[LITERATURE REVIEW]

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The Efficacy of Exercise Therapy for Rotator Cuff–Related Shoulder Pain According to the FITT Principle: A Systematic Review With Meta-analyses

Rotator cuff–related shoulder pain (RCRSP) is an umbrella term for a range of shoulder pain diagnoses including rotator cuff tendinopathy, subacromial impingement syndrome or subacromial pain syndrome.[30] Symptoms are described as pain in the anterolateral part of the shoulder and difficulties during shoulder elevation and rotation, with attribution to the structures around the subacromial space, the proximal humerus, rotator cuff tendons, and bursa.[30] The etiology is multifactorial including age, loading history, biomechanical factors, psychosocial factors, lifestyle, and general health.[30] First-line treatment of RCRSP should be nonoperative[49] and include exercise prescription with or without pharmacological treatments or other modalities such as manual therapy.[12,27] Exercise, along with education, are core components of nonoperative management of RCRSP.[27,46] The components of exercise therapy reported in clinical trials include exercises for the neck and thoracic muscles, scapula-focused exercises, motor control exercises, concentric or eccentric strengthening, and variable levels of high- or low-intensity resistance training, as well as whole-body exercises and aerobic conditioning.[7,31] These exercise programs are proposed to reduce pain and disability, increase muscle strength and endurance, improve neuromuscular control, and increase range of motion and load tolerance.[30]

OBJECTIVE: To evaluate the efficacy of exercise interventions with differing frequency, intensity, type, and time (FITT) on shoulder pain and disability in people with rotator cuff–related shoulder pain (RCRSP).

DESIGN: Intervention systematic review with meta-analyses.

LITERATURE SEARCH: Electronic searches were conducted up to May 2023.

STUDY SELECTION CRITERIA: Randomized controlled trials (RCTs) comparing the effects of exercise interventions differing in prescription according to the FITT principle, in people with RCRSP.

DATA SYNTHESIS: Separate meta-analyses comparing exercise type (specific versus nonspecific exercise) and intensity (high versus low) were conducted. Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to evaluate the certainty of evidence.

RESULTS: Twenty-two RCTs (n = 1281) were included. There was moderate-certainty evidence that motor control exercise programs, when compared to nonspecific exercise programs, significantly reduced disability in the short (SMD: −0.29; 95% CI: −0.51, −0.07; n = 323; 7 RCTs) and medium terms (SMD: −0.33; 95% CI: −0.57, −0.09; n = 286; 5 RCTs), but not pain in the short term (SMD: −0.19; 95% CI: −0.41, 0.03; n = 323; 7 RCTs). Uncertainties remained regarding other exercise types (eccentric and scapula-focused exercise programs) versus nonspecific exercise programs, and exercise intensity due to low- to very low–certainty evidence. No trials were identified that compared different frequencies or times.

CONCLUSION: For adults with RCRSP, motor control exercise programs were probably slightly superior to nonspecific exercise programs. However, it is unclear if the effects were due to motor control exercise or to other program characteristics such as progression and tailoring. *J Orthop Sports Phys Ther 2024;54(8):499-512. Epub 7 June 2024. doi:10.2519/jospt.2024.12453*

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While exercise therapy is effective for RCRSP, there is no consensus on the specific exercise types and whether specific or general exercises are the most effective. There is also a lack of guidance for

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clinicians on how to design and prescribe an effective exercise program for individual patients.[49] Littlewood et al[31] examined patient and contextual factors in people with RCRSP, reporting data on exercise types, content, and dosage. The narrative synthesis stated that higher dosage for sets and repetitions, and the application of resistance may be more beneficial, but also that poor reporting hampered definitive conclusions. Supervised exercise programs do not appear to be an important factor, with a recent review finding similar effectiveness for supervised and home-based exercise programs for individuals with RCRSP.[16]

In reporting the outcome of an exercise intervention, information regarding specific elements of exercise prescription is critical to permit replication. The FITT (frequency, intensity, type, and time) principle describes specific components within an exercise prescription, like in a medication prescription, providing necessary details for replication.[38] However, there has been no systematic review to date examining the evidence for exercise programs in people with RCRSP, related to the FITT principle. Using the FITT principle as a framework in a systematic review, it is possible to evaluate which specific elements of the exercise program are the most important for improving patient-reported outcomes. It may be possible to give more specific guidance to clinicians on exercise prescription for RCRSP.[40]

The aims of this systematic review were to appraise the available evidence on exercise programs with different FITT parameters for individuals with RCRSP, and to evaluate their effects on self-reported outcomes of shoulder pain, disability, and quality of life (QoL).

METHODS

The systematic review is registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero/; registration number: CRD42019127912). There were 2 deviations from the protocol: (1) exercise delivery modes in terms of supervised compared to home-based exercises were not assessed as a systematic review addressing this question was recently published,[16] and (2) meta-regressions were not performed as there were fewer than 10 studies in the meta-analyses.[20]

This systematic review and meta-analyses were conducted according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines.[39]

A qualitative thematic analysis was also performed by presenting characteristics of the different exercise programs: exercise types, exercise parameters, required material, instructions to patients, exercise program duration, and frequency. This is presented in a separate article.[14]

Eligibility Criteria

Randomized controlled trials (RCTs) published in peer-reviewed journals and written in English were included. Publications were included if (1) participants were described as having RCRSP or synonymous conditions (eg, rotator cuff tendinopathy, subacromial impingement, subacromial pain syndrome, subacromial bursopathy, long head biceps tendinopathy, or partial-thickness rotator cuff tear); (2) they examined the efficacy of any exercise intervention as a stand-alone intervention or as part of an active exercise multimodal approach; (3) they compared 2 or more exercise interventions, which differed in prescriptions of the FITT principles, ie, in frequency, intensity, type, or time (duration of intervention); (4) they examined the effects of exercise on at least 1 self-reported outcome measure related to pain, disability, or health-related QoL.

Publications were excluded if (a) participants with full-thickness rotator cuff tear, adhesive capsulitis, arthritis, fractures, and joint instability were specifically included; (b) interventions combined exercise with passive treatment modalities such as joint mobilizations and manipulations, electrotherapy, cryotherapy, and pain-relieving adjuvants, unless applied to both exercise groups; and (c) they involved a comparison of modes of delivery but not different exercise type or prescription, eg, home-based compared to supervised exercise, or exercise groups that differed only in feedback mechanisms (eg, biofeedback).

Literature Search

An electronic literature search of the following databases was conducted: Allied and Complementary Medicine Database (AMED), CINAHL, MEDLINE (PubMed), SPORTDiscus, Cochrane Register of Controlled Trials (CENTRAL), Physiotherapy Evidence Database (PEDro), EMBASE, and Web of Science. All databases were initially searched from the date of inception up until March 2020, and updated searches were completed up to December 2021 and May 2023 (excluding the AMED database). Subject headings were specific to each database. Search terms were searched individually and then combined using relevant Boolean terms. Full search strategies are available in the **SUPPLEMENTAL APPENDIX**. Reference lists of included studies and previous systematic reviews in the field were screened for additional relevant references.

Study Selection

Pairs of researchers (K.M. and LK, or M.C. and M.O.D.) independently screened titles and abstracts for inclusion criteria and determined the list of articles for full-text review. Two researchers assessed the full texts for inclusion criteria. A third researcher (B.J.K. or S.L.) was consulted if there were any disagreements about study eligibility. Two researchers grouped the articles into the FITT categories for meta-analyses. The list of selected articles, along with our inclusion criteria, was sent to 4 shoulder expert researchers within this field, to ensure no trials had been missed.

Data Extraction

Data were extracted independently by 2 researchers for each trial (K.M., B.J.K., L.K., or S.L.). Data extraction included study design, sample size, diagnosis, details of the interventions in relation to the FITT principles, and outcome data.

"Frequency" was defined as the number of days per week the exercise was prescribed. To be included in the "intensity" category, the trial had to include a comparison of high- versus low-intensity exercise, with a clear difference in exercise intensity between groups. This could either be in terms of the amount of resistance used, total number of repetitions per exercise session, or overall load per session.[26,32] Trials could be included in both the "type" and "intensity" categories if they met the respective criteria.

