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Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials

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ABSTRACT

OBJECTIVE

Low-level laser therapy (LLLT) is not recommended in major knee osteoarthritis (KOA) treatment guidelines. We investigated whether a LLLT dose-response relationship exists in KOA.

DESIGN

We conducted a systematic review and meta-analysis of randomized placebo-controlled trials. The included trials were subgrouped by dose using the World Association for Laser Therapy treatment recommendations.

DATA SOURCES

We searched for eligible articles using PubMed, Embase, CINAHL, PEDro, and CENTRAL on the 18th February 2019, reference lists of eligible articles, related reviews, a book, citations, and experts in the field.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

We solely included randomized placebo-controlled trials involving participants with KOA according to the American College of Rheumatology and/or Kellgren/Lawrence criteria in which LLLT was applied to participants' knee(s). There were no language restrictions.

RESULTS

22 trial articles were included in the meta-analysis (N = 1063). Overall, pain was significantly reduced by LLLT compared to placebo-control at the end of therapy (14.23 mm VAS [95% CI: 7.31-21.14]) and during follow-ups 2-12 weeks later (15.92 mm VAS [95% CI: 6.47-25.37]). The subgroup analysis revealed that more pain was significantly reduced by the recommended LLLT doses compared to the placebo-control at the end of therapy (18.71 mm [95% CI: 9.42-27.99]) and during follow-ups 2-12 weeks later (23.23 mm VAS [95% CI: 10.60-35.86]). The pain reduction provided by the recommended LLLT doses peaked during follow-ups 2-4 weeks after the end of therapy at 31.87 mm VAS significantly beyond placebo ([95% CI: 18.18-45.56]). A similar positive

statistically significant trend for disability was found in comparing LLLT to placebo-control. No adverse events were reported.

CONCLUSION

LLLT is safe and offers disability reduction and clinically relevant pain relief in KOA at 4-7 Joules with 785-860 nm wavelength or 1-3 Joules with 904 nm wavelength per treatment spot.

STUDY REGISTRATION

PROSPERO registration number: CRD42016035587.

Keywords Phototherapy; Laser therapy; Knee osteoarthritis; Systematic review; Meta-analysis

Strengths and limitations of this study

- The review was conducted in conformance with an a priori published protocol including a detailed plan for statistical analysis.
- No language restrictions were applied; four (18%) of the included trials were reported in non-English language.
- Three persons each independently extracted the data for meta-analysis and resolved data disagreements by consensus-based discussions.
- A series of analyses were conducted to estimate the effectiveness of low-level laser therapy on pain over time.
- No quality of life meta-analysis was performed as this outcome was only assessed in a single included trial.

Introduction

Approximately 13% of women and 10% of men in the population aged ≥ 60 years suffer from knee osteoarthritis (KOA) in the USA.[1] KOA is a degenerative inflammatory disease affecting the entire joint and is characterised by progressive loss of cartilage and associated with pain, disability and reduced quality of life.[1] Increased inflammatory activity is associated with higher pain intensity and more rapid KOA disease progression.[1 2]

Some of the conservative intervention options for KOA are exercise therapy, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and anti-inflammatory Low-Level Laser Therapy (LLLT). There is evidence that exercise therapy reduces pain and disability and improves quality of life (QoL) in persons with KOA.[3 4] NSAIDs are recommended in most KOA clinical treatment guidelines and is probably the most frequently prescribed therapy category for osteoarthritis, despite intake of these drugs is associated with negative side effects[5], which is problematic, especially in chronic diseases, such as OA, which require long-term treatment. Furthermore, the results of a network meta-analysis indicate that the pain relieving effect from NSAIDs in KOA beyond placebo is small to moderate (depending on drug type)[6], and the effect of using the NSAID tiaprofenic acid, for example, is probably gone within less than two weeks, unless the treatment is continued.[7]

LLLT is a non-invasive treatment modality[8 9] with an anti-inflammatory effect[9-14], which has been compared to that of a NSAID in rats with KOA by Tomazoni et al.; NSAID (10 mg diclofenac/knee/session) and LLLT (6 Joules 830 nm wavelength laser/knee/session) reduced similar levels of inflammatory cells and metalloproteinase (MP 3 and 13). In addition, LLLT reduced the expression of pro-inflammatory cytokines (interleukin-1β, interleukin-6, and tumour necrosis factor α), myeloperoxidase, and prostaglandin E_2 significantly more than NSAID did.[10 11]

LLLT is not recommended in major osteoarthritis treatment guidelines. LLLT for KOA was mentioned in the European League Against Rheumatism (EULAR) osteoarthritis guidelines (2018) but not recommended[15], and in the Osteoarthritis Research Society International (OARSI)

guidelines (2018), it was stressed that LLLT should not be considered a core intervention in the management of KOA.[16]
This may be partly due to conflicting results of two recently published reviews on the current topic (Huang et al. 2015 and Rayegani et al. 2017).[8 17] The conflicting results may arise from omission of relevant trials [8 17-23] and LLLT dose-related issues. Only Huang et al. conducted a LLLT dose-response relationship investigation in KOA, i.e., by subgrouping the trials by laser dose, but they did not consider that World Association for Laser Therapy (WALT) recommends applying four times the laser dose with continuous irradiation compared to highly pulsed irradiation.[17 22 24-26]
Thus, it was unknown whether LLLT is effective in KOA, and we believed it necessitated conducting a new systematic review.
The objectives of the current review were to estimate the effectiveness of LLLT in KOA regarding knee pain, disability and quality of life (QoL), and we only considered randomized placebo-controlled clinical trials (RCTs) for inclusion to minimize risk of bias.

Methods

This review was conducted in adherence to a PROSPERO protocol (number CRD42016035587) and it is reported in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis statement 2009.[27]

Literature search and selection of studies

Any identified study was included if it was a randomized placebo-controlled trial involving participants with KOA according to the American College of Rheumatology tool and/or a radiographic inspection with the Kellgren/Lawrence (K/L) criteria, focusing on LLLT applied to participants' knee(s) and self-reported pain, disability, and/or QoL was reported. There were no language restrictions.
We updated a search for eligible articles indexed in PubMed, Embase, CINAHL, PEDro, and CENTRAL on the 18th February 2019. The database search strings contained synonyms for LLLT, KOA, and RCT, and keywords were added when optional (a search string is provided in the PROSPERO protocol). The search was continued by reading reference lists of all the eligible trial and relevant review articles[8 17 28], citations[29-33], and a laser book[34], and involving experts in the field.
Two reviewers (MBS and JMB) each independently selected the trial articles. Both reviewers scrutinized the titles/abstracts of all the publications identified in the search, and any accessible full-text article was retrieved if it was judged potential eligible by at least one reviewer. Both reviewers evaluated the full texts of all potentially eligible retrieved articles and made an independent decision to include or exclude each article, with close attention to the inclusion criteria. When selection disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Any retrieved article not fulfilling the inclusion criteria was omitted and listed with reason for exclusion.

Risk of bias analysis

Two reviewers (MBS and JJ) each independently evaluated all included trials for risk of bias at the outcome level, using the Cochrane Collaboration's risk of bias tool.[35] When risk of bias disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Likelihood of publication bias was assessed with graphical funnel plots.[35]

Data-extraction and meta-analysis

Three reviewers (MBS, JMB, and KVF) each independently extracted the data for meta-analysis. Two of the reviewers (MBS and KVF) each independently collected the other trial characteristics. The data-extraction forms were subsequently compared, and data disagreements were resolved by consensus-based discussions. Summary data were extracted, unless published individual participant data were available.[21] The results from the included trials for statistical analysis were selected from outcome scales in adherence to hierarchies published by Juhl et al.[36]

Pain intensity was the primary outcome. As pain reported with continuous, numeric and categorical/Likert scales highly correlates with pain measured using the Visual Analogue Scale (VAS), the scores of all pain scales were transformed to 0-100%, corresponding to 0-100 mm VAS.[37] The pain results were combined with the Mean Difference (MD) method, primarily using change scores, i.e., when only final scores could be obtained from a trial, change and final scores were mixed in the analysis, since the MD method allows for this without introducing bias.[35]

Self-reported disability and QoL results were synthesized using the Standardized Mean Difference (SMD) method using change scores solely. The SMD was adjusted to Hedges' *g* and interpreted as follows: SMDs of 0.2, ~ 0.5, and > 0.8 represent a small, moderate, and large effect, respectively.[35]

Random effects meta-analyses were conducted, and impact from heterogeneity (inconsistency) on the analyses was examined using I^2 statistics. An I^2 value of 0% indicates no inconsistency, and an I^2 value of 100% indicates maximal inconsistency[35]; the values were categorized as low (25%), moderate (50%), and high (75%).[38]

Standard deviations (SD) for analysis were extracted or estimated from other variance data in a pre-specified prioritized order: (1) SD, (2) standard error, (3) 95% confidence interval, (4) P-value, (5) interquartile range, (6) median of correlations, (7) visually from graph, or (8) other methods.[35]

The trials were subgrouped by adherence and non-adherence to the WALT recommendations for laser dose per treatment spot, as pre-specified. WALT recommends irradiating the knee joint line/synovia with the following laser doses per treatment spot: ≥ 4 Joules applied with 5-500 mW mean power using 780-860 nm wavelength and/or ≥ 1 Joules applied with 5-500 mW mean power (> 1000 mW peak power) using 904 nm wavelength.[24 25]

The main meta-analyses were conducted using two pre-specified time points of assessment, i.e., immediately after the end of LLLT and last time point of assessment 1-12 weeks after the end of LLLT (follow-up).

MBS performed the meta-analyses, under supervision of JMB, using the software programs Excel 2016 (Microsoft) and Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

Results

In total, 2735 publications were identified in the search, of which 22 trial articles were judged eligible and included in the review (N = 1089) (fig 1 and table 1-2) with data for meta-analysis (N = 1063). Four included trials were not reported in the English language[19 21 23 39] and one included trial was unpublished (Gur and Oktayoglu). Excluded articles initially judged potentially eligible were listed with reasons for omission (supplementary material).

Fig 1 | Flow chart illustrating the trial identification process
LLLT = low-level laser therapy; ACR = American College of Rheumatology; K/L = Kellgren/Lawrence.

At the group level, the mean age of the participants was 60.25 (50.11-69) years (data from 19 trials), the mean percentage of women was 69.63 (0-100) (data from 17 trials), the mean BMI of the

participants was 29.55 (25.8-38) (data from 14 trials), the mean of median K/L grades was 2.37 (data from 13 trials) and the mean baseline pain was 63.61 mm VAS (35.25-92) (data from 22 trials). LLLT was used as an adjunct to exercise therapy in eleven trials. The mean duration of the treatment periods was 3.53 weeks with the recommended LLLT doses and 3.89 weeks with the non-recommended LLLT doses (table 1-2). Non-recommended LLLT doses were applied in nine of the trials. That is, Al Rashoud et al.[31], Bülow et al.[20], Tascioglu et al.[40], and Bagheri et al.[23] applied too few (< 4) Joules per treatment spot with 830 nm wavelength, Jensen et al.[21], Nivbrant et al.[19] and Hinman et al.[41] applied too few (< 1) Joules per treatment spot with 904 nm wavelength, and Youssef et al.[42] (one group) and Rayegani et al.[43] used continuous laser with too long of a wavelength (880 nm) (table 2). No adverse event was reported by any of the trial authors. None of the authors stated receiving funding from the laser industry (supplementary material).

Table 1 | Characteristics of the included trials

First author	Intervention group at baseline	Control group at baseline	Intervention vs control programme	Outcome scales, week of assessment after baseline
Al Rashoud 2014[31]	N: 26 Women: 62% Age: 52 years BMI: 38 VAS pain: 64 mm K/L: -	N: 23 Women: 65% Age: 56 years BMI: 37.1 VAS pain: 59 mm K/L: -	3 weeks of exercise therapy, advice, and LLLT vs 3 weeks of exercise therapy, advice, and sham LLLT	Pain: VAS (movement) Disability: SKFS QoL: - Week of assessment: 2, **3**, **9**, 29
Alfredo 2011/2018[29] [44]	N: 24 Women: 75% Age: 61.15 years BMI: 30.16 VAS pain: 53.2 mm K/L: 3	N: 22 Women: 80% Age: 62.25 years BMI: 29.21 VAS pain: 35.4 mm K/L: 2	3 weeks of LLLT followed by 8 weeks of exercise therapy vs 3 weeks of sham LLLT followed by 8 weeks of exercise therapy	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, **11**, 24, 37
Alghadir 2014[32]	N: 20 Women: 50% Age: 55.2 years BMI: 32.34 VAS pain: 74.5 mm K/L: 2	N: 20 Women: 40% Age: 57 years BMI: 33.09 VAS pain: 75.5 mm K/L: 2	4 weeks of exercise therapy, heat packs, and LLLT vs 4 weeks of exercise therapy, heat packs, and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **4**
Bagheri 2011[23]	N: 18 Women: 83.13% Age: 58.32 years BMI: 28.87 VAS pain: 67 mm K/L: -	N: 18 Women: 83.13% Age: 56.14 years BMI: 27.66 VAS pain: 59 mm K/L: -	5 weeks of exercise therapy, therapeutic ultrasound, TENS, and LLLT vs 5 weeks of exercise therapy, therapeutic ultrasound, TENS, and sham LLLT	Pain: WOMAC (VAS) 0-100 Disability: WOMAC QoL: - Week of assessment: **5**
Bülow 1994[20]	N: 14 Women: - Age: - BMI: - VAS pain: 65.08 mm K/L: -	N: 15 Women: - Age: - BMI: - VAS pain: 56.35 mm K/L: -	3 weeks of LLLT vs 3 weeks of sham LLLT	Pain: 0-121 Likert scale (movement/rest) Disability: - QoL: - Week of assessment: **3**, **6**
Delkhosh 2018[39]	N: 15 Women: 100% Age: 55.9 years BMI: 26.5 VAS pain: 57 mm K/L: -	N: 15 Women: 100% Age: 58.3 years BMI: 27.8 VAS pain: 45 mm K/L: -	2 weeks of exercise therapy, therapeutic ultrasound, TENS, and LLLT vs 2 weeks of exercise therapy, therapeutic ultrasound, TENS, and sham LLLT	Pain: VAS Disability: WOMAC QoL: - Week of assessment: **2**, **8**
Fukuda 2011[30]	N: 25 Women: 80% Age: 63 years BMI: 30 VAS pain: 61 mm K/L: 2	N: 22 Women: 64% Age: 63 years BMI: 30 VAS pain: 62 mm K/L: 2	3 weeks of LLLT vs 3 weeks of sham LLLT	Pain: VNSP (movement) Disability: Lequesne QoL: - Week of assessment: **3**
Gur 2003[33] (1.5 Joules)	N: 30 Women: 83.3% Age: 58.64 years BMI: 31.17 VAS pain: 73.2 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**
Gur 2003[33] (1 Joules)	N: 30 Women: 76.7%	N: 30 Women: 80%	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks	Pain: VAS (movement) Disability: -

	Age: 59.8 years BMI: 28.49 VAS pain: 74.4 mm K/L: 2	Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	of exercise and 2 weeks of sham LLLT	QoL: - Week of assessment: 6, 10, **14**
Gur and Oktayoglu	N: 40 Women: 75% Age: 58.2 years BMI: 29.11 VAS pain: 88 mm K/L: 3	N: 40 Women: 72.5% Age: 58.26 years BMI: 30.11 VAS pain: 92 mm K/L: 3	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**
Gworys 2012[18]	N: 34 Women: - Age: 57.6 BMI: - VAS pain: 54 mm K/L: -	N: 31 Women: - Age: 67.7 BMI: - VAS pain: - K/L: -	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: VAS Disability: Lequesne QoL: - Week of assessment: **2**
Hegedus 2009[45]	N: 18 Women: - Age: - BMI: - VAS pain: 57.5 mm K/L: 2	N: 17 Women: - Age: - BMI: - VAS pain: 56.2 mm K/L: 2	4 weeks of LLLT vs 4 weeks of sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**, 6, **12**
Helianthi 2016[46]	N: 30 Women: 60% Age: 69 years BMI: 25.8 VAS pain: 60.2 mm K/L: 3	N: 29 Women: 82.8% Age: 68 years BMI: 26.3 VAS pain: 54.1 mm K/L: 3	5 weeks of LLLT vs 5 weeks of sham LLLT	Pain: VAS (movement) Disability: Lequesne QoL: - Week of assessment: 2, **5**, **7**
Hinman 2014[41]	N: 71 Women: 39% Age: 63.4 years BMI: 30.7 VAS pain: 41.5 mm K/L: -	N: 70 Women: 56% Age: 63.8 years BMI: 28.8 VAS pain: 43 mm K/L: -	12 weeks of LLLT vs 12 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: AQoL-6D Week of assessment: **12**, 52
Jensen 1987[21]	N: 13 Women: - Age: - BMI: - VAS pain: 67 mm K/L: -	N: 16 Women: - Age: - BMI: - VAS pain: 72.6 mm K/L: -	1 week of LLLT vs 1 week of sham LLLT	Pain: 0-21 (movement) Disability: - QoL: - Week of assessment: **1**
Kheshie 2014[47]	N: 18 Women: 0% Age: 56.56 years BMI: 28.62 VAS pain: 76.8 mm K/L: 2.5	N: 15 Women: 0% Age: 55.6 years BMI: 28.51 VAS pain: 78.7 mm K/L: 2.5	6 weeks of exercise and LLLT vs 6 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **6**
Koutenaei 2017[48]	N: 20 Women: 85% Age: 52.3 years BMI: 28.4 VAS pain: 74 mm K/L: 3	N: 20 Women: 80% Age: 53 years BMI: 28.6 VAS pain: 65.5 mm K/L: 3	2 weeks of exercise and LLLT vs 2 weeks of exercise and sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: **2**, **4**
Mohammed 2018[49]	N: 20 Women: 85% Age: 55.25 years BMI: ≥ 25 VAS pain: 70 mm K/L: 2	N: 20 Women: 85% Age: 50.11 years BMI: ≥ 25 VAS pain: 80 mm K/L: 2	4 weeks of LLLT vs 4 weeks of sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**
Nambi 2016[50]	N: 17 Women: - Age: 58 BMI: 26.9 VAS pain: 78 mm K/L: 3.1	N: 17 Women: - Age: 60 BMI: 28.3 VAS pain: 76 mm K/L: 3.2	4 weeks of exercise, kinesio tape, and LLLT vs 4 weeks of exercise, kinesio tape, and sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**, **8**
Nivbrant 1992[19]	N: 15 Women: 69.2% Age: 69 years BMI: - VAS pain: 67 mm K/L: -	N: 15 Women: 84.6% Age: 66 years BMI: - VAS pain: 58 mm K/L: -	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: VAS (movement) Disability: Walking disability QoL: - Week of assessment: **2**, 3, **6**
Rayegani 2012[43]	N: 12 Women: 83.3%	N: 13 Women: 92.3%	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC

	Age: 61.7 years BMI: - VAS pain: 63 mm K/L: < 4	Age: 61.2 years BMI: - VAS pain: 52 mm K/L: < 4		QoL: - Week of assessment: 6, **14**
Tascioglu 2004[40] (3 Joules)	N: 20 Women: 70% Age: 62.86 years BMI: 27.56 VAS pain: 68 mm K/L: 2	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	10 days of LLLT vs 10 days of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, 26
Tascioglu 2004[40] (1.5 Joules)	N: 20 Women: 75% Age: 59.92 years BMI: 28.63 VAS pain: 65.72 mm K/L: 2.5	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	10 days of LLLT vs 10 days of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, 26
Youssef 2016[42] (904 nm)	N: 18 Women: 66.7% Age: 67.5 BMI: < 40 VAS pain: 51.67 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: < 40 VAS pain: 50.00 mm K/L: 2	8 weeks of exercise and LLLT vs 8 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **8**
Youssef 2016[42] (880 nm)	N: 18 Women: 61.1% Age: 67.3 BMI: < 40 VAS pain: 52.50 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: < 40 VAS pain: 50.00 mm K/L: 2	8 weeks of exercise and LLLT vs 8 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **8**

VAS = Visual Analogue Scale; VNPS = visual numerical pain scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NRS = Numeric Rating Scale; DIQ = Disability Index Questionnaire; SKFS = Saudi Knee Function Scale; QoL = Quality of life; AQoL-6D = Assessment of Quality of Life 6 Dimensions; TENS = transcutaneous electrical nerve stimulation.
The values for age and body mass index (BMI) are means, and the values for the Kellgren/Lawrence (K/L) grade are medians. Baseline VAS scores have been extracted or estimated as described in the method section. Week of assessment in bold denotes time point used for the main meta-analyses.

Table 2 | Laser characteristics of the included trials

First author	Treated area	Wave-length (nm)	Joules per treatment spot	Mean output (mW)	Seconds per treated spot	Number of spots treated	Sessions/ sessions per week
Al Rashoud 2014[31]*	Knee joint line (medial and lateral) and acupoints (SP9, SP10, ST36)	830	1.2	30	40	5	9/3
Alfredo 2011, 2018[29] [44]	Knee joint line (medial and lateral)	904	3	60	50	9	9/3
Alghadir 2014[32]	Knee condyles, joint line (medial and lateral), and popliteal fossa	850	6	100	60	8	8/2
Bagheri 2011[23]*	Knee joint line	830	3	30	100	10	10/5
Bülow 1994[20]*	Painful spots in 0-10 cm radius of the knee joint line	830	1.5-4.5	25	60-180	5-15	9/3
Delkhosh 2018[39]	Knee joint	830	5	30	167	5	10/5
Fukuda 2011[30]	Front knee capsule	904	3	60	50	9	9/3
Gur 2003[33] (1.5 Joules)	Antero-lateral and antero-medial portal of the knee	904	1.5	10	150	2	10/2
Gur 2003[33] (1 Joules)	Antero-lateral and antero-medial portal of the knee	904	1	11.2	90	2	10/2
Gur and Oktayoglu	Antero-lateral and antero-medial portal of the knee	904	1.5	10	150	2	10/2
Gworys 2012[18]	Knee joint line, patellofemoral joint, and popliteal fossa	810	6.6	400	16	7	10/2
Hegedus 2009[45]	Knee joint line, popliteal fossa, and condyles	830	6	50	120	8	8/2
Helianthi 2016[46]	Knee joint line (lateral) and acupoints (ST36, SP9, GB34, EX-LE-4)	785	4	50	80	5	10/2
Hinman 2014[41]*	Acupoints (locations not stated)	904	0.2	10	20	6	8-12/0.67-1

Jensen 1987[21]*	Knee joint line (medial and lateral), apex and basis of patellae	904	0.054	0.3	180	4	5/5
Kheshie 2014[47]#	Front knee	830	-	160	-	-	12/2
Koutenaei 2017[48]	Front knee, popliteal fossa, and femur condyles in the popliteal cavity	810	7	100	70	8	10/5
Mohammed 2018[49]	Knee joint line (lateral) and acupoints (ST36, Sp10, GB, ashi)	808	5.4	90	60	7	12/3
Nambi 2016[50]	Knee joint line, condyles, and popliteal fossa	904	1.5	25	60	8	12/4
Nivbrant 1992[19]*	Knee joint line (medial and lateral) and acupoints (ST34, SP10, X32)	904	0.72	4	180	7	6/3
Rayegani 2012[43]*	Knee joint line and popliteal fossa	880	6	50	120	8	10/5
Tascioglu 2004[40] (3 Joules)*	Painful spots on the knee	830	3	50	60	5	10/5
Tascioglu 2004[40] (1.5 Joules)*	Painful spots on the knee	830	1.5	50	30	5	10/5
Youssef 2016[42] (904 nm)	Knee joint line (medial and lateral)	904	3	60	50	9	16/2
Youssef 2016[42] (880 nm)*	Knee joint line (medial and lateral), epicondyles and popliteal fossa	880	6	50	120	8	16/2

* Non-recommended LLLT dose; # 1250 Joules per session.

Regardless of laser doses applied, pain was significantly reduced by LLLT compared to the placebo-control at the end of therapy (14.23 mm VAS [95% CI: 7.31 to 21.14]; I^2 = 93%; N = 816) (fig 2) and during follow-ups 2-12 weeks later (15.92 mm VAS [95% CI: 6.47 to 25.37]; I^2 = 93%; N = 581) (fig 3). The dose subgroup analyses demonstrated that more pain was significantly reduced by the recommended LLLT doses compared to the placebo-control at the end of therapy (18.71 mm [95% CI: 9.42 to 27.99]; I^2 = 95%; N = 480) (fig 2) and during follow-ups 2-12 weeks later (23.23 mm VAS [95% CI: 10.60 to 35.86]; I^2 = 95%; N = 392) (fig 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the non-recommended LLLT doses compared to placebo-control at the end of therapy (6.34 mm VAS [95% CI: 1.26 to 11.41]; I^2 = 44%; N = 336) (fig 2), but the difference during follow-ups 2-12 weeks later was not significant (6.20 mm VAS [95% CI: -0.65 to 13.05]; I^2 = 38%; N = 189) (fig 3). The between-subgroup differences in pain results (recommended vs non-recommended doses) were significantly in favour of the recommended LLLT doses regarding both time points (P = 0.02 and 0.02) (fig 2-3).
Regardless of laser doses applied, disability was significantly reduced by LLLT compared to placebo-control at the end of therapy (SMD = 0.59 [95% CI: 0.33 to 0.86]; I^2 = 57%; N = 617) (fig 4) and during follow-ups 2-12 weeks later (SMD = 0.66 [95% CI: 0.23 to 1.09]; I^2 = 67%; N = 289) (fig 5). The dose subgroup analyses demonstrated that more disability was significantly reduced by the recommended LLLT doses compared to placebo-control at the end of therapy (SMD = 0.75 [95% CI: 0.46 to 1.03]; I^2 = 34%; N = 339) (fig 4) and during follow-ups 2-8 weeks later (SMD = 1.31 [95% CI: 0.92 to 1.69]; I^2 = 0%; N = 129) (fig 5). The dose subgroup analyses demonstrated that disability was neither significantly reduced by the non-recommended LLLT doses compared to placebo-control at the end of therapy (SMD = 0.36 [95% CI: -0.02 to 0.73]; I^2 = 49%; N = 278) (fig 4) nor during follow-ups 2-12 weeks later (SMD = 0.26 [95% CI: -0.06 to 0.58]; I^2 = 0%; N = 160) (fig 5). The between-subgroup difference in disability results was significantly in favour of the recommended LLLT doses over the non-recommended LLLT doses regarding one of two time points (P = 0.11 and < 0.0001) (fig 4-5).
No QoL meta-analysis was performed because this outcome was only assessed in a single trial, i.e., by Hinman et al. who applied a non-recommended LLLT dose and reported insignificant results.[41]
The funnel plots revealed no publication bias (supplementary material). Additionally, the point effect estimates only changed negligible by changing to fixed effect models post hoc, indicating that the effect estimates were not influenced by small study biases (supplementary material).
Post hoc analyses showed that LLLT was significantly superior to the placebo-control both with and without exercise therapy as cointervention (P ≤ 0.007) (supplementary material).

The therapists were not blinded in six of the trials (fig 6), however, post hoc analyses revealed that there was no statistically significant interaction between the effect estimates and any of the risk of bias domains judged and no drop in statistical heterogeneity (supplementary material). The same applied to the statistical heterogeneity when we changed from the MD to the SMD method post hoc (supplementary material).

