

RESEARCH ARTICLE

Exercise-based rehabilitation reduces reinjury following acute lateral ankle sprain: A systematic review update with meta-analysis

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Abstract

Research questions

- 1) Do exercise-based rehabilitation programs reduce re-injury following acute ankle sprain?;
- 2) Is rehabilitation effectiveness moderated by the exercise's therapeutic quality, content and volume?

Methods

This systematic review with meta-analysis (PROSPERO: CRD42020210858) included randomized controlled trials in which adults who sustained an acute ankle sprain received exercise-based rehabilitation as an intervention. Databases CINAHL, Web of Science, SPORTDiscus, Cochrane Central Register of Controlled Trials, PEDro and Google Scholar were searched for eligible articles (last search: March 2021). ROB II screening tool by Cochrane was used to assess risk of bias and the i-CONTENT tool was used to assess quality of interventions. Both qualitative analysis and quantitative data synthesis were performed.

Results

Fourteen randomized controlled trials comprising 2182 participants were included. Five studies were judged overall low risk of bias and i-CONTENT assessment showed poor to moderate therapeutic quality of exercise across all included articles. Pooled data found significant reductions in re-injury prevalence at 12 months, in favour of the exercise-based rehabilitation group vs usual care (OR: 0.60; 95%CI: 0.36 to 0.99). Pooled data for re-injury incidence showed not-significant results (MD: 0.027; 95%CI: -2.14 to 2.19). Meta-regression displayed no statistically significant association between training volume and odds of re-injury ($r = -0.00086$; SD: 0.00057; 95%CI: -0.00197 to 0.00025). Results from patient-reported outcomes and clinical outcomes were inconclusive at 1 month, 3–6 months and 7–12 months of follow up.

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Conclusion

Exercise-based rehabilitation reduces the risk of recurrent ankle sprain compared to usual care, but there is insufficient data to determine the optimal content of exercise-based interventions. Training volume varied considerably across studies but did not affect the odds of sustaining a re-injury. Effects on patient-reported outcomes and clinical outcomes are equivocal. Future research should compare different exercise contents, training volumes and intensities after ankle sprain.

Introduction

Ankle sprains are amongst the most common musculoskeletal injuries in sports [1]. Doherty et al. [2] pooled data from prospective studies, reporting a cumulative incidence rate of 11.5 ankle sprains/1000 exposures and a prevalence of 11.8%. Lateral ankle sprains (LAS) are the most common [2–4], and usually involve excessive inversion-internal rotation either with or without plantar flexion. The Anterior Talofibular Ligament (ATFL) [5] has the lowest load tolerance [5] and is most frequently injured [1, 5–10]. In more severe ankle sprains the Calcaneofibular Ligament (CFL) [5, 6, 8, 10], Anterior Inferior Tibiofibular Ligament (AITFL) [6, 8], Posterior Inferior Tibiofibular Ligament (PITFL) [5, 6, 8] or even the Deltoid Ligament [6] are involved.

The average time to return to sport after lateral ankle sprain is 16 to 24 days [5, 11–15], but a large proportion of athletes experience re-injury or other long-term problems [1, 4, 16–21]. Epidemiology data of recurrent ankle sprains in athletes range from 12% to 47%, with the largest re-injury rates occurring in junior basketball (47%), volleyball (46%) and American Football (43%) [22]. Chronic ankle instability (CAI) is characterised by recurrent ankle sprains, feelings of the ankle “giving away” and perceived instability [4, 23–25]. It is estimated that up to 40% of people develop CAI, which may also be an important mediator for post traumatic osteoarthritis [4]. Ankle sprains incur a substantial economic impact [26], mostly because of the substantial indirect costs due to decreased physical activity, diminished productivity and lower quality of life [4].

A previous systematic review based on studies published up to 2017 [7], included seven randomized controlled trials (RCTs) examining the effectiveness of rehabilitation exercises after an acute ankle sprain. Their pooled data found significant reductions in re-injury risk over a 12 month period with exercise based rehabilitation, but a sensitivity analysis also indicated that effect magnitudes were reduced in higher quality studies. The authors were also unable to make any clear recommendation on the optimal content and volume of the exercise-based intervention programs, due to insufficient reporting. Total rehabilitation time has been shown to be a key moderator of treatment effect in other musculoskeletal research; for example, the risk of anterior cruciate ligament (ACL) injury is optimally reduced with higher training doses (>0.75 hours/week) and more than 14 months of follow-up [27].

It is important to update existing evidence, as new studies emerge and new methods develop. Since January 2017, many new studies have been published in this field. The most recent systematic review in this field focused primarily on re-injury outcomes. Recent guidelines informing clinical assessment and return to play decisions after ankle sprain [8, 28] highlight the importance of quantifying both mechanical and sensorimotor impairments, using a combination of clinical and patient reported outcomes. The ankle sprain literature has also not

yet been examined using the international Consensus on Therapeutic Exercise and Training tool (i-CONTENT tool), which provides an objective evaluation of the therapeutic quality of ankle sprain rehabilitation programs, and the potential impact on treatment effect estimates [29]. The aim of this review is to update the evidence base informing the management of acute ankle sprains, by including newly emerged studies, performing a more comprehensive review of clinical and patient reported outcomes, objectively assessing quality of interventions, and by including quantitative analysis to examine the effect of training volume on re-injury. The specific research questions are: 1) Does exercise-based rehabilitation reduce reinjury following acute ankle sprain?; 2) Is rehabilitation effectiveness moderated by the exercise's therapeutic quality, content, and volume?

Methods

Selection and search strategy

The protocol was registered a priori with the International Prospective Registration Register of Systematic Reviews (PROSPERO) on November 24th, 2020 (registration number: CRD42020210858, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020210858). The preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) guidelines were followed, and depicted in [S3](#) and [S4](#) Files [30]. The MEDLINE search strategy is shown in [S1 File](#). This search strategy was modified as required and applied across multiple databases (CINAHL, Web of Science, SPORTDiscus, Cochrane Central Register of Controlled Trials, Physiotherapy Evidence Database (PEDro) and Google Scholar). All databases were searched from their inception through March 2021. Furthermore, additional literature was hand-searched, by going over reference lists of screened articles. To be included in this study, articles had to meet the following predetermined eligibility criteria ([Box 1](#)). Eligibility screening was done by two independent reviewers (JW & AS) in two phases: first screening of titles and abstracts, then reading full texts. The Rayyan app was used for both screening phases [31]. Studies which were excluded in the second phase of screening are referenced in [S2 File](#). In case of disagreement a third reviewer (CB) was invited to reach consensus.

Data extraction

Data extraction was also undertaken independently by two reviewers (JW & AS) as per the published protocol. Extraction of data comprised methodological data (authors, year of publication, language, study design, participants demographics, inclusion/exclusion criteria, recruitment site and time, time since injury at recruitment, diagnosis, ankle injury history, time of follow-up, content of exercise-based intervention and comparison intervention) and details of exercise interventions (duration of the intervention, number of sessions, time per rehabilitation session). We also calculated the total rehabilitation time to estimate training volume. This calculation was based on duration of one rehabilitation session (minutes), duration of the entire intervention program (weeks) and number of rehabilitation sessions included in the intervention program. Any disparities regarding extracted data were resolved by consensus discussion with the third reviewer (CB).

Risk of bias

Risk of bias was independently evaluated (JW & AS) using the Risk of Bias in randomized controlled trials (ROB II) [32]. This is screening tool which is based on five categories: 1) randomisation process; 2) deviation from the intended intervention; 3) missing outcome data; 4) measurement of the outcome; 5) selection of the reported results. Each domain comprises

Box 1. Eligibility criteria

Study design	Randomized controlled trials
Participants	Patients with acute ankle sprain
Intervention	Exercise-based rehabilitation strategies, in isolation or as an adjunct to usual care
Outcome measures	Re-injury Pain Patient-reported outcome measures Clinical outcomes
Comparison	Exercise-based rehabilitation compared to usual care Usual care plus exercise-based rehabilitation compared to usual care Different types of exercise-based rehabilitation compared to each other

relevant questions and a judgement for each respective domain via an algorithm that considers the answers to the relevant questions to propose a final judgement [32]. Consensus was reached by consulting the third reviewer (CB), in case of disparities.

Quality of intervention

The international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) tool, published in 2020 [29], assesses seven items: patient selection, dosage of the exercise programme, type of exercise programme, qualified supervisor, type and timing of outcome assessment, safety of the exercise programme and adherence to the exercise programme [29]. All items were independently evaluated (JW & AS) as either “low risk” or “high risk” of ineffectiveness of the exercise intervention. In case of equivocality, the item could also be evaluated as “probably done” or “probably not done”. Each evaluation should be substantiated by a rationale to support the evaluation.

