Relative efficacy of prehabilitation interventions and their components: systematic review with network and component network meta-analyses of randomised controlled trials

Daniel I McIsaac,[1] Gurlavine Kidd,[2] Chelsia Gillis,[3] Karina Branje,[2] Mariam Al-Bayati,[2] Adir Baxi,[2] Alexa L Grudzinski,[4] Laura Boland,[5] Areti-Angeliki Veroniki,[6] Dianna Wolfe,[2] Brian Hutton[2]

[1]Department of Anesthesiology and Pain Medicine, University of Ottawa, Clinical Epidemiology Program, Ottawa Hospital Research Institute, School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

[2]Clinical Epidemiology Program, the Ottawa Hospital Research Institute, Ottawa, ON, Canada

[3]McGill University, School of Human Nutrition, Montreal, QC, Canada

[4]Department of Anaesthesiology and Pain Medicine, University of Ottawa, Ottawa, ON, Canada

[5]Public Health Agency of Canada, Ottawa, ON, Canada

[6]Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

Correspondence to: D McIsaac (@mcisaac_d) dmcisaac@toh.ca (ORCID 0000-0002-8543-1859)

Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVE
To estimate the relative efficacy of individual and combinations of prehabilitation components (exercise, nutrition, cognitive, and psychosocial) on critical outcomes of postoperative complications, length of stay, health related quality of life, and physical recovery for adults who have received surgery.

DESIGN
Systematic review with network and component network meta-analyses of randomised controlled trials.

DATA SOURCES
Medline, Embase, PsycINFO, CINAHL, Cochrane Library, and Web of Science were initially searched 1 March 2022, and updated on 25 October 2023. Certainty in findings were assessed using the Confidence in Network Meta-Analysis (CINeMA) approach.

MAIN OUTCOME MEASURES
To compare treatments and to compare individual components informed by partnership with patients, clinicians, researchers, and health system leaders using an integrated knowledge translation framework. Eligible studies were any randomised controlled trial including adults preparing for major surgery who were allocated to prehabilitation interventions or usual care, and where critical outcomes were reported.

RESULTS
186 unique randomised controlled trials with 15 684 participants were included. When comparing treatments using random-effects network meta-analysis, isolated exercise (odds ratio 0.50 (95% confidence interval (CI) 0.39 to 0.64); very low certainty of evidence), isolated nutritional (0.62 (0.50 to 0.77); very low certainty of evidence), and combined exercise, nutrition, plus psychosocial (0.64 (0.45 to 0.92); very low certainty of evidence) prehabilitation were most likely to reduce complications compared with usual care. Combined exercise and psychosocial (−2.44 days (95% CI −3.85 to −1.04); very low certainty of evidence), combined exercise and nutrition (−1.22 days (−2.54 to 0.10); moderate certainty of evidence), isolated exercise (−0.93 days (−1.27 to −0.58); very low certainty of evidence), and isolated nutritional prehabilitation (−0.99 days (−1.49 to −0.48); very low certainty of evidence) were most likely to decrease length of stay. Combined exercise, nutrition, plus psychosocial prehabilitation was most likely to improve health related quality of life (mean difference on Short Form-36 physical component scale 3.48 (95% CI 0.82 to 6.14); very low certainty of evidence) and physical recovery (mean difference in meters on the six min walk test 43.43 (95% CI 5.96 to 80.91); very low certainty of evidence).When comparing individual components using component network meta-analysis, exercise and nutrition were the individual components most likely to improve all critical outcomes. The certainty of evidence for all comparisons across all outcomes was generally low to very low due to trial level risk of bias and imprecision; however, results for exercise and nutritional prehabilitation were robust with exclusion of high risk of bias trials.

CONCLUSIONS
Consistent and potentially meaningful effect estimates suggest that exercise prehabilitation, nutritional prehabilitation, and multicomponent interventions including exercise may benefit adults preparing for surgery and could be considered in clinical care. However, multicentre trials that are appropriately powered for high priority outcomes and that have a low risk of bias are required to have greater certainty in prehabilitation's efficacy.

REGISTRATION
International prospective registry of systematic reviews CRD42023353710.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Postoperative complications, prolonged length of stay, and difficult patient centred recovery after surgery are common and have major implications for patients, clinicians, and health system leaders

Prehabilitation of one or multiple components that aim to increase patients' reserves before surgery may help to improve outcomes, but certainty of its efficacy is low, and what components are most efficacious is unknown

WHAT THIS STUDY ADDS

Multicomponent interventions that include exercise, as well as isolated exercise and nutrition are most likely to improve complication rates, length of stay, health related quality of life and physical recovery after surgery

The certainty of prehabilitation interventions' efficacy remain low due to trial level risks of bias and imprecision

Introduction

Prehabilitation means actively preparing patients for surgery through exercise, nutritional enhancement, psychological support, cognitive training, or a combination of these components.[1-3] With more than 300 million surgeries performed worldwide each year,[4] patients, the public, clinicians, scientists, and health system leaders have identified prehabilitation

as a high priority intervention for research and future implementation.[5-7] Postoperative complications and impaired functional recovery remain common (each >20% incidence) after major surgery. By helping patients to enhance their physical, physiological, psychological or cognitive reserve before surgery, prehabilitation represents a promising intervention to prevent these complications.[8-10]

Despite the prioritisation and promise of prehabilitation, evidence highlights several barriers to routine application of prehabilitation for patients preparing for surgery. Many reviews,[11-14] including an umbrella review that synthesised 55 unique systematic reviews,[1] suggest that prehabilitation may have protective effects in reducing complications, length of stay, and improving functional recovery. However, the overall certainty of benefit is low for several reasons.[1] Although prehabilitation directly targets patients' health behaviours and requires meaningful effort from individuals to participate,[15] most available systematic reviews are rated as low quality[1 16] and have not included patient and public perspectives.[1] Reviews typically estimate one effect for either a single prehabilitation component (eg, exercise only) or pool heterogeneous interventions together.[1 14 17 18] As an often multicomponent intervention where different components (eg, exercise and nutrition) may modify the other's efficacy,[7 19] this limits our ability to understand what prehabilitation components, or combinations of components, are most likely to be efficacious. Consequently, patients and clinicians are uncertain about what prehabilitation approaches should be incorporated into clinical practice, while researchers aiming to optimally design future prehabilitation interventions and trials are left with limited insights.

To move the science of prehabilitation forward, high quality evidence synthesis is required, based on best practice methods to identify relevant primary studies, and appropriate analyses that can estimate the relative efficacy of different prehabilitation components. Network meta-analysis and component network meta-analysis allow estimation of separate effects for specific combinations of components, and individual components, respectively, through direct and indirect comparisons.[20] We undertook a systematic review along with network meta-analysis and component network meta-analysis that was informed by patient and public partnerships using an integrated knowledge translation framework.[21] Our aim was to identify which prehabilitation components and combinations of components were most likely to improve critical postoperative outcomes (complications, length of stay, health related quality of life, and physical recovery) in adults preparing for surgery.

Methods

This systematic review incorporated treatment level network meta-analysis and component network meta-analysis. A protocol was developed, prospectively registered (CRD42023353710), and published.[22] This report was prepared in keeping with guidance from the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement, the PRISMA statement extension for network meta-analysis,[23 24] and the guidance for reporting involvement of patients and the public-2 checklist (appendix 1).[25]

Search strategy

A search strategy was developed by an information specialist, and peer reviewed using best practices[27] prior to performance in the following databases: Ovid Medline, Embase, the CINAHL, PsycINFO, Web of Science, and the Cochrane CENTRAL Register of Controlled Trials. We also reviewed clinical trials registration websites to identify unpublished data, and reviewed reference lists of included studies to identify missed citations. The literature search (appendix 2) was initially run on 1 March 2022 and was updated on 25 October 2023.

Intervention definition

While no universal definition of prehabilitation exists,[3] we defined prehabilitation as a unimodal intervention consisting of exercise (eg, aerobic, strength, functional or stretching, or respiratory focused interventions), nutrition (eg, counselling, supplementation, or other interventions to improve oral or enteral intake), cognitive (eg, interventions to improve or maintain cognitive function), or psychosocial (eg, interventions to improve mood, affect, or motivation) training or support, or a multimodal intervention that combined exercise, nutrition, cognitive or psychosocial components, or a combination, undertaken for seven or more days before surgery.[1 2 14] No restrictions were placed on daily or overall programme duration, location, or supervisory approaches.

Inclusion and exclusion criteria

We included randomised controlled trials that enrolled adults (>18 years) undergoing elective surgery who were allocated to a prehabilitation intervention versus a comparator intervention or usual or standard care, and that reported any critical outcomes. We excluded studies that evaluated isolated preoperative risk factor management (eg, smoking cessation, anaemia treatment, and management of medical conditions), where the prehabilitation intervention was for fewer than seven days (to differentiate prehabilitation interventions from related interventions such as enhanced recovery programmes, and to ensure programmes had adequate time for effect, based on established operational definition of prehabilitation developed using integrated knowledge translation approach[1]), or where the study design was quasi-experimental or non-randomised. No restrictions regarding language of publication were applied.

