

Accepted Manuscript

Exercise prehabilitation in elective intra-cavity surgery: A role within the ERAS pathway? A narrative review

Samuel T. Orange, Matthew J. Northgraves, Phil Marshall, Leigh A. Madden, Rebecca V. Vince



PII: S1743-9191(18)30741-6

DOI: [10.1016/j.ijso.2018.04.054](https://doi.org/10.1016/j.ijso.2018.04.054)

Reference: IJSU 4626

To appear in: *International Journal of Surgery*

Received Date: 17 February 2018

Revised Date: 26 March 2018

Accepted Date: 30 April 2018

Please cite this article as: Orange ST, Northgraves MJ, Marshall P, Madden LA, Vince RV, Exercise prehabilitation in elective intra-cavity surgery: A role within the ERAS pathway? A narrative review, *International Journal of Surgery* (2018), doi: 10.1016/j.ijso.2018.04.054.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2018. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <http://creativecommons.org/licenses/by-nc-nd/4.0/>

Exercise Prehabilitation in Elective Intra-cavity Surgery: a Role within the ERAS Pathway? A Narrative Review

Samuel T. Orange¹, Matthew J. Northgraves^{1,2}, Phil Marshall¹, Leigh A. Madden³, and Rebecca V. Vince^{1*}.

¹Sport, Health and Exercise Science, School of Life Sciences, University of Hull, Hull, UK.

²Department of Health Sciences, University of York, York, UK.

³Centre of Biomedical Research, School of Life Sciences, University of Hull, Hull, UK.

Running heading: Exercise Prehabilitation: a Narrative Review

Corresponding author

*Rebecca Vince¹, PhD

¹Sport, Health and Exercise Science, School of Life Sciences, University of Hull, Hull, UK,
HU6 7RX.

Email: rebecca.vince@hull.ac.uk

Telephone: +44 (0)1482 463176

1 **Exercise Prehabilitation in Elective Intra-cavity Surgery: a Role within the**

2 **ERAS Pathway? A Narrative Review**

3 **Running heading:** Exercise Prehabilitation: a Narrative Review

4

ACCEPTED MANUSCRIPT

5 **Abstract**

6 The Enhanced Recovery after Surgery (ERAS) model integrates several elements of
7 perioperative care into a standardised clinical pathway for surgical patients. ERAS
8 programmes aim to reduce the rate of complications, improve surgical recovery, and limit
9 postoperative length of hospital stay (LOHS). One area of growing interest that is not
10 currently included within ERAS protocols is the use of exercise prehabilitation (PREHAB)
11 interventions. PREHAB refers to the systematic process of improving functional capacity of
12 the patient to withstand the upcoming physiological stress of surgery. A number of recent
13 systematic reviews have examined the role of PREHAB prior to elective intra-cavity surgery.
14 However, the results have been conflicting and a definitive conclusion has not been obtained.
15 Furthermore, a summary of the research area focussing exclusively on the therapeutic
16 potential of exercise prior to intra-cavity surgery is yet to be undertaken. Clarification is
17 required to better inform perioperative care and advance the research field. Therefore, this
18 “review of reviews” provides a critical overview of currently available evidence on the effect
19 of exercise PREHAB in patients undergoing i) coronary artery bypass graft surgery (CABG),
20 ii) lung resection surgery, and iii) gastrointestinal and colorectal surgery. We discuss the
21 findings of systematic reviews and meta-analyses and supplement these with recently
22 published clinical trials. This article summarises the research findings and identifies pertinent
23 gaps in the research area that warrant further investigation. Finally, studies are conceptually
24 synthesised to discuss the feasibility of PREHAB in clinical practice and its potential role
25 within the ERAS pathway.

26 **Keywords**

27 Exercise training; Prehabilitation; Presurgical period; Intra-cavity surgery; Enhanced
28 Recovery after Surgery

29 1. Introduction

30 Major surgery represents a considerable stressor for older adults. The majority of surgical
31 patients are over 60 years old [1] and often present multiple comorbidities with a decreased
32 ability to cope with trauma. These age-related impairments in physiological function, coupled
33 with the raft of metabolic and hormonal perturbations that occur in response to surgery, often
34 lead to a longer convalescence for elderly patients [2]. In particular, major intra-abdominal
35 resections are associated with an in-hospital stay of up to 10-days [3] and complication rates
36 of 15-20% [4, 5].

37 The Enhanced Recovery after Surgery (ERAS) pathway was initiated in the 1990s by a group
38 of academic surgeons to improve perioperative care in these patients [6]. The ERAS model
39 was originally developed for colorectal surgery but has now been applied to almost all major
40 surgical specialities [7] and represents a paradigm shift towards a multimodal, patient-centred
41 approach to surgical care. ERAS is designed to modify the physiological and psychological
42 response to surgical trauma by integrating a range of evidence-based components into a
43 standardised clinical pathway. Ultimately, ERAS programmes aim to reduce the rate of
44 complications, improve surgical recovery, and limit postoperative length of hospital stay
45 (LOHS). Indeed, a number of recent meta-analytic reviews have reported a 30% to 50%
46 reduction in LOHS and complication rates in colorectal surgery patients receiving treatment
47 through the ERAS pathway compared to traditional perioperative care [8-12]. Furthermore,
48 this reduction has been achieved without compromising patient safety [10] and is associated
49 with lower healthcare costs [9].

