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Review

Time to Prioritise Quality Over Quantity in Prehabilitation Trials: A Literature Review

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Abstract

The increasing number of prehabilitation randomised controlled trials (RCTs) for cancer surgery patients emphasises the need for high-quality evidence. Therefore, this study aims to assess reporting quality and risk of bias in prehabilitation RCTs.

A comprehensive search was conducted across multiple databases, including MEDLINE, Embase, The Cochrane Library, CINAHL, AMED, and PsycINFO to identify RCTs evaluating the effectiveness of exercise, nutrition, and/or psychological interventions on postoperative complications and/or length of hospital stay in adult patients undergoing cancer surgery. Trials were assessed for risk of bias, reporting quality and other relevant metrics.

Of the 74 included RCTs, 55 had a high risk of bias. Deviations from intended interventions (55%) and missing outcome data (32%) were the most frequently identified items with a high risk of bias. Only nine of 13 TIDieR items were adequately reported, and just nine RCTs provided information on intervention modifications. 55% of trials provided a protocol, with 68% altering primary and/or secondary aims.

Prehabilitation RCTs exhibit poor reporting quality and high risk of bias. More transparent trials are needed to assess the effectiveness of prehabilitation programs. Identifying barriers to improving the quality would assist in enhancing the reliability of future trials.

Keywords: Adult, preoperative exercise, checklist, length of stay, postoperative complications, randomised controlled trials as topic

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Major surgery leads to significant haemodynamic and metabolic disturbances. To date, most interventions intended to improve postoperative outcomes have focused on modifications to anaesthesia or the surgical procedure itself. Major postoperative concerns include increased mortality and postoperative complication rate, longer length of stay and slow recovery of functional status.[1] Prehabilitation, a healthcare discipline which focuses on optimising functional capacity before surgery, is a novel method of addressing these issues. For example, cardiopulmonary exercise can be used to mitigate postoperative declines in cardiorespiratory fitness, and supplementation of preoperative nutrition may reduce infectious complications and mortality rates.[2, 3] Preoperative immunonutrition involves

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the provision of amino acids and nucleotides in the preoperative period and is thought to counteract excessive inflammation caused by the surgical stress response.[4]

In the past two decades, the number of trials referring to prehabilitation has increased by a factor of around 30-50.[5, 6] However, the amount of literature on the quality of these studies is limited. A recent work published by Cuijpers et al (2022), assessing the reporting quality of 12 prehabilitation trials[7] using a checklist derived from the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement,[8, 9] found the reporting quality to be poor. Only 15 out of 24 items assessed were reported by more than half of the identified trials. One particular item, "feasibility criteria", was only reported by four out 12 trials (33.3%). Previous reviews of randomised controlled trials (RCTs) in surgery or anaesthetics have revealed similarly poor reporting quality and high risk of bias. Specifically, protocol registration, protocol adherence, recruitment status, funding status, randomisation and blinding presented a high risk of bias.[10-13] Common reasons for these findings include conduct difficulties (e.g., difficulty in standardising surgical procedures, lack of placebo and blinding, varying experience levels of surgeons,[14, 15] and inadequate funding.[15] High risk of bias can also occur due to unavoidable methodological processes, for example where blinding is impractical due to the inherent requirements of exercise-based prehabilitation interventions.

With the rapidly increasing number of trials in prehabilitation, it is important to ensure the trials adhere to high standards of methodological and reporting quality. Chalmers et al., (2009) found that 85% of global investment in research is wasted, with a substantial amount of waste attributable to methodological flaws which jeopardise study validity, thus limiting their usefulness in evidence-based medicine.[16] In response to such findings, several tools and checklists (e.g., CONSORT and the Template for Intervention Description and Replication (TIDieR)) have been introduced in the past decade to improve transparency and methodological/reporting quality, with the goal of increasing reporting quality and lowering risk of bias.[17, 18]

To address these issues, a review was conducted to determine the risk of bias and reporting quality of the interventions in RCTs investigating the effectiveness of prehabilitation interventions in cancer patients undergoing surgery.

Methods

Study Design

We performed an analysis of RCTs in cancer patients undergoing prehabilitation. The protocol for the review was published on the Open Science Framework at https://osf.io/9p8gf. This review was written according to the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis.[19]

Article Selection Process

We performed a search in MEDLINE, Embase, The Cochrane Library, CINAHL, AMED and PsycINFO. The search strategy was developed in conjunction with an experienced librarian from The University of Sydney and was based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions for randomised controlled trials, combined with medical subject headings and keywords to identify potential articles.[18] In addition to the electronic medical databases searches, forward and backwards citation tracking was conducted for additional relevant articles.

This review identified RCTs investigating the effectiveness of preoperative exercise, nutrition and/or psychological interventions on postoperative complications and/or length of hospital stay in adult cancer patients undergoing surgery in the thorax, abdomen and pelvic regions. Quasi-randomised controlled trials, trials including samples with >5% presenting with non-malignant disease, and interventions delivered during the intraoperative and postoperative periods were excluded.

The complete screening process was performed by two independent review authors (DS and JB) and was conducted using the Covidence online software (Covidence, Melbourne, VIC, Australia[20]). In the first stage, titles and abstracts were screened for eligibility and clearly irrelevant trials were excluded. In the second stage, full-text articles were obtained for each potentially eligible study and assessed to check if the study fulfilled the inclusion criteria. Consensus between the two reviewers were used to resolve any disagreement. If consensus could not be reached, a third reviewer (MS or CK) was consulted. We provide the primary exclusion reason for the exclusion of all full text trials screened in Figure 1. There were no language or publication restrictions applied to the search strategy, and translations were attempted for non-English published trials.