Outcomes

Using an integrated knowledge translation approach, we were able to prespecify four outcomes based on input from patients, clinicians, health system leaders, and scientists: (1) any postoperative medical

or surgical complications during the initial surgical hospital duration or up to 30 days after surgery; (2) length of hospital stay; (3) health related quality of life (generic or disease specific: up to 90 days after surgery); (4) physical recovery (eg, six min walk test and short physical performance battery; up to 90 days postoperative). Where more than one measure of a critical outcome was reported in an included trial, a prespecified prioritisation scheme was used to select the specific outcome measure for data synthesis (appendix 3). We used the following effect sizes to guide the interpretation of results that were potentially clinically meaningful: complications (odds ratio <0.80),[28] length of stay (1 day), health related quality of life (3 points on the Short-Form 36, physical component scale),[29] and physical recovery (20 metres on the six min walk test).[30 31]

Study selection
Screening of titles and abstracts, and then full text review, were conducted in duplicate by two independent reviewers using DistillerSR (Evidence Partners, Ottawa, Canada). At each stage, the study lead (DIM) reviewed and resolved any conflicts, or ratings marked as uncertain, for final inclusion using a consensus based approach.

Data extraction and risk of bias assessment
Once the final set of included randomised controlled trials was identified, data were extracted using a standardised collection form designed a priori for this study (appendix 4). Each data point was extracted by a first reviewer and verified by one of two lead data extractors. Sample size, population characteristics, and outcome data were collected for each trial. For the dichotomous outcome (complications), we collected data at the treatment arm level (number of participants and events) and its measure of uncertainty (eg, 95% confidence intervals (CIs)). For continuous outcomes (length of stay, health related quality of life, and physical recovery), we preferentially collected data at the treatment arm level (ie, number of participants, mean, and standard deviation) over effect estimates (eg, mean difference and 95% CI). For health related quality of life and physical recovery, where both baseline and final measures were reported, final measures were preferred over within group differences. Where medians and ranges (interquartile range or range from minimum to maximum value) were reported instead of means and standard deviations, data were transformed using the methods of Wan and colleagues.[32] Where group level baseline scores and change scores were reported for quality of life and physical recovery, we calculated final scores and estimated standard deviation using a correlation coefficient of 0.70, which was selected in consultation with clinical experts. Other data formats were converted as necessary, using published methods.[33 34] Missing data were sought directly from study authors, with at least two emails sent at least two weeks apart before data were considered missing. All risk of bias assessments were duplicated, one by the study lead and a second by another reviewer, using the Cochrane risk of bias tool.[35] For each study, overall risk of bias was classified as low (no domains rated high, low risk of bias for allocation concealment, less than three domains unclear), moderate (one domain rated high, low risk of bias for allocation concealment, fewer than three domains unclear), or high (all other cases).

Data syntheses and analyses
Descriptive summaries of study level characteristics prioritised by the research team were computed (appendix 5). We generated network diagrams for each outcome to assess network connectivity and to present the evidence base for each outcome. Between trial heterogeneity and appropriateness of the transitivity assumption for network meta-analysis were assessed using box plots, bar charts, and evidence tables to examine differences in potential study-level effect modifiers (eg, surgery type, control group outcome risk or mean, publication year, mean age, proportion female, and risk of bias) and study design. All analyses were performed in R statistical software (version 4.3.3; R Core Team 2024; netmeta, gemtc, rjags, and BUGSnet packages).[36-38] Results were considered to have strong statistical evidence based on an alpha of 5% unless otherwise specified.

Treatment level network meta-analysis
We prespecified use of frequentist random-effects network meta-analysis models for all outcomes. Binary endpoints were directly modelled using the extracted counts of events and participants for each study, with odds ratios as the summary effect measure. Studies with no events in either group did not contribute to the meta-analysis, while defaults (ie, no continuity correction) in netmeta were used for studies with zero events in one arm as treatment effects did not assume infinite values.[36] Continuous endpoints were modelled with mean differences, or standardised mean differences when an outcome was measured on different scales across studies (ie, health related quality of life, and physical recovery). Where outcomes were measured before and after surgery (health related quality of life and physical recovery), only final values were included in the analyses. We back-transformed standardised mean differences[39] to the scale most frequently reported in included studies (Short Form (SF)-36 physical component score for health related quality of life and the six min walk test for physical recovery (details in appendix 6)). All pooled effects were estimated along with 95% CIs and 95% prediction intervals.[33 40] Consistency within treatment level network meta-analysis was assessed using global (ie, design-by-treatment interaction test[41]) and local tests (ie, comparison of direct and indirect treatment effects, using a back-calculation approach[42]). We also calculated the I^2 statistic to estimate the percentage of variability due to heterogeneity rather than chance,[33] which can be inflated in network meta-analyses due to potential inconsistency across different studies and designs.[43] Between study variance (τ^2) was estimated

using the restricted maximum likelihood method.[44] Results of all treatment level network meta-analysis were reported using forest plots, with usual care as the reference group, and league tables of all pair-wise treatment comparisons. Treatments were ranked using P scores, which can be interpreted as the mean extent of certainty that a given treatment is more efficacious than any other.[45] P scores vary from 0 to 1, with values closer to 1 representing greater probability of being most efficacious. Relative treatment rankings were reported using rank-heat plots of P scores to allow comparison of treatment ranks across all outcomes.[46] Effects from small studies (potential publication bias) were assessed through visual inspection of contour-enhanced funnel plots and incorporated into assessments of the certainty of the evidence.[36 47] We considered several sensitivity analyses for the treatment level network meta-analysis to explore evidence of heterogeneity or inconsistency, or both. (1) We did network meta-regressions by surgery type (oncological *v* non-oncological and orthopaedic *v* non-orthopaedic) and used control group outcome risk or mean; network meta-regressions were performed in a Bayesian framework as these methods are unavailable within frequentist network meta-analysis packages. (2) We removed studies that were potentially outliers based on magnitude or direction of treatment effect relative to other studies of the same treatment comparison. (3) We used modelling the ratio of geometric means for length of stay data,[48] which follow a skewed distribution. (4) We did a restriction of network meta-analysis to studies judged to be at overall low risk of bias (appendix 7).

Component network meta-analysis
To explore the relative efficacy of individual components (ie, exercise, nutrition, psychological, and cognitive) within and across treatments, we performed component network meta-analysis in a frequentist setting.[20] Additive component network meta-analysis assumes that the effects of individual components are additive (ie, the effect of a treatment comprised of exercise and nutrition components would be the sum of the expected effects of exercise and nutrition alone).[20] We tested the additivity assumption by comparing the difference in Cochrane's Q-statistics of the additive component network meta-analysis model and the treatment level (ie, full-interaction) network meta-analysis model at a cut-off determined by the difference in the models' degrees of freedom.[20 49] When significantly different Q-statistics were found, the additivity assumption was considered violated and interaction component network meta-analysis models were fit in a forward selection process, as described elsewhere.[49] Further details on component network meta-analysis implementation are provided in appendix 7.

Certainty of evidence assessment
Certainty of treatment effect estimates for each outcome at the treatment level were assessed using the Confidence in Network Meta-Analysis (CINeMA) approach, covering six domains of bias: within study bias, across study bias, indirectness, imprecision, heterogeneity, and inconsistency.[50 51] For each outcome, we generated CINeMA certainty ratings with levels of high, moderate, low, or very low. We used the risk of bias due to missing evidence in network meta-analysis (ROB-MEN) tool to assess reporting bias, which includes the assessment of effects from small studies.[52] Details of the ROB-MEN and CINeMA assessment methods are available in appendix 8. Overall CINeMA assessments for each comparison reported in the main text were based on the average risk of bias assessment and the average indirectness assessment for that comparison.

