RESEARCH ARTICLE





a systematic review and meta-analysis ZhiBo Deng¹, JiangPing Wu¹, KaiYing Tang¹, Han Shu¹, Ting Wang¹, FuBing Li^{2*} and Mao Nie^{1*}

with open reduction and internal fixation:

beneficial for distal radius fractures treated

In adults, early mobilization may be

Abstract

Objectives: It remains debatable if early mobilization (EM) yields a better clinical outcome than the late mobilization (LM) in adults with an acute and displaced distal radial fracture (DRF) of open reduction internal fixation (ORIF). Therefore, we aimed to perform a systematic review and meta-analysis of randomized controlled trials (RCTs), comparing clinical results with the safety of EM with LM following ORIF.

Methods: Databases such as Medline, Cochrane Central Register, and Embase were searched from Jan 1, 2000, to July 31, 2021, and RCTs comparing EM with LM for DRF with ORIF were included in the analysis. The primary outcome of study included disabilities of the Arm, Shoulder, and Hand (DASH) score at different follow-up times. Wherever the secondary outcomes included patient-rated wrist evaluation (PRWE), grip strength (GS), visual analog scale (VAS), wrist range of motion (WROM), and associated complications, the two independent reviewers did data extraction for the analysis. Effect sizes of outcome for each group were pooled using random-effects models; thereafter, the results were represented in the forest plots.

Results: Nine RCTs with 293 EM and 303 LM participants were identified and included in the study. Our analysis showed that the DASH score of the EM group was significantly better than LM group at the six weeks postoperatively (-10.15; 95% CI - 15.74 to - 4.57, P < 0.01). Besides, the EM group also had better outcomes in PRWE, GS and WROM at 6 weeks. However, EM showed potential higher rate for implant loosening and/or fracture re-displacement complication (3.00; 95% CI 1.02–8.83, P = 0.05).

Conclusion: Functionally, at earlier stages, EM for patients with DRF of ORIF may have a beneficial effect than LM. The mean differences in the DASH score at 6 weeks surpassed the minimal clinically important difference; however, the potentially higher risk of implant loosening and/or fracture re-displacement cannot be ignored. Due to the lack of definitive evidence, multicenter and large sample RCTs are required for determining the optimal rehabilitation protocol for DRF with ORIF.

PROSPERO registration number: CRD42021240214 2021/2/28.

Keywords: Meta-analysis, Distal radius fracture, Open reduction internal fixation, Early mobilization, Late mobilization

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Introduction

Distal radius fracture (DRF) is one of the most common fracture [1, 2]. Particularly in an aging society, the incidence of DRF will continue to grow [3, 4]. Despite

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the existing variations, in the view of significantly better results in the reduction and functional recovery of open reduction internal fixation (ORIF) [5], it has become the primary surgical technique for the treatment of such fractures [6, 7]. However, rehabilitation type and immobilization duration following the plate fixation of DRFs remain uncertain [8], whereas persistent plaster fixation has been repeatedly questioned as a conventional rehabilitation program [9]. For patients in the early mobilization (EM) group, the satisfaction level remains higher due to the self-opportunity of maintaining basic hygiene without any protective measures [10]. However, EM is controversial due to the local pain-associated complications, poor wound healing, implant loosening, loss of reduction, and internal fixation failure [11].

A randomized controlled study demonstrated that EM positively impacted the surgical treatment outcome and caused no additional complications compared to late immobilization (LM) [12]. Furthermore, a prospective study revealed that EM had better patient-reported outcomes and wrist range of motion (WROM). Meanwhile, it did not require multiple follow-ups and guidance from physiotherapists during rehabilitation [13]. Another study reported that the LM does not lead to decreased wrist motion compared to initial wrist motion [10, 14]. Furthermore, Andrade et al., have reported the comparative more use of opioids in the early active groups [15]. In the light of these results, after the surgery, the postoperative fixation time ranges from immediate mobilization to the 6 weeks of cast immobilization, based on the different practices of the surgeons [13, 16–18].

To the best of our knowledge, no evidence-based medical study compared the EM with the conventional LM after ORIF of DRF. Therefore, we performed systematic review and meta-analysis based on randomized controlled studies (RCTs) for exploring the advantage of EM protocol over LM protocol in respect to clinical outcomes and complications.

Materials and methods

Study method

Our systematic review with meta-analysis performed on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Additional file 1) [19]. Search strategy, trial selection, eligibility criteria, data collection, risk of bias assessment, and analysis process were duly conducted according to the predefined protocol (https://www.crd.york.ac.uk/PROSPERO/; PROSPERO: CRD42021240214).

Search strategy and trial selection

The databases such as Medline, Cochrane Central Register, and Embase were searched from Jan 1, 2000, to June 30, 2021. The keywords used to explore the potential published RCTs were as follows: "Early mobilization," "Accelerated rehabilitation," "Delayed motion," "Distal radius fractures," "Distal radius," and "Randomized Controlled Trials." After dataset de-duplication, all titles were further filtered, and only relevant abstracts were reviewed again. Finally, the full text of eligible trials was studied before making the final inclusion. Reference lists of identified studies were also cross-checked to prevent any overlooked relevant trials.

Inclusion criteria

Inclusion criteria were defined based on Population, Intervention, Comparison, and Outcome (PICO) method [20].

- 1. Population: Adults \geq 18 years with a diagnosed DRF from acute trauma and open reduction internal fixation treatment.
- 2. Type of Intervention: Early mobilization group (immobilization period of ≤ 2 weeks); accelerated rehabilitation scheme (beginning of a passive and/ or active wrist exercise program, immediately after internal fixation).
- 3. Type of Comparison: Late mobilization group (more immobilization period>2 weeks, and then start of exercise program); standard rehabilitation scheme (No movement of the wrist until the cast removal).
- 4. Outcomes: At least one of the following results was required: Disabilities of the Arm, Shoulder, and Hand (DASH), Patient-Rated Wrist Evaluation (PRWE), grip strength (GS), visual analog scale (VAS), wrist range of motion (WROM) and associated complications.
- 5. Type of Study Design: Prospective controlled clinical trials or Randomized Controlled Trials (RCTs) published in English.

Exclusion Criteria: (1) Studies on other limb fractures other than DRF and (2) studies reporting only the radiological result.

Data extraction

Two independent authors (KY T and HS) extracted raw data from the included studies using pre-designed data extraction tables. In the study, three or more arms were included. Then, the data were pooled from the treatment arms with the earliest motion group and the last motion group. In the studies not reporting numeric value, manual measurements of published charts were performed. Also, in the dataset, not written in standard form, the standard deviations were approximately as range/4 [21]. It is worth noting that the QuickDASH is



a concept-retention version of DASH, which is similar to the complete DASH in terms of properties and scores [22]. We contacted the corresponding author to obtain the dataset, for studies containing the result of interest but with original data non-availability. Besides, any disagreements in the process were also resolved by the general consensus.

Risk of bias assessment

The risk of bias assessment was conducted based on the Cochrane Risk of Bias Tool [23]. In addition, the quality of included RCTs was also evaluated from the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blind outcome assessment, incomplete outcome data, selective reporting, and other sources of biases in the study. As a result, the overall quality of each study was classified as unclear, low, or high risk of bias. Meanwhile, articles with low risk of bias were also defined as four or more meeting criteria.

Evidence assessment with the GRADE approach

The evidence assessment was performed using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The outcomes were assessed for the following elements: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Statistical analysis

Review Manager Software (Revman 5.3.3, Cochrane Collaboration, Oxford, United Kingdom) was used for the pooled data statistical analyses. The continuous variable outcomes (DASH, PRWE, VAS, GS, WROM) were represented as mean difference (MD) with a 95% confidence interval (95% CI). Similarly, dichotomous outcomes (complications) were represented as risk ratio (RR) with 95% CI. Heterogeneity among the studies was also assessed using the I^2 test [24], where $I^2 > 50\%$ indicates significant heterogeneity and $I^2 < 50\%$ was considered to have low heterogeneity; thus for the analysis,



the random-effect model and fixed-effect model were used, respectively. Additionally, a P value of < 0.05 was considered statistically significant. Meanwhile, the MD of DASH was compared with the minimal clinically important difference (MCID), estimated at 10 in DRF to evaluate its clinical relevance [25]. The sensitivity analysis was performed to explore the reliability of the outcomes. Furthermore, publication bias was examined by Begg's rank correlation and Egger's weighted regression method.

Results

Search outcomes and trial characteristics

As shown in Fig. 1, a total of 981 potentially relevant articles were retrieved from all the databases, but only 243 of them were retained for study, after the removal

of the duplicates. Following the screening of the titles and abstracts, 221 articles were further excluded. The remaining 22 full-text articles were carefully evaluated, and 13 were excluded after the final screening due to variable reasons. Finally, 9 RCTs meeting the inclusion criteria were taken for comprehensive evaluation of this meta-analysis [10, 12–15, 17, 18, 26, 27]. Quality assessment of the included studies is shown in Fig. 2, and no investigation was excluded on bias concern. The essential characteristics of the included studies are also tabulated in Table 1. The sample sizes of the 9 studies ranged between 30 and 119. Whereas between the 293 EM and 303 LM cases, no significant differences were observed in participants demographics or fracture type.

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References	Country	No. of	Age(years) (EM/LM)	Male (%) (EM/LM)	AO classification	Intervention		Outcome measures
		patients (EM/LM)			(%	EM	ΓW	
Lozano [14]	USA	30/30	55/51	37/33	40:3:57/37:23:40	Removed patients' thermoplastic splint and performed active and active-assisted wrist motion exercises at post- operative 1st week	Wore thermoplastic splint at all times. Wrist motion exercises were initiated at 6-weeks	DASH, VAS, WROM, GS, complications
Brehmer [26]	USA	36/42	49.8/55.3	25/29	67:3:30/55:5:40	Started wrist/forearm pas- sive range of motion and strengthened exercise at 2-weeks	Started wrist passive range of motion and strength- ened exercise at 6-weeks	DASH, WROM, GS, complica- tions
Quadlbauer [12]	Austria	15/15	49.1 ± 15.4/58.8 ± 12.1	13/15	7:7:86/0:0:100	Wore a removable thermo- plastic splint on day 1 after surgery for 1 week	Wore a non-removable plaster cast for 5 weeks after surgery	DASH, PRWE, VAS, WROM, complications
Watson [17]	Australia	46/46	54.0 ± 15.6/52.0 ± 15.9	37/24.4	9:77:14/11:67:22	After cast removal at 1st week postoperatively, a standardized education and exercise program was adopted for 6 weeks	After cast removal at 6-weeks, a standardized education and exercise program was adopted for 6 weeks	DASH, PRWE, VAS, WROM, GS, complications
Andrade [15]	Brazil	19/20	51.2 土 16.6/47.6 土 15.1	42/45	0:0:19/0:5:95	Early wrist mobilization with inelastic bandage after surgery	A short forearm splint for 2 weeks after surgery	DASH, PRWE, VAS, WROM, GS, complications
Clementsen [13]	Norway	57/62	55 土 12.4/55 土 11.9	7/11	100.00/100.00	Plaster splint was removed at postoperative 2–3 days. Patients met with the institution's physiotherapist every other week during the first 3 months	Patients wore dorsal splint for 2 weeks and only met with the physiotherapist once splint was removed	DASH, PRWE, VAS, WROM, GS, complications
Sørensen [10]	Denmark	47/48	67.1 ± 8.4/67 ± 8.5	X	36:19:45/33:10:57	Wore removable orthosis (wrist lacer) last 2 weeks, and then started non- weight-bearing exercises of fingers and wrist from the postoperative 1st day	Wore standard dorsal plaster cast for 2 weeks, and then wore removable orthosis to exercises	DASH, WROM, GS, complica- tions
Dennison [18]	USA	18/15	54.9 ± 18.4/53.1 ± 14.6	6/7	67:33:0/67:33:0	Initiated an active and pas- sive wrist motion protocol at postoperative 14 days	Delayed wrist motion was initiated at postoperative 5 weeks	DASH, PRWE, VAS, WROM, GS, complications