Data analysis

Meta-analysis was performed on re-injury data by one data analyst (JT). All Meta-analyses and forest plots were conducted and established using Comprehensive Meta-analysis software (CMA 2nd version- Biostat, Englewood, USA). If a study reported no re-injuries, the value “1” was added to both groups to be able to calculate Odds Ratio’s (OR). When studies only reported graphical data, values were estimated using the WebPlotDigitizer app (<https://automeris.io/WebPlotDigitizer>) [33]. An a priori set random effects-model was used to pool individual study results. The DerSimonian and Laird inversed variance method was applied to calculate weight factors [34]. Studies were examined for clinical homogeneity, based on outcome, intervention and time of follow-up. To test the null hypothesis of no between studies heterogeneity a chi-square test with degrees of freedom and its corresponding p-value was applied. The degree of heterogeneity, i.e., the part of the total observed heterogeneity which

can be explained by the true between studies heterogeneity, was expressed by Higgins' I^2 . Higgins' I^2 benchmarking was used for interpretation of the calculated I^2 values: around 25%: low heterogeneity; around 50%: moderate heterogeneity; around or above 75%: high heterogeneity [35]. The overall weighted, pooled estimate was expressed as an OR for re-injury prevalence or MD for re-injury incidence, with its corresponding 95% confidence interval. A subgroup meta-analysis was performed based on time of follow-up: ≤ 6 months of follow-up and 7–12 months of follow-up. Sensitivity analysis was performed to determine if quality of the exercise programs had an influence on pooled effect sizes. A fixed effect meta-regression was used to examine the effect of total rehabilitation time on re-injury risk. The association between the covariate (total rehabilitation time) and the primary outcome (log OR) was quantified using unstandardized regression coefficient (B), 95% CI and the corresponding p-value. Small study effects were examined using a funnel plot (standard error by log OR) and a classic fail-safe N test used to determine the number of statistically not significant studies it would need to bring the overall weighted mean effect size to statistically not significant [36]. Data extracted from individual studies regarding clinical and patient-reported outcomes were recalculated and expressed as between-group mean differences and effect sizes with 95%CI's. For all statistical analyses level of error was set at 5% ($p < .05$).

Results

Search results and study flow

The literature search yielded a total of 7241 articles. After the removal of duplicates and both screening phases, fourteen eligible studies [37–50] were included for qualitative synthesis, of which eleven [37–42, 44, 46, 48–50] were included in meta-analysis. Full details of the review process are shown in the PRISMA flow diagram (Fig 1). A reference list containing studies which appeared to meet the eligibility criteria, but were excluded in the last phase of screening is provided in S2 File.

Study characteristics

Table 1 summarizes the study characteristics. A total of 14 studies were included [37–50], representing a total of 2184 participants (52% male; 48% female). Study size varied from $n = 20$ to $n = 522$. Six [39, 43–46, 50] of the 14 studies failed to mention an a priori sample size calculation. The time of follow-up ranged from 1.5 months to 12 months. Participants were recruited from emergency departments, clinical practices, or from general practitioners, with time since injury at recruitment varying from day of injury to 11 weeks post sprain. In two studies, participants were recruited based on self-reported ankle sprains [42, 48], whereas all other studies used clinical assessments. Three studies specified a history of ankle sprain within the previous year or two years as a criterium for exclusion [40, 47, 49], and only two specified ankle syndesmosis injury as a criterion for exclusion [44, 45]. Six studies [39, 43, 46, 48–50] did not report on previous ankle sprain; in the others, this ranged from 42.5% [37] to 71% [42]. Exercise programs comprised postural balance exercises in all but 2 studies [37, 43]. The majority of studies used rehabilitation content which was either exclusively [46, 47, 50] or primarily based on postural balance training [39, 41, 42, 44, 45, 48, 49]. Nine [38–42, 44, 45, 48, 49] of the 12 studies used single-leg stance exercises, with applicable variations.

Risk of bias assessment

Table 2 shows the scores assigned to each study by the Risk of Bias (ROB) II Cochrane tool [32]. All studies showed low risk of bias for missing outcome data. Only one study [40] was

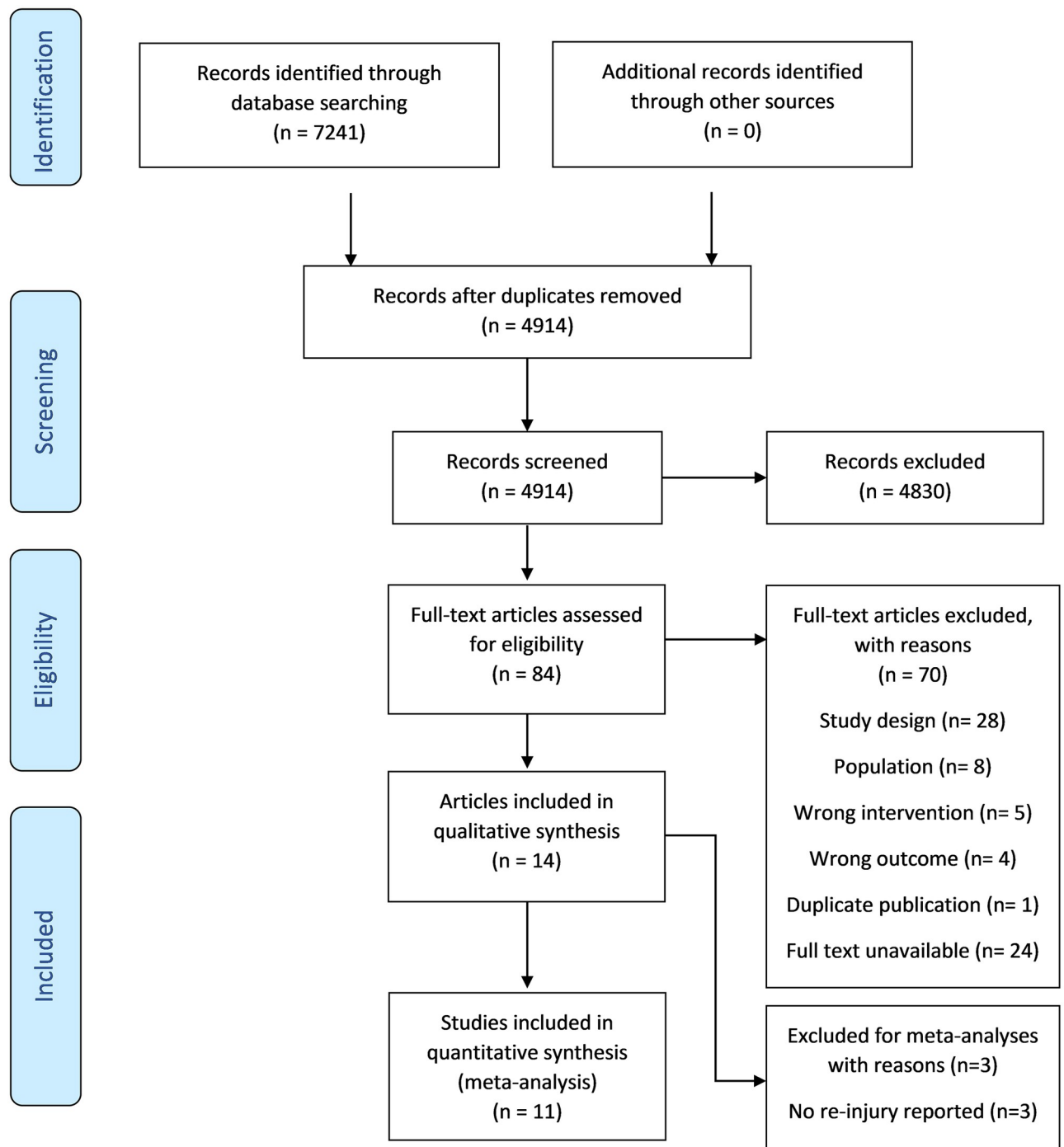


Fig 1. PRISMA flow diagram of the review process.

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judged to have some concerns regarding deviations from the intended interventions and one other study [43] was also deemed to have some concerns regarding measurement of the outcomes. Six studies [39, 40, 43, 46, 47, 50] did not pre-register their protocol or publish their methods, resulting in a judgement of “some concerns” for the category of selection of the reported results. Also six studies [39, 40, 43, 46, 48, 50] did not apply adequate randomisation,

Table 1. Study characteristics.

