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Complete List of Authors:	McIsaac, Daniel; University of Ottawa, Department of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Hutton, Brian; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Veroniki, Areti; St Michael's Hospital, Knowledge Translation Program Gill, Marlyn; Patient Partner Boland, L.; Ottawa Hospital Research Institute, Centre for Practice-Changing Research Branje, Karina; University of Ottawa, Department of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Grudzinski, Alexa L; University of Ottawa, Department of Anesthesiology and Pain Medicine Hladkowicz, Emily; Ottawa Hospital, Departments of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Shaw, Julia; University of Ottawa, Department of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Gillis, Chelsia; McGill University, School of Human Nutrition The Prehabilitation Knowledge Network, Group Authorship; NA
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Identifying relative efficacy of components of prehabilitation in adult surgical patients: protocol for a systematic review and component network meta-analysis

Corresponding Author: Daniel I McIsaac MD, MPH, FRCPC
Associate Professor of Anesthesiology and Pain Medicine, University of Ottawa
Associate Scientist, Ottawa Hospital Research Institute
Email: dmcisaac@toh.ca
Phone-613-761-4940/Fax-613-761-5209
Department of Anesthesiology, The Ottawa Hospital Civic Campus
Room B311, 1053 Carling Ave
Ottawa, ON K1Y 4E9

Authors: McIsaac, Daniel I MD, MPH, FRCPC[1,2,3*]; Hutton, Brian PhD[2,3]; Veroniki, Areti Angeliki PhD[4]; Gill, Marlyn MSW[5]; Boland, Laura SLP(c), PhD[6]; Branje, Karina MSc[1,2]; Grudzinski, Alexa L MD[1]; Hladkowicz, Emily MA.Ed[1,2,]; Shaw, Julia MSc[1,2]; Gillis, Chelsia RD, PhD[7]; the Prehabilitation Knowledge Network Authorship Group*

Affiliations:
1 Department of Anesthesiology and Pain Medicine, University of Ottawa, Ottawa, Canada
2 Clinical Epidemiology Program, the Ottawa Hospital Research Institute, Ottawa, Canada
3 School of Epidemiology & Public Health, University of Ottawa, Ottawa, Canada
4 Knowledge Translation Program, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Canada
5 Patient Partner, Calgary, Canada
6 Centre for Practice-Changing Research, Ottawa Hospital Research Institute, Ottawa, Canada
7 Department of Human Nutrition, McGill University, Montreal, Canada

***Individual collaborators with group authorship:** Shamsuddin Akhtar, Marlis Atkins, Sylvie Aucoin, Rebecca Auer, Carlota Basualdo-Hammond, Paul Beaule, Mary Brindle, Gregory Bryson, Franco Carli, Antoine Eskander, Dean Fergusson, Julio F Fiore Jr., Alan Forster, Melani Gillam, Leah Gramlich, Jayna Holroyd-Leduc, Timothy Jackson, Rachel Khadaroo, Manoj Lalu, Cameron Love, Guillaume Martel, Colin McCartney, Dolores McKeen, Amanda Meliambro, Husein Moloo, Ronald Moore, John Muscedere, Julie Nantel, Stephane Poitras, Celena Scheede-Bergdahl, Risa Shorr, Monica Taljaard, Tom Wallace, Duminda Wijeysundera

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ABSTRACT

Introduction: Prehabilitation is a high-priority intervention for patients, the public, clinicians, and health systems. However, existing knowledge syntheses are generally low quality and do not provide insights regarding the relative efficacy of different prehabilitation components (e.g., exercise, nutrition, psychosocial or cognitive interventions). The objective of the planned review is to evaluate the relative efficacy of different prehabilitation components to inform current care, implementation, and future research.

Methods and analysis: We will perform a systematic review and component network meta-analysis (CNMA). We will use a peer-reviewed search strategy to identify all randomized trials of prehabilitation in adult surgical patients from Ovid Medline, Embase, the CINAHL, PsychINFO, Web of Science, and the Cochrane Central Register of Controlled Trials, along with grey literature. All stages of the review and data extraction process will be performed in duplicate following recommended best practices. To compare the relative efficacy of different prehabilitation components (prespecified as exercise, nutrition, psychosocial or cognitive interventions), we will use CNMA, an extension of network meta-analysis that allows estimation of the contributions to efficacy of each component of a multicomponent intervention through direct and indirect comparisons. We will use additive CNMA models for critical outcomes (post-operative complications, patient-reported recovery, physical recovery, and length of stay); standard care will be the common reference condition. Pre-specified sensitivity and subgroup analyses will be conducted.

Ethics and dissemination: This review of published data does not require ethical review. Results will be disseminated via scientific conferences, peer reviewed publications, social and traditional media and via our research network to target partners and organizations.

Strengths and limitations of this study

-A prespecified protocol based on best practices for systematic review and meta-analysis will guide conduct of the study

-All stages of the study will be done in collaboration with patient and knowledge user partners so that findings will be co-produced in an integrated knowledge translation framework

-Component network meta-analysis will allow comparison of the relative efficacy of different prehabilitation components, even when multiple components are delivered simultaneously

-If assumptions underlying component network meta-analysis are not met, we may be unable to estimate relative efficacy of different components

Introduction

Globally, >300 million surgical procedures are performed each year.[1,2] These surgeries mostly occur on a planned (also referred to as 'elective') basis,[3] meaning that wait-times can be positively leveraged to optimize patient status prior to surgery. Patient optimization is critical in supporting high value surgical care as adverse postoperative events that matter to patients and the healthcare system are common.[4] Complications such as cardiopulmonary events, infections and major bleeding occur in 10-20% of patients.[5–7] Impaired functional recovery or new clinically significant disability develop in more than 1 in 5 surgical patients; such adverse events are even more common amongst older patients and those with poor baseline health. [8–12] Effective strategies to improve outcomes for the millions of people having surgery each year are urgently needed.

Prehabilitation is a process undertaken in advance of surgery, which has the specific intent of improving an individual's functional, physiologic, cognitive and/or mental health status through targeted interventions.[13,14] Patients, the public, and international specialty societies identify prehabilitation as a high priority intervention, including multiple James Lind Alliance priority setting partnerships.[15–17] However, despite the face validity and enthusiasm for prehabilitation interventions, a recently completed umbrella review of 55 prehabilitation systematic reviews found that existing evidence synthesis is insufficient to inform practice.[18] Several key knowledge gaps preclude translation of current evidence into practice. First, existing systematic reviews have major methodologic shortcomings; 51 of 55 prehabilitation reviews synthesized in a recent umbrella review were rated as low quality.[18,19] Second, prehabilitation interventions are heterogeneous, as they may consist of different components, including exercise, nutrition, psychosocial and cognitive interventions, or combinations thereof.[18] Existing prehabilitation reviews have typically focused only on single component interventions, or pooled all types of prehabilitation components or interventions together. This means that patients, clinicians, researchers, and health system planners are unable to determine what specific components, or combinations of components, contribute the most to prehabilitation efficacy and deserve the greatest focus in implementation and future research.

Understanding how the current evidence network can be leveraged to detect differences between the effects of interventions and their individual components would help to address these important gaps.

Component network meta-analysis (CNMA), an extension to network meta-analysis, allows estimation of separate effects for each component of a multicomponent intervention through direct and indirect comparison, even when these are delivered in combination.[20,21] We propose a CNMA based on an up-to-date, high-quality systematic review, to address important knowledge gaps in the prehabilitation evidence base. Our objective is to estimate which prehabilitation components contribute the greatest efficacy in improving critical outcomes, including postoperative complication rates, patient-reported recovery, physical recovery, and length of stay in adult patients preparing for surgery.

Methods

Design

This study will be a systematic review with CNMA. This protocol has been prepared in consideration of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines, the PRISMA extension for network meta-analysis, and specific considerations for CNMA.[22–24] Methods for the review are directly informed by the Cochrane Handbook and Methodological Expectations of Cochrane Intervention Reviews (MECIR).[25,26] Findings will be reported according to PRISMA guidance.[23,27,28] Any deviations from our prespecified methodology will be described in the final report (with rationale).[29] The protocol has been submitted for registration to the International Prospective Register of Systematic Reviews (PROSPERO).

Patient and public involvement

This review will be conducted and co-produced with partners using an integrated knowledge translation (iKT) framework.[30–32] Specifically, patients who will be impacted by the research and knowledge users who will implement evidence in practice have been, and will continue to be, regularly engaged through meetings, surveys and one-on-one discussions. A start-up meeting occurred June 3rd, 2022; mid-study, post-synthesis and wrap up team meetings will also be held to ensure meaningful input can be obtained throughout the course of the study. Patient and public involvement will be reported according to the Guidance for Reporting Involvement of Patients and the Public-2 checklist.[33]

Intervention definition

A prehabilitation intervention is intended to improve physical, physiologic, cognitive or psychosocial function and to correct deficiencies in these domains in advance of surgery.[13,14] We will define and operationalize the following working definition of prehabilitation based on consistent descriptions of prehabilitation provided in the literature: a unimodal intervention consisting of exercise (e.g., aerobic, strength or flexibility focused interventions), nutrition (e.g., advice, supplementation or other interventions to improve oral or enteral macro or micronutrient intake), cognitive (e.g., interventions to improve or maintain cognitive function), or psychosocial (e.g., interventions to improve mood, affect or motivation)

training, or a multimodal intervention that combines exercise, nutrition, cognitive, and/or psychosocial training with or without other interventions, undertaken for 7 or more days before surgery.[13,34–36] No limitations will be placed on duration, location or supervisory approaches to the prehabilitation intervention. For the purposes of CNMA, intervention components will be classified as: exercise, nutrition, cognitive or psychosocial. The reference category will be standard care, which is the most common comparator in existing randomized trials and meta-analyses of prehabilitation.[18]

Inclusion criteria

Selection criteria will be informed by our Population-Intervention-Comparator-Outcome question. We will include randomized trials addressing a population of adults (≥18 years; provision of pediatric surgical care is substantively different from adults) undergoing major elective surgery where participants were exposed to a prehabilitation intervention prior to surgery compared to individuals receiving standard care or a different prehabilitation intervention (e.g., another prehabilitation intervention consisting of different components) reporting prespecified outcomes (see *Outcomes* section below).