Data Collection

Two review authors (WJ and SK) extracted information on author, journal (e.g., impact factor) and study characteristics, for each study, using a data extraction form developed in Microsoft Excel (Microsoft Corp., Redmond, Washington, USA), and the data was checked by two other reviewers (MS and CK). We resolved discrepancies by reviewer discussion. The data extraction form was also used to collect data on risk of bias with the Risk of Bias 2 (RoB 2) tool[17] and the TIDieR checklist.[21] Risk of bias assessment was conducted using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) tool. Each study was rated at 'low', 'some concerns' or 'high' risk of bias for each of the five domains (randomisation, deviation, missing outcome data, measurement and selection); this was followed by an overall judgement for the study. Domain 2 was assessed twice for all trials, once to consider the effect of 'assignment to inter-

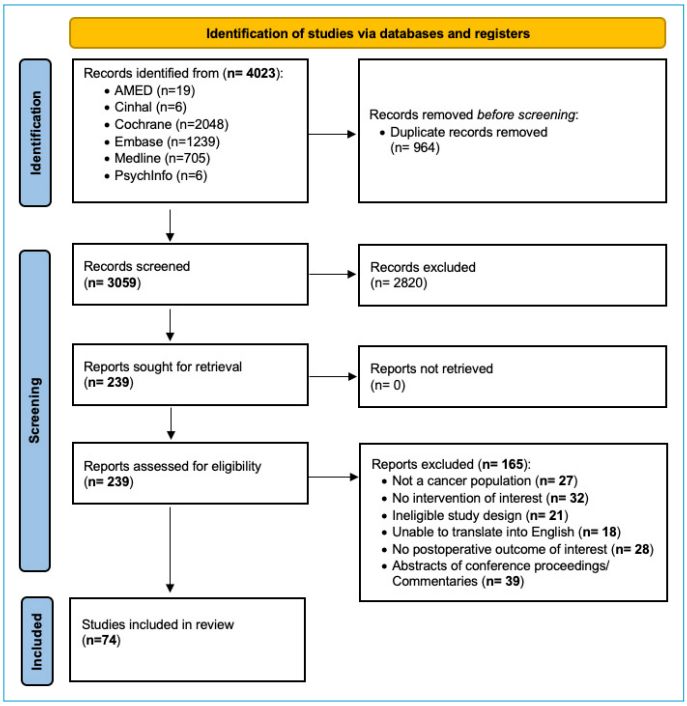

Figure 1. PRISMA Flow Diagram.

vention' on risk of bias due to deviations from the intended interventions, and a second time to examine the effect of 'adherence to intervention'. For every study, each of the 12 TIDieR items were rated as 'present', 'absent', 'not applicable', or 'insufficient information'.

Each published trial was also compared with its publicly available protocol (if available) to assess whether the primary and secondary aims were maintained, whether the planned sample size was achieved and time between trial commencement year and year of publication. The other collected variables of interest were journal impact factor, journal specialty, profession delivering the intervention, country of study, centre status (single or multi-centre), type of cancer, trial commencement year, funding and conflict of interest.

Data Synthesis

All data was synthesised descriptively. All outcomes of interest are presented as frequency (percentage). An ad-hoc analysis was performed to compare the risk of bias of trials published before and after the introduction of the Cochrane Risk of Bias 2 instrument (August 2019).[17]

Results

Study Characteristics

A total of 74 trials were identified.[22-95] The PRISMA flow diagram for the article selection process is shown in Figure 1. The included trials were published between 1982 and 2021, with a mean sample size of 53 (range: 19 - 241). The characteristics of the included trials are presented in Table 1.

Risk of Bias

A total of 55 trials (74%) were rated as having high risk of bias, with most of the bias observed in Domain 2: bias due to deviations from intended interventions (55% were rated at high risk when effect of adherence to intervention was considered) and Domain 3: bias due to missing outcome data (32% were rated at high risk in this domain). The summary information for risk of bias is presented in Figure 2 and Supplements 1-3. When assignment to intervention was the focus of Domain 2, 32%, 38% and 30% of trials were rated as low, some concerns and high risk of bias, respectively. However, when adherence was considered, the percentages of trials rated as low, some concerns and high risk of bias were 45%, 0% and 55% respectively. Furthermore, when the effect of adherence was assessed, only one trial was found to be at a low risk of bias, whereas no studies were at a low risk of bias when the effect of assignment was considered.[56] Conversely, 72 out of 73 trials (99%) were rated as having low risk of bias for 'bias in measurement of outcome'.