Study	Participants A	Recruitment site (country)	Time since injury at recruitment	Diagnosis (n)	n. Previous ankle injury (%)	% re-injury: UC vs EB	Follow-up
Bleakley [37]	n = 101; 51–50	ED, sports injury clinic (Northern Ireland)	<7 days	Grade 1 (29)	42.5	4 vs 4	4 months
	69–32 (68–32%)			Grade 2 (73)			
	26y, SD: 8y						
Brisson [38]	n = 503; 250–254	ED (Canada)	<72 hours	Grade 1 (149)	59.4	8.4 vs 7.5	6 months
	223–280 (44–56%)			Grade 2 (354)			
	30y, SD: 13y						
Holme [39]	n = 71; 42–29	ED (Denmark)	Day of injury	Grade 1 (21)	Not stated	29 vs 7	12 months
	44–27 (62–38%)			Grade 2 (38)			
	26y, SD: 4y			Grade 3 (12)			
Hultman [40]	n = 65; 32–33	ED (Sweden)	Day of injury	Grade 1 (21)	44.6	6 vs 3	3 months
	35–30 (54–46%)			Grade 2 (38)			
	35y, SD: 14y			Grade 3 (12)			
Hupperets [41]	n = 522; 256–266	ED, general practice, physical therapy offices (Netherlands)	<2 months	LAS	47	34 vs 30	12 months
	274–248 (52–48%)						
	28 y, SD: 12 y						
Janssen [42]*	n = 340; 113–107–120	Sport federations (Netherlands)	<2 months	Grade 1 (68)	71	15 vs 27 vs 19	12 months
	157–183 (46–54%)			Grade 2/3 (272)			
	34 y, SD: 13 y						
Kachanathu [43]	n = 40; 20–20	University hospitals (Saudi Arabia)	Not stated	Grade 2 LAS	Not stated	Not stated	No follow-up
	24–16 (60–40%)						
	21.8 y, SD: 2.9 y						
Lazarou [44, 45]	n = 20; 10–10	Rehabilitation centre (Greece)	≥ 11 weeks	Grade 1 (29)	50	20 vs 0	12 months
	6–14 (30–70%)			Grade 2 (73)			
	22 y, SD: 3 y						
Mohammadi [46]*	n = 60; 20–20–20	Sports club (Iran)	Not stated	Grade 1 (29)	Not stated	40 vs 5 vs 20	10 months
	60–0 (100–0%)			Grade 2 (73)			
	24.6 y, SD: 2.63 y						
Punt [47]*	n = 90; 30–30–30	ED (Switzerland)	4 weeks	Grade 1 (55)	60	0.03**	1.5 months
	51–39 (64–36%)			Grade 2 (35)			
	32.7 y, SD: 11 y						
Van Reijen [48]	n = 220; 110–110	Clinical practice, advertising (Netherlands)	<2 months	Grade 1 (91)	Not stated	63 vs 64	12 months
	110–110 (50–50%)			Grade 2 (64)			
	37.9 y, SD: 13.4 y			Grade 3 (18)			
Van Rijn [49]	n = 102; 53–49	General practitioner, ED (Netherlands)	<1 week	Grade 1 (43)	Not stated	31 vs 27	12 months
	59–43 (58–42%)			Grade 2 (42)			
	37 y, SD: 11.9 y			Grade 3 (4)			

(Continued)

Table 1. (Continued)

Study	Participants A	Recruitment site (country)	Time since injury at recruitment	Diagnosis (n)	n. Previous ankle injury (%)	% re-injury: UC vs EB	Follow-up
Wester [50]	n = 48; 24–24	ED (Denmark)	Day of injury	Primary LAS; grade 2	Not stated	54 vs 25	8 months
	29–19 (60–40%)						
	25 y, SD: 7 y						

^A Participants: total amount; amount usual care—exercise-based rehabilitation; male-female (%); mean age, SD.

Abbreviations: n = amount; SD = Standard Deviation; UC = Usual care; EB: Exercise-based rehabilitation; SD: Standard deviation; ED = Emergency Department, LAS = lateral ankle sprain, ROM = range of motion.

*These studies included a 2-arm comparison: usual care—exercise-based intervention 1—Exercise-based intervention 2.

**No distinction was made.

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blinding participants and therapists, baseline comparability or allocation concealment, and where thus determined as “high risk” for the category of randomisation process.

Therapeutic quality of exercise programs assessment

Each i-CONTENT criterion, and respective scores are stated in Table 3. There was a low risk of bias for patient selection, safety and exercise adherence. In all cases the type of exercise was deemed suitable and where applicable, a qualified supervisor was employed. The type and timing of outcome assessment was most inconsistent, with three of the included intervention programmes [43, 46] scoring high risk of bias and one [39] judged as probably not done due to insufficient information.

Effect of interventions

Eleven of the included studies [37–39, 41, 42, 44–48, 50] compared no intervention or usual care to an exercise-based intervention. Four studies [40, 43, 47, 48] compared different exercise-based intervention modalities.

Table 2. Risk of bias—ROB II Cochrane tool.

Study	1	2	3	4	5
Bleakley [36]	LR	LR	LR	LR	LR
Brison [37]	LR	LR	LR	LR	LR
Holme [38]	HR	LR	LR	LR	Q
Hultman [39]	HR	Q	LR	LR	Q
Hupperets [40]	LR	LR	LR	LR	LR
Janssen [41]	LR	LR	LR	LR	LR
Kachanathu [42]	HR	LR	LR	Q	Q
Lazarou [43, 44]	LR	LR	LR	LR	LR
Mohammadi [45]	HR	LR	LR	LR	Q
Punt [46]	LR	LR	LR	LR	Q
Van Reijen [47]	HR	LR	LR	LR	LR
Van Rijn [48]	LR	LR	LR	LR	LR
Wester [49]	HR	LR	LR	LR	Q

1. Randomisation process; 2. Deviations from the intended interventions; 3. Missing outcome data; 4. Measurement of the outcome; 5. Selection of the reported results

Abbreviations: LR = Low risk; Q = questionable/ Some concerns; HR = High risk.

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Table 3. Therapeutic quality of exercise program (i-CONTENT tool).

Study	1	2	3	4	5	6	7
Bleakley [37]	LR	LR	LR	NA	LR	LR	LR
Brison [38]	LR	PD	LR	LR	LR	LR	LR
Holme [39]	LR	PD	LR	PD	PnD	LR	LR
Hultman [40]	LR	LR	LR	LR	LR	LR	LR
Hupperets [41]	LR	LR	LR	NA	LR	LR	LR
Janssen [42]	LR	LR	LR	NA	LR	LR	LR
Kachanathu [43]	LR	PD	LR	LR	HR	LR	LR
Lazarou [44, 45]	LR	LR	LR	LR	LR	LR	LR
Mohammadi [46]—proprioception	LR	PD	LR	NA	HR	LR	LR
Mohammadi [46]—Strength*	LR	HR	LR	NA	HR	LR	LR
Punt [47]	LR	LR	LR	NA	LR	LR	LR
Van Reijen [48]	LR	LR	LR	NA	LR	LR	LR
Van Rijn [49]	LR	LR	LR	LR	LR	LR	LR
Wester [50]	LR	LR	LR	NA	LR	LR	LR

1. Patient selection; 2. Dosage of exercise program; 3. Type of the exercise program; 4. Qualified supervisor; 5. Type and timing of outcome assessment; 6. Safety of exercise program; 7. Adherence to the exercise program

Abbreviations: LR = “low risk” of ineffectiveness; HR = “High risk” of ineffectiveness; PD = Probably done; PnD = Probably not done; NA = Not applicable

* This study compared different types of exercise based intervention to usual care.

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Usual care vs exercise-based intervention

Re-injury

In Fig 2, pooled data from nine studies [37–39, 41, 42, 44, 46, 49, 50], comprising ten intervention comparisons, shows a reduction in re-injury in favour of the exercise-based intervention group (OR: 0.61; 95%CI: 0.38 to 0.98). Subgroup analyses based on follow up time found statistically non-significant between group difference at ≤ 6 months in favour of the exercise-based intervention group (OR: 0.90; 95%CI: 0.31 to 2.71), while effect at 7–12 month follow up was statistically significant, again in favour of the exercise-based intervention group (OR: 0.53; 95%CI: 0.30 to 0.94). Sensitivity analysis excluding one study [46] which contained two intervention programs judged with a “high risk” of ineffectiveness [46], displayed that re-injury reductions in favour of the exercise-based rehabilitation group lost statistical significance, for both overall (OR: 0.68; 95%CI: 0.40 to 1.15) and subgroup analysis at 7–12 months follow-up (OR: 0.61; 95%CI: 0.33 to 1.13).

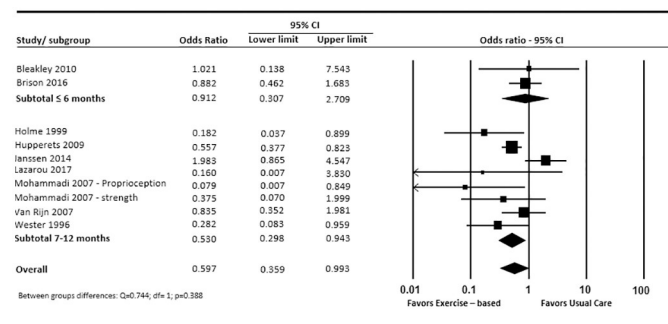


Fig 2. Forest plot (re-injury prevalence: Usual care vs exercise-based intervention).