Exclusion criteria

Studies evaluating isolated preoperative risk factor management (e.g., smoking cessation, anemia treatment, medication management in isolation), or interventions applied immediately (≤7 days) before surgery (a time frame consistent with enhanced recovery after surgery)[37,38] will be excluded to be consistent with accepted definitions of prehabilitation.[18] No language exclusions will be applied. Quasi experimental and other non-randomized designs will be excluded.

Outcomes

Consultation with partners (patients, clinicians, health system leaders, scientists) and a recent umbrella review performed by our team informed pre-specification of outcomes.[18] This led to the choice of critical and exploratory outcomes that are prioritized by knowledge users and that will be adequately reported in prehabilitation trials. Critical outcomes include: 1) a composite of any postoperative medical or surgical complications during the index hospitalization or within 30 days (a core outcome in surgery and

perioperative medicine[39,40]) as it is a key step on the causal pathway between prehabilitation and improved recovery after surgery,[10] and is the most commonly reported outcome in prehabilitation RCTs;[36] 2) patient-reported recovery (e.g., disability or quality of life; most distal reported measure up to 90-days after surgery); 3) physical recovery (e.g., 6-minute walk test, short physical performance battery; most distal reported measure up to 90-days after surgery); and 4) length of hospital stay (LoS). Exploratory outcomes will be organized per the Institute for Healthcare Improvement Triple Aim domains, and will include health (non-home discharge, mortality), experience (pain, satisfaction), and resource use (costs).[36,41,42] These exploratory outcomes will be analyzed if adequate data and resources are available.

Search strategy

Our search strategy (Supplementary file 1) has been developed with our team's information specialist, and has undergone the Peer Review of Electronic Search Strategies (PRESS) review process with a second, independent information specialist.[43] Grey literature sources will be searched.[26,44] We will translate and apply our search strategy to Ovid Medline, Embase, the CINAHL, PsychINFO, Web of Science, and the Cochrane CENTRAL Register of Controlled Trials. We will assess reference lists of included trials and related reviews to identify citations missed by our search.

Study review and selection

All stages of the review will be conducted in duplicate by two independent reviewers using Distiller SR (Evidence Partners, Ottawa, Canada). At each stage of the review, the first 50 citations will be assessed, followed by a meeting of reviewers with study leads to review decisions, identify any issues related to disagreements and/or interpretation of selection criteria, and recalibrate reviewers' approaches as needed. The first stage will include title and abstract review. After full text review by two independent authors, any conflicts will be resolved through consensus in a meeting between study leads and reviewers; reasons for exclusion at full text review will be documented and provided in the final publication.

Data extraction

Data will be extracted using a form specifically designed for this review following a piloting exercise by the review team. Key to the implementation of CNMA as our analytic approach, we will collect

full descriptions of comparator conditions (e.g., standard care, other prehabilitation interventions). All data will be extracted in duplicate; disagreements will be resolved by reviewers through cooperative review of the primary source with a study lead. A full description of all anticipated data points is included in Supplementary file 2. Sample size, population characteristics, and missing data will be collected for each trial. For binary outcomes, we will collect the 2x2 table, event rates and/or effect measures (e.g., odds ratios or risk ratios) along with a measure of uncertainty (e.g., 95% confidence intervals [CIs], p-values). For continuous outcomes we will collect means and standard deviations, and/or effect estimates such as mean differences along with their 95% CIs and p-values. Any missing data will be sought directly from study authors.

Assessment of bias in included studies

The Cochrane Risk of Bias 2 tool will be applied in duplicate to each included RCT[45] to assess within-study bias of the included evidence. Where ≥10 studies are available in a meta-analysis, funnel plots and Egger's test will be used to assess for possible publication bias and small-study effects.[46]

Assessment of certainty of evidence

We will use the GRADE working group classification to assess the certainty of evidence for each outcome,[47] including modifications specific to certainty assessment in network meta-analysis.[48] This will allow us to categorize evidence as high/moderate/low/very-low certainty, which will be reported using appropriate statements.[49]

Intervention effect estimates

Pooled effect estimates will be reported as odds ratios (binary outcomes), mean differences (continuous outcomes on a single scale (e.g., LoS)), or standardized mean differences (SMDs) (continuous outcomes on multiple scales (e.g., functional recovery)); point estimates along with 95% CIs will be reported. Where SMDs are calculated from different scales that capture related conceptual outcomes (e.g., patient-reported recovery via quality of life or disability scales), directionality will be standardized prior to analysis. Where multiple scales that reflect functional recovery are reported within a single included study, we will preferentially select for pooling generic (vs. disease specific) scales to enhance generalizability,

and quality of life (vs. other concepts) scales, as our previous work demonstrates that quality of life is reported far more frequently in prehabilitation studies than related measures like disability.[18] Where continuous outcome measures are not reported as means and standard deviations, we will use the methods of Wan and colleagues to estimate means and standard deviations from reported measures such as medians and interquartile or overall ranges.[50] Effect estimates derived from cluster randomized trials will be pooled using the reported effect adjusted for clustering, or if not available, a corrected estimate accounting for an estimated design effect.[51]

Data syntheses and analyses

Our approach to analysis will follow previous recommendations, whereby sequential and complimentary techniques will be used to estimate the pooled effects of prehabilitation and its components.[20,52]

Pairwise meta-analysis

Pair-wise meta-analysis will first be used to estimate whether any prehabilitation intervention, or prespecified components (exercise, nutrition, psychosocial or cognitive) improve critical outcomes compared to standard care or comparator interventions (separately). All meta-analysis models will use random-effects, as existing knowledge suggests that assumptions for fixed-effect meta-analysis will not be met (in particular due to heterogeneity related to different surgical procedures).[18] We will use the Hartung-Knapp-Sidik-Jonkman method to derive appropriate CIs.[53] Between-study variance will be estimated using the restricted maximum likelihood method and its 95% CI using the Q-profile approach.[54–56] We will also calculate the I^2 statistic to quantify the percentage of variability due to between-study heterogeneity rather than random error. If substantial heterogeneity exists, sources will be explored using subgroup analysis and meta-regression, based on prespecified postulated effect modifiers (type of surgery, age, type of prehabilitation, baseline functional status).

Assessment of assumptions for NMA and CNMA

We will assess for transitivity (the assumption that two components can be validly compared via common control condition) both visually and statistically. Visual evaluation will be conducted via

assessment of the distribution of effect modifiers in tabular and graphical presentations across treatment comparisons. We will visually inspect similarity of the distribution of the following effect modifiers: type of surgery, age, baseline functional status, comorbidity or American Society of Anesthesiologists' Score, presence of cancer, presence of malnutrition. Statistical assessment of transitivity will involve a global assessment of consistency using the design-by-treatment interaction model,[57] and a local assessment through the node-splitting approach.[58] For the CNMA, we will assess the additivity assumption using the method of Rucker and colleagues based on the difference in Q statistics between the additive CNMA and standard NMA model.[24]

Network meta-analysis

Next, we will conduct a standard NMA, also referred to as a full interaction model in CNMA,[20] and generate network plots to visually explore the available evidence base. We will perform a random-effects NMA assuming a common between-studies variance (τ^2) across the whole network, using the restricted maximum likelihood method.[59] We will estimate summary effect measures (odds ratios, mean differences, weighted mean differences) along with 95% CIs and 95% prediction intervals. To assess the magnitude of heterogeneity we will compare the estimated τ^2 with an empirical distribution for dichotomous data.[60] We will obtain a treatment hierarchy using P-scores, which take values between 0 and 1, and which is based on the estimated treatment effects and their associated uncertainty.[61]

Component network meta-analysis

We will use an additive CNMA model to evaluate the influence of the individual components, where each component has its own effect, and the total effect of an intervention will be equal to the sum of the relative component effects. It should be noted that common components in comparisons of interventions cancel out (i.e., $mean\ difference_{A+B\ vs.\ A+C}$ is identical to the effect of $mean\ difference_{B\ vs.\ C}$).

Model Implementation

All analyses will be performed in the R programming language (R Foundation for Statistical Computing, Vienna, Austria). We will fit pair-wise meta-analysis models in R using the *meta* package,[62] and will conduct all NMA, CNMAs, design-by-treatment interaction models, node-splitting models, subgroup and sensitivity analyses in R using the *netmeta* package.[63]

Sensitivity analyses

If adequate data are available and network geometry is not substantively changed, we will re-estimate our additive CNMA models limited to low risk of bias trials only.