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References	Country	No. of	Age(years) (EM/LM)	Male (%) (EM/LM)	AO classification	Intervention		Outcome measures
		patients (EM/LM)			(% of A:B:C) (EM/ LM)	EM	ΓW	
Zeckey [27]	Germany	25/25	82 ± 3/80 ± 3.5	6/8	16:4:80/8:8:84	Performing patients'own training frequency with early mobilization and a pain-adapted increase in weight-bearing without immobilization	Wrist orthosis in a func- tional position for 4 weeks	WROM, GS, complications

EM early motion, LM late motion, NR not report, DASH the Disabilities of the Arm, Shoulder, and Hand, PRWE Patient-Rated Wrist Evaluation, WROM wrist range of motion, GS grip strength



Primary outcome DASH scores

As shown in Fig. 3, DASH scores were available in 8 studies [10, 12–15, 17, 18, 26] for total of 546 patients. The DASH scores in EM were significantly better when compared with LM at 6 and 24 weeks postoperatively, with mean differences (MDs) of -10.15 (95% CI -15.74 to -4.57, P < 0.01) and -1.77 (95% CI -3.09 to -0.45, P < 0.01), respectively. Interestingly, MD at the 6th week reached the MCID value of 10. However, EM had a similar outcome to LM at the 12th and 48th week postoperatively, with MDs of -1.61 (95% CI -4.37-1.14, P = 0.25) and 0.37 (95% CI -1.05-1.79,

P = 0.61), respectively. The summarized outcomes were also evaluated as a moderate or lower heterogeneity, with $I^2 = 77\%$, 53%, 0%, and 0% for the 6th, 12th, 24th, and 48th week postoperatively, respectively.

Secondary outcomes PRWE scores

As shown in Fig. 4, four studies [12, 13, 17, 18] with 274 patients reported data on PRWE and lower heterogeneity ($l^2=31\%$, $l^2=12\%$, $l^2=0\%$) for PRWE scores at 6th, 12th, and 48th week postoperatively. The outcome showed that the EM group had improved PRWE scores



	early	y moti	on	late	motio	on		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
4.1.1 6 weeks									
Andrade 2019	2.8	2	19	2.2	2.8	20	1.6%	0.60 [-0.92, 2.12]	
Clementsen 2019	1.8	1.8	57	2.2	1.7	62	9.4%	-0.40 [-1.03, 0.23]	
Dennison 2020	0.8	1.1	18	1.5	1.5	15	4.5%	-0.70 [-1.61, 0.21]	
Quadibauer 2017	1.54	1.18	15	2.24	1.96	15	2.8%	-0.70 [-1.86, 0.46]	
Subtotal (95% CI)			109			112	18.3%	-0.43 [-0.88, 0.02]	
Heterogeneity: Tau ² =	: 0.00; C	hi² = 2	.31, df=	= 3 (P =	0.51);	$ ^{2} = 0\%$			
Test for overall effect:	Z=1.87	' (P = 0	0.06)						
4.1.2 12 weeks									
Andrade 2019	0.7	1	19	1.8	2.6	20	2.5%	-1.10 [-2.32, 0.12]	
Clementsen 2019	1.1	1.6	57	1	1.2	62	14.3%	0.10 (-0.41, 0.61)	
Lozano 2008	2.4	2.25	30	2.4	2.25	30	2.9%	0.00 [-1.14, 1.14]	
Quadibauer 2017	0.6	0.99	15	0.88	0.95	15	7.8%	-0.28 [-0.97, 0.41]	
Subtotal (95% CI)			121			127	27.5%	-0.15 [-0.56, 0.26]	
Heterogeneity: Tau ² =	: 0.02; C	hi² = 3	.41, df=	= 3 (P =	0.33);	I ² = 12 ⁹	%		
Test for overall effect:	Z = 0.72	! (P = 0	0.47)						
4.1.3 24 weeks									
Andrade 2019	1.1	1.4	19	1.7	2.9	20	1.9%	-0.60 [-2.02, 0.82]	
Clementsen 2019	0.7	1.8	57	0.7	1.2	62	12.2%	0.00 [-0.55, 0.55]	
Lozano 2008	1.5	0.75	30	1.9	1.5	30	10.4%	-0.40 [-1.00, 0.20]	
Quadibauer 2017	0.13	0.52	15	0.25	0.47	15	29.8%	-0.12 [-0.47, 0.23]	
Subtotal (95% CI)			121			127	54.2%	-0.16 [-0.43, 0.10]	◆
Heterogeneity: Tau ² =	: 0.00; C	hi ² = 1	.35, df=	= 3 (P =	0.72);	$ ^{2} = 0\%$			
Test for overall effect:	Z=1.22	! (P = 0).22)						
Total (95% CI)			351			366	100.0%	-0.20 [-0.40, -0.01]	◆
Heterogeneity: Tau ² =	: 0.00; C	hi² = 8	.31. df=	= 11 (P :	= 0.69): $I^2 = 0^9$	%		<u> </u>
Test for overall effect:	Z = 2.05	i (Ρ = (0.04)						-2 -1 0 1 2
To at fay and avanual diff							~~		early motion late motion
rest for subdroup din	rerences	Chi-	= 1.12.	df = 2 (i	r = 0.5	o∩. ⊨=	0%		

	early	y motio	n	lat	e motior	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
5.1.1 2 weeks									
Brehmer 2014	11.8	6.5	36	10	6.5	36	5.0%	1.80 [-1.20, 4.80]	
Zeckey 2020	7.9	3	25	5.5	1.5	25	7.4%	2.40 [1.09, 3.71]	
Subtotal (95% CI)			61			61	12.4%	2.30 [1.10, 3.51]	•
Heterogeneity: Tau ² =	0.00; C	hi² = 0.1	13, df=	= 1 (P =	0.72); I ²	= 0%			
Test for overall effect:	Z= 3.75	5(P = 0)	.0002)						
5.1.2 6 weeks									
Brehmer 2014	22.2	10	36	16.8	10	36	3.2%	5.40 [0.78, 10.02]	
Clementsen 2019	13.6	7.7	57	12.2	5.9	62	5.7%	1.40 [-1.08, 3.88]	
Quadibauer 2017	14.46	9.18	15	4.56	3.92	15	2.8%	9.90 [4.85, 14.95]	
Sorensen 2020	11	5.4	47	9.2	5.7	48	6.1%	1.80 [-0.43, 4.03]	+
Watson 2018	14.9	9.9	46	12	9.1	46	3.9%	2.90 [-0.99, 6.79]	
Zeckey 2020	10.45	3.6	25	8.25	3.61	25	6.4%	2.20 [0.20, 4.20]	
Subtotal (95% CI)			226			232	28.1%	3.11 [1.27, 4.95]	-
Heterogeneity: Tau² =	2.66; C	hi ² = 11	.00, dt	f= 5 (P =	= 0.05);	r = 55°	%		
Test for overall effect:	Z = 3.32	2 (P = 0	.0009)						
5.1.3 12 weeks									
Brehmer 2014	31.7	9.5	36	29.5	9.5	36	3.4%	2.20 [-2.19, 6.59]	
Clementsen 2019	21.2	8.5	57	20.5	7.7	62	5.1%	0.70 [-2.22, 3.62]	
Lozano 2008	18.4	10.4	30	19.9	7.6	30	3.2%	-1.50 [-6.11, 3.11]	
Quadibauer 2017	22.73	7.58	15	16.29	9.73	15	2.1%	6.44 [0.20, 12.68]	
Sorensen 2020	17.6	6	47	16.6	7	48	5.5%	1.00 [-1.62, 3.62]	
Zeckey 2020	13.5	3.03	25	13.75	3.59	25	6.7%	-0.25 [-2.09, 1.59]	
Subtotal (95% CI)			210			216	25.9%	0.61 [-0.72, 1.93]	-
Heterogeneity: Tau ² =	= 0.30; C	hi ² = 5.	57, df=	= 5 (P =	0.35); l²	= 10%			
Test for overall effect:	Z = 0.89	9 (P = 0	.37)						
5.1.4 24 weeks									
Brehmer 2014	31.2	98	36	25.9	9.8	36	3.2%	5 30 10 77, 9 831	
Lozano 2008	23	10	30	24.9	13	30	2.3%	-1.90 [-7.77.3.97]	
Quadibauer 2017	26.96	7.09	15	20.98	10.84	15	1.9%	5.98 (-0.57, 12,53)	
Sorensen 2020	20.6	7.2	47	20.5	8.2	48	4.8%	0.10 (-3.00, 3.20)	
Watson 2018	22.7	12.4	46	24.5	16.8	46	2.2%	-1.80 [-7.83, 4.23]	
Zeckev 2020	14.45	3	25	18.6	5.03	25	6.0%	-4.15 [-6.45, -1.85]	
Subtotal (95% CI)			199			200	20.5%	0.27 [-3.17, 3.70]	
Heterogeneity: Tau ² =	12.67; 0	Chi² = 1	9.63,	df = 5 (F	= 0.001); ² = 3	75%		
Test for overall effect:	Z= 0.15	5 (P = 0	.88)						
5.1.5 48 weeks									
Quadibauer 2017	27.99	8.03	15	24.45	11.71	15	1.7%	3.54 [-3.65, 10.73]	
Sorensen 2020	22.2	6.8	47	21.9	8.6	48	4.8%	0.30 [-2.81, 3.41]	
Zeckey 2020	19	2.77	25	18.8	3.63	25	6.7%	0.20 [-1.59, 1.99]	
Subtotal (95% CI)			87			88	13.2%	0.37 [-1.14, 1.89]	—
Heterogeneity: Tau ² =	= 0.00; C	nr= 0.1	/8,df=	= 2 (P =	0.68); l²	= 0%			
Test for overall effect:	∠=0.48	5 (P = 0	.03)						
Total (95% CI)			783			797	100.0%	1.44 [0.40, 2.49]	◆
Heterogeneity: Tau ² =	3.34; C	hi² = 57	.15, di	í = 22 (F	< 0.000)1); l² =	62%	· · · · ·	
Test for overall effect:	Z= 2.72	2 (P = 0	.007)						-10 -5 U 5 10
Test for subaroup dif	ferences	: Chi ² =	9.00.	df = 4 (l	P = 0.06). I ² = 5	5.6%		eany motion rate motion
Fig. 6 Forest plot of g	rip stren	gth in a	meta	-analysi	S				

than the LM group, with MD of - 12.47 (95% CI - 18.10 to - 6.84, $P\!<\!0.01)$ at 6 weeks postoperatively.