For exercise "type," trials were grouped into one of the categories below, according to the trial authors' descriptions of the experimental exercise program, and/or a clearly identifiable difference in exercise type between groups:

1. Motor control exercise programs: focused on specific muscle control and/or coordination, dynamic muscular stabilization exercises, proprioceptive exercises, specific movements, or movement control exercises.[28,44]
2. Scapula-focused exercise programs: focused on scapular muscles and/or were aimed at increasing scapular postural awareness and/or stability.[37]
3. Eccentric exercise programs: focused on eccentric movements, that involved lengthening under the load of the rotator cuff and/or other shoulder muscles.[42]
4. Nonspecific exercise programs: more generic shoulder resistance or strengthening exercise programs without emphasis on muscle control, scapular muscles/stability, or eccentric exercises.[28]

A specific group could be included in 2 categories if the intervention satisfied the criteria of 2 exercise types (eg, an exercise program involving scapula-focused motor control exercises).

The "time" category examined the total duration of the intervention in weeks. For data extraction and analysis, the follow-up periods were defined according to these categories:

- Immediate: within 1 day.
- Short term: closest follow-up time to 1 month but less than 2 months.
- Medium term: closest follow-up time to 3 months with a range between 2 to 6 months.
- Long term: closest follow-up time to 12 months with a range between 6 and 18 months.
- Very long term: follow-up beyond 18 months after the initiation of care.

Risk-of-Bias Assessment

Included trials were appraised independently by 2 researchers (K.M., L.K. and/or S.L.) using the Cochrane Risk of Bias tool version 2 (RoB 2).[45] Risk-of-bias judgments were made in the specific context of the trial. There are 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We judged a trial was at "high risk of bias" when high risk was identified in any domain or if "some concerns" was identified in 3 or more domains. We judged a trial had "some concerns" when "some concerns" was identified in 1 or 2 domains. A trial was at "low risk of bias" if all domains were judged as "low risk." Results were compared and disagreements resolved by discussion.

Data Synthesis

For pain, the outcome measures were all numerical or visual analogue scales based on a 0-to-10 or 0-to-100 scale with high scores indicating more pain. All the extracted scores were adjusted to a 0-to-10 scale for pooling. For disability measures, a lower score indicated lower disability and the sign of the score was adjusted with a negative value when needed (ie, Shoulder Rating Questionnaire in which higher score indicate more function). Random-effects model meta-analyses were performed using Review Manager (RevMan 5.4, The Cochrane Collaboration, Copenhagen, Denmark).

For all meta-analyses, alpha levels were set at 0.05 and 95% confidence intervals (CIs) were calculated. The effect of exercise therapy in the individual trials was expressed as standardized mean differences (SMDs) on pain, disability, and QoL, separately. A negative SMD indicated a beneficial effect on pain, disability, or QoL in favor of the experimental intervention. As secondary analyses, pain outcomes were also expressed as mean differences (MDs) in different meta-analyses. The visual analog scale (VAS) and the numeric pain-rating scale were considered as similar tools, and results were pooled to calculate MD. When multiple disability measures were reported, we used the trial's primary outcome and if it was not specified by authors, we used the validated disability outcome that was the most represented in the analysis. Sensitivity analyses excluding high-risk-of-bias RCTs were performed for each analysis. Sensitivity analyses excluding scapula-focused trials from the motor control meta-analyses and excluding a trial analyzing both exercise intensity and type were performed, as well as analyses on pain mean differences.

Heterogeneity was evaluated using the Cochrane's Q test and I^2 (percentage of total variation due to between-study heterogeneity) using Review Manager, as well as prediction intervals, which were calculated for each meta-analysis including at least 3 studies using the Comprehensive Meta-Analysis Prediction Intervals software.[5] Funnel plots were not inspected as all meta-analysis included fewer than 10 trials. Effect size interpretation was as per Cohen,[10] where <0.2 was trivial, 0.2 to 0.49 was small, 0.5 to 0.79 was moderate, and ≥0.8 was large.

GRADE Assessment

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework was used to judge the certainty of evidence and to formulate recommendations based on the main results.[17] Levels of evidence were downgraded for serious risk of bias based on the Cochrane RoB 2, for serious imprecision based on the magnitude of the CIs and for serious inconsistency based on the I^2 and prediction intervals. Levels of evidence were interpreted as follows:

- High certainty: Very confident the true effect lies close to the calculated estimate.
- Moderate certainty: Moderately confident in the effect estimate. The true effect is likely to be close to the estimate, but there is still a possibility that it may differ substantially.
- Low certainty: Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate.
- Very low certainty: Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate.

RESULTS

FROM THE 9622 POTENTIALLY RELEVANT articles identified through titles and abstract review, 22 trials met the eligibility criteria after full-text review (**FIGURE 1**). Reasons for excluding full texts and references of excluded manuscripts are available in **SUPPLEMENTAL APPENDIX**. Characteristics of included trials and exercise programs are presented in **SUPPLEMENTAL APPENDIX** and are further discussed in a separate article.[14] Two articles described the same trial and were treated as a single trial.[18,21]

Risk-of-Bias Assessment of Included Trials

A summary of the risk-of-bias assessment for each trial is presented in **TABLE 1**. Six trials were at low risk of bias,[6,9,13,22,24,25] nine had some concerns regarding the risk of bias[1-4,11,23,33,34,47] and seven were at high risk of bias.[8,15,19,21,36,41,48] Missing outcome data were the main domain of potential bias.

Participants

In total, 1281 participants with RCRSP were included (53% female) with sample sizes ranging between 21 and 200 participants per trial (median = 48). Mean participant age among all included patients was 47.8 years.

Intervention Characteristics

Frequency and Time For frequency, most of the included trials prescribed daily exercise sessions; some prescribed as few as 2 exercise sessions per week. For time, the length of intervention ranged between 5