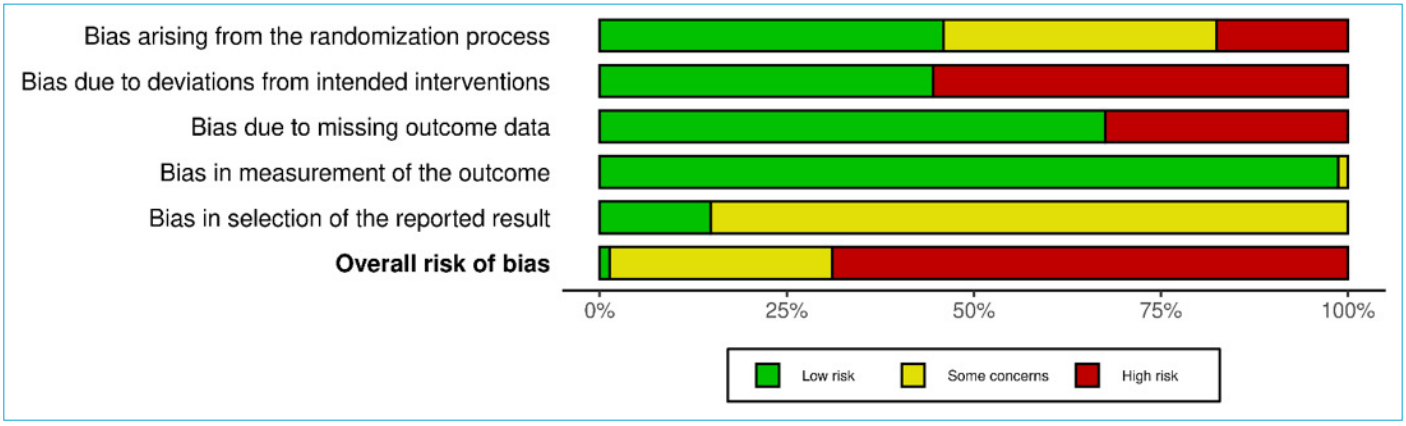

Figure 2. Risk of Bias Summary with Domain 2 Examining Adherence.

Table 1. Study Characteristics

Author, year	Registered protocol	Changed primary/ secondary outcomes	Planned N (Final N)	Journal specialty (impact factor)	Profession delivering intervention	Population	Recruitment start date	Funding	Conflicts of Interest*
Aiko, 2012	NR	NR	NR (26)	Gastroenterology (2.80)	NR	Country: Japan Site: Single-centre Type of cancer: Oesophageal	NR	NR	NR
Amraoui, 2018	Yes	No	150 (150)	General medicine (13.40)	Anaesthetist	Country: France Site: Multicentre Type of cancer: Breast	1/09/2014	Present	Yes
Ashida, 2019	Yes	No	24 (20)	General surgery (2.50)	NR	Country: Japan Site: Single-centre Type of cancer: Pancreatic	NR	Present	NR
Ausania, 2019	NR	NR	NR (40)	Gastroenterology (2.10)	Multidisciplinary	Country: Spain Site: Single-centre Type of cancer: Pancreatic	NR	Absent	NR
Banerjee, 2018	NR	NR	NR (55)	Oncology (2.70)	Exercise physiologist	Country: United Kingdom Site: Multicentre Type of cancer: Bladder	1/01/2012	NR	No
Bartels, 2004	NR	NR	NR (47)	Nutrition science (7.05)	NR	Country: Germany Site: Single-centre Type of cancer: Liver	NR	NR	NR
Barth, 2019	Yes	Yes	110 (60)	Surgery (13.79)	Dietician	Country: United States Site: Multicentre Type of cancer: Liver	1/06/2012	NR	No
Benzo, 2011	NR	NR	NR (19)	Oncology (5.71)	NR	Country: United States Site: Multicentre Type of cancer: Lung	NR	Present	No
Blackwell, 2020	Yes	Yes	48 (40)	Urology & Nephrology (5.55)	Doctor	Country: United Kingdom Site: NR Type of cancer: Mixed	1/08/2016	NR	No
Braga, 2002	NR	NR	NR (100)	Surgery (3.36)	NR	Country: Italy Site: NR Type of cancer: CRC	NR	NR	NR
Braga, 2012	Yes	Yes	36 (36)	Surgery (3.36)	NR	Country: Italy Site: NR Type of cancer: Pancreatic	NR	NR	NR
Burden, 2011	NR	NR	NR (116)	Nutrition science (3.09)	NR	Country: United Kingdom Site: NR Type of cancer: CRC	NR	Present	No
Burden, 2017	Yes	Yes	126 (101)	Geriatrics & Gerontology (12.51)	Nutritionist	Country: United Kingdom Site: Multicentre Type of cancer: CRC	1/11/2013	Present	Yes

Table 1. Cont.