VAS scores

As shown in Fig. 5, five studies [12–15, 18] with 281 patients had data on VAS scores. Lower heterogeneity was found for the VAS scores ($I^2 = 0\%$, $I^2 = 12\%$, $I^2 = 0\%$)

at 6th, 12th, and 48th week postoperatively, although no significant differences were observed between EM and LM group (P > 0.05).

	ear	ly motio	n	late	e motior	n		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
6.1.1 2 weeks									
Brehmer 2014	36	11.66	36	29	11.66	42	4.4%	7.00 [1.81, 12.19]	
Zeckey 2020	30	13.1	25	20	5	25	4.3%	10.00 [4.50, 15.50]	
Subtotal (95% CI)			61			67	8.8%	8.41 [4.64, 12.19]	◆
Heterogeneity: Tau ² =	0.00; C	hi² = 0.6	0, df =	1 (P = 0	.44); 2 =	:0%			
Test for overall effect:	Z = 4.37	' (P < 0.0	0001)						
6.1.2 6 weeks									
Brehmer 2014	56	21.86	36	39	21.86	42	3.2%	17.00 [7.27, 26.73]	
Clementsen 2019	38.2	16	57	37.7	15.6	62	4.3%	0.50 [-5.19, 6.19]	
Quadibauer 2017	45.33	8.76	15	20.77	11.88	15	3.8%	24.56 [17.09, 32.03]	
Sorensen 2020	25.4	9.3	47	27.8	12.1	48	4.6%	-2.40 [-6.73, 1.93]	
Watson 2018	52.3	15.9	46	39.8	15.2	46	4.1%	12.50 [6.14, 18.86]	
Zeckey 2020	40	10	25	25	9.4	25	4.4%	15.00 [9.62, 20.38]	
Subtotal (95% CI)			226			238	24.5%	10.87 [2.30, 19.45]	
Heterogeneity: Tau ² =	103.38;	Chi ² = 5	59.36,	df = 5 (P	< 0.000	001); I²	= 92%		
Test for overall effect:	Z = 2.49) (P = 0.0	01)						
6.1.3 12 weeks									
Brehmer 2014	75	13.33	36	67	13.33	42	4.2%	8.00 [2.07, 13.93]	
Clementsen 2019	51.4	14.8	57	51	11.1	62	4.5%	0.40 [-4.33, 5.13]	
Lozano 2008	55	12.5	30	56	18.75	30	3.7%	-1.00 [-9.06, 7.06]	
Quadibauer 2017	60.33	10.26	15	50	17.56	15	3.1%	10.33 [0.04, 20.62]	
Sorensen 2020	45.2	8.8	47	43.2	11.6	48	4.7%	2.00 [-2.14, 6.14]	
Zeckey 2020	50	5	25	30	11.25	25	4.5%	20.00 [15.17, 24.83]	
Subtotal (95% CI)			210			222	24.7%	6.62 [-0.42, 13.65]	
Heterogeneity: Tau² =	66.40; 0	Chi² = 45	5.09, di	f = 5 (P ·	< 0.0000	01); I ² =	89%		
Test for overall effect:	Z = 1.84	(P = 0.0	07)						
6.1.4 24 weeks									
Brehmer 2014	65	11.05	36	60	11.05	42	4.5%	5.00 [0.08, 9.92]	
Lozano 2008	68	13.75	30	67	15.25	30	3.9%	1.00 [-6.35, 8.35]	
Quadibauer 2017	69.67	9.72	15	58.85	15.96	15	3.3%	10.82 [1.36, 20.28]	
Sorensen 2020	51.8	8	47	51.3	11.7	48	4.7%	0.50 [-3.52, 4.52]	
Watson 2018	61	15	46	61.7	11.1	46	4.4%	-0.70 [-6.09, 4.69]	
Zeckey 2020	40	5	25	40	8.15	25	4.8%	0.00 [-3.75, 3.75]	
Subtotal (95% CI)			199			206	25.5%	1.72 [-0.84, 4.29]	
Heterogeneity: Tau* =	3.04; C	nr= 7.1	9, dt =	5 (P = U	.21); 1*=	: 30%			
Test for overall effect:	Z = 1.32	? (P = 0.1	19)						
6 4 E 40 weeke									
0.1.5 40 weeks	60.7	107	67	64	40.2	60	1.00	4 20 / 5 60 2 001	
Ciementsen 2019	59.7	13.7	57	01	10.3	62	4.0%	-1.30 [-5.68, 3.08]	
Quadibauer 2017	08.07 50.5	10.86	15	63.40	14.05	15	3.4%	5.21 [-3.78, 14.20]	
Sorensen 2020	50.5	9.7	47	54.0	11	48	4.7%	1.90 [-2.27, 0.07]	
Zeckey ZUZU	50	12.5	25	40	15	25	3.8%	10.00 [2.35, 17.65]	
Subtore (95% CI)	10.07	Chiz - C	07 46	- 2 /0 -	0.001-12	100	10.5%	2.97 [-1.45, 7.58]	
Test for everall offerst	7 4 22	UNE = 0.	o/,u⊺≎ ∖o∖	= 3 (P =	0.08); 1*	= 50%			
rest for overall effect:	2 = 1.32	: (P = 0.1	19)						
Total (95% CI)			840			883	100.0%	6 15 [3 30, 9 01]	•
Heteroneneity Tou? -	40.97.0	Chi≅ = 14	15 02	df = 23 /	P<000	10011-1	2 = 84%	0110 [0100, 0101]	
Test for overall effect	7 = 4.22) (P < 0 (10011	ui – 20 (, -0.00	,001),1	- 04 70		-20 -10 0 10 20
Test for subaroun diff	2 - 4.22	: (1 5 0.0	11 46	df = A/P	2 = 0.02) Z - 6	51%		early motion late motion
	vior ir		- 1.40. opelus	ai – 4 (r	- 0.02	0	0.170		
rig. / Forest plot of fle	exion in	a meta-	andiysi	15					

GS

As shown in Fig. 6, seven studies [10, 12–14, 17, 26, 27] with 518 patients described data on the grip strength (Kg). The summarized outcomes were evaluated as a slightly moderate or lower heterogeneity, with $I^2 = 0\%$, 55%, 10%, 75%, and 0% at the 2nd, 6th, 12th, 24th, and 48th week postoperatively. Meta-analysis showed that

the EM group had a statistically better grip strength than the LM group at 2nd and 6th week postoperatively, with MD of 2.30 (95% CI 1.10–3.51, P<0.01) and 3.11 (95% CI 1.27–4.95, P<0.01), respectively.

	ear	y motio	n	late	e motior	ı		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
6.2.1 2 weeks									
Brehmer 2014	44	8.98	36	42	8.98	42	4.6%	2.00 [-2.00, 6.00]	- +-
Zeckey 2020	30	6.25	25	20	6.25	25	4.7%	10.00 [6.54, 13.46]	
Subtotal (95% CI)			61			67	9.3%	6.06 [-1.77, 13.90]	
Heterogeneity: Tau ² =	28.36; (Chi² = 8.	79, df =	= 1 (P =	0.003);	r = 899	6		
Test for overall effect:	Z = 1.52	: (P = 0.1	13)						
6 2 2 6 wooks									
Drohmor 2014	62	16.66	96	60	16.66	42	2606	10 00 (2 60 17 42)	
Clementeen 2019	46.0	10.00	50	42.0	17.00	42 62	2.0%	10.00 [2.36, 17.42] 4.00 [-2.42, 10.42]	
Ouedlbeuer 2017	40.9	976	15	42.9	11.9	15	2.9%	24.66 [17.09.32.03]	
Soronson 2020	40.00	10.70	47	20.77	127	40	J. J. A 466	-0.20[17:09, 32:03]	
Watson 2018	457	14.5	46	37.8	13.0	46	4.4%	7 90 (2 10 13 70)	
Zeckey 2020	40.7	14.5	25	20	6.85	25	4.17%	10.00 [6.68, 13.32]	
Subtotal (95% CI)	50		226	20	0.00	238	24.4%	9.06 [3.24, 14.88]	
Heterogeneity: Tau ² =	43.83: 0	Chi ^z = 33	3.89. di	'= 5 (P ·	< 0.0000	1): I ² =	85%		
Test for overall effect:	Z = 3.05	i (P = 0.0	002)	0 (,	0.0000	.,,, .	00 %		
0.2.3 12 Weeks	70	44.94	20		44.94		0.00		
Brehmer 2014	72	14.24	36	68	14.24	42	3.9%	4.00 [-2.34, 10.34]	
Clementsen 2019	62.2	14.5	5/	60.1	14.3	62	4.3%	2.10 [-3.08, 7.28]	
Lozano 2008	49	12.5	30	51	13.75	30	3.8%	-2.00 [-8.65, 4.65]	
Quadibauer 2017	59.33	11.48	15	50.39	12.10	15	3.3%	8.94 [0.48, 17.40]	
Sorensen 2020 Zookou 2020	53.0	9.3	47	50.7	11.2	48	4.5%	2.90 [-1.24, 7.04]	
Zeckey 2020 Subtotal (05% CI)	40	5	20	40	10	20	4.5%	0.00 [-4.38, 4.38]	
Hotorogonoity: Tou? -	0.62.01	hi2 - 6 2	2 10 4 df -	6 /D = 0	201-12-	60	24.470	2.00 [-0.22, 4.34]	-
Test for overall effect:	7 - 1.77	/D = 0.0	4, ui – 10\	5 (F - 0	.30),1 -	0.20			
restion overall ellect.	2-1.0	(F = 0.0	50)						
6.2.4 24 weeks									
Brehmer 2014	70	7.72	36	69	7.72	42	4.7%	1.00 [-2.44, 4.44]	
Lozano 2008	56	12.5	30	59	12.5	30	3.9%	-3.00 [-9.33, 3.33]	
Quadibauer 2017	72.33	11.32	15	58.85	12.27	15	3.3%	13.48 [5.03, 21.93]	
Sorensen 2020	59.8	8.3	47	58.5	9.3	48	4.7%	1.30 [-2.24, 4.84]	
Watson 2018	54.4	13.4	46	58.3	8.7	46	4.4%	-3.90 [-8.52, 0.72]	
Zeckey 2020	42.5	5	25	55	10	25	4.5%	-12.50 [-16.88, -8.12]	
Subtotal (95% CI)			199			206	25.6%	-1.09 [-6.60, 4.41]	
Heterogeneity: Tau ² =	40.24; ($Chi^2 = 41$	1.89, di	'= 5 (P ·	< 0.0000	11); I ^z =	88%		
l est for overall effect:	Z = 0.39	(P = 0.7	(U)						
6.2.5 48 weeks									
Clementsen 2019	67.4	12.9	57	69.1	8.6	62	4.6%	-1.70 [-5.67, 2.27]	
Quadibauer 2017	74	10.04	15	67.31	11.11	15	3.6%	6.69 [-0.89, 14.27]	+
Sorensen 2020	63.5	8.5	47	61.7	10	48	4.6%	1.80 [-1.93, 5.53]	
Zeckey 2020	50	16.25	25	50	10	25	3.6%	0.00 [-7.48, 7.48]	
Subtotal (95% CI)			144			150	16.4%	0.99 [-2.03, 4.01]	-
Heterogeneity: Tau² =	2.67; C	hi² = 4.1	6, df =	3 (P = 0	.24); I² =	28%			
Test for overall effect:	Z = 0.64	(P = 0.5	52)						
Total (95% CI)			840			883	100.0%	3.30 [0.70, 5.90]	•
Heterogeneity Tau ² =	34.28 (Chi ² = 14	54.20	df = 23 (′P < ∩ ∩∩	0011.1	² = 85%		+ + + +
Test for overall effect	Z = 2.49	(P = 0 0)1)	20 (. 0.00		- 00 10		-20 -10 0 10 20
Test for subarous diff	erences	: Chi ² =	8.28. d	f=4 (P	= 0,08)	² = 51	7%		early motion late motion
Fig. 8 Forest plot of ex	ktension	in a me	eta-ana	lysis	0.007.				
-				· ·					