50 There are 24 core elements of ERAS that are distributed along the patient pathway, as
51 outlined recently by Ljungqvist and colleagues [7]. One area that is not currently included
52 within ERAS protocols, although it is a growing field of interest, is the use of preoperative

53 exercise or prehabilitation (PREHAB) interventions. PREHAB refers to the systematic
54 process of improving functional capacity of the patient to withstand the upcoming
55 physiological stress of surgery [13]. The concept of PREHAB is contingent on the principle
56 that patients with higher levels of fitness generally exhibit reduced postoperative
57 complications and improved clinical outcomes [14]. The application of PREHAB prior to
58 intra-abdominal and intra-thoracic surgery has received considerable attention in recent years
59 [15-19]. However, the results of existing systematic reviews have been conflicting.
60 Clarification is required to better inform perioperative care and to identify pertinent gaps in
61 the research area that warrant further investigation.

62 To address this issue, a recent scoping review [20] has provided an extensive overview of the
63 PREHAB literature. The review included all types of surgery and non-exercise pulmonary
64 interventions, such as inspiratory muscle training (IMT) and incentive spirometry. Given that
65 the effectiveness of PREHAB may differ between various types of surgery and different
66 methods of preoperative therapy, a “review of reviews” that focuses exclusively on exercise
67 interventions prior to intra-cavity resection is warranted. Therefore, this review aimed to
68 evaluate the effect of exercise PREHAB on physical fitness, LOHS and postoperative
69 complications in patients undergoing elective major intra-abdominal and intra-thoracic
70 surgery.

71 **2. Process of review**

72 We conducted the literature search in PubMed (MEDLINE) and Google Scholar databases
73 from 2006 to 2016 using a combination of keywords such as prehabilitation, preoperative,
74 surgery, aerobic exercise, resistance training, physical function, abdominal, thoracic, cardiac,
75 colorectal, and lung. Keywords were also combined with the following Medical Subject
76 Headings (only relevant for search in PubMed): preoperative period, thoracic surgery,

77 colorectal surgery, exercise, and exercise therapy. Focus was on systematic reviews and
78 meta-analyses, although these were also supplemented with available individual studies. We
79 defined *PREHAB* as a structured regimen of aerobic and/or resistance training, either home-
80 based or in a supervised setting, prior to major elective intra-cavity surgery. *Intra-cavity*
81 *surgery* was defined as elective intra-abdominal and intra-thoracic surgery [16]. In the cases
82 of systematic reviews or meta-analyses that cited studies that included other types of surgery
83 (e.g. orthopaedic) or the predominant use of pulmonary interventions (e.g. IMT), pertinent
84 individual studies cited within the meta-analyses were reviewed independently. Finally, we
85 discuss whether the current evidence-base supports the inclusion of PREHAB within ERAS
86 pathways.

87 **3. PREHAB in Intra-Thoracic Surgery**

88 **3.1. Coronary Artery Bypass Graft Surgery**

89 Two well-designed meta-analyses [21, 22] have reviewed the effects of PREHAB in cardiac
90 patients awaiting coronary artery bypass graft (CABG) surgery. The majority of studies cited
91 within these reviews, however, exclusively involved educational interventions and/or IMT.
92 For example, Hulzebos and colleagues [21] reviewed eight randomised controlled trials
93 (RCTs), six of which only included the use of non-exercise pulmonary interventions. We
94 identified just three studies, all of which were RCTs that involved the predominant use of
95 exercise training as the PREHAB intervention [23-25]. In a small pilot RCT using the six
96 minute walk test (6MWT) distance as the primary outcome [23], 17 patients engaged in eight
97 weeks of aerobic exercise (walking and cycling at 85% maximal oxygen consumption
98 [VO_{2max}]) and resistance exercises (body weight and resistance bands) twice per week.
99 Compared with control, the PREHAB group improved 6MWT distance and 5-metre gait
100 speed at the preoperative (6MWT: 136 metres; 5-metre gait speed: -1.6 sec) and 3-month

101 postoperative (6MWT: 123 metres; 5-metre gait speed: -1.2 sec) reassessments. No reduction
102 in LOHS was found between groups (PREHAB = 5.3 ± 1.0 days; CON = 5.1 ± 1.4 days),
103 suggesting that the improvement in functional capacity may not translate into favourable
104 clinical outcomes. A lack of change in LOHS was also reported following 10 weeks of
105 combined aerobic exercise training (40 minutes at 60% maximum heart rate [HR_{max}]) and
106 mental stress reduction in 117 patients scheduled for CABG and/or valve surgery (PREHAB
107 = 6 days [range: 5 to 8]; CON = 6 days [range: 5 to 8]) [24]. The absence of an objective
108 measure of physical fitness means it is unknown whether PREHAB improved patients'
109 fitness prior to surgery. Moreover, it is important to note that the sample sizes for both studies
110 were calculated in order to provide power to detect changes in either objective [23] or
111 subjective [24] measures of function, rather than clinical outcomes.

112 In the only RCT conducted with CABG patients that had LOHS as the primary outcome
113 measure, 246 patients awaiting elective surgery for CABG were randomised to receive either
114 a multi-dimensional preoperative intervention or usual care [25]. The intervention consisted
115 of 30 minutes of supervised aerobic exercise (40 – 70% of VO_{2max}), in addition to a variety of
116 mobility exercises, twice weekly for approximately eight weeks (mean duration: 8.3 weeks).
117 Patients who received the PREHAB intervention spent one less day in hospital overall (95%
118 CI: 0.0 to 1.0), and 2.1 hours less time in ICU (95% CI: -1.2 to 16.0) compared to the control
119 group. The PREHAB group also displayed a greater quality of life during the waiting period
120 (measured by the SF-36), which continued up to six months after surgery. Thus, engaging in
121 PREHAB in the waiting period for CAGB surgery provided an imminent patient benefit that
122 is likely to be meaningful. Furthermore, the authors calculated the cost of PREHAB would be
123 C\$342 per day, and that an exercise test before the intervention would cost C\$240 [25].
124 Based on the rate of one day in a Canadian hospital (C\$715), a one day reduction in LOHS
125 would provide a net cost savings of approximately C\$133 per patient per day.