Post hoc analyses were performed to more precisely estimate the pain time-effect profile for the recommended LLLT doses by imputing the results of the trials with these doses in subgroups with narrower time intervals. Pain was significantly reduced by the recommended LLLT doses compared to the placebo-control immediately after therapy week 2-3 and 4-8 and at follow-ups 2-4, 6-8 and 12 weeks later; the peak point was 2-4 weeks after the end of therapy (31.87 mm VAS beyond placebo [95% CI: 18.18 to 45.56]; $I^2 = 93\%$; N = 322). The 21- and 34-weeks follow-up pain results were not statistically significant (fig 7 and supplemental material). The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high ($I^2 = 95\%$) (fig 2-3) but the mean statistical heterogeneity of the six subgroups covering the same time period was only moderate ($I^2 = 58\%$) (fig 7 and supplementary material).

Fig 2 | Pain results from immediately after the end of therapy

Fig 3 | Pain results from 2-12-weeks follow-ups

Fig 4 | Disability results from immediately after the end of therapy

Fig 5 | Disability results from 2-12-weeks follow-ups

Fig 6 | Risk of bias plot of the included trials
The trials are ranked by pain point effect estimates, i.e., more LLLT positive results in the bottom of the fig; the plot is based on the results from the main pain analyses (immediately after the end of therapy, primarily). Support for our judgements and risk of bias statistical analyses are available (supplementary material).

Fig 7 | Pain time-effect profile (recommended LLLT doses vs placebo-control)
Values on the y-axis are mm VAS pain results. Positive VAS score indicates the recommended LLLT doses are superior to the placebo-control. The related forest plot is available (supplementary material).
VAS = Visual Analogue Scale.
* Recommended LLLT doses are statistically significantly superior to the placebo-control ($P \leq 0.05$); ** Recommended LLLT doses are statistically significantly superior to the placebo-control ($P \leq 0.01$).

Discussion

Our meta-analyses showed that pain and disability were significantly reduced by LLLT compared to the placebo-control, regardless of the laser doses applied. Subsequently, we sub-grouped the included trials according to the WALT recommendations (2010) for laser dose per treatment spot, and this revealed a dose-response relationship. The subgroup analyses demonstrated that pain was reduced significantly more by the recommended LLLT doses compared to the placebo-control at the end of therapy and that the pain relief improved slightly during the time of follow-up. The non-recommended LLLT doses provided no or little positive effect beyond placebo.

The statistical heterogeneity in the pain analyses of the recommended LLLT doses was high, and some of it is due to the increase and subsequent decrease in pain reduction with time. The pain sensitivity analysis for time showed a drop in the mean statistical heterogeneity to a moderate level. The time-effect profile demonstrated that pain was significantly reduced by the recommended LLLT doses compared to the placebo-control, even at follow-up 12 weeks post-therapy, and that the pain reduction provided by these doses peaked during the follow-ups 2-4 weeks post-therapy at 31.87 mm VAS highly significantly beyond placebo. Our pain results are between-group (placebo-

controlled) estimates and a mix of pain during movement (primarily) and global pain. In comparison, the estimated minimal clinically important pain reduction within-subject is 19.9 mm VAS pain (depending on, e.g., the level of baseline pain) or 40.8% during movement.[51] Thus, our results clearly demonstrate that the recommended LLLT doses offer a clinically important level of KOA pain relief.

Our analyses also demonstrated that disability was significantly more reduced by the recommended LLLT doses compared to the placebo-control at the end of therapy (SMD = 0.75) and during follow-ups 2-8 weeks later (SMD = 1.31).

Furthermore, we found that LLLT appears effective as a single therapy as well as an adjunct to exercise therapy.

Subgrouping all the trials by risk of bias judgements in pain and disability analyses only altered the statistical heterogeneity by negligible levels, indicating that the trials were generally of high methodological quality.

According to WALT, the osteoarthritic knee should be laser irradiated to reduce inflammation and promote tissue repair.[24 25 52] One of the discrepancies from our review and previously published reviews of the same topic is that we omitted the RCT by Yurtkuran et al.[8 17 28 53], as they solely applied laser to an acupoint located distally from the knee joint (spleen 9).[53]

In line with our findings and the WALT dose recommendations, Joensen et al. (2012) observed that the percentage of laser penetrating rat skin at 810 and 904 nm wavelength was 20 and 38-58, respectively. That is, to deliver the same dose beneath the skin, 2.4 times the energy on the skin surface is required with an 810 nm laser compared to a 904 nm laser device. This may be due to the different wavelengths and/or because 904 nm laser is super-pulsed (pulse peak power ≥ 10000 mW typically), whereas shorter wavelength laser is delivered continuously or with less intense pulsation.[26] The estimated median dose applied with the recommended LLLT was six and three Joules per treatment spot with 785-860 and 904 nm wavelength laser, respectively. Most of the trial authors reported LLLT parameters in detail but did not state whether the laser devices were calibrated. That is, in the LLLT trials with non-significant effect estimates, equipment failure cannot be ruled out.

It is important to note that no adverse events were reported by any of the trial authors and the dropout rate was minor, indicating that LLLT is harmless.

The positive effect from LLLT lasts longer than those of widely recommended painkiller drugs[7], and future trials with booster sessions of LLLT should be conducted to see if the effect can be prolonged. Analyses of LLLT vs NSAIDs in terms of cost-effectiveness would also provide valuable information.

Limitations

This review lacks QoL analyses and direct comparisons between LLLT and other interventions.

Conclusions

LLLT is safe and offers disability reduction and clinically relevant pain relief in KOA at 4-7 Joules with 785-860 nm wavelength or 1-3 Joules with 904 nm wavelength per treatment spot on the knee joint.

Contributors: MBS, JMB, and HL wrote the PROSPERO protocol. MBS and JMB selected the trials, with the involvement of IFN when necessary. MBS and JJ judged the risk of bias, with the involvement of IFN when necessary. MBS and IFN did the translations. MBS, JMB, and KVF extracted the data. MBS performed the analyses, under supervision of JMB. All the authors participated in interpreting of the results. MBS drafted the manuscript, and subsequently revised it, based on comments by RABLM, HS, and all the other authors. All the authors read and accepted the final version of the manuscript.

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Ethical approval: Not required.
Data sharing: The dataset for meta-analysis is available from the corresponding author upon reasonable request. The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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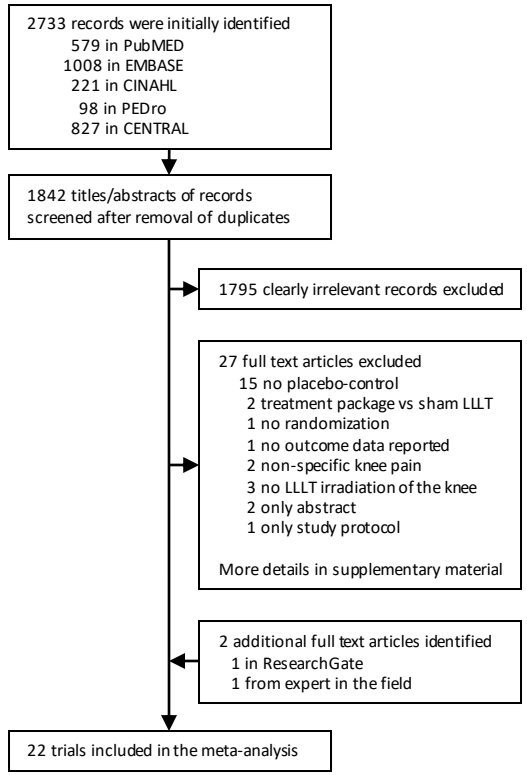
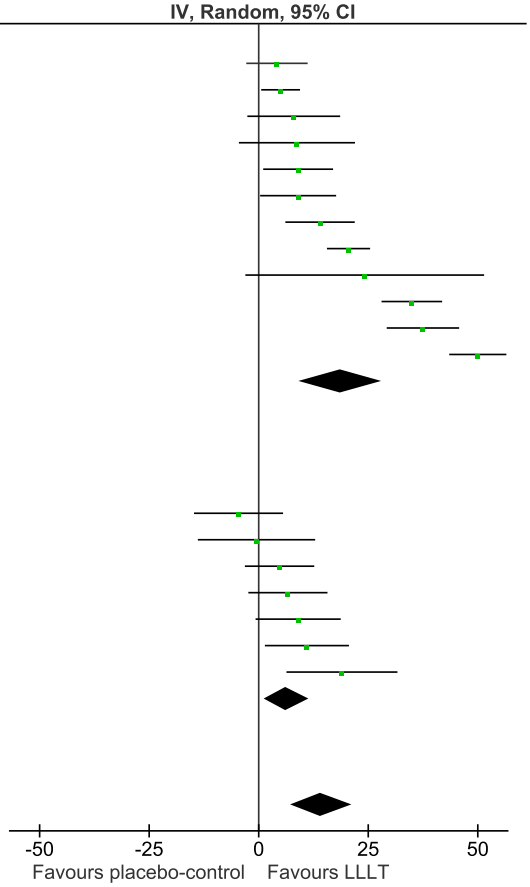
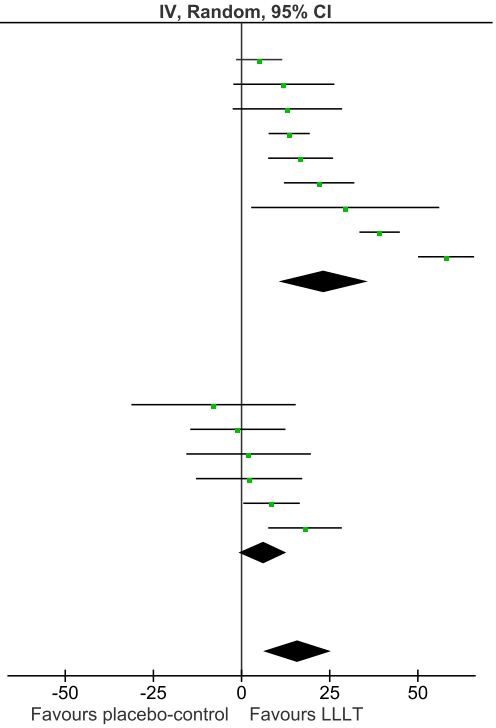

2733 records were initially identified
579 in PubMED
1008 in EMBASE
221 in CINAHL
98 in PEDro
827 in CENTRAL
1842 titles/abstracts of records screened after removal of duplicates
1795 clearly irrelevant records excluded
27 full text articles excluded
15 no placebo-control
2 treatment package vs sham LLLT
1 no randomization
1 no outcome data reported
2 non-specific knee pain
3 no LLLT irradiation of the knee
2 only abstract
1 only study protocol
More details in supplementary material
2 additional full text articles identified
1 in ResearchGate
1 from expert in the field
22 trials included in the meta-analysis

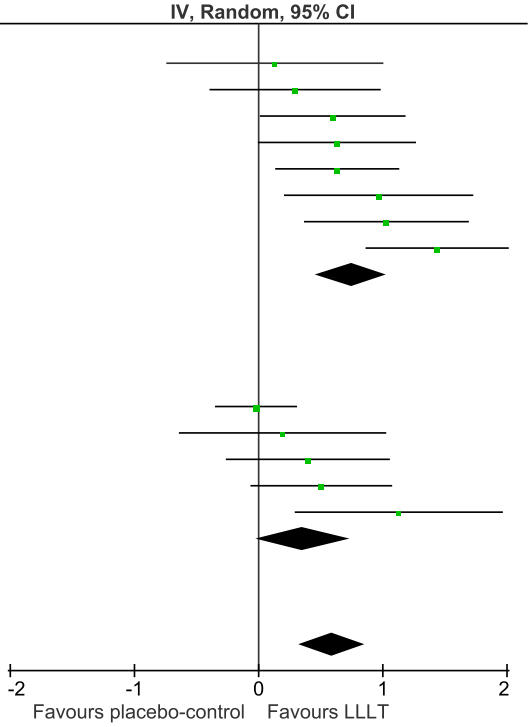
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Recommended LLLT dose vs placebo-control								
Youssef 2016 (904 nm)	6.667	13.34	18	2.5	4.492	7	5.6%	4.17 [-2.84, 11.17]
Gworys 2012	20	8	34	15	10	31	5.8%	5.00 [0.57, 9.43]
Fukuda 2011	17	22.67	25	9	13.78	22	5.2%	8.00 [-2.59, 18.59]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	4.9%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	5.5%	9.00 [1.03, 16.97]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	5.4%	9.00 [0.33, 17.67]
Delkhosh 2018	25	14	15	11	7	15	5.5%	14.00 [6.08, 21.92]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	5.8%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	3.1%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	5.6%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	5.5%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	5.6%	50.00 [43.48, 56.52]
Subtotal (95% CI)			**255**			**225**	**63.4%**	**18.71 [9.42, 27.99]**
Heterogeneity: Tau² = 243.24; Chi² = 201.44, df = 11 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.95 (P < 0.0001)								
1.1.2 Non-recommended LLLT dose vs placebo-control								
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	5.3%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	4.9%	-0.50 [-13.88, 12.88]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	5.5%	4.76 [-3.15, 12.68]
Youssef 2016 (880 nm)	9.167	18.343	18	2.5	4.492	8	5.4%	6.67 [-2.36, 15.69]
Bagheri 2011	28	18.5	18	19	10	18	5.3%	9.00 [-0.72, 18.72]
Al Rashoud 2014	32	13.617	26	21	19.656	23	5.3%	11.00 [1.41, 20.59]
Nivbrant 1992	23	15.31	13	4	17.556	13	4.9%	19.00 [6.34, 31.66]
Subtotal (95% CI)			**173**			**163**	**36.6%**	**6.34 [1.26, 11.41]**
Heterogeneity: Tau² = 20.17; Chi² = 10.65, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 2.45 (P = 0.01)								
Total (95% CI)			**428**			**388**	**100.0%**	**14.23 [7.31, 21.14]**
Heterogeneity: Tau² = 209.90; Chi² = 243.08, df = 18 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 4.03 (P < 0.0001)								
Test for subgroup differences: Chi² = 5.25, df = 1 (P = 0.02), I² = 80.9%								



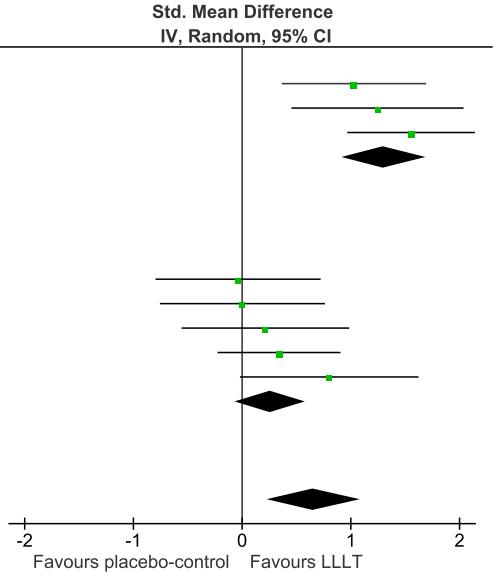
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Recommended LLLT dose vs placebo-control								
Gur and Oktayoglu	45	17.267	37	40	10.479	35	7.4%	5.00 [-1.56, 11.56]
Gur 2003 (1 Joules, 904 nm)	36.4	23.113	30	24.4	23.113	15	6.5%	12.00 [-2.33, 26.33]
Gur 2003 (1.5 Joules, 904 nm)	37.4	25.039	30	24.4	25.039	15	6.4%	13.00 [-2.52, 28.52]
Koutenaei 2017	26	10.053	20	12.5	8.732	20	7.4%	13.50 [7.66, 19.34]
Alfredo 2011	21.5	14.855	20	4.75	14.855	20	7.1%	16.75 [7.54, 25.96]
Delkhosh 2018	29	17	15	7	10	15	7.1%	22.00 [12.02, 31.98]
Hegedus 2009	-11.8	11.194	18	-41.2	40.05	9	4.8%	29.40 [2.73, 56.07]
Helianthi 2016	40.47	14.8	30	1.32	6	29	7.5%	39.15 [33.42, 44.88]
Nambi 2016	66	11.265	17	8	12.357	17	7.3%	58.00 [50.05, 65.95]
Subtotal (95% CI)			**217**			**175**	**61.4%**	**23.23 [10.60, 35.86]**
Heterogeneity: Tau² = 335.90; Chi² = 149.09, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.60 (P = 0.0003)								
2.1.2 Non-recommended LLLT dose vs placebo-control								
Bülow 1994	0.794	31.986	14	8.73	31.986	15	5.2%	-7.94 [-31.23, 15.36]
Tascioglu 2004 (3 Joules, 830 nm)	0.4	16.771	20	1.45	18.254	10	6.6%	-1.05 [-14.54, 12.44]
Nivbrant 1992	9	22.474	13	7	23.462	13	6.0%	2.00 [-15.66, 19.66]
Tascioglu 2004 (1.5 Joules, 830 nm)	3.6	22.697	20	1.45	18.254	10	6.4%	2.15 [-12.91, 17.21]
Rayegani 2012	12.5	10.215	12	4	10.215	13	7.3%	8.50 [0.49, 16.51]
Al Rashoud 2014	34	17.331	26	16	19.656	23	7.0%	18.00 [7.56, 28.44]
Subtotal (95% CI)			**105**			**84**	**38.6%**	**6.20 [-0.65, 13.05]**
Heterogeneity: Tau² = 26.43; Chi² = 8.03, df = 5 (P = 0.15); I² = 38%								
Test for overall effect: Z = 1.77 (P = 0.08)								
Total (95% CI)			**322**			**259**	**100.0%**	**15.92 [6.47, 25.37]**
Heterogeneity: Tau² = 303.25; Chi² = 190.87, df = 14 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 3.30 (P = 0.0010)								
Test for subgroup differences: Chi² = 5.40, df = 1 (P = 0.02), I² = 81.5%								

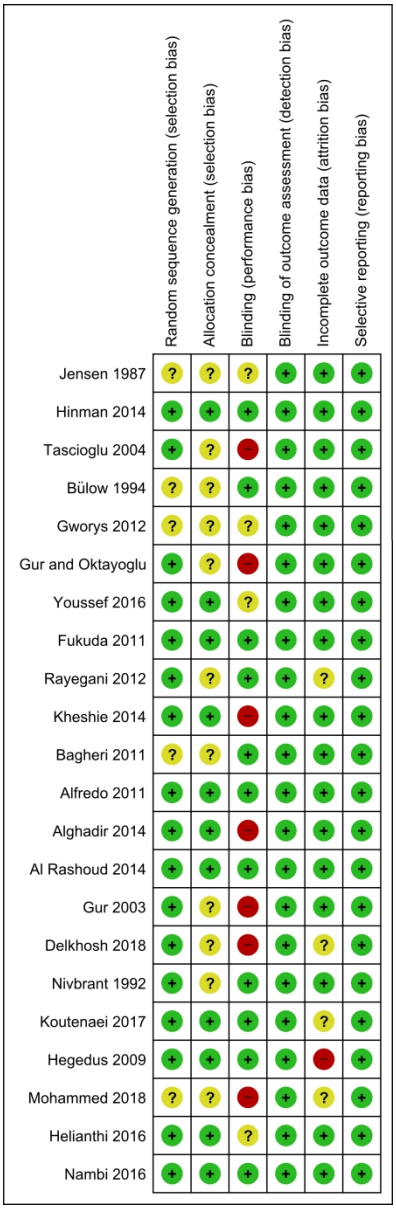


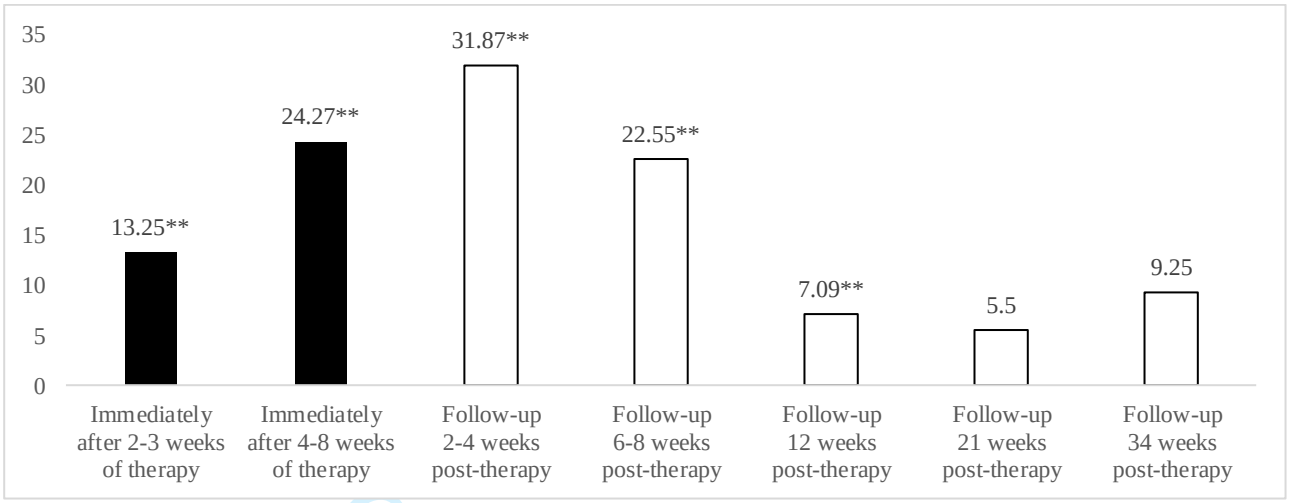
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Random, 95% CI
7.1.1 Recommended LLLT dose vs placebo-control								
Youssef 2016 (904 nm)	6.575	13.157	18	4.932	8.86	7	5.5%	0.13 [-0.74, 1.00]
Kheshie 2014	13.56	11.395	18	10.4	9.315	15	7.2%	0.29 [-0.40, 0.98]
Fukuda 2011	3.2	4.267	25	1	2.717	22	8.3%	0.60 [0.01, 1.18]
Alghadir 2014	15.95	5.364	20	12.5	5.364	20	7.8%	0.63 [-0.01, 1.27]
Gworys 2012	1.06	0.6	34	0.5	1.1	31	9.4%	0.63 [0.13, 1.13]
Delkhosh 2018	7.9	4.9	15	4.1	2.3	15	6.5%	0.97 [0.20, 1.73]
Alfredo 2011	9.7	9.48	20	-0.25	9.48	20	7.5%	1.03 [0.37, 1.69]
Helianthi 2016	5.2	3.9	30	-0.7	4.2	29	8.5%	1.44 [0.86, 2.01]
Subtotal (95% CI)			**180**			**159**	**60.7%**	**0.75 [0.46, 1.03]**
Heterogeneity: Tau² = 0.06; Chi² = 10.67, df = 7 (P = 0.15); I² = 34%								
Test for overall effect: Z = 5.19 (P < 0.00001)								
7.1.2 Non-recommended LLLT dose vs placebo-control								
Hinman 2014	-0.5	23.422	71	0	23.422	70	11.7%	-0.02 [-0.35, 0.31]
Youssef 2016 (880 nm)	7.671	15.35	18	4.932	8.86	8	5.8%	0.19 [-0.64, 1.03]
Bagheri 2011	27.5	19	18	21	12.4	18	7.5%	0.40 [-0.26, 1.06]
Al Rashoud 2014	35	32.185	26	19	30.063	23	8.5%	0.50 [-0.07, 1.08]
Nivbrant 1992	22	16.967	13	4	13.756	13	5.8%	1.13 [0.29, 1.97]
Subtotal (95% CI)			**146**			**132**	**39.3%**	**0.36 [-0.02, 0.73]**
Heterogeneity: Tau² = 0.09; Chi² = 7.78, df = 4 (P = 0.10); I² = 49%								
Test for overall effect: Z = 1.86 (P = 0.06)								
Total (95% CI)			**326**			**291**	**100.0%**	**0.59 [0.33, 0.86]**
Heterogeneity: Tau² = 0.13; Chi² = 27.92, df = 12 (P = 0.006); I² = 57%								
Test for overall effect: Z = 4.44 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.62, df = 1 (P = 0.11), I² = 61.8%								



Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Random, 95% CI
8.1.1 Recommended LLLT dose vs placebo-control								
Alfredo 2011	14.35	10.052	20	3.8	10.052	20	13.1%	1.03 [0.36, 1.69]
Delkhosh 2018	8.5	4.6	15	3.1	3.8	15	11.6%	1.25 [0.45, 2.04]
Helianthi 2016	5.3	4.5	30	-1.2	3.7	29	14.1%	1.55 [0.97, 2.14]
Subtotal (95% CI)			**65**			**64**	**38.7%**	**1.31 [0.92, 1.69]**
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0%								
Test for overall effect: Z = 6.65 (P < 0.00001)								
8.1.2 Non-recommended LLLT dose vs placebo-control								
Tascioglu 2004 (3 Joules, 830 nm)	1.56	9.292	20	1.93	10.337	10	12.0%	-0.04 [-0.80, 0.72]
Tascioglu 2004 (1.5 Joules, 830 nm)	1.96	11.831	20	1.93	10.337	10	12.0%	0.00 [-0.76, 0.76]
Nivbrant 1992	12	17.329	13	8	18.815	13	11.8%	0.21 [-0.56, 0.99]
Al Rashoud 2014	31	33.423	26	20	30.063	23	14.3%	0.34 [-0.23, 0.90]
Rayegani 2012	2.2	0.845	12	1.5	0.845	13	11.2%	0.80 [-0.02, 1.62]
Subtotal (95% CI)			**91**			**69**	**61.3%**	**0.26 [-0.06, 0.58]**
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 4 (P = 0.59); I² = 0%								
Test for overall effect: Z = 1.60 (P = 0.11)								
Total (95% CI)			**156**			**133**	**100.0%**	**0.66 [0.23, 1.09]**
Heterogeneity: Tau² = 0.25; Chi² = 20.90, df = 7 (P = 0.004); I² = 67%								
Test for overall effect: Z = 2.99 (P = 0.003)								
Test for subgroup differences: Chi² = 16.73, df = 1 (P < 0.0001), I² = 94.0%								




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Jensen 1987
Hinman 2014
Tascioglu 2004
Bülow 1994
Gworys 2012
Gur and Oktayoglu
Youssef 2016
Fukuda 2011
Rayegani 2012
Kheshie 2014
Bagheri 2011
Alfredo 2011
Alghadir 2014
Al Rashoud 2014
Gur 2003
Delkhosh 2018
Nivbrant 1992
Koutenaei 2017
Hegedus 2009
Mohammed 2018
Helianthi 2016
Nambi 2016



Supplementary material for the article by Stausholm et al. entitled *Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials*

Table of content

Excluded articles 1
Pain time-effect profile of LLLT 2
Publication and small study bias assessment 3
Risk of bias impact analysis 5
Support for risk of bias judgments and funding of the included trials 9
LLLT with and without exercise therapy 16
Mean Difference vs Standardized Mean Difference 17
References 19

Excluded articles

Table 1 | Excluded articles initially judged potentially eligible

First author	Reason for exclusion
Alayat 2017[1]	HILT, not LLLT
Ciechanowska 2008[2]	No placebo-control
Coelho[3]	Only study protocol
de Matos 20184[4]	No placebo-control
de Meneses[5]	Full-text not available (emailed)
de Paula 2018[6]	NBLT + LLLT vs sham LLLT alone
Giavelli 1998[7]	No placebo-control
Götte 1995[8]	No outcome data reported
Kujawa 2004[9]	No placebo-control
Leal-Junior 2014[10]	Non-specific knee pain
Lepilina 1990[11]	No placebo-control
Marquina 2012[12]	Non-specific knee pain
Montes-Molina 2009[13]	No placebo-control
Nakamura 2014[14]	No placebo-control
Paolillo 2018[15]	No placebo-control
Pinfildi[16]	Full-text not available (emailed)
Ren 2010[17]	No placebo-control
Shen 2009[18]	LLLT + moxibustion vs sham LLLT alone
Soleimanpour 2014[19]	No placebo-control
Stelian 1992[20]	NBLT, not laser
Trelles 1991[21]	No placebo-control
Wang 2013[22]	No randomization
Yavuz 2013[23]	No placebo-control
Yurtkuran 2006[24]	Irradiated acupoint spleen 9, not the knee joint
Yuvarani 2018[25]	No placebo-control
Zhao 2010[26]	No placebo-control
Zou 2017[27]	No placebo-control

NBLT = narrow-band light therapy; LLLT = low-level laser therapy; HILT = high intensity laser therapy; ACR = American College of Rheumatology; K/L = Kellgren/Lawrence.