Author, year	Registered protocol	Changed primary/ secondary outcomes	Planned N (Final N)	Journal specialty (impact factor)	Profession delivering intervention	Population	Recruitment start date	Funding	Conflicts of Interest*
Chen, 2017	NR	NR	NR (120)	General medicine (0.22)	NR	Country: China Site: NR Type of cancer: Gastric	1/01/2014	Present	NR
Christensen, 2019	Yes	Yes	50 (50)	Surgery (6.94)	Personal trainer	Country: Denmark Site: Single-centre Type of cancer: GEJ	1/04/2016	Present	Yes
Dettling, 2013	NR	NR	NR (83)	Physiotherapy (1.87)	Physiotherapy	Country: Netherlands Site: NR Type of cancer: Oesophageal	NR	NR	NR
Dronkers, 2010	NR	NR	NR (42)	Rehabilitation medicine (1.77)	Physiotherapy	Country: Netherlands Site: Single-centre Type of cancer: CRC	NR	NR	NR
Dunne, 2016	Yes	Yes	40 (37)	Surgery (6.94)	NR	Country: United Kingdom Site: Type of cancer:	1/07/2011	Present	No
Fan, 1989	NR	NR	NR (40)	Nutrition science (8.23)	NR	Country: Hong Kong Site: NR Type of cancer: Liver	NR	NR	NR
Fang, 2013	NR	NR	NR (44)	Basic principles of medicine (6.78)	NR	Country: China Site: Single-centre Type of cancer: Lung	NR	NR	NR
Fujitani, 2012	Yes	Yes	231 (231)	Surgery (6.94)	NR	Country: Japan Site: NR Type of cancer: Gastric	NR	NR	No
Garcia, 2017	Yes	Yes	22 (22)	Rehabilitation medicine (1.77)	Physiotherapy	Country: Spain Site: NR Type of cancer: Lung	1/10/2013	Present	No
Giger-Pabst, 2013	NR	NR	NR (108)	Nutrition science (3.42)	NR	Country: Switzerland Site: Multicentre Type of cancer: Mixed	1/01/2006	Present	Yes
Gil, 1997	NR	NR	NR (41)	Nutrition science (3.42)	NR	Country: Spain Site: Single-centre Type of cancer: Mixed	1/01/1987	NR	NR
Gunerhan, 2009	NR	NR	NR (33)	Gastroenterology (5.74)	NR	Country: Turkey Site: Single-centre Type of cancer: Gastric	NR	NR	NR
Hamamoto, 2018	Yes	No	64 (64)	General surgery (3.75)	NR	Country: Japan Site: NR Type of cancer: CRC	1/07/2013	NR	No

Table 1. Cont.

Author, year	Registered protocol	Changed primary/ secondary outcomes	Planned N (Final N)	Journal specialty (impact factor)	Profession delivering intervention	Population	Recruitment start date	Funding	Conflicts of Interest*
Hogan, 2020	Yes	Yes	108 (108)	Nutrition science (3.90)	Nutritionist	Country: Australia Site: Single-centre Type of cancer: Pelvic	1/08/2015	NR	No
Horvat, 2010	NR	NR	NR (68)	General medicine (1.17)	NR	Country: Slovenia Site: NR Type of cancer: CRC	NR	NR	No
Huang, 2017	NR	NR	NR (80)	Surgery (13.40)	NR	Country: China Site: Single-centre Type of cancer: Lung	1/03/2015	Present	No
Huang, 2017b	NR	NR	NR (90)	Respiratory medicine (2.37)	Multidisciplinary	Country: China Site: Single-centre Type of cancer: Lung	1/11/2015	Present	No
Jin, 1999	NR	NR	NR (46)	Nutrition science (3.90)	NR	Country: China Site: Single-centre Type of cancer: Mixed	NR	Present	NR
Kabata, 2014	Yes	Yes	102 (102)	Oncology (2.70)	NR	Country: Poland Site: Single-centre Type of cancer: Mixed	1/05/2011	NR	No
Karlsson, 2019	Yes	Yes	30 (21)	General medicine (3.75)	Physiotherapy	Country: Sweden Site: Single-centre Type of cancer: CRC	1/09/2016	Present	No
Kaya, 2016	NR	NR	NR (58)	Cardiothoracic surgery (4.62)	NR	Country: Turkey Site: Single-centre Type of cancer: Lung	1/01/2014	Absent	No
Kikuchi, 2016	Yes	Yes	80 (77)	Oncology (5.34)	NR	Country: Japan Site: Single-centre Type of cancer: Liver	1/10/2011	NR	NR
Kitagawa, 2017	Yes	Yes	29 (29)	Surgery (0.91)	NR	Country: Japan Site: Single-centre Type of cancer:	1/05/2013	NR	No
Koet, 2021	NR	NR	NR (75)	Oncology (2.70)	Nursing	Country: Netherlands Site: Single-centre Type of cancer: CRC	1/03/2013	NR	No
Lai, 2017	Yes	No	288 (60)	Surgery (2.20)	Physiotherapy	Country: China Site: Single-centre Type of cancer: Lung	1/06/2015	NR	No
Lai, 2017b	Yes	Yes	288 (101)	Cardiothoracic surgery (1.98)	NR	Country: China Site: Single-centre Type of cancer: Lung	NR	Present	No

Table 1. Cont.