WROM

As shown in Figs. 7, 8, 9, 10, 11 and 12, the WROM was reported in six directions in the pooled flexion, extension, supination, pronation, radial deviation, and ulnar deviation. At the 6th week, flexion (MD=10.87, 95% CI 2.30–19.45, P=0.01), extension (MD=9.06, 95% CI 3.24–14.88, P<0.01), pronation (MD=3.93, 95%

CI 1.37–6.50, P<0.01), supination (MD=5.63, 95% CI 2.10–9.16, P<0.01) and radial deviation (MD=1.99, 95% CI 0.46–3.51, P=0.01) had better performance in the EM group in comparison with the LM group.

	ear	ly motio	n	lat	e motio	n		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
6.3.1 6 weeks									
Brehmer 2014	75	15	36	66	15	42	3.9%	9.00 [2.32, 15.68]	· · · · · · · · · · · · · · · · · · ·
Clementsen 2019	60.4	27.4	57	59.8	26.5	62	2.0%	0.60 [-9.10, 10.30]	
Quadibauer 2017	57	22.27	15	43.85	15.02	15	1.1%	13.15 [-0.44, 26.74]	· · · · · · · · · · · · · · · · · · ·
Sorensen 2020	64.8	15.6	47	62.4	16.8	48	4.1%	2.40 [-4.12, 8.92]	
Watson 2018	65.9	15.6	46	59.7	17.2	46	3.9%	6.20 [-0.51, 12.91]	
Subtotal (95% CI)			201			213	15.0 %	5.63 [2.10, 9.16]	
Heterogeneity: Tau ² =	= 0.64; C	hi² = 4.1	6, df =	4 (P = 0)	.39); i ² =	= 4%			
Test for overall effect:	Z = 3.12	2 (P = 0.0	002)						
6.3.2 12 weeks									
Brehmer 2014	86	13.32	36	82	13.32	42	4.7%	4.00 [-1.93, 9.93]	
Clementsen 2019	75.8	18.5	57	78.6	15.5	62	4.4%	-2.80 [-8.96, 3.36]	
Lozano 2008	80	11.25	30	83	11.25	30	5.0%	-3.00 [-8.69, 2.69]	
Quadibauer 2017	73.67	15.64	15	70.38	17.61	15	1.4%	3.29 [-8.63, 15.21]	
Sorensen 2020	77.6	10.8	47	75.2	11.4	48	7.1%	2.40 [-2.06, 6.86]	
Subtotal (95% CI)			185			197	22.7%	0.59 [-2.37, 3.55]	
Heterogeneity: Tau ² =	= 1.91; C	hi² = 4.7	9, df =	4 (P = 0	l.31); I ² =	: 16%			
Test for overall effect:	Z = 0.39	9 (P = 0.7	70)						
6.3.3 24 weeks									
Brehmer 2014	84	13.22	36	79	13.22	42	4.8%	5.00 [-0.89, 10.89]	+
Lozano 2008	88	3.75	30	88	6.25	30	12.8%	0.00 [-2.61, 2.61]	_ _
Quadibauer 2017	83.67	7.67	15	75.39	12.66	15	3.2%	8.28 [0.79, 15.77]	
Sorensen 2020	82	7.7	47	80.2	8.2	48	10.6%	1.80 [-1.40, 5.00]	- +-
Watson 2018	72	12.6	46	70.5	11.3	46	6.3%	1.50 [-3.39, 6.39]	
Subtotal (95% CI)			174			181	37.7%	2.03 [-0.24, 4.29]	◆
Heterogeneity: Tau ² =	= 2.03; C	hi² = 5.8	0, df =	4 (P = 0	.21); I ² =	: 31%			
Test for overall effect:	Z=1.75	5 (P = 0.0	08)						
6.3.4 48 weeks									
Clementsen 2019	84.5	10.8	57	85.9	6.3	62	10.5%	-1.40 [-4.61, 1.81]	
Quadibauer 2017	82	11.46	15	79.23	11.88	15	2.7%	2.77 [-5.58, 11.12]	
Sorensen 2020	84.5	7	47	82.8	7.7	48	11.4%	1.70 [-1.26, 4.66]	- <u>+</u>
Subtotal (95% CI)			119			125	24.7%	0.44 [-1.87, 2.75]	•
Heterogeneity: Tau ² =	= 0.53; C	hi² = 2.2	6, df =	2 (P = 0	.32); I ² =	: 11%			
Test for overall effect:	Z = 0.37	? (P = 0.7	71)						
Total (95% CI)			679			716	100.0%	1.89 [0.43, 3.34]	◆
Heterogeneity: Tau² =	= 2.55; C	hi² = 23.	90, df=	= 17 (P :	= 0.12);	l² = 299	%		
Test for overall effect:	Z= 2.54	(P = 0.0	D1)	-					-10 -5 0 5 10
Test for subaroup dif	ferences	: Chi ² =	6.52. d	lf = 3 (P	= 0.09).	I ² = 54	.0%		eany motion rate motion
Fig. 9 Forest plot of su	upinatio	n in a m	eta-an	alysis					
-				/					

Complications

As shown in Fig. 13, nine RCTs [10, 12–15, 17, 18, 26, 27] with 596 patients recorded related complication rates. However, no heterogeneity ($I^2 = 0\%$, $I^2 = 0\%$) from the implant loosening and/or fracture re-displacement complication and overall complications was detected. Interestingly, the pooled result on the rate of implant loosening and/or fracture re-displacement complications showed that the EM led to a potentially higher proportion than LM, with RR of 3.00 (95% CI 1.02–8.83, P=0.05). The overall complications rate outcome had no statistical difference between the two groups (RR=1.16, 95% CI 0.72–1.87, P=0.54). The detailed occurrence of complications is listed in Table 2.

Heterogeneity analyses

Heterogeneity in data was resulted due to the inconsistencies found in the intervention protocol between the included RCTs. The sensitivity analysis was conducted to explore the impact of individual studies by excluding one study at each time. In the DASH, GS, flexion, extension, pronation, and ulnar deviation pooled analysis, heterogeneity showed a significant reduction when excluding one or two studies. Still, no significant difference was observed in comparison with previous results. The detailed outcomes are shown in Additional file 2.