Protocol deviations
All protocol deviations are reported in appendix 9. As described, our team of patient and knowledge user partners emphasised reporting of the treatment level network meta-analysis as the primary analysis (over the component network meta-analysis) because of the clinical and statistical considerations for component network meta-analysis (which was a recognised possibility in our published protocol).[22]

Patient and public involvement
The focus of this review was directly informed by three patients and 10 knowledge user partners using an integrated knowledge translation approach.[21 26] Using this approach meant that patients with lived experience of having surgery, and knowledge users with lived experience of providing and delivering perioperative care and prehabilitation participated as partners on the research team. Partners collaborated in all aspects of the research process, from question formation through to dissemination (including preparation and approval of the final manuscript). Partnerships were fostered through formal and informal meetings, discussions, and email. We used team-wide questionnaires to identify what prehabilitation components to evaluate and to choose critical outcomes. Prehabilitation is a complex intervention, and component network meta-analysis and network meta-analysis are complex statistical approaches with many underlying assumptions. For this reason, a major focus of team meetings, which included small group breakout sessions, was to discuss how the clinical considerations of prehabilitation should inform the application of statistical assumptions to our data. These discussions were also used to guide interpretation, once results were available. From meetings and discussions, the patient and knowledge user team decided to place a primary focus on the treatment level network meta-analysis results rather than component level component network meta-analysis results because partners expressed a strong belief in the likely underlying clinically meaningful interaction of different prehabilitation components in multimodal prehabilitation programmes (eg, many partners expressed a belief that exercise and nutrition would act synergistically[19]). Therefore, results from
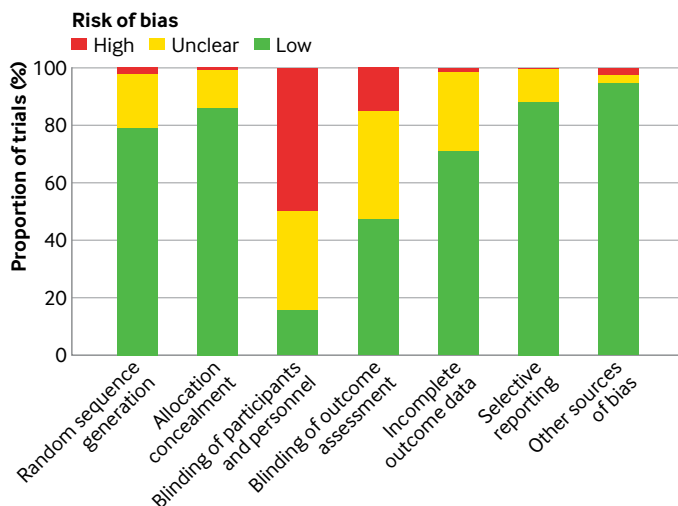
Fig 1 | Proportion of included studies with high, unclear, and low risk of bias for each bias domain of the Cochrane collaboration's risk of bias 1 tool

treatment level network meta-analysis were thought to be most clinically relevant, and knowledge users expressed a preference for relying less on the more complex statistical assumptions underlying component network meta-analysis.[20]

Results

We screened 6106 unique titles and abstracts, followed by full text review of 1114 records, resulting in the inclusion of 186 unique randomised controlled trials (n=15 684) (PRISMA diagram, appendix 10; included studies, appendix 11; excluded studies with rationale, appendix 12). No included studies reported any patient or public partnership. Among included trials, 43 (23%) were low risk of bias, 66 (36%) were moderate, and 77 (41%) were high risk (fig 1, appendix 13).

The mean age of trial participants was 62 years, the median proportion of participants who were women or identified as women(distinction between sex and gender in included studies was poor) was 45%. The distribution of surgery types was as follows: 43 (23%) orthopaedic, 20 (11%) major non-oncology, 20 (11%) cardiac or vascular, 84 (45%) oncology, and 19 (10%) mixed. An exercise prehabilitation component was reported in 133 randomised controlled trials (72%), nutritional in 68 (37%), psychosocial in 31 (17%), and cognitive in four (2%) (appendix 11).

Network characteristics and review of assumptions

Network diagrams for all four outcomes are presented in figure 2. All outcomes except physical recovery had one closed loop; physical recovery had a star-shaped network. For each outcome, we assessed transitivity through visual inspection of patient characteristics across studies informing the network meta-analysis. The findings showed, on average, minor differences between treatment comparisons in mean age and the proportion of enrolled women, mainly for comparisons

with smaller numbers of studies (appendix 14). In cases where evidence showed intransitivity, we downgraded CINeMA certainty ratings in the indirectness domain (appendix 8). We also noted some variability in observed risk of complications and central values of length of stay, health related quality of life, and physical recovery in the usual care group (appendix 14, along with results of prespecified control group risk (or mean) network meta-regressions mentioned later). Statistical heterogeneity was substantial for length of stay, health related quality of life, and physical recovery; however, none of our a priori specified effect modifiers meaningfully explained this variability. Small study effects may have been present for exercise, nutrition, plus psychosocial and isolated nutritional prehabilitation for complications and length of stay outcomes; isolated exercise for health related quality of life; and exercise, nutrition, plus psychosocial prehabilitation for physical recovery. For all outcomes, prediction intervals suggested that estimated effects may not always be reliably replicated in different clinical scenarios, reflecting potential heterogeneity in treatment response (appendices 15, 16, 17, and 18 for details). No evidence of global inconsistency was suggested for any endpoint, while a minor deviation detected in the local tests of inconsistency for the complications outcome downgraded certainty ratings for one comparison.

Complications

Complications were reported in 106 trials comprising 8816 participants (fig 2, complications). Reported complication types were predominantly a composite of any complication (49 (46%)), or cardiopulmonary (21 (20%)) or infectious complications (21 (20%)) (appendix 15). All interventions except for isolated psychosocial prehabilitation directionally reduced the odds of complications compared with usual care (fig 3, complications). The four highest ranked treatments versus usual care were isolated exercise prehabilitation (odds ratio 0.50 (95% CI 0.39 to 0.64); P score 0.85; very low certainty of evidence), exercise plus nutrition (0.52 (0.26 to 1.05); P score 0.75; very low certainty), isolated nutritional prehabilitation (odds ratio 0.62 (0.50 to 0.77); P score 0.62; very low certainty), and combined exercise, nutrition, plus psychosocial prehabilitation (odds ratio 0.64 (0.45 to 0.92); P score 0.59; very low certainty) (fig 3, complications). No significant differences were found between active treatments (see league tables in appendix 15). Statistical heterogeneity was moderate in the whole network (I^2=30.7%; τ^2=0.15). Network meta-regression on surgery type did not reduce statistical heterogeneity, and model fit was worse compared with the primary model when baseline risk meta-regression was conducted (appendix 15). Certainty of evidence from direct comparisons were rated as very low for all treatment comparisons except exercise plus nutrition versus usual care (low; appendix 15). Reduced certainty was mainly due to concerns regarding within-study bias and imprecision.
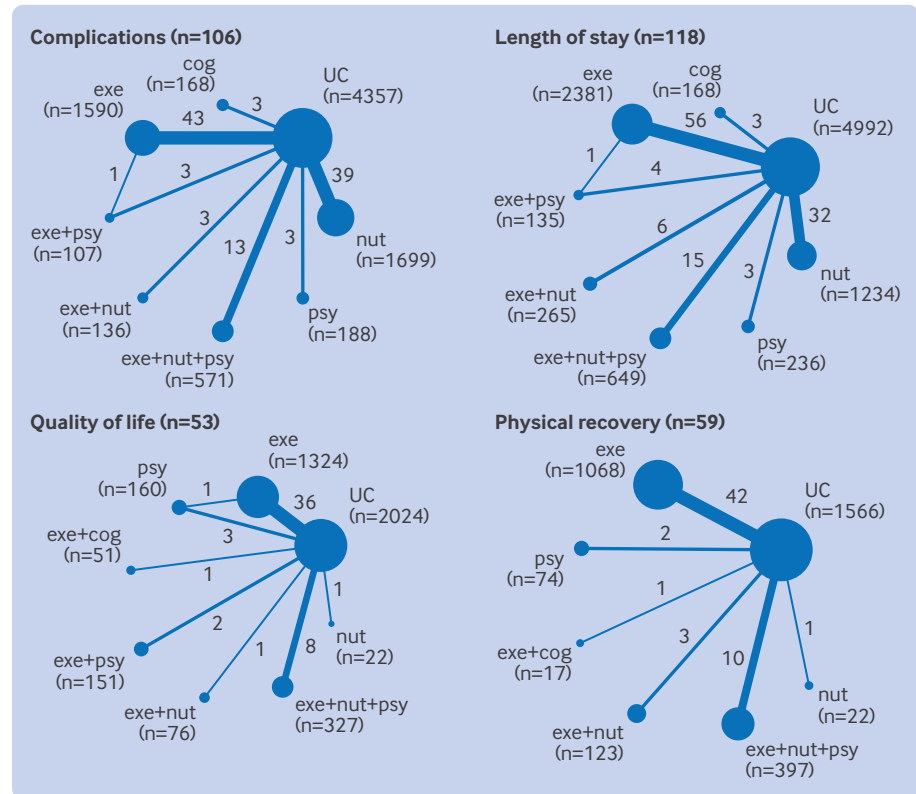
Fig 2 | Network diagrams for all critical outcomes (postoperative complications, length of stay in hospital, quality of life, and physical recovery). Network diagrams display the evidence base that informed network meta-analysis for each outcome. Nodes are proportionally sized to reflect the total numbers of patients randomised to each intervention, while edges are proportionally sized to reflect the numbers of randomised controlled trials informing each treatment comparison. cog=cognitive; exe=exercise; nut=nutrition; psy=psychosocial; UC=usual care

For the component network meta-analysis model, no statistical evidence suggested violation of the additivity assumption (appendix 15). Exercise (odds ratio 0.53 (95% CI 0.42 to 0.66)) and nutrition (0.66 (0.54 to 0.81)) components both significantly reduced the odds of postoperative complications (appendix 15). Evidence for the psychosocial component was more consistent with harm (1.75 (1.17 to 2.61)). Heterogeneity was unchanged from the treatment level network meta-analysis (I²=30.3%; τ²=0.14).