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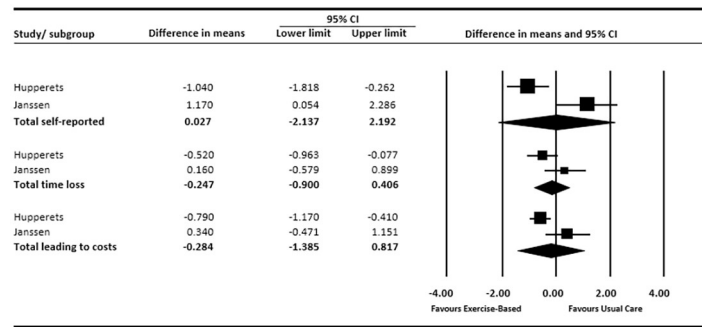


Fig 3. Forest plot (reinjury incidence: Usual care vs exercise-based intervention).

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Two studies [41, 42] reported re-injury incidence rates, documented per 1000 hours of sports exposure. Pooled data in Fig 3, shows inconsistent effects across the two studies. The pooled effects were statistically non-significant for incidence of self-reported re-injury (MD: 0.027; 95%CI: -2.14 to 2.19), time-loss re-injury (MD: -0.25; 95%CI: -0.90 to 0.41) and costs (MD: -0.28; 95%CI: -1.39 to 0.82).

Training volume

The majority of the included studies [38, 41–43, 46–49], reported a rehabilitation duration of 30 minutes per session with all other studies using durations between 10 and 60 minutes [37, 39, 40, 44, 45, 50]. The number of rehabilitation sessions ranged from 5 to 84 sessions, and the duration of rehabilitation ranged from 1 to 12 weeks. Total rehabilitation time was estimated for two studies [40, 43], and one study [46] failed to provide any information. In the remaining studies, total rehabilitation time ranged from 3.5 hours to 21 hours, with a median of 12 hours.

A fixed-method meta-regression analysis with pooled total rehabilitation time data from studies comparing usual care or no intervention to an exercise-based intervention showed no association between odds of re-injury and increasing training volume ($r = -0.00086$; SD: 0.00057; 95%CI: -0.00197 to 0.00025).

Patient-reported outcomes

Fig 4 presents measurement methods, between-group mean differences and effect sizes with 95%CI's for all patient-reported outcomes of studies comparing usual care to exercise-based rehabilitation at 1 month, 3 to 6 months and 7 to 9 months of follow up.

Perceived instability. Two [49, 50] studies assessing perceived instability favoured exercise-based intervention, but only the findings of Wester et al. [50] were statistically significant ($p < 0.01$).

Self-reported function. Three studies [37, 38, 49] recorded self-reported function. Self-reported function results reported by Bleakley et al. [37] were consistently better for the usual care group at 1 month (ES: -1.01, 95%CI: -1.41 to 0.59) and 3–6 months of follow-up (ES: -0.28, 95%CI: -0.67 to 0.12), although only significant 1 month post injury. Results of Brison et al. [38] and Van Rijn et al. [49] were conflicting between different time points.

Pain. Three studies [37, 45, 50] reported pain outcomes at 1 month, 3–6 months or 7–12 months of follow up. Only Lazarou et al. [45] found significant differences between groups on pain outcomes. These results were in favour of the exercise-based intervention group after 3 to 6 months of follow-up for the pain rating index (ES: 1.34, 95%CI: 0.32 to 2.25) and present pain index (ES: 6.32, 95%CI: 3.99 to 8.13).

Study	Measurement method	Difference between groups	Effect size-direction		95% CI
			UC	EB	
Self-reported function					
1 month					
Bleakley 2010	LEFS (0-80)	3,00		0.4	0.00 to 0.79
	Karlisson Score (0-100)	4,80*		-1.01	-1.41 to 0.59
Brison 2016	FAOS (0-500)	3,37		0.04	-10.14 to 16.87
3-6 months					
Bleakley 2010	Karlisson Score (0-100)	1,10		-0.28	-0.67 to 0.12
Brison 2016	FAOS (0-500)	8,45		-0.10	-23.48 to 6.57
Van Rijn 2007	Subjective recovery (0-10)	0,33		0.14	-0.25 to 0.54
7-12 months					
Van Rijn 2007	Subjective recovery (0-10)	0,28		-0.12	-0.51 to 0.28
Pain					
1 month					
Bleakley 2010	0-100 scale (rest)	0,20		-0.04	-0.43 to 0.35
	0-100 scale (activity)	0,60		-0.04	-0.43 to 0.35
3-6 months					
Lazarou 2018	PRI (0-45)	3,00*		1.34	0.32 to 2.25
	VAS (0-10)	0,80		0.93	-0.03 to 1.81
	PPI (0-5)	1,00*		6.32	3.99 to 8.13

Fig 4. Patient-reported outcomes (usual care vs exercise-based rehabilitation). Abbreviations: UC = usual care; EB = exercise-based rehabilitation; 95% CI = 95% confidence interval; LEFS = Lower extremity function score; FAOS = Foot and ankle outcome score; PRI: Pain rating index; VAS = Visual analogue scale; PPI = Present pain index. * Significant difference ($p < .05$).

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Clinical outcomes

Fig 5 depicts measurement methods, mean between-group differences and effect sizes with 95% CI of all clinical outcomes of studies comparing usual care to exercise-based rehabilitation at 1 month, 3 to 6 months and 7 to 9 months of follow up.

Swelling. Swelling was assessed in three studies [37, 38, 50], with two studies [37, 38] using the same method. Yet, results for this outcome were conflicting.

Muscle strength. Three studies [38, 39, 44] assessed muscle strength. Results of Brison et al. [38] and Holme et al. [39] were inconsistent, while Lazarou et al. [44] displayed significant effect sizes in favour of the exercise-based group for plantarflexion torque at 120°/s (ES: 1.32; 95%CI: 0.31 to 2.23) and eversion torque at 30°/s (ES: 1.50; 95%CI: 0.45 to 2.42) at 3–6 months of follow-up.

Range of motion

Dorsiflexion range of motion (ROM) was evaluated by Brison et al. [38], Lazarou et al. [45] and Van Rijn et al. [49]. Results were inconsistent for both plantarflexion and dorsiflexion ROM at either 1 month and 3–6 months of follow up.

Proprioception. Two studies [39, 44] reported proprioception. Both studies found results favouring the exercise-based intervention group; however the largest effects were for plantarflexion joint position sense at 15° (ES: 1.34; 95%CI: 0.32 to 2.25) and 30° (ES: 1.00; 95%CI: 0.03 to 1.88) [44].

Sensory motor control. Three studies [39, 45, 49] assessed different components of sensorimotor control (postural sway, balance, single leg hop for distance, single leg hop for time, functional stability) at 3–6 months follow up. Effects were in favour of the exercise-based intervention group, except for balance performance. The only significant between group difference was for single-leg hop for distance (ES: 1.33; 95%CI: 0.31 to 2.23) [45].

Ankle function. Bleakley et al. [37] assessed ankle function at 1 month follow up using the sports ankle rating scale, reporting statistically significant effects in favour of usual care (ES: -0.72; 95%CI: -1.11 to -0.31). Lazarou et al. [45] assessed ankle function 3–6 months post ankle sprain and found results in favour of the exercise-based intervention group, although statistically not significant (ES: 0.68; 95%CI: -0.25 to 1.55).