Pain time-effect profile of LLLT

Analyses were performed to estimate the pain time-effect profile of the recommended LLLT doses by imputing the results of the trials with these doses in subgroups with narrower time intervals (fig 1).

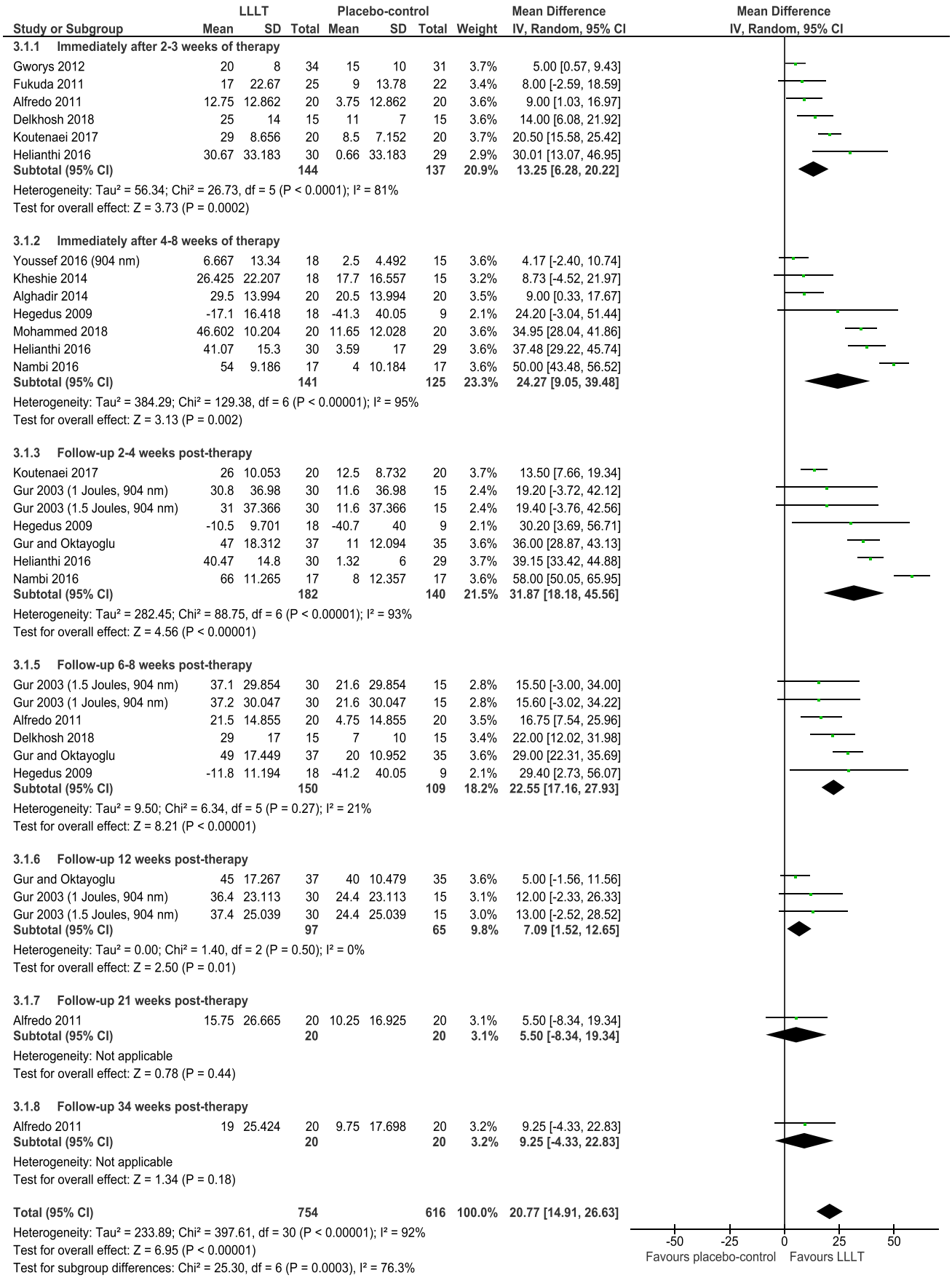


Fig 1 | Pain time-effect profile (recommended LLLT doses vs placebo-control)

Publication and small study bias assessment

Funnel plots were performed using the results from the main analyses (immediately after the end of therapy, primarily). There were no clear indications of publication bias (fig 2-3). Moreover, a subsequent change from random to fixed effects models only caused a slight change in point effect estimates: Pain results from 13.22 to 14.14 mm VAS (fig 4-5) and disability from 0.57 to 0.48 (SMD) (fig 6-7).

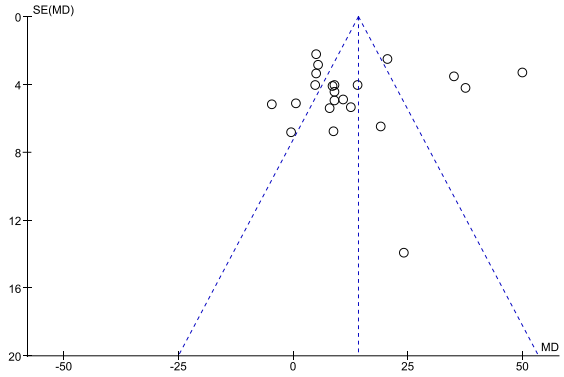


Fig 2 | Funnel plot (pain)

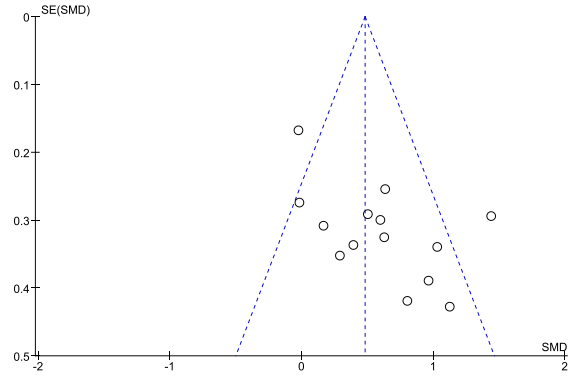


Fig 3 | Funnel plot (disability)

Study or Subgroup	LLLT Mean	SD	Total	Placebo-control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	4.5%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	4.1%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (both intervention groups)	2	19.764	40	1.45	18.254	20	4.5%	0.55 [-9.53, 10.63]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.7%	4.76 [-3.15, 12.68]
Gur and Oktayoglu	45	17.267	37	40	10.479	35	4.9%	5.00 [-1.56, 11.56]
Gworys 2012	20	8	34	15	10	31	5.0%	5.00 [0.57, 9.43]
Youssef 2016 (both intervention groups)	7.917	15.858	36	2.5	4.492	15	4.9%	5.42 [-0.24, 11.07]
Fukuda 2011	17	22.67	25	9	13.78	22	4.5%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.7%	8.50 [0.49, 16.51]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	4.1%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.7%	9.00 [1.03, 16.97]
Bagheri 2011	28	18.5	18	19	10	18	4.6%	9.00 [-0.72, 18.72]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	4.7%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	4.6%	11.00 [1.41, 20.59]
Gur 2003 (both intervention groups)	36.9	23.895	60	24.4	24.076	30	4.5%	12.50 [1.97, 23.03]
Delkhosh 2018	25	14	15	11	7	15	4.7%	14.00 [6.08, 21.92]
Nivbrant 1992	23	15.31	13	4	17.556	13	4.2%	19.00 [6.34, 31.66]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	5.0%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	2.5%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	4.8%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.7%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	4.9%	50.00 [43.48, 56.52]
Total (95% CI)			**577**			**486**	**100.0%**	**13.22 [7.15, 19.29]**

Heterogeneity: Tau² = 185.88; Chi² = 260.56, df = 21 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.27 (P < 0.0001)

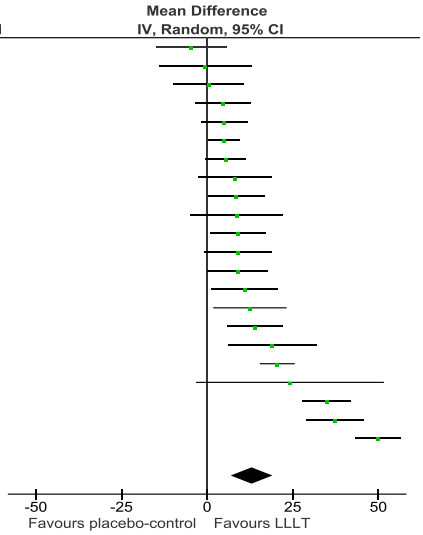


Fig 4 | Random effects model (pain)

Study or Subgroup	LLLT Mean	SD	Total	Placebo-control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	2.7%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	1.6%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (both intervention groups)	2	19.764	40	1.45	18.254	20	2.7%	0.55 [-9.53, 10.63]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.4%	4.76 [-3.15, 12.68]
Gur and Oktayoglu	45	17.267	37	40	10.479	35	6.5%	5.00 [-1.56, 11.56]
Gworys 2012	20	8	34	15	10	31	14.1%	5.00 [0.57, 9.43]
Youssef 2016 (both intervention groups)	7.917	15.858	36	2.5	4.492	15	8.7%	5.42 [-0.24, 11.07]
Fukuda 2011	17	22.67	25	9	13.78	22	2.5%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.3%	8.50 [0.49, 16.51]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	1.6%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.4%	9.00 [1.03, 16.97]
Bagheri 2011	28	18.5	18	19	10	18	2.9%	9.00 [-0.72, 18.72]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	3.7%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	3.0%	11.00 [1.41, 20.59]
Gur 2003 (both intervention groups)	36.9	23.895	60	24.4	24.076	30	2.5%	12.50 [1.97, 23.03]
Delkhosh 2018	25	14	15	11	7	15	4.4%	14.00 [6.08, 21.92]
Nivbrant 1992	23	15.31	13	4	17.556	13	1.7%	19.00 [6.34, 31.66]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	11.5%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	0.4%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	5.8%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.1%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	6.5%	50.00 [43.48, 56.52]
Total (95% CI)			**577**			**486**	**100.0%**	**14.14 [12.48, 15.81]**

Heterogeneity: Chi² = 260.56, df = 21 (P < 0.00001); I² = 92%
Test for overall effect: Z = 16.64 (P < 0.00001)

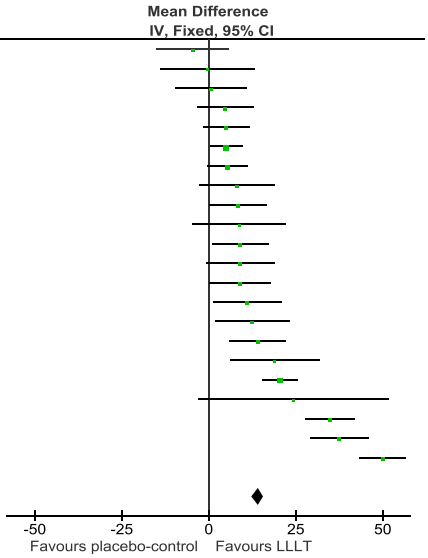


Fig 5 | Fixed effects model (pain)

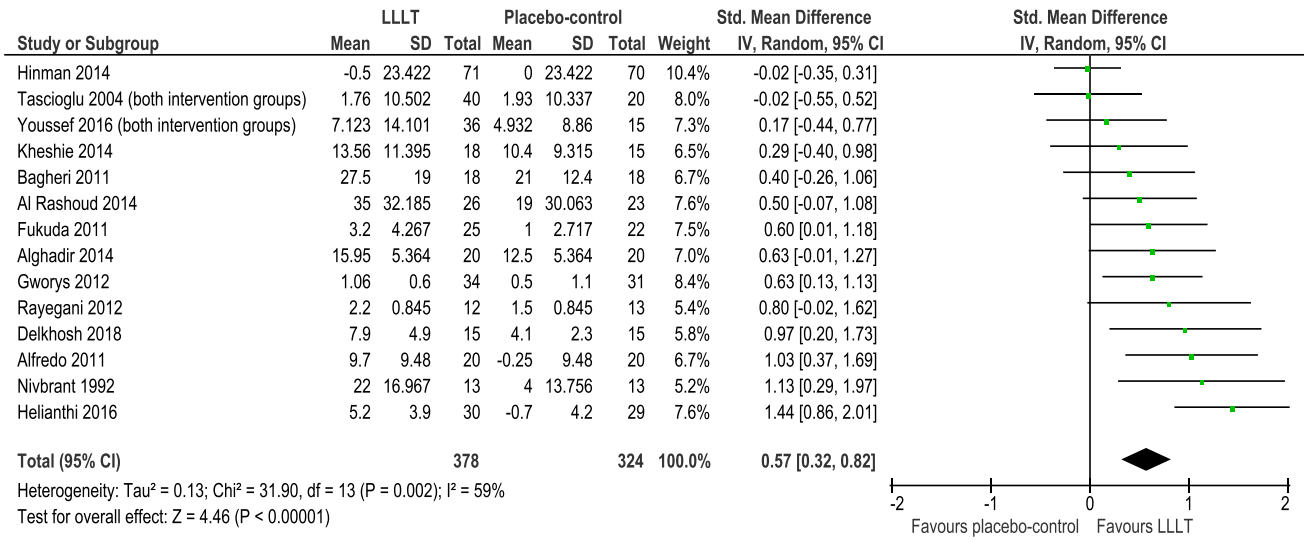


Fig 6 | Random effects model (disability)

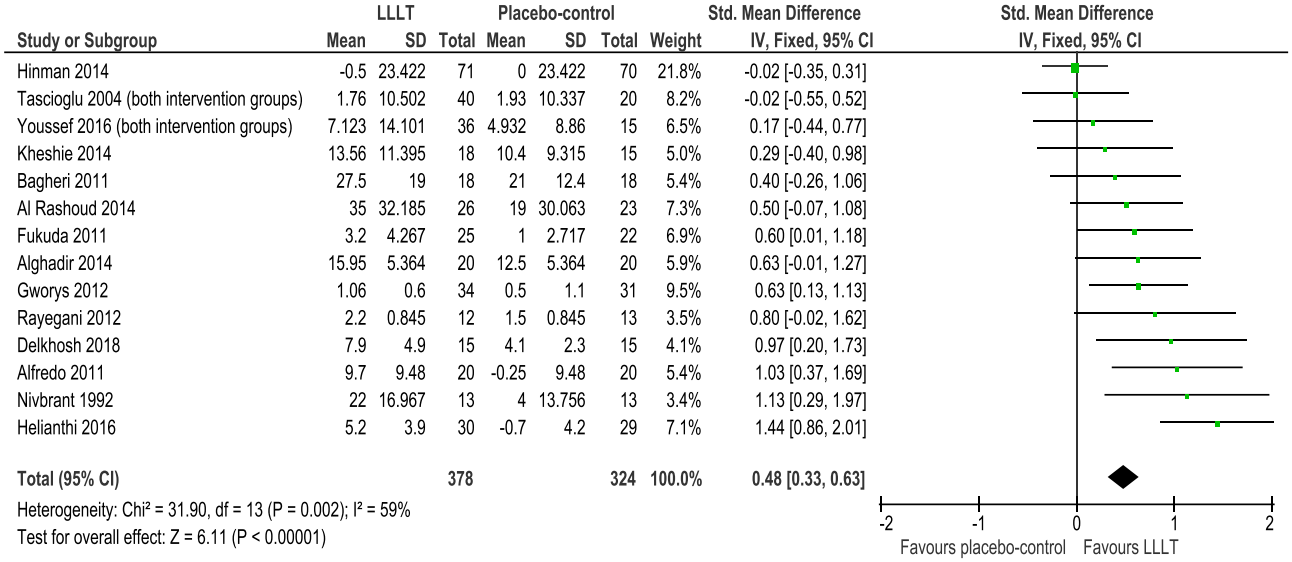


Fig 7 | Fixed effects model (disability)

Risk of bias impact analysis

Risk of bias impact analyses were performed using the results from the main analyses (immediately after the end of therapy, primarily). The mean statistical heterogeneity of the subgroup analyses were similar to the overall levels (fig 8-15).

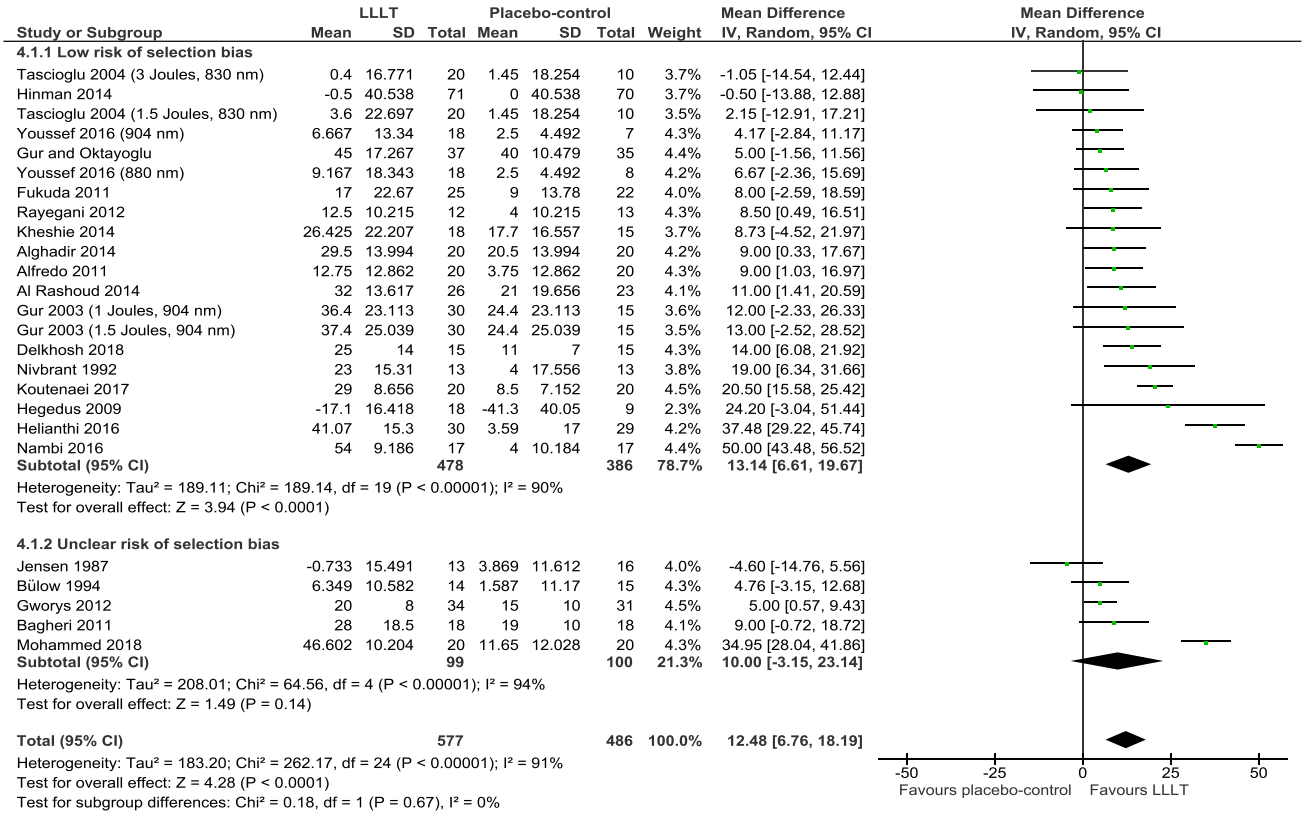


Fig 8 | Pain results - risk of selection bias (random sequence generation)

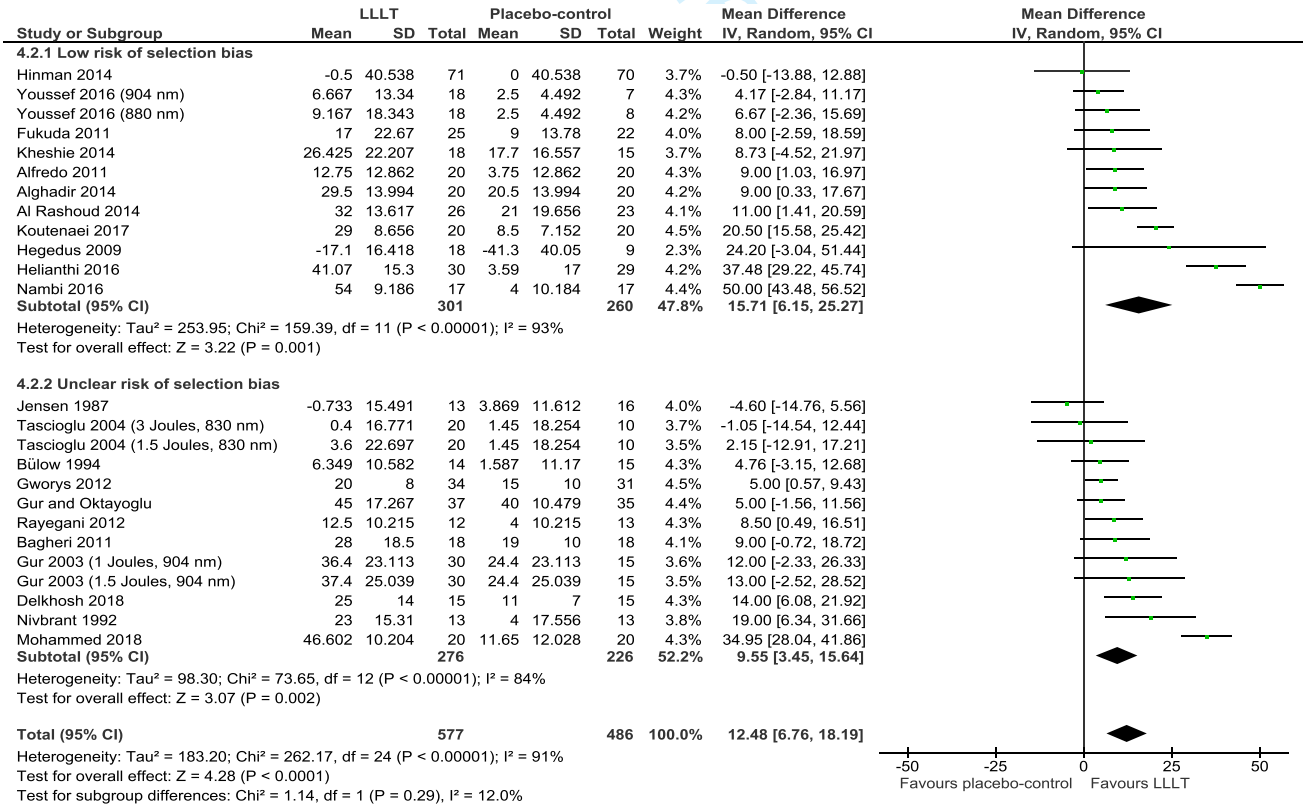


Fig 9 | Pain results - risk of selection bias (allocation concealment)

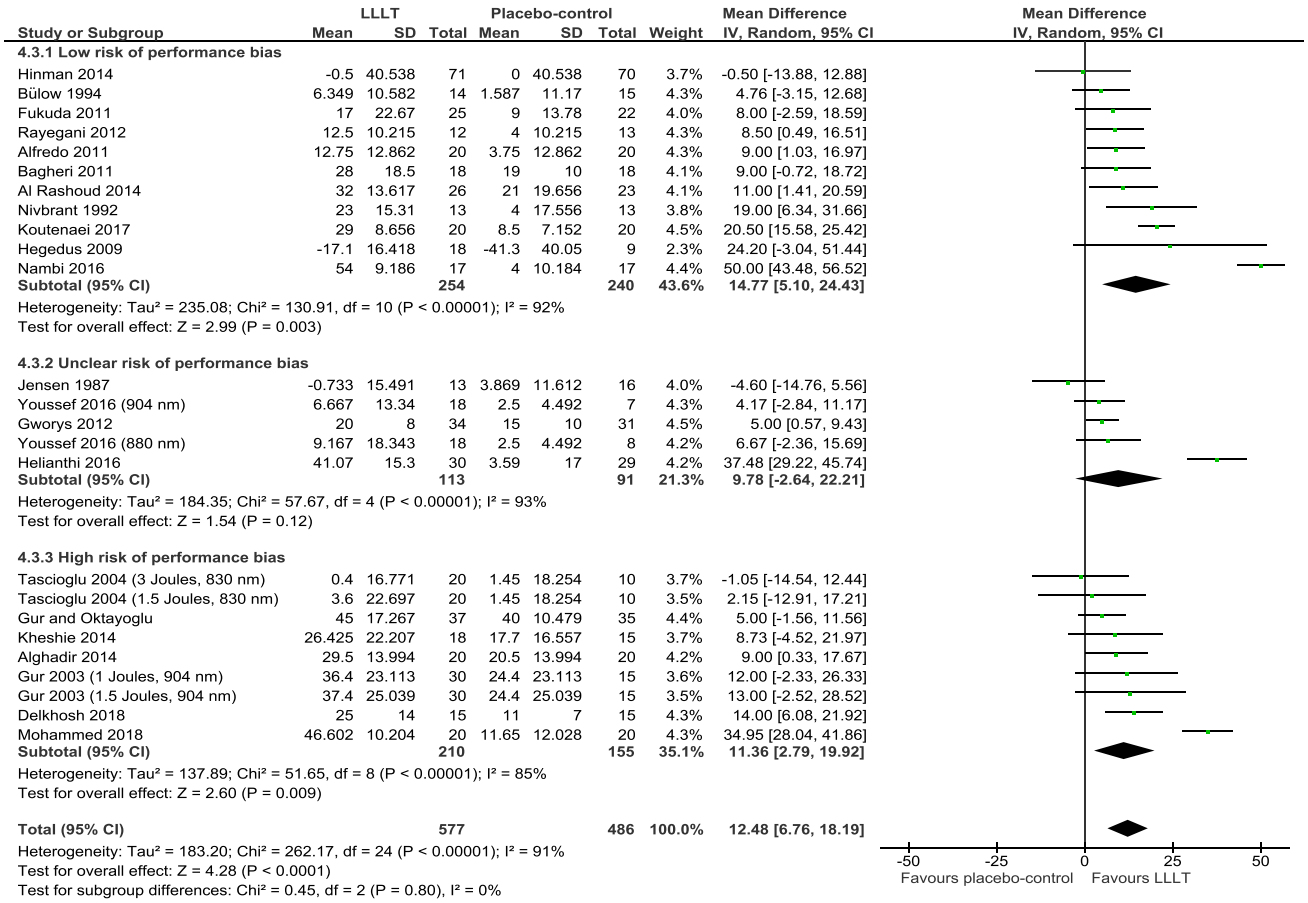


Fig 10 | Pain results - risk of performance bias (blinding of therapist)