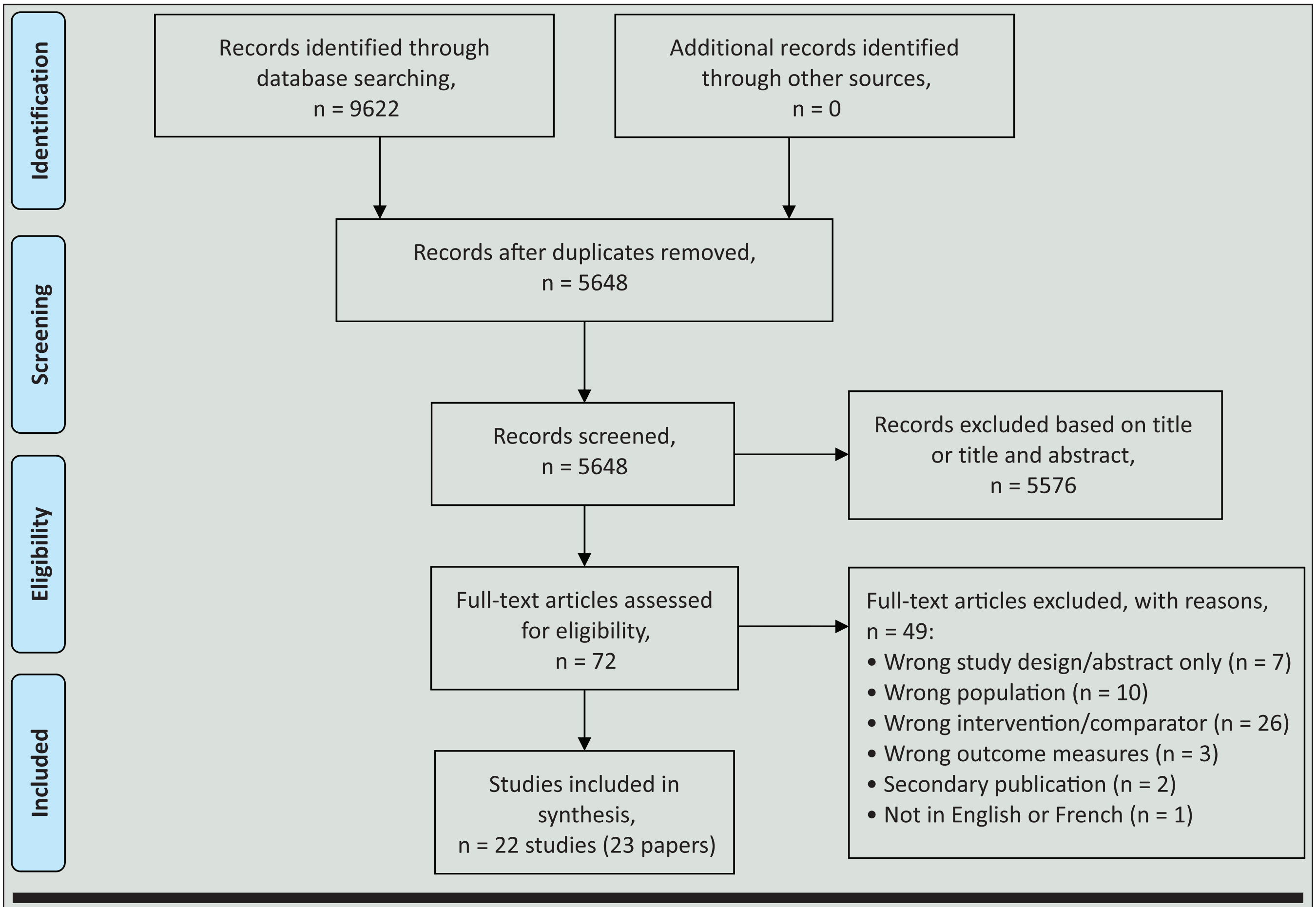

FIGURE 1. Schematic breakdown of literature search results.

TABLE 1 Risk of Bias of Included Randomized Controlled Trials

Study	D1	D2	D3	D4	D5	Overall
Baskurt 2011	+	+	+	+	-	-
Beaudreuil 2011	+	+	+	+	-	-
Bek Clausen 2021	+	+	+	+	+	+
Berg 2020	-	+	+	-	-	-
Blume 2015	+	+	+	+	-	-
Boudreau 2019	+	+	+	+	+	+
Chaconas 2017	+	+	X	+	-	X
Dejaco 2017	+	+	+	-	-	-
Dube 2023	+	+	+	+	+	+
Fatima 2021	-	-	X	+	-	X
Heron 2017	+	+	X	-	-	X
Holmgren & Hallgren 2012	+	X	X	+	-	X
Hotta 2020	+	+	+	+	+	+
Hui 2022	+	+	+	-	+	-
Ingwersen 2017	+	+	+	+	+	+
Kamonseki 2022	+	+	+	+	+	+
Macias Hernadez 2021	+	+	+	+	-	-
Maenhout 2012	+	+	-	+	-	-
Marzetti 2014	+	+	X	+	-	X
Osteras 2010	+	+	X	+	-	X
Struyf 2013	+	+	-	-	-	-
Turgut 2017	+	+	X	+	-	X

Risk-of-Bias Domains

Domains:
D1: Bias arising from the randomization process
D2: Bias due to deviations from intended intervention
D3: Bias due to missing outcome data
D4: Bias in measurement of the outcome
D5: Bias in selection of the reported result

Judgement
X High
- Some concerns
+ Low

and 12 weeks. Although frequency and duration of the intervention varied, no trial directly compared these parameters between groups. Therefore, we were unable to conduct a meta-analysis examining these parameters.

Intensity Six trials compared high- versus low-load exercise programs.[3,9,18,19,21,24,41]

Type Three main categories were identified: motor control exercise programs compared to nonspecific exercise programs comprising 8 trials,[1,2,6,13,25,36,47,48] eccentric exercise programs compared to nonspecific exercise programs comprising 6 trials,[4,8,11,15,33,34] scapula-focused exercise programs compared to nonspecific exercise programs comprising 5 trials.[1,21,22,47,48] One trial compared Yi Jin Bang exercises, which consists of 10 mind-body movements that involve the shoulder and that are performed with the help of a stick, for strengthening and stretching exercises.[23] Nonspecific exercise programs were defined as a control and generic exercise program in all RCTs except in the work of Dubé et al[13] in which it consisted of an exercise program aimed to increase shoulder strength based on the 1-repetition maximum of each individual. In the work of Boudreau et al,[6] the motor control exercise program involved the same exercises as in the nonspecific programs, but with coactivation of pectoralis and latissimus dorsi.

Further details regarding the description of the exercise interventions are provided in the associated publication.[14]

Exercise Type

Motor Control Exercise Programs Compared to Nonspecific Exercise Programs Motor control exercise programs significantly reduced pain in the medium (SMD: –0.38; 95% CI: –0.71, –0.05; n = 286; 5 RCTs) and long terms (SMD: –0.57; 95% CI: –0.98, –0.16; n = 96; 2 RCTs), but not in the short term (SMD: –0.19; 95% CI: –0.41, 0.03; n = 323; 7 RCTs) when compared to nonspecific exercise programs (**FIGURE 2**). For disability, motor control exercise programs significantly reduced disability in the short (SMD: –0.29; 95% CI: –0.51, –0.07; n = 323; 7 RCTs), medium (SMD: –0.33; 95% CI: –0.57, –0.09; n = 286; 5 RCTs), and long terms (SMD: –0.48; 95% CI: –0.88, –0.07; n = 96; 2 RCTs) when compared to nonspecific exercise programs as presented in **FIGURE 2**.

Eccentric Exercise Programs Compared to Nonspecific Exercise Programs Eccentric exercise programs significantly reduced pain in the medium (SMD: –0.57; 95% CI: –0.88, –0.26; n = 167; 3