Length of stay

Length of stay was reported in 118 randomised controlled trials (n=10 060; fig 2). A network meta-analysis at the treatment level found that all interventions, except for isolated cognitive prehabilitation, directionally reduced length of stay compared with usual care (fig 3, length of stay). The four highest ranked treatments all reduced length of stay by a potentially clinically meaningful difference of about one day versus usual care, including exercise plus psychosocial prehabilitation (mean difference −2.44 days (95% CI −3.85 to −1.04); very low certainty of evidence), exercise plus nutrition (−1.22 days (−2.54 to 0.10); P score 0.71; moderate certainty), isolated nutritional prehabilitation (−0.99 days (−1.49 to −0.48); P score 0.67; very low certainty),

and isolated exercise prehabilitation (−0.93 days (−1.27 to −0.58); P score 0.63; very low certainty). Combined exercise plus psychosocial prehabilitation was associated with significantly greater reductions in length of stay compared with each of isolated exercise (−1.52 days (−2.94 to −0.09); very low certainty); exercise, nutrition, plus psychosocial (−1.91 days (−3.47 to −0.36); very low certainty); isolated psychosocial (−2.18 days (−4.08 to −0.29); very low certainty); and isolated cognitive (−2.80 days (−4.79 to −0.82); very low certainty) interventions; no significant differences were noted between any other active treatment comparisons (see league tables in appendix 16). Statistical heterogeneity was high across the whole network (I² =83.3%; τ² =1.09). Certainty in the effect estimates for direct comparisons was moderate for exercise plus nutrition and exercise, nutrition, plus psychosocial versus usual care, and very low for all others. Downgrades were mainly due to concerns regarding within-study bias and imprecision. For comparison specific assessments, see appendix 16.

Sensitivity analyses using the ratio of geometric means effect measure resulted in only minor changes in clinical interpretations relative to the primary analysis (appendix 16). Other sensitivity analyses excluding outlier studies in the loop did not reduce heterogeneity. Meta-regression on surgery type did not

significantly improve model fit, while meta-regression on the mean length of stay of the control group did significantly improve model fit (appendix 16). Adjustment mean length of stay of the for control group also strengthened effect estimates for all treatments compared with usual care (appendix 16). The effects of exercise, nutrition, plus psychosocial and exercise plus nutrition reached statistical significance; the effect of cognitive prehabilitation reversed direction to become beneficial; and treatment rankings shifted so that usual care became the lowest ranked treatment.

For the component network meta-analysis model, statistical evidence suggested that the additivity assumption did not hold (appendix 16). A model containing a two way interaction term between exercise and nutrition and a three way interaction term between exercise, nutrition, and psychosocial components improved model fit. Findings from the interaction model suggested that exercise and nutrition components significantly reduced length of stay (exercise: mean difference −0.96 days (95% CI −1.30 to −0.61); nutrition: −0.99 days (−1.49 to −0.48)). However, the interaction terms suggested that the incremental effects of the exercise and nutrition components were reduced in the other's presence (ie, the reduction in length of stay was not as large as their sum), and inclusion of a psychosocial component further reduced the expected effect of the intervention. The effects of psychosocial and cognitive components were imprecise (appendix 16). Heterogeneity was unchanged from the treatment level network meta-analysis (I^2=83.2%; τ^2=1.07).

Health related quality of life

Health related quality of life was reported in 53 randomised controlled trials (n=4135; fig 2, panel C) and measured on various scales, most commonly the SF-36 or SF-12 physical component score (n=14 studies; 26%) and the EQ-5D visual analogue scale (n=8; 15%). Findings are presented as mean differences after back-transformation to the SF-36 physical component score (as well as standardised mean differences in appendix 17). Treatment level network meta-analysis found that all interventions except isolated psychosocial prehabilitation and exercise plus cognitive prehabilitation directionally improved health related quality of life measures compared with usual care (fig 3). Compared with usual care, the two highest ranked treatments increased health related quality of life by a potentially clinically meaningful difference (mean difference=3), including exercise, psychosocial, plus nutrition (mean difference 3.48 (95% CI 0.82 to 6.14); P score 0.81; very low certainty of evidence) and isolated nutritional prehabilitation (3.28 (−5.03 to 11.60); P score 0.68; moderate certainty). Isolated exercise (2.29 (0.96 to 3.62); P score 0.66; very low certainty), and exercise plus psychosocial (1.31 (−3.36 to 5.98); P score 0.51; low certainty) prehabilitation were third and fourth highest ranked versus usual care, but pooled point estimates were not larger than a potentially meaningful difference (fig 3, quality of life). No significant differences were found between active treatments (see league tables in appendix 17). Statistical heterogeneity was moderate in the whole network (I^2=60.0%; τ^2=0.09). Certainty in direct effect estimates were moderate for one intervention (nutrition v usual care), low for three (exercise plus nutrition and exercise plus psychosocial v usual care; exercise v psychosocial) and very low for four comparisons (exercise, psychosocial, exercise plus cognitive, and exercise, nutrition, plus psychosocial v usual care). Downgrades were mainly due to concerns regarding within study bias and imprecision (appendix 17). Network meta-regressions on surgery type and control group standardised mean did not improve model fit (appendix 17).

For the component network meta-analysis model, no evidence suggested violation of the additivity assumption from statistical tests. Amongst components, only exercise was associated with a statistically significant improvement in health related quality of life (mean difference 2.20 (95% CI 1.00 to 3.50); appendix 17). Heterogeneity was unchanged from the treatment level network meta-analysis (I^2=59.0%; τ^2=0.08).

Physical recovery

Physical recovery was reported in 59 randomised controlled trials (n=3267; fig 2) and was measured on various scales, most commonly the six min walk test (34 studies). Findings are presented as mean differences after back-transformation to the six min walk test (measured in meters; standardised mean differences in appendix 18). Treatment level network meta-analysis found that all interventions directionally improved physical recovery compared with usual care (fig 3, physical recovery). The four highest ranked treatments compared with usual care all increased physical recovery by a potentially clinically meaningful difference (six min walk test 20 m), including exercise, psychosocial, plus nutrition (mean difference v usual care 43.43 m (95% CI 5.96 to 80.91); P score 0.72; very low certainty of evidence), exercise plus nutrition (40.52 m (−32.33 to 113.38); P score 0.65; very low certainty), isolated psychosocial (34.50 m (−45.75 to 114.76); P score 0.60; very low certainty), and isolated exercise (25.73 m (6.11 to 45.35); P score 0.54; low certainty) (fig 3, physical recovery). No significant differences were noted between active treatments (see league tables in appendix 18). Statistical heterogeneity was moderate to high in the whole network (I^2=66.0%; τ^2=0.16). Certainty in the effect estimates were very low for all treatment comparisons mainly due to concerns regarding within-study bias, imprecision, and incoherence (appendix 18). Network meta-regressions on surgery type did not improve model fit.

For the component network meta-analysis model, no evidence from statistical testing suggested that the additivity assumption was violated. Amongst components, only exercise was associated with a statistically significant improvement in physical recovery (mean difference 26.25 (6.25 to 45.00);
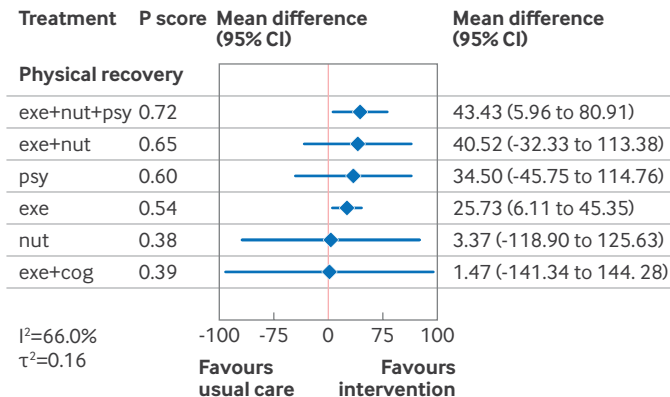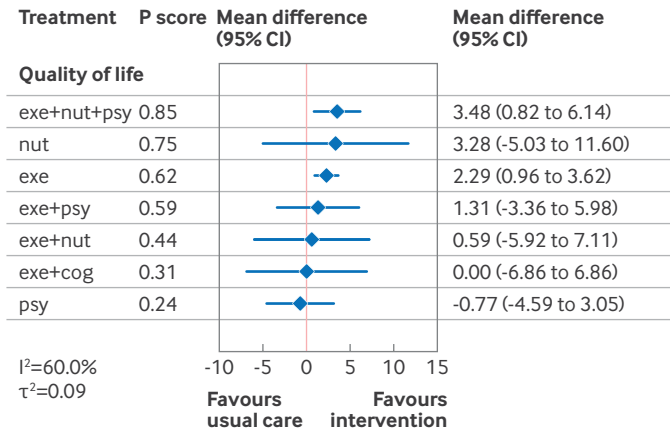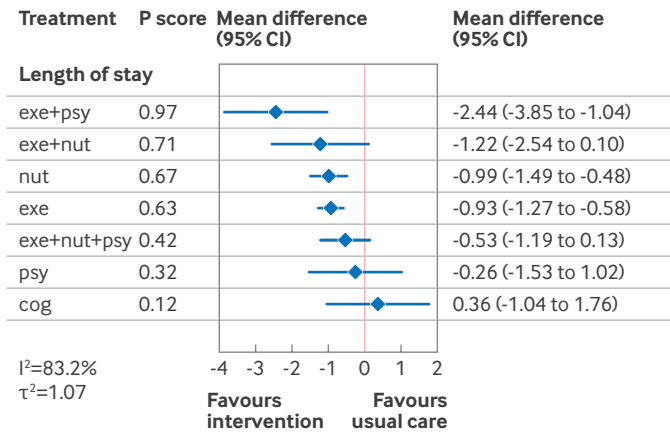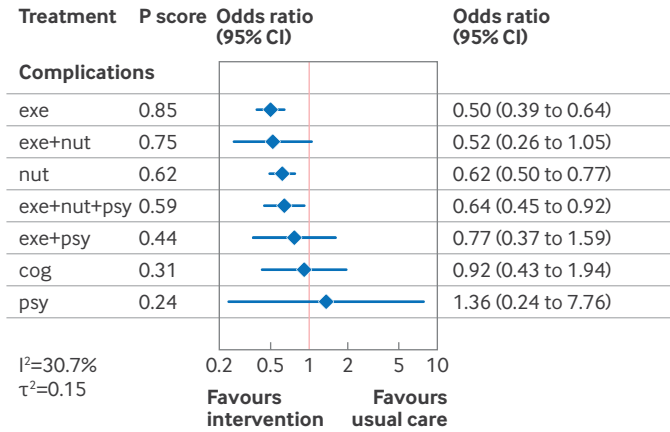
Complications