While we have prespecified, based on prior umbrella review, exercise, nutrition, psychosocial and cognitive interventions as the components that we will compare using CNMA, theoretically each component can be further subdivided. If adequate data are available, we will explore CNMA analyses by subcomponent (e.g., exercise: aerobic, strength, other; nutrition: supplementation, counselling, other; psychosocial: anxiety reduction, mood stabilization, other; although ultimately some subcomponents listed here may require further merging or disaggregation based on their distribution between studies) to further refine our understanding of intervention component efficacy. If missing data are present and unaccounted for in primary reports, we will complete sensitivity analyses using appropriate techniques to impute missing values and assess consistency between primary and imputed results.

Dissemination

Results will be disseminated through presentations at scientific conferences and submission of peer-reviewed manuscripts. Using our iKT approach, we will also perform targeted dissemination to partner organizations and via our investigator network. Social and traditional media will also be used to spread results to a larger audience.

Limitations

Component network meta-analysis requires specific assumptions and acknowledgement of limitations. Assumptions underlying CNMA are similar to those of network meta-analyses,[64] and will require assessment prior to analysis. Because network comparisons (direct and indirect) depend upon a common reference condition (i.e., standard care), detailed description of standard care conditions in existing

trials will be described to allow meaningful clinical interpretation of results. Should assumption-violating differences between RCTs be identified, we will incorporate baseline risk meta-regression (i.e., control rate meta-regression) in our analyses.[65] Some indirect (i.e., via the standard care reference condition) comparisons may not be possible due to a lack of relevant RCT comparators. We have defined our components as exercise, nutrition, psychosocial and cognitive. However, we recognize that these components could be subdivided further, and have therefore pre-specified exploratory investigation of sub-components (e.g., strength vs aerobic exercise) should adequate data be available. Sparse data can also limit the power to detect meaningful differences, especially in CNMA models with interactions and for meta-regression.[20,66,67]

Conclusion

Prehabilitation is a promising and high-priority intervention from the perspective of patients, the public, clinicians, scientists, and health systems. The proposed review will provide a high-quality synthesis of all prehabilitation trials. Use of CNMA will allow estimation of the relative efficacy of different prehabilitation components. The findings will directly inform current care, health system implementation and design of future interventions and trials.

Collaborators: Prehabilitation Knowledge Network: Shamsuddin Akhtar, Marlis Atkins, Sylvie Aucoin, Rebecca Auer, Carlota Basualdo-Hammond, Paul Beaule, Mary Brindle, Gregory Bryson, Franco Carli, Antoine Eskander, Dean Fergusson, Julio Fiore Jr., Alan Forster, Melani Gillam, Leah Gramlich, Jayna Holroyd-Leduc, Timothy Jackson, Rachel Khadaroo, Manoj Lalu, Cameron Love, Guillaume Martel, Colin McCartney, Dolores McKeen, Amanda Meliambro, Husein Moloo, Ronald Moore, John Muscedere, Julie Nantel, Stephane Poitras, Celena Scheede-Bergdahl, Risa Shorr, Monica Taljaard, Tom Wallace, Duminda Wijeysundera

Please include the collaborator listing on the manuscript and associated pubmed citation.

Author's Contributions: DIM is the Principal Investigator. DIM, MG, LB, BH, AA, CG, KB, ALG, JS, and EH were involved in the conception and design of the study. DIM wrote the initial draft of the protocol and this manuscript. All authors provided critical input regarding the design of the study. DM, BH, and AA designed the data analysis plan. All authors revised the protocol critically for important intellectual content and approved the final version to be published. DIM, MG, LB, BH, AA, CG, KB, ALG, JS, and EH agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors, including the Prehabilitation Knowledge Network, have critically reviewed and approved the final protocol.

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Supplementary file 1 – Search strategies

Ovid MEDLINE(R) ALL

1 (prehab* or pre-hab*).tw,kf.
2 (preoperative* rehabilitation or preoperative* training).tw,kw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 Preoperative Exercise/
5 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
6 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).tw,kf.
7 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*))).tw,kf.
8 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (diet or dietary or nutrit*)).tw,kf.
2008
9 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (resistance or strength or weight or muscle) adj2 training).tw,kf.
10 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (food adj3 (counsel* or support* or modif*))).tw,kf.
11 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((energy or protein) adj3 supplement*)).tw,kf.
12 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (exercise or exercises or stretch* or aerobic* or physical activit*)).tw,kf.
13 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (cbt or cognitive behavio?r*)).tw,kf.
14 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 counsel*).tw,kf.
15 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 supplement*).tw,kf.
16 or/1-15
17 *Preoperative Care/ or *Preoperative Period/ or (preoperat* or pre-operat* or presurg* or pre-surg*).ti.
18 exp Exercise Therapy/ or Exercise/
19 Physical Fitness/
20 (exercise or exercises or stretch* or aerobic* or physical activit*).tw,kw.
21 ((resistance or strength or weight or muscle) adj2 training).tw.
22 diet therapy/ or Nutrition Therapy/ or Nutritional Support/
23 (diet or dietary or nutrit*).tw,kw.
24 (food adj3 (counsel* or support* or modif*)).tw.
25 ((energy or protein) adj3 supplement*).tw.
26 Dietary Supplements/
27 Physical Therapy Modalities/ or (physical therap* or physiotherap*).tw,kw.
28 Counseling/ or counsel?ing.tw,kw.
29 behavior therapy/ or cognitive behavioral therapy/ or Psychotherapy/ or Relaxation Therapy/
30 Stress, Psychological/rh, th
31 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*)).tw.

32 or/18-31
33 17 and 32
34 16 or 33
35 randomized controlled trial.pt.
36 controlled clinical trial.pt.
37 random*.tw.
38 placebo.ab.
39 clinical trials as topic.sh.
40 trial.ti.
41 or/35-40
42 exp animals/ not humans/
43 (infant/ or child/ or adolescent/) not adult/
44 41 not (42 or 43)
45 34 and 44
46 45 use medall

Embase Classic+Embase

1 (prehab* or pre-hab*).mp.
2 (preoperative* rehabilitation or preoperative* training).tw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).tw.
5 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (diet or dietary or nutrit*)).tw.
6 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*))).tw.
7 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (resistance or strength or weight or muscle) adj2 training).tw.
8 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (food adj3 (counsel* or support* or modif*))).tw.
9 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((energy or protein) adj3 supplement*)).tw.
10 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (stretch* or aerobic*)).tw.
11 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
12 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (cbt or cognitive behavio?r*)).tw.
13 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 counsel*).tw.
14 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 supplement*).tw.
15 or/1-14
16 *preoperative care/ or *preoperative period/ or (preoperat* or pre-operat* or presurg* or pre-surg*).ti.
17 exp *kinesiotherapy/
18 exp *exercise/
19 (exercise or exercises or stretch* or aerobic* or physical activit*).ti.
20 ((resistance or strength or weight or muscle) adj2 training).ti.
21 diet therapy/ or diet supplementation/
22 (diet or dietary or nutrit*).ti.

23 (food adj3 (counsel* or support* or modif*)).ti.
24 ((energy or protein) adj3 supplement*).tw.
25 physiotherapy/
26 (physical therap* or physiotherap*).ti.
27 counseling/ or nutritional counseling/
28 behavior therapy/
29 cognitive behavioral therapy/ or cognitive therapy/
30 psychotherapy/
31 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*)).ti.
32 or/17-31
33 16 and 32
34 15 or 33
35 double-blind*.mp. or placebo*.tw. or blind*.tw. or trial.ti.
36 random*.ti.
37 (random* adj2 (trial* or stud*)).tw.
38 35 or 36 or 37
39 34 and 38
40 (child/ or childhood/ or infant/) not adult/
41 (exp animal/ or nonhuman/) not exp human/
42 39 not (40 or 41)

EBM Reviews - Cochrane Central Register of Controlled Trials

1 (prehab* or pre-hab*).tw,kw.
2 (preoperative* rehabilitation or preoperative* training).tw,kw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).tw.
5 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj4 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).ti.
6 Preoperative Exercise/
7 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
8 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*))).tw.
9 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 (diet or dietary or nutrit*)).tw.
10 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (resistance or strength or weight or muscle) adj2 training).tw.
11 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (food adj3 (counsel* or support* or modif*))).tw.
12 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((energy or protein) adj3 supplement*)).tw.
13 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (exercise or exercises or stretch* or aerobic* or physical activit*)).tw.
14 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (cbt or cognitive behavio?r*)).tw.
15 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 counsel*).tw.
16 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 supplement*).tw.