Study	Measurement method	Difference between groups	Effect size-direction		95% CI
			UC	EB	
Swelling					
<i>1 month</i>					
Bleakley 2010	Figure-of-8 method (cm)	0.30		0.26	-0.13 to 0.65
Brison 2016	Figure-of-8 method (cm)	3.10		-0.18	-0.35 to 0.00
<i>3-6 months</i>					
Brison 2016	Figure-of-8 method (cm)	2.24		-0.11	-5.99 to 1.51
Wester 1997	Volumetric measurement (ml)	0.60		0.07	
Plantar flexion muscle strength					
<i>1 month</i>					
Brison 2016	ID (torque-Nm)	4.63		0.14	-1.17 to 10.43
	ID (Power-Watts)	1.45		0.15	-0.17 to 3.08
<i>3-6 months</i>					
Brison 2016	ID (torque-Nm)	5.53		0.15	-0.90 to 11.95
	ID (Power-Watts)	1.59		0.17	-0.18 to 3.36
Holme 1999	ID (torque-Nm)	5.00		0.18	-0.29 to 0.65
Lazarou 2017	ID (30/s) (torque-Nm)	12.00		0.58	-0.34 to 1.45
	ID (120/s) (torque-Nm)	14.10*		1.32	0.31 to 2.23
Dorsiflexion muscle strength					
<i>1 month</i>					
Brison 2016	ID (torque-Nm)	0.71			-1.31 to 2.73
	ID (Power-Watts)	0.26			-0.42 to 0.94
<i>3-6 months</i>					
Brison 2016	ID (torque-Nm)	0.09		0.00	-2.12 to 2.30
	ID (Power-Watts)	0.29		0.07	-0.40 to 0.98
Holme 1999	ID (torque-Nm)	0.20		-0.01	-0.48 to 0.46
Lazarou 2017	ID (30/s) (torque-Nm)	0.50		-0.08	-0.95 to 0.80
	ID (120/s) (torque-Nm)	2.70		0.56	-0.36 to 1.43
Inversion muscle strength					
<i>3-6 months</i>					
Holme 1999	ID (torque-Nm)	0.60		-0.07	-0.55 to 0.40
Lazarou 2017	ID (30/s) (torque-Nm)	3.40		0.41	-0.50 to 1.27
	ID (120/s) (torque-Nm)	6.10		0.82	-0.13 to 1.69
Eversion muscle strength					
<i>3-6 months</i>					
Holme 1999	ID (torque-Nm)	2.70		0.45	-0.03 to 0.92
Lazarou 2017	ID (30/s) (torque-Nm)	4.90*		1.50	0.45 to 2.42
	ID (120/s) (torque-Nm)	2.50		0.82	-0.12 to 1.69
Plantar flexion ROM					
<i>1 month</i>					
Brison 2016	ID-Active (degrees)	0.52		0.05	-1.32 to 2.36
	ID-Passive (degrees)	0.42		-0.04	-2.12 to 1.27
<i>3-6 months</i>					
Brison 2016	ID-Active (degrees)	0.22		0.02	-1.94 to 2.38
	ID-Passive (degrees)	0.19		0.02	-2.21 to 1.83
Dorsiflexion ROM					
<i>1 month</i>					
Brison 2016	ID-Active (degrees)	0.62		0.09	-0.68 to 1.91
	ID-Passive (degrees)	0.49			-1.49 to 0.51
	Lunge test (mm)	0.50		0.02	-4.27 to 5.27
<i>3-6 months</i>					
Brison 2016	ID-Active (degrees)	0.27		-0.02	-1.93 to 1.39
	ID-Passive (degrees)	0.88		-0.11	-2.19 to 0.43
	Lunge test (mm)	0.59		-0.02	-6.56 to 5.68
Lazarou 2018	Goniometer (degrees)	0.00		0.00	-0.88 to 0.88
Van Rijn 2007	Digital inclinometer-Active (degrees)	1.82		-0.25	-0.69 to 0.18
Proprioception					
<i>3-6 months</i>					
Holme 1999	ID-JPS (Degrees)	3.10		0.09	-0.39 to 0.56
Lazarou 2017	ID-JPS (DF 10) (degrees)	1.00		0.39	-0.51 to 1.26
	ID-JPS (15 PF) (degrees)	3.00*		1.34	0.32 to 2.25
	ID-JPS (30 PF) (degrees)	2.00*		1.00	0.03 to 1.88
Sensory motor function					
<i>3-6 months</i>					
Holme 1999	Postural sway (cm)	10.00		0.16	-0.32 to 0.63
Lazarou 2018	Single-leg hop for distance (cm)	33.00*		1.33	0.31 to 2.23
	Single-leg hop for time (s)	0.10		-0.28	-1.15 to 0.61
	Balance (stability index)	0.50		0.83	-0.11 to 1.71
Van Rijn 2007	Functional stability	0.12		0.63	0.27 to 1.48
Ankle function					
<i>1 month</i>					
Bleakley 2010	Sports ankle rating scale (0-60)	1.90*		0.72	-1.11 to -0.31
<i>3-6 months</i>					
Lazarou 2018	Foot - heel raises	2.50		0.68	-0.25 to 1.55

Fig 5. Clinical outcomes (usual care vs exercise-based rehabilitation). Abbreviations: UC = usual care; EB = exercise-based rehabilitation; 95% CI = 95% confidence interval; ID = Isokinetic dynamometer; JPS = Joint position sense; ROM = Range of motion. * Significant difference (p < .05).

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Comparison between exercise-based interventions

Hultman et al. [40] compared supervised exercise-based intervention based on either two or four visits from a physiotherapist. Patients receiving four visits recorded a statistically non-significant reduction in re-injury (OR: 0.47; 95%CI: 0.04 to 5.44) (Fig 6). The group receiving four visits did have statistically better self-reported function (p<0.05), and lower pain (p = 0.025) at 3–6 months (Fig 8). There were no differences between groups for ankle

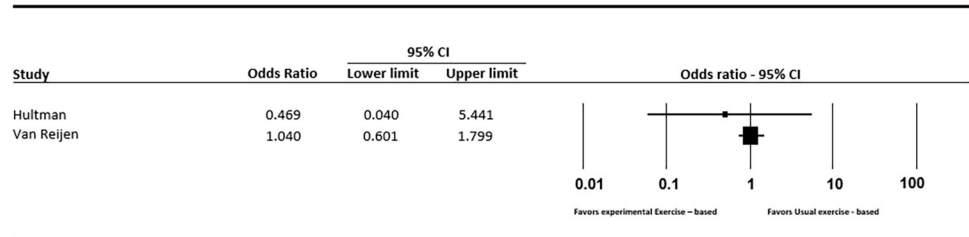


Fig 6. Forest plot (re-injury prevalence: Usual exercise-based vs experimental exercise-based).

<https://doi.org/10.1371/journal.pone.0262023.g006>

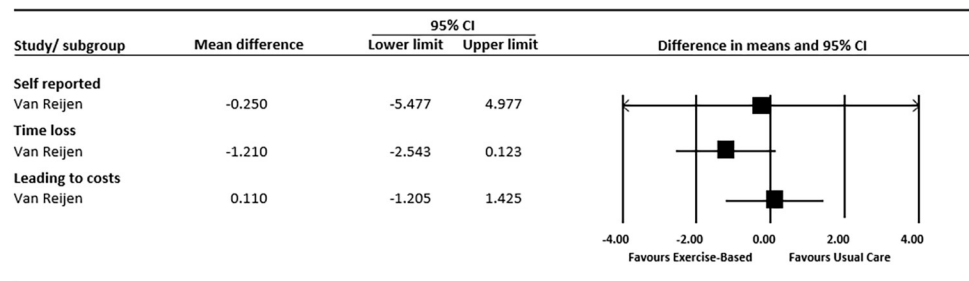


Fig 7. Forest plot (re-injury incidence: Usual exercise-based vs experimental exercise-based).

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plantarflexion and dorsiflexion ROM ($p > .05$), functional ankle stability ($p = 0.86$) and ankle function ($p = 0.54$).

Van Reijen et al. [48] compared an exercise-based rehabilitation program delivered via a phone application, to the same program provided in printed booklet. There was a small reduction in re-injury in favour of the booklet group (OR: 1.04; 95%CI: 0.60 to 1.80) but this was not statistically significant (Fig 6). Effects for self-reported re-injury incidence rates, presented as re-injuries per 1000 hours of sports exposure, favoured the phone application group, but again these were not statistically significant (MD: -0.25; 95%CI: -5.48 to 4.98). There were similar patterns for time-loss injuries (MD: -1.21; 95%CI: -2.54 to 0.12) (Fig 7). Self-reported function evaluated at 1 month, 3–6 months and 7–12 months follow up, also shows conflicting results (Fig 8).

Study	Measurement method	Difference between groups	Effect size-direction		95% CI
			U-EB	E-EB	
Self-reported function					
1 month					
Van Reijen 2017	FADI (0-100)	0.61		0.07	-0.19 to 0.34
3-6 months					
Hultman 2010	FAOS (0-500)	44.86*		-	-
Van Reijen 2017	FADI (0-100)	0.77		0.10	-0.17 to 0.36
7-12 months					
Van Reijen 2017	FADI (0-100)	0.68		-0.10	-0.37 to 0.16
Pain					
3-6 months					
Hultman 2010	FAOS pain (0-100)	10.89*		-	-

Fig 8. Patient-reported outcomes (usual exercise-based vs experimental exercise-based). Abbreviations: U-EB = Usual exercise-based rehabilitation; E-EB = Experimental exercise-based rehabilitation; 95% CI = 95% confidence interval; FADI = Foot and ankle disability index; FOAS = Foot and ankle outcome score. * Significant difference ($p < .05$).

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Discussion

Summary of findings

Following a published decision framework [51], it was timely to update a previous systematic review [7]. The review doubles the number of included trials, with aggregate data from 2184 participants (48% female) across 14 RCTs. We found further evidence that exercise-based rehabilitation reduces the risk of recurrent ankle sprain vs minimal usual care. We used i-CONTENT to formally assess the therapeutic quality of the exercise interventions; and a sensitivity analysis found reduced effect magnitude (for re-injury risk), when lower quality interventions were removed from the meta-analysis. The content and volume of exercise interventions continues to vary, and using a planned meta-regression, there was a weak and non-significant trend that higher training volumes were most effective. Although, we extracted all available data on clinical and patient-reported outcomes, results were generally conflicting at most follow up time points.