Author, year	Registered protocol	Changed primary/ secondary outcomes	Planned N (Final N)	Journal specialty (impact factor)	Profession delivering intervention	Population	Recruitment start date	Funding	Conflicts of Interest*
Lai, 2019	Yes	No	200 (68)	Translational medicine (8.44)	Physiotherapy	Country: China Site: NR Type of cancer: Lung	NR	NR	No
Licker, 2017	Yes	Yes	390 (151)	Oncology (15.61)	Physiotherapy	Country: Switzerland Site: Multicentre Type of cancer: Lung	1/10/2011	NR	No
Liu, 2020	Yes	Yes	73 (73)	Anaesthetics (5.18)	Not applicable	Country: China Site: NR Type of cancer: Lung	1/04/2017	Absent	No
Lopez-Rodriguez, 2021	Yes	Yes	130 (20)	Oncology (2.70)	NR	Country: Spain Site: Single-centre Type of cancer: CRC	1/10/2018	NR	No
Manzanares, 2017	NR	NR	NR (84)	Surgery (0.36)	NR	Country: Spain Site: Single-centre Type of cancer: CRC	1/12/2010	NR	No
McCarter, 1998	NR	NR	NR (38)	Nutrition science (3.90)	NR	Country: United States Site: NR Type of cancer: Mixed	NR	Present	NR
Mikagi, 2011	NR	NR	NR (26)	General medicine (0.12)	NR	Country: Japan Site: NR Type of cancer: Liver	1/02/2005	NR	NR
Mina, 2018	Yes	No	100 (86)	Surgical oncology (3.45)	Nursing	Country: Canada Site: Multicentre Type of cancer: Prostate	1/02/2014	Present	No
Minnella, 2018	Yes	No	51 (51)	Surgery (16.68)	Multidisciplinary	Country: Canada Site: Single-centre Type of cancer: Mixed	1/01/2013	Present	No
Minnella, 2020	Yes	No	42 (42)	Anaesthetics (4.14)	Multidisciplinary	Country: Canada Site: Single-centre Type of cancer: CRC	1/01/2016	Present	No
Minnella, 2021	Yes	No	70 (70)	Urology & Nephrology (7.30)	Multidisciplinary	Country: Canada Site: Single-centre Type of cancer: Bladder	1/08/2013	Present	Yes
Morano, 2013	Yes	Yes	21 (21)	Rehabilitation medicine (2.70)	Physiotherapy	Country: Brazil Site: Single-centre Type of cancer: Lung	1/03/2008	NR	NR
Moriya, 2014	Yes	Yes	90 (85)	Gastroenterology (1.55)	NR	Country: Japan Site: Single-centre Type of cancer: CRC	1/10/2005	NR	NR

Table 1. Cont.

Author, year	Registered protocol	Changed primary/ secondary outcomes	Planned N (Final N)	Journal specialty (impact factor)	Profession delivering intervention	Population	Recruitment start date	Funding	Conflicts of Interest*
Moug, 2019	Yes	Yes	80 (40)	General surgery (1.82)	Not applicable	Country: United Kingdom Site: Multicentre Type of cancer: CRC	1/08/2014	NR	No
Mueller, 1982	NR	NR	NR (125)	General medicine (202.73)	NR	Country: Germany Site: Single-centre Type of cancer: Mixed	1/12/1978	NR	NR
Nakamura, 2005	NR	NR	NR (26)	Nutrition science (4.34)	NR	Country: Japan Site: NR Type of cancer: Mixed	NR	NR	NR
Okamoto, 2009	NR	NR	NR (60)	Surgery (3.28)	NR	Country: Japan Site: Multicentre Type of cancer: Gastric	1/04/2005	NR	NR
Ozdemir, 2019	Yes	Yes	120 (85)	OB/GYN (3.01)	Multidisciplinary	Country: Turkey Site: Single-centre Type of cancer: Mixed	1/01/2018	NR	No
Pehlivan, 2011	NR	NR	NR (60)	Cardiothoracic surgery (4.62)	Physiotherapy	Country: Turkey Site: Single-centre Type of cancer: Lung	1/01/2007	NR	No
Pexe-Machado, 2013	Yes	Yes	22 (22)	Nutrition science (4.34)	NR	Country: Brazil Site: Single-centre Type of cancer: Mixed	1/03/2010	Present	No
Polakowski, 2019	NR	NR	NR (73)	Nutrition science (4.34)	NR	Country: Brazil Site: Single-centre Type of cancer: CRC	NR	NR	NR
Reis, 2019	NR	NR	NR (33)	Surgery (1.13)	NR	Country: Brazil Site: Single-centre Type of cancer: CRC	1/05/2017	Absent	No
Rizvanovic, 2019	Yes	No	50 (50)	General surgery (1.82)	NR	Country: Bosnia and Herzegovina Site: Single-centre Type of cancer: CRC	1/05/2018	NR	No
Rovera, 1989	NR	NR	NR (28)	Nutrition science (N/A)	Dietician	Country: Italy Site: Single-centre Type of cancer: Bladder	NR	NR	NR
Russell, 2019	Yes	Yes	32 (32)	Hepatology (3.17)	NR	Country: New Zealand Site: Single-centre Type of cancer: Liver	1/11/2012	Present	No
Shukla, 2020	Yes	Yes	24 (24)	Not applicable	Physiotherapy	Country: Australia Site: Multicentre Type of cancer: Lung	1/07/2015	Present	NR

Table 1. Cont.

Author, year	Registered protocol	Changed primary/ secondary outcomes	Planned N (Final N)	Journal specialty (impact factor)	Profession delivering intervention	Population	Recruitment start date	Funding	Conflicts of Interest*
Steffens, 2021	Yes	Yes	22 (22)	General medicine (8.78)	Physiotherapy	Country: Australia Site: Single-centre Type of cancer: Mixed	21/09/2017	Present	NR
Torrinhas, 2013	Yes	No	63 (63)	Nutrition science (7.05)	Pharmacist	Country: Brazil Site: Single-centre Type of cancer: Mixed	1/04/2006	Present	No
Uno, 2016	Yes	No	40 (40)	Surgery (3.36)	Nursing	Country: Japan Site: Single-centre Type of cancer: Liver	1/05/2009	NR	NR
Valkenet, 2018	Yes	Yes	241 (241)	Surgery (3.36)	Physiotherapy	Country: Netherlands Site: Multicentre Type of cancer: Oesophageal	1/09/2013	Present	No
van Adrichem, 2014	Yes	Yes	60 (39)	Surgery (3.36)	Physiotherapy	Country: Netherlands Site: Single-centre Type of cancer: Oesophageal	1/12/2009	Present	No
Wierdak, 2021	Yes	Yes	26 (26)	Oncology (6.64)	NR	Country: Poland Site: Single-centre Type of cancer: CRC	1/11/2017	Present	No
Xu, 2006	NR	NR	NR (60)	Surgery (3.36)	NR	Country: China Site: Single-centre Type of cancer: Mixed	1/01/2003	NR	NR
Yamana, 2015	Yes	NR	60 (60)	General surgery (3.45)	Physiotherapy	Country: Japan Site: Single-centre Type of cancer: Oesophageal	1/04/2011	NR	No
Zelic, 2012	NR	NR	NR (40)	General medicine (5.45)	NR	Country: Croatia Site: NR Type of cancer: CRC	NR	NR	NR