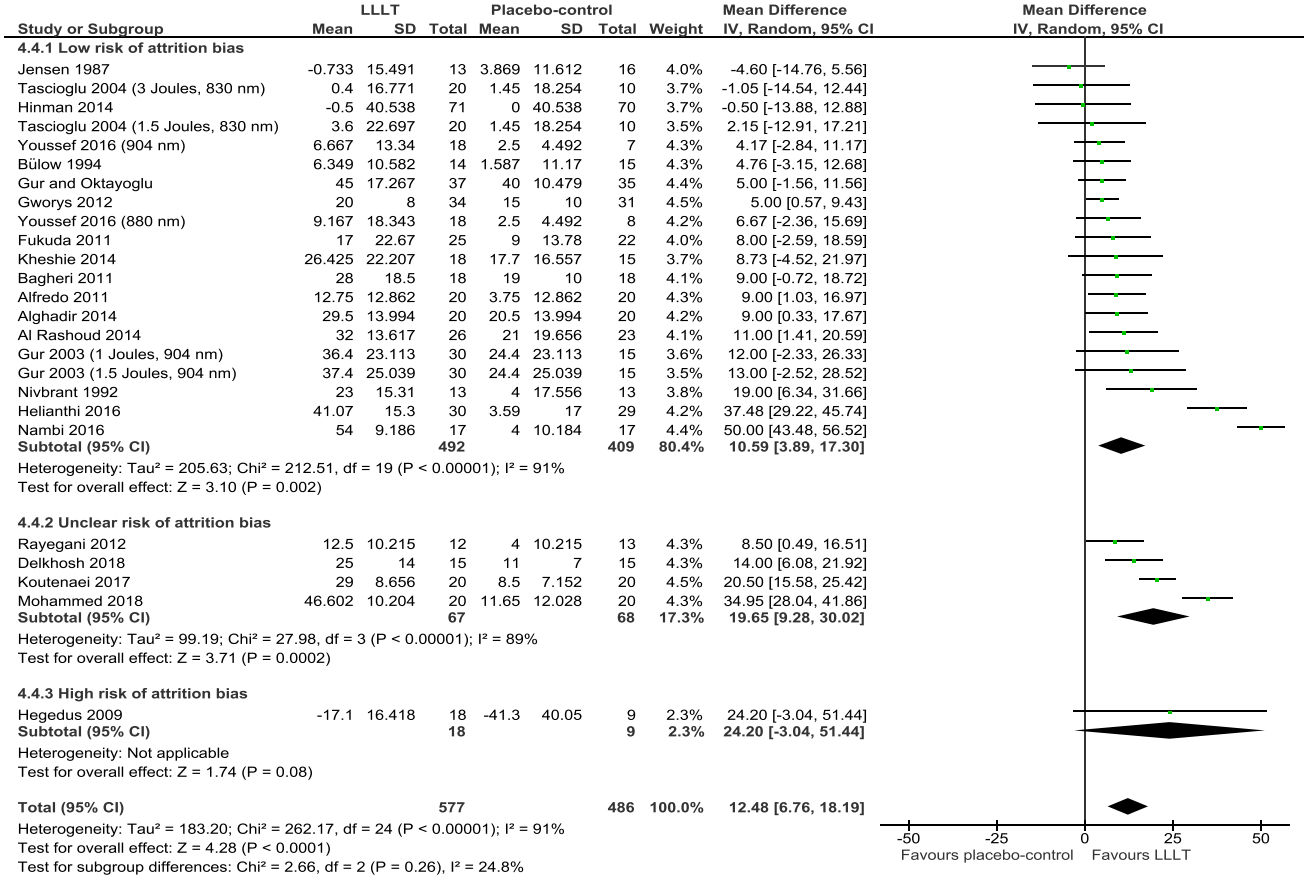


Fig 11 | Pain results - risk of attrition bias (incomplete outcome data)

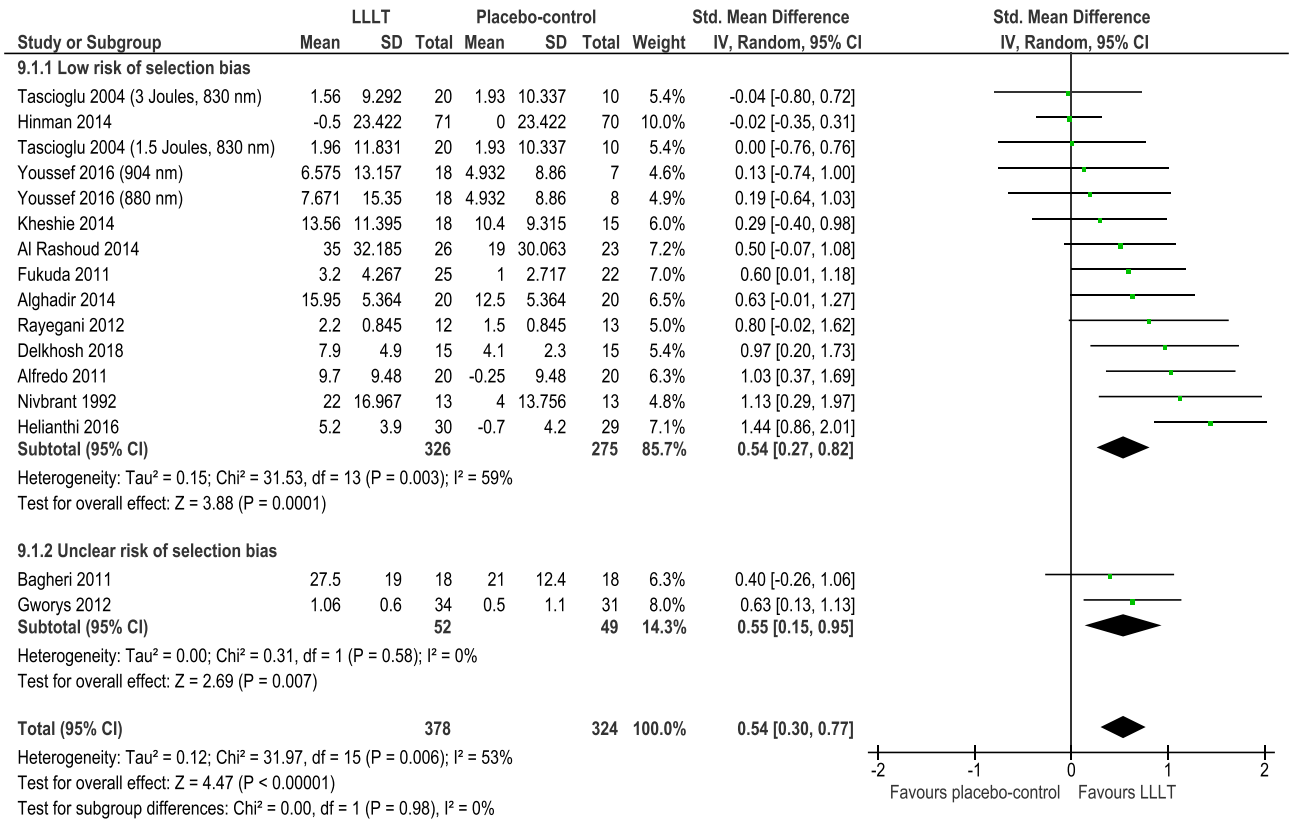


Fig 12 | Disability results - risk of selection bias (random sequence generation)

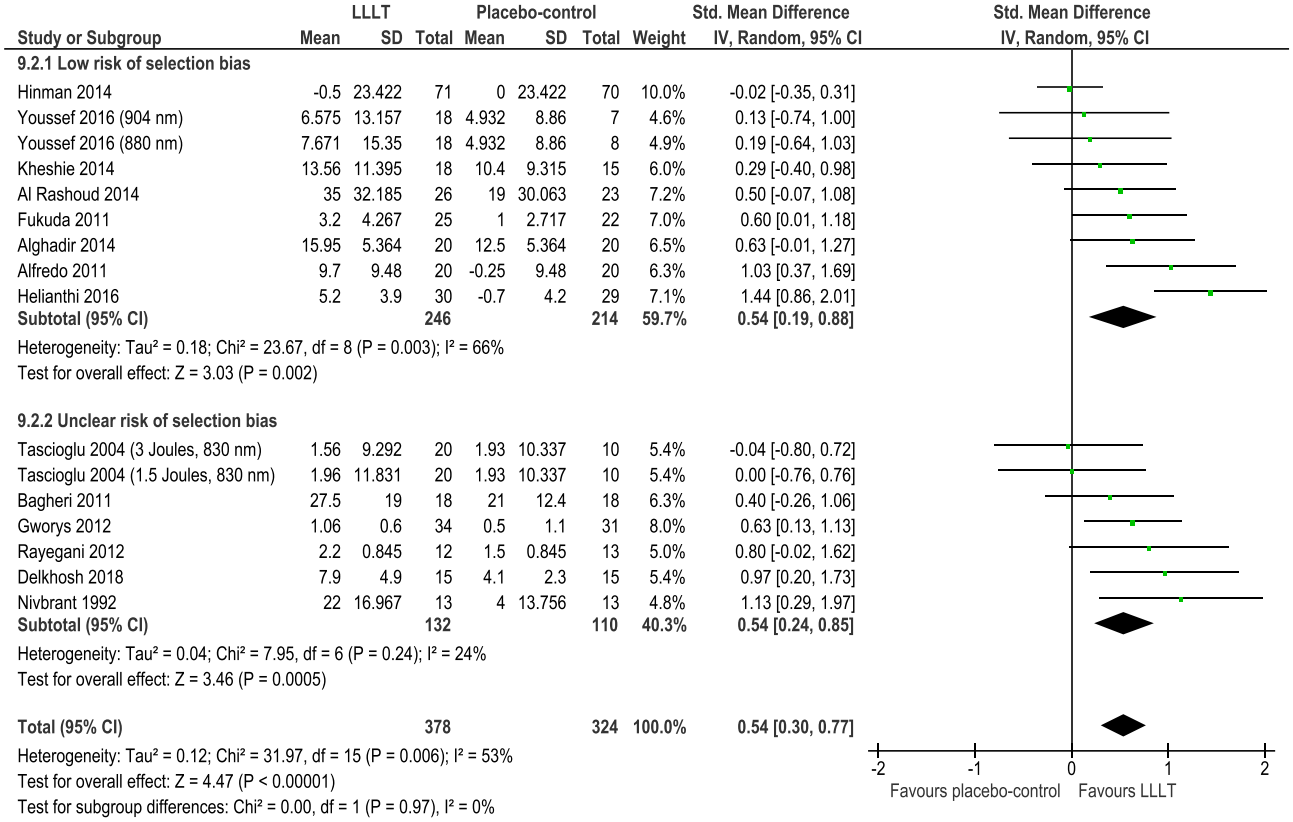


Fig 13 | Disability results - risk of selection bias (allocation concealment)

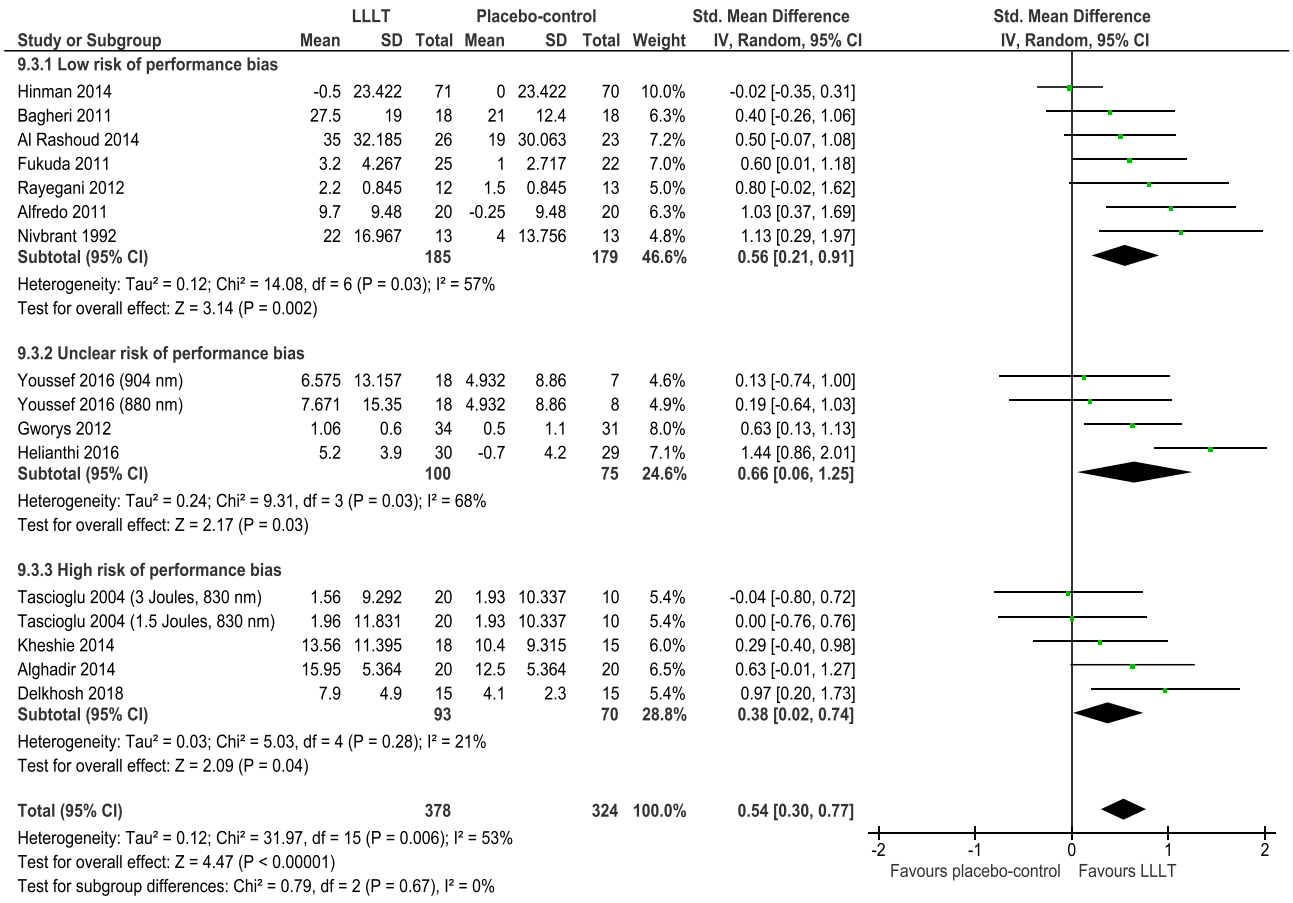


Fig 14 | Disability results - risk of performance bias (blinding of therapist)

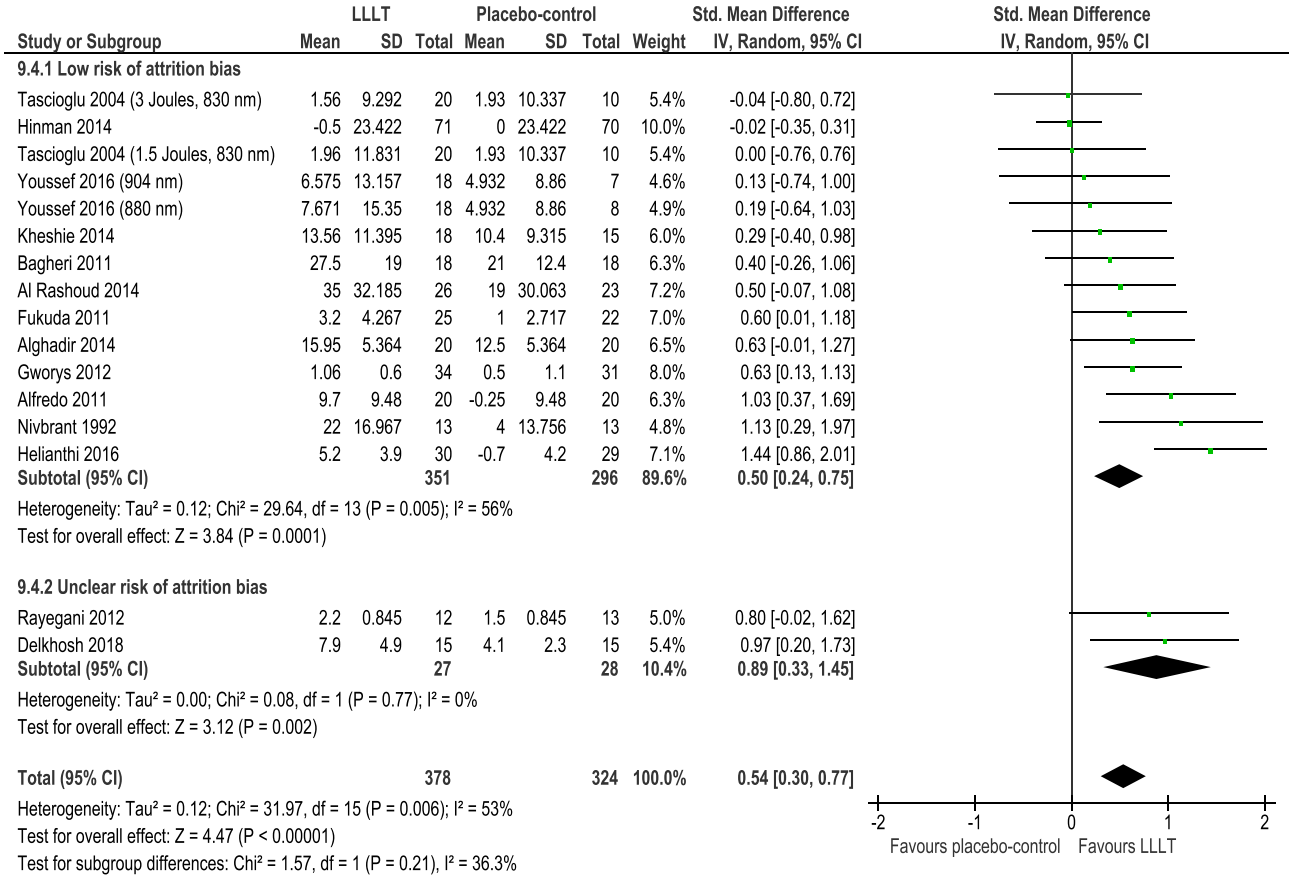


Fig 15 | Disability results - risk of attrition bias (incomplete outcome data)

Support for risk of bias judgments and funding of the included trials

Al Rashoud et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"... a randomization list was produced using software-generated randomised numbers to the randomisation depended on random blocks of 10."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	Low risk	Quote: *"Neither investigator nor the patient knew whether a placebo or active treatment was being administered to only the research assistant had the identifying code to determine which treatment was given."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"Forty-nine patients with knee osteoarthritis were assigned at random into two groups: Active laser group (n = 26) and placebo laser group (n = 23)", "... 49 completed the study ..."*. Our comment: Probably true.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (International Standard Randomised Controlled Trials Number: ISRCTN24010862).

Funding – quote: *"The project was funded by general administration for medical services of Ministry of Interior, Security Forces Hospital; Riyadh, Saudi Arabia."*.

Alfredo et al. 2011

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed by using sealed, randomly filled envelopes describing the treatment group. Patients and the physiotherapist responsible for the evaluation were unaware of randomization results"*. Our comment: Probably done. It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Allocation concealment	Low risk	Quote: *"Patients and the physiotherapist responsible for the randomization were unaware of the randomization results"*. Our comment: Probably true.
Blinding of participants and personnel	Low risk	Quote: "*All patients were treated by the same physiotherapist who had not taken part in the evaluations". "The laser equipment had two identical pens, one for the active treatment and one for the placebo treatment (sealed)".* Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"All participants were evaluated by the same blinded physiotherapist"* Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 13% of the included participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Reported in adherence to a protocol (Clinical Trials number: CT01306435).

Funding - quote: *"This study was supported financially by: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) – Foundation of Research Support of São Paulo State and Coordenação de Aperfeic¸oamentode Pessoalde Ni´vel Superior (CAPES) – Coordination for the Improvement of Higher Level – or Education – Personnel. Biostatistics Support Group, Department of Dentistic, School of Odontology, University of São Paulo, São Paulo, Brazil."*.

Alghadir et al. 2013

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed using sealed, randomly filled envelopes"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	High risk	Quote: *"The treatment parameters were identical, but without switching on the machine"*. Our comment: Probably done. The study is described as single-blinded. The experimental group was treated with invisible laser. The physiotherapists treating the participants were not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"(...) all of them completed the study period."*. Our comment: Probably true.
Selective reporting	Low risk	Our comment: Reported as stated in the protocol.

Funding – quote: *"The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project NO RGP-VPP-209."*.

Bagheri et al. 2010

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Quote (translated from Farsi): *"The random distribution of people was done in such a way that the number of male and female patients is the same in both groups"*. Our comment: Not enough information to make a qualified judgment.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Low risk	Quote (translated from Farsi): *"The presence of active or inactive lasers was not known"*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded. The experimental group was treated with invisible laser.
Incomplete data	Low risk	Our comment: 10% of the participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Sponsored by the Semnan University of Science.

Bülow et al. 1994

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized, but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Low risk	Quote: *"The nurse in charge of the randomization key selected the laser or placebo-laser before each treatment"* and *"The blinded settings for patient and physician were maintained"*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcomes of interest described in the method section is missing in the result section.

Funding – quote: *"The study was sponsored by Henny and Helge Holgersen's Foundation and the Bodil Petersen Foundation."*.

Delkhosh et al. 2018

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"… volunteers are randomly allocated to three groups by lottery."*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	High risk	Quotes: *"The patients were randomly assigned to three groups: 1-standard treatment with placebo laser…"* and *"Not blinded"*. Our comment: The investigators claimed the trial was placebo-controlled which is probably true as the participants were treated with invisible laser. Therefore, it seems likely that the investigators statement regarding lack of blinding refers to the therapist.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (Iranian Registry of Clinical Trials number: IRCT201502224549N8).

Funding – quote: *"Vice chancellor for research, Semnan University of Medical Sciences."*.

Fukuda et al. 2011

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"This distribution was made by a secretary who was not involved in the treatment or evaluation, through a draw of sealed opaque envelopes. The envelopes were taken directly to the therapist without the patient having access to the result."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"(...) two identical pens, of which one was active (laser) and the other was sealed (placebo). These were labelled A and B by the project secretary, and only this person knew the true identification of the pens."*. Our comment to the quote: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Physical Therapy Sector, Irmandade da Santa Casa de Misericórdia de São Paulo (ISCMSP), São Paulo, São Paulo, Brazil.

Gur & Oktayoglu

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Patients were randomly assigned to three treatment groups by one of the non-treating authors by drawing 1 of 120 envelopes."*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were sequentially numbered, opaque, and sealed.
Blinding of participants and personnel	High risk	Quote: *"The study was conducted in a double-blind fashion. Subjects and physician were unaware of the code for active or placebo laser until the data analysis was completed but therapist was aware of the code for active or placebo laser."*. Our comment: Probably true. The experimental group was treated with invisible laser. The participants were probably blinded, but the therapist was not.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 7.5% of the participants allocated to the laser group were not evaluated. 12.5% of the participants allocated to the control group were not evaluated. These numbers are unlikely to introduce a relevant bias. Reasons for dropout across groups are similar.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Gur et al. 2003

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Patients were randomly assigned to three treatment groups by one of the non-treating authors by drawing of 1 of 90 envelopes"*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were sequentially numbered, opaque, and sealed.
Blinding of participants and personnel	High risk	Quote: *"The study was conducted in a double-blind fashion. Subjects and physician were unaware of the code for active or placebo laser until the data analysis was completed but therapist was aware of the code for active or placebo laser."*. Our comment: Probably true. The experimental group was treated with invisible laser. The participants were probably blinded, but the therapist was not.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Gworys et al. 2012

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized, but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: *"(…) a placebo group where laser therapy procedures were simulated without actual irradiation."*. Our comment: Probably done. The experimental group was treated with invisible laser. The participants were probably blinded, but there is too little information to judge whether the therapists were blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"laser the therapy sessions were performed once a day, 5 days a week over 2 weeks. Each patient attended 10 sessions."*. Our comment: All participants probably attended to all 10 sessions. The outcomes were assessed immediately after the 10 sessions. Thus, there were probably no dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Hegedus et al. 2009

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was ensured by having patients randomly choose sealed envelopes from a bowl"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. Our comment: Probably true. All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	High risk	Our comment: 50% of the participants in the control group were not evaluated while 100% of the participants in the laser group were evaluated. These numbers are likely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"The authors wish to thank Dr. Gábor Deák for the Doppler examinations and András Tóth for taking the numerous thermographic images."*.

Helianti et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"a randomization list was created using a computer-generated table containing random numbers."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	Unclear risk	Quote: *"Both investigator and participants did not know whether laser acupuncture active treatment or placebo treatment was being administered. Only the researcher and her assistant had the code to determine which treatment was given. Both groups used the same laser device and the same study site. Participant blinding was optimized by using eye mask and headset (…)"*. Our comment: The experimental group was treated with invisible laser. The investigator and participants were probably blinded, but it is unclear who administered the therapy and if this person was blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 4.8% of the participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding sources: Not stated.

Hinman et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"An investigator (K.N.) accessed the computerized randomization to reveal allocation."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Participant codes for randomized laser treatment groups were pre-programmed into the laser machines by an independent biomechanical engineer to permit blinding of acupuncturist and participants in these groups."*. Our comment: Probably true.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 8.45% and 17.14% had dropped out from the experimental and placebo group at week 12, respectively. Intention to treat analysis was used and this analysis and the results did not differ from the per-protocol analysis.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (Australian New Zealand Clinical Trials Registry Number: ACTRN12609001001280).

Funding – quote: *"Funding/Support: This trial was funded by the National Health and Medical Research Council (project 566783). Drs Hinman and Bennell are both funded in part by Australian Research Council Future Fellowships (FT130100175 and FT0991413, respectively). Dr McCrory is funded in part by a National Health and Medical Research Council Practitioner Fellowship (1026383). Dr Pirotta is funded in part by a National Health and Medical Research Council Career Development Fellowship (1050830). Dr Williamson was funded in part by a National Health and Medical Research Council grant (1004233). Role of the Funder/Sponsor: The study sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; reparation, review, or approval of the manuscript; and decision to submit the manuscript for publication."*.

Jensen et al. 1987

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: (Translated from Danish) *"Two coded laser devices of the same appearance was utilized in the trial. One of the devices was inactive and served as control. The other was active with infrared laser."*. Our comment: The experimental group was treated with invisible laser. The participants were probably blinded, but it is unknown whether the therapists were blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are assessed and reported by the participants. The experimental group was treated with invisible laser.
Incomplete data	Low risk	Our comment: 1 participant was not evaluated.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Kheshie et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed simply by assigning a specific identification number for each patient. These numbers were randomized into three groups using the SPSS program"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	High risk	Our comment: The study is described as single-blinded and the participants were probably blinded. Thus, the therapist was not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 15% and 0% dropped out of the placebo and experimental group, respectively. These numbers are unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"This research received a grant from the Institute of Scientific Research and Revival of Islamic Heritage at Umm Al-Qura University, Makkah, Saudi Arabia."*.

Koutenaei et al. 2017

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"…were assigned randomly (using random blocks) …"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: The use of random blocks was probably sufficient.
Blinding of participants and personnel	Low risk	Quote: *"The placebo group also lasted for 70 seconds in these places, but the laser had no output"*. Our comment: Both participants and therapists were probably blinded because they described the study as double-blinded and treated the intervention group with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"The study was supported by the Department of Physiotherapy at the University of Social Welfare and Rehabilitation Sciences."*.