Study or Subgroup Mean SD Total Weight N. Random, 95% CI N. Random, 95% CI 64.16 Weeks Brehmer 2014 80 10.92 36 77 10.92 42 3.0% 3.00 [1.86, 7.86] Clementsen 2019 713 13.4 45 74.2 15.2 62 2.7% 5.10 [L0.04, 10.24] Quadibauer 2017 61.67 13.97 15 15.0 1.052 [0.67, 20.37] Sorensen 2020 74.9 8.3 47 73.1 17 48 2.5% 1.80 [3.366, 7.16] Valson 2018 74.2 1.0 2.01 2.13 11.0% 3.03 [1.37, 6.50] Heterogeneity Tau ² = 0.00 (P = 2.06, 01 = 2.66, 01 = 4 (P = 0.62); P = 0.% Test for overall effect Z = 3.00 (P = 0.03) 6.4 4.8 1.00 [5.68, 7.68] Commentson 2019 83.6 13.5 7.7 1.00 [2.36, 5.76] Commentson 2019 82.6 1.0 1.02% 0.00 [2.37, 2.36] Commentson 2016 82.2 5.4 4.2 4.8% -2.00 [5.76, 1.76] Commentson 2016 82.		ear	y motio	n	late	e motio	n		Mean Difference	Mean Difference
6.4.16 weeks Derkmer 2014 80 10.92 36 77 10.92 42 3.0% 3.00 [+1.86, 7.86] Clementsen 2019 79.3 13.4 57 74.2 15.2 62 2.7% $5.10 [0.04, 10.24]$ Quadbauer 2017 61.67 13.97 15 51.15 13.66 15 0.0% $10.52 [0.67, 20.37]$ Sorensen 2020 74.9 8.3 47 72.1 17 48 2.5% $4.00 [>2.14, 10.14]$ Subtotal (95% C) 201 213 11.0% $3.33 [1.37, 6.50]$ Heterogeneity: Tau"= 0.00; Chi"= 2.66, df = 4 (P = 0.62); P = 0% Test for overall effect Z = 3.00 (P = 0.003) 6.4.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% $1.00 [>5.68, 7.68]$ Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% $1.70 [>2.36, 57.6]$ Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% $1.70 [>2.36, 57.6]$ Clementsen 2019 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% C1) 125 53.1 13.37 15 1.4% $1.89 [>5.71, 9.09]$ Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% C1) 157 5.31 13.37 15 1.4% $1.89 [>5.71, 9.09]$ 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% $-2.00 [>5.76, 1.76]$ Lozano 2008 90 2.5 30 90 1.75 30 23.6% $0.00 [>1.02, 1.2, 1.2, 74]$ Heterogeneity: Tau" = 0.00; Chi" = 0.50; df = 4 (P = 0.73); P = 0% Fest for overall effect Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% $-2.00 [>5.76, 1.76]$ Lozano 2008 90 2.5 30 90 1.75 30 23.6% $0.20 [>3.73, 4.79]$ Subtotal (95% C1) 174 181 48.0% $0.63 [-1.07, 2.34]$ Heterogeneity: Tau" = 1.73; Chi" = 9.33, df = 4 (P = 0.08); P = 51% Test for overall effect Z = 0.73 (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% $1.00 [+1.18, 3.18]$ Quadbauer 2017 81.67 7.86 15 62.31 9.27 77 13.7% $0.83 [-1.20, 2.85]$ Heterogeneity: Tau" = 0.54; Chi" = 1.51, df = 16 (P = 0.24); P = 18% Test for overall effect Z = 0.54; Chi" = 1.68, df = 2 (P = 0.18), P = 38.1% Test for overall effect Z = 0.54; Chi" = 1.67, P = 0.01; P = 38.1%	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Brehmer 2014 80 10.92 36 77 10.92 42 30% 3.00 [+1.85, 7.86] Clementsen 2019 73 13.4 57 74.2 15.2 62 2.7% 510 [-0.04, 10.24] Quadibauer 2017 61.67 13.97 15 51.15 13.66 15 0.8% $10.52(0.67, 20.37)$ Sorensen 2020 74.9 8.3 47 73.1 17 48 2.5% 1.80 [+3.66], 7.16] Viston 2018 74.2 14.4 46 70.2 15.6 46 1.9% 4.00 [>2.14, 10.14] Subtotal (95% CI) 201 201 213 11.0% 3.33 [1.37, 6.50] Heterogeneity: Tau ⁺ = 0.00; Ch ⁺ = 2.66, df = 4 (P = 0.62); P = 0% Test for overall effect Z = 3.00 (P = 0.003) 64.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [>5.86, 7.68] Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 [>2.36, 5.76] Lozano 2008 88 5 30 88 4.25 30 10.2% 0.00 [>2.35, 2.35] Ouadibauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.89 [>5.77, 19.09] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ⁺ = 0.00; Ch ⁺ = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect Z = 1.68 (P = 0.09) 64.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% 0.201 [>3.76, 1.76] Ouadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.901 [>3.96, 5.76] Sorensen 2020 84.6 42 47 81.6 5.9 48 12.3% 3.001 [>4, 5.68] Sorensen 2020 84.6 42 47 81.6 5.9 48 12.3% 3.001 [>4, 5.68] Subtotal (95% CI) 72 2.33, df = 4 (P = 0.08); P = 51% Test for overall effect Z = 0.73 (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.001 [>1.18, 3.18] Quadibauer 2017 82.592 15 2.31 9.27 77 13.7% 0.83 [-1.20, 2.2.85] Heterogeneity: Tau ⁺ = 0.54; Ch ⁺ = 1.51, df = 1 (P = 0.24); P = 0.8% Test for overall effect Z = 0.80 (P = 0.24) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ⁺ = 0.54; Ch ⁺ = 1.51, df = 1 (P = 0.24); P = 38.1% Test for overall effect Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% Test for overall effect Z = 0.54; Ch ⁺ = 1.51, df = 1 (P = 0.24); P = 38.1% Test for verall effect Z = 0.54; Ch ⁺ = 1.54; df = 34, df = 34, P = 0.18), P = 38.1\%	6.4.1 6 weeks									
Clementsen 2019 79.3 13.4 57 74.2 15.2 62 2.7% 5.10 [+0.4, 10.24] Ouadhauer 2017 61.67 13.97 15 51.15 13.6 15 0.2% 10.52 0.67, 20.37] Serensen 2020 74.9 8.3 47 73.1 17 48 2.5% 10.92 65.7.6] Viatson 2018 74.2 14.4 46 70.2 15.6 46 1.9% 4.00 [+2.14, 10.14] Subtotal (95% C) 201 213 11.0% Subtotal (95% C) 201 213 11.0% Test for overall effect Z = 3.00 ($P = 0.003$) 6.4.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [+5.68, 7.68] Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 [+2.3, 5.76] Ouadhauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.69 [+5.7, 10.00] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% Subtotal (95% C) 195 2.5.5 (df = 4 ($P = 0.73$); $P = 0\%$ Test for overail effect Z = 1.88 ($P = 0.08$) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [+5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [+1.00, 1.09] Ouadhauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [+3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Heterogeneity: Tau ² = 0.03 ($P = 0.47$) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 0.00 [+3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Fest for overail effect Z = 0.73 ($P = 0.47$) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 0.00 [+3.96, 5.76] Subtotal (95% C) 72 77 13.7% 0.83 [+1.20, 2.2.8] Heterogeneity: Tau ² = 0.05 ($P = 0.47$) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 0.00 [+1.8, 3.18] Ouadhauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [+5.85, 5.26] Subtotal (95% C) 72 77 13.7% 0.83 [+1.20, 2.2.8] Heterogeneity: Tau ² = 0.54; ($P = 0.47$); $P = 0.87$; $P = 0.8$ Test for overail effect Z = 0.54; ($P = 0.29$); $P = 38.1\%$ Test for overail effect Z = 0.54; ($P = 0.48$) $P = 0.18$); $P = 38.1\%$ Test for overail effect Z = 0.54; ($P = 0.18$); $P = 38.1\%$	Brehmer 2014	80	10.92	36	77	10.92	42	3.0%	3.00 [-1.86, 7.86]	
Ouadbauer 2017 61.67 13.37 15 51.15 13.56 15 0.8% 10.52 (0.67, 20.37) Watson 2018 74.2 14.4 46 70.2 15.6 46 1.9% 4.00 [>2.14, 10.14] Subtratal (95% CI) 201 213 11.0% 3.33 [1.37, 6.50] Heterogeneity: Tau" = 0.00; Ch" = 2.66, df = 4 (P = 0.62); P = 0% Test for overall effect Z = 3.00 (P = 0.003) 6.4.212 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [>5.68, 7.66] Lozano 2008 88 5 30 81 4.25 30 10.2% 0.00 [>2.35, 2.35] Guadbauer 2017 77 75.21 15.37 15 1.4% 1.69 [>5.76], 1.90] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtratal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] 1.26 [-0.21, 2.74] Heterogeneity: Tau" = 0.00; Ch" = 2.05, df = 4 (P = 0.73); P = 0% 3.00 [0.94, 5.06] 3.00 [0.94, 5.06] 3.00 [0.94, 5.06] 3.00 [0.94, 5.06] 3.00 [0.94, 5.06] <	Clementsen 2019	79.3	13.4	57	74.2	15.2	62	2.7%	5.10 [-0.04, 10.24]	
Sorensen 2020 74.9 8.3 47 73.1 17 48 2.5% 1.80 $(-3.56, 7.16)$ Watson 2018 74.2 14.4 46 70.2 15.6 46 1.9% 4.00 $(-3.44, 10.14)$ Stubtotal (95% CI) 20.00; Chi ² = 2.66, df = 4 (P = 0.62); P = 0% Test for overall effect. Z = 3.00 (P = 0.003) 6.4.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 $(-5.68, 7.68)$ Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 $(-2.36, 5.76)$ Lozano 2008 88 5 30 88 4.25 30 10.2% 0.00 $(-2.35, 2.35)$ Guadbauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.89 $(-5.71, 5.09)$ Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 (D.02, 4.78) Subtotal (95% CI) 185 197 27.4% 1.26 $(-0.24, 2.74)$ Heterogeneity: Tau ² = 0.00; Chi ² = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect. Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 $(-5.76, 1.76)$ Lozano 2008 90 2.5 30 90 1.75 30 23.8% 0.000 $(-1.08, 1.09)$ Quadbauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.309 $(-3.96, 5.76)$ Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 (D.94, 5.06) Watson 2018 78.3 10.2 46 78.1 9.3 46 4.23% 0.201 $(-3.78, 4.19)$ Guadbauer 2017 81.67 5.86 15 80.77 7.6 15 3.0% 0.307, 3.79, 4.19] Subtotal (95% CI) 174 46 (P = 0.08); P = 51% Test for overall effect. Z = 0.54; Chi ² = 158, 3(f = 4 (P = 0.08); P = 51% Test for overall effect. Z = 0.73 (P = 0.47) 6.4.48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 $(-1.18, 3.18)$ Guadbauer 2017 82 5.92 15 82.31 9.27 15 2.3% $(-3.11, 5.8, 8, 5.26)$ Subtotal (95% CI) 72 77 13.7% 0.83 $(-1.20, 2.285)$ Heterogeneity: Tau ² = 0.54; Chi ² = 158, (f = 0.06) Test for overall effect. Z = 0.73 (P = 0.47) 6.4.48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 $(-1.18, 3.18)$ Guadbauer 2017 82 5.92 15 82.31 9.27 15 2.3% $(-3.11, 5.8, 8, 5.26)$ Subtotal (95% CI) 72 77 13.7% 0.83 $(-1.20, 2.2.85)$ Heterogeneity: Tau ² = 0.54; Chi ² = 156 (P = 0.24); F = 18% Test for overall effect. Z = 0.76 (P = 0.000) Test for overall effect. Z = 0.76 (P = 0.00) Test for overall effect. Z = 0.76 (P = 0.00) Test for overa	Quadibauer 2017	61.67	13.97	15	51.15	13.56	15	0.8%	10.52 [0.67, 20.37]	
Watson 2018 74.2 14.4 46 70.2 15.6 46 1.9% 4.00 [2.14, 10.14] Subtotal (95% C) 201 213 11.0% 3.93 [1.37, 6.50] Heterogeneity: Tau" = 0.00; Chi" = 2.66, df = 4 ($P = 0.62$); $P = 0\%$ Test for overall effect: Z = 3.00 ($P = 0.003$) 6.4.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [5.68, 7.68] Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 [-2.36, 5.76] Lozano 2008 88 5 30 88 4.25 30 10.2% 0.00 [-2.35, 2.35] Ouadibauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.69 [5.71, 9.09] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% C) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau" = 0.00; Chi" = 2.05, df = 4 ($P = 0.73$); $P = 0\%$ Test for overall effect: Z = 1.68 ($P = 0.09$) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.9% -2.00 [5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.901-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.201-3.79, 4.19] Subtotal (95% C) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau" = 1.73; Chi" = 8.23, df = 4 ($P = 0.08$); $P = 51\%$ Test for overall effect: Z = 0.73 ($P = 0.47$) 6.4.4 49 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.86, 5.26] Subtotal (95% C) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau" = 0.54; Chi" = 19.51; df = 16 ($P = 0.24$; $I = 18\%$ Test for overall effect: Z = 0.73 ($P = 0.42$) Total (95% C) 632 668 100.0% Heterogeneity: Tau" = 0.54; Chi" = 1.84, df = 3 ($P = 0.18$); $P = 38.1\%$ Test for overall effect: Z = 0.76 ($P = 0.04$) Test for overall effect: Z = 0.76 ($P = 0.06$) Test for overall effect: Z = 0.76 ($P = 0.06$) Test for overall effect: Z = 0.76 ($P = 0.08$); $P = 38.1\%$	Sorensen 2020	74.9	8.3	47	73.1	17	48	2.5%	1.80 [-3.56, 7.16]	
Subtotal (95% C) 201 213 11.0% 3.33 [1.37, 6.50] Heterogeneity: Tau ² = 0.00; Ch ² = 2.66, df = 4 (P = 0.62); P = 0% Test for overall effect Z = 3.00 (P = 0.003) 6.4.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [5.68, 7.68] Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 [-2.36, 5.76] Lozano 2008 88 5 30 88 4.25 30 10.2% 0.00 [-3.35, 2.35] Guadibauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.69 [-5.71, 9.09] Sortensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% CI) 195 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Ch ² = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.8% 0.00 [-1.09, 1.09] Ouadibauer 2017 81.6 5.88 81 65.9 48 12.3% 3.00 [0.94, 5.06] Valson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% CI) 174 181 48.4% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Ch ² = 8.23; df = 4 (P = 0.08); P = 51% Test for overall effect Z = 0.73 (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Ouadibauer 2017 82 5.92 15 82.31 9.27 17 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 71 3.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Ch ² = 0.18, df = 1 (P = 0.67); P = 0% Test for overall effect Z = 0.73 (P = 0.47) Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Ch ² = 1.9.51; df = 16 (P = 0.24); P = 18% Test for overall effect Z = 0.76 (P = 0.18), P = 38.1% Test for overall effect Z = 0.76 (P = 0.18), P = 38.1%	Watson 2018	74.2	14.4	46	70.2	15.6	46	1.9%	4.00 [-2.14, 10.14]	
Heterogeneity: Tau ² = 0.00; Chi ² = 2.66, df = 4 (P = 0.62); P = 0% Test for overall effect: Z = 3.00 (P = 0.003) 6.4.212 weeks Drehmer 2014 82 15 36 81 15 42 1.7% 1.00 [-5.68, 7.68] Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 [-2.36, 5.76] Lozano 2008 88 5 30 88 4.25 30 10.2% 0.00 [-2.35, 2.35] Guadibauer 2017 75 592 15 75.31 13.37 15 1.4% 1.69 [-5.71, 9.09] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Chi ² = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect: Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 2.8% 0.00 [-1.09, 1.09] Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Valson 2018 78.3 10.2 4 6 78.1 3.3 46 4.3% 0.20 [-5.78, 1.76] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); P = 51% Test for overall effect: Z = 0.73 (P = 0.47) 6.4.4 84 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.02, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.24); P = 18% Test for overall effect: Z = 0.77 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 18.54, df = 3 (P = 0.18), P = 38.1% Test for verall effect: Z = 0.77 (P = 0.18), ff = 16 (P = 0.24); P = 18% Test for verall effect: Z = 0.77 (P = 0.18), P = 38.1%	Subtotal (95% CI)			201			213	11.0%	3.93 [1.37, 6.50]	
Test for overall effect: $Z = 3.00$ (P = 0.003) 6.4.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [-5.68, 7.68] Clementser 2019 836 10.3 57 81.9 12.3 62 4.2% 1.70 [-2.36, 5.76] Lozano 2008 88 5 30 88 4.25 30 10.2% 0.00 [-2.35, 2.35] Quadibauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.69 [-5.71, 9.09] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Ch ² = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect: $Z = 1.68$ (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadibauer 2017 81.6 7 5.88 15 80.77 7.6 15 30.% 0.30 [0.34, 5.06] Watson 2018 7.8.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Ch ² = 8.23; df = 4 (P = 0.08); P = 51% Test for overall effect: $Z = 0.73$ (P = 0.18), df = 1 (P = 0.67); P = 0% Test for overall effect: $Z = 0.00$ (Ch ² = 0.18), df = 1 (P = 0.67); P = 0% Test for overall effect: $Z = 0.00$ (Ch ² = 0.67); P = 0.67 Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Ch ² = 19.51, df = 16 (P = 0.24); P = 18% Test for overall effect: $Z = 0.76 (P = 0.47)$ Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Ch ² = 19.51, df = 16 (P = 0.24); P = 18% Test for overall effect: $Z = 0.76 (P = 0.47)$ Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Ch ² = 19.51, df = 16 (P = 0.24); P = 18% Test for overall effect: $Z = 0.76 (P = 0.08)$ Test for overall effect: $Z = 0.76 (P = 0.08)$ Test for overall effect: $Z = 0.76 (P = 0.18)$, P = 38.1%	Heterogeneity: Tau² =	: 0.00; Cl	hi² = 2.6	6, df =	4 (P = 0	.62); I² =	:0%			
6.4.2 12 weeks Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [-5.68, 7.68] Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 [-2.36, 5.76] Guadlbauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.69 [-5.71, 9.09] Soutbotal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Chi ² = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect Z = 1.88 (P = 0.09) 6.4.324 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 3.02 [-3.68, 5.76] 30 90 1.57 1.03 1.00 [-1.09, 1.09] 1.00 Quadlbauer 2017 81.67 5.88 15 80.77 7.6 15 3.00 0.09 [-3.66, 5.76] 50 50 Sorensen 2020 84.6 4.2 4.78 8.3 4.84 3.300 [.0.94, 5.06] 1.02 1.02, 8.26	Test for overall effect:	Z = 3.00	(P = 0.0	003)						
Brehmer 2014 82 15 36 81 15 42 1.7% 1.00 [-5.68, 7.68] Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% 1.70 [-3.65, 7.6] Lozano 2008 88 5 30 88 425 30 10.2% 0.00 [-2.35, 2.35, 7.6] Quadlbauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.69 [-5.71, 9.09] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Ch ² = 2.05, df = 4 ($P = 0.73$); $P = 0\%$ Test for overall effect Z = 1.68 ($P = 0.09$) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadlbauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.30 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 65.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 65.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 6.5.9 48 12.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 0.00; Ch ² = 0.47) 6.4.448 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadlbauer 2017 82 5.92 15 80.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Ch ² = 0.18), P = 0.87, P = 0.87 Test for overall effect Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Ch ² = 1.9.51, df = 16 (P = 0.24); P = 18% Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for o	6.4.2 12 weeks									