Re-injury

Pooled data from nine studies, found statistically significant reductions in re-injury in favour of the exercise-based rehabilitation group. The prevalence of recurrent ankle sprains was 22% in the usual care group, which aligns with previous prospective research [52]. By comparison, pooled prevalence of re-injury in the exercise group was 16%, equating to an absolute risk reduction of 6%. This effect magnitude is clinically important, and these findings must be disseminated to healthcare professionals, athletes and the general public. Research in the United States (US) shows ankle sprains to have the highest recurrence rates out of any musculoskeletal injury [53], yet many of the practitioners treating these injuries have a moderate understanding of their epidemiology and often limit management to rest-ice-compression-elevation [54]. Furthermore, the public perception, that ankle sprains are innocuous, remains widespread, and it is estimated that less than 50% of individuals who incur an ankle sprain, consult a medical professional [55].

The magnitude of re-injury risk reduction varied across the present set of studies. Four studies [39, 41, 46, 50] showed statistically significant reductions in odds of sustaining a re-injury in the exercise-based intervention group. Whereas others showed no difference between groups [37], or non-significant trends in favour of the usual care group [42] or the exercise-based rehabilitation group [38, 44, 46, 49]. Treatment effect may be moderated by many clinical factors, such as injury history, severity and method of diagnosis. In the current review, only two studies [44, 45] specified involvement of the ankle syndesmosis as a criterion for exclusion. It is estimated that 1 in 5 ankle sprains have syndesmotic involvement [56]; these injuries are associated with prolonged recovery [56] and therefore require a more conservative management strategy.

Only two studies compared different types of exercise-based interventions, but data pooling was not undertaken due to heterogeneity. Subsequently, no conclusion can be drawn regarding different types of exercise-based interventions. There was also some variation across studies, regarding the therapeutic quality of their exercise interventions based on the i-CONTENT tool. It was interesting that the study employing exercise interventions at highest risk of ineffectiveness (based on type and timing of outcomes, and their exercise dosage) [46], also reported the largest effect magnitudes. Again, we must acknowledge that there are many factors influencing effect estimate magnitude and direction. In particular, this study [46] also showed suboptimal methodological study quality [32], and failed to incorporate adequate allocation concealment, blinding of subjects, therapists and assessors, and

intention-to-treat analysis. These limitations can yield wide CI's and thus over estimate treatment effects [57].

Exercise-based intervention

A pre-planned meta-regression showed a small decrease in odds of re-injury with increased training volume, although this was not statistically significant. We also found preliminary evidence from a single study [40] that four supervised training sessions is superior to two supervised sessions. We calculated training volume based on frequency, duration and timing, but a limitation was that no information regarding intensity was considered [58]. Training intensity is a key variable influencing training volume [59], but this has not yet been considered in the ankle literature. This may explain why, in contrast to other common lower limb injuries [27], we did not find a significant association between training volume and odds of re-injury. Consensus regarding optimal training volume and the effect of training volume on recurrent ankle sprains is still lacking in current literature. Moreover, consistency in intervention duration, number of rehabilitation sessions and time per rehabilitation session is warranted for further studies comparing ankle sprain rehabilitation.

Clinical and patient-reported outcomes

Although our results displayed overall re-injury reductions, effects of rehabilitation on other important clinical outcome measures and patient-reported outcome measures are inconsistent. Others have shown that the course of recovery from an acute ankle sprain varies significantly, across clinical constructs (e.g., pain, subjective instability) [60, 61]. It is therefore important that this is reflected in the timing of outcome assessments.

The fifth criterium of the i-CONTENT tool [29], type and timing of outcome assessments, also displayed inconsistent results. This may also explain why our findings regarding re-injury reduction are conflicting with results of the secondary outcomes. Only Brison et al. [38] applied a criteria-based progression in their rehabilitation programme, addressing specific impairments, whereas all other studies applied a general intervention program independent of the progress made by the study participants. The rehabilitation progression of common musculoskeletal conditions such as Anterior Cruciate Ligament reconstruction (ACLR), calf muscle strain and hamstring injury are guided by evidence-based criteria. There are currently no criteria for rehabilitation progression after an acute ankle sprain [62].

Strengths and limitations

Although we were able to double the amount of included studies of the previous review, only 9 studies were included for meta-analysis. Therefore, publication bias cannot be excluded [63]. Results of the ROB II assessment showed that only five [37, 38, 41, 42, 49] of these studies have low risk of bias [32]. Furthermore, after sensitivity analysis based on results of the i-CONTENT-tool both overall effect sizes and effect sizes at 7–12 months were not significant anymore. There was little consistency in measurement time points for clinical outcomes and patient-reported outcomes, and many studies provided insufficient data to calculate effect sizes; this limited the potential for data pooling. Where possible, we presented effect size estimates for individual studies, and we extracted outcome data at three clinically relevant time points: 1 months, 3–6 months and 7–12 months post ankle sprain. Guidelines for reporting outcomes in clinical trials are currently in development [64], which must be applied in future research. Similar to the previous review [7], we were unable to conclude the optimal exercise-based program based on content and volume, advocating future ankle sprain rehabilitation

research to compile exercise-based rehabilitation programs in accordance with the Consensus on Exercise Reporting Template [65].

Conclusion

Rehabilitation reduces the risk of recurrent ankle sprain by 40% compared to usual care or doing nothing. The effect of rehabilitation on other PROMs and clinical outcomes is conflicting. Exercise interventions were generally well reported but there was no evidence to suggest an optimal rehabilitation protocol or training volume. Better understanding of rehabilitation effect could be achieved through consistent measurement methods, with key focus on CAI prevalence and a minimal follow up of 12 months. Future research should examine which variables (duration, exercise content, intensity) have the greatest moderating effect on rehabilitation outcomes.

Supporting information

S1 File. MEDLINE search strategy. Search terms implemented for MEDLINE, modified as required and applied across other databases.

(DOCX)

S2 File Reference list Reference list of studies which might appear to meet inclusion criteria, but were excluded in second phase of screening.

(DOCX)

S3 File. PRISMA 2020 checklist.

(DOCX)

S4 File. PRISMA 2020 abstract checklist.

(DOCX)

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References

1. Doherty C, Bleakley C, Delahunt E, Holden S. Treatment and prevention of acute and recurrent ankle sprain: an overview of systematic reviews with meta-analysis. *British journal of sports medicine*. 2017; 51(2):113–25. <https://doi.org/10.1136/bjsports-2016-096178> PMID: 28053200