Mohammed et al. 2017

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	High risk	Quote: *"(…) placebo laser (laser probe is directed to the same acupoints while the device is off).".* Our comment: Probably done. The experimental group was treated with invisible laser. The study is described as single-blinded and the participants were probably blinded. As there was no description of a blinding procedure of the therapist, we assume that this person was not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: Not stated. The authors state: *"The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication."*.

Nambi et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Thirty-four subjects were randomized into two groups (active and placebo) by an investigator who is not involved in assessment, diagnosis or treatment. Randomization was performed by using sealed randomly filled envelopes from a bowl containing an equal number of slips with either number 1 or 2"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Subjects and the physiotherapist responsible for the evaluation were unaware of randomization results.". "super pulsed laser with (…) or with a placebo probe (…) of the same appearance and display."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"All subjects were evaluated by the same blinded physiotherapist"*. Our comment: Probably done. All outcomes of interest are assessed and reported by the participants who were probably blinded.
Incomplete data	Low risk	Quote: *"The required sample for the study was 17 subjects per group". "All 34 subjects completed the study with the 8-week follow-up evaluation.".* Our comment: Probably true.
Selective reporting	Low risk	Our comment: No outcomes of interest described in the method section was missing in the result section.

Funding - quote: *"Authors are grateful to the Deanship of scientific Research, Prince Sattam Bin Abdul Aziz University, Al-Kharj, Saudi Arabia for the financial support to carry out this project no 2015/01/4375. Research funding program: Specialized Research Grant program (He alth)."*.

Nivbrant et al. 1992

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Our comment: Randomization was performed by drawing of randomly filled envelopes describing the treatment group.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were sequentially numbered, opaque and sealed.
Blinding of participants and personnel	Low risk	Quote (translated from Swedish): *"The placebo emitter was visually identical to the active laser. A practitioner otherwise not involved in the trial treated the participants with laser. The practitioner was unaware of which was the active and inactive laser."*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor (detection bias)	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 13% in each group were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Rayegani et al. 2012

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Randomization was ensured by having patients randomly choose sealed envelopes from a bowl.
Allocation concealment	Unclear risk	Our comment: It is unclear whether the envelopes were opaque.
Blinding of participants and personnel	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. *"The placebo group was treated with an ineffective probe (power 0 mW) and with the same method."*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Tascioglu et al. 2004

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Sixty patients, who fulfilled the entry criteria, were admitted to the study and they were randomly divided into three groups using numbered envelopes"*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether the envelopes were sealed and opaque.
Blinding of participants and personnel	High risk	Our comment: The study is described as single-blinded and the participants were probably blinded. Thus, the therapist was probably not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are assessed and reported by the participants who were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Youssef et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"They were assigned randomly to three groups by a blinded and independent research assistant who opened sealed envelopes that contained a computer-generated randomization card according to the recruitment diagram."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: *"(...) in the placebo group, procedure was identical but without emission of energy. The laser equipment had two identical pens, one for the active treatment and one for the placebo treatment (sealed)."*. Our comment: Probably done. The experimental group was treated with invisible laser. The participants were probably blinded, but there was no information regarding blinding of therapists.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	1 participant was not evaluated.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

LLLT with and without exercise therapy

Subgroup analyses were performed to assess the impact of exercise therapy on the effect of LLLT in a treatment package (results are from immediately after the end of therapy, primarily). LLLT was significantly superior to the placebo-control both with and without exercise therapy (fig 16-17). The levels of statistical heterogeneity were unaltered in the pain analyses (fig 16), and slightly lowered in the disability analysis (fig 17).

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
16.1.1 With exercise therapy								
Youssef 2016 (904 nm)	6.667	13.34	18	2.5	4.492	7	4.3%	4.17 [-2.84, 11.17]
Gur and Oktayoglu (unpublished)	45	17.267	37	40	10.479	35	4.4%	5.00 [-1.56, 11.56]
Youssef 2016 (880 nm)	9.167	18.343	18	2.5	4.492	8	4.2%	6.67 [-2.36, 15.69]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	3.7%	8.73 [-4.52, 21.97]
Bagheri 2011	28	18.5	18	19	10	18	4.1%	9.00 [-0.72, 18.72]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.3%	9.00 [1.03, 16.97]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	4.2%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	4.1%	11.00 [1.41, 20.59]
Gur 2003 (1 Joules, 904 nm)	36.4	23.113	30	24.4	23.113	15	3.6%	12.00 [-2.33, 26.33]
Gur 2003 (1.5 Joules, 904 nm)	37.4	25.039	30	24.4	25.039	15	3.5%	13.00 [-2.52, 28.52]
Delkhosh 2018	25	14	15	11	7	15	4.3%	14.00 [6.08, 21.92]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	4.5%	20.50 [15.58, 25.42]
Nambi 2016	54	9.186	17	4	10.184	17	4.4%	50.00 [43.48, 56.52]
Subtotal (95% CI)			**287**			**228**	**53.4%**	**13.41 [5.46, 21.37]**
Heterogeneity: Tau² = 190.29; Chi² = 143.84, df = 12 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 3.31 (P = 0.0009)								
16.1.2 Without exercise therapy								
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	4.0%	-4.60 [-14.76, 5.56]
Tascioglu 2004 (3 Joules, 830 nm)	0.4	16.771	20	1.45	18.254	10	3.7%	-1.05 [-14.54, 12.44]
Hinman 2014	-0.5	40.538	71	0	40.538	70	3.7%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (1.5 Joules, 830 nm)	3.6	22.697	20	1.45	18.254	10	3.5%	2.15 [-12.91, 17.21]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.3%	4.76 [-3.15, 12.68]
Gworys 2012	20	8	34	15	10	31	4.5%	5.00 [0.57, 9.43]
Fukuda 2011	17	22.67	25	9	13.78	22	4.0%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.3%	8.50 [0.49, 16.51]
Nivbrant 1992	23	15.31	13	4	17.556	13	3.8%	19.00 [6.34, 31.66]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	2.3%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	4.3%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.2%	37.48 [29.22, 45.74]
Subtotal (95% CI)			**290**			**258**	**46.6%**	**11.39 [2.72, 20.07]**
Heterogeneity: Tau² = 198.98; Chi² = 113.75, df = 11 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 2.57 (P = 0.01)								
Total (95% CI)			**577**			**486**	**100.0%**	**12.48 [6.76, 18.19]**
Heterogeneity: Tau² = 183.20; Chi² = 262.17, df = 24 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%								

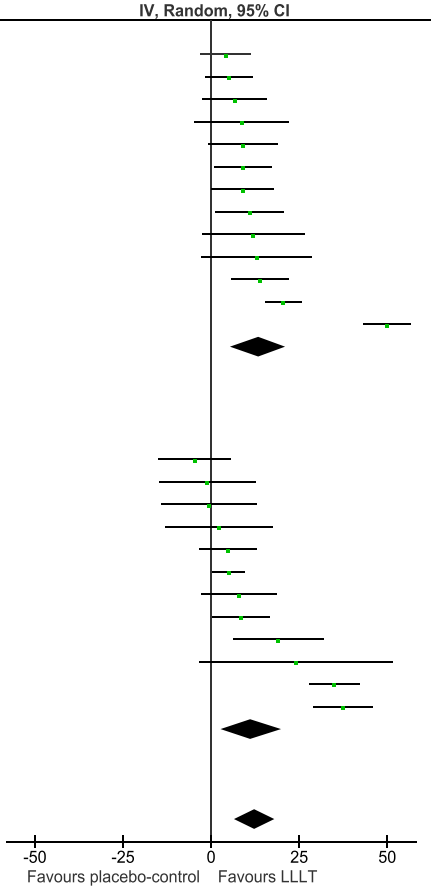


Fig 16 | LLLT with and without exercise therapy (pain)

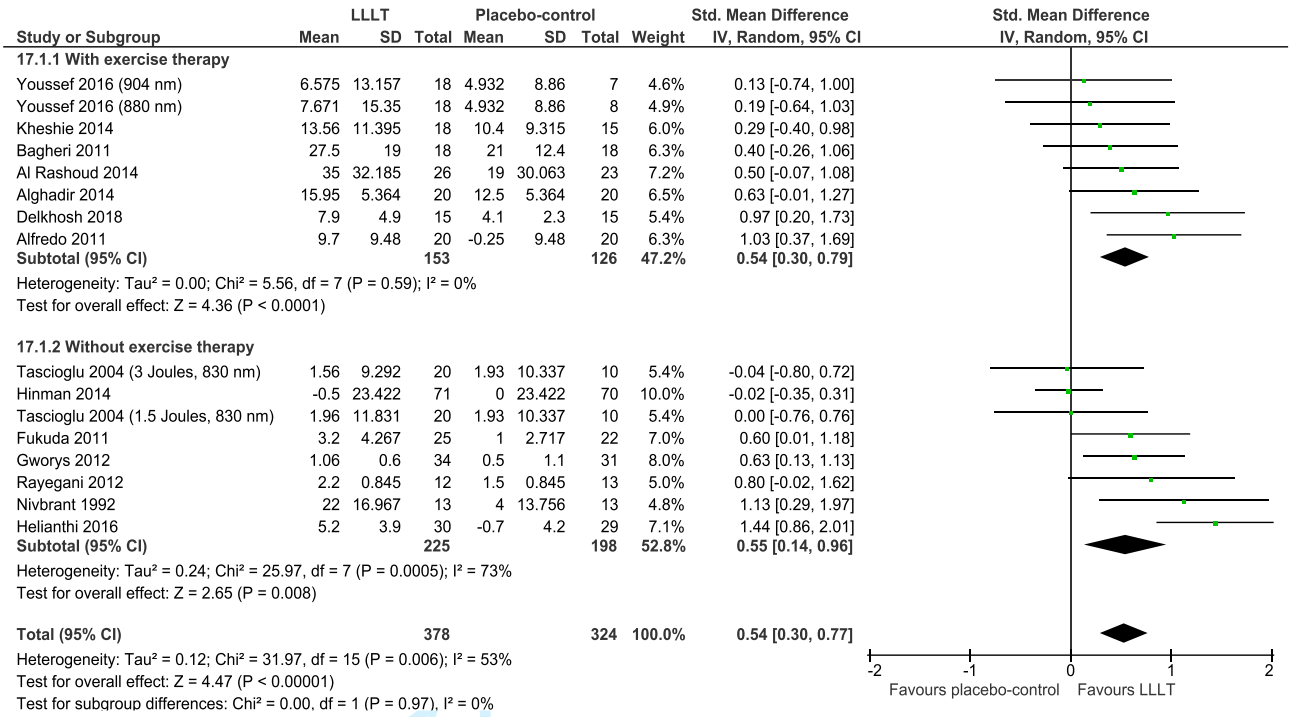


Fig 17 | LLLT with and without exercise therapy (disability)

Mean Difference vs Standardized Mean Difference

The levels of statistical heterogeneity changed only negligible when we switched from the Mean Difference (MD) method to the Standardized Mean Difference (SMD) method (fig 18-21). The trial by Hegedus et al. was omitted from these analyses as they solely reported final scores, and it is inappropriate to mix final scores with change scores in SMD analyses (fig 18-19).

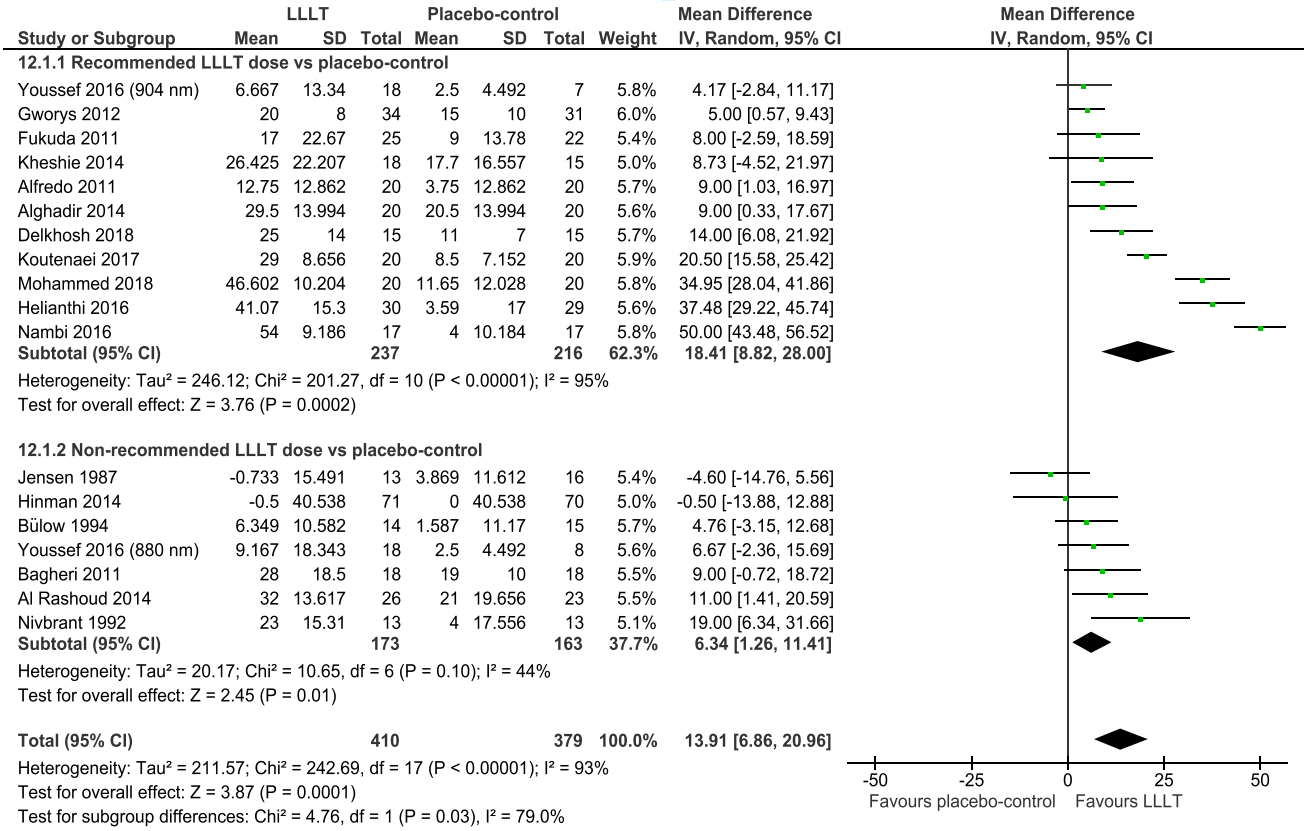


Fig 18 | Mean Difference (pain results from immediately after the end of therapy)

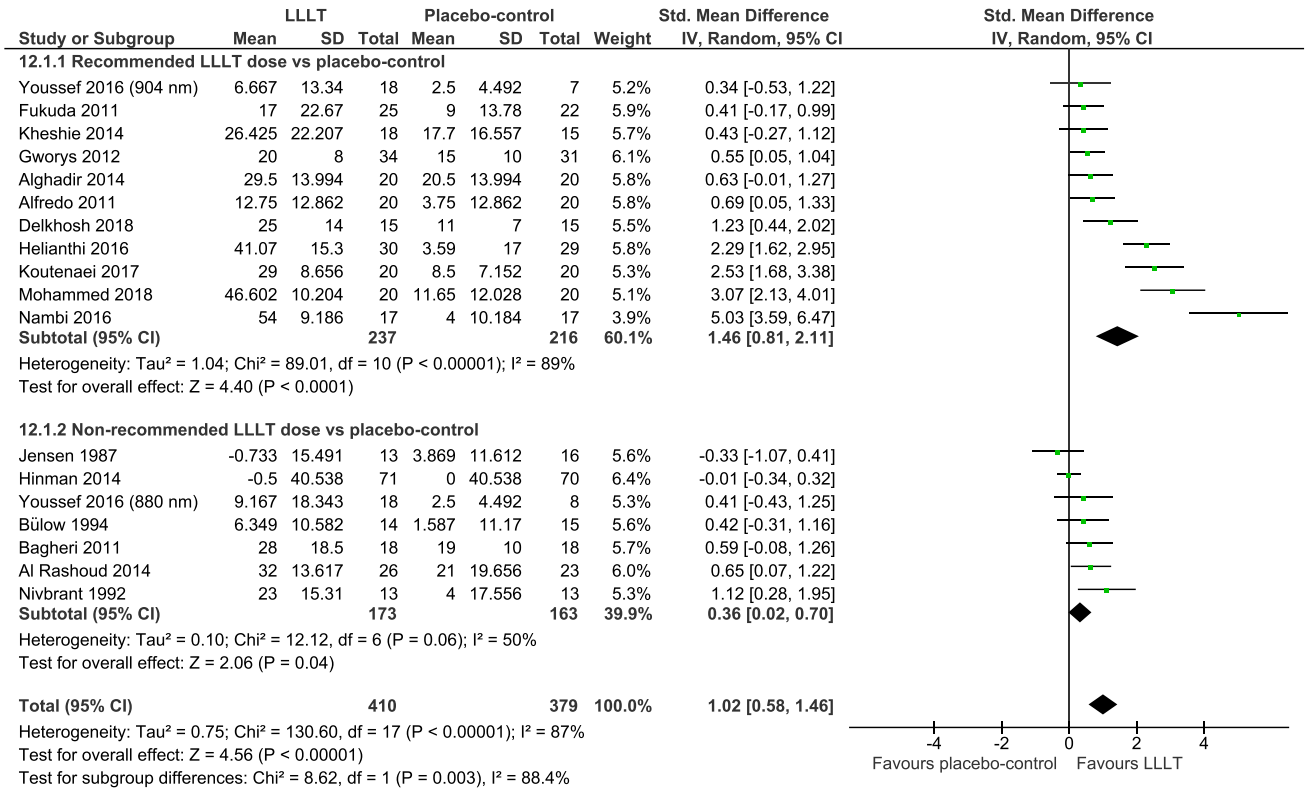


Fig 19 | Standardized Mean Difference (pain results from immediately after the end of therapy)

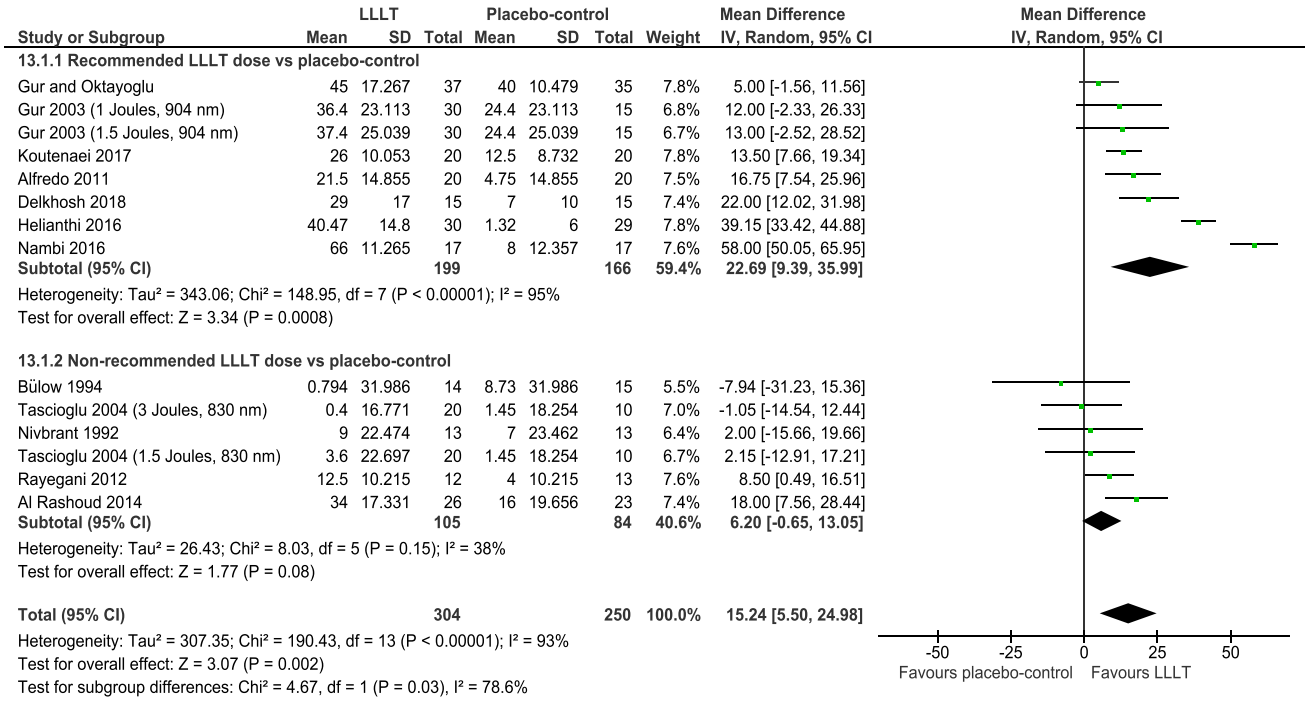


Fig 20 | Mean Difference (pain results from 2-12-weeks follow-ups)

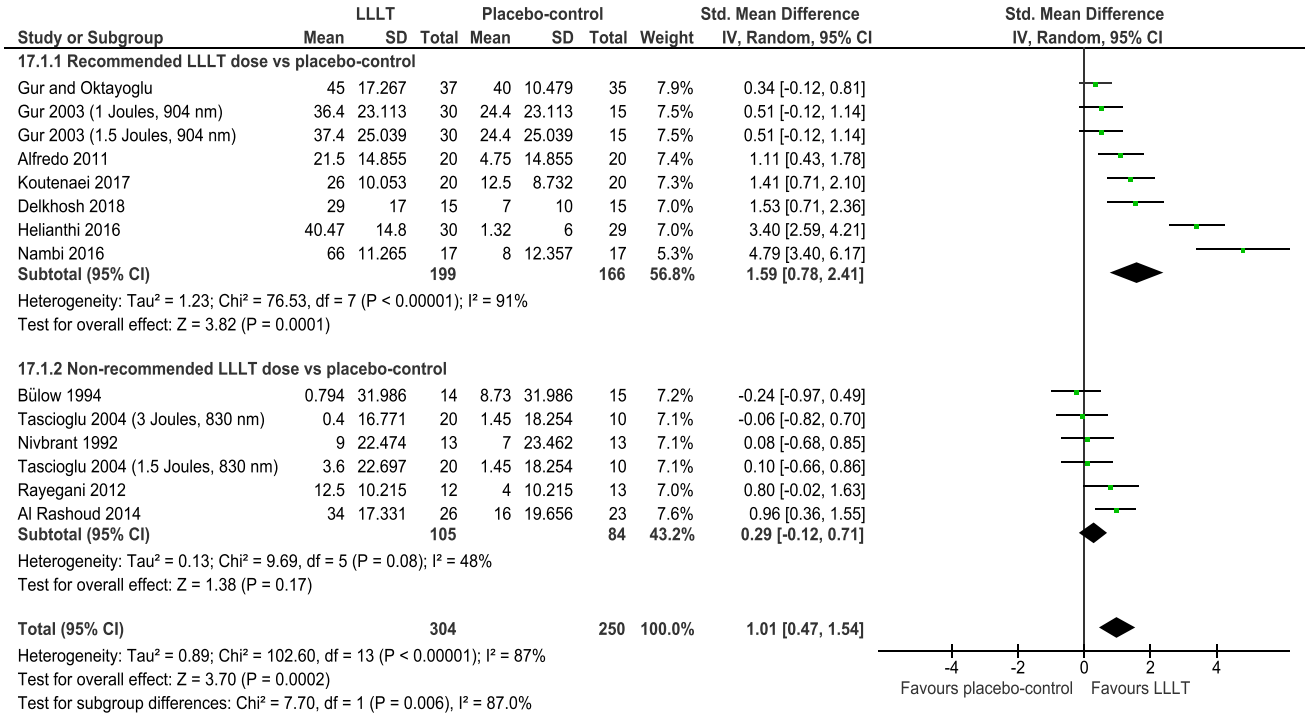


Fig 21 | Standardized Mean Difference (pain results from 2-12-weeks follow-ups)

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PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3 + PROSPERO protocol
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3-4 + PROSPERO protocol
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 3 + PROSPERO protocol
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	PROSEPRO protocol
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 3-4 + PROSPERO protocol
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4 + PROSPERO protocol
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4-8 (table 1-2) + PROSPERO protocol
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 3 + PROSPERO protocol + supplementary material
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4 + PROSPERO protocol
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4 + supplementary material + PROSPERO protocol

PRISMA checklist (continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 3 + supplementary material
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8-9 + supplementary material
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 4 + supplementary material (table of excluded articles)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 4-8 (table 1-2)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 8 (figure 6) + supplementary material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	figure 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 8-9 + figure 2-5 + supplementary material
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 8 + supplementary material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 8-9 + supplementary material
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 10 + PROSPERO protocol

BMJ Open

Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials

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Keywords:	Photobiomodulation therapy, Laser therapy < DERMATOLOGY, Knee osteoarthritis, Systematic review, Meta-analysis

Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials

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Word count, excluding title page, abstract, references, figures and tables: 3757

Abstract

Objectives Low-Level Laser Therapy (LLLT) is not recommended in major knee osteoarthritis (KOA) treatment guidelines. We investigated whether a LLLT dose-response relationship exists in KOA, with funding from University of Bergen.

Design Systematic review and meta-analysis.

Data sources Eligible articles were identified through PubMed, Embase, CINAHL, PEDro and CENTRAL on the 18th February 2019, reference lists, a book, citations and experts.

Eligibility criteria for selecting studies We solely included randomized placebo-controlled trials involving participants with KOA according to the American College of Rheumatology and/or Kellgren/Lawrence criteria, in which LLLT was applied to participants' knee(s). There were no language restrictions.

Data extraction and synthesis The included trials were synthesised with random effects meta-analyses and subgrouped by dose using the World Association for Laser Therapy treatment recommendations. Cochrane's risk of bias tool was used.

Results 22 trials (N = 1063) were meta-analysed. Risk of bias was insignificant. Overall, pain was significantly reduced by LLLT compared to placebo at the end of therapy (14.23 mm VAS [95% CI: 7.31-21.14]) and during follow-ups 2-12 weeks later (15.92 mm VAS [95% CI: 6.47-25.37]). The subgroup analysis revealed that pain was significantly reduced by the recommended LLLT doses compared to placebo at the end of therapy (18.71 mm [95% CI: 9.42-27.99]) and during follow-ups 2-12 weeks later (23.23 mm VAS [95% CI: 10.60-35.86]). The pain reduction from the recommended LLLT doses peaked during follow-ups 2-4 weeks after the end of therapy (31.87 mm VAS significantly beyond placebo [95% CI: 18.18-45.56]). Disability was also significantly reduced by LLLT. No adverse events were reported.

Conclusion LLLT is safe and offers clinically relevant pain relief and a moderate to large amount of disability reduction in KOA at 4-7 Joules with 785-860 nm wavelength and at 1-3 Joules with 904 nm wavelength per treatment spot.

PROSPERO registration number CRD42016035587.

Keywords Phototherapy; Laser therapy; Knee osteoarthritis; Systematic review; Meta-analysis

Strengths and limitations of this study

- The review was conducted in conformance with a detailed a priori published protocol, which included e.g. laser dose subgroup criteria.
- No language restrictions were applied; four (18%) of the included trials were reported in non-English language.
- A series of meta-analyses were conducted to estimate the effect of Low-Level Laser Therapy on pain over time.
- Three persons each independently extracted the outcome data from the included trial articles to ensure high reproducibility of the meta-analyses.
- The review lack quality of life analyses and direct comparisons between Low-Level Laser Therapy and other interventions.