126 3.2. PREHAB in Lung Resection Surgery

127 Overall, the quality of evidence for PREHAB in lung resection surgery is poor, with the
128 research area being dominated by RCTs with small sample sizes and single-group
129 observational trials. In a recent systematic review [19] of 10 studies consisting of 277
130 participants (Table 1), only four studies were RCTs, with one study being a case control
131 study and the remaining five studies were prospective cohort trials. Furthermore, only four
132 studies included in the review were considered as 'good quality' or above according to the
133 Physiotherapy Evidence Database (PEDro) scale. Notwithstanding the lack of high quality
134 studies, the findings indicated that PREHAB may have beneficial effects on physical fitness,
135 which is consistent with another systematic review in patients undergoing elective intra-
136 cavity surgery [16]. The authors also suggested that LOHS and complication rates may be
137 reduced with PREHAB [19]. However, this conclusion was based on only two RCTs, both of
138 which included less than 30 participants. In a meta-analysis of 21 studies (5 RCTs) that
139 included 1189 patients from 2005 to 2013 [15], PREHAB reduced LOHS by -4.83 days (95%
140 CI: -5.9 to -3.76) and decreased the relative risk for developing postoperative complications
141 (RR 0.45; 95% CI: 0.28 to 0.74) based on pooled data from nine studies. While the meta-
142 analysis did not quantify changes in exercise capacity, several included studies reported
143 statistically significant improvements in 6MWT distance and VO_{2max} , ranging from 20 metres
144 [26] to 170 metres [27] and from $2.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ [28] to $6.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ [27],
145 respectively. Furthermore, two studies also demonstrated an increment in the maximal
146 workload achieved during the cardiopulmonary exercise test [29, 30].

147 Interestingly, simple walking regimens have been shown to evoke discernible benefits to
148 patients awaiting lung resection. In an RCT with LOHS as the primary outcome measurement
149 [31], 60 patients with non-small cell lung cancer (NSCLC) received either usual care, or
150 engaged in walking exercise on a treadmill three times per day for one week (intensity and

151 duration not reported) in addition to chest physiotherapy (breathing exercises and incentive
152 spirometry). The PREHAB group registered a significantly reduced LOHS in comparison
153 to the control group (5.4 ± 2.7 vs. 9.7 ± 3.1 days, respectively). Compared with baseline
154 values, the PREHAB group also significantly increased their pre-surgical walking duration
155 (18.2 ± 7.4 vs. 39.7 ± 16.2 minutes), distance (614 ± 415 vs. 991 ± 535 metres), and speed
156 (4.0 ± 1.0 vs. 5.0 ± 1.1 mph), although the testing involved non-standardised procedures and
157 the change in walking capacity was measured within groups because the control group did
158 not participate in exercise testing. Nevertheless, improvements in clinical and functional
159 outcomes have also been reported following a similar four-week walking (10 – 30 minutes at
160 80% VO_{2max} , three times per week) and IMT (10 – 30 minutes daily) intervention prior to
161 lung cancer resection [32]. Compared to patients receiving conventional chest physiotherapy
162 (breathing exercises for lung expansion), the PREHAB group increased 6MWT distance (-4.6
163 ± 20.3 vs. 50 ± 16.2 metres), reduced LOHS (12.2 ± 3.6 vs. 7.8 ± 4.8 days), had fewer days
164 with chest tubes (7.4 ± 2.6 vs. 4.5 ± 2.9 days) and exhibited less postoperative pulmonary
165 complications (7 vs. 2), respectively. Though the inclusion of IMT is likely to have
166 augmented the effects of exercise, these studies [31, 32] suggest that a short-term, simple
167 PREHAB protocol may improve pre-surgical functional capacity and can have a substantial
168 benefit on convalescence, at least in patients awaiting lung resection.

169 In the only home-based study, Coats et al. [33] investigated the effects of a 4 week PREHAB
170 intervention in NSCLC patients. The intervention included 30 minutes of aerobic exercise at
171 60-80% of peak workload and free-weight resistance exercises (1-2 sets of 10-15 repetitions
172 with 1-2 kg dumbbells) for 3-5 times per week. In contrast to several previous studies, no
173 significant improvement was found in the VO_{2max} of the 13 patients to complete the
174 intervention. The lack of supervision in Coats et al. [33] may have contributed to the
175 difference between studies; supervised programmes tend to be more effective than

176 unsupervised programmes for improving function in older adults [34]. Despite the lack of
177 change in VO_{2max} , Coats et al. [33] reported significant and clinically meaningful
178 improvements in the constant endurance test (from 264 ± 79 seconds to 421 ± 241 seconds)
179 and 6MWT distance (540 ± 98 metres to 568 ± 101 metres). Small improvements were also
180 noted in deltoid ($\Delta 1.8 \pm 2.8$ kg), triceps ($\Delta 1.3 \pm 1.8$ kg) and hamstring ($\Delta 3.4 \pm 3.7$ kg)
181 muscle strength following PREHAB. While these changes were potentially trivial, an
182 increase in muscle strength prior to surgery may play an important role in facilitating early
183 mobilisation, which is a key component of the ERAS pathway. For this reason, measures of
184 muscle strength should be considered important in future studies to assess the efficacy of
185 PREHAB in context of ERAS.