17 or/1-16
18 (infant/ or child/ or adolescent/) not adult/
19 17 not 18
20 remove duplicates from 19

APA PsycInfo

1 (prehab* or pre-hab*).tw.
2 (preoperative* rehabilitation or preoperative* training).tw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
5 1 or 2 or 3 or 4
6 surgical patients/ or (preoperat* or pre-operat* or presurg* or pre-surg*).ti.
7 exp exercise/ or physical activity/ or physical fitness/
8 (exercise or exercises or stretch* or aerobic* or physical activit*).tw.
9 ((resistance or strength or weight or muscle) adj2 training).tw.
10 Diets/
11 Nutrition/ or Dietary Supplements/
12 (diet or dietary or nutrit*).tw.
13 (food adj3 (counsel* or support* or modif*)).tw.
14 ((energy or protein) adj3 supplement*).tw.
15 physical therapy/ or physical treatment methods/
16 (physical therap* or physiotherap*).tw.
17 Counseling/
18 counsel?ing.tw.
19 Behavior Therapy/ or Cognitive Behavior Therapy/ or Cognitive Therapy/
20 Psychotherapy/
21 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*)).tw.
22 or/7-21
23 6 and 22
24 5 or 23
25 exp Clinical Trials/ or Placebo/ or (random* or sham or placebo* or ((singl* or doubl*) adj (blind* or dumm* or mask*)) or ((tripl* or trebl*) adj (blind* or dumm* or mask*)) or (control* adj3 (study or studies or trial* or group*)) or Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or allocated or ((open label or open-label) adj5 (study or studies or trial*)) or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)) or ((pragmatic or practical) adj3 trial*) or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)) or (phase adj3 (III or "3") adj3 (study or studies or trial*))).ti,ab,hw.
26 24 and 25

CinahlComplete

#	Query
S1	(MH "Prehabilitation")
S2	TI ((prehab* or pre-hab*)) OR AB ((prehab* or pre-hab*))
S3	TI ((preoperative* rehabilitation or preoperative* training)) OR AB ((preoperative* rehabilitation or preoperative* training))
S4	TI (((perioperat* or peri operat*) N3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing))) OR AB (((perioperat* or peri operat*) N3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)))
S5	S1 OR S2 OR S3 OR S4
S6	(MH "Preoperative Care") or (MH "Preoperative Period") or TI (preoperat* or pre-operat* or presurg* or pre-surg)
S7	(MH "Therapeutic Exercise+")
S8	(MH "Exercise+")
S9	(MH "Physical Fitness+")
S10	TI ((exercise or exercises or stretch* or aerobic* or physical activit*)) OR AB ((exercise or exercises or stretch* or aerobic* or physical activit*))
S11	TI ((resistance or strength or weight or muscle) N2 training) OR AB ((resistance or strength or weight or muscle) N2 training)
S12	(MH "Diet Therapy+")
S13	(MH "Nutritional Support+")

S14	TI ((diet or dietary or nutrit*)) OR AB ((diet or dietary or nutrit*))
S15	TI (food N3 (counsel* or support* or modif*)) OR AB (food N3 (counsel* or support* or modif*))
S16	TI ((energy or protein) N3 supplement*) OR AB ((energy or protein) N3 supplement*)
S17	(MH "Dietary Supplementation")
S18	(MH "Physical Therapy+")
S19	(MH "Physical Therapy Service")
S20	TI ((physical therap* or physiotherap*)) OR AB ((physical therap* or physiotherap*))
S21	(MH "Counseling+")
S22	TI counsel?ing OR AB counsel?ing
S23	(MH "Behavior Therapy") OR (MH "Cognitive Therapy")
S24	(MH "Psychotherapy+")
S25	TI ((psychological or psychosocial or cognitive) N3 (intervention* or therap*)) OR AB ((psychological or psychosocial or cognitive) N3 (intervention* or therap*))
S26	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
S27	S6 AND S26
S28	TI ((preoperat* or pre-operat* or presurg* or pre-surg*) N3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)) OR AB ((preoperat* or pre-operat* or presurg* or pre-surg*) N3 (exercis* or physiotherap* or

	physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning))
S29	TI (((preoperat* or pre-operat* or presurg* or pre-surg*)N5 ((psychological or psychosocial or cognitive) N3 (intervention* or therap*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*)N5 ((psychological or psychosocial or cognitive) N3 (intervention* or therap*)))
S30	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (diet or dietary or nutrit*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (diet or dietary or nutrit*)))
S31	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (resistance or strength or weight or muscle) N2 training)) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (resistance or strength or weight or muscle) N2 training))
S32	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 ((energy or protein) N3 supplement*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 ((energy or protein) N3 supplement*)))
S33	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (exercise or exercises or stretch* or aerobic* or physical activit*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (exercise or exercises or stretch* or aerobic* or physical activit*)))
S34	TI ((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (cbt or cognitive behavior* or cognitive behaviour))) OR AB ((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (cbt or cognitive behavior* or cognitive behaviour)))
S35	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 counsel*)) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 counsel*))
S36	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 supplement) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 supplement)

S37	S5 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36
S38	(MH (randomized controlled trials OR double-blind studies OR single-blind studies OR random assignment OR pretest-posttest design OR cluster sample) OR TI (randomised OR randomized) OR AB random* OR TI trial OR ((MH (sample size) AND AB (assigned OR allocated OR control))) OR MH (placebos OR crossover design OR comparative studies) OR AB ((control W5 group) OR (cluster W3 RCT) OR PT (randomized controlled trial))) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human))
S39	S37 AND S38
S40	(MH "Child+") NOT (MH "Adult+")
S41	S39 NOT S40

Web of Science

(infant/ or child/ or adolescent/) not adult/

((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (cbt or cognitive behavior* or cognitive behaviour)).

1. (ALL=(prehab*)) OR ALL=("pre habilitation")

2. (TI=((preoperat* OR pre-operat* OR presurg* OR pre-surg*))) AND TI=(exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel* OR condition*)

3. (TI=((preoperat* OR pre-operat* OR presurg* OR pre-surg*))) AND TI=(counsel* OR psych* OR behavior therap* OR behaviour therap*)

4. (TI=(preoperat* OR pre-operat* OR presurg* OR pre-surg*)) AND TI=(nutrition OR diet OR supplement OR dietary)

5. (TI=(exercise* or diet or nutrition* counsel*)) AND TI=(surgery or surgical)

6. ((((#1) OR #2) OR #3) OR #4) OR #5

7. Search

(TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))) NOT TS=(animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot

or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes))

8. (#6) AND #7

Supplementary file 2 – Datapoints extracted from included RCTs

1. Author
2. Year of publication
3. Countries of origin
4. Study start and end dates
5. Patient partners
    a. As authors
        i. Demographics
        ii. Roles
    b. As acknowledged collaborators
        i. Demographics
        ii. Roles
6. Prehabilitation definition
    a. In introduction or background
    b. In methods
7. Prehabilitation characteristics
    a. Multimodal (y/n)
8. Prehabilitation Components (eg, exercise, nutrition, psychosocial, cognitive)
    a. Type of exercise
        i. Unimodal
        ii. Multimodal
        iii. Interval training
        iv. Other
        v. Components (eg, cardio, strength, stretching, respiratory exercise)
    b. Type of nutrition
        i. Counselling
        ii. Supplementation
        iii. Combined
        iv. Other
    c. Type of psychosocial
        i. Motivational interviewing
        ii. Anxiety management
        iii. Stress management
        iv. Other
    d. Type of cognitive
    e. Other co-interventions
9. Enhanced recovery after surgery (ERAS) (y/n)
10. Weight loss objective (y/n)
11. Duration of prehabilitation
    a. Average
    b. Program
        i. Minimum participation
        ii. Maximum participation
    c. Per session
12. Frequency of prehabilitation
13. Intervention time-point
    a. Preoperative only
    b. Preoperative plus rehab after surgery
14. Location of prehabilitation

a. Home
b. Facility
c. Combined

15. Supervision
    a. Self-directed
    b. Coach-led
    c. Combined
16. Session format
    a. Individual
    b. Group
    c. Combined
17. Personalization
    a. Description of personalization
18. Motivation techniques
    a. Description of motivation techniques
    b.
19. Control (eg, standard care or active controls such as rehabilitation after surgery)
    a. Standard care
        i. Description of standard care
    b. Static instructions
        i. Description of static instructions
    c. Other prehabilitation
        i. Description of other prehabilitation
    d. Rehabilitation
        i. Description of rehabilitation
    e. Other
        i. Description of other
20. Surgical specialty
    a. Orthopedic
    b. Major non-oncology
    c. Cardiac/vascular
    d. Oncology
    e. Mixed
    f. Other
21. Surgical procedure(s)
22. Population characteristics
    a. Total sample size
    b. Sample size per arm
    c. Age (average, range)
    d. Sex (% females vs. males)
    e. Gender (% women vs. men vs. non-binary/transgender/other)
    f. Presence of specific risk factors
        i. Multimorbidity (≥2 comorbidities)
        ii. ASA score
        iii. Frailty
        iv. Malnutrition
        v. Obesity
        vi. Baseline functional status
        vii. Disability
        viii. Presence of cancer
            1. Use of neoadjuvant therapies

23. Outcomes (counts, summary statistics, effect estimates with 95%CI; per time window)
    a. Health
        i. Complications
            1. Any
            2. Cardiopulmonary
            3. Surgical
            4. Infectious
        ii. Discharge disposition
        iii. Physical functional recovery
        iv. Disability
        v. Quality of life
        vi. Mortality
    b. Experience
        i. Pain
        ii. Patient satisfaction
    c. Resource use
        i. Length of stay
        ii. Costs
    d. Intervention Safety
        i. Any intervention-attributable adverse events
        ii. Cardiopulmonary adverse events during intervention period
        iii. Falls during intervention period
        iv. Assessor-confirmed intervention-attributable adverse events
24. Adherence
    a. Outcome type
        i. Binary
            1. Threshold used
        ii. Continuous
    b. Adherence rate
    c. Method of measurement
25. Feasibility measures
26. Barriers and facilitators to implementation

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	14
Sponsor	5b	Provide name for the review funder and/or sponsor	14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	14
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8 Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9 Appendix 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9 Appendix 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Identifying relative efficacy of components of prehabilitation in adult surgical patients: protocol for a systematic review and component network meta-analysis