2. Doherty C, Delahunt E, Caulfield B, Hertel J, Ryan J, Bleakley C. The incidence and prevalence of ankle sprain injury: a systematic review and meta-analysis of prospective epidemiological studies. *Sports Med.* 2014; 44(1):123–40. <https://doi.org/10.1007/s40279-013-0102-5> PMID: 24105612
3. Fong DT, Hong Y, Chan LK, Yung PS, Chan KM. A systematic review on ankle injury and ankle sprain in sports. *Sports Med.* 2007; 37(1):73–94. <https://doi.org/10.2165/00007256-200737010-00006> PMID: 17190537
4. Gribble PA, Bleakley CM, Caulfield BM, Docherty CL, Fourchet F, Fong DT, et al. Evidence review for the 2016 International Ankle Consortium consensus statement on the prevalence, impact and long-term consequences of lateral ankle sprains. *British journal of sports medicine.* 2016; 50(24):1496–505. <https://doi.org/10.1136/bjsports-2016-096189> PMID: 27259753
5. D'Hooghe P, Cruz F, Alkhelaifi K. Return to Play After a Lateral Ligament Ankle Sprain. *Curr Rev Musculoskelet Med.* 2020; 13(3):281–8. <https://doi.org/10.1007/s12178-020-09631-1> PMID: 32377961
6. Swenson DM, Collins CL, Fields SK, Comstock RD. Epidemiology of U.S. high school sports-related ligamentous ankle injuries, 2005/06–2010/11. *Clin J Sport Med.* 2013; 23(3):190–6. <https://doi.org/10.1097/JSM.0b013e31827d21fe> PMID: 23328403
7. Bleakley CM, Taylor JB, Dischiavi SL, Doherty C, Delahunt E. Rehabilitation Exercises Reduce Reinjury Post Ankle Sprain, But the Content and Parameters of an Optimal Exercise Program Have Yet to Be Established: A Systematic Review and Meta-analysis. *Arch Phys Med Rehabil.* 2019; 100(7):1367–75. <https://doi.org/10.1016/j.apmr.2018.10.005> PMID: 30612980
8. Delahunt E, Bleakley CM, Bossard DS, Caulfield BM, Docherty CL, Doherty C, et al. Clinical assessment of acute lateral ankle sprain injuries (ROAST): 2019 consensus statement and recommendations of the International Ankle Consortium. *British journal of sports medicine.* 2018; 52(20):1304–10. <https://doi.org/10.1136/bjsports-2017-098885> PMID: 29886432
9. Doherty C, Bleakley C, Hertel J, Caulfield B, Ryan J, Delahunt E. Recovery From a First-Time Lateral Ankle Sprain and the Predictors of Chronic Ankle Instability: A Prospective Cohort Analysis. *The American journal of sports medicine.* 2016; 44(4):995–1003. <https://doi.org/10.1177/0363546516628870> PMID: 26912285
10. Hertel J, Corbett RO. An Updated Model of Chronic Ankle Instability. *J Athl Train.* 2019; 54(6):572–88. <https://doi.org/10.4085/1062-6050-344-18> PMID: 31162943
11. Cloke DJ, Ansell P, Avery P, Deehan D. Ankle injuries in football academies: a three-centre prospective study. *British journal of sports medicine.* 2011; 45(9):702–8. <https://doi.org/10.1136/bjism.2009.067900> PMID: 20511620
12. Cloke DJ, Spencer S, Hodson A, Deehan D. The epidemiology of ankle injuries occurring in English Football Association academies. *British journal of sports medicine.* 2009; 43(14):1119–25. <https://doi.org/10.1136/bjism.2008.052050> PMID: 19106152
13. Waldén M, Häggglund M, Ekstrand J. Time-trends and circumstances surrounding ankle injuries in men's professional football: an 11-year follow-up of the UEFA Champions League injury study. *British journal of sports medicine.* 2013; 47(12):748–53. <https://doi.org/10.1136/bjsports-2013-092223> PMID: 23813486
14. Woods C, Hawkins R, Hulse M, Hodson A. The Football Association Medical Research Programme: an audit of injuries in professional football: an analysis of ankle sprains. *British journal of sports medicine.* 2003; 37(3):233–8. <https://doi.org/10.1136/bjism.37.3.233> PMID: 12782548
15. Woods C, Hawkins R, Hulse M, Hodson A. The Football Association Medical Research Programme: an audit of injuries in professional football-analysis of preseason injuries. *British journal of sports medicine.* 2002; 36(6):436–41; discussion 41. <https://doi.org/10.1136/bjism.36.6.436> PMID: 12453838
16. Hertel J. Functional Anatomy, Pathomechanics, and Pathophysiology of Lateral Ankle Instability. *J Athl Train.* 2002; 37(4):364–75. PMID: 12937557
17. Anandacoomarasamy A, Barnsley L. Long term outcomes of inversion ankle injuries. *British journal of sports medicine.* 2005; 39(3):e14; discussion e. <https://doi.org/10.1136/bjism.2004.011676> PMID: 15728682
18. Konradsen L, Bech L, Ehrenbjerg M, Nickelsen T. Seven years follow-up after ankle inversion trauma. *Scand J Med Sci Sports.* 2002; 12(3):129–35. <https://doi.org/10.1034/j.1600-0838.2002.02104.x> PMID: 12135444
19. Valderrabano V, Pagenstert G, Horisberger M, Knupp M, Hintermann B. Sports and recreation activity of ankle arthritis patients before and after total ankle replacement. *The American journal of sports medicine.* 2006; 34(6):993–9. <https://doi.org/10.1177/0363546505284189> PMID: 16452268
20. Valderrabano V, Horisberger M, Russell I, Dougall H, Hintermann B. Etiology of ankle osteoarthritis. *Clin Orthop Relat Res.* 2009; 467(7):1800–6. <https://doi.org/10.1007/s11999-008-0543-6> PMID: 18830791

21. Saltzman CL, Zimmerman MB, O'Rourke M, Brown TD, Buckwalter JA, Johnston R. Impact of comorbidities on the measurement of health in patients with ankle osteoarthritis. *The Journal of bone and joint surgery American volume*. 2006; 88(11):2366–72. <https://doi.org/10.2106/JBJS.F.00295> PMID: [17079392](https://pubmed.ncbi.nlm.nih.gov/17079392/)
22. Herzog MM, Kerr ZY, Marshall SW, Wikstrom EA. Epidemiology of Ankle Sprains and Chronic Ankle Instability. *J Athl Train*. 2019; 54(6):603–10. <https://doi.org/10.4085/1062-6050-447-17> PMID: [31135209](https://pubmed.ncbi.nlm.nih.gov/31135209/)
23. Gribble PA, Delahunt E, Bleakley CM, Caulfield B, Docherty CL, Fong DT, et al. Selection criteria for patients with chronic ankle instability in controlled research: a position statement of the International Ankle Consortium. *J Athl Train*. 2014; 49(1):121–7. <https://doi.org/10.4085/1062-6050-49.1.14> PMID: [24377963](https://pubmed.ncbi.nlm.nih.gov/24377963/)
24. Gribble PA, Delahunt E, Bleakley C, Caulfield B, Docherty C, Fouchet F, et al. Selection criteria for patients with chronic ankle instability in controlled research: a position statement of the International Ankle Consortium. *British journal of sports medicine*. 2014; 48(13):1014–8. <https://doi.org/10.1136/bjsports-2013-093175> PMID: [24255768](https://pubmed.ncbi.nlm.nih.gov/24255768/)
25. Gribble PA, Delahunt E, Bleakley C, Caulfield B, Docherty CL, Fouchet F, et al. Selection criteria for patients with chronic ankle instability in controlled research: a position statement of the International Ankle Consortium. *The Journal of orthopaedic and sports physical therapy*. 2013; 43(8):585–91. <https://doi.org/10.2519/jospt.2013.0303> PMID: [23902805](https://pubmed.ncbi.nlm.nih.gov/23902805/)
26. Bielska IA, Wang X, Lee R, Johnson AP. The health economics of ankle and foot sprains and fractures: A systematic review of English-language published papers. Part 2: The direct and indirect costs of injury. *Foot (Edinburgh, Scotland)*. 2019; 39:115–21. <https://doi.org/10.1016/j.foot.2017.07.003> PMID: [29174064](https://pubmed.ncbi.nlm.nih.gov/29174064/)
27. Gagnier JJ, Morgenstern H, Chess L. Interventions Designed to Prevent Anterior Cruciate Ligament Injuries in Adolescents and Adults: A Systematic Review and Meta-analysis. *The American journal of sports medicine*. 2013; 41(8):1952–62. <https://doi.org/10.1177/0363546512458227> PMID: [22972854](https://pubmed.ncbi.nlm.nih.gov/22972854/)
28. Smith MD, Vicenzino B, Bahr R, Bandholm T, Cooke R, Mendonça LM, et al. Return to sport decisions after an acute lateral ankle sprain injury: introducing the PAASS framework—an international multidisciplinary consensus. *British journal of sports medicine*. 2021. <https://doi.org/10.1136/bjsports-2021-104087> PMID: [34158354](https://pubmed.ncbi.nlm.nih.gov/34158354/)
29. Hoogbeem TJ, Kousemaker MC, van Meeteren NL, Howe T, Bo K, Tugwell P, et al. i-CONTENT tool for assessing therapeutic quality of exercise programs employed in randomised clinical trials. *British journal of sports medicine*. 2020:bjsports-2019-101630. <https://doi.org/10.1136/bjsports-2019-101630> PMID: [33144350](https://pubmed.ncbi.nlm.nih.gov/33144350/)
30. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372:n71. <https://doi.org/10.1136/bmj.n71> PMID: [33782057](https://pubmed.ncbi.nlm.nih.gov/33782057/)
31. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews*. 2016; 5(1):210. <https://doi.org/10.1186/s13643-016-0384-4> PMID: [27919275](https://pubmed.ncbi.nlm.nih.gov/27919275/)
32. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj*. 2019; 366:l4898. <https://doi.org/10.1136/bmj.l4898> PMID: [31462531](https://pubmed.ncbi.nlm.nih.gov/31462531/)
33. Drevon D, Fursa SR, Malcolm AL. Intercoder Reliability and Validity of WebPlotDigitizer in Extracting Graphed Data. *Behavior modification*. 2017; 41(2):323–39. <https://doi.org/10.1177/0145445516673998> PMID: [27760807](https://pubmed.ncbi.nlm.nih.gov/27760807/)
34. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemporary Clinical Trials*. 2015; 45:139–45. <https://doi.org/10.1016/j.cct.2015.09.002> PMID: [26343745](https://pubmed.ncbi.nlm.nih.gov/26343745/)
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*. 2002; 21(11):1539–58. <https://doi.org/10.1002/sim.1186> PMID: [12111919](https://pubmed.ncbi.nlm.nih.gov/12111919/)
36. Orwin RG. A Fail-SafeN for Effect Size in Meta-Analysis. *Journal of Educational Statistics*. 1983; 8(2):157–9.
37. Bleakley CM, O'Connor SR, Tully MA, Rocke LG, Macauley DC, Bradbury I, et al. Effect of accelerated rehabilitation on function after ankle sprain: randomised controlled trial. *Bmj*. 2010; 340:c1964. <https://doi.org/10.1136/bmj.c1964> PMID: [20457737](https://pubmed.ncbi.nlm.nih.gov/20457737/)
38. Brison RJ, Day AG, Pelland L, Pickett W, Johnson AP, Aiken A, et al. Effect of early supervised physiotherapy on recovery from acute ankle sprain: randomised controlled trial. *BMJ*. 2016; 355:i5650. <https://doi.org/10.1136/bmj.i5650> PMID: [27852621](https://pubmed.ncbi.nlm.nih.gov/27852621/)
39. Holme E, Magnusson SP, Becher K, Bieler T, Aagaard P, Kjaer M. The effect of supervised rehabilitation on strength, postural sway, position sense and re-injury risk after acute ankle ligament sprain.

