistic studies.

Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study **BMJ , 2013**

Although limited in quantity, existing randomised trial evidence on exercise interventions suggests that exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes

“Marginal gains theory”

“the principle of multiple, seemingly miniscule, improvements throughout any given process, collectively achieving a far superior output”

- Identifying every single small step
- Bundle of evidence-based elements

Dave Brailsford, director of British Cycling Team , 2012