Study or Subgroup	Motor Control Exercise Mean	SD	Total	Nonspecific Exercises Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.3.1 Pain - short term								
Baskurt 2011	1.93	1.32	20	2.3	1.95	20	12.4%	−0.22 [−0.84, 0.40]
Boudreau 2019	3.53	1.95	20	4.06	2.12	19	12.1%	−0.26 [−0.89, 0.38]
Dubé 2023	2.08	1.63	41	2.38	1.5	41	25.5%	−0.19 [−0.62, 0.24]
Kamonseki 2022	2.67	2.03	32	2.77	2.13	32	20.0%	−0.05 [−0.54, 0.44]
Marzetti 2014	3.73	3.4995	24	4.1	3.4995	24	15.0%	−0.10 [−0.67, 0.46]
Struyf 2013	2.15	1.7	10	3.7	2.3	10	5.8%	−0.73 [−1.65, 0.18]
Turgut 2017	0.76	1.27	15	0.99	1.34	15	9.3%	−0.17 [−0.89, 0.55]
Subtotal (95% CI)			**162**			**161**	**100.0%**	**−0.19 [−0.41, 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 6 (*P* = .93); I² = 0%								
Test for overall effect: Z = 1.70 (*P* = .09)								
3.3.2 Pain - medium term								
Beaudreuil 2011	−12.2	2.8	30	-9.9	2.9	32	20.8%	−0.80 [−1.32, −0.28]
Dubé 2023	1.13	1.4	41	1.9	1.53	41	24.2%	−0.52 [−0.96, −0.08]
Kamonseki 2022	1.83	2.23	32	1.5	1.47	32	22.0%	0.17 [−0.32, 0.66]
Marzetti 2014	2.46	3.5172	24	3.76	3.5172	24	18.8%	−0.36 [−0.93, 0.21]
Turgut 2017	0.13	0.34	15	0.66	1.77	15	14.1%	−0.40 [−1.13, 0.32]
Subtotal (95% CI)			**142**			**144**	**100.0%**	**−0.38 [−0.71, −0.05]**
Heterogeneity: Tau² = 0.07; Chi² = 7.74, df = 4 (*P* = .10); I² = 48%								
Test for overall effect: Z = 2.23 (*P* = .03)								
3.3.3 Pain - long term								
Beaudreuil 2011	−13.1	2	22	−10.8	3.7	26	48.6%	−0.74 [−1.33, −0.15]
Marzetti 2014	1.86	3.5172	24	3.33	3.5172	24	51.4%	−0.41 [−0.98, 0.16]
Subtotal (95% CI)			**46**			**50**	**100.0%**	**−0.57 [−0.98, −0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (*P* = .43); I² = 0%								
Test for overall effect: Z = 2.73 (*P* = .006)								
3.3.4 Disability - short term								
Baskurt 2011	−82.61	10.33	20	−70.82	19.7	20	11.8%	−0.73 [−1.38, −0.09]
Boudreau 2019	28.9	17.1	20	31	17.9	19	12.3%	−0.12 [−0.75, 0.51]
Dubé 2023	22.5	13	41	23.5	11.5	41	25.9%	−0.08 [−0.51, 0.35]
Kamonseki 2022	17.6	13	32	19.6	13	32	20.2%	−0.15 [−0.64, 0.34]
Marzetti 2014	19.41	13.185	24	23.24	13.185	24	15.0%	−0.29 [−0.85, 0.28]
Struyf 2013	35	14	10	48.7	11.3	10	5.4%	−1.03 [−1.98, −0.09]
Turgut 2017	20.18	20.45	15	27.95	16.75	15	9.3%	−0.40 [−1.13, 0.32]
Subtotal (95% CI)			**162**			**161**	**100.0%**	**−0.29 [−0.51, −0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 5.78, df = 6 (*P* = .45); I² = 0%								
Test for overall effect: Z = 2.57 (*P* = .01)								
3.3.5 Disability - medium term								
Beaudreuil 2011	−16.4	4	30	−13.9	4.8	32	21.3%	−0.56 [−1.07, −0.05]
Dubé 2023	12.1	11.9	41	15.6	12.6	41	28.6%	−0.28 [−0.72, 0.15]
Kamonseki 2022	10.9	15.3	32	10.6	10.9	32	22.9%	0.02 [−0.47, 0.51]
Marzetti 2014	18.09	13.2027	24	22.9	13.2027	24	17.1%	−0.36 [−0.93, 0.21]
Turgut 2017	9.23	11.21	15	22.18	20.16	15	10.1%	−0.77 [−1.52, −0.03]
Subtotal (95% CI)			**142**			**144**	**100.0%**	**−0.33 [−0.57, −0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 4.16, df = 4 (*P* = .38); I² = 4%								
Test for overall effect: Z = 2.73 (*P* = .006)								
3.3.6 Disability - long term								
Beaudreuil 2011	−17.6	3.4	22	−15.4	4.4	26	49.4%	−0.54 [−1.12, 0.03]
Marzetti 2014	17	13.185	24	22.48	13.185	24	50.6%	−0.41 [−0.98, 0.16]
Subtotal (95% CI)			**46**			**50**	**100.0%**	**−0.48 [−0.88, −0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (*P* = .74); I² = 0%								
Test for overall effect: Z = 2.29 (*P* = .02)								

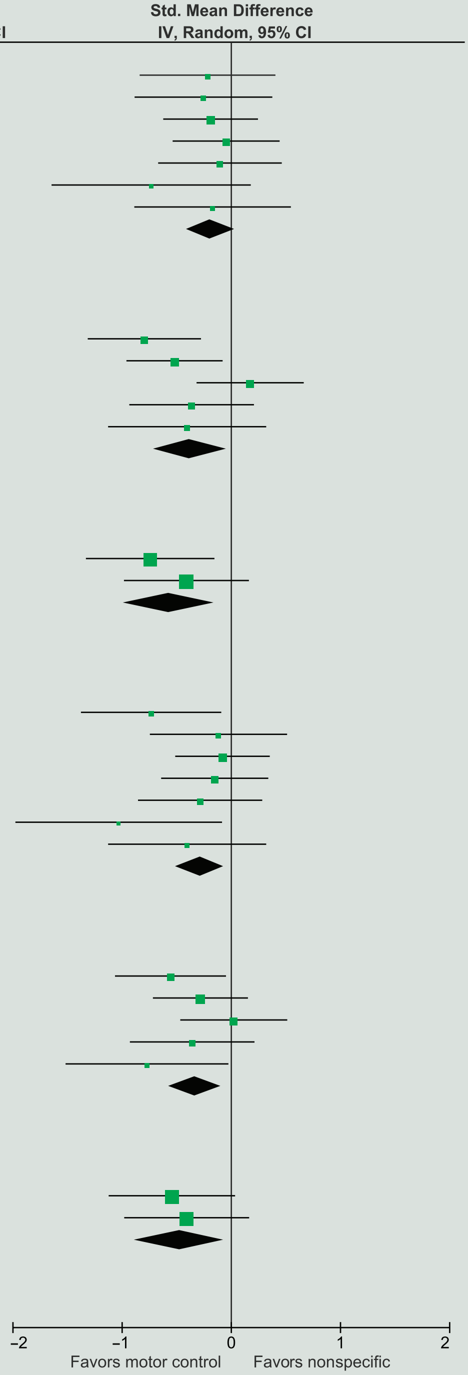

FIGURE 2. Efficacy of motor control exercises programs compared to nonspecific exercises programs for change in self-reported pain and disability in adults with rotator cuff tendinopathy in the short, medium, and long terms. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation; Std, standardized.

RCTs), but not in the short term (SMD: −0.32; 95% CI: −0.75, 0.12; n = 82; 2 RCTs) when compared to nonspecific exercise programs as presented in **FIGURE 3**. For disability, eccentric exercise programs did not significantly reduce disability in the short (SMD: 0.10; 95% CI: −0.65, 0.86; n = 177; 4 RCTs) and medium terms (SMD: −0.30; 95% CI: −0.86, 0.27; n = 262; 5 RCTs) when compared to nonspecific exercise programs (**FIGURE 3**). One trial was not included as