- Scand J Med Sci Sports. 1999; 9(2):104–9. <https://doi.org/10.1111/j.1600-0838.1999.tb00217.x> PMID: 10220845
40. Hultman K, Fältström A, Öberg U. The effect of early physiotherapy after an acute ankle sprain. *Advances in Physiotherapy*. 2010; 12(2):65–73.
 41. Hupperets MD, Verhagen EA, van Mechelen W. Effect of unsupervised home based proprioceptive training on recurrences of ankle sprain: randomised controlled trial. *Bmj*. 2009; 339:b2684. <https://doi.org/10.1136/bmj.b2684> PMID: 19589822
 42. Janssen KW, van Mechelen W, Verhagen EA. Bracing superior to neuromuscular training for the prevention of self-reported recurrent ankle sprains: a three-arm randomised controlled trial. *British journal of sports medicine*. 2014; 48(16):1235–9. <https://doi.org/10.1136/bjsports-2013-092947> PMID: 24398222
 43. Kachanathu SJ, Hafez AR, Alenazi AM, Hassan SM, Algarni AD, Albarrati A. Wirksamkeit von Übungen in geschlossenen und offenen kinematischen Ketten zur Rehabilitation von Distorsionen der Knöchelregion. *Physikalische Medizin, Rehabilitationsmedizin, Kurortmedizin*. 2016; 26(01):28–31.
 44. Lazarou L, Kofotolis N, Malliou P, Kellis E. Effects of two proprioceptive training programs on joint position sense, strength, activation and recurrent injuries after ankle sprains. *Isokinetics and Exercise Science*. 2017; 25:289–300.
 45. Lazarou L, Kofotolis N, Pafis G, Kellis E. Effects of two proprioceptive training programs on ankle range of motion, pain, functional and balance performance in individuals with ankle sprain. *Journal of Back and Musculoskeletal Rehabilitation*. 2018; 31:437–46. <https://doi.org/10.3233/BMR-170836> PMID: 28946541
 46. Mohammadi F. Comparison of 3 preventive methods to reduce the recurrence of ankle inversion sprains in male soccer players. *The American journal of sports medicine*. 2007; 35(6):922–6. <https://doi.org/10.1177/0363546507299259> PMID: 17379918
 47. Punt IM, Ziltener JL, Monnin D, Allet L. Wii Fit™ exercise therapy for the rehabilitation of ankle sprains: Its effect compared with physical therapy or no functional exercises at all. *Scand J Med Sci Sports*. 2016; 26(7):816–23. <https://doi.org/10.1111/sms.12509> PMID: 26076737
 48. Van Reijen M, Vriend I, Zuidema V, van Mechelen W, Verhagen EA. The "Strengthen your ankle" program to prevent recurrent injuries: A randomized controlled trial aimed at long-term effectiveness. *Journal of science and medicine in sport*. 2017; 20(6):549–54. <https://doi.org/10.1016/j.jsams.2016.12.001> PMID: 27988093
 49. van Rijn RM, van Os AG, Kleinrensink GJ, Bernsen RM, Verhaar JA, Koes BW, et al. Supervised exercises for adults with acute lateral ankle sprain: a randomised controlled trial. *The British journal of general practice: the journal of the Royal College of General Practitioners*. 2007; 57(543):793–800. PMID: 17925136
 50. Wester JU, Jespersen SM, Nielsen KD, Neumann L. Wobble board training after partial sprains of the lateral ligaments of the ankle: a prospective randomized study. *The Journal of orthopaedic and sports physical therapy*. 1996; 23(5):332–6. <https://doi.org/10.2519/jospt.1996.23.5.332> PMID: 8728532
 51. Garner P, Hopewell S, Chandler J, MacLehose H, Akl EA, Beyene J, et al. When and how to update systematic reviews: consensus and checklist. *BMJ*. 2016; 354:i3507. <https://doi.org/10.1136/bmj.i3507> PMID: 27443385
 52. Pourkazemi F, Hiller CE, Raymond J, Black D, Nightingale EJ, Refshauge KM. Predictors of recurrent sprains after an index lateral ankle sprain: a longitudinal study. *Physiotherapy*. 2018; 104(4):430–7. <https://doi.org/10.1016/j.physio.2017.10.004> PMID: 29325691
 53. Swenson DM, Yard EE, Fields SK, Dawn Comstock R. Patterns of Recurrent Injuries among US High School Athletes, 2005–2008. *The American journal of sports medicine*. 2009; 37(8):1586–93. <https://doi.org/10.1177/0363546509332500> PMID: 19372270
 54. Corbett RO, Vela L, Harris PC, Saliba S, Hertel J. Athletic Trainers' Perception on Treating and Managing Ankle Sprains. *Journal of Athletic Training*. 2020.
 55. Hiller CE, Nightingale EJ, Raymond J, Kilbreath SL, Burns J, Black DA, et al. Prevalence and impact of chronic musculoskeletal ankle disorders in the community. *Arch Phys Med Rehabil*. 2012; 93(10):1801–7. <https://doi.org/10.1016/j.apmr.2012.04.023> PMID: 22575395
 56. Roemer FW, Jomaah N, Niu J, Almusa E, Roger B, D'Hooghe P, et al. Ligamentous Injuries and the Risk of Associated Tissue Damage in Acute Ankle Sprains in Athletes: A Cross-sectional MRI Study. *The American journal of sports medicine*. 2014; 42(7):1549–57. <https://doi.org/10.1177/0363546514529643> PMID: 24753239
 57. Armijo-Olivo S, Fuentes J, da Costa BR, Saltaji H, Ha C, Cummings GG. Blinding in Physical Therapy Trials and Its Association with Treatment Effects: A Meta-epidemiological Study. *American journal of physical medicine & rehabilitation*. 2017; 96(1):34–44. <https://doi.org/10.1097/PHM.0000000000000521> PMID: 27149591

58. Jette AM. The Importance of Dose of a Rehabilitation Intervention. *Physical therapy*. 2017; 97(11):1043-. <https://doi.org/10.1093/ptj/pzx085> PMID: 29099967
59. Baechle TR, Earle RW, National Strength & Conditioning Association (U.S.). *Essentials of strength training and conditioning*. 3rd ed. Champaign, IL: Human Kinetics; 2008. xiv, 641 p. p.
60. van Rijn RM, van Os AG, Bernsen RM, Luijsterburg PA, Koes BW, Bierma-Zeinstra SM. What is the clinical course of acute ankle sprains? A systematic literature review. *The American journal of medicine*. 2008; 121(4):324–31.e6. <https://doi.org/10.1016/j.amjmed.2007.11.018> PMID: 18374692
61. Terrier P, Piotton S, Punt IM, Ziltener J-L, Allet L. Predictive Factors of Recovery after an Acute Lateral Ankle Sprain: A Longitudinal Study. *Sports*. 2021; 9(3):41. <https://doi.org/10.3390/sports9030041> PMID: 33803881
62. Tassignon B, Verschueren J, Delahunt E, Smith M, Vicenzino B, Verhagen E, et al. Criteria-Based Return to Sport Decision-Making Following Lateral Ankle Sprain Injury: a Systematic Review and Narrative Synthesis. *Sports Medicine*. 2019; 49(4):601–19. <https://doi.org/10.1007/s40279-019-01071-3> PMID: 30747379
63. Borenstein M. *Introduction to meta-analysis*. Chichester, U.K.: John Wiley & Sons; 2009. xxviii, 421 p. p.
64. Butcher NJ, Mew EJ, Monsour A, Chan A-W, Moher D, Offringa M. Outcome reporting recommendations for clinical trial protocols and reports: a scoping review. *Trials*. 2020; 21(1):620. <https://doi.org/10.1186/s13063-020-04440-w> PMID: 32641085
65. Slade SC, Dionne CE, Underwood M, Buchbinder R, Beck B, Bennell K, et al. Consensus on Exercise Reporting Template (CERT): Modified Delphi Study. *Physical therapy*. 2016; 96(10):1514–24. <https://doi.org/10.2522/ptj.20150668> PMID: 27149962