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Complete List of Authors:	McIsaac, Daniel; University of Ottawa, Department of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Hutton, Brian; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Veroniki, Areti; St Michael's Hospital, Knowledge Translation Program Gill, Marlyn; Patient Partner Boland, L.; Ottawa Hospital Research Institute, Centre for Practice-Changing Research Branje, Karina; University of Ottawa, Department of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Grudzinski, Alexa L; University of Ottawa, Department of Anesthesiology and Pain Medicine Hladkowicz, Emily; Ottawa Hospital, Departments of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Shaw, Julia; University of Ottawa, Department of Anesthesiology and Pain Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Gillis, Chelsia; McGill University, School of Human Nutrition The Prehabilitation Knowledge Network, Group Authorship; NA
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	SURGERY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, REHABILITATION MEDICINE

Identifying relative efficacy of components of prehabilitation in adult surgical patients: protocol for a systematic review and component network meta-analysis

Corresponding Author: Daniel I McIsaac MD, MPH, FRCPC
Associate Professor of Anesthesiology and Pain Medicine, University of Ottawa
Associate Scientist, Ottawa Hospital Research Institute
Email: dmcisaac@toh.ca
Phone-613-761-4940/Fax-613-761-5209
Department of Anesthesiology, The Ottawa Hospital Civic Campus
Room B311, 1053 Carling Ave
Ottawa, ON K1Y 4E9

Authors: McIsaac, Daniel I MD, MPH, FRCPC[1,2,3*]; Hutton, Brian PhD[2,3]; Veroniki, Areti Angeliki PhD[4]; Gill, Marlyn MSW[5]; Boland, Laura SLP(c), PhD[6]; Branje, Karina MSc[1,2]; Grudzinski, Alexa L MD[1]; Hladkowicz, Emily MA.Ed[1,2,]; Shaw, Julia MSc[1,2]; Gillis, Chelsia RD, PhD[7]; the Prehabilitation Knowledge Network Authorship Group*

Affiliations:
1 Department of Anesthesiology and Pain Medicine, University of Ottawa, Ottawa, Canada
2 Clinical Epidemiology Program, the Ottawa Hospital Research Institute, Ottawa, Canada
3 School of Epidemiology & Public Health, University of Ottawa, Ottawa, Canada
4 Knowledge Translation Program, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Canada
5 Patient Partner, Calgary, Canada
6 Centre for Practice-Changing Research, Ottawa Hospital Research Institute, Ottawa, Canada
7 Department of Human Nutrition, McGill University, Montreal, Canada

***Individual collaborators with group authorship:** Shamsuddin Akhtar, Marlis Atkins, Sylvie Aucoin, Rebecca Auer, Carlota Basualdo-Hammond, Paul Beaule, Mary Brindle, Gregory Bryson, Franco Carli, Antoine Eskander, Dean Fergusson, Julio F Fiore Jr., Alan Forster, Melani Gillam, Leah Gramlich, Jayna Holroyd-Leduc, Timothy Jackson, Rachel Khadaroo, Manoj Lalu, Cameron Love, Guillaume Martel, Colin McCartney, Dolores McKeen, Amanda Meliambro, Husein Moloo, Ronald Moore, John Muscedere, Julie Nantel, Stephane Poitras, Celena Scheede-Bergdahl, Risa Shorr, Monica Taljaard, Tom Wallace, Duminda Wijeysundera

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ABSTRACT

Introduction: Prehabilitation is a high-priority intervention for patients, the public, clinicians, and health systems. However, existing knowledge syntheses are generally low quality and do not provide insights regarding the relative efficacy of different prehabilitation components (e.g., exercise, nutrition, psychosocial or cognitive interventions). The objective of the planned review is to evaluate the relative efficacy of different prehabilitation components to inform current care, implementation, and future research.

Methods and analysis: We will perform a systematic review and component network meta-analysis (CNMA). We will use a peer-reviewed search strategy to identify all randomized trials of prehabilitation in adult surgical patients from Ovid Medline, Embase, the CINAHL, PsychINFO, Web of Science, and the Cochrane Central Register of Controlled Trials, along with grey literature. All stages of the review and data extraction process will be performed in duplicate following recommended best practices. To compare the relative efficacy of different prehabilitation components (prespecified as exercise, nutrition, psychosocial or cognitive interventions), we will use CNMA, an extension of network meta-analysis that allows estimation of the contributions to efficacy of each component of a multicomponent intervention through direct and indirect comparisons. We will use additive CNMA models for critical outcomes (post-operative complications, patient-reported recovery, physical recovery, and length of stay); standard care will be the common reference condition. Pre-specified sensitivity and subgroup analyses will be conducted.

Ethics and dissemination: This review of published data does not require ethical review. Results will be disseminated via scientific conferences, peer reviewed publications, social and traditional media and via our research network to target partners and organizations.

Strengths and limitations of this study

-A prespecified protocol based on best practices for systematic review and meta-analysis will guide conduct of the study

-All stages of the study will be done in collaboration with patient and knowledge user partners so that findings will be co-produced in an integrated knowledge translation framework

-Component network meta-analysis will allow comparison of the relative efficacy of different prehabilitation components, even when multiple components are delivered simultaneously

-If assumptions underlying component network meta-analysis are not met, we may be unable to estimate relative efficacy of different components

Introduction

Globally, >300 million surgical procedures are performed each year.[1,2] These surgeries mostly occur on a planned (also referred to as 'elective') basis,[3] meaning that wait-times can be positively leveraged to optimize patient status prior to surgery. Patient optimization is critical in supporting high value surgical care as adverse postoperative events that matter to patients and the healthcare system are common.[4] Complications such as cardiopulmonary events, infections and major bleeding occur in 10-20% of patients.[5-7] Impaired functional recovery or new clinically significant disability develop in more than 1 in 5 surgical patients; such adverse events are even more common amongst older patients and those with poor baseline health.[8-12] Effective strategies to improve outcomes for the millions of people having surgery each year are urgently needed.

Prehabilitation is a process undertaken in advance of surgery, which has the specific intent of improving an individual's functional, physiologic, cognitive and/or mental health status through targeted interventions.[13,14] Patients, the public, and international specialty societies identify prehabilitation as a high priority intervention, including multiple James Lind Alliance priority setting partnerships.[15-17] However, despite the face validity and enthusiasm for prehabilitation interventions, a recently completed umbrella review of 55 prehabilitation systematic reviews found that existing evidence synthesis is insufficient to inform practice.[18] Several key knowledge gaps preclude translation of current evidence into practice. First, existing systematic reviews have major methodologic shortcomings; 51 of 55 prehabilitation reviews synthesized in a recent umbrella review were rated as low quality.[18,19] Second, prehabilitation interventions are heterogeneous, as they may consist of different components, including exercise, nutrition, psychosocial and cognitive interventions, or combinations thereof.[18] Existing prehabilitation reviews have typically focused only on single component interventions, or pooled all types of prehabilitation components or interventions together. This means that patients, clinicians, researchers, and health system planners are unable to determine what specific components, or combinations of components, contribute the most to prehabilitation efficacy and deserve the greatest focus in

implementation and future research. Understanding how the current evidence network can be leveraged to detect differences between the effects of interventions and their individual components would help to address these important gaps.

Component network meta-analysis (CNMA), an extension to network meta-analysis, allows estimation of separate effects for each component of a multicomponent intervention through direct and indirect comparison, even when these are delivered in combination.[20,21] We propose a CNMA based on an up-to-date, high-quality systematic review, to address important knowledge gaps in the prehabilitation evidence base. Our objective is to estimate which prehabilitation components contribute the greatest efficacy in improving critical outcomes, including postoperative complication rates, patient-reported recovery, physical recovery, and length of stay in adult patients preparing for surgery.

Methods

Design

This study will be a systematic review with CNMA. The study began in March 2022 and has an anticipated end date of March 2023. This protocol has been prepared in consideration of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines, the PRISMA extension for network meta-analysis, and specific considerations for CNMA.[22-24] Methods for the review are directly informed by the Cochrane Handbook and Methodological Expectations of Cochrane Intervention Reviews (MECIR).[25,26] Findings will be reported according to PRISMA guidance.[23,27,28] Any deviations from our prespecified methodology will be described in the final report (with rationale).[29] The protocol has been submitted for registration to the International Prospective Register of Systematic Reviews (PROSPERO).

Patient and public involvement

This review will be conducted and co-produced with partners using an integrated knowledge translation (iKT) framework.[30-32] Specifically, patients who will be impacted by the research and knowledge users who will implement evidence in practice have been, and will continue to be, regularly engaged through meetings, surveys and one-on-one discussions. A start-up meeting occurred June 3rd, 2022; mid-study, post-synthesis and wrap up team meetings will also be held to ensure meaningful input can be obtained throughout the course of the study. Patient and public involvement will be reported according to the Guidance for Reporting Involvement of Patients and the Public-2 checklist.[33]

Intervention definition

A prehabilitation intervention is intended to improve physical, physiologic, cognitive or psychosocial function and to correct deficiencies in these domains in advance of surgery.[13,14] We will define and operationalize the following working definition of prehabilitation based on consistent descriptions of prehabilitation provided in the literature: a unimodal intervention consisting of exercise (e.g., aerobic, strength or flexibility focused interventions), nutrition (e.g., advice, supplementation or other

interventions to improve oral or enteral macro or micronutrient intake), cognitive (e.g., interventions to improve or maintain cognitive function), or psychosocial (e.g., interventions to improve mood, affect or motivation) training, or a multimodal intervention that combines exercise, nutrition, cognitive, and/or psychosocial training with or without other interventions, undertaken for 7 or more days before surgery.[13,34-36] No limitations will be placed on duration, location or supervisory approaches to the prehabilitation intervention. For the purposes of CNMA, intervention components will be classified as: exercise, nutrition, cognitive or psychosocial. The reference category will be standard care, which is the most common comparator in existing randomized trials and meta-analyses of prehabilitation.[18]

Inclusion criteria

Selection criteria will be informed by our Population-Intervention-Comparator-Outcome question. We will include randomized trials addressing a population of adults (≥18 years; provision of pediatric surgical care is substantively different from adults) undergoing major elective surgery where participants were exposed to a prehabilitation intervention prior to surgery compared to individuals receiving standard care or a different prehabilitation intervention (e.g., another prehabilitation intervention consisting of different components) reporting prespecified outcomes (see *Outcomes* section below).