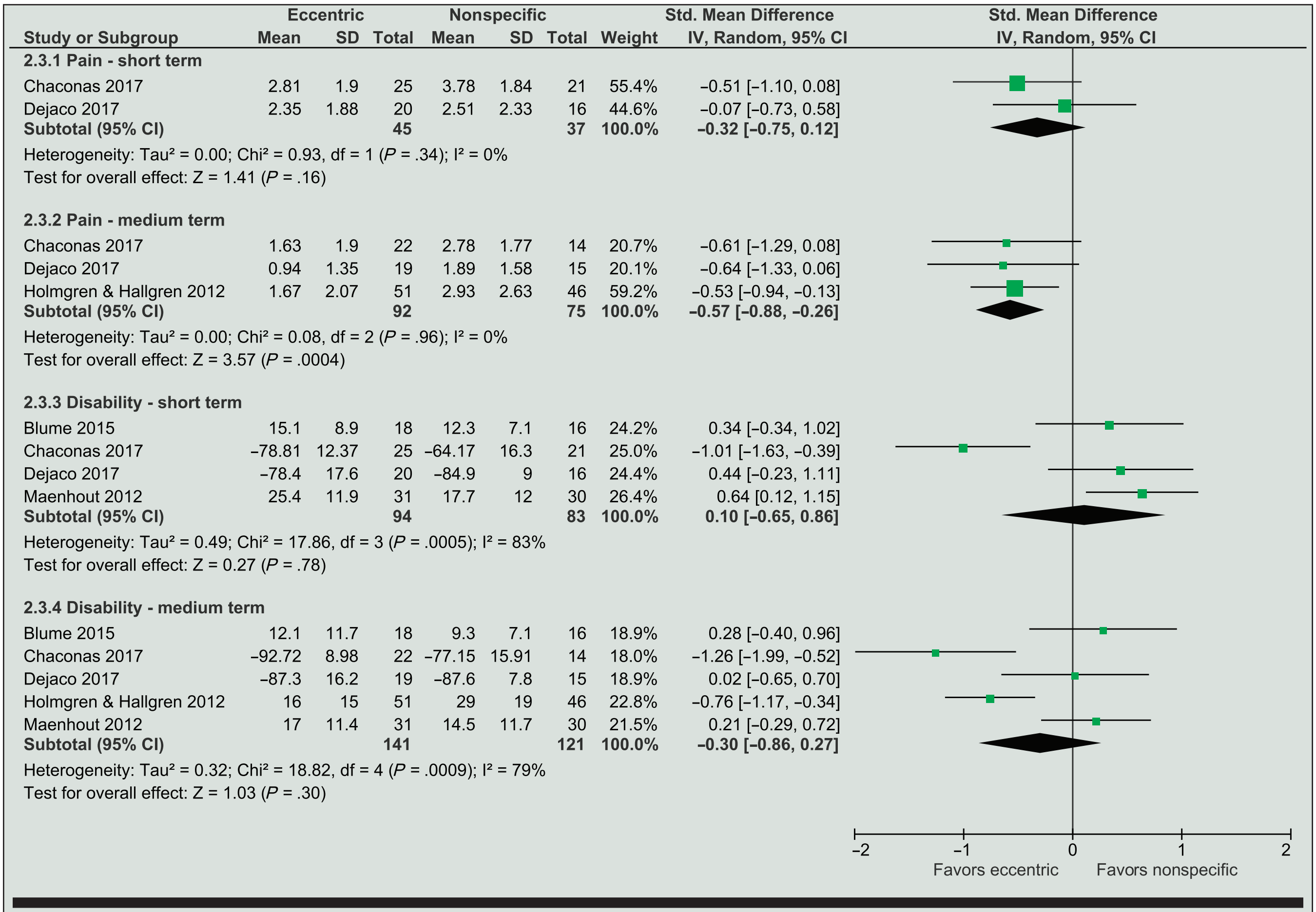

FIGURE 3. Efficacy of eccentric exercises programs compared to nonspecific exercises programs for change in self-reported pain and disability in adults with rotator cuff tendinopathy in the short and medium terms. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation; Std, standardized.

mean, and nonspecific deviations were not available.[15]

Scapula-Focused Exercise Programs Compared To Nonspecific Exercise Programs Scapula-focused exercise programs significantly reduced pain in the medium term (SMD: −0.45; 95% CI: −0.74, −0.16; n = 187; 3 RCTs), but not in the short term (SMD: −0.1; 95% CI: −0.54, 0.35; n = 150; 4 RCTs) when compared to nonspecific exercise programs (**FIGURE 4**). For disability, scapula-focused exercise programs significantly reduce disability in the medium term (SMD: −0.51; 95% CI: −1.01, −0.02; n = 187; 3 RCTs), but not in the short term (SMD: −0.42; 95% CI: −0.99, 0.16; n = 150; 4 RCTs) when compared to nonspecific exercise programs (**FIGURE 4**).

Jin Bang Exercise Program Compared To Nonspecific Exercise Programs Based on 1 RCT,[23] Jin Bang exercise program was comparable to nonspecific exercise programs to reduce pain and disability in the medium term.

Intensity: High-Load Exercise Programs Compared to Low-Load Exercise Programs

High-load exercise programs, when compared to low-load exercise programs, did not significantly reduce pain in the short (SMD: −0.15; 95% CI: −0.93, 0.62; n = 221; 2 RCTs) and medium terms (SMD: −0.19; 95% CI: −0.49, 0.11; n = 453; 4 RCTs) and did not significantly reduce disability in the short (SMD: −0.21; 95% CI: −0.72, 0.29; n = 301; 3 RCTs) and medium terms (SMD: −0.49; 95% CI: −1.02, 0.05; n = 453; 4 RCTs) (**FIGURE 5**). High-load exercise programs did not significantly improve QoL in the medium term (SMD: −0.29; 95% CI: −0.99, 0.42; n = 297; 2 RCTs) when compared to low-load exercise programs (**FIGURE 5**).

Sensitivity and Secondary Analyses

Sensitivity analyses excluding RCTs with a high risk of bias, and analyses excluding scapula-focused trials in the motor control meta-analyses or excluding the Holmgren trial in each meta-analysis, were performed. Overall, estimated mean effects were only minimally altered in these analyses (change range in SMD = 0 to 0.14) and are reported in **TABLE 2** and in the **SUPPLEMENTAL APPENDIX**. Secondary

Study or Subgroup	Scapula Stability Mean	Scapula Stability SD	Scapula Stability Total	Nonspecific Mean	Nonspecific SD	Nonspecific Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.3.1 Pain - short term								
Baskurt 2011	1.93	1.32	20	2.3	1.95	20	27.2%	−0.22 [−0.84, 0.40]
Hotta 2020	2.7	3.3	30	1.5	2.9	30	32.9%	0.38 [−0.13, 0.89]
Struyf 2013	2.15	1.7	10	3.7	2.3	10	16.8%	−0.73 [−1.65, 0.18]
Turgut 2017	0.76	1.27	15	0.99	1.34	15	23.1%	−0.17 [−0.89, 0.55]
Subtotal (95% CI)			**75**			**75**	**100.0%**	**−0.10 [−0.54, 0.35]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 5.27$, df = 3 ($P = .15$); $I^2 = 43\%$								
Test for overall effect: Z = 0.43 ($P = .67$)								
4.3.2 Pain - medium term								
Holmgren & Hallgren 2012	1.67	2.07	51	2.93	2.63	46	51.3%	−0.53 [−0.94, −0.13]
Hotta 2020	0.5	1.7	30	1.2	2.4	30	32.5%	−0.33 [−0.84, 0.18]
Turgut 2017	0.13	0.34	15	0.66	1.77	15	16.1%	−0.40 [−1.13, 0.32]
Subtotal (95% CI)			**96**			**91**	**100.0%**	**−0.45 [−0.74, −0.16]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 2 ($P = .83$); $I^2 = 0\%$								
Test for overall effect: Z = 3.01 ($P = .003$)								
4.3.3 Disability - short term								
Baskurt 2011	−82.61	10.33	20	−70.82	19.7	20	26.4%	−0.73 [−1.38, −0.09]
Hotta 2020	49.8	23.7	30	43.5	27.8	30	30.2%	0.24 [−0.27, 0.75]
Struyf 2013	35	14	10	48.7	11.3	10	19.1%	−1.03 [−1.98, −0.09]
Turgut 2017	20.18	20.45	15	27.95	16.75	15	24.3%	−0.40 [−1.13, 0.32]
Subtotal (95% CI)			**75**			**75**	**100.0%**	**−0.42 [−0.99, 0.16]**
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 8.48$, df = 3 ($P = .04$); $I^2 = 65\%$								
Test for overall effect: Z = 1.42 ($P = .16$)								
4.3.4 Disability - medium term								
Holmgren & Hallgren 2012	16	15	51	29	19	46	40.2%	−0.76 [−1.17, −0.34]
Hotta 2020	32.8	26	30	34.2	30	30	35.2%	−0.05 [−0.56, 0.46]
Turgut 2017	9.23	11.21	15	22.18	20.16	15	24.6%	−0.77 [−1.52, −0.03]
Subtotal (95% CI)			**96**			**91**	**100.0%**	**−0.51 [−1.01, −0.02]**
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 5.04$, df = 2 ($P = .08$); $I^2 = 60\%$								
Test for overall effect: Z = 2.03 ($P = .04$)								

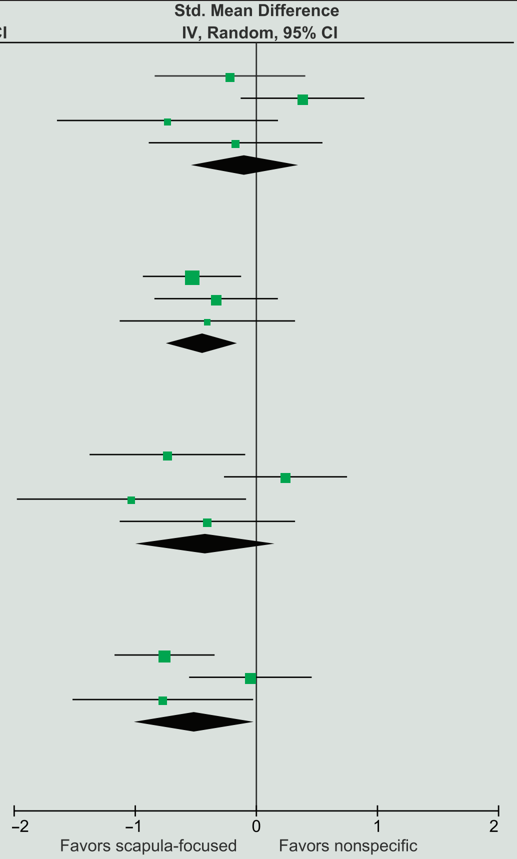

FIGURE 4. Efficacy of scapula-focused exercises programs compared to nonspecific exercises programs for change in self-reported pain and disability in adults with rotator cuff tendinopathy in the short and medium terms. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation; Std, standardized.

analyses reporting mean differences in pain were conducted and are reported in the **SUPPLEMENTAL APPENDIX**.