186 In summary, there is some evidence that PREHAB can improve physical fitness prior to lung
187 resection surgery. These improvements appear to be meaningful and may translate into
188 favourable clinical outcomes. For example, studies measuring 6MWT distance reported an
189 increase of between 20 and 170 metres following PREHAB, with the majority of
190 improvements exceeding the minimal important difference previously reported in lung cancer
191 patients (22 - 42 metres) [35]. In addition, Coats and colleagues [33] provided preliminary
192 evidence that PREHAB can enhance the force-generating capacity of skeletal muscle. Even
193 so, the research area is dominated by poor quality studies, mainly involving single-group
194 observational trials with small sample sizes. It is also pertinent to note that the majority of
195 studies consisted of at least five hospital-based supervised exercise sessions a week, therefore
196 a considerable time and resource (money, facility and staffing availability) burden would be
197 placed on both the exercise provider and patient in order to participate in the intervention.
198 Older persons are more likely to engage in exercise interventions that are easily accessible,
199 do not require transport, and involve no out-of-pocket costs [36].

200 **4. PREHAB in Intra-Abdominal Surgery**

201 **4.1. Gastrointestinal and Colorectal Surgery**

202 There are several published systematic reviews in the topic of PREHAB and surgery that
203 have included gastrointestinal and colorectal patients, and a further four reviews that have
204 focused solely on colorectal and/or abdominal surgery [16-18, 37]. In 2014, a meta-analysis
205 [38] suggested that no recommendation can currently be made regarding exercise training as
206 a routine intervention for colorectal cancer patients. However, this study [38] involved all
207 stages of the perioperative pathway. In the only systematic review to date specifically
208 evaluating PREHAB in patients awaiting surgery for colorectal cancer, Boereboom et al. [17]
209 identified eight studies with a total of 518 patients from 2009 to 2015, including five RCTs,
210 two prospective cohort trials and one non-randomised interventional study. Results indicated
211 that exercise PREHAB improves functional capacity, and to a lesser extent cardiorespiratory
212 fitness prior to colorectal cancer resection. 6MWT distance was the preferred primary
213 outcome measure in five of the included studies (two studies analysed the same data [39,
214 40]), with reported improvements of between 4 metres [41] and 42 metres [42] compared
215 with control. However, there was no evidence of reduced LOHS or complications rates, and
216 thus the improvement in fitness may not translate into reduced perioperative risk or improved
217 postoperative outcomes.

218 A similar finding was reported in a systematic review by O'Doherty and colleagues [16]
219 including 10 studies from 1981 to 2011, containing 524 patients awaiting elective intra-cavity
220 surgery. Four of the studies were RCTs and six were observational. It was concluded that
221 PREHAB is effective in improving physical fitness, however, the evidence for augmented
222 postoperative clinical outcome is limited. Seven of the studies reported VO_{2max} or predicted
223 VO_{2max} as the primary outcome measure, with increases of up to $8 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ found in
224 patients undergoing gastrointestinal surgery [43]. A beneficial effect of PREHAB on
225 objective measures of cardiorespiratory performance has also been demonstrated recently by

226 West and colleagues [44] in neoadjuvant chemoradiotherapy (NACRT) patients, although a
227 non-randomised design was used and the intervention lasted six weeks, which may not be
228 applicable for colorectal surgery patients not receiving NACRT because the duration exceeds
229 the median wait time between surgical consultation and resection (~31 days) [45].

230 There appears to be a collective difficulty of converting promising results in a laboratory
231 environment into meaningful improvements in the clinical setting. This may be related to the
232 design and conduct of exercise interventions, or because all studies in this research area
233 report measures of physical fitness as the primary outcome measure and are underpowered to
234 detect differences in clinical outcomes. It has been suggested that 400 participants would be
235 required to detect a 10% reduction in the incidence of absolute postoperative complications
236 with an alpha of 0.05 and a power of 0.80 [17]; to date, these data do not currently exist.

237 In another systematic review [18] based on six RCTs (673 patients) from 1997 to 2010, the
238 authors concluded that PREHAB may be effective in enhancing physical fitness in surgical
239 patients awaiting abdominal resection. However, when considering the primary data from the
240 individual studies included within the review, no study actually reported a PREHAB-induced
241 increase in physical fitness. Of the three studies to measure physical fitness prior to surgery,
242 Kim et al. [41] and Dronkers et al. [46] failed to show changes in VO_{2max} and predicted
243 VO_{2max} , respectively. Furthermore, Carli et al. [39] showed that the proportion of patients
244 with an improvement of ≥ 20 metres in the 6MWT was actually greater in a sham
245 intervention group compared with the PREHAB group (47% vs. 22% preoperatively, and
246 41% vs. 11% postoperatively). Patients in the PREHAB group were instructed to cycle seven
247 days per week (20-30 min at 50% of HR_{max} , progressing by 10% each week as tolerated) and
248 perform resistance training three times per week (bodyweight and free-weight exercises until
249 volitional failure), whereas the sham intervention consisted of a recommendation to walk for
250 30 minutes every day. While task specificity (e.g. walking intervention and walking-based

251 outcome measure) and the multiple imputation of large amounts of data (i.e. due to the high
252 attrition rates) may have contributed to the results, only 16% of the PREHAB group fully
253 adhered to the protocol. Thus, patients with a low baseline fitness level may have found the
254 intensive and time-consuming design of the bike/strengthening programme intimidating or
255 too difficult. This highlights the necessity to find an appropriate balance between an exercise
256 stimulus that is sufficient to improve physical fitness, but also to maximise patient
257 engagement and safety.