Exclusion criteria

Studies evaluating isolated preoperative risk factor management (e.g., smoking cessation, anemia treatment, medication management in isolation), or interventions applied immediately (≤7 days) before surgery (a time frame consistent with enhanced recovery after surgery)[37,38] will be excluded to be consistent with accepted definitions of prehabilitation.[18] No language exclusions will be applied. Quasi experimental and other non-randomized designs will be excluded.

Outcomes

Consultation with partners (patients, clinicians, health system leaders, scientists) and a recent umbrella review performed by our team informed pre-specification of outcomes.[18] This led to the choice of critical and exploratory outcomes that are prioritized by knowledge users and that will be adequately

reported in prehabilitation trials. Critical outcomes include: 1) a composite of any postoperative medical or surgical complications during the index hospitalization or within 30 days (a core outcome in surgery and perioperative medicine)[39,40] as it is a key step on the causal pathway between prehabilitation and improved recovery after surgery,[10] and is the most commonly reported outcome in prehabilitation RCTs;[36] 2) patient-reported recovery (e.g., disability or quality of life; most distal reported measure up to 90-days after surgery); 3) physical recovery (e.g., 6-minute walk test, short physical performance battery; most distal reported measure up to 90-days after surgery); and 4) length of hospital stay (LoS). Exploratory outcomes will be organized per the Institute for Healthcare Improvement Triple Aim domains, and will include health (non-home discharge, mortality), experience (pain, satisfaction), and resource use (costs).[36,41,42] These exploratory outcomes will be analyzed if adequate data and resources are available.

Search strategy

Our search strategy (Supplementary file 1) has been developed with our team's information specialist, and has undergone the Peer Review of Electronic Search Strategies (PRESS) review process with a second, independent information specialist.[43] Grey literature sources will be searched.[26,44] We will translate and apply our search strategy to Ovid Medline, Embase, the CINAHL, PsychINFO, Web of Science, and the Cochrane CENTRAL Register of Controlled Trials. We will assess reference lists of included trials and related reviews to identify citations missed by our search.

Study review and selection

All stages of the review will be conducted in duplicate by two independent reviewers using Distiller SR (Evidence Partners, Ottawa, Canada). At each stage of the review, the first 50 citations will be assessed, followed by a meeting of reviewers with study leads to review decisions, identify any issues related to disagreements and/or interpretation of selection criteria, and recalibrate reviewers' approaches as needed. The first stage will include title and abstract review. After full text review by two independent authors, any conflicts will be resolved through consensus in a meeting between study leads and reviewers; reasons for exclusion at full text review will be documented and provided in the final publication.

Data extraction

Data will be extracted using a form specifically designed for this review following a piloting exercise by the review team. Key to the implementation of CNMA as our analytic approach, we will collect full descriptions of comparator conditions (e.g., standard care, other prehabilitation interventions). All data will be extracted in duplicate; disagreements will be resolved by reviewers through cooperative review of the primary source with a study lead. A full description of all anticipated data points is included in Supplementary file 2. Sample size, population characteristics, and missing data will be collected for each trial. For binary outcomes, we will collect the 2x2 table, event rates and/or effect measures (e.g., odds ratios or risk ratios) along with a measure of uncertainty (e.g., 95% confidence intervals [CIs], p-values). For continuous outcomes we will collect means and standard deviations, and/or effect estimates such as mean differences along with their 95% CIs and p-values. Any missing data will be sought directly from study authors.

Assessment of bias in included studies

The Cochrane Risk of Bias 2 tool will be applied in duplicate to each included RCT[45] to assess within-study bias of the included evidence. Where ≥10 studies are available in a meta-analysis, funnel plots and Egger's test will be used to assess for possible publication bias and small-study effects.[46]

Assessment of certainty of evidence

We will use the GRADE working group classification to assess the certainty of evidence for each outcome,[47] including modifications specific to certainty assessment in network meta-analysis.[48] This will allow us to categorize evidence as high/moderate/low/very-low certainty, which will be reported using appropriate statements.[49]

Intervention effect estimates

Pooled effect estimates will be reported as odds ratios (binary outcomes), mean differences (continuous outcomes on a single scale (e.g., LoS)), or standardized mean differences (SMDs) (continuous outcomes on multiple scales (e.g., functional recovery)); point estimates along with 95% CIs will be reported. Where SMDs are calculated from different scales that capture related conceptual outcomes (e.g., patient-reported recovery via quality of life or disability scales), directionality will be standardized prior to

analysis. Where multiple scales that reflect functional recovery are reported within a single included study, we will preferentially select for pooling generic (vs. disease specific) scales to enhance generalizability, and quality of life (vs. other concepts) scales, as our previous work demonstrates that quality of life is reported far more frequently in prehabilitation studies than related measures like disability.[18] Where continuous outcome measures are not reported as means and standard deviations, we will use the methods of Wan and colleagues to estimate means and standard deviations from reported measures such as medians and interquartile or overall ranges.[50] Effect estimates derived from cluster randomized trials will be pooled using the reported effect adjusted for clustering, or if not available, a corrected estimate accounting for an estimated design effect.[51]

Data syntheses and analyses

Our approach to analysis will follow previous recommendations, whereby sequential and complimentary techniques will be used to estimate the pooled effects of prehabilitation and its components.[20,52]

Pairwise meta-analysis

Pair-wise meta-analysis will first be used to estimate whether any prehabilitation intervention, or prespecified components (exercise, nutrition, psychosocial or cognitive) improve critical outcomes compared to standard care or comparator interventions (separately). All meta-analysis models will use random-effects, as existing knowledge suggests that assumptions for fixed-effect meta-analysis will not be met (in particular due to heterogeneity related to different surgical procedures).[18] We will use the Hartung-Knapp-Sidik-Jonkman method to derive appropriate CIs.[53] Between-study variance will be estimated using the restricted maximum likelihood method and its 95% CI using the Q-profile approach.[54-56] We will also calculate the I^2 statistic to quantify the percentage of variability due to between-study heterogeneity rather than random error. If substantial heterogeneity exists, sources will be explored using subgroup analysis and meta-regression, based on prespecified postulated effect modifiers (type of surgery, age, type of prehabilitation, baseline functional status).

Assessment of assumptions for NMA and CNMA

We will assess for transitivity (the assumption that two components can be validly compared via common control condition) both visually and statistically. Visual evaluation will be conducted via assessment of the distribution of effect modifiers in tabular and graphical presentations across treatment comparisons. We will visually inspect similarity of the distribution of the following effect modifiers: type of surgery, age, baseline functional status, comorbidity or American Society of Anesthesiologists' Score, presence of cancer, presence of malnutrition. Statistical assessment of transitivity will involve a global assessment of consistency using the design-by-treatment interaction model,[57] and a local assessment through the node-splitting approach.[58] For the CNMA, we will assess the additivity assumption using the method of Rucker and colleagues based on the difference in Q statistics between the additive CNMA and standard NMA model.[24]

Network meta-analysis

Next, we will conduct a standard NMA, also referred to as a full interaction model in CNMA,[20] and generate network plots to visually explore the available evidence base. We will perform a random-effects NMA assuming a common between-studies variance (τ^2) across the whole network, using the restricted maximum likelihood method.[59] We will estimate summary effect measures (odds ratios, mean differences, weighted mean differences) along with 95% CIs and 95% prediction intervals. To assess the magnitude of heterogeneity we will compare the estimated τ^2 with an empirical distribution for dichotomous data.[60] We will obtain a treatment hierarchy using P-scores, which take values between 0 and 1, and which is based on the estimated treatment effects and their associated uncertainty.[61]

Component network meta-analysis

We will use an additive CNMA model to evaluate the influence of the individual components, where each component has its own effect, and the total effect of an intervention will be equal to the sum of the relative component effects. It should be noted that common components in comparisons of interventions cancel out (i.e., $mean\ difference_{A+B\ vs.\ A+C}$ is identical to the effect of $mean\ difference_{B\ vs.\ C}$).

Model Implementation

All analyses will be performed in the R programming language (R Foundation for Statistical Computing, Vienna, Austria). We will fit pair-wise meta-analysis models in R using the *meta* package,[62] and will conduct all NMA, CNMAs, design-by-treatment interaction models, node-splitting models, subgroup and sensitivity analyses in R using the *netmeta* package.[63]

Sensitivity analyses

If adequate data are available and network geometry is not substantively changed, we will re-estimate our additive CNMA models limited to low risk of bias trials only.