Certainty of Evidence

Certainty of the evidence regarding the efficacy of motor control exercise programs to reduce pain and disability in the short, medium, and long terms was considered low or moderate. Certainty of the evidence was low regarding the efficacy of eccentric exercise programs to reduce pain in the short and medium terms and for the efficacy of scapula-focused exercise programs to reduce pain in the medium term. All other analyses were of very low certainty. Certainty of evidence was downgraded by 1 or 2 points for risk of bias, inconsistency (heterogeneity), or imprecision of the estimates (**TABLE 2**).

DISCUSSION

For adults with RCRSP, motor control exercise programs were probably slightly superior to nonspecific exercise programs for reducing pain and disability in the short to long terms. Uncertainties remain for eccentric and scapula-focused exercise programs, which might be slightly superior to nonspecific exercise programs to reduce pain in the medium term, while it is very uncertain if they result in a greater reduction in disability. The evidence comparing high- and low-load exercise programs was very uncertain. There was no evidence to inform exercise prescription concerning the parameters of frequency or duration/time.

Clinical Implications

Based on low- to moderate-certainty evidence, motor control exercise programs probably outperform nonspecific exercise programs for reducing pain and disability in the short, medium, and long terms. Consistency of the results was observed across the 6 meta-analyses and the CIs included small to large effects in favor of these programs to trivial effect in favor of motor control exercise programs in 5 out of 6 analyses (trivial effect in favor of nonspecific exercise programs for the remaining analysis). Although most of the sensitivity analyses reported nonstatistically significant differences due to higher imprecision, the SMD estimates only slightly differ than the primary analyses SMD estimates, indicating that our results are robust. Sensitivity analyses on pain mean difference reported similar results. Therefore, the superior effect of motor control exercise programs appears to be small, although it may be

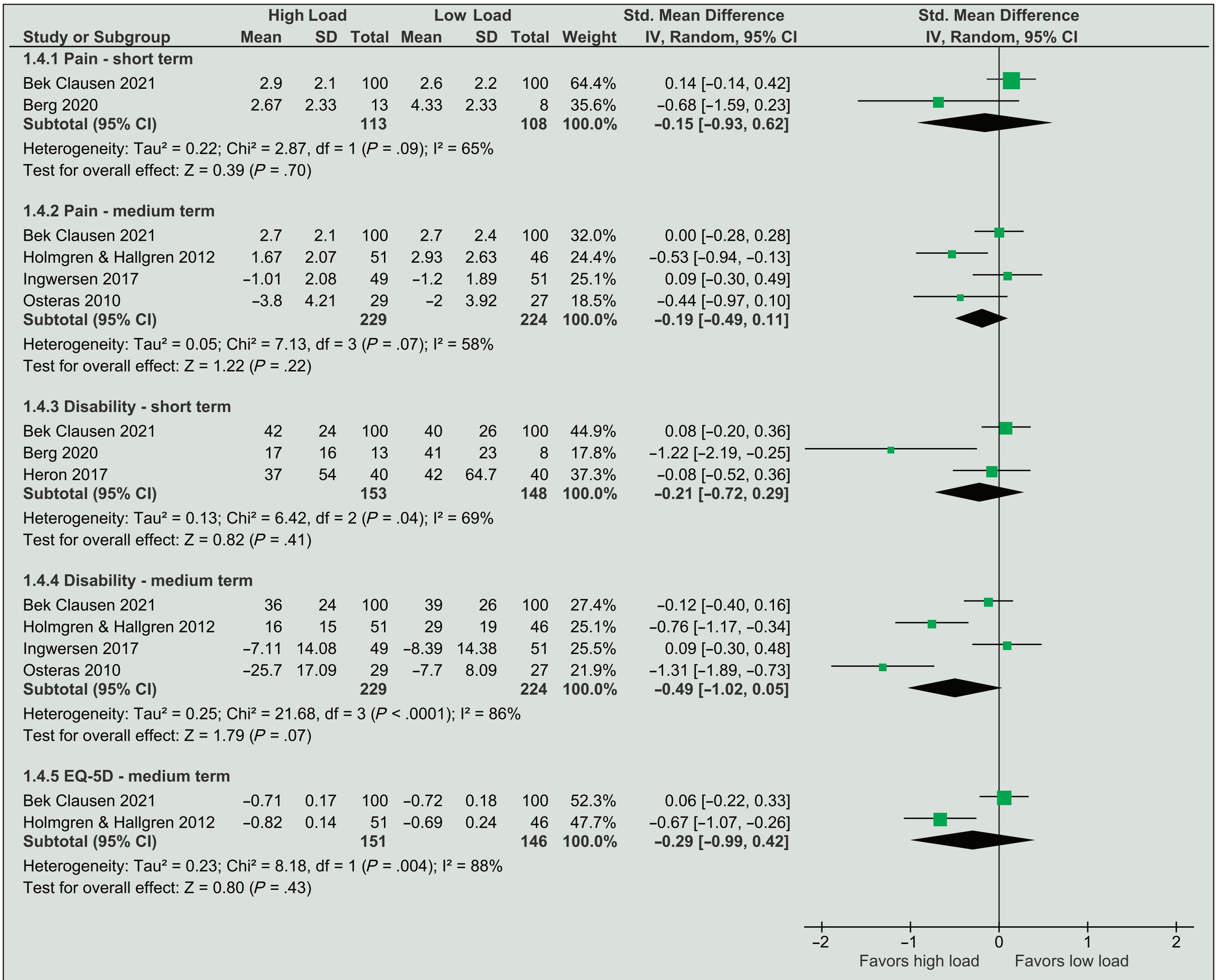

FIGURE 5. Efficacy of high-load exercises programs compared to low-load exercises programs for change in self-reported pain, disability, and EQ-5D in adults with rotator cuff tendinopathy in the short and medium terms. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation; Std, standardized.

trivial, moderate, or large based on the CIs. Other exercise program factors, such as exercise progression and pain levels during exercise, might contribute to these outcomes. A nonspecific exercise program was considered as a control intervention in 6 of the 8 RCTs, suggesting that these programs are more generic and less tailored to each individual. Therefore, some uncertainty remains as to whether the observed superiority of motor control exercise programs was due to the inclusion of motor control exercise or due to one of the abovementioned factors.

The efficacy of eccentric and scapula-focused exercise programs compared to nonspecific exercise programs also remains uncertain. All meta-analyses were of very low to low certainty of evidence and the reported CIs were large and often not statistically significant. While the analyses on pain at medium terms suggest a superiority of eccentric and scapula-focused exercises, further evidence is essential before reaching a definitive conclusion.

Comparison With Previous Systematic Reviews

Overall, there is a general agreement between the conclusions of previous systematic reviews and ours. Our review builds upon new RCTs and used the GRADE approach offering an updated perspective taking into account the certainty of the evidence.