258 In order to improve exercise compliance, the same research group have since conducted three
259 trimodal home-based RCTs [42, 47, 48]. In all three studies the frequency of aerobic exercise
260 was decreased from daily to three times per week, the training intensity did not exceed 50%
261 HR_{max} , and patients were allowed to choose their preferred type of exercise. The exercise
262 interventions lasted four weeks and were also appended with whey protein supplementation
263 and psychological support. The PREHAB group displayed a greater improvement in 6MWT
264 distance compared with controls in all three studies (from 29.1 metres [47] to 41.6 metres
265 [48]), which was also associated with faster postoperative recovery of 6MWT performance 8
266 weeks following resection [from 45.2 metres [48] to 85.4 metres [42]]. Compliance in the
267 preoperative period was above 75% in all three studies, suggesting that exercising at home
268 may facilitate adherence to PREHAB programmes. Indeed, home-based cardiac rehabilitation
269 programmes have tended to show greater adherence and maintenance rates than supervised
270 hospital-based programmes [49]. However, consistent with other studies investigating
271 PREHAB in abdominal surgery, no differences between PREHAB and control groups were
272 found in LOHS, 30-day complication rate, or complication severity.

273 Generally, the literature shows that PREHAB prior to colorectal resection enhances walking
274 capacity by approximately 25 to 40 metres, and can also induce small improvements
275 cardiorespiratory fitness. The promotion of walking capacity prior to surgery has led to

276 improved postoperative recovery of physical fitness, which is parallel with the objectives of
277 the ERAS pathway. However, the magnitude of change in physical fitness appears
278 insufficient or unable to translate into favourable clinical outcomes, such as reduced LOHS
279 and complication rate. The lack of multi-centred adequately powered RCTs certainly
280 underpin, at least in part, the negligible changes in perioperative outcomes. It is also
281 conceivable that the current modalities of exercise PREHAB, rather than the theory of
282 PREHAB *per se*, also contribute to the absence of improvement in outcome measures.

283 There is a distinct lack of standardised PREHAB guidelines for patients undergoing major
284 intra-abdominal and intra-thoracic surgery, ostensibly due to the conflicting findings in the
285 current literature. The majority of studies have involved generic prescriptions of moderate-
286 intensity aerobic exercise, with resistance training less frequently included within PREHAB
287 protocols. Likewise, the primary endpoint was usually a measurement of cardiorespiratory
288 fitness such as VO_{2max} or 6MWT, presumably based on the well-established relationship
289 between VO_{2max} and perioperative outcome [14]. When resistance training has been
290 prescribed in PREHAB protocols, pertinent programme design variables have largely been
291 ignored and/or not reported. Given that PREHAB is defined as the systematic process of
292 improving functional capacity of the patient to withstand surgical stress [13], and strength
293 training has consistently been shown to augment functional ability in older adults [50],
294 further work is required to investigate the therapeutic benefits of individualised resistance
295 training programmes prior to intra-cavity surgery.

296 **5. A Role for PREHAB in the ERAS Pathway?**

297 PREHAB appears to be effective for improving physical fitness prior to elective intra-cavity
298 surgery. Some studies have also reported an accelerated recovery of postoperative functional
299 capacity, which is a central tenet of ERAS pathways [7]. However, the rate of complications

300 and LOHS are also important endpoints for ERAS care, and there is limited evidence
301 suggesting that PREHAB can modify these clinical outcomes. Indeed, there appears to be a
302 collective difficulty of translating favourable changes in functional capacity into a reduction
303 in complication rates or LOHS. Furthermore, the majority of studies in the PREHAB
304 literature are included in multiple systematic reviews, meaning there are a small number of
305 primary studies and most of them are single-centred and inadequately powered to detect
306 changes in any clinical endpoint.

307 The ERAS Society have published guidelines for evidence-based perioperative care in
308 elective colonic surgery [51]. The preoperative components of the ERAS model are presented
309 in Table 2. For PREHAB to be considered a worthwhile addition to the ERAS pathway,
310 evidence is required demonstrating that the benefits of presurgical exercise exceed current
311 practice in the preoperative period. Only two studies to date, both involving colorectal cancer
312 patients, have administered PREHAB in the context of ERAS. Li et al. [42] compared
313 PREHAB to a control group receiving standard ERAS care, whereas Gillis et al. [48]
314 compared PREHAB to a group undergoing exercise rehabilitation within ERAS. In
315 agreement with the totality of literature, both studies reported an increase in walking capacity
316 following PREHAB, but there were no improvements in LOHS nor complication rates when
317 compared to a standard ERAS programme [42, 48]. Further research is required directly
318 comparing the effects of ERAS *with* PREHAB versus ERAS *without* PREHAB in patients
319 undergoing intra-cavity surgery.

320 In addition to the well-established clinical benefits, studies have shown ERAS programmes to
321 be cost-effective across a range of surgical specialities, including abdominal and thoracic
322 surgery [52, 53]. This is thought to be a consequence of shorter convalescence and reductions
323 in morbidity and complication rates [53]. In contrast, there is a paucity of data concerning the
324 cost-effectiveness of PREHAB. However, the lack of benefit to clinical outcomes suggests

325 that, currently, PREHAB may not be economically worthwhile for service providers. The
326 adoption of any new intervention in the healthcare system requires rigorous justification due
327 to significant financial considerations and constraints. The absence of improvements in
328 LOHS and complications, coupled with a lack of savings, impedes the potential uptake of
329 PREHAB into existing ERAS pathways.