NR= Not reported; *= No indicates that the authors declared no conflict of interest, Yes indicates that the authors declared a conflict of interest, NR indicates that no information on conflict of interest was provided.

Ad hoc analysis showed a modest decrease in risk of bias when comparing trials published before and after the introduction of the Cochrane risk of bias 2 instrument. When 'adherence' was considered for Domain 2, 44 of 62 trials (70.1%) published before the advent of the Cochrane risk of bias instrument were rated at high risk of bias. However, this number decreased to 7 out of 12 trials (58.3%) for trials published after introduction of the Cochrane risk of bias instrument. Similarly, when 'assignment' was considered, the proportion of trials presenting a high risk of bias declined from 54.8% to 33.3% after the introduction of RoB 2.

Reporting Quality

TIDieR items were generally poorly reported across all trials, with the most poorly reported item being item 10 (intervention modification), which was only reported by nine trials (12%). Item 5 (who provided the intervention) was only reported by 34 (46%) of the included trials. However, some items were well reported: 100% of trials reported item 1 (intervention name) and item 2 (rationale/goal of intervention). A summary of the reporting quality of the included trials is presented in Figure 3.

Other Outcomes

A total of 40 (55%) trials had a registered protocol, of which 22 (55%) were registered on ClinicalTrials.gov. However, it is worth noting that some manuscripts had reported protocols, or protocol registration codes which linked to a different study.[50, 51, 59, 60] Median impact factor of the journals in which the trials were published was 3.8 (range: 0.1 – 202.7). The journals most commonly focused on surgery, (n=25, 34%)[24, 28, 31, 32, 36, 40, 43, 47, 50, 55, 57, 60, 65, 69, 73, 76, 78, 81, 82, 85, 89-91, 93, 94] nutrition science, (n=13, 18%)[27, 34, 37, 41, 44, 45, 48, 52, 66, 75, 79, 80, 96] oncology (n=8, 11%)[26, 29, 53, 56, 58, 62, 64, 92] and general medicine (n=8, 11%).[23, 35, 49, 54, 67, 74, 88, 95]

Discussion

Statement of Principal Findings

We identified 74 published prehabilitation trials, with most presenting high risk of bias. Notably, 34 (45%) of the identified trials did not have a publicly available protocol. Of those with a registered protocol, 20 (59%) changed their research question and/or have not achieved the planned sample size.

Mechanisms and Implications

There are several possible reasons for the high risk of bias observed in the included studies. In exercise-based trials, where blinding was only possible for the assessors collecting the data, risk of bias may have been inherently elevated (as per Domain 2: Risk of bias due to deviations from the intended interventions, from the RoB 2 tool). Among the 56 trials which were rated at a high risk of bias, assessor blinding was not particularly well done either, with item 4.3 (Were outcome assessors aware of the intervention received by study participants?) being reported as 'no' or 'probably no' by only 37 studies. Trials with a subjective outcome (e.g., acceptability/feasibility of treatment, pain scores) may have naturally had a higher risk of bias, where a variety of confounding factors such as individual pain tolerance, distance from home to treatment centre, and personal preferences may influence the results. Unlike exercise interventions, immunonutrition trials could have a placebo arm, which lowered their risk of bias due to the blinding effect of a placebo. Despite this, 47 out of 48 (98%) immunonutrition trials were still rated at 'some concerns' or 'high' risk of bias.

A major contributor to the high risk of bias in Domain 5 (Risk of bias in selection of the reported result) is the low rate of protocol registration across the trials. Because item 5.1 assesses whether the trial data was analysed in accordance with a pre-specified plan, the absence of such a plan increases the risk of reporting bias.

With regard to reporting quality, we were unable to find evidence of any journal formally endorsing the TIDieR checklist. In addition, none of the included trials mentioned the checklist, which may explain the poor reporting quality of the included trials. Assessing reporting quality using different checklists can lead to varying scores. To ensure the reliability of our findings, it may be useful to apply another checklist to the included studies. For example, if we use a different tool and find that the studies are well-reported, this would support the validity of our results. To address the variation in reporting quality scores which arise from the application of different checklists, researchers may wish to develop a specialised set of guidelines for prehabilitation trials and explore potential variables that could be used to assess the quality of a study when participant blinding is not possible, such as whether randomisation is stratified based on confounding variables.[10]

It appears that the conclusions of current prehabilitation trials should be interpreted with caution, as the generalisability of their results is limited by a high risk of bias. Systematic reviews and meta-analyses which include such RCTs may also have unreliable conclusions, as unreported confounding factors are a factor in heterogeneity.[10, 97] The results of Cuijpers (2022) are aligned with our findings, showing that the limitations in reporting quality are not evenly distributed across items and domains. For example, "a clear description of the criteria for assessing success of