Lafrance et al reported similar results in terms of the efficacy of motor control exercise programs compared to nonspecific exercise programs to reduce pain and disability for adults with various

TABLE 2 Summary of Clinical Efficacy of Exercise Programs for Adults With Rotator Cuff–Related Shoulder Pain

Interventions and Comparison	Outcomes	Differential Effect of the Intervention vs Comparison (95% CI)	Heterogeneity Prediction Intervals (I^2)	No. of Participants (Trials)	Certainty of the Evidence (GRADE)	Comments
Motor control exercise programs compared to nonspecific exercise programs	Pain - Short term	SMD **0.19 lower** (0.41 lower to 0.03 higher)[1,13]	Common effect size* (0%)	323 (7 RCTs)	⊕⊕⊕◯ Moderate[a]	**It is likely** that motor control exercise programs, when compared to nonspecific exercise programs, result in **small effect in favor of motor control to trivial effect in favor of nonspecific exercise** to reduce pain in the short term.
	Pain - Medium term	SMD **0.38 lower** (0.71 lower to 0.05 lower)[2,14]	−1.38 to 0.62 (48%)	286 (5 RCTs)	⊕⊕◯◯ Low[a,b]	The **evidence suggests** that motor control exercise programs, when compared to nonspecific exercise programs, result in **moderate to trivial** effects to reduce pain in the medium term.
	Pain - Long term	SMD **0.57 lower** (0.98 lower to 0.16 lower)	NA** (0%)	96 (2 RCTs)	⊕⊕◯◯ Low[a,b]	The **evidence suggests** that motor control exercise programs when compared to nonspecific exercise programs, result in **large to trivial** effects to reduce pain in the long term.
	Disability - Short term	SMD **0.29 lower** (0.51 lower to 0.07 lower)[3,15]	Common effect size* (0%)	323 (7 RCTs)	⊕⊕⊕◯ Moderate[a]	**It is likely** that motor control exercise programs, when compared to nonspecific exercise programs, result in **moderate to trivial** effects to reduce disability in the short and medium terms.
	Disability - Medium term	SMD **0.33 lower** (0.57 lower to 0.09 lower)[4,16]	Common effect size* (0%)	286 (5 RCTs)	⊕⊕⊕◯ Moderate[a]	
	Disability - Long term	SMD **0.48 lower** (0.88 lower to 0.07 lower)	NA** (0%)	96 (2 RCTs)	⊕⊕◯◯ Low[a,b]	The **evidence suggests** that motor control exercise programs when compared to nonspecific exercise programs, result in **large to trivial** effects to reduce disability in the long term.
Eccentric exercise programs compared to nonspecific exercise programs	Pain - Short term	SMD **0.32 lower** (0.75 lower to 0.12 higher)	NA** (0%)	82 (2 RCTs)	⊕⊕◯◯ Low[a,c]	The **evidence suggests** that eccentric exercise programs, when compared to nonspecific exercise programs, result in a **moderate effect in favor of eccentric to trivial effect in favor of nonspecific exercise** to reduce pain in the short term.
	Pain - Medium term	SMD **0.57 lower** (0.88 lower to 0.26 lower)[17]	Common effect size* (0%)	167 (3 RCTs)	⊕⊕◯◯ Low[a,c]	The **evidence suggests** that eccentric exercise programs, when compared to nonspecific exercise programs, result in a **large effect in favor of eccentric to trivial effect in favor of nonspecific exercise** to reduce pain in the short term.
	Disability - Short term	SMD **0.10 higher** (0.65 lower to 0.86 higher)[5]	−3.33 to 3.54 (83%)	177 (4 RCTs)	⊕◯◯◯ Very low[a,b,e]	The **evidence is very uncertain**. The confidence intervals are large and include small to large effects in favor of both interventions.
	Disability - Medium term	SMD **0.30 lower** (0.86 lower to 0.27 higher)[6,18]	−2.31 to 1.71(79%)	262 (5 RCTs)	⊕◯◯◯ Very low[a,b,e]	
Scapula-focused exercise programs compared to nonspecific exercise programs	Pain - Short term	SMD **0.1 lower** (0.54 lower to 0.35 higher)[7]	−1.70 to 1.49 (43%)	150 (4 RCTs)	⊕◯◯◯ Very low[a,b,c]	The **evidence is very uncertain**. The confidence intervals are large and include moderate effects in favor of scapula-focused exercise programs to small effects in favor of nonspecific exercise programs.
	Pain - Medium term	SMD **0.45 lower** (0.74 lower to 0.16 lower)[19]	Common effect size* (0%)	187 (3 RCTs)	⊕⊕◯◯ Low[a,c]	The **evidence suggests** that scapula-focused exercise programs when compared to nonspecific exercise programs, result in **moderate to trivial** effects to reduce pain in the medium term.
	Disability - Short term	SMD **0.42 lower** (0.99 lower to 0.16 higher)[8]	−2.79 to 1.94 (65%)	150 (4 RCTs)	⊕◯◯◯ Very low[a,b,c]	The **evidence is very uncertain**. The confidence intervals are large and include large effects in favor of scapula-focused exercise programs to trivial effects in favor of nonspecific exercise programs.
	Disability - Medium term	SMD **0.51 lower** (1.01 lower to 0.02 lower)[20]	−5.87 to 4.84 (60%)	187 (3 RCTs)	⊕◯◯◯ Very low[a,b,c]	The **evidence is very uncertain**. The confidence intervals are large and include large to trivial effects in favor of scapula-focused exercise programs.

High-load exercise programs compared to low-load exercise programs	Pain - Short term	SMD **0.15 lower** (0.93 lower to 0.62 higher)[9]	NA** (65%)	221 (2 RCTs)	⊕◯◯◯ Very low[b,e]	The **evidence is very uncertain**. The confidence intervals are large and include small to large effects in favor of high-load exercise programs and trivial to moderate effects in favor of low-load exercise programs.
	Pain - Medium term	SMD **0.19 lower** (0.49 lower to 0.11 higher)[10,21]	−1.36 to 0.98 (58%)	453 (4 RCTs)	⊕◯◯◯ Very low[a,b,c]	
	Disability - Short term	SMD **0.21 lower** (0.72 lower to 0.29 higher)[11]	−5.86 to 5.43 (69%)	301 (3 RCTs)	⊕◯◯◯ Very low[a,c,d]	
	Disability - Medium term	SMD **0.49 lower** (1.02 lower to 0.05 higher)[12,22]	−2.93 to 1.96 (86%)	453 (4 RCTs)	⊕◯◯◯ Very low[a,c,d]	
	EQ-5D - Medium term	SMD **0.29 lower** (0.99 lower to 0.42 higher)[23]	NA** (88%)	297 (2 RCTs)	⊕◯◯◯ Very low[a,b,e]	