330 It is unknown whether PREHAB is simply unable to improve clinical outcomes, or that
331 currently prescribed exercise interventions are insufficient to drive the necessary adaptations.
332 The exercise programmes within this body of literature are largely heterogeneous, although
333 the vast majority of studies have involved generic prescriptions of moderate-intensity aerobic
334 exercise. While these protocols have generally induced changes in aerobic fitness, a more
335 precise manipulation of training variables may improve the training stimulus and better
336 prepare the patient for the upcoming physiological stress of surgery. Therefore, future work
337 should compare the effectiveness of different training modalities and adhere to exercise trial
338 reporting guidelines (e.g. [54]) to advance our understanding of the optimal exercise
339 PREHAB characteristics and ultimately help develop consensus exercise guidelines for this
340 patient population.

341 **6. Conclusion**

342 To conclude, the current evidence-base on PREHAB for patients undergoing elective intra-
343 cavity surgery is limited by inadequately powered RCTs, single-group observational trials
344 and a lack of evidence demonstrating favourable changes in clinical endpoints. Considering
345 these drawbacks in the literature, and that only two studies have administered PREAB in the
346 context of ERAS [42, 48], this review cannot recommend that PREHAB be introduced into
347 existing ERAS pathways. Further randomised clinical trials should be powered to detect
348 changes in clinical outcomes rather than changes in physical fitness. For example,

349 prospective studies are needed to better characterise the impact of PREHAB on length of stay
350 and complication rate. In addition, the quality of prescribed exercise PREHAB interventions
351 must be examined in order to advance this research area.

352 **Funding** This research did not receive any specific grant from funding agencies in the public,
353 commercial, or not-for-profit sectors.

ACCEPTED MANUSCRIPT

References

- 354 1. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA: A
355 Cancer Journal for Clinicians. 2001;51(1):15-36.
- 356 2. Baquero GA, Rich MW. Perioperative care in older adults. J Geriatr Cardiol.
357 2015;12(5):465-9.
- 358 3. Schoetz DJ, Jr., Bockler M, Rosenblatt MS, Malhotra S, Roberts PL, Murray JJ, et al.
359 "Ideal" length of stay after colectomy: whose ideal? Dis Colon Rectum. 1997;40(7):806-10.
- 360 4. Basse L, Hjort Jakobsen D, Billesbolle P, Werner M, Kehlet H. A clinical pathway to
361 accelerate recovery after colonic resection. Ann Surg. 2000;232(1):51-7.
- 362 5. Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey SG, Brewer D, et al.
363 Postoperative morbidity and mortality following resection of the colon and rectum for cancer.
364 Dis Colon Rectum. 1995;38(5):480-6; discussion 6-7.
- 365 6. Kehlet H. Multimodal approach to control postoperative pathophysiology and
366 rehabilitation. Br J Anaesth. 1997;78(5):606-17.
- 367 7. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review.
368 JAMA Surg. 2017;152(3):292-8.
- 369 8. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery
370 program in colorectal surgery: a meta-analysis of randomized controlled trials. World Journal
371 of Surgery. 2014;38(6):1531-41.
- 372 9. Roulin D, Donadini A, Gander S, Griesser AC, Blanc C, Hübner M, et al.
373 Cost-effectiveness of the implementation of an enhanced recovery protocol for colorectal
374 surgery. British Journal of Surgery. 2013;100(8):1108-14.
- 375 10. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The
376 enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective

- 377 open colorectal surgery: a meta-analysis of randomized controlled trials. *Clinical Nutrition*.
378 2010;29(4):434-40.
- 379 11. Zhuang CL, Ye XZ, Zhang XD, Chen BC, Yu Z. Enhanced recovery after surgery
380 programs versus traditional care for colorectal surgery: a meta-analysis of randomized
381 controlled trials. *Dis Colon Rectum*. 2013;56(5):667-78.
- 382 12. Lv L, Shao YF, Zhou YB. The enhanced recovery after surgery (ERAS) pathway for
383 patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled
384 trials. *Int J Colorectal Dis*. 2012;27(12):1549-54.
- 385 13. Topp R, Ditmyer M, King K, Doherty K, Hornyak J. The effect of bed rest and
386 potential of prehabilitation on patients in the intensive care unit. *AACN Advanced Critical*
387 *Care*. 2002;13(2):263-76.
- 388 14. Levett DZ, Grocott MP. Cardiopulmonary exercise testing for risk prediction in major
389 abdominal surgery. *Anesthesiology Clinics*. 2015;33(1):1-16.
- 390 15. Garcia RS, Brage MI, Moolhuyzen EG, Granger CL, Denehy L. Functional and
391 postoperative outcomes after preoperative exercise training in patients with lung cancer: a
392 systematic review and meta-analysis. *Interactive Cardiovascular and Thoracic Surgery*.
393 2016;23(3):486-97.
- 394 16. O'Doherty AF, West M, Jack S, Grocott MP. Preoperative aerobic exercise training in
395 elective intra-cavity surgery: a systematic review. *British Journal of Anaesthesia*.
396 2013;110(5):679-89.
- 397 17. Boereboom C, Doleman B, Lund JN, Williams JP. Systematic review of pre-operative
398 exercise in colorectal cancer patients. *Techniques in Coloproctology*. 2016;2016(20):2.
- 399 18. Pouwels S, Stokmans RA, Willigendael EM, Nienhuijs SW, Rosman C, van
400 Ramshorst B, et al. Preoperative exercise therapy for elective major abdominal surgery: a
401 systematic review. *International Journal of Surgery*. 2014;12(2):134-40.