Treatment	P score	Odds ratio (95% CI)
exe	0.85	0.50 (0.39 to 0.64)
exe+nut	0.75	0.52 (0.26 to 1.05)
nut	0.62	0.62 (0.50 to 0.77)
exe+nut+psy	0.59	0.64 (0.45 to 0.92)
exe+psy	0.44	0.77 (0.37 to 1.59)
cog	0.31	0.92 (0.43 to 1.94)
psy	0.24	1.36 (0.24 to 7.76)

I^2=30.7%
τ^2=0.15

0.2 0.5 1 2 5 10
Favours intervention — Favours usual care

Length of stay

Treatment	P score	Mean difference (95% CI)
exe+psy	0.97	-2.44 (-3.85 to -1.04)
exe+nut	0.71	-1.22 (-2.54 to 0.10)
nut	0.67	-0.99 (-1.49 to -0.48)
exe	0.63	-0.93 (-1.27 to -0.58)
exe+nut+psy	0.42	-0.53 (-1.19 to 0.13)
psy	0.32	-0.26 (-1.53 to 1.02)
cog	0.12	0.36 (-1.04 to 1.76)

I^2=83.2%
τ^2=1.07

-4 -3 -2 -1 0 1 2
Favours intervention — Favours usual care

Quality of life

Treatment	P score	Mean difference (95% CI)
exe+nut+psy	0.85	3.48 (0.82 to 6.14)
nut	0.75	3.28 (-5.03 to 11.60)
exe	0.62	2.29 (0.96 to 3.62)
exe+psy	0.59	1.31 (-3.36 to 5.98)
exe+nut	0.44	0.59 (-5.92 to 7.11)
exe+cog	0.31	0.00 (-6.86 to 6.86)
psy	0.24	-0.77 (-4.59 to 3.05)

I^2=60.0%
τ^2=0.09

-10 -5 0 5 10 15
Favours usual care — Favours intervention

Physical recovery

Treatment	P score	Mean difference (95% CI)
exe+nut+psy	0.72	43.43 (5.96 to 80.91)
exe+nut	0.65	40.52 (-32.33 to 113.38)
psy	0.60	34.50 (-45.75 to 114.76)
exe	0.54	25.73 (6.11 to 45.35)
nut	0.38	3.37 (-118.90 to 125.63)
exe+cog	0.39	1.47 (-141.34 to 144. 28)

I^2=66.0%
τ^2=0.16

-100 -75 0 75 100
Favours usual care — Favours intervention

Fig 3 | Treatment effects obtained from treatment level network meta-analysis for all outcomes (active interventions vs usual care; postoperative complications, length of stay in hospital, quality of life, physical recovery). P score measures of treatment ranking are also provided (range 0-1, where values nearer 1 indicate preferred interventions). cog=cognitive; exe=exercise; nut=nutrition; psy=psychosocial; UC=usual care

appendix 18). Heterogeneity was unchanged from the treatment level network meta-analysis (I^2=64.9%; τ^2=0.14).

Treatment rankings across outcomes
Based on P scores rankings, in treatment level network meta-analysis, isolated exercise and multicomponent interventions that included exercise were typically most probable to improve critical outcomes, while isolated psychosocial and cognitive interventions and usual care were less probable to improve outcomes (fig 4). Similar results were found in component network meta-analysis, with exercise and nutrition components most consistently ranked higher than other components across critical outcomes (appendix 19).

Sensitivity analyses
Sensitivity analyses showed that the beneficial effects of isolated exercise and nutritional prehabilitation on critical outcomes were robust to the impacts of risk of bias at the study level. The effect of nutrition interventions strengthened when studies assessed to have high risk of bias were removed from the network (appendix 20). Similarly, nutrition alone was found to further reduce length of stay when studies that had high risk of bias were removed; although the effect of exercise alone was reduced, and no studies assessed to have low risk of bias evaluated exercise plus psychosocial interventions. Health related quality of life and physical recovery networks became sparse when studies that had a high risk of bias were removed, resulting in widening of confidence intervals for exercise, although the magnitude of effect changed minimally in both analyses. Effect estimates for all other interventions generally either remained stable or moved toward the null in risk of bias sensitivity analyses across all outcomes.

Discussion
In this systematic review with treatment level network and component network meta-analyses of 186 randomised controlled trials with more than 15 000 participants, we found consistent directional evidence that prehabilitation interventions based on exercise or nutrition, or multicomponent interventions that included exercise, may meaningfully reduce complication rates and length of stay, and may improve health related quality of life and physical recovery for adults preparing for major surgery. While trial level risk of bias and imprecision reduced the certainty of our effect estimates, pooled effect sizes may represent

clinically meaningful improvements, and estimates for exercise and nutrition were robust after exclusion of high risk of bias trials. These data suggest that multicentre trials that have low risk of bias are required to confirm the benefits and generalisability of exercise, nutritional, and multicomponent prehabilitation, with high levels of certainty. Patients, clinicians, and health system leaders might concurrently consider strategies to feasibly implement promising prehabilitation strategies, especially exercise and nutrition, into preoperative care.

Prehabilitation is a complex intervention that typically consists of multiple components, requires substantial behaviour change for participants, relies on the expertise of staff delivering the programme, and requires skill development by participants. Additionally, prehabilitation can be delivered in various contexts (eg, home or facility based) and by various means (eg, direct coaching or virtual programming). While several elements must be considered in the development, evaluation, and implementation phases of a complex intervention, determining intervention efficacy remains a key phase.[53] In the case of prehabilitation, a lack of clarity regarding which components, or combinations of components, are efficacious in improving critical

outcomes remains despite publication of more than 100 randomised controlled trials and dozens of systematic reviews.[1 12 14 17 18 54] While this uncertainty is multifactorial, leading contributors are a lack of rigour in conduct of existing reviews, use of quantitative methods that do not align with the multicomponent nature of prehabilitation interventions, and risk of bias at the trial level.[1]

To overcome the limitations of previous reviews, we partnered with patients, clinicians, researchers, and health system leaders to inform development and evaluation of prehabilitation by applying best practices in systematic review method.[33] We identified all randomised controlled trials of prehabilitation using exercise, nutrition, or psychological or cognitive (or both) interventions that reported data for effect on outcomes that our partners considered critical (ie, complications, length of stay, health related quality of life, and physical recovery).[21] We then applied network meta-analysis and component network meta-analysis to identify what combinations of components, and individual components, were most likely to be efficacious in improving outcomes.[20 55] Our results show that the overall certainty in prehabilitation' efficacy remain mostly low to very low, in keeping with previous reviews.[1 14 56 57] However, important insights
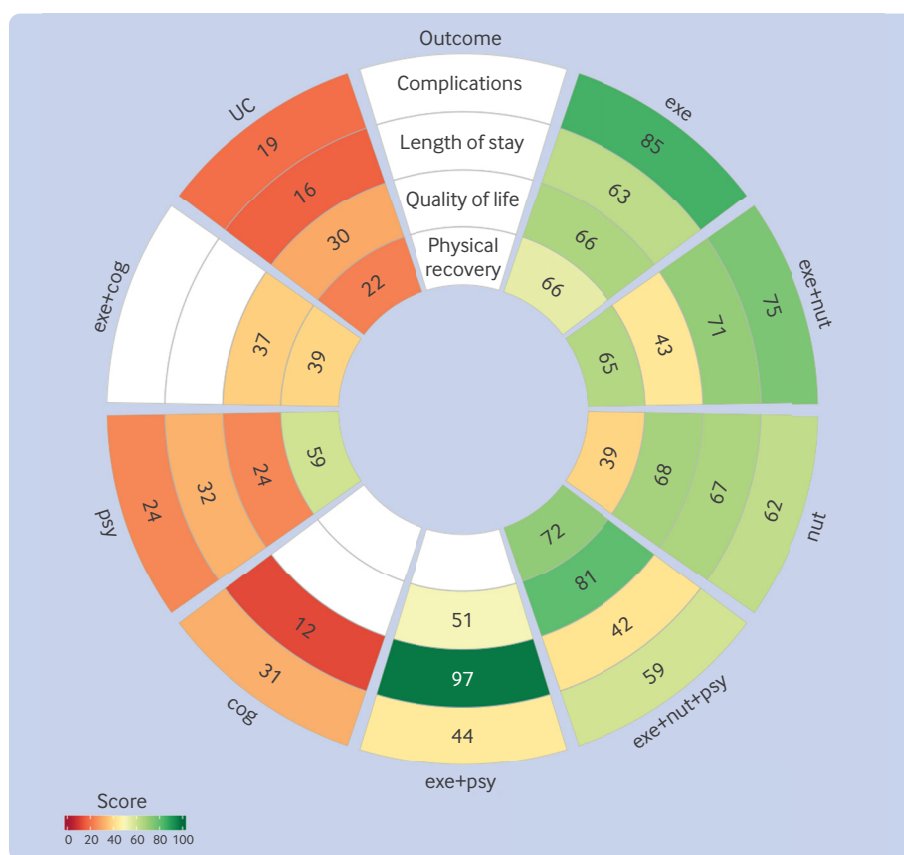