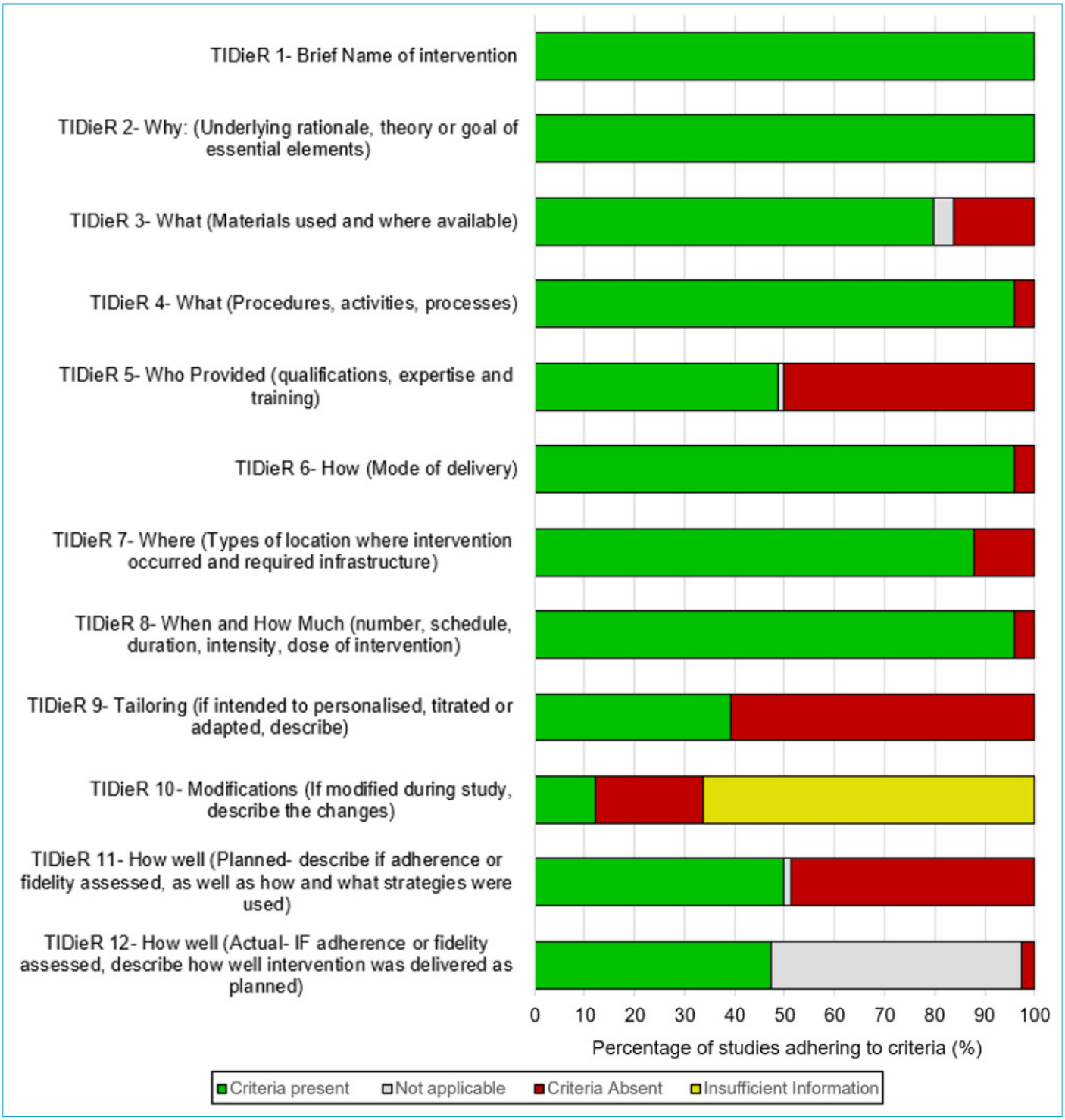

Figure 3. Description of the intervention details (TIDieR Checklist).

feasibility" is poorly reported in Cuijpers (2022), and "a description of whether the intervention personalised, titrated or adapted" is poorly reported in our study. Thus, it is advisable for the authors of future prehabilitation RCTs to pay particular attention to those domains.

As a first step in improving the quality of prehabilitation research, we suggest that more journals endorse the use of reporting guidelines such as PRISMA, CONSORT and TIDieR. Alongside this, journals may translate reporting guidelines to make them more accessible, hold workshops to train researchers and clinicians on the use of guidelines, and provide feedback to authors on the quality of their manu-

scripts. Maintaining a high standard of reporting quality will allow a more accurate risk of bias assessment and enable researchers to assess the replicability of trial results. To facilitate adherence to reporting guidelines, journals may endorse the use of AI-powered tools to check manuscripts. An example of such a tool is Penelope.ai, which has been endorsed by BMJ Open.[11] Furthermore, journals adding a requirement for a pre-published protocol would help to reduce reporting bias and improve transparency in research. At the time of writing of this article, the implementation of some of these measures is already underway.[98-100] While these measures appear to work in theory, their implementation may be limited by funding, time, ethical issues, or other practical concerns.