- 402 19. Pouwels S, Fiddelaers J, Tejjink JA, ter Woorst JF, Siebenga J, Smeenk FW.
403 Preoperative exercise therapy in lung surgery patients: A systematic review. *Respiratory*
404 *Medicine*. 2015;109(12):1495-504.
- 405 20. Pouwels S, Hageman D, Gommans LN, Willigendael EM, Nienhuijs SW, Scheltinga
406 MR, et al. Preoperative exercise therapy in surgical care: a scoping review. *J Clin Anesth*.
407 2016;33:476-90.
- 408 21. Hulzebos EH, Smit Y, Helden PP, van Meeteren NL. Preoperative physical therapy
409 for elective cardiac surgery patients. *The Cochrane Library*. 2012;11:CD010118.
- 410 22. Snowdon D, Haines TP, Skinner EH. Preoperative intervention reduces postoperative
411 pulmonary complications but not length of stay in cardiac surgical patients: a systematic
412 review. *Journal of Physiotherapy*. 2014;60(2):66-77.
- 413 23. Sawatzky JA, Kehler DS, Ready AE, Lerner N, Boreskie S, Lamont D, et al.
414 Prehabilitation program for elective coronary artery bypass graft surgery patients: a pilot
415 randomized controlled study. *Clinical Rehabilitation*. 2014;28(7):648-57.
- 416 24. Rosenfeldt F, Braun L, Spitzer O, Bradley S, Shepherd J, Bailey M, et al. Physical
417 conditioning and mental stress reduction-a randomised trial in patients undergoing cardiac
418 surgery. *BMC Complementary and Alternative medicine*. 2011;11:20.
- 419 25. Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative
420 intervention on preoperative and postoperative outcomes in low-risk patients awaiting
421 elective coronary artery bypass graft surgery: a randomized, controlled trial. *Annals of*
422 *Internal Medicine*. 2000;133(4):253-62.
- 423 26. Bradley A, Marshall A, Stonehewer L, Reaper L, Parker K, Bevan-Smith E, et al.
424 Pulmonary rehabilitation programme for patients undergoing curative lung cancer surgery.
425 *European Journal of Cardio-Thoracic Surgery*, . 2013;44(4):e266-71.

- 426 27. Divisi D, Di Francesco C, Di Leonardo G, Crisci R. Preoperative pulmonary
427 rehabilitation in patients with lung cancer and chronic obstructive pulmonary disease.
428 *European Journal of Cardio-Thoracic Surgery*. 2013;43(2):293-6.
- 429 28. Jones LW, Peddle CJ, Eves ND, Haykowsky MJ, Courneya KS, Mackey JR, et al.
430 Effects of presurgical exercise training on cardiorespiratory fitness among patients
431 undergoing thoracic surgery for malignant lung lesions. *Cancer*. 2007;110(3):590-8.
- 432 29. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, Carbognani P, et al.
433 Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small
434 cell lung cancer. *European Journal of Cardio-Thoracic Surgery*. 2008;33(1):95-8.
- 435 30. Fang Y, Zhao Q, Huang D. The impact of exercise training on surgery tolerability in
436 lung cancer patients with impaired pulmonary function. *Chinese Journal of Rehabilitation
437 Medicine*. 2013;28:619-23.
- 438 31. Pehlivan E, Turna A, Gurses A, Gurses HN. The effects of preoperative short-term
439 intense physical therapy in lung cancer patients: a randomized controlled trial. *Annals of
440 Thoracic and Cardiovascular Surgery*. 2011;17(5):461-8.
- 441 32. Morano MT, Araújo AS, Nascimento FB, da Silva GF, Mesquita R, Pinto JS, et al.
442 Preoperative pulmonary rehabilitation versus chest physical therapy in patients undergoing
443 lung cancer resection: a pilot randomized controlled trial. *Archives of Physical Medicine and
444 Rehabilitation*. 2013;94(1):53-8.
- 445 33. Coats V, Maltais F, Simard S, Frechette E, Tremblay L, Ribeiro F, et al. Feasibility
446 and effectiveness of a home-based exercise training program before lung resection surgery.
447 *Canadian Respiratory Journal*. 2013;20(2):e10-e6.
- 448 34. Lacroix A, Hortobagyi T, Beurskens R, Granacher U. Effects of Supervised vs.
449 Unsupervised Training Programs on Balance and Muscle Strength in Older Adults: A
450 Systematic Review and Meta-Analysis. *Sports Med*. 2017.

- 451 35. Granger CL, Holland AE, Gordon IR, Denehy L. Minimal important difference of the
452 6-minute walk distance in lung cancer. *Chronic respiratory Disease*. 2015;12(2):146-54.
- 453 36. Franco MR, Howard K, Sherrington C, Ferreira PH, Rose J, Gomes JL, et al. Eliciting
454 older people's preferences for exercise programs: a best-worst scaling choice experiment.
455 *Journal of Physiotherapy*. 2015;61(1):34-41.
- 456 37. Pouwels S, Willigendael EM, van Sambeek MR, Nienhuijs SW, Cuypers PW, Teijink
457 JA. Beneficial Effects of Pre-operative Exercise Therapy in Patients with an Abdominal
458 Aortic Aneurysm: A Systematic Review. *European Journal of Vascular and Endovascular
459 Surgery*. 2015;49(1):66-76.
- 460 38. Cramer H, Lauche R, Klose P, Dobos G, Langhorst J. A systematic review and
461 meta-analysis of exercise interventions for colorectal cancer patients. *European Journal of
462 Cancer Care* 2014;23(1):3-14.
- 463 39. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized
464 clinical trial of prehabilitation in colorectal surgery. *British Journal of Surgery*.
465 2010;97(8):1187-97.
- 466 40. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, et al. Impact of
467 preoperative change in physical function on postoperative recovery: argument supporting
468 prehabilitation for colorectal surgery. *Surgery*. 2011;150(3):505-14.
- 469 41. Kim DJ, Mayo NE, Carli F, Montgomery DL, Zavorsky GS. Responsive measures to
470 prehabilitation in patients undergoing bowel resection surgery. *The Tohoku Journal of
471 Experimental Medicine*. 2009;217(2):109-15.
- 472 42. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal
473 prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study.
474 *Surgical Endoscopy*. 2013;27(4):1072-82.