While we have prespecified, based on prior umbrella review, exercise, nutrition, psychosocial and cognitive interventions as the components that we will compare using CNMA, theoretically each component can be further subdivided. If adequate data are available, we will explore CNMA analyses by subcomponent (e.g., exercise: aerobic, strength, other; nutrition: supplementation, counselling, other; psychosocial: anxiety reduction, mood stabilization, other; although ultimately some subcomponents listed here may require further merging or disaggregation based on their distribution between studies) to further refine our understanding of intervention component efficacy. If missing data are present and unaccounted for in primary reports, we will complete sensitivity analyses using appropriate techniques to impute missing values and assess consistency between primary and imputed results.

Ethics and Dissemination

Results will be disseminated through presentations at scientific conferences and submission of peer-reviewed manuscripts. Using our iKT approach, we will also perform targeted dissemination to partner organizations and via our investigator network. Social and traditional media will also be used to spread results to a larger audience. Ethics approval was not required as this study does not require participation of human subjects.

Limitations

Component network meta-analysis requires specific assumptions and acknowledgement of limitations. Assumptions underlying CNMA are similar to those of network meta-analyses,[64] and will

require assessment prior to analysis. Because network comparisons (direct and indirect) depend upon a common reference condition (i.e., standard care), detailed description of standard care conditions in existing trials will be described to allow meaningful clinical interpretation of results. Should assumption-violating differences between RCTs be identified, we will incorporate baseline risk meta-regression (i.e., control rate meta-regression) in our analyses.[65] Some indirect (i.e., via the standard care reference condition) comparisons may not be possible due to a lack of relevant RCT comparators. We have defined our components as exercise, nutrition, psychosocial and cognitive. However, we recognize that these components could be subdivided further, and have therefore pre-specified exploratory investigation of sub-components (e.g., strength vs aerobic exercise) should adequate data be available. Sparse data can also limit the power to detect meaningful differences, especially in CNMA models with interactions and for meta-regression.[20,66,67]

Collaborators: Prehabilitation Knowledge Network: Shamsuddin Akhtar, Marlis Atkins, Sylvie Aucoin, Rebecca Auer, Carlota Basualdo-Hammond, Paul Beaule, Mary Brindle, Gregory Bryson, Franco Carli, Antoine Eskander, Dean Fergusson, Julio Fiore Jr., Alan Forster, Melani Gillam, Leah Gramlich, Jayna Holroyd-Leduc, Timothy Jackson, Rachel Khadaroo, Manoj Lalu, Cameron Love, Guillaume Martel, Colin McCartney, Dolores McKeen, Amanda Meliambro, Husein Moloo, Ronald Moore, John Muscedere, Julie Nantel, Stephane Poitras, Celena Scheede-Bergdahl, Risa Shorr, Monica Taljaard, Tom Wallace, Duminda Wijeysundera

Please include the collaborator listing on the manuscript and associated pubmed citation.

Author's Contributions: DIM is the Principal Investigator. DIM, MG, LB, BH, AA, CG, KB, ALG, JS, and EH were involved in the conception and design of the study. DIM wrote the initial draft of the protocol and this manuscript. All authors provided critical input regarding the design of the study. DM, BH, and AA designed the data analysis plan. All authors revised the protocol critically for important intellectual content and approved the final version to be published. DIM, MG, LB, BH, AA, CG, KB, ALG, JS, and EH agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors, including the Prehabilitation Knowledge Network, have critically reviewed and approved the final protocol.

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Supplementary file 1 – Search strategies

Ovid MEDLINE(R) ALL

1 (prehab* or pre-hab*).tw,kf.
2 (preoperative* rehabilitation or preoperative* training).tw,kw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 Preoperative Exercise/
5 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
6 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).tw,kf.
7 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*))).tw,kf.
8 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (diet or dietary or nutrit*)).tw,kf. 2008
9 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (resistance or strength or weight or muscle) adj2 training).tw,kf.
10 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (food adj3 (counsel* or support* or modif*))).tw,kf.
11 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((energy or protein) adj3 supplement*)).tw,kf.
12 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (exercise or exercises or stretch* or aerobic* or physical activit*)).tw,kf.
13 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (cbt or cognitive behavio?r*)).tw,kf.
14 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 counsel*).tw,kf.
15 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 supplement*).tw,kf.
16 or/1-15
17 *Preoperative Care/ or *Preoperative Period/ or (preoperat* or pre-operat* or presurg* or pre-surg*).ti.
18 exp Exercise Therapy/ or Exercise/
19 Physical Fitness/
20 (exercise or exercises or stretch* or aerobic* or physical activit*).tw,kw.
21 ((resistance or strength or weight or muscle) adj2 training).tw.
22 diet therapy/ or Nutrition Therapy/ or Nutritional Support/
23 (diet or dietary or nutrit*).tw,kw.
24 (food adj3 (counsel* or support* or modif*)).tw.
25 ((energy or protein) adj3 supplement*).tw.
26 Dietary Supplements/
27 Physical Therapy Modalities/ or (physical therap* or physiotherap*).tw,kw.
28 Counseling/ or counsel?ing.tw,kw.
29 behavior therapy/ or cognitive behavioral therapy/ or Psychotherapy/ or Relaxation Therapy/
30 Stress, Psychological/rh, th
31 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*)).tw.

32 or/18-31
33 17 and 32
34 16 or 33
35 randomized controlled trial.pt.
36 controlled clinical trial.pt.
37 random*.tw.
38 placebo.ab.
39 clinical trials as topic.sh.
40 trial.ti.
41 or/35-40
42 exp animals/ not humans/
43 (infant/ or child/ or adolescent/) not adult/
44 41 not (42 or 43)
45 34 and 44
46 45 use medall

Embase Classic+Embase

1 (prehab* or pre-hab*).mp.
2 (preoperative* rehabilitation or preoperative* training).tw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).tw.
5 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (diet or dietary or nutrit*)).tw.
6 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*))).tw.
7 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (resistance or strength or weight or muscle) adj2 training).tw.
8 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (food adj3 (counsel* or support* or modif*))).tw.
9 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((energy or protein) adj3 supplement*)).tw.
10 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (stretch* or aerobic*)).tw.
11 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
12 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (cbt or cognitive behavio?r*)).tw.
13 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 counsel*).tw.
14 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 supplement*).tw.
15 or/1-14
16 *preoperative care/ or *preoperative period/ or (preoperat* or pre-operat* or presurg* or pre-surg*).ti.
17 exp *kinesiotherapy/
18 exp *exercise/
19 (exercise or exercises or stretch* or aerobic* or physical activit*).ti.
20 ((resistance or strength or weight or muscle) adj2 training).ti.
21 diet therapy/ or diet supplementation/
22 (diet or dietary or nutrit*).ti.

23 (food adj3 (counsel* or support* or modif*)).ti.
24 ((energy or protein) adj3 supplement*).tw.
25 physiotherapy/
26 (physical therap* or physiotherap*).ti.
27 counseling/ or nutritional counseling/
28 behavior therapy/
29 cognitive behavioral therapy/ or cognitive therapy/
30 psychotherapy/
31 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*)).ti.
32 or/17-31
33 16 and 32
34 15 or 33
35 double-blind*.mp. or placebo*.tw. or blind*.tw. or trial.ti.
36 random*.ti.
37 (random* adj2 (trial* or stud*)).tw.
38 35 or 36 or 37
39 34 and 38
40 (child/ or childhood/ or infant/) not adult/
41 (exp animal/ or nonhuman/) not exp human/
42 39 not (40 or 41)

EBM Reviews - Cochrane Central Register of Controlled Trials

1 (prehab* or pre-hab*).tw,kw.
2 (preoperative* rehabilitation or preoperative* training).tw,kw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).tw.
5 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj4 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)).ti.
6 Preoperative Exercise/
7 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
8 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*))).tw.
9 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 (diet or dietary or nutrit*)).tw.
10 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (resistance or strength or weight or muscle) adj2 training).tw.
11 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 (food adj3 (counsel* or support* or modif*))).tw.
12 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj5 ((energy or protein) adj3 supplement*)).tw.
13 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (exercise or exercises or stretch* or aerobic* or physical activit*)).tw.
14 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (cbt or cognitive behavio?r*)).tw.
15 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 counsel*).tw.
16 ((preoperat* or pre-operat* or presurg* or pre-surg*) adj2 supplement*).tw.