Negative values favor the intervention exercise programs.
Abbreviations: CI, confidence interval; RCT, randomized controlled trial; SMD, standardized mean difference.
**Common effect size means that there is no heterogeneity and that the prediction interval is equal to the imprecision of the mean estimate (eg, motor control exercise programs; disability - short term, prediction interval = 0.51 lower to 0.07 lower).*
***Prediction interval can only be calculated if there are more than 2 trials.*
[a]Certainty was downgraded for serious risk of bias.
[b]Certainty was downgraded for serious inconsistency (heterogeneity).
[c]Certainty was downgraded for serious imprecision.
[d]Certainty was downgraded twice for very serious inconsistency (heterogeneity).
[e]Certainty was downgraded twice for very serious imprecision.
Sensitivity analyses excluding high-risk-of-bias trials. Forest plots are available in supplemental materials.
1. Motor control, pain – short term: SMD: −0.21 (−0.46 to 0.04), n = 245 (5 RCTs)
2. Motor control, pain – medium term: SMD: −0.38 (−0.93 to 0.17), n = 208 (3 RCTs)
3. Motor control, disability – short term: SMD: −0.31 (−0.62 to 0), n = 245 (5 RCTs)
4. Motor control, disability – medium term: SMD: −0.27 (−0.58 to 0.04), n = 208 (3 RCTs)
5. Eccentric, disability – short term: SMD: 0.5 (0.15 to 0.85), n = 131 (3 RCTs)
6. Eccentric, disability – medium term: SMD: 0.18 (−0.17 to 0.53), n = 129 (3 RCTs)
7. Scapula-focused, pain – short term: SMD: −0.11 (−0.72 to 0.50), n = 120 (3 RCTs)
8. Scapula-focused, disability – short term: SMD: −0.45 (−1.25 to 0.35), n = 120 (3 RCTs)
9. High load, pain – short term: SMD: −0.15 (−0.93 to 0.62), n = 221 (2 RCTs)
10. High load, pain – medium term: SMD: 0.03 (−0.19 to 0.26), n = 300 (2 RCTs)
11. High load, disability – short term: SMD: −0.48 (−1.75 to 0.78), n = 221 (2 RCTs)
12. High load, disability – medium term: SMD: −0.05 (−0.28 to 0.18), n = 300 (2 RCTs)
Sensitivity analyses excluding scapula-focused trials in the motor control analyses
13. Motor control, pain – short term: SMD: −0.14 (−0.4 to 0.11), n = 233 (4 RCTs)
14. Motor control, pain – medium term: SMD: −0.38 (−0.78 to 0.03), n = 256 (4 RCTs)
15. Motor control, disability – short term: SMD: −0.15 (−0.41 to 0.11), n = 233 (4 RCTs)
16. Motor control, disability – medium term: SMD: −0.28 (−0.53 to −0.04), n = 256 (4 RCTs)
Sensitivity analyses excluding the Holmgren & Hallgren trial
17. Eccentric, pain – medium term: SMD: −0.62 (−1.11 to −0.13), n = 70 (2 RCTs)
18. Eccentric, disability– medium term: SMD: −0.16 (−0.81 to 0.49), n = 165 (4 RCTs)
19. Scapula-focused, pain – medium term: SMD: −0.36 (−0.77 to 0.06), n = 90 (2 RCTs)
20. Scapula-focused, disability – medium term: SMD: −0.36 (−1.06 to 0.34), n = 90 (2 RCTs)
21. High load, pain – medium term: SMD: −0.05 (−0.31 to 0.2), n = 356 (3 RCTs)
22. High load, disability – medium term: SMD: −0.4 (−1.07 to 0.26), n = 356 (3 RCTs)
23. High load, EQ-5D – medium term: SMD: −0.4 (−1.07 to 0.26), n = 356 (3 RCTs)

upper and lower extremity musculoskeletal disorders including but not limited to RCRSP.[28]

Shire et al compared specific exercise programs including motor control and scapula-focused exercises to nonspecific exercise programs for adults with RCRSP. They concluded that there was insufficient evidence to determine if specific exercise programs are superior to nonspecific exercise programs. This systematic review, which was published 6 years ago, used different eligibility criteria and, thus, did not include any recent trials.[43]

Regarding eccentric exercise programs, Larsson et al reported similar results for pain and disability reduction at 6 to 8 weeks and at 12 weeks. Their conclusion was somewhat more definitive regarding pain reduction of eccentric exercise programs as they combined 6- to 12-week follow-ups in their primary analysis, while we differentiated these 2 timeframes as short and medium terms. They concluded that low-certainty evidence suggested that eccentric exercise programs may provide a small but likely not clinically important pain reduction when compared to other types of exercise programs at 6 to 12 weeks follow-up among adults with RCRSP.[29]

Regarding exercise intensity, Malliaras et al reported similar results and concluded that there was conflicting evidence regarding the efficacy of high-load exercise programs compared to low-load exercise programs to reduce pain and disability among adults with RCRSP.[35]

Unanswered Questions and Future Research

Several of the included trials did not thoroughly report all programs and exercise characteristics related to the FITT principles. While the frequency and duration of the intervention varied between the trials, no trial directly compared these parameters between groups, meaning these principles could not be separately examined in the current meta-analyses. Ideal exercise program frequency and duration remain unknown. Motor control exercise programs are probably slightly superior to nonspecific exercise programs. However, it is not clear if this superiority is due to the motor control exercises themselves or due to other components of the exercise programs such as the exercise progression and tailoring levels, which may explain the benefits observed compared to nonspecific exercise programs. Future trials should compare motor control and nonspecific exercise programs with similar load, progression, and tailoring levels to isolate the motor control components. Exercise adherence could also be an important factor in the effect of the exercise program and should be assessed in future trials. Trials comparing identical exercise types, but prescribed with different exercise frequency or duration would further inform exercise prescription in people with RCRSP.

Limitations

There are no important methodological limitations in the present review as it conforms to the PRISMA and Cochrane Collaboration guidelines.[20,39] Prediction intervals were also calculated to examine heterogeneity. Certainty of the evidence was assessed using the GRADE approach, and conclusions were made accordingly. However, the limited number of trials per meta-analysis should be highlighted, especially for eccentric or scapula-focused exercise programs and for higher-load exercise programs. There were wider CIs and lower certainty of the evidence. Lack of trials also limited subgroup analyses or meta-regression, which could have highlighted which factors are associated with greater improvement.

Most of the included RCTs had moderate to high risk of bias, with only 6 at low risk of bias. Sample size is another limitation, with most of the trials including fewer than 50 patients (median = 48). Although it might not be considered as a methodological limitation, exercise programs labeling is a challenge. We classified some RCTs into both motor control exercise and scapula-focused exercise programs. A different classification of some trials in our review regarding the types of exercise could lead to slightly different results. To assess the robustness of our results, we conducted several sensitivity analyses, which all reported similar results and did not alter our conclusions. Certain components of the specific exercise programs, such as eccentric exercises or scapula-specific exercises, were also included as part of some of the nonspecific exercise programs.

CONCLUSION

Motor control exercise programs resulted in greater to comparable pain and disability reductions when compared to nonspecific exercise programs in the short, medium, and long terms. The differential clinical effect of motor control exercise programs may be trivial to moderate. Motor control exercise programs are probably slightly superior to nonspecific exercise programs. For eccentric and scapula-focused exercise programs versus nonspecific exercise programs and for higher- versus lower-load exercise programs, uncertainties persist due to low to very low certainty of evidence. ◉

KEY POINTS

FINDINGS: In adults with RCRSP, motor control exercise programs are probably slightly superior to nonspecific exercise programs to reduce pain and disability in the short to long terms. However, it is not clear if these effects are due to the motor control exercises itself or because of other components of the exercise programs such as the exercise progression and tailoring levels. In adults with RCRSP, the efficacy of eccentric and scapula-focused exercise programs compared to nonspecific exercise programs, and high-intensity programs compared to those with lower intensity, remains uncertain. There is no evidence for the efficacy of different frequencies or time parameters of exercise programs for RCRSP.
IMPLICATIONS: When prescribing an exercise program, clinicians should consider the exercise types (such as motor

control), progression, and tailor the program to patients' needs and preferences as these programs (especially motor control exercise programs) appear to be superior to nonspecific and more generic exercise programs.

CAUTION: Our findings should be interpreted with caution as our results are of very low to moderate certainties. For motor control and scapula-focused exercises, the exercise type was not fully isolated in the included trials as other factors such as the progression and tailoring level differed between the exercise groups.

STUDY DETAILS

AUTHOR CONTRIBUTIONS: Concept/idea/research design: Simon Lafrance, Maxime Charron, François Desmeules, Birgit Juul-Kristensen, and Karen McCreesh. Acquisition of data: Maxime Charron, Marc-Olivier Dubé, Birgit Juul-Kristensen, Leonora Kennedy, and Karen McCreesh. Analysis and interpretation of data: Simon Lafrance, Leonora Kennedy, and Karen McCreesh. Writing/review/editing of manuscript: Simon Lafrance, Maxime Charron, Marc-Olivier Dubé, François Desmeules, Jean-Sébastien Roy, Birgit Juul-Kristensen, Leonora Kennedy, and Karen McCreesh. Final approval of the manuscript: Simon Lafrance, Maxime Charron, Marc-Olivier Dubé, François Desmeules, Jean-Sébastien Roy, Birgit Juul-Kristensen, Leonora Kennedy, and Karen McCreesh. Acquisition of funding: François Desmeules and Karen McCreesh.

DATA SHARING: All data relevant to the study are included in the article or are available as **SUPPLEMENTAL APPENDIX**.

PATIENT AND PUBLIC INVOLVEMENT: Patients and the public were not involved in the research.

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