- 475 43. Timmerman H, de Groot JF, Hulzebos HJ, de Knikker R, Kerckamp HEM, Van
476 Meeteren NLU. Feasibility and preliminary effectiveness of preoperative therapeutic exercise
477 in patients with cancer: a pragmatic study. *Physiotherapy Theory and Practice*.
478 2011;27(2):117-24.
- 479 44. West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, et al. Effect
480 of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in
481 preoperative rectal cancer patients: a blinded interventional pilot study. *British Journal of*
482 *Anaesthesia*. 2015;114(2):244-51.
- 483 45. Gillis A, Dixon M, Smith A, Law C, Coburn NG. A patient-centred approach toward
484 surgical wait times for colon cancer: a population-based analysis. *Can J Surg*. 2014;57(2):94-
485 100.
- 486 46. Dronkers JJ, Lamberts H, Reutelingsperger IM, Naber RH, Dronkers-Landman CM,
487 Veldman A, et al. Preoperative therapeutic programme for elderly patients scheduled for
488 elective abdominal oncological surgery: a randomized controlled pilot study. *Clinical*
489 *Rehabilitation*. 2010;24(7):614-22.
- 490 47. Chen BP, Awasthi R, Sweet SN, Minnella EM, Bergdahl A, Santa Mina D, et al.
491 Four-week prehabilitation program is sufficient to modify exercise behaviors and improve
492 preoperative functional walking capacity in patients with colorectal cancer. *Supportive Care*
493 *in Cancer*. 2016;25(1):33-40.
- 494 48. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus
495 Rehabilitation: A Randomized Control Trial in Patients Undergoing Colorectal Resection for
496 Cancer. *The Journal of the American Society of Anesthesiologists*. 2014;121(5):937-47.
- 497 49. Buckingham SA, Taylor RS, Jolly K, Zawada A, Dean SG, Cowie A, et al. Home-
498 based versus centre-based cardiac rehabilitation: abridged Cochrane systematic review and
499 meta-analysis. *Open Heart*. 2016;3(2):e000463.

- 500 50. Liu CJ, Latham NK. Progressive resistance strength training for improving physical
501 function in older adults. *Cochrane Database Syst Rev.* 2009(3):Cd002759.
- 502 51. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al.
503 Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After
504 Surgery (ERAS((R))) Society recommendations. *World J Surg.* 2013;37(2):259-84.
- 505 52. Scarci M, Solli P, Bedetti B. Enhanced recovery pathway for thoracic surgery in the
506 UK. *J Thorac Dis.* 2016;8(Suppl 1):S78-83.
- 507 53. Stowers MD, Lemanu DP, Hill AG. Health economics in Enhanced Recovery After
508 Surgery programs. *Can J Anaesth.* 2015;62(2):219-30.
- 509 54. Slade SC, Dionne CE, Underwood M, Buchbinder R. Consensus on Exercise
510 Reporting Template (CERT): Explanation and Elaboration Statement. *Br J Sports Med.* 2016.

511

512

513 **Table Captions**514 **Table 1.** Overview of the included reviews

515 Table 2. Preoperative components of the Enhanced Recovery After Surgery (ERAS) Pathway

ACCEPTED MANUSCRIPT

Table 1. Overview of the included reviews

516

Authors	Type of Review	Type of Surgery	Number of studies [RCTs]	Number of patients
Pouwels et al. [19]	SR	Lung	10 [4]	277
Garcia et al. [15]	SR and meta-analysis	Lung	21 [5]	1189
Boereboom et al. [17]	SR	Colorectal	8 [5]	518
O'Doherty et al. [16]	SR	Abdominal Cardiac	10 [4]	524
Pouwels et al. [18]	SR	Abdominal	6 [6]	673

RCT- randomised controlled trial, SR- systematic review

Table 2. Preoperative components of the Enhanced Recovery After Surgery (ERAS)

Pathway

Component	Rationale
Cessation of smoking and excessive alcohol consumption	Reduce complications
Structured preoperative information, education and counselling	Reduce fear and anxiety
Preoperative carbohydrate treatment	Reduce insulin resistance and possibly improve recovery
Not routinely using preoperative bowel preparation	Reduce dehydration, prolonged ileus and risk of anastomotic leakage
Prophylaxis against thromboembolism	Reduce thromboembolic complications
Preoperative prophylaxis against infection	Reduce rate of infections

518

519

520

Highlights

- Prehabilitation appears to be effective for improving physical fitness prior to surgery
- Changes in physical fitness may not translate into improved perioperative outcomes
- The literature is dominated by small RCTs and single-group observational trials
- Most prehabilitation interventions involve generic prescriptions of aerobic exercise

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

None

Please state any sources of funding for your research

none

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

none

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry and the unique identifying number of the study. You can register your research at <http://www.researchregistry.com> to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

none

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

All authors contributed to the writing of the review manuscript

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Rebecca Vince