Fig 4 | Rank-heat plot obtained from treatment-level network meta-analysis. The rank heat plot presents a summary of P scores (range 0-100) for each intervention across outcomes, where darker shades of green represent more benefit and darker shades of red represent less benefit. cog=cognitive; exe=exercise; nut=nutrition; psy=psychosocial; UC=usual care

have emerged that should inform further development and refinement of prehabilitation interventions, their evaluation, and future implementation.

Multicentre prehabilitation trials that are low risk of bias are urgently needed. To reduce trial level risk of bias, trialists will need to focus on improving blinding of personnel and participants, while ensuring outcome data are complete. Although the impact of blinding on effect size estimates is uncertain, blinding may be especially important when outcomes are patient reported.[58] [59] While blinding in non-drug studies, especially for exercise interventions, is challenging, existing reviews synthesise a number of potential approaches.[60] [61] Building on these insights, low risk of bias trials should aim to estimate the effectiveness of exercise, nutrition, and multicomponent interventions that include exercise. Designs need to be adequately powered to detect meaningful differences in outcomes, particularly health related quality of life and physical recovery.

While certainty in pooled estimates for all components and combinations was downgraded because of within trial bias and imprecision across all outcomes, data for health related quality of life and physical recovery were especially sparse. The scarcity of patient reported and physical recovery data were especially pertinent as patient perspectives and core outcome sets increasingly stress the importance of patient reported and functional outcome measures after surgery.[7] [62-65] While our results suggest that prehabilitation likely has moderate effects on complications and length of stay, estimated prediction intervals indicate that intervention effects may vary substantially, further highlighting the urgent need for design and conduct of robust prehabilitation trials. In designing such multicentre trials, the generalisability of trial results would be enhanced through inclusion of equity deserving groups.[66] Adequate power may also be supported by using more conservative effect sizes (such as the upper boundary of the estimated 95% CIs[67]) in estimating sample size requirements given identified concerns about risk of bias and imprecision in underlying trials. Where available, established minimally important differences should be incorporated into trials designed to evaluate patient reported outcomes and functional recovery.[30] [68]

Previous reviews and our partners have identified that prehabilitation's efficacy in improving outcomes may be heterogenous.[1] [14] [18] [54] This heterogeneity, as well as the overall uncertainty identified in our review, is reflected in existing guidelines that discuss prehabilitation. In particular, current areas of focus are older age and the presence of frailty, as well as defined states of malnutrition.[69] [70] [71] In developing our protocol, partners postulated that surgery type may be an important potential effect modifier.[22] While statistical heterogeneity was substantial for all outcomes other than complications, accounting for surgery type as an effect modifier did not reduce statistical heterogeneity or improve model fit for any outcome. This suggests that surgery type may not be an important modifier of prehabilitation efficacy and might support design and evaluation of prehabilitation programmes that could span multiple surgical populations. Knowledge synthesis focused on newly emerging within-component interventions (eg, aerobic v strength v inspiratory muscle training as approaches to exercise) will further help to untangle heterogeneity.[57] Evaluation of other prioritised effect modifiers, as well as whether prehabilitation trials are reflective of target populations and their diversity, will require more consistent reporting of participant and programme characteristics. This reporting could be supported by development of prehabilitation specific reporting guidelines or extensions.[72]

Our findings also provide valuable insights for patients, clinicians, and health system leaders interested in actionable, evidence informed strategies to implement prehabilitation to improve outcomes. Most importantly, our data suggest that exercise is the prehabilitation component most likely to improve critical outcomes. This finding was consistent in primary results from treatment level network meta-analysis models, where isolated exercise was the most likely intervention to decrease complications, and multicomponent interventions that included exercise had the highest probability of improving length of stay, health related quality of life and physical recovery. In component network meta-analysis models, exercise was the only component to improve all critical outcomes in a statistically significant manner; had the greatest effect for complications, health related quality of life, and physical recovery; and had the highest or second highest probability of being the most efficacious component for three of four critical outcomes. In addition to exercise, nutritional prehabilitation should also be strongly considered because isolated nutrition and multicomponent interventions that included nutrition significantly improved all critical outcomes and had a high probability of being the most efficacious component in all component network meta-analysis analyses. For cognitive and psychosocial prehabilitation components, available evidence was sparse for all outcomes and these interventions were not widely applied across different surgical populations. Future research is needed to provide greater insights into the efficacy of isolated psychosocial and cognitive prehabilitation, as well as their roles in multicomponent programmes.

Strengths and limitations

This review was conducted according to best practices for systematic reviews, network meta-analyses, and component network meta-analyses. Our protocol was developed in partnership with patients, clinicians, health system leaders, and researchers, and was registered and published a priori. Partners were also involved in all subsequent stages of the review, including interpretation of results and reporting. As prehabilitation systematic reviews and randomised trials to date have rarely included patient partners and knowledge users, our integrated knowledge translation

informed approach could act as an exemplar for future partnered research. Through conduct and reporting of both network and component network meta-analyses, our results provide insights into the efficacy of both combinations of, and individual, prehabilitation components.

Despite inclusion of 186 trials providing data for more than 15 000 participants, certainty in our estimates was low to very low for most analyses. Low certainty ratings largely reflected study level risk of bias, especially blinding, which is a major consideration in patient reported and performance based outcomes, as well as imprecision. Heterogeneity within pooled components (eg, different types of exercise programmes were all pooled as exercise interventions) may also account for some of the estimated imprecision. Future syntheses could consider more granular exploration of subcomponents and combinations within subcomponents. Some heterogeneity could also be due to different timing of outcome ascertainment within prespecified follow up periods. The duration that an intervention must be implemented before surgery to be considered prehabilitation has no consensus. Our specification of seven days was thought to allow differentiation from related interventions such as enhanced recovery programmes and aligned with published knowledge synthesis. How inclusion of interventions spanning a different time frame (eg, under the assumption that more than seven days may be required to achieve efficacy) would impact pooled results in unknown. Sparse data related to psychological and cognitive prehabilitation, as well as limited representation of these components across surgery types, may have limited our ability to provide robust estimates of their efficacy.

Conclusions

In a systematic review with network and component network meta-analyses at the treatment level, we found evidence for prehabilitation efficacy with moderate effect sizes in reducing complications rates, and potentially clinically meaningful improvements in length of stay, health related quality of life, and physical recovery for adults preparing for major surgery. The strongest evidence supports isolated exercise and nutritional prehabilitation, as well as multicomponent interventions including exercise. Overall certainty in this evidence, however, was low to very low and reflects an urgent need for multicentre trials that are low risk of bias and appropriately powered to detect realistic and meaningful effect sizes in representative surgical populations.

Canadian Prehabilitation Knowledge Network: Sylvie Aucoin, Rebecca Auer, Paul Beaule, Gregory Bryson, Franco Carli, Antoine Eskander, Dean Fergusson, Julio Fiore Jr, Alan Forster, Jayna Holroyd-Leduc, Rachel Khadaroo, Manoj Lalu, Guillaume Martel, Colin McCartney, Julie Nantel, Stephane Poitras, Celena Scheede-Bergdahl, Monica Taljaard, Duminda Wijeysundera, Shamsuddin Akhtar, Marlis Atkins, Carlota Basualdo-Hammond, Mary Brindle, Melani Gillam, Leah Gramlich, Timothy Jackson, Cameron Love, Dolores McKeen, Amanda Meliambo, Husein Moloo, Ronald Moore, John Muscedere, Risa Shorr, Tom Wallace, Emily Hladkowicz, Al Crawford, Mandy Li, Cian Devine, Taylor Gilmore, Rahul Mor, Julien LeBlanc, David Schramm, Lana Ramic, Marta I Berrio Valencia, Emily Liang, Nathaniel Neilipovitz, Samantha Dunlop.