Introduction

Approximately 13% of women and 10% of men in the population aged ≥ 60 years suffer from knee osteoarthritis (KOA) in the USA.[1] KOA is a degenerative inflammatory disease affecting the entire joint and is characterised by progressive loss of cartilage and associated with pain, disability and reduced quality of life (QoL).[1] Increased inflammatory activity is associated with higher pain intensity and more rapid KOA disease progression.[1 2]

Some of the conservative intervention options for KOA are exercise therapy, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and anti-inflammatory Low-Level Laser Therapy (LLLT). There is evidence that exercise therapy reduces pain and disability and improves QoL in persons with KOA.[3 4] NSAIDs are recommended in most KOA clinical treatment guidelines and is probably the most frequently prescribed therapy category for osteoarthritis, despite intake of these drugs is associated with negative side effects[5], which is problematic, especially since the disease requires long-term treatment. Furthermore, a recently published network meta-analysis indicates that the pain relieving effect of NSAIDs in KOA beyond placebo is small to moderate (depending on drug type).[6] Likewise, in the first systematic review on this topic, the pain relieving effect of NSAIDs was estimated to only 10.1 mm on the 0-100 mm Visual Analoge Scale (VAS) better than placebo.[7]

LLLT is a non-invasive treatment modality[8 9], which has been reported to induce anti-inflammatory effects[9-14]. LLLT was compared to NSAID in rats with KOA by Tomazoni et al. in a laboratory; NSAID (10 mg diclofenac/knee/session) and LLLT (830 nm wavelength, 6 Joules/knee/session) reduced similar levels of inflammatory cells and metalloproteinase (MP-3 and MP-13). In addition, LLLT reduced the expression of pro-inflammatory cytokines (interleukin-1β and -6 and tumour necrosis factor α), myeloperoxidase and prostaglandin E_2 significantly more than NSAID did.[10 11]

LLLT has been applied to rabbits with KOA three times per week for eight weeks in a placebo-controlled experiment by Wang et al. At the end of treatment week six, they found that LLLT had significantly reduced pain and synovitis and the production of interleukin-1β, inducible nitric oxide synthase and MP-3 and slowed down loss of Metallopeptidase Inhibitor 1. Two weeks later, LLLT had significantly reduced MP-1 and MP-13 and slowed down loss of collagen II, aggrecan and transforming growth factor beta, and the previous changes were sustained.[12] These findings indicate that the effects of LLLT increase over time.

Pallotta et al. conducted a study on LLLT in rats with acute knee inflammation, which demonstrated that even though LLLT (810 nm) significantly enhanced cyclooxygenase (COX-1 and -2) expression it significantly reduced several other inflammatory makers, i.e., leukocyte infiltration,

myeloperoxidase, interleukin-1 and -6 and especially prostaglandin E_2. Pallotta et al. hypothesised that the increase in COX levels by LLLT was involved in a production of inflammatory mediators related to the resolution of the inflammatory process.[14]

LLLT is not recommended in major osteoarthritis treatment guidelines. LLLT for KOA was mentioned in the European League Against Rheumatism (EULAR) osteoarthritis guidelines (2018) but not recommended[15], and in the Osteoarthritis Research Society International (OARSI) guidelines (2018), it was stressed that LLLT should not be considered a core intervention in the management of KOA.[16]

This may be partly due to conflicting results of two recently published reviews on the current topic (Huang et al. 2015 and Rayegani et al. 2017).[8 17] The conflicting results may arise from omission of relevant trials[8 17-23] and inadequately addressed LLLT dose-related issues. Only Huang et al. conducted a LLLT dose-response relationship investigation in KOA, i.e., by subgrouping the trials by laser dose, but they did not consider that World Association for Laser Therapy (WALT) recommends applying four times the laser dose with continuous irradiation compared to super-pulsed irradiation.[17 22 24-26] Thus, it was unknown whether LLLT is effective in KOA, and we saw a need for a new systematic review.

The objectives of the current review were to estimate the effectiveness of LLLT in KOA regarding knee pain, disability and QoL, and we only considered randomized placebo-controlled clinical trials (RCTs) for inclusion to minimize risk of bias.

Methods

This review was conducted in adherence to a PROSPERO protocol (number CRD42016035587) and is reported in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis statement 2009.[27]

Literature search and selection of studies

Any identified study was included if it was a randomized placebo-controlled trial involving participants with KOA according to the American College of Rheumatology tool and/or a radiographic inspection with the Kellgren/Lawrence (K/L) criteria, in which LLLT was applied to participants' knee(s) and self-reported pain, disability and/or QoL was reported. There were no language restrictions.

We updated a search for eligible articles indexed in PubMed, Embase, CINAHL, PEDro and CENTRAL on the 18th February 2019. The database search strings contained synonyms for LLLT and KOA, and keywords were added when optional. The PubMed search string is available in the supplementary material. The search was continued by reading reference lists of all the eligible trial and relevant review articles[8 17 28], citations[29-33], and a laser book[34] and involving experts in the field. Two reviewers (MBS and JMB) each independently selected the trial articles. Both reviewers scrutinised the titles/abstracts of all the publications identified in the search, and any accessible full-text article was retrieved if it was judged potential eligible by at least one reviewer. Both reviewers evaluated the full texts of all potentially eligible retrieved articles and made an independent decision to include or exclude each article, with close attention to the inclusion criteria. When selection disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Any retrieved article not fulfilling the inclusion criteria was omitted and listed with reason for exclusion.

Risk of bias analysis

Two reviewers (MBS and JJ) each independently evaluated all included trials for risk of bias at the outcome level, using the Cochrane Collaboration's risk of bias tool.[35] When risk of bias

disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Likelihood of publication bias was assessed with graphical funnel plots.[35]

Data-extraction and meta-analysis

Three reviewers (MBS, JMB and KVF) each independently extracted the data for meta-analysis. Two of the reviewers (MBS and KVF) each independently collected the other trial characteristics. The data-extraction forms were subsequently compared, and data disagreements were resolved by consensus-based discussions. Summary data were extracted, unless published individual participant data were available.[21] The results from the included trials for statistical analysis were selected from outcome scales in adherence to hierarchies published by Juhl et al.[36]

Pain intensity was the primary outcome. As pain reported with continuous, numeric and categorical/Likert scales highly correlates with pain measured using the VAS, the scores of all pain scales were transformed to 0-100%, corresponding to 0-100 mm VAS.[37] The pain results were combined with the Mean Difference (MD) method, primarily using change scores, i.e., when only final scores could be obtained from a trial, change and final scores were mixed in the analysis, since the MD method allows for this without introducing bias.[35]

Self-reported disability results were synthesized using the Standardized Mean Difference (SMD) method using change scores solely. The SMD was adjusted to Hedges' *g* and interpreted as follows: SMDs of 0.2, ~ 0.5, and > 0.8 represent a small, moderate, and large effect, respectively.[35]

Lack of QoL data prohibited an analysis of this outcome.

Random effects meta-analyses were conducted, and impact from heterogeneity (inconsistency) on the analyses was examined using I^2 statistics. An I^2 value of 0% indicates no inconsistency, and an I^2 value of 100% indicates maximal inconsistency[35]; the values were categorised as low (25%), moderate (50%) and high (75%).[38]

Standard deviations (SD) for analysis were extracted or estimated from other variance data in a pre-specified prioritised order: (1) SD, (2) standard error, (3) 95% confidence interval, (4) P-value, (5) interquartile range, (6) median of correlations, (7) visually from graph or (8) other methods.[35]

The trials were subgrouped by adherence and non-adherence to the WALT recommendations for laser dose per treatment spot, as pre-specified. WALT recommends irradiating the knee joint line/synovia with the following laser doses per treatment spot: ≥ 4 Joules applied with 5-500 mW mean power using 780-860 nm wavelength and/or ≥ 1 Joules applied with 5-500 mW mean power (> 1000 mW peak power) using 904 nm wavelength.[24 25]

The main meta-analyses were conducted using two pre-specified time points of assessment, i.e., immediately after the end of LLLT and last time point of assessment 1-12 weeks after the end of LLLT (follow-up).

MBS performed the meta-analyses, under supervision of JMB, using the software programs Excel 2016 (Microsoft) and Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

Results

In total, 2735 publications were identified in the search, of which 22 trial articles were judged eligible and included in the review (N = 1089) (figure 1 and table 1-2) with data for meta-analysis (N = 1063). Four included trials were not reported in the English language[19 21 23 39] and one included

trial was unpublished (Gur and Oktayoglu). Excluded articles initially judged potentially eligible were listed with reasons for omission (supplementary material).

Figure 1 | Flow chart illustrating the trial identification process
LLLT = low-level laser therapy.

At the group level, the mean age of the participants was 60.25 (50.11-69) years (data from 19 trials), the mean percentage of women was 69.63 (0-100) (data from 17 trials), the mean BMI of the participants was 29.55 (25.8-38) (data from 14 trials), the mean of median K/L grades was 2.37 (data from 13 trials) and the mean baseline pain was 63.61 mm VAS (35.25-92) (data from 22 trials). LLLT was used as an adjunct to exercise therapy in eleven trials. The mean duration of the treatment periods was 3.53 weeks with the recommended LLLT doses and 3.89 weeks with the non-recommended LLLT doses (table 1-2). Non-recommended LLLT doses were applied in nine of the trials. That is, Al Rashoud et al.[31], Bülow et al.[20], Tascioglu et al.[40] and Bagheri et al.[23] applied too few (< 4) Joules per treatment spot with 830 nm wavelength, Jensen et al.[21], Nivbrant et al.[19] and Hinman et al.[41] applied too few (< 1) Joules per treatment spot with 904 nm wavelength and Youssef et al.[42] (one group) and Rayegani et al.[43] used continuous laser with too long of a wavelength (880 nm) (table 2). No adverse event was reported by any of the trial authors. None of the authors stated receiving funding from the laser industry (supplementary material).

Table 1 | Characteristics of the included trials

First author	Intervention group at baseline	Control group at baseline	Intervention vs control programme	Outcome scales, week of assessment after baseline
Al Rashoud 2014[31]	N: 26 Women: 62% Age: 52 years BMI: 38 VAS pain: 64 mm K/L: -	N: 23 Women: 65% Age: 56 years BMI: 37.1 VAS pain: 59 mm K/L: -	3 weeks of exercise therapy, advice, and LLLT vs 3 weeks of exercise therapy, advice, and sham LLLT	Pain: VAS (movement) Disability: SKFS QoL: - Week of assessment: 2, **3**, **9**, 29
Alfredo 2011/2018[29] [44]	N: 24 Women: 75% Age: 61.15 years BMI: 30.16 VAS pain: 53.2 mm K/L: 3	N: 22 Women: 80% Age: 62.25 years BMI: 29.21 VAS pain: 35.4 mm K/L: 2	3 weeks of LLLT followed by 8 weeks of exercise therapy vs 3 weeks of sham LLLT followed by 8 weeks of exercise therapy	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, **11**, 24, 37
Alghadir 2014[32]	N: 20 Women: 50% Age: 55.2 years BMI: 32.34 VAS pain: 74.5 mm K/L: 2	N: 20 Women: 40% Age: 57 years BMI: 33.09 VAS pain: 75.5 mm K/L: 2	4 weeks of exercise therapy, heat packs, and LLLT vs 4 weeks of exercise therapy, heat packs, and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **4**
Bagheri 2011[23]	N: 18 Women: 83.13% Age: 58.32 years BMI: 28.87 VAS pain: 67 mm K/L: -	N: 18 Women: 83.13% Age: 56.14 years BMI: 27.66 VAS pain: 59 mm K/L: -	5 weeks of exercise therapy, therapeutic ultrasound, TENS, and LLLT vs 5 weeks of exercise therapy, therapeutic ultrasound, TENS, and sham LLLT	Pain: WOMAC (VAS) 0-100 Disability: WOMAC QoL: - Week of assessment: **5**
Bülow 1994[20]	N: 14 Women: - Age: - BMI: - VAS pain: 65.08 mm K/L: -	N: 15 Women: - Age: - BMI: - VAS pain: 56.35 mm K/L: -	3 weeks of LLLT vs 3 weeks of sham LLLT	Pain: 0-121 Likert scale (movement/rest) Disability: - QoL: - Week of assessment: **3**, **6**
Delkhosh 2018[39]	N: 15 Women: 100% Age: 55.9 years BMI: 26.5 VAS pain: 57 mm K/L: -	N: 15 Women: 100% Age: 58.3 years BMI: 27.8 VAS pain: 45 mm K/L: -	2 weeks of exercise therapy, therapeutic ultrasound, TENS, and LLLT vs 2 weeks of exercise therapy, therapeutic ultrasound, TENS, and sham LLLT	Pain: VAS Disability: WOMAC QoL: - Week of assessment: **2**, **8**
Fukuda 2011[30]	N: 25 Women: 80%	N: 22 Women: 64%	3 weeks of LLLT vs 3 weeks of sham LLLT	Pain: VNSP (movement) Disability: Lequesne

	Age: 63 years BMI: 30 VAS pain: 61 mm K/L: 2	Age: 63 years BMI: 30 VAS pain: 62 mm K/L: 2		QoL: - Week of assessment: **3**
Gur 2003[33] (1.5 Joules)	N: 30 Women: 83.3% Age: 58.64 years BMI: 31.17 VAS pain: 73.2 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**
Gur 2003[33] (1 Joules)	N: 30 Women: 76.7% Age: 59.8 years BMI: 28.49 VAS pain: 74.4 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**
Gur and Oktayoglu	N: 40 Women: 75% Age: 58.2 years BMI: 29.11 VAS pain: 88 mm K/L: 3	N: 40 Women: 72.5% Age: 58.26 years BMI: 30.11 VAS pain: 92 mm K/L: 3	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**
Gworys 2012[18]	N: 34 Women: - Age: 57.6 BMI: - VAS pain: 54 mm K/L: -	N: 31 Women: - Age: 67.7 BMI: - VAS pain: - K/L: -	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: VAS Disability: Lequesne QoL: - Week of assessment: **2**
Hegedus 2009[45]	N: 18 Women: - Age: - BMI: - VAS pain: 57.5 mm K/L: 2	N: 17 Women: - Age: - BMI: - VAS pain: 56.2 mm K/L: 2	4 weeks of LLLT vs 4 weeks of sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**, 6, **12**
Helianthi 2016[46]	N: 30 Women: 60% Age: 69 years BMI: 25.8 VAS pain: 60.2 mm K/L: 3	N: 29 Women: 82.8% Age: 68 years BMI: 26.3 VAS pain: 54.1 mm K/L: 3	5 weeks of LLLT vs 5 weeks of sham LLLT	Pain: VAS (movement) Disability: Lequesne QoL: - Week of assessment: 2, **5**, **7**
Hinman 2014[41]	N: 71 Women: 39% Age: 63.4 years BMI: 30.7 VAS pain: 41.5 mm K/L: -	N: 70 Women: 56% Age: 63.8 years BMI: 28.8 VAS pain: 43 mm K/L: -	12 weeks of LLLT vs 12 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: AQoL-6D Week of assessment: **12**, 52
Jensen 1987[21]	N: 13 Women: - Age: - BMI: - VAS pain: 67 mm K/L: -	N: 16 Women: - Age: - BMI: - VAS pain: 72.6 mm K/L: -	1 week of LLLT vs 1 week of sham LLLT	Pain: 0-21 (movement) Disability: - QoL: - Week of assessment: **1**
Kheshie 2014[47]	N: 18 Women: 0% Age: 56.56 years BMI: 28.62 VAS pain: 76.8 mm K/L: 2.5	N: 15 Women: 0% Age: 55.6 years BMI: 28.51 VAS pain: 78.7 mm K/L: 2.5	6 weeks of exercise and LLLT vs 6 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **6**
Koutenaei 2017[48]	N: 20 Women: 85% Age: 52.3 years BMI: 28.4 VAS pain: 74 mm K/L: 3	N: 20 Women: 80% Age: 53 years BMI: 28.6 VAS pain: 65.5 mm K/L: 3	2 weeks of exercise and LLLT vs 2 weeks of exercise and sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: **2**, **4**
Mohammed 2018[49]	N: 20 Women: 85% Age: 55.25 years BMI: ≥ 25 VAS pain: 70 mm K/L: 2	N: 20 Women: 85% Age: 50.11 years BMI: ≥ 25 VAS pain: 80 mm K/L: 2	4 weeks of LLLT vs 4 weeks of sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**
Nambi 2016[50]	N: 17 Women: -	N: 17 Women: -	4 weeks of exercise, kinesio tape, and LLLT vs 4 weeks	Pain: VAS Disability: -

	Age: 58 BMI: 26.9 VAS pain: 78 mm K/L: 3.1	Age: 60 BMI: 28.3 VAS pain: 76 mm K/L: 3.2	of exercise, kinesio tape, and sham LLLT	QoL: - Week of assessment: **4**, **8**
Nivbrant 1992[19]	N: 15 Women: 69.2% Age: 69 years BMI: - VAS pain: 67 mm K/L: -	N: 15 Women: 84.6% Age: 66 years BMI: - VAS pain: 58 mm K/L: -	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: VAS (movement) Disability: Walking disability QoL: - Week of assessment: **2**, 3, **6**
Rayegani 2012[43]	N: 12 Women: 83.3% Age: 61.7 years BMI: - VAS pain: 63 mm K/L: < 4	N: 13 Women: 92.3% Age: 61.2 years BMI: - VAS pain: 52 mm K/L: < 4	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: 6, **14**
Tascioglu 2004[40] (3 Joules)	N: 20 Women: 70% Age: 62.86 years BMI: 27.56 VAS pain: 68 mm K/L: 2	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	10 days of LLLT vs 10 days of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, 26
Tascioglu 2004[40] (1.5 Joules)	N: 20 Women: 75% Age: 59.92 years BMI: 28.63 VAS pain: 65.72 mm K/L: 2.5	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	10 days of LLLT vs 10 days of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, 26
Youssef 2016[42] (904 nm)	N: 18 Women: 66.7% Age: 67.5 BMI: < 40 VAS pain: 51.67 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: < 40 VAS pain: 50.00 mm K/L: 2	8 weeks of exercise and LLLT vs 8 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **8**
Youssef 2016[42] (880 nm)	N: 18 Women: 61.1% Age: 67.3 BMI: < 40 VAS pain: 52.50 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: < 40 VAS pain: 50.00 mm K/L: 2	8 weeks of exercise and LLLT vs 8 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **8**

VAS = Visual Analogue Scale; VNPS = visual numerical pain scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NRS = Numeric Rating Scale; DIQ = Disability Index Questionnaire; SKFS = Saudi Knee Function Scale; QoL = Quality of life; AQoL-6D = Assessment of Quality of Life 6 Dimensions; TENS = transcutaneous electrical nerve stimulation.
The values for age and Body Mass Index (BMI) are means and the values for the Kellgren/Lawrence (K/L) grade are medians. Baseline VAS scores have been extracted or estimated as described in the method section. Week of assessment in bold denotes time point used for the main meta-analyses.

Table 2 | Laser characteristics of the included trials

First author	Treated area	Wave-length (nm)	Joules per treatment spot	Mean output (mW)	Seconds per treated spot	Number of spots treated	Sessions/ sessions per week
Al Rashoud 2014[31]*	Knee joint line (medial and lateral) and acupoints (SP9, SP10, ST36)	830	1.2	30	40	5	9/3
Alfredo 2011, 2018[29] [44]	Knee joint line (medial and lateral)	904	3	60	50	9	9/3
Alghadir 2014[32]	Knee condyles, joint line (medial and lateral), and popliteal fossa	850	6	100	60	8	8/2
Bagheri 2011[23]*	Knee joint line	830	3	30	100	10	10/5
Bülow 1994[20]*	Painful spots in 0-10 cm radius of the knee joint line	830	1.5-4.5	25	60-180	5-15	9/3
Delkhosh 2018[39]	Knee joint	830	5	30	167	5	10/5
Fukuda 2011[30]	Front knee capsule	904	3	60	50	9	9/3
Gur 2003[33] (1.5 Joules)	Antero-lateral and antero-medial portal of the knee	904	1.5	10	150	2	10/2

Gur 2003[33] (1 Joules)	Antero-lateral and antero-medial portal of the knee	904	1	11.2	90	2	10/2
Gur and Oktayoglu	Antero-lateral and antero-medial portal of the knee	904	1.5	10	150	2	10/2
Gworys 2012[18]	Knee joint line, patellofemoral joint, and popliteal fossa	810	6.6	400	16	7	10/2
Hegedus 2009[45]	Knee joint line, popliteal fossa, and condyles	830	6	50	120	8	8/2
Helianthi 2016[46]	Knee joint line (lateral) and acupoints (ST36, SP9, GB34, EX-LE-4)	785	4	50	80	5	10/2
Hinman 2014[41]*	Acupoints (locations not stated)	904	0.2	10	20	6	8-12/0.67-1
Jensen 1987[21]*	Knee joint line (medial and lateral), apex and basis of patellae	904	0.054	0.3	180	4	5/5
Kheshie 2014[47]#	Front knee	830	-	160	-	-	12/2
Koutenaei 2017[48]	Front knee, popliteal fossa, and femur condyles in the popliteal cavity	810	7	100	70	8	10/5
Mohammed 2018[49]	Knee joint line (lateral) and acupoints (ST36, Sp10, GB, ashi)	808	5.4	90	60	7	12/3
Nambi 2016[50]	Knee joint line, condyles, and popliteal fossa	904	1.5	25	60	8	12/4
Nivbrant 1992[19]*	Knee joint line (medial and lateral) and acupoints (ST34, SP10, X32)	904	0.72	4	180	7	6/3
Rayegani 2012[43]*	Knee joint line and popliteal fossa	880	6	50	120	8	10/5
Tascioglu 2004[40] (3 Joules)*	Painful spots on the knee	830	3	50	60	5	10/5
Tascioglu 2004[40] (1.5 Joules)*	Painful spots on the knee	830	1.5	50	30	5	10/5
Youssef 2016[42] (904 nm)	Knee joint line (medial and lateral)	904	3	60	50	9	16/2
Youssef 2016[42] (880 nm)*	Knee joint line (medial and lateral), epicondyles and popliteal fossa	880	6	50	120	8	16/2

* Non-recommended LLLT dose; # 1250 Joules per session.

Overall, pain was significantly reduced by LLLT compared to the placebo-control at the end of therapy (14.23 mm VAS [95% CI: 7.31 to 21.14]; I^2 = 93%; N = 816) (figure 2) and during follow-ups 2-12 weeks later (15.92 mm VAS [95% CI: 6.47 to 25.37]; I^2 = 93%; N = 581) (figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the recommended LLLT doses compared to placebo at the end of therapy (18.71 mm [95% CI: 9.42 to 27.99]; I^2 = 95%; N = 480) (figure 2) and during follow-ups 2-12 weeks later (23.23 mm VAS [95% CI: 10.60 to 35.86]; I^2 = 95%; N = 392) (figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the non-recommended LLLT doses compared to placebo at the end of therapy (6.34 mm VAS [95% CI: 1.26 to 11.41]; I^2 = 44%; N = 336) (figure 2), but the difference during follow-ups 2-12 weeks later was not significant (6.20 mm VAS [95% CI: -0.65 to 13.05]; I^2 = 38%; N = 189) (figure 3). The between-subgroup differences (recommended vs non-recommended doses) in pain results were significantly in favour of the recommended LLLT doses regarding both time points (P = 0.02 and 0.02) (figure 2-3).

Overall, disability was significantly reduced by LLLT compared to placebo at the end of therapy (SMD = 0.59 [95% CI: 0.33 to 0.86]; I^2 = 57%; N = 617) (figure 4) and during follow-ups 2-12 weeks later (SMD = 0.66 [95% CI: 0.23 to 1.09]; I^2 = 67%; N = 289) (figure 5). The dose subgroup analyses demonstrated that disability was significantly reduced by the recommended LLLT doses compared to placebo at the end of therapy (SMD = 0.75 [95% CI: 0.46 to 1.03]; I^2 = 34%; N = 339) (figure 4) and during follow-ups 2-8 weeks later (SMD = 1.31 [95% CI: 0.92 to 1.69]; I^2 = 0%; N = 129) (figure 5). The dose subgroup analyses demonstrated that disability was neither significantly reduced by the non-recommended LLLT doses compared to placebo at the end of therapy (SMD = 0.36 [95% CI: -0.02 to 0.73]; I^2 = 49%; N = 278) (figure 4) nor during follow-ups 2-12 weeks later (SMD = 0.26 [95% CI: -0.06 to 0.58]; I^2 = 0%; N = 160) (figure 5). The between-subgroup differences in disability results were in favour of the recommended LLLT doses over the non-

recommended LLLT doses but only significantly regarding one of two time points (P = 0.11 and < 0.0001) (figure 4-5).
No QoL meta-analysis was performed because this outcome was only assessed in a single trial, i.e., by Hinman et al. who applied a non-recommended LLLT dose and reported insignificant results.[41]
The funnel plots indicated that there was no publication bias (supplementary material). We additionally checked for small study bias by reducing the statistical weight of the smallest studies through a change from random to fixed effects models and this led to similar mean effect estimates, indicating that there was no small study bias (supplementary material).[35]
Methodological quality of the included trials was judged adequate (low risk of bias), unclear (unclear risk of bias) and inadequate (high risk of bias) in 76%, 18% and 6% instances, respectively. Risk of detection bias and reporting bias appeared low in all the trials. There was a lack of information regarding random sequence generation in five trials, allocation concealment in eleven trials, blinding of therapist in four trials and incomplete outcome data in four trials. Therapist blinding was inadequate in seven trials and there was an inadequate handling of data in a single trial (figure 6). However, risk of bias subgroup-analyses conducted post hoc revealed that there was no statistically significant interaction between the effect estimates and risk of bias, and they did not display a drop in statistical heterogeneity (supplementary material). Support for our risk of bias judgments is available (supplementary material).
The statistical heterogeneity remained the same when we changed from the MD to the SMD method post hoc (supplementary material).
Post hoc analyses demonstrated that LLLT was significantly superior to the placebo both with exercise therapy (P = 0.0009 for pain and P < 0.0001 for disability) and without exercise therapy (P = 0.01 for pain and P = 0.008 for disability) as co-intervention (supplementary material).
Post hoc analyses were performed to more precisely estimate the pain time-effect profile for the recommended LLLT doses by imputing the results of the trials with these doses in subgroups with narrower time intervals. Pain was significantly reduced by the recommended LLLT doses compared to placebo immediately after therapy week 2-3 and 4-8 and at follow-ups 2-4, 6-8 and 12 weeks later; the peak point was 2-4 weeks after the end of therapy (31.87 mm VAS beyond placebo [95% CI: 18.18 to 45.56]; I^2 = 93%; N = 322). The 21- and 34-weeks follow-up pain results were not statistically significant (figure 7 and supplementary material). The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high (I^2 = 95%) (figure 2-3) but the mean statistical heterogeneity of the six subgroups covering the same time period was only moderate (I^2 = 58%) (figure 7 and supplementary material).

Figure 2 | Pain results from immediately after the end of therapy

Figure 3 | Pain results from 2-12-weeks follow-ups

Figure 4 | Disability results from immediately after the end of therapy

Figure 5 | Disability results from 2-12-weeks follow-ups

Figure 6 | Risk of bias plot of the included trials
The trials are ranked by pain point effect estimates, i.e., more LLLT positive results in the bottom of the figure; the plot is based on the results from the main pain analyses (immediately after the end of therapy, primarily). Support for our judgements and risk of bias statistical analyses are available (supplementary material).

Figure 7 | Pain time-effect profile (recommended LLLT doses vs placebo-control)
Values on the y-axis are mm VAS pain results. Positive VAS score indicates the recommended LLLT doses are superior to the placebo-control. The related forest plot is available (supplementary material).

VAS = Visual Analogue Scale.
** Recommended LLLT doses are highly statistically significantly superior to the placebo ($P \leq 0.01$).

Discussion

Our meta-analyses showed that pain and disability were significantly reduced by LLLT compared to placebo. We sub-grouped the included trials according to the WALT recommendations (2010) for laser dose per treatment spot, and this revealed a significant dose-response relationship. We conclude that the recommended LLLT doses offers clinically relevant pain relief in KOA. The non-recommended LLLT doses provided no or little pain and disability reduction.

The absolute Minimally Clinically Important Improvement (MCII) of pain in KOA has been estimated to 19.9, 17 and 9 units on a 0-100 scale in 2005, 2012 and 2015, respectively.[51-53] It is important to note that the MCII of pain is a within-subject improvement and depends on baseline pain intensity.[51-53]

The pain reduction from the recommended LLLT doses was significantly superior to placebo even at follow-ups 12 weeks after the end of therapy, and the difference was greater than 20 mm VAS from the final 4-8 weeks of therapy through follow-ups 6-8 weeks after the end of therapy. Interestingly, the pain reduction from the recommended LLLT doses peaked at follow-ups 2-4 weeks after the end of therapy (31.87 mm VAS highly significantly beyond placebo).

Disability was significantly reduced by the recommended LLLT doses compared to placebo at the end of therapy by a moderate extent (SMD = 0.75) and during follow-ups 2-8 weeks later to a large extent (SMD = 1.31).

Our clinical findings that the effect of LLLT progresses over time is in line with in vivo results of Wang et al.[12]

Furthermore, we found that LLLT appeared equally effective in KOA patients undergoing and not undergoing exercise therapy.

Risk of bias of the included trials appeared insignificant and could not explain the statistical heterogeneity (supplementary material). We find it plausible that some of the statistical heterogeneity of the overall analyses is associated with the dose subgroup criteria (wavelength specific laser doses per treatment spot) since the mean levels of statistical heterogeneity of the subgroup analyses were consistently lower than the overall levels.

It is unknown to us whether other differences in the LLLT protocols impacted the results.

The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high, and some of it can be explained by the pooling of results from various time points of assessment given the pain reduction increased and subsequent decreased with time; the pain reduction time profile showed a drop in statistical heterogeneity to a moderate level.

According to WALT, the osteoarthritic knee should be laser irradiated to reduce inflammation and promote tissue repair.[24 25 54] One of the discrepancies from our review and previously published reviews of the same topic is that we omitted the RCT by Yurtkuran et al.[8 17 28 55], as they solely applied laser to an acupoint located distally from the knee joint (spleen 9).

In line with our findings and the WALT dose recommendations, Joensen et al. (2012) observed that the percentage of laser penetrating rat skin at 810 and 904 nm wavelength was 20 and 38-58, respectively. That is, to deliver the same dose beneath the skin, 2.4 times the energy on the skin surface is required with an 810 nm laser compared to a 904 nm laser device. This may be due to the different wavelengths and/or because 904 nm laser is super-pulsed (pulse peak power ≥ 10000 mW typically), whereas shorter wavelength laser is delivered continuously or with less intense pulsation.[26] The estimated median dose applied with the recommended LLLT was six and three Joules per treatment spot with 785-860 and 904 nm wavelength laser, respectively. Most of the trial authors reported LLLT parameters in detail but did not state whether the laser devices were

calibrated. That is, in the LLLT trials with non-significant effect estimates, equipment failure cannot be ruled out.
It is important to note that no adverse events were reported by any of the trial authors and the dropout rate was minor, indicating that LLLT is harmless.
The positive effect from LLLT lasts longer than those of widely recommended painkiller drugs[56], and future trials with booster sessions of LLLT should be conducted to see if the effect can be prolonged. The effect of using the NSAID tiaprofenic acid, for example, is probably gone within a week, unless the treatment is continued.[56] Analyses of LLLT vs NSAIDs in terms of cost-effectiveness would also provide valuable information.

Strengths and limitations of this study
In contrast to previous reviews on the current topic, our review was conducted in conformance with an a priori published protocol[8 17 28], which included a detailed plan for statistical analysis (e.g. laser dose subgroup criteria).
Furthermore, this is the first review on this topic without language restrictions[8 17 28], and this expansion proved important since four (18%) of the included trials were reported in non-English language.[19 21 23 39]
We conducted a series of meta-analyses illustrating effect of LLLT on pain over time. Three persons each independently extracted the outcome data from the included trial articles to ensure high reproducibility of the meta-analyses.
This review lacks QoL analyses and direct comparisons between LLLT and other interventions.

Conclusions
LLLT is safe and offers clinically relevant pain relief and a moderate to large amount of disability reduction in KOA at 4-7 Joules with 785-860 nm wavelength and at 1-3 Joules with 904 nm wavelength per treatment spot on the knee joint.

Contributors: MBS, JMB and HL wrote the PROSPERO protocol. MBS and JMB selected the trials, with the involvement of IFN when necessary. MBS and JJ judged the risk of bias, with the involvement of IFN when necessary. MBS and IFN did the translations. MBS, JMB and KVF extracted the data. MBS performed the analyses, under supervision of JMB. All the authors participated in interpreting of the results. MBS drafted the first version of the manuscript, and subsequently revised it, based on comments by RABLM, HS and all the other authors. All the authors read and accepted the final version of the manuscript.
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Competing interests: JMB and RABLM are post-presidents and former board members of World Association for Laser Therapy, a non-for-profit research organization from which they have never received funding, grants or fees. The other authors declared that they had no conflict of interests related to this work.
Ethical approval: Not required.
Data sharing: The dataset for meta-analysis is available from the corresponding author upon reasonable request. The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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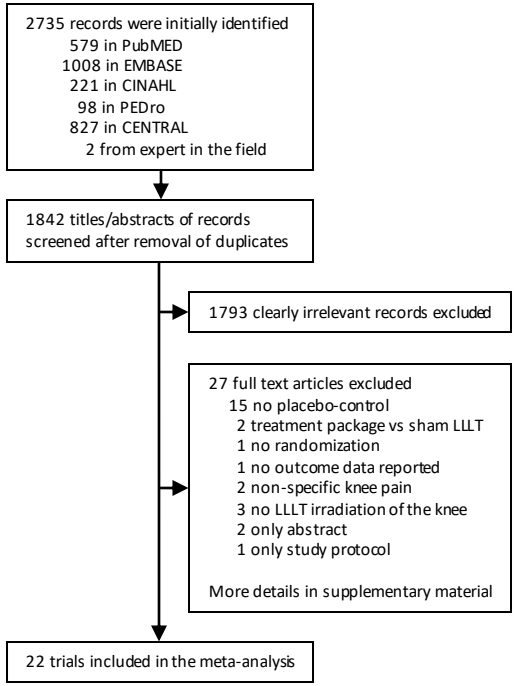
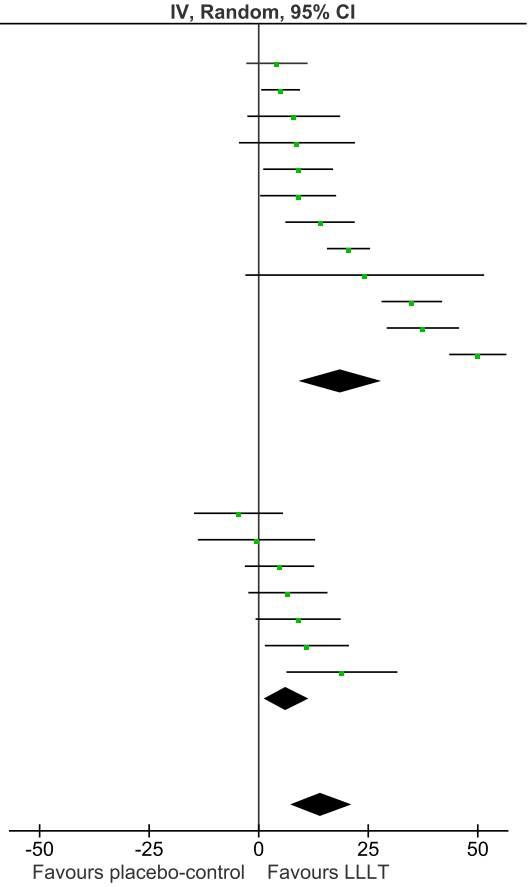
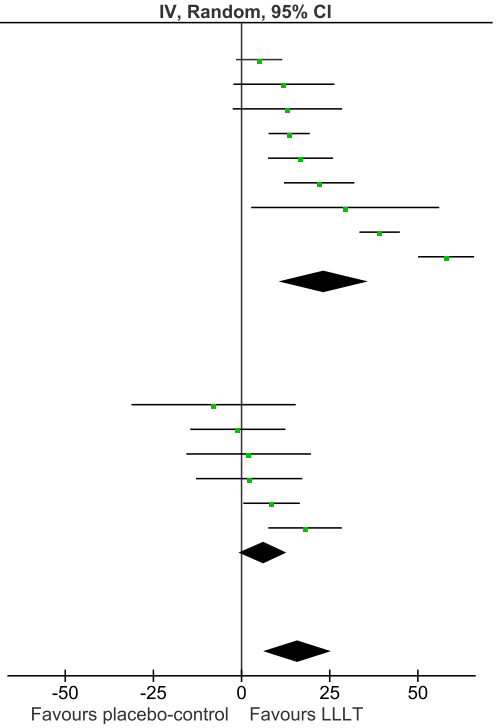

2735 records were initially identified
579 in PubMED
1008 in EMBASE
221 in CINAHL
98 in PEDro
827 in CENTRAL
2 from expert in the field
1842 titles/abstracts of records screened after removal of duplicates
1793 clearly irrelevant records excluded
27 full text articles excluded
15 no placebo-control
2 treatment package vs sham LLLT
1 no randomization
1 no outcome data reported
2 non-specific knee pain
3 no LLLT irradiation of the knee
2 only abstract
1 only study protocol
More details in supplementary material
22 trials included in the meta-analysis

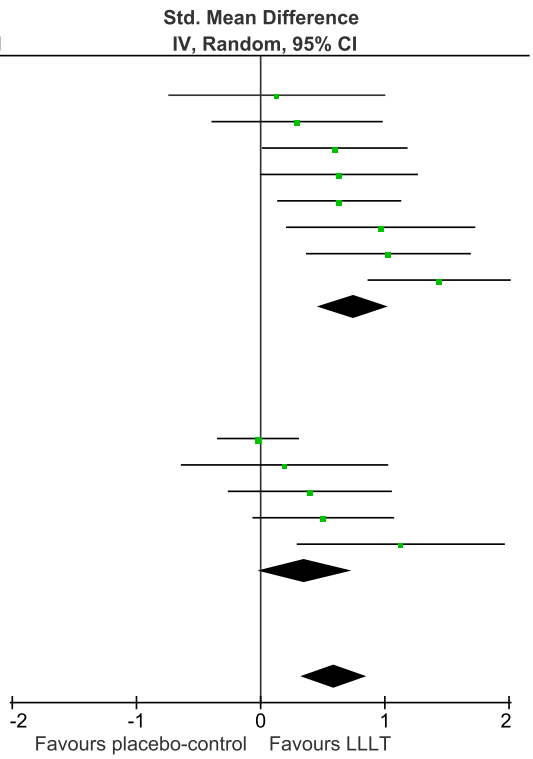
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Recommended LLLT dose vs placebo-control								
Youssef 2016 (904 nm)	6.667	13.34	18	2.5	4.492	7	5.6%	4.17 [-2.84, 11.17]
Gworys 2012	20	8	34	15	10	31	5.8%	5.00 [0.57, 9.43]
Fukuda 2011	17	22.67	25	9	13.78	22	5.2%	8.00 [-2.59, 18.59]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	4.9%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	5.5%	9.00 [1.03, 16.97]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	5.4%	9.00 [0.33, 17.67]
Delkhosh 2018	25	14	15	11	7	15	5.5%	14.00 [6.08, 21.92]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	5.8%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	3.1%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	5.6%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	5.5%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	5.6%	50.00 [43.48, 56.52]
Subtotal (95% CI)			**255**			**225**	**63.4%**	**18.71 [9.42, 27.99]**
Heterogeneity: Tau² = 243.24; Chi² = 201.44, df = 11 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.95 (P < 0.0001)								
1.1.2 Non-recommended LLLT dose vs placebo-control								
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	5.3%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	4.9%	-0.50 [-13.88, 12.88]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	5.5%	4.76 [-3.15, 12.68]
Youssef 2016 (880 nm)	9.167	18.343	18	2.5	4.492	8	5.4%	6.67 [-2.36, 15.69]
Bagheri 2011	28	18.5	18	19	10	18	5.3%	9.00 [-0.72, 18.72]
Al Rashoud 2014	32	13.617	26	21	19.656	23	5.3%	11.00 [1.41, 20.59]
Nivbrant 1992	23	15.31	13	4	17.556	13	4.9%	19.00 [6.34, 31.66]
Subtotal (95% CI)			**173**			**163**	**36.6%**	**6.34 [1.26, 11.41]**
Heterogeneity: Tau² = 20.17; Chi² = 10.65, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 2.45 (P = 0.01)								
Total (95% CI)			**428**			**388**	**100.0%**	**14.23 [7.31, 21.14]**
Heterogeneity: Tau² = 209.90; Chi² = 243.08, df = 18 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 4.03 (P < 0.0001)								
Test for subgroup differences: Chi² = 5.25, df = 1 (P = 0.02), I² = 80.9%								



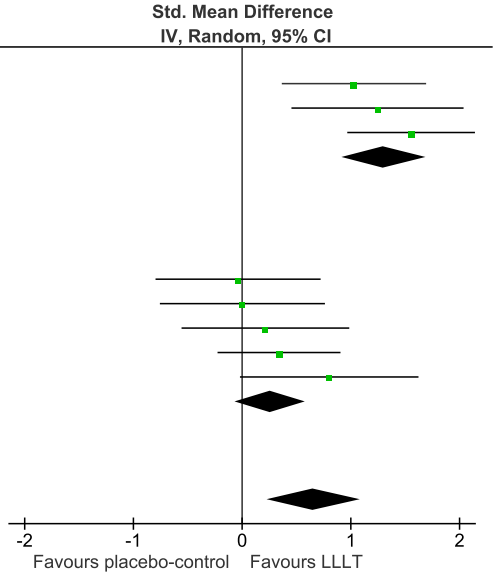
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Recommended LLLT dose vs placebo-control								
Gur and Oktayoglu	45	17.267	37	40	10.479	35	7.4%	5.00 [-1.56, 11.56]
Gur 2003 (1 Joules, 904 nm)	36.4	23.113	30	24.4	23.113	15	6.5%	12.00 [-2.33, 26.33]
Gur 2003 (1.5 Joules, 904 nm)	37.4	25.039	30	24.4	25.039	15	6.4%	13.00 [-2.52, 28.52]
Koutenaei 2017	26	10.053	20	12.5	8.732	20	7.4%	13.50 [7.66, 19.34]
Alfredo 2011	21.5	14.855	20	4.75	14.855	20	7.1%	16.75 [7.54, 25.96]
Delkhosh 2018	29	17	15	7	10	15	7.1%	22.00 [12.02, 31.98]
Hegedus 2009	-11.8	11.194	18	-41.2	40.05	9	4.8%	29.40 [2.73, 56.07]
Helianthi 2016	40.47	14.8	30	1.32	6	29	7.5%	39.15 [33.42, 44.88]
Nambi 2016	66	11.265	17	8	12.357	17	7.3%	58.00 [50.05, 65.95]
Subtotal (95% CI)			**217**			**175**	**61.4%**	**23.23 [10.60, 35.86]**
Heterogeneity: Tau² = 335.90; Chi² = 149.09, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.60 (P = 0.0003)								
2.1.2 Non-recommended LLLT dose vs placebo-control								
Bülow 1994	0.794	31.986	14	8.73	31.986	15	5.2%	-7.94 [-31.23, 15.36]
Tascioglu 2004 (3 Joules, 830 nm)	0.4	16.771	20	1.45	18.254	10	6.6%	-1.05 [-14.54, 12.44]
Nivbrant 1992	9	22.474	13	7	23.462	13	6.0%	2.00 [-15.66, 19.66]
Tascioglu 2004 (1.5 Joules, 830 nm)	3.6	22.697	20	1.45	18.254	10	6.4%	2.15 [-12.91, 17.21]
Rayegani 2012	12.5	10.215	12	4	10.215	13	7.3%	8.50 [0.49, 16.51]
Al Rashoud 2014	34	17.331	26	16	19.656	23	7.0%	18.00 [7.56, 28.44]
Subtotal (95% CI)			**105**			**84**	**38.6%**	**6.20 [-0.65, 13.05]**
Heterogeneity: Tau² = 26.43; Chi² = 8.03, df = 5 (P = 0.15); I² = 38%								
Test for overall effect: Z = 1.77 (P = 0.08)								
Total (95% CI)			**322**			**259**	**100.0%**	**15.92 [6.47, 25.37]**
Heterogeneity: Tau² = 303.25; Chi² = 190.87, df = 14 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 3.30 (P = 0.0010)								
Test for subgroup differences: Chi² = 5.40, df = 1 (P = 0.02), I² = 81.5%								

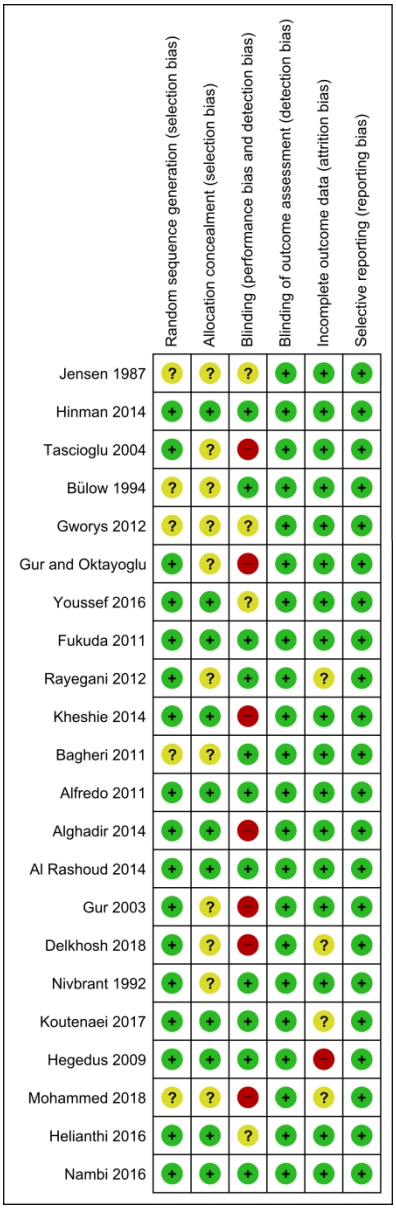


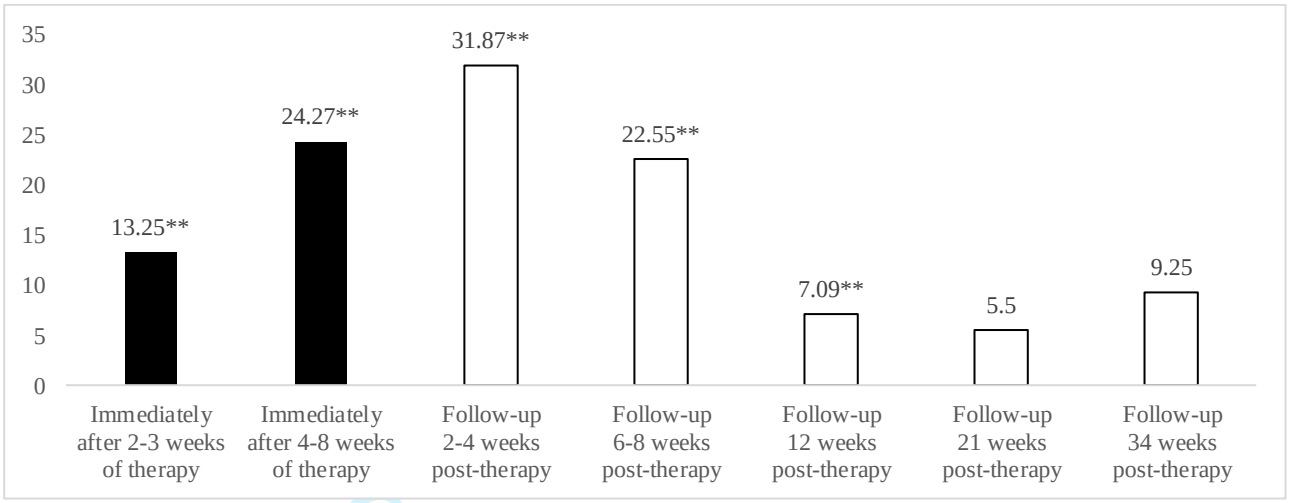
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Random, 95% CI
7.1.1 Recommended LLLT dose vs placebo-control								
Youssef 2016 (904 nm)	6.575	13.157	18	4.932	8.86	7	5.5%	0.13 [-0.74, 1.00]
Kheshie 2014	13.56	11.395	18	10.4	9.315	15	7.2%	0.29 [-0.40, 0.98]
Fukuda 2011	3.2	4.267	25	1	2.717	22	8.3%	0.60 [0.01, 1.18]
Alghadir 2014	15.95	5.364	20	12.5	5.364	20	7.8%	0.63 [-0.01, 1.27]
Gworys 2012	1.06	0.6	34	0.5	1.1	31	9.4%	0.63 [0.13, 1.13]
Delkhosh 2018	7.9	4.9	15	4.1	2.3	15	6.5%	0.97 [0.20, 1.73]
Alfredo 2011	9.7	9.48	20	-0.25	9.48	20	7.5%	1.03 [0.37, 1.69]
Helianthi 2016	5.2	3.9	30	-0.7	4.2	29	8.5%	1.44 [0.86, 2.01]
Subtotal (95% CI)			**180**			**159**	**60.7%**	**0.75 [0.46, 1.03]**
Heterogeneity: Tau² = 0.06; Chi² = 10.67, df = 7 (P = 0.15); I² = 34%								
Test for overall effect: Z = 5.19 (P < 0.00001)								
7.1.2 Non-recommended LLLT dose vs placebo-control								
Hinman 2014	-0.5	23.422	71	0	23.422	70	11.7%	-0.02 [-0.35, 0.31]
Youssef 2016 (880 nm)	7.671	15.35	18	4.932	8.86	8	5.8%	0.19 [-0.64, 1.03]
Bagheri 2011	27.5	19	18	21	12.4	18	7.5%	0.40 [-0.26, 1.06]
Al Rashoud 2014	35	32.185	26	19	30.063	23	8.5%	0.50 [-0.07, 1.08]
Nivbrant 1992	22	16.967	13	4	13.756	13	5.8%	1.13 [0.29, 1.97]
Subtotal (95% CI)			**146**			**132**	**39.3%**	**0.36 [-0.02, 0.73]**
Heterogeneity: Tau² = 0.09; Chi² = 7.78, df = 4 (P = 0.10); I² = 49%								
Test for overall effect: Z = 1.86 (P = 0.06)								
Total (95% CI)			**326**			**291**	**100.0%**	**0.59 [0.33, 0.86]**
Heterogeneity: Tau² = 0.13; Chi² = 27.92, df = 12 (P = 0.006); I² = 57%								
Test for overall effect: Z = 4.44 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.62, df = 1 (P = 0.11), I² = 61.8%								



Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Random, 95% CI
8.1.1 Recommended LLLT dose vs placebo-control								
Alfredo 2011	14.35	10.052	20	3.8	10.052	20	13.1%	1.03 [0.36, 1.69]
Delkhosh 2018	8.5	4.6	15	3.1	3.8	15	11.6%	1.25 [0.45, 2.04]
Helianthi 2016	5.3	4.5	30	-1.2	3.7	29	14.1%	1.55 [0.97, 2.14]
Subtotal (95% CI)			**65**			**64**	**38.7%**	**1.31 [0.92, 1.69]**
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0%								
Test for overall effect: Z = 6.65 (P < 0.00001)								
8.1.2 Non-recommended LLLT dose vs placebo-control								
Tascioglu 2004 (3 Joules, 830 nm)	1.56	9.292	20	1.93	10.337	10	12.0%	-0.04 [-0.80, 0.72]
Tascioglu 2004 (1.5 Joules, 830 nm)	1.96	11.831	20	1.93	10.337	10	12.0%	0.00 [-0.76, 0.76]
Nivbrant 1992	12	17.329	13	8	18.815	13	11.8%	0.21 [-0.56, 0.99]
Al Rashoud 2014	31	33.423	26	20	30.063	23	14.3%	0.34 [-0.23, 0.90]
Rayegani 2012	2.2	0.845	12	1.5	0.845	13	11.2%	0.80 [-0.02, 1.62]
Subtotal (95% CI)			**91**			**69**	**61.3%**	**0.26 [-0.06, 0.58]**
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 4 (P = 0.59); I² = 0%								
Test for overall effect: Z = 1.60 (P = 0.11)								
Total (95% CI)			**156**			**133**	**100.0%**	**0.66 [0.23, 1.09]**
Heterogeneity: Tau² = 0.25; Chi² = 20.90, df = 7 (P = 0.004); I² = 67%								
Test for overall effect: Z = 2.99 (P = 0.003)								
Test for subgroup differences: Chi² = 16.73, df = 1 (P < 0.0001), I² = 94.0%								




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias and detection bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Jensen 1987
Hinman 2014
Tascioglu 2004
Bülow 1994
Gworys 2012
Gur and Oktayoglu
Youssef 2016
Fukuda 2011
Rayegani 2012
Kheshie 2014
Bagheri 2011
Alfredo 2011
Alghadir 2014
Al Rashoud 2014
Gur 2003
Delkhosh 2018
Nivbrant 1992
Koutenaei 2017
Hegedus 2009
Mohammed 2018
Helianthi 2016
Nambi 2016



Supplementary material for the article by Stausholm et al. entitled *Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials*

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Mean Difference vs Standardized Mean Difference 17
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PubMed database search string

The PubMed database search string was: ("Osteoarthritis, Knee"[Mesh] OR "Knee Joint"[Mesh] OR "Knee"[Mesh] OR "Osteoarthritis"[Mesh] OR Knee[Title/Abstract] OR Knees[Title/Abstract] OR Osteoarthr*[Title/Abstract]) AND ("Low-Level Light Therapy"[Mesh] OR LLLT[Title/Abstract] OR "low level"[Title/Abstract] OR "low power"[Title/Abstract] OR laser therap*[Title/Abstract] OR "laser acupuncture"[Title/Abstract] OR "narrow band"[Title/Abstract] OR "HeNe"[Title/Abstract] OR "632 nm"[Title/Abstract] OR "Ga-Al-As"[Title/Abstract] OR "820 nm"[Title/Abstract] OR "830 nm"[Title/Abstract] OR "850 nm"[Title/Abstract] OR "GaAs"[Title/Abstract] OR "904 nm"[Title/Abstract])

Excluded articles

Table 1 | Excluded articles initially judged potentially eligible

First author	Reason for exclusion
Alayat 2017[1]	HILT, not LLLT
Ciechanowska 2008[2]	No placebo-control
Coelho[3]	Only study protocol
de Matos 20184[4]	No placebo-control
de Meneses[5]	Full-text not available (emailed)
de Paula 2018[6]	NBLT + LLLT vs sham LLLT alone
Giavelli 1998[7]	No placebo-control
Götte 1995[8]	No outcome data reported
Kujawa 2004[9]	No placebo-control
Leal-Junior 2014[10]	Non-specific knee pain
Lepilina 1990[11]	No placebo-control
Marquina 2012[12]	Non-specific knee pain
Montes-Molina 2009[13]	No placebo-control
Nakamura 2014[14]	No placebo-control
Paolillo 2018[15]	No placebo-control
Pinfildi[16]	Full-text not available (emailed)
Ren 2010[17]	No placebo-control
Shen 2009[18]	LLLT + moxibustion vs sham LLLT alone
Soleimanpour 2014[19]	No placebo-control
Stelian 1992[20]	NBLT, not laser
Trelles 1991[21]	No placebo-control
Wang 2013[22]	No randomization
Yavuz 2013[23]	No placebo-control
Yurtkuran 2006[24]	Irradiated acupoint spleen 9, not the knee joint
Yuvarani 2018[25]	No placebo-control
Zhao 2010[26]	No placebo-control
Zou 2017[27]	No placebo-control

NBLT = narrow-band light therapy; LLLT = low-level laser therapy; HILT = high intensity laser therapy.

Pain time-effect profile of LLLT

Analyses were performed to estimate the pain time-effect profile of the recommended LLLT doses by imputing the results of the trials with these doses in subgroups with narrower time intervals (figure 1).

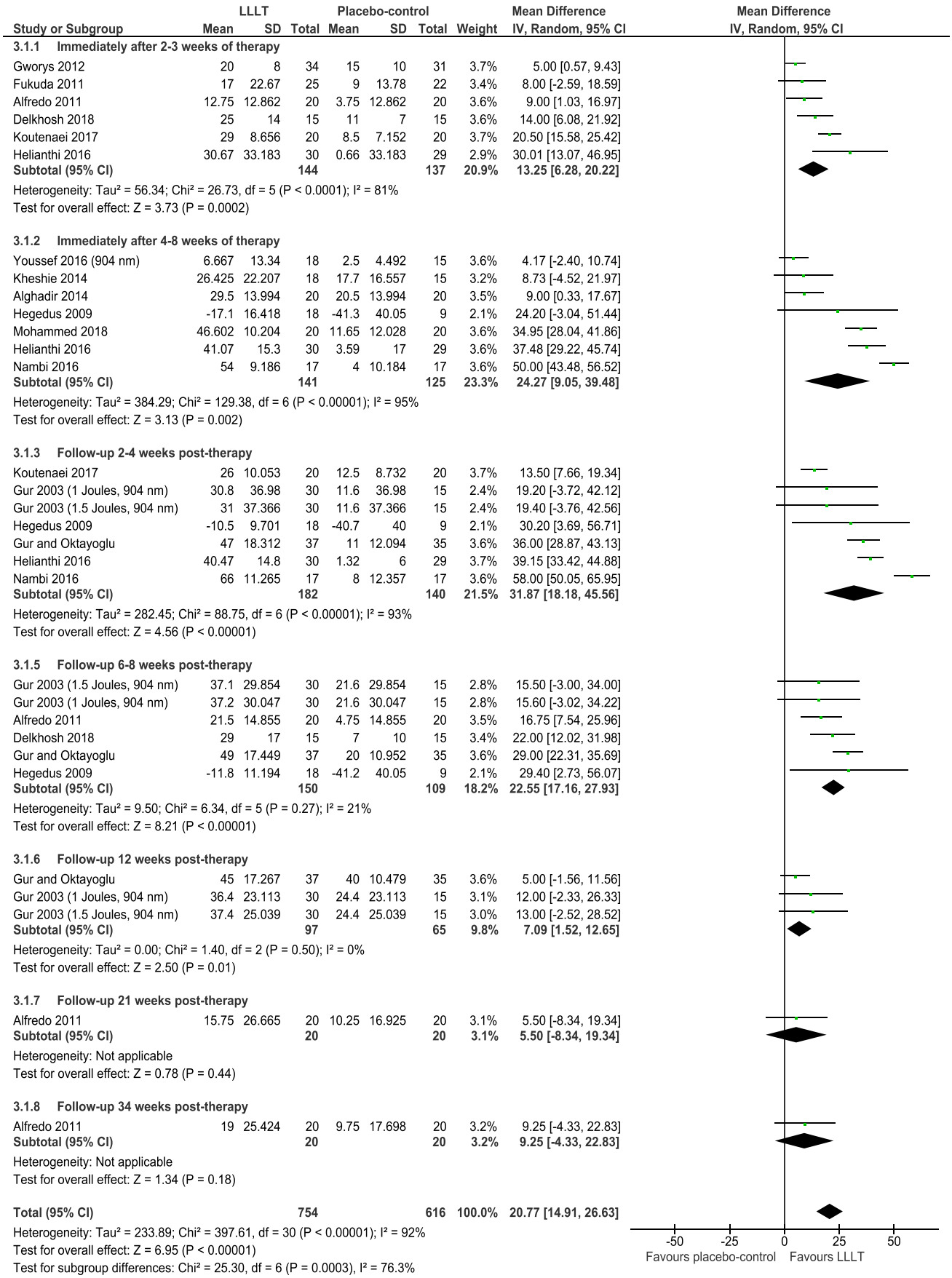

Figure 1 | Pain time-effect profile (recommended LLLT doses vs placebo-control)

Publication and small study bias assessment

Funnel plots were performed using the results from the main analyses (immediately after the end of therapy, primarily). There were no clear indications of publication bias (figure 2-3). Moreover, a subsequent change from random to fixed effects models only caused a slight change in point effect estimates: Pain results from 13.22 to 14.14 mm VAS (figure 4-5) and disability from 0.57 to 0.48 (SMD) (figure 6-7).

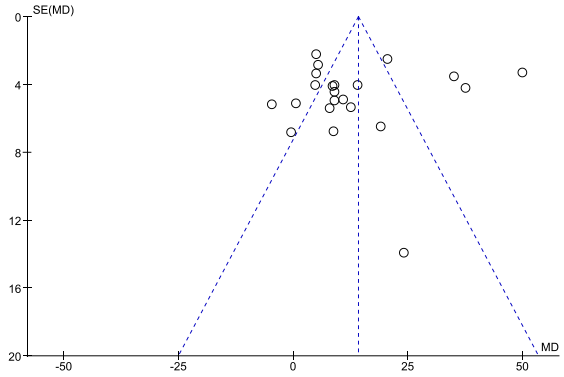

Figure 2 | Funnel plot (pain)

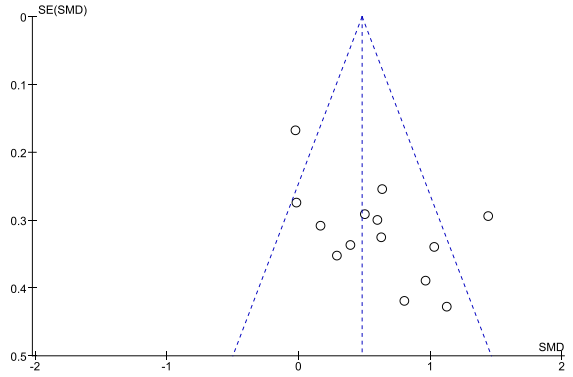

Figure 3 | Funnel plot (disability)

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	4.5%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	4.1%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (both intervention groups)	2	19.764	40	1.45	18.254	20	4.5%	0.55 [-9.53, 10.63]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.7%	4.76 [-3.15, 12.68]
Gur and Oktayoglu	45	17.267	37	40	10.479	35	4.9%	5.00 [-1.56, 11.56]
Gworys 2012	20	8	34	15	10	31	5.0%	5.00 [0.57, 9.43]
Youssef 2016 (both intervention groups)	7.917	15.858	36	2.5	4.492	15	4.9%	5.42 [-0.24, 11.07]
Fukuda 2011	17	22.67	25	9	13.78	22	4.5%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.7%	8.50 [0.49, 16.51]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	4.1%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.7%	9.00 [1.03, 16.97]
Bagheri 2011	28	18.5	18	19	10	18	4.6%	9.00 [-0.72, 18.72]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	4.7%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	4.6%	11.00 [1.41, 20.59]
Gur 2003 (both intervention groups)	36.9	23.895	60	24.4	24.076	30	4.5%	12.50 [1.97, 23.03]
Delkhosh 2018	25	14	15	11	7	15	4.7%	14.00 [6.08, 21.92]
Nivbrant 1992	23	15.31	13	4	17.556	13	4.2%	19.00 [6.34, 31.66]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	5.0%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	2.5%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	4.8%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.7%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	4.9%	50.00 [43.48, 56.52]
Total (95% CI)			**577**			**486**	**100.0%**	**13.22 [7.15, 19.29]**

Heterogeneity: Tau² = 185.88; Chi² = 260.56, df = 21 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.27 (P < 0.0001)

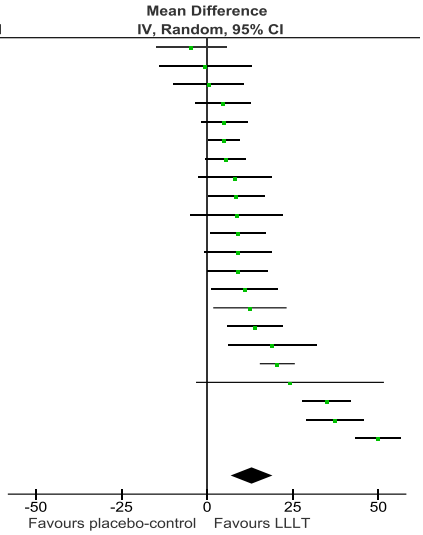

Figure 4 | Random effects model (pain)

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Fixed, 95% CI
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	2.7%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	1.6%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (both intervention groups)	2	19.764	40	1.45	18.254	20	2.7%	0.55 [-9.53, 10.63]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.4%	4.76 [-3.15, 12.68]
Gur and Oktayoglu	45	17.267	37	40	10.479	35	6.5%	5.00 [-1.56, 11.56]
Gworys 2012	20	8	34	15	10	31	14.1%	5.00 [0.57, 9.43]
Youssef 2016 (both intervention groups)	7.917	15.858	36	2.5	4.492	15	8.7%	5.42 [-0.24, 11.07]
Fukuda 2011	17	22.67	25	9	13.78	22	2.5%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.3%	8.50 [0.49, 16.51]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	1.6%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.4%	9.00 [1.03, 16.97]
Bagheri 2011	28	18.5	18	19	10	18	2.9%	9.00 [-0.72, 18.72]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	3.7%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	3.0%	11.00 [1.41, 20.59]
Gur 2003 (both intervention groups)	36.9	23.895	60	24.4	24.076	30	2.5%	12.50 [1.97, 23.03]
Delkhosh 2018	25	14	15	11	7	15	4.4%	14.00 [6.08, 21.92]
Nivbrant 1992	23	15.31	13	4	17.556	13	1.7%	19.00 [6.34, 31.66]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	11.5%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	0.4%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	5.8%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.1%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	6.5%	50.00 [43.48, 56.52]
Total (95% CI)			**577**			**486**	**100.0%**	**14.14 [12.48, 15.81]**

Heterogeneity: Chi² = 260.56, df = 21 (P < 0.00001); I² = 92%
Test for overall effect: Z = 16.64 (P < 0.00001)

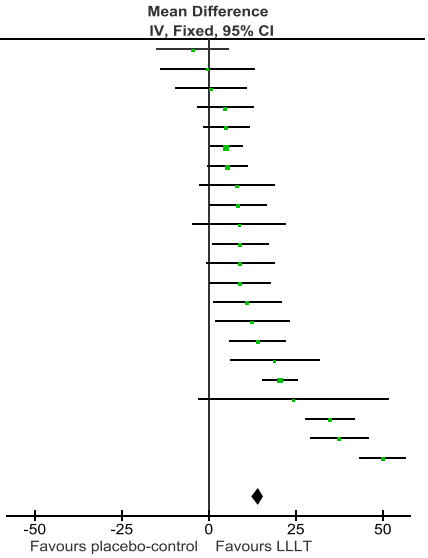

Figure 5 | Fixed effects model (pain)

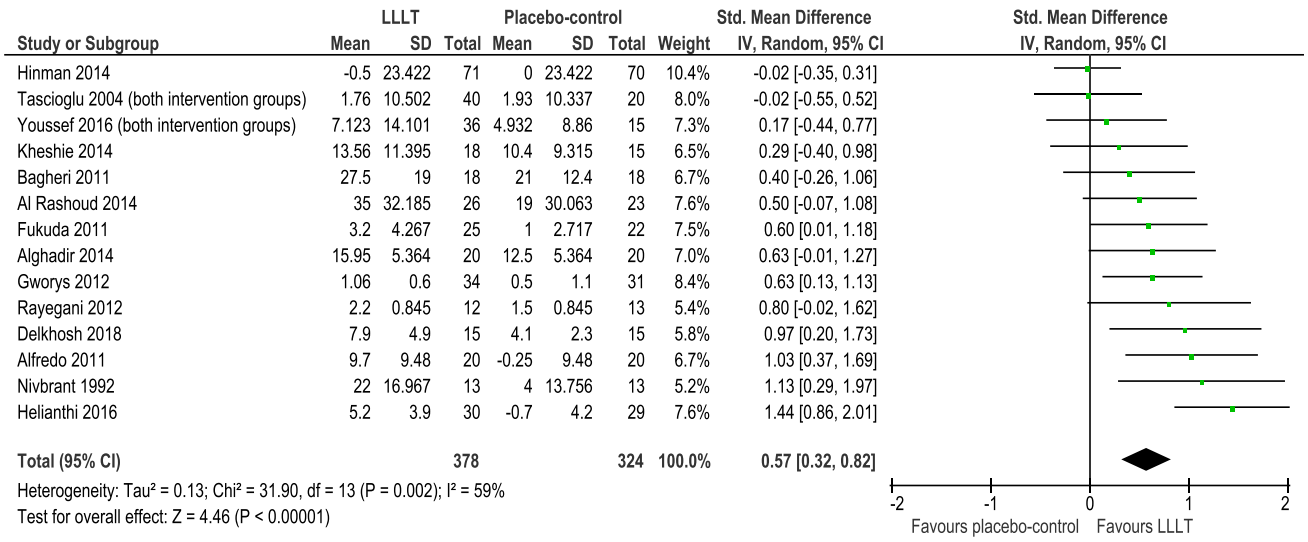

Figure 6 | Random effects model (disability)

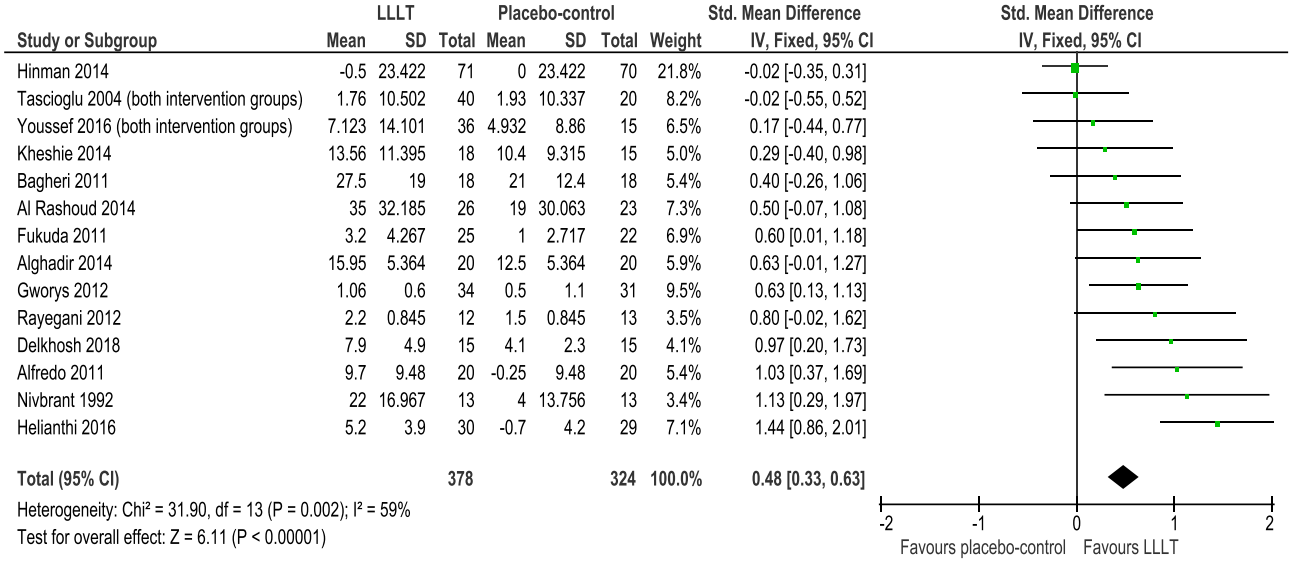

Figure 7 | Fixed effects model (disability)

Risk of bias impact analysis

Risk of bias impact analyses were performed using the results from the main analyses (immediately after the end of therapy, primarily). The mean statistical heterogeneity of the subgroup analyses were similar to the overall levels (figure 8-15).

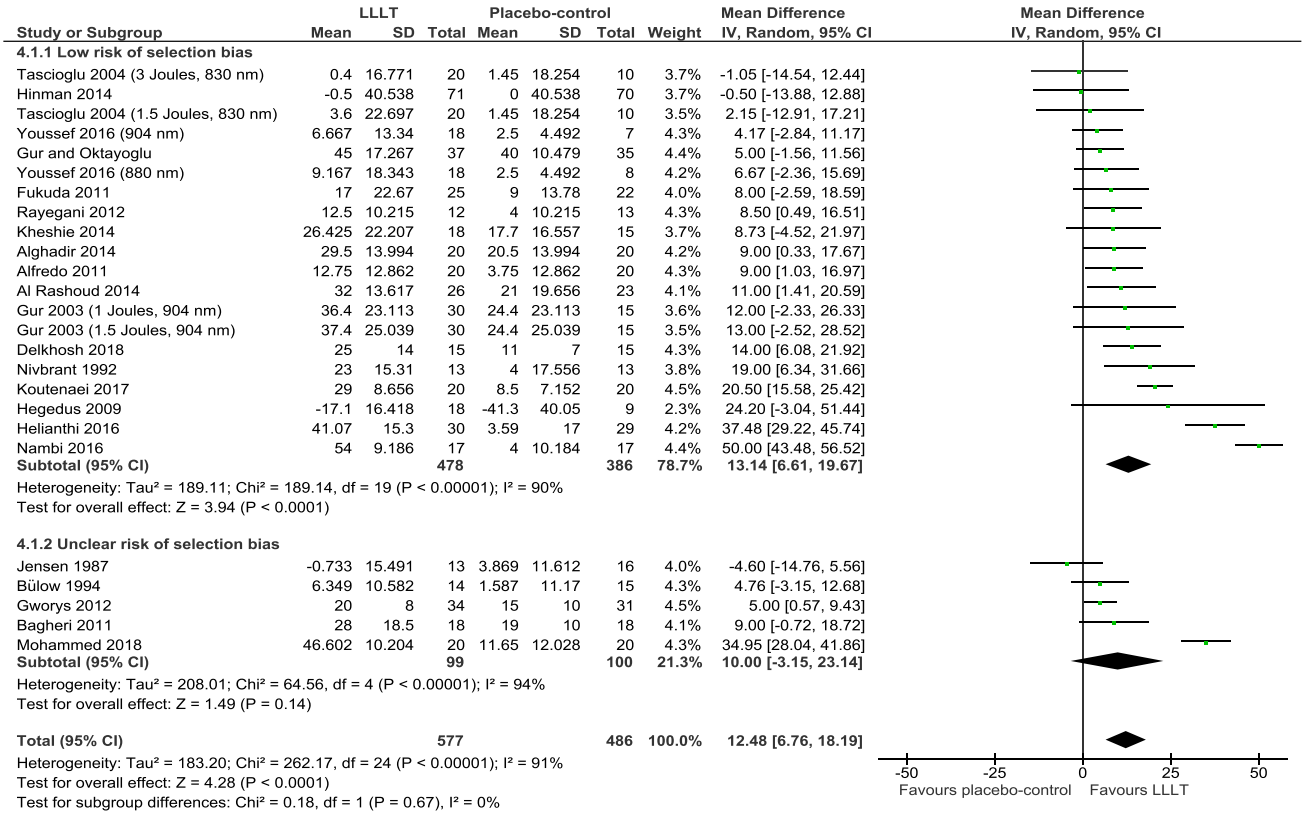

Figure 8 | Pain results - risk of selection bias (random sequence generation)

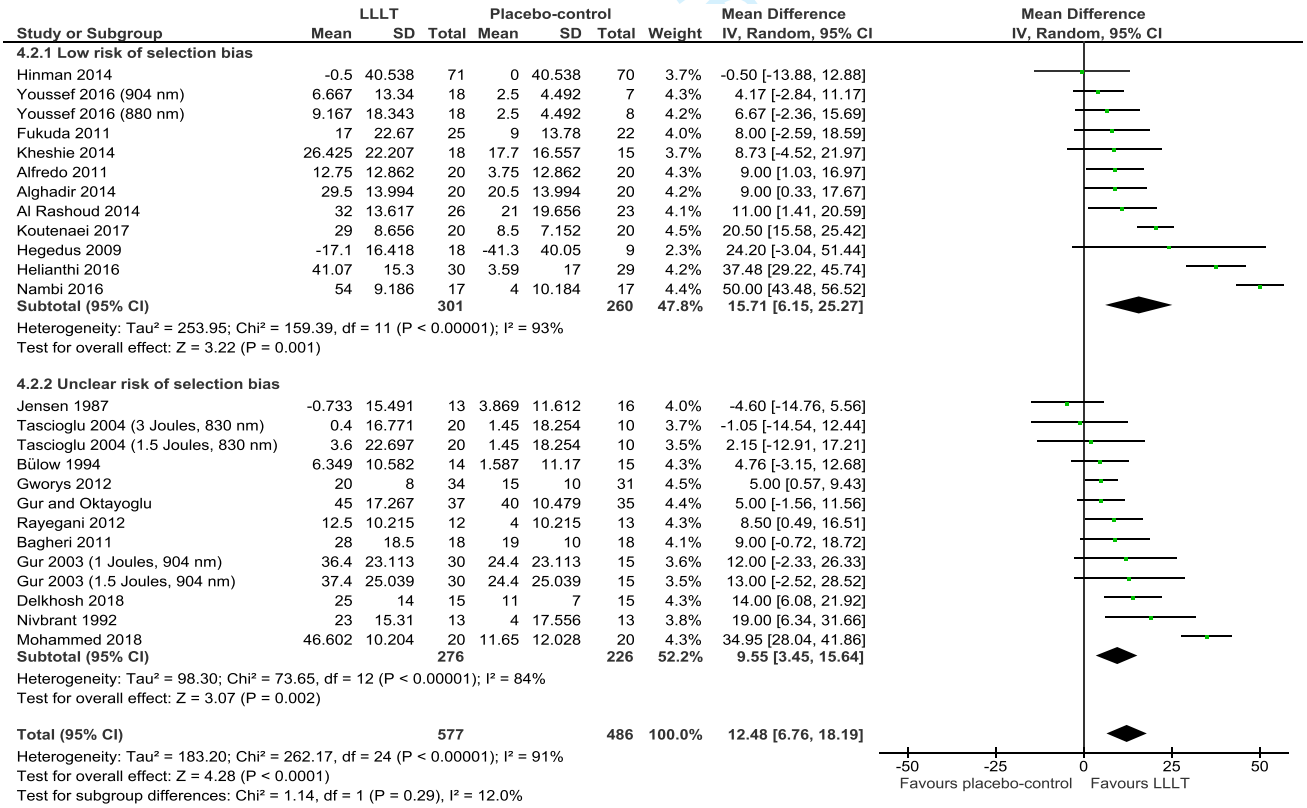

Figure 9 | Pain results - risk of selection bias (allocation concealment)

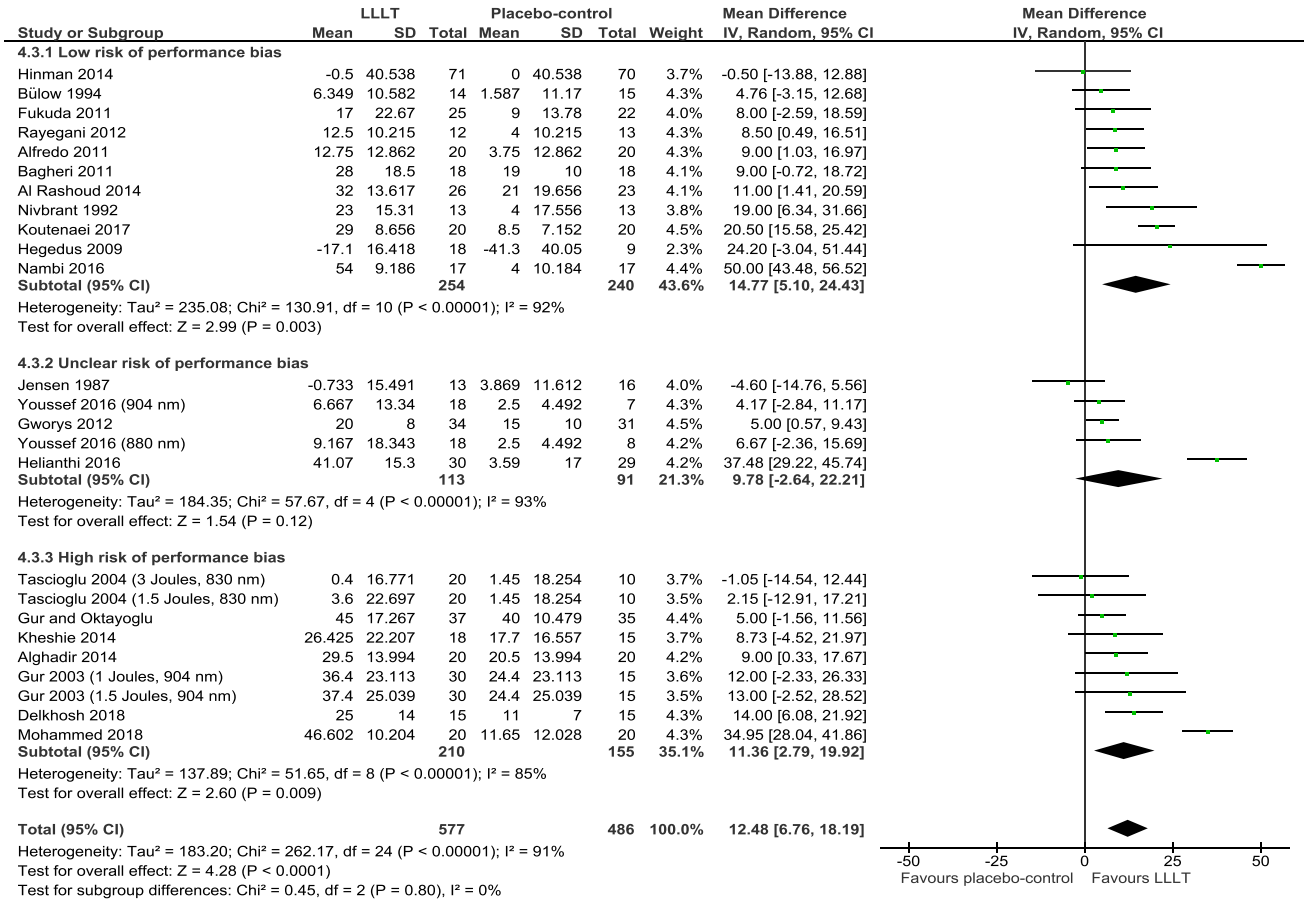

Figure 10 | Pain results - risk of performance bias (blinding of therapist)