Clementsen 2019 83.6 10.3 57 81.9 12.3 62 4.2% $1.70 [+2.36, 5.76]$ Lozano 2008 88 5 30 88 4.25 30 10.2% $0.00 [+2.36, 2.35]$ Quadibauer 2017 77 5.92 15 75.31 13.37 15 1.4% $1.68 [+5.71, 9.09]$ Subtotal (95% CI) 185 197 27.4% $1.26 [-0.21, 2.74]$ Heterogeneity: Tau ² = 0.00; Ch ² = 2.05 df = 4 (P = 0.73); P = 0% Test for overall effect: Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2017 81.6 75.88 15 80.77 7.6 15 3.0% $0.00 [+3.96, 5.76]$ Soutbotal (95% CI) 174 18.6 5.9 48 12.3% $0.00 [+3.96, 5.76]$ Subtotal (95% CI) 174 18.4 4.4 $(P = 0.08); P = 51\%$ Test for overall effect: Z = 0.73 (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% $1.00 [+1.18, 3.18]$ Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% $-0.31 [+5.86, 5.26]$ Subtotal (95% CI) 72 77 13.7% $0.83 [-1.20, 2.85]$ Heterogeneity: Tau ² = 0.00; Ch ² = 0.18, df = 1 (P = 0.67); P = 0% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Ch ² = 19.51, df = 16 (P = 0.24); P = 18% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Ch ² = 19.51, df = 16 (P = 0.24); P = 18.7 Test for overall effect: Z = 0.76 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for suboroud differences: Chi ² = 4.84. df = 3 (P = 0.18), P = 38.1%	Brehmer 2014	82	15	36	81	15	42	1.7%	1.00 (-5.68, 7.68)	
Lozano 2008 88 5 30 88 4.25 30 10.2% $0.00 [-2.35, 2.35]$ Guadibauer 2017 77 5.92 15 75.31 13.37 15 1.4% 1.89 [-5.71, 9.09] Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 [0.02, 4.78] Subtotal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Chi ² = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect: Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% CI) 174 181 48.0% 0.20 [-3.79, 4.19] Subtotal (95% CI) 72 77 13.7% 0.33 [-1.20, 2.85] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23; df = 4 (P = 0.08); P = 51% Test for overall effect: Z = 0.73 (P = 0.47) 6.4.48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.33 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.24); I ² = 18% Test for overall effect: Z = 0.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for suborou differences: Chi ² = 4.84, df = 3 (P = 0.18), I ² = 38.1%	Clementsen 2019	83.6	10.3	57	81.9	12.3	62	4.2%	1.70 [-2.36, 5.76]	
Quadibater 2017 77 5.92 15 75.31 13.37 15 1.4% $1.68[5.71, 8.09]$ Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% $2.40[0.02, 4.78]$ Subtotal (95% CI) 185 197 27.4% $1.26[-0.21, 2.74]$ Heterogeneity: Tau" = 0.00; Chi" = 2.05, df = 4 (P = 0.73); I" = 0% $Test for overall effect Z = 1.68 (P = 0.09)$ $6.4.324$ weeks Brehmer 2014 81 8.44 42 4.8% $-2.00[-5.76, 1.76]$ Quadibauer 2017 81.67 5.8 15 80.77 7.6 15 3.0% $0.00[-1.09, 1.09]$ Quadibauer 2017 81.67 5.8 15 80.77 7.6 15 3.0% $0.20[-3.79, 4.19]$ Subtotal (95% CI) 174 818 48.0% $0.20[-3.79, 4.19]$ $0.63[-1.07, 2.34]$ Heterogeneity: Tau" = 1.73; Chi" = 8.23, df = 4 (P = 0.08); I" = 51\% $1.00[+1.18, 3.18]$ $0.63[-1.20, 2.85]$ Quadibauer 2017 82 5.92 15 82.31 9.27 77 13.7% $0.83[-1.20, 2.85]$	Lozano 2008	88	5	30	88	4.25	30	10.2%	0.00 (-2.35, 2.35)	
Sorensen 2020 82.2 5.4 47 79.8 6.4 48 10.0% 2.40 (0.02, 4.78) Subtotal (95% C)) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Chi ² = 2.05, df = 4 (P = 0.73); P = 0% Test for overall effect Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadbauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% C)) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); P = 51% Test for overall effect Z = 0.73 (P = 0.47) 6.4.4 89 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% C)) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); P = 0% Test for overall effect Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); P = 18% Test for overall effect Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 1.951, df = 16 (P = 0.24); P = 38.1%	Quadibauer 2017	77	5.92	15	75.31	13.37	15	1.4%	1.69 [-5.71, 9.09]	
Subtotal (95% CI) 185 197 27.4% 1.26 [-0.21, 2.74] Heterogeneity: Tau ² = 0.00; Chi ² = 2.05, df = 4 (P = 0.73); I ² = 0% Test for overall effect Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadtbauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.98, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.78, 4.19] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); I ² = 51% Test for overall effect Z = 0.73 (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadtbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% Test for overall effect Z = 0.70 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 2.67 (P = 0.008) Test for overall effect Z = 0.64, df = 3 (P = 0.18), I ² = 38.1%	Sorensen 2020	82.2	5.4	47	79.8	6.4	48	10.0%	2.40 [0.02, 4.78]	
Heterogeneity: Tau ² = 0.00; Chi ² = 2.05, df = 4 (P = 0.73); l ² = 0% Test for overall effect: Z = 1.68 (P = 0.09) 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% Cl) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); l ² = 51% Test for overall effect: Z = 0.73 (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% Cl) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); l ² = 0% Test for overall effect: Z = 0.70 (P = 0.42) Total (95% Cl) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18% Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 2.67 (P = 0.008) Test for overall effect: Z = 0.79 (P = 0.18), l ² = 38.1%	Subtotal (95% CI)			185			197	27.4%	1.26 [-0.21, 2.74]	◆
Test for overall effect: $Z = 1.68 (P = 0.09)$ 6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadlbauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); i ² = 51% Test for overall effect: $Z = 0.73 (P = 0.47)$ 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadlbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); i ² = 0% Test for overall effect: $Z = 0.80 (P = 0.42)$ Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); i ² = 18% Test for overall effect: $Z = 2.67 (P = 0.008)$ Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18), P = 38.1%	Heterogeneity: Tau ² =	0.00; Cl	hi² = 2.0	5. df =	4 (P = 0	.73); I ² =	: 0%			
6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% $3.00 [0.94, 5.06]$ Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); I ² = 51% Test for overall effect Z = 0.73 (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% Test for overall effect Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% Test for overall effect: Z = 2.67 (P = 0.008) Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18), I ² = 38.1%	Test for overall effect:	Z=1.68	(P = 0.0)9)						
6.4.3 24 weeks Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [-5.76, 1.76] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); i ² = 51% Test for overall effect: $Z = 0.73$ (P = 0.47) 6.4.4 88 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); i ² = 0% Test for overall effect: $Z = 0.80$ (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); i ² = 18% Test for overall effect: $Z = 2.67$ (P = 0.008) Test for overall effect: $Z = 2.67$ (P = 0.08) Test for suboroup differences: Chi ² = 4.84. df = 3 (P = 0.18), i ² = 38.1%										
Brehmer 2014 81 8.44 36 83 8.44 42 4.8% -2.00 [$5.76, 1.76$] Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [$1.09, 1.09$] Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [$3.96, 5.76$] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [$0.94, 5.06$] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [$3.79, 4.19$] Subtotal (95% CI) 174 181 48.0% 0.63 [$-1.07, 2.34$] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); I ² = 51% Test for overall effect: $Z = 0.73$ (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [$-1.18, 3.18$] Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [$-5.88, 5.26$] Subtotal (95% CI) 72 77 13.7% 0.83 [$-1.20, 2.85$] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% Test for overall effect: $Z = 0.80$ (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% Test for overall effect: $Z = 2.67$ (P = 0.008) Test for overall effect: $Z = 2.67$ (P = 0.008) Test for overall effect: $Z = 2.67$ (P = 0.008) Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18). I ² = 38.1%	6.4.3 24 weeks									
Lozano 2008 90 2.5 30 90 1.75 30 23.6% 0.00 [-1.09, 1.09] Quadlbauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% 0.90 [-3.96, 5.76] Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% 3.00 [0.94, 5.06] Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtoal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); l ² = 51% Test for overall effect: $Z = 0.73$ (P = 0.47) 6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadlbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtoal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); l ² = 0% Test for overall effect: $Z = 0.80$ (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18% Test for overall effect: $Z = 2.67$ (P = 0.008) Test for subarous differences: Chi ² = 4.84. df = 3 (P = 0.18). l ² = 38.1%	Brehmer 2014	81	8.44	36	83	8.44	42	4.8%	-2.00 [-5.76, 1.76]	
Quadibauer 2017 81.67 5.88 15 80.77 7.6 15 3.0% $0.90 [-3.96, 5.76]$ Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% $3.00 [0.94, 5.06]$ Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% $0.20 [-3.79, 4.19]$ Subtotal (95% CI) 174 181 48.0% $0.63 [-1.07, 2.34]$ Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); l ² = 51\%Test for overall effect: $Z = 0.73$ (P = 0.47)6.4.4 48 weeksClementsen 2019 87 6.1 57 86 6 2 11.3% $1.00 [-1.18, 3.18]$ Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% $-0.31 [-5.88, 5.26]$ Subtotal (95% CI) 72 77 13.7% $0.83 [-1.20, 2.85]$ Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); l ² = 0%Test for overall effect: $Z = 0.80$ (P = 0.42)Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18%Test for subarous differences: Chi ² = 4.84. df = 3 (P = 0.18). l ² = 38.1%Lie 1000000Ifferences: Chi ² = 4.84. df = 3 (P = 0.18). l ² = 38.1%	Lozano 2008	90	2.5	30	90	1.75	30	23.6%	0.00 [-1.09, 1.09]	_
Sorensen 2020 84.6 4.2 47 81.6 5.9 48 12.3% $3.00 [0.94, 5.06]$ Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% $0.20 [-3.79, 4.19]$ Subtotal (95% Cl) 174 181 48.0% $0.63 [-1.07, 2.34]$ Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); I ² = 51% Test for overall effect: $Z = 0.73$ (P = 0.47) 6.4.4 8 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% $1.00 [-1.18, 3.18]$ Quadibauer 2017 82 5.92 15 82.31 9.27 15 2.3% $-0.31 [-5.88, 5.26]$ Subtotal (95% Cl) 72 77 13.7% $0.83 [-1.20, 2.85]$ Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% Test for overall effect: $Z = 0.80$ (P = 0.42) Total (95% Cl) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% Test for overall effect: $Z = 2.67$ (P = 0.008) Test for subaroup differences: Chi ² = 4.84, df = 3 (P = 0.18), I ² = 38.1%	Quadibauer 2017	81.67	5.88	15	80.77	7.6	15	3.0%	0.90 [-3.96, 5.76]	
Watson 2018 78.3 10.2 46 78.1 9.3 46 4.3% 0.20 [-3.79, 4.19] Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); l ² = 51% Test for overall effect: Z = 0.73 (P = 0.47) 0.63 [-1.07, 2.34] 6.4.4 88 weeks Clementsen 2019 87 6.1 57 86 6 22 11.3% 1.00 [-1.18, 3.18] QuadIbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] -0.31 [-5.88, 5.26] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); l ² = 0% 1.20 [0.32, 2.08] -10 -5 0 5 10 Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18% 1.20 [0.32, 2.08] -10 -5 0 5 10 Test for overall effect: Z = 2.67 (P = 0.008) 1.29 = 38.1% -10 -5 0 5 10 Early motion Iate motion Iate motion Iate motion Iate motion	Sorensen 2020	84.6	4.2	47	81.6	5.9	48	12.3%	3.00 [0.94, 5.06]	
Subtotal (95% CI) 174 181 48.0% 0.63 [-1.07, 2.34] Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); I ² = 51% Test for overall effect: Z = 0.73 (P = 0.47) 6.4.4 88 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] QuadIbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 632 668 100.0% Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% Test for overall effect: Z = 2.67 (P = 0.008) Test for subaroup differences: Chi ² = 4.84, df = 3 (P = 0.18). I ² = 38.1%	Watson 2018	78.3	10.2	46	78.1	9.3	46	4.3%	0.20 [-3.79, 4.19]	
Heterogeneity: Tau ² = 1.73; Chi ² = 8.23, df = 4 (P = 0.08); I ² = 51% Test for overall effect: $Z = 0.73$ (P = 0.47) 6.4.4 8 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% Cl) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% Test for overall effect: $Z = 0.80$ (P = 0.42) Total (95% Cl) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% Test for overall effect: $Z = 2.67$ (P = 0.008) Test for subaroup differences: Chi ² = 4.84, df = 3 (P = 0.18). I ² = 38.1%	Subtotal (95% CI)			174			181	48.0%	0.63 [-1.07, 2.34]	-
Test for overall effect: $Z = 0.73$ (P = 0.47) 6.4.4 8 weeks Clementsen 2019 87 6.1 57 86 6 62 11.3% 1.00 [-1.18, 3.18] Quadbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% Cl) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); i ² = 0% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% Cl) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); i ² = 18% Test for overall effect: Z = 2.67 (P = 0.008) Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18). i ² = 38.1%	Heterogeneity: Tau² =	: 1.73; C	hi² = 8.2	3, df =	4 (P = 0	.08); I² =	: 51%			
6.4.4 48 weeks Clementsen 2019 87 6.1 57 86 6 2 11.3% 1.00 [-1.18, 3.18] QuadIbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); l ² = 0% 1.20 [0.32, 2.08] Test for overall effect: Z = 0.80 (P = 0.42) 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18% 1.20 [0.32, 2.08] Test for overall effect: Z = 2.67 (P = 0.008) 1.20 [0.32, 2.08] Test for subarooub differences: Chi ² = 4.84, df = 3 (P = 0.18). l ² = 38.1% 1.00 -5 Sin 40.5 (Subto differences: Chi ² = 4.84, df = 3 (P = 0.18). l ² = 38.1% -10 -5 0 5 10	Test for overall effect:	Z = 0.73	(P = 0.4	47)						
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QuadIbauer 2017 82 5.92 15 82.31 9.27 15 2.3% -0.31 [-5.88, 5.26] Subtotal (95% CI) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% 0.83 [-1.20, 2.85] Test for overall effect: Z = 0.80 (P = 0.42) 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% 1.20 [0.32, 2.08] Test for overall effect: Z = 2.67 (P = 0.008) 1.20 [0.32, 2.08] Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18). I ² = 38.1% 1.0	Clementsen 2019	87	6.1	57	86	6	62	11.3%	1.00 [-1.18, 3.18]	
Subtotal (95% Cl) 72 77 13.7% 0.83 [-1.20, 2.85] Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% 0.83 [-1.20, 2.85] Test for overall effect: Z = 0.80 (P = 0.42) 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% 1.20 [0.32, 2.08] Test for overall effect: Z = 2.67 (P = 0.008) 1.20 [0.32, 2.08] Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18). I ² = 38.1% 1.20 [0.32, 2.08]	Quadibauer 2017	82	5.92	15	82.31	9.27	15	2.3%	-0.31 [-5.88, 5.26]	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.18, df = 1 (P = 0.67); I ² = 0% Test for overall effect: $Z = 0.80$ (P = 0.42) Total (95% Cl) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); I ² = 18% Test for overall effect: $Z = 2.67$ (P = 0.008) Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18). I ² = 38.1% Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18). I ² = 38.1%	Subtotal (95% CI)			72			77	13.7%	0.83 [-1.20, 2.85]	-
Test for overall effect: $Z = 0.80$ (P = 0.42) Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18% Test for overall effect: $Z = 2.67$ (P = 0.008) Test for subgroup differences: Chi ² = 4.84, df = 3 (P = 0.18). l ² = 38.1% End of the former of	Heterogeneity: Tau² =	: 0.00; Cl	hi² = 0.1	8, df =	1 (P = 0	.67); I² =	:0%			
Total (95% CI) 632 668 100.0% 1.20 [0.32, 2.08] Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18% -10 -5 0 5 10 Test for overall effect: Z = 2.67 (P = 0.008) Test for subroub differences: Chi ² = 4.84, df = 3 (P = 0.18). l ² = 38.1% -10 -5 0 5 10 "I'm 100" Found for the foundation of the provided formed by th	Test for overall effect:	Z = 0.80	(P = 0.4	42)						
Heterogeneity: Tau ² = 0.54; Chi ² = 19.51, df = 16 (P = 0.24); l ² = 18% -1 -1 -1 -1 Test for overall effect: Z = 2.67 (P = 0.008) -10 -5 0 5 10 Test for subaroup differences: Chi ² = 4.84. df = 3 (P = 0.18). l ² = 38.1% -10 -5 0 5 10 Fin 4.26 Ferry definition -10 -5 0 5 10	Total (95% CI)			632			668	100.0%	1.20 [0.32, 2.08]	◆
Test for overall effect: Z = 2.67 (P = 0.008) Test for subaroup differences: Chi ² = 4.84. df = 3 (P = 0.18). I ² = 38.1% Test for subaroup differences: Chi ² = 4.84. df = 3 (P = 0.18). I ² = 38.1%	Heterogeneity: Tau ² =	0.54; Cl	hi² = 19.	51, df=	= 16 (P =	= 0.24);	l ² = 189	%		
Test for subaroup differences: Chi ² = 4.84, df = 3 (P = 0.18), l ² = 38.1%	Test for overall effect:	Z = 2.67	(P = 0.0	008)						-10 -5 0 5 10
Fin 10 Franktalst of any action in a sector combined	Test for subaroup dif	ferences	: Chi² =	4.84. d	f= 3 (P	= 0.18).	I ² = 38	.1%		early motion rate motion
Fig. 10 Forest plot of pronation in a meta-analysis	Fig. 10 Forest plot of	pronatio	n in a m	neta-ar	nalysis					