Canadian Perioperative Anaesthesia Clinical Trials (PACT) Group: W Scott Beattie, André Denault, Richard Hall, C David Mazer, Stuart McCluskey, Kathryn Sparrow, Jessica Spence, Alexis Turgeon, Faraj Abdallah, Jamal Alkadri, Saleh Al-Nahdi, Shelly Au, Siniana Avramescu, Leyla Baghirzada, Hema Bagry, Jonathan Bailey, Daniel Bainbridge, Alex Bak, Gabriele Baldinii, Jean-Marie Bamvita, Jillian Banfield, Justyna Bartoszko, Michael Bautista, Jean Beaubien, William Beaubien-Souligny, Nicolas Beaudet, Pierre Beaulieu, Emilie Belley-Côté, Gianluca Bertolizio, Sylvain Boet, Guillaume Bousquet-Dion, David Boyle, Connor Brenna, Scott Brudney, Norman Buckley, Neville Burke, Jean Bussières, Matthew Cameron, Daenis Camire, Francois M Carrier, Françoise Chagnon, Nidhi Charan, Anton Chau, Marshall Cheng, Gilles Chiniara, Janice Chisholm, Michelle Chiu, Stephen Choi, Chris Christodoulou, Jason Chui, Frances Chung, Hance Clarke, Etienne Couture, Brian Cuthbertson, Frédérick D'Aragon, Pieter de Jager, Megan Deck, Ainsley Decker, Alain Deschamps, Derek Dillane, George Djaiani, Gary Dobson, Pierre Drolet, Daniel Dubois, Catherine Duclos, Laura Duggan, Tristan Dumbarton, Deborah DuMerton Shore, Kaylene Duttchen, Darcie Earle, Nicola Edwards, Alana Flexman, John Fuller, Marie-Pierre Gagne, Nicole Gibson, Andres-Felipe Gil, Ian Gilron, Martin Girard, Bryan Glezerson, Neil Goldenberg, Talha Gondal, Matthias Gorges, Daniel Gottesman, James Green, Alexander Gregory, Hilary Grocott, Alexander Grunfeld, Gregory Hare, Tyrone Harrison, Peter Hedlin, Thomas Hemmerling, Jennifer Héroux, Orlando Hung, Michael Jacka, Angela Jerath, Naheed Jivraj, Keyvan Karkouti, Lilia Kaustov, Janny Ke, Brent Kennedy, Brad Kerr, James Kim, Margot Klemmer, Stephen Kowalski, Karim Ladha, Wing Lam, Danielle Lapierre, Michael Law, Jean-Sebastian Lebon, Vincent Lecluyse, Susan M. Lee, Alexandre Lefebvre, Christian Lehmann, Jordan Leitch, Francois Lellouche, Edmond Li, Andy Liu, Nagappa Mahes, Heather McDonald, William McKay, Sarah McMullen, Jason McVicar, Andrew Milne, Perseus Missirlis, Glenio Mizubuti, Peter Moliner, Corentin Monfort, Janice Montbriand, Michelle Mozel, Maliha Muneer, Allana Munro, Thomas Mutter, Bhanu Nalla, Wayne Nates, David Neilpovitz, Angela Neufeld, Curtis Nickel, Jennifer O'Brien, Beverley Orser, Angélica Ostiguy, Charles Overbeek, Jean P. Gelinas, Joel Parlow, James Paul, Heather Pierce, Gilles Plourde, Christopher Prabhakar, Jeremy Pridham, Mateen Raazi, Rakesh Sondekoppam, Ramiro Arellano, Tim Ramsay, Saifee Rashiq, Ravi Jayas, Ravi Taneja, Rebecca Grey, Rene Martin, Renee El-Gabalawy, Tracey Rice, Richard N Merchant, David Roach, Roanne Preston, Roberta DiDonato, Ron Ree, Ronald George, Rosaleen Chun, David Rosen, Roupen Hatzakorzian, Jean-Dennis Roy, Olivier Royer, Rudy Noppens, Samantha Russell, Ruth Graham, Ryan McGinn, Ryan Ramos, Tarit Saha, Sonia Sampson, Corey Sawchuk, Michael Schmidt, Thomas Schricker, Stephan Schwarz, Seyed Mahdi Sedighi, Herman Sehmbi, Daniel Sellers, Harsha Shanthanna, Faisal Siddiqui, Naveed Siddiqui, Surita Sidhu, I Singh, Stephanie Sobotie, Sabri Soussi, Summer Sukh Brar, Louise Sun, Terri Sun, Varun Suresh, Vanessa Sweet, Linda Szabo, Edmond Tan, Jordan Tarshis, Mullein Thorleifson, Andrea Todd, Diem Tran, Victor Tran, Vatsal Trivedi, Vishal Uppal, Michaël Verret, Victor Neira, Dianshi Wang, George Wang, Louie Wang, Geoff Warden, Marcin Wasowicz, Jean Wong, Kim Wong, Vincent Wourms, Stuart Wright, Homer Yang, Stephen Yang, Cynthia Yarnold, Doreen Yee.

1   McIsaac DI, Gill M, Boland L, et al, Prehabilitation Knowledge Network. Prehabilitation in adult patients undergoing surgery: an umbrella review of systematic reviews. *Br J Anaesth* 2022;128:244-57. doi:10.1016/j.bja.2021.11.014

2   Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? *Anaesthesia* 2019;74(Suppl 1):20-6. doi:10.1111/anae.14505

3   Fleurent-Grégoire C, Burgess N, McIsaac DI, et al. Towards a common definition of surgical prehabilitation: a scoping review of randomised trials. *Br J Anaesth* 2024;133:305-15. doi:10.1016/j.bja.2024.02.035

4   Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;372:139-44. doi:10.1016/S0140-6736(08)60878-8

5   Boney O, Bell M, Bell N, et al. Identifying research priorities in anaesthesia and perioperative care: final report of the joint National Institute of Academic Anaesthesia/James Lind Alliance Research Priority Setting Partnership. *BMJ Open* 2015;5:e010006. doi:10.1136/bmjopen-2015-010006

6   McKeen DM, Banfield JC, McIsaac DI, et al, Perioperative Anesthesia Clinical Trials Group (PACT). Top ten priorities for anesthesia and perioperative research: a report from the Canadian Anesthesia Research Priority Setting Partnership. *Can J Anaesth* 2020;67:641-54. doi:10.1007/s12630-020-01607-6

7   Raichurkar P, Denehy L, Solomon M, et al, Prehabilitation Expert Collaborative. Research Priorities in Prehabilitation for Patients Undergoing Cancer Surgery: An International Delphi Study. *Ann Surg Oncol* 2023;30:7226-35. doi:10.1245/s10434-023-14192-x

8   Hallet J, Jerath A, Turgeon A, et al. The association between anesthesia provider-volume and short-term outcomes in complex gastrointestinal cancer surgery: a population-based analysis. *JAMA Surg* (Accepted).

9   Wijeysundera DN, Pearse RM, Shulman MA, et al, METS study investigators. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018;391:2631-40. doi:10.1016/S0140-6736(18)31131-0

10   International Surgical Outcomes Study group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016;117:601-9. doi:10.1093/bja/aew316

11   Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. *World J Surg* 2019;43:1661-8. doi:10.1007/s00268-019-04950-y

12   Punnoose A, Claydon-Mueller LS, Weiss O, Zhang J, Rushton A, Khanduja V. Prehabilitation for patients undergoing orthopedic surgery: a systematic review and meta-analysis. *JAMA Netw Open* 2023;6:e238050. doi:10.1001/jamanetworkopen.2023.8050

13   Marmelo F, Rocha V, Moreira-Gonçalves D. The impact of prehabilitation on post-surgical complications in patients undergoing non-urgent cardiovascular surgical intervention: Systematic review and meta-analysis. *Eur J Prev Cardiol* 2018;25:404-17. doi:10.1177/2047487317752373

14   Gillis C, Buhler K, Bresee L, et al. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. *Gastroenterology* 2018;155:391-410.e4. doi:10.1053/j.gastro.2018.05.012

15   Barnes K, Hladkowicz E, Dorrance K, et al. Barriers and facilitators to participation in exercise prehabilitation before cancer surgery for older adults with frailty: a qualitative study. *BMC Geriatr* 2023;23:356. doi:10.1186/s12877-023-03990-3

16   Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008. doi:10.1136/bmj.j4008

17   Falz R, Bischoff C, Thieme R, et al. Effects and duration of exercise-based prehabilitation in surgical therapy of colon and rectal cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol* 2022;148:2187-213. doi:10.1007/s00432-022-04088-w

18   Clifford K, Woodfield JC, Tait W, Campbell HA, Baldi JC. Association of preoperative high-intensity interval training with cardiorespiratory fitness and postoperative outcomes among adults undergoing major surgery: a systematic review and meta-analysis. *JAMA Netw Open* 2023;6:e2320527. doi:10.1001/jamanetworkopen.2023.20527