17 or/1-16
18 (infant/ or child/ or adolescent/) not adult/
19 17 not 18
20 remove duplicates from 19

APA PsycInfo

1 (prehab* or pre-hab*).tw.
2 (preoperative* rehabilitation or preoperative* training).tw.
3 ((perioperat* or peri operat*) adj3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)).tw.
4 ((exercise* or diet or nutrition* counsel?ing) and (surgery or surgical)).ti.
5 1 or 2 or 3 or 4
6 surgical patients/ or (preoperat* or pre-operat* or presurg* or pre-surg*).ti.
7 exp exercise/ or physical activity/ or physical fitness/
8 (exercise or exercises or stretch* or aerobic* or physical activit*).tw.
9 ((resistance or strength or weight or muscle) adj2 training).tw.
10 Diets/
11 Nutrition/ or Dietary Supplements/
12 (diet or dietary or nutrit*).tw.
13 (food adj3 (counsel* or support* or modif*)).tw.
14 ((energy or protein) adj3 supplement*).tw.
15 physical therapy/ or physical treatment methods/
16 (physical therap* or physiotherap*).tw.
17 Counseling/
18 counsel?ing.tw.
19 Behavior Therapy/ or Cognitive Behavior Therapy/ or Cognitive Therapy/
20 Psychotherapy/
21 ((psychological or psychosocial or cognitive) adj3 (intervention* or therap*)).tw.
22 or/7-21
23 6 and 22
24 5 or 23
25 exp Clinical Trials/ or Placebo/ or (random* or sham or placebo* or ((singl* or doubl*) adj (blind* or dumm* or mask*)) or ((tripl* or trebl*) adj (blind* or dumm* or mask*)) or (control* adj3 (study or studies or trial* or group*)) or Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or allocated or ((open label or open-label) adj5 (study or studies or trial*)) or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)) or ((pragmatic or practical) adj3 trial*) or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)) or (phase adj3 (III or "3") adj3 (study or studies or trial*))).ti,ab,hw.
26 24 and 25

CinahlComplete

#	Query
S1	(MH "Prehabilitation")
S2	TI ((prehab* or pre-hab*)) OR AB ((prehab* or pre-hab*))
S3	TI ((preoperative* rehabilitation or preoperative* training)) OR AB ((preoperative* rehabilitation or preoperative* training))
S4	TI (((perioperat* or peri operat*) N3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing))) OR AB (((perioperat* or peri operat*) N3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing)))
S5	S1 OR S2 OR S3 OR S4
S6	(MH "Preoperative Care") or (MH "Preoperative Period") or TI (preoperat* or pre-operat* or presurg* or pre-surg)
S7	(MH "Therapeutic Exercise+")
S8	(MH "Exercise+")
S9	(MH "Physical Fitness+")
S10	TI ((exercise or exercises or stretch* or aerobic* or physical activit*)) OR AB ((exercise or exercises or stretch* or aerobic* or physical activit*))
S11	TI ((resistance or strength or weight or muscle) N2 training) OR AB ((resistance or strength or weight or muscle) N2 training)
S12	(MH "Diet Therapy+")
S13	(MH "Nutritional Support+")

S14	TI ((diet or dietary or nutrit*)) OR AB ((diet or dietary or nutrit*))
S15	TI (food N3 (counsel* or support* or modif*)) OR AB (food N3 (counsel* or support* or modif*))
S16	TI ((energy or protein) N3 supplement*) OR AB ((energy or protein) N3 supplement*)
S17	(MH "Dietary Supplementation")
S18	(MH "Physical Therapy+")
S19	(MH "Physical Therapy Service")
S20	TI ((physical therap* or physiotherap*)) OR AB ((physical therap* or physiotherap*))
S21	(MH "Counseling+")
S22	TI counsel?ing OR AB counsel?ing
S23	(MH "Behavior Therapy") OR (MH "Cognitive Therapy")
S24	(MH "Psychotherapy+")
S25	TI ((psychological or psychosocial or cognitive) N3 (intervention* or therap*)) OR AB ((psychological or psychosocial or cognitive) N3 (intervention* or therap*))
S26	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
S27	S6 AND S26
S28	TI ((preoperat* or pre-operat* or presurg* or pre-surg*) N3 (exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning)) OR AB ((preoperat* or pre-operat* or presurg* or pre-surg*) N3 (exercis* or physiotherap* or

	physical therapy or diet or nutrition* or physical activit* or counsel?ing or conditioning))
S29	TI (((preoperat* or pre-operat* or presurg* or pre-surg*)N5 ((psychological or psychosocial or cognitive) N3 (intervention* or therap*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*)N5 ((psychological or psychosocial or cognitive) N3 (intervention* or therap*)))
S30	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (diet or dietary or nutrit*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (diet or dietary or nutrit*)))
S31	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (resistance or strength or weight or muscle) N2 training)) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (resistance or strength or weight or muscle) N2 training))
S32	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 ((energy or protein) N3 supplement*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 ((energy or protein) N3 supplement*)))
S33	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (exercise or exercises or stretch* or aerobic* or physical activit*))) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (exercise or exercises or stretch* or aerobic* or physical activit*)))
S34	TI ((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (cbt or cognitive behavior* or cognitive behaviour))) OR AB ((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (cbt or cognitive behavior* or cognitive behaviour)))
S35	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 counsel*)) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 counsel*))
S36	TI (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 supplement) OR AB (((preoperat* or pre-operat* or presurg* or pre-surg*) N2 supplement)

S37	S5 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36
S38	(MH (randomized controlled trials OR double-blind studies OR single-blind studies OR random assignment OR pretest-posttest design OR cluster sample) OR TI (randomised OR randomized) OR AB random* OR TI trial OR ((MH (sample size) AND AB (assigned OR allocated OR control))) OR MH (placebos OR crossover design OR comparative studies) OR AB ((control W5 group) OR (cluster W3 RCT) OR PT (randomized controlled trial))) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human))
S39	S37 AND S38
S40	(MH "Child+") NOT (MH "Adult+")
S41	S39 NOT S40

Web of Science

(infant/ or child/ or adolescent/) not adult/

((preoperat* or pre-operat* or presurg* or pre-surg*) N5 (cbt or cognitive behavior* or cognitive behaviour)).

1. (ALL=(prehab*)) OR ALL=("pre habilitation")

2. (TI=((preoperat* OR pre-operat* OR presurg* OR pre-surg*))) AND TI=(exercis* or physiotherap* or physical therapy or diet or nutrition* or physical activit* or counsel* OR condition*)

3. (TI=((preoperat* OR pre-operat* OR presurg* OR pre-surg*))) AND TI=(counsel* OR psych* OR behavior therap* OR behaviour therap*)

4. (TI=(preoperat* OR pre-operat* OR presurg* OR pre-surg*)) AND TI=(nutrition OR diet OR supplement OR dietary)

5. (TI=(exercise* or diet or nutrition* counsel*)) AND TI=(surgery or surgical)

6. ((((#1) OR #2) OR #3) OR #4) OR #5

7. Search

(TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))) NOT TS=(animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot

or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes))

8. (#6) AND #7

Supplementary file 2 – Datapoints extracted from included RCTs

1. Author
2. Year of publication
3. Countries of origin
4. Study start and end dates
5. Patient partners
    a. As authors
        i. Demographics
        ii. Roles
    b. As acknowledged collaborators
        i. Demographics
        ii. Roles
6. Prehabilitation definition
    a. In introduction or background
    b. In methods
7. Prehabilitation characteristics
    a. Multimodal (y/n)
8. Prehabilitation Components (eg, exercise, nutrition, psychosocial, cognitive)
    a. Type of exercise
        i. Unimodal
        ii. Multimodal
        iii. Interval training
        iv. Other
        v. Components (eg, cardio, strength, stretching, respiratory exercise)
    b. Type of nutrition
        i. Counselling
        ii. Supplementation
        iii. Combined
        iv. Other
    c. Type of psychosocial
        i. Motivational interviewing
        ii. Anxiety management
        iii. Stress management
        iv. Other
    d. Type of cognitive
    e. Other co-interventions
9. Enhanced recovery after surgery (ERAS) (y/n)
10. Weight loss objective (y/n)
11. Duration of prehabilitation
    a. Average
    b. Program
        i. Minimum participation
        ii. Maximum participation
    c. Per session
12. Frequency of prehabilitation
13. Intervention time-point
    a. Preoperative only
    b. Preoperative plus rehab after surgery
14. Location of prehabilitation

a. Home
b. Facility
c. Combined

15. Supervision
    a. Self-directed
    b. Coach-led
    c. Combined
16. Session format
    a. Individual
    b. Group
    c. Combined
17. Personalization
    a. Description of personalization
18. Motivation techniques
    a. Description of motivation techniques
    b.
19. Control (eg, standard care or active controls such as rehabilitation after surgery)
    a. Standard care
        i. Description of standard care
    b. Static instructions
        i. Description of static instructions
    c. Other prehabilitation
        i. Description of other prehabilitation
    d. Rehabilitation
        i. Description of rehabilitation
    e. Other
        i. Description of other
20. Surgical specialty
    a. Orthopedic
    b. Major non-oncology
    c. Cardiac/vascular
    d. Oncology
    e. Mixed
    f. Other
21. Surgical procedure(s)
22. Population characteristics
    a. Total sample size
    b. Sample size per arm
    c. Age (average, range)
    d. Sex (% females vs. males)
    e. Gender (% women vs. men vs. non-binary/transgender/other)
    f. Presence of specific risk factors
        i. Multimorbidity (≥2 comorbidities)
        ii. ASA score
        iii. Frailty
        iv. Malnutrition
        v. Obesity
        vi. Baseline functional status
        vii. Disability
        viii. Presence of cancer
            1. Use of neoadjuvant therapies

23. Outcomes (counts, summary statistics, effect estimates with 95%CI; per time window)
    a. Health
        i. Complications
            1. Any
            2. Cardiopulmonary
            3. Surgical
            4. Infectious
        ii. Discharge disposition
        iii. Physical functional recovery
        iv. Disability
        v. Quality of life
        vi. Mortality
    b. Experience
        i. Pain
        ii. Patient satisfaction
    c. Resource use
        i. Length of stay
        ii. Costs
    d. Intervention Safety
        i. Any intervention-attributable adverse events
        ii. Cardiopulmonary adverse events during intervention period
        iii. Falls during intervention period
        iv. Assessor-confirmed intervention-attributable adverse events
24. Adherence
    a. Outcome type
        i. Binary
            1. Threshold used
        ii. Continuous
    b. Adherence rate
    c. Method of measurement
25. Feasibility measures
26. Barriers and facilitators to implementation

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	14
Sponsor	5b	Provide name for the review funder and/or sponsor	14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	14
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8 Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9 Appendix 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9 Appendix 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.