Publication bias

Begg's rank correlation and Egger's weighted regression analysis were performed separately to investigate the publication bias. A *P* value of < 0.05 was considered publication bias. The *P* values for all pooled analyses are presented in Additional file 3(all P > 0.05). No obvious publication bias was found in all the studied outcomes.

Quality of the evidence in the GRADE system

As shown in Additional file 4, a total of 43 outcomes, including subgroup analysis of this meta-analysis, were evaluated by the GRADE system. The evidence quality for all outcomes was either moderate or low, suggesting our meta-analysis had overall moderate evidence quality.

Discussion

The primary finding of this study revealed that EM yielded a significantly better DASH score than LM at 6 weeks (MD of -10.15 points) postoperatively, in patients with acute displaced DRFs followed by ORIF. Moreover, this difference reached the MCID defined as 10 points in DASH [28]. Although the mean difference at 24-week DASH between EM and LM was statistically different (MD = -1.77 points, P < 0.05), which did not reach MCID (10 points). EM group also outperformed the LM group in PRWE at 6 weeks. However, the EM group had a similar clinical outcome score at 12 weeks to final follow-up (\geq 1 year) compared to the LM. The primary finding revealed that at the earlier stages, the function of injured limbs recovers more quickly in EM cohorts with DRF of ORIF.



Secondary findings at postoperative 2^{nd} and 6^{th} week showed a significantly better GS for EM compared to the LM. Nonetheless, comparing with LM, EM might be involved in a similar VAS score at 1-year followup. Regarding WROM, in postoperative 6^{th} week, EM showed significant improvement in terms of flexion, extension, pronation, supination, and radial deviation than LM. However, EM showed a potentially higher proportion of implant loosening and/or fracture re-displacement complications than LM (P=0.05).