19   Gillis C, Hasil L, Kasvis P, et al. Nutrition care process model approach to surgical prehabilitation in oncology. *Front Nutr* 2021;8:644706. doi:10.3389/fnut.2021.644706

20   Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biom J* 2020;62:808-21. doi:10.1002/bimj.201800167

21   Boland L, Kothari A, McCutcheon C, Graham ID, Integrated Knowledge Translation Research Network. Building an integrated knowledge translation (IKT) evidence base: colloquium proceedings and research direction. *Health Res Policy Syst* 2020;18:8. doi:10.1186/s12961-019-0521-3

22   McIsaac DI, Hutton B, Veroniki A, et al, Prehabilitation Knowledge Network Authorship Group. Identifying relative efficacy of components of prehabilitation in adult surgical patients: protocol for a systematic review and component network meta-analysis. *BMJ Open* 2022;12:e068797. doi:10.1136/bmjopen-2022-068797

23   Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84. doi:10.7326/M14-2385

24   Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71

25   Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ* 2017;358:j3453. doi:10.1136/bmj.j3453

26   Graham ID, Tetroe J, Pearson A. *Turning Knowledge Into Action: Practical Guidance on how to Do Integrated Knowledge Translation Research.* 1st ed. Lippincott Williams & Wilkins, 2014.

27   McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;75:40-6. doi:10.1016/j.jclinepi.2016.01.021

28   Rosenthal JA. Qualitative descriptors of strength of association and effect size. *J Soc Serv Res* 1996;21:37-59. doi:10.1300/J079v21n04_02.

29   Maruish ME. *User's Manual for the SF-36v2 Health Survey.* Quality Metric Incorporated, 2011.

30   Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017;23:377-81. doi:10.1111/jep.12629

31   Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006;54:743-9. doi:10.1111/j.1532-5415.2006.00701.x

32   Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. doi:10.1186/1471-2288-14-135

33   Higgins J, Thomas J, Chandler J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* Cochrane Collaboration, 2019. doi:10.1002/9781119536604.

34   Harrer M. *Doing meta-analysis with R: a hands-on guide.* 1st ed. CRC Press/Taylor & Francis Group, 2022.

35 Higgins JPT, Altman DG, Gøtzsche PC, et al, Cochrane Bias Methods GroupCochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928-5928. doi:10.1136/bmj.d5928

36 Balduzzi S, Rücker G, Nikolakopoulou A, et al. netmeta: An *R* package for network meta-analysis using frequentist methods. *J Stat Softw* 2023;106. doi:10.18637/jss.v106.i02.

37 van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods* 2016;7:80-93. doi:10.1002/jrsm.1167

38 Béliveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. *BMC Med Res Methodol* 2019;19:196. doi:10.1186/s12874-019-0829-2

39 Murad MH, Wang Z, Chu H, Lin L. When continuous outcomes are measured using different scales: guide for meta-analysis and interpretation. *BMJ* 2019;364:k4817. doi:10.1136/bmj.k4817

40 Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549-549. doi:10.1136/bmj.d549

41 Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98-110. doi:10.1002/jrsm.1044

42 Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932-44. doi:10.1002/sim.3767

43 Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013;13:35. doi:10.1186/1471-2288-13-35

44 Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* 2016;7:55-79. doi:10.1002/jrsm.1164

45 Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;15:58. doi:10.1186/s12874-015-0060-8

46 Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. *J Clin Epidemiol* 2016;76:193-9. doi:10.1016/j.jclinepi.2016.02.016

47 NMAstudio. https://www.nmastudioapp.com/ (accessed 19 March 2024)

48 Friedrich JO, Adhikari NKJ, Beyene J. Ratio of geometric means to analyze continuous outcomes in meta-analysis: comparison to mean differences and ratio of arithmetic means using empiric data and simulation. *Stat Med* 2012;31:1857-86. doi:10.1002/sim.4501

49 Petropoulou M, Rücker G, Weibel S, Kranke P, Schwarzer G. Model selection for component network meta-analysis in connected and disconnected networks: a simulation study. *BMC Med Res Methodol* 2023;23:140. doi:10.1186/s12874-023-01959-9

50 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082. doi:10.1371/journal.pmed.1003082

51 Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Syst Rev* 2020;16:e1080. doi:10.1002/cl2.1080

52 Chiocchia V, Holloway A, Salanti G. Semi-automated assessment of the risk of bias due to missing evidence in network meta-analysis: a guidance paper for the ROB-MEN web-application. *BMC Med Res Methodol* 2023;23:223. doi:10.1186/s12874-023-02038-9

53 Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021;374:n2061. doi:10.1136/bmj.n2061

54 Freeman SC, Scott NW, Powell R, Johnston M, Sutton AJ, Cooper NJ. Component network meta-analysis identifies the most effective components of psychological preparation for adults undergoing surgery under general anesthesia. *J Clin Epidemiol* 2018;98:105-16. doi:10.1016/j.jclinepi.2018.02.012

55 Ades AE, Welton NJ, Dias S, et alTwenty years of network meta-analysis: Continuing controversies and recent developments. *Res Synth Methods* 2024;jrsm.1700. doi:10.1002/jrsm.1700

56 Stiger RJ, Williams MA, Gustafson OD, Woods A, Collett J. The effectiveness of prehabilitation interventions on biopsychosocial and service outcomes pre and post upper gastrointestinal surgery: a systematic review. *Disabil Rehabil* 2024;46:5676-99. doi:10.1080/09638288.2024.2310765

57 Ricci C, Alberici L, Serbassi F, et al. Physical prehabilitation in patients who underwent major abdominal surgery: a comprehensive systematic review and component network meta-analysis using GRADE and CINeMA Approach. *Ann Surg Oncol* 2024;31:1725-38. doi:10.1245/s10434-023-14632-8

58 Moustgaard H, Clayton GL, Jones HE, et al. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. *BMJ* 2020;368:l6802. doi:10.1136/bmj.l6802

59 Participants in the 5th Cochrane Rehabilitation Methodological Meeting, Arienti C, Armijo-Olivo S, et al.The influence of bias in randomized controlled trials on rehabilitation intervention effect estimates: what we have learned from meta-epidemiological studies. *Eur J Phys Rehabil Med* 2024;60:135-44. doi:10.23736/S1973-9087.23.08310-7

60 Hohenschurz-Schmidt D, Draper-Rodi J, Vase L, et al. Blinding and sham control methods in trials of physical, psychological, and self-management interventions for pain (article I): a systematic review and description of methods. *Pain* 2023;164:469-84. doi:10.1097/j.pain.0000000000002723

61 Armijo-Olivo S, Fuentes J, da Costa BR, Saltaji H, Ha C, Cummings GG. Blinding in physical therapy trials and its association with treatment effects: a meta-epidemiological study. *Am J Phys Med Rehabil* 2017;96:34-44. doi:10.1097/PHM.0000000000000521

62 Abdellatif S, Hladkowicz E, Lalu MM, et alPatient-prioritization of routine and patient-reported postoperative outcome measures: a prospective, nested cross-sectional study. *Can J Anaesth* 2021; doi:10.1007/s12630-022-02191-7

63 Myles PS, Boney O, Botti M, et al, StEP–COMPAC Group. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: patient comfort. *Br J Anaesth* 2018;120:705-11. doi:10.1016/j.bja.2017.12.037

64 Moonesinghe SR, Jackson AIR, Boney O, et al, Standardised Endpoints in Perioperative Medicine-Core Outcome Measures in Perioperative and Anaesthetic Care (StEP-COMPAC) Group. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine initiative: patient-centred outcomes. *Br J Anaesth* 2019;123:664-70. doi:10.1016/j.bja.2019.07.020

65 McNair AGK, Whistance RN, Forsythe RO, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. *PLoS Med* 2016;13:e1002071. doi:10.1371/journal.pmed.1002071

66 Schwartz AL, Alsan M, Morris AA, Halpern SD. Why Diverse Clinical Trial Participation Matters. *N Engl J Med* 2023;388:1252-4. doi:10.1056/NEJMp2215609

67 Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 2012;65:301-8. doi:10.1016/j.jclinepi.2011.07.011

68 Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life-a systematic review. *J Clin Epidemiol* 2017;89:188-98. doi:10.1016/j.jclinepi.2017.06.009

69 American College of Surgeons. Strong for Surgery. Chicago, Il: American College of Surgeons.

70 Perioperative Care of People Living with Frailty. Centre for perioperative care. https://cpoc.org.uk/guidelines-resources-guidelines/perioperative-care-people-living-frailty (accessed 27 March 2023)

71 NIHR; Royal College of Anaesthetists; Macmillan Cancer Support. Prehabilitation for people with cancer: Principles and guidance for prehabilitation within the management and support of people with cancer. 2019.

72 Engel D, Testa GD, McIsaac DI, et al. Reporting quality of randomized controlled trials in prehabilitation: a scoping review. *Perioper Med (Lond)* 2023;12:48. doi:10.1186/s13741-023-00338-8

Web appendix: Extra material supplied by authors