Strengths and Weaknesses of the Study

Our study had a number of strengths. Six databases and the reference lists of included articles were searched, and no language or publication date restrictions were applied to the search. These measures helped reduce the degree of selection bias in our study by capturing as many trials as possible. The data extraction on trial characteristics was thoroughly checked by two other reviewers (DS, SK), thus preventing errors, and strengthening the reliability of our findings and conclusions. Through a focused evaluation of RCTs, which form the foundation of clinical decision making, our study contributes to the ongoing process of quality improvement in prehabilitation research.

However, our review also has limitations. 18 studies could not be translated and were therefore excluded. The reporting quality and risk of bias assessments were only conducted by one reviewer, which may have increased the risk of bias of our own study. During the risk of bias assessment process, we did not consider the impossibility of blinding and/or standardising certain types of interventions, such as physiotherapy. Furthermore, some trials were pilot or feasibility studies which are not subject to the stringent methodological standards of RCTs.[101] Thus, these trials may have been assigned a higher risk of bias rating by the nature of their design. In light of this, the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool may be a more suitable tool for such trials.[102]

Strengths and Weaknesses in Relation to Other Studies, Discussing Particularly any Differences in Results

To our knowledge, our study is the first to assess both the reporting quality and risk of bias in prehabilitation trials. Furthermore, our study may be more generalisable than previous studies as it assessed prehabilitation trials in patients with a range of cancers and a variety of outcomes as compared to previous studies which focused solely on one outcome e.g. feasibility. Although Cuijpers (2022) and our study used different checklists and focused on different outcomes, we both concluded that reporting quality was poor in prehabilitation trials.[7]

Unanswered Questions and Future Research

By allocating research funds away from cohort studies, retrospective studies, and case series, and towards large-scale, double-blinded RCTs, researchers can produce a smaller number of high-quality trials. This approach can help prevent research waste and improve the overall quality of the evidence.

This review has only assessed the quality of RCTs as the eligibility criteria excluded cohort studies and other study designs. It would be of interest for future studies to assess prehabilitation trials with these designs to see if they are at a similar risk of bias. Since the results of this study were qualitatively summarised, future studies could conduct a statistical analysis to investigate the relationship between trial characteristics and study quality. We hypothesise that articles published in higher impact factor journals will present high methodological quality, as such journals have more stringent requirements for submission. Authors may wish to explore variations in risk of bias and reporting quality between studies amenable to blinding (e.g., immunonutrition) and those that cannot be blinded (e.g., physiotherapy). Further investigations may wish to compare the risk of bias and reporting quality in prehabilitation trials published before and after the introduction of TIDieR and RoB 2 guidelines.

Future authors could also investigate the barriers and enablers to improving quality in prehabilitation studies via a survey. This information can subsequently form the basis for further solutions to these issues. We anticipate that their implementation will improve the quality of evidence-based medicine and, thus, maximise clinical benefit for prehabilitation patients.

Conclusions

Prehabilitation RCTs in cancer patient populations are poorly reported and have a high risk of bias, providing unreliable conclusions to clinicians. Interventions are needed to improve adherence to reporting checklists and risk of bias guidelines. Surveys and interviews of the authors of prehabilitation RCTs may be useful in elucidating the barriers and enablers to higher quality research.

Disclosures

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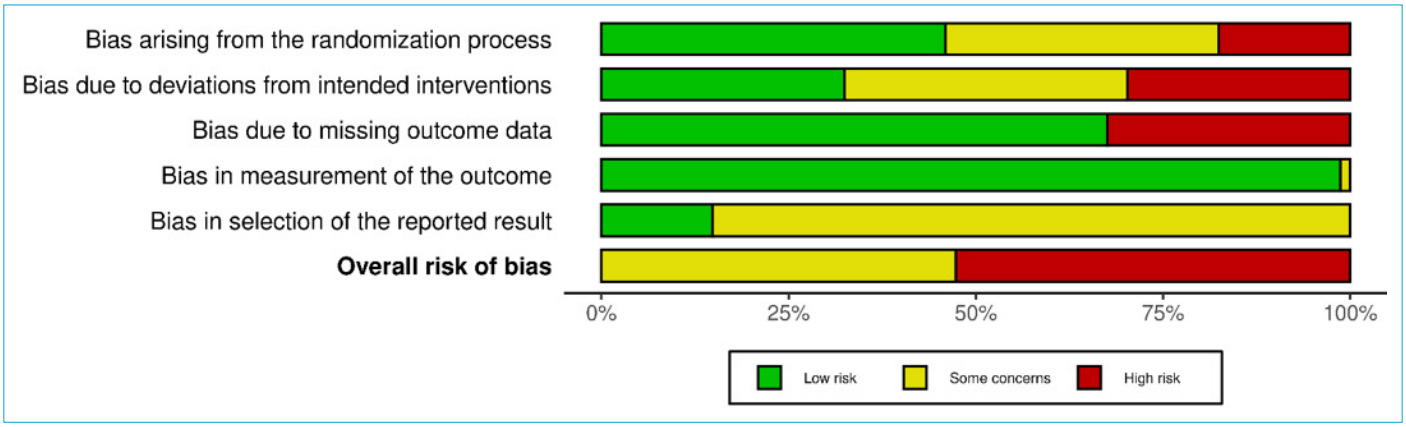

Supplement 1. Risk of Bias Summary with Domain 2 Examining Assignment.