Postoperative EM improved the patient's quality of life and physical comfort [10, 29], and therefore assures the individuals early return to activities of daily living and work. Despite the lack of supporting studies demonstrating its effectiveness, immobilization has been empirically used to provide analgesia after surgery [30, 31]. The latest Cochrane Database Review published in 2015 by Handoll et al. [8] on rehabilitation for DRFs pointed out that as in

2006 [32], there is a lack of sufficient evidence about the effectiveness of the various rehabilitation programs after ORIF for DRF. Considering the biomechanical studies, the fixation of DRFs with a locking plate provides a five times higher stability than the forces caused by the active finger movement [33], suggesting the internal fixation treatment offers a strong fixation that meets the need for the early mobilization of these patients. However, the included studies had slight variable definitions of early mobilization. For example, Sørensen et al. [10] instructed the EM group to start nonweight-bearing exercises of the wrist and fingers from the postoperative first day, whereas Dennison et al. [18] required EM patients to gradually start active and passive wrist exercises on the 14th day after surgery. However, most of the studies included gradual movement of the wrist joints without a rigid fixation within 2 weeks or immediately after the operation.

	early	y motio	n	late	e motior	ı		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
6.6.1 6 weeks									
Clementsen 2019	26.9	13	57	24.8	12.9	62	6.3%	2.10 [-2.56, 6.76]	
Quadibauer 2017	27.67	8.21	15	14.62	8.53	15	4.8%	13.05 [7.06, 19.04]	
Sorensen 2020	30.1	8	47	29.6	8.2	48	8.1%	0.50 [-2.76, 3.76]	_ _
Watson 2018	18	7.9	46	15.1	7.4	46	8.3%	2.90 [-0.23, 6.03]	
Subtotal (95% CI)			165			171	27.5%	4.08 [-0.18, 8.33]	
Heterogeneity: Tau ² =	:14.14; (Chi²=1	3.22,	df = 3 (F	e = 0.004	l); l² = 7	77%		
Test for overall effect:	Z = 1.88	8 (P = 0.	.06)						
6.6.2 12 weeks									
Clementsen 2019	33.4	13	57	33.9	12.3	62	6.4%	-0.50 [-5.06, 4.06]	
Lozano 2008	33	10	30	36	10.75	30	5.6%	-3.00 [-8.25, 2.25]	
Quadibauer 2017	31.67	4.88	15	27.31	5.99	15	7.2%	4.36 [0.45, 8.27]	
Sorensen 2020	39.8	7.7	47	38.4	8.5	48	8.1%	1.40 [-1.86, 4.66]	
Subtotal (95% CI)			149			155	27.3%	0.93 [-1.88, 3.75]	-
Heterogeneity: Tau ² =	3.73; C	hi² = 5.9	51, df=	= 3 (P =	0.14); I²	= 46%			
Test for overall effect:	Z = 0.65	5 (P = 0.	.52)						
6.6.3 24 weeks									
Quadibauer 2017	35.67	5.3	15	29.23	3.44	15	8.2%	6.44 [3.24, 9.64]	
Sorensen 2020	43.6	8.4	47	44.1	8.4	48	8.0%	-0.50 [-3.88, 2.88]	
Watson 2018	19.7	8.4	46	19.5	6.6	46	8.4%	0.20 [-2.89, 3.29]	
Subtotal (95% CI)			108			109	24.6%	2.06 [-2.26, 6.38]	
Heterogeneity: Tau ² = Test for overall effect:	: 11.88; (Z = 0.93	Chi² = 1 } (P = 0	0.81,± .35)	df = 2 (F	r = 0.005	5); I² = 8	31%		
			,						
6.6.4 48 weeks									
Clementsen 2019	37.8	13.2	57	38.1	12.8	62	6.2%	-0.30 [-4.98, 4.38]	
Quadibauer 2017	35	6.55	15	30	4.56	15	7.0%	5.00 [0.96, 9.04]	
Sorensen 2020	45	9.2	47	46	9.7	48	7.4%	-1.00 [-4.80, 2.80]	
Subtotal (95% CI)			119	a (5		125	20.6%	1.26 [-2.57, 5.08]	
Heterogeneity: I auf =	6.92; C	nr= 5.0	U8, 01 =	= 2 (P =	0.08); 1-	= 61%			
l est for overall effect:	Z = 0.64	(P = 0.	.52)						
Total (95% CI)			541			560	100.0%	2.04 [0.31, 3.77]	◆
Heterogeneity: Tau ² =	6.82; C	hi² = 36	i.62, di	f = 13 (F	= 0.000)5); I ² =	64%		+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
Test for overall effect:	Z = 2.31	(P = 0.	.02)						early motion late motion
Test for subaroup diff	erences	: Chi²=	: 1.56.	df = 3 (i	P = 0.67). I ² = O	%		sany motion rate motion
Fig. 12 Forest plot of u	ulnar de	viation	in a m	eta-ana	lysis				

To obtain a comparable and conclusive outcome, researches on EM versus LM after ORIF for DRFs with more high-quality large RCTs were included. The results suggested that patients treated with EM may get better clinical outcomes at an early stages which was inconcurrence with the previous studies [13, 17, 18, 26, 27]. As there was no statistical difference observed for the long term between the two groups, the difference in the functional results during the early stages between the two groups might have caused by the residual rigidity of the cast in the LM group [17]. However, at the 6th week, the pain scores of the two groups were similar, which was consistent with the study of Dennison et al. [17]. Furthermore, these results were possibly influenced by the imbalance in opioid use between the two groups. Andrade et al. [15] have shown that patients with EM tend to use more tramadol; therefore, we could not make a clear conclusion on the pain score. However, the pooled analysis showed that the EM group had a potentially higher risk of implant loosening and/or fracture re-displacement complication (P=0.05), which occurred 5.5 times more (11:2) in EM than the LM group. Although the slight difference in implant loosening could be a complication resulting from immature surgical technology [10], which is still a new discovery compared to the previous literatures that compared EM with LM [13, 17, 27]. EM for patients with DRF after ORIF fracture positively affects functional recovery, but the risk of failure for fracture healing must also be considered [17], as it increases the risk of secondary surgery for these patients. The complications do have negative impact on healthcare budget as well as on the patient's total well-being. Consequently, EM is not completely safe and flawless, so we recommend in exercise caution for extrapolating our outcomes, especially for the health care policymakers and patients.

The current study had some limitations. Firstly, our study was limited by the number of matches and available RCTs in the database; therefore, we could not

	early mo	otion	late mo	tion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
6.7.1 Implant looseni	ing and/or t	fractur	e re-displ	laceme	nt		
Andrade 2019	1	19	0	20	1.9%	3.15 [0.14, 72.88]	
Brehmer 2014	1	36	0	42	1.9%	3.49 [0.15, 83.03]	
Clementsen 2019	2	57	0	62	2.1%	5.43 [0.27, 110.77]	
Lozano 2008	1	30	1	30	2.5%	1.00 [0.07, 15.26]	
Sorensen 2020	1	47	0	48	1.9%	3.06 [0.13, 73.33]	
Watson 2018	4	46	1	46	4.1%	4.00 [0.46, 34.44]	
Zeckey 2020	1	25	0	25	1.9%	3.00 [0.13, 70.30]	
Subtotal (95% CI)		260		273	16.3%	3.00 [1.02, 8.83]	
Total events	11		2				
Heterogeneity: Tau ² =	= 0.00; Chi ^a	² = 0.86,	df = 6 (P	= 0.99)	; I² = 0%		
Test for overall effect:	Z = 2.00 (F	P = 0.05	i)				
6.7.2 Overall complic	cations						
Andrade 2019	1	19	0	20	1.9%	3.15 [0.14, 72.88]	
Brehmer 2014	4	36	2	42	7.0%	2.33 [0.45, 12.00]	
Clementsen 2019	7	57	8	62	21.0%	0.95 [0.37, 2.46]	
Dennison 2020	4	18	4	15	13.0%	0.83 [0.25, 2.78]	
Lozano 2008	3	30	2	30	6.4%	1.50 [0.27, 8.34]	
Quadibauer 2017	2	15	1	15	3.6%	2.00 [0.20, 19.78]	
Sorensen 2020	4	47	5	48	12.1%	0.82 [0.23, 2.86]	
Watson 2018	6	46	5	46	15.2%	1.20 [0.39, 3.66]	
Zeckey 2020	2	25	1	25	3.5%	2.00 [0.19, 20.67]	
Subtotal (95% CI)		293		303	83.7%	1.16 [0.72, 1.87]	-
Total events	33		28				
Heterogeneity: Tau ² =	= 0.00; Chi ²	= 2.37	df = 8 (P	= 0.97)	; I² = 0%		
Test for overall effect:	Z = 0.62 (F	P = 0.54)				
Total (95% CI)		553		576	100.0%	1.36 [0.88, 2.09]	-
Total events	44		30				
Heterogeneity: Tau ² =	= 0.00; Chi ²	= 5.81	df = 15 (l	P = 0.98	3); I² = 0%	b	
Test for overall effect:	Z=1.37 (F	P = 0.17)				early motion late motion
Test for subaroup dif	ferences: C	Chi² = 2.	50. df = 1	(P = 0.	11). I ^z = 6	0.0%	
Fig. 13 Forest plot of co	omplicatior	ns in a n	neta-analy	/sis			

 Table 2
 Details of complications

No. of studies	EM	LM
7	9	15
5	10	10
5	3	1
7	11	2
	No. of studies 7 5 5 7 7	No. of studies EM 7 9 5 10 5 3 7 11

perform the subgroup analysis and the pooled analysis for radiographic outcomes. Secondly, the included patients in each of the 9 RCTs were slightly different for the age bracket and mechanism of injury, as DRF in the elderly is often caused by low energy injury, while in young people, it is often associated with high energy injury and accompanied by polytrauma. Therefore, our results may vary due to variable age range. Thirdly, variation in internal fixed implants of included studies may also affect the outcomes. Fourthly, our research does not have a cost-benefit analysis as we could not remark on the potential cost differences of EM from the perspective of patients or society. Consequently, we could not remark on whether EM has the theoretical advantage of returning to work faster than LM. Lastly, each study had a different detailed rehabilitation program for the EM, which had an inherent impact on the functional scores.

Conclusion

We showed that although EM had significantly better DASH, PRWE, GM, and WROM at earlier stages, EM and LM had similar clinical outcomes during the longterm follow-up period. Moreover, studied cases had a higher potential for implant loosening and/or fracture redisplacement complication rate when subjected to EM. Therefore, in the future, the optimal rehabilitation protocol for DRF of ORIF should be individualized, depending on the fracture types and degree of osteoporosis.

Abbreviations

DRF: Distal radius fracture; ORIF: Open reduction internal fixation; EM: Early mobilization; LM: Late mobilization; DASH: Disabilities of the Arm, Shoulder, and Hand; PRWE: Patient-Rated Wrist Evaluation; VAS: Visual analog scale; GS: Grip strength; WROM: Wrist range of motion; MCID: Minimal clinically important difference.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-021-02837-0.

Additional file 1. PRISMA checklist.

Additional file 2. Heterogeneity analyses.

Additional file 3. Publication bias of all summarized outcomes.

Additional file 4. Quality of evidence according to the GRADE criteria.

Acknowledgements

Mao Nie was supported by the Kuanren Talents Program of the second affiliated hospital of Chongqing Medical University.

Authors contributions

All named authors have substantially contributed to conducting the underlying research and drafting this manuscript. ZB D and JP W designed the experiments. KYT and HS searched articles, extracted data. TW made the analysis. ZB D and JP W wrote this manuscript. FB L and MN examined the original study data, reviewed the analysis of data, and approved the final manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The data sets supporting the results of this article are included within the article.

Declarations

Ethics approval and consent to participate Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Competing interests

The authors declare that no competing interests.

Received: 29 August 2021 Accepted: 10 November 2021 Published online: 24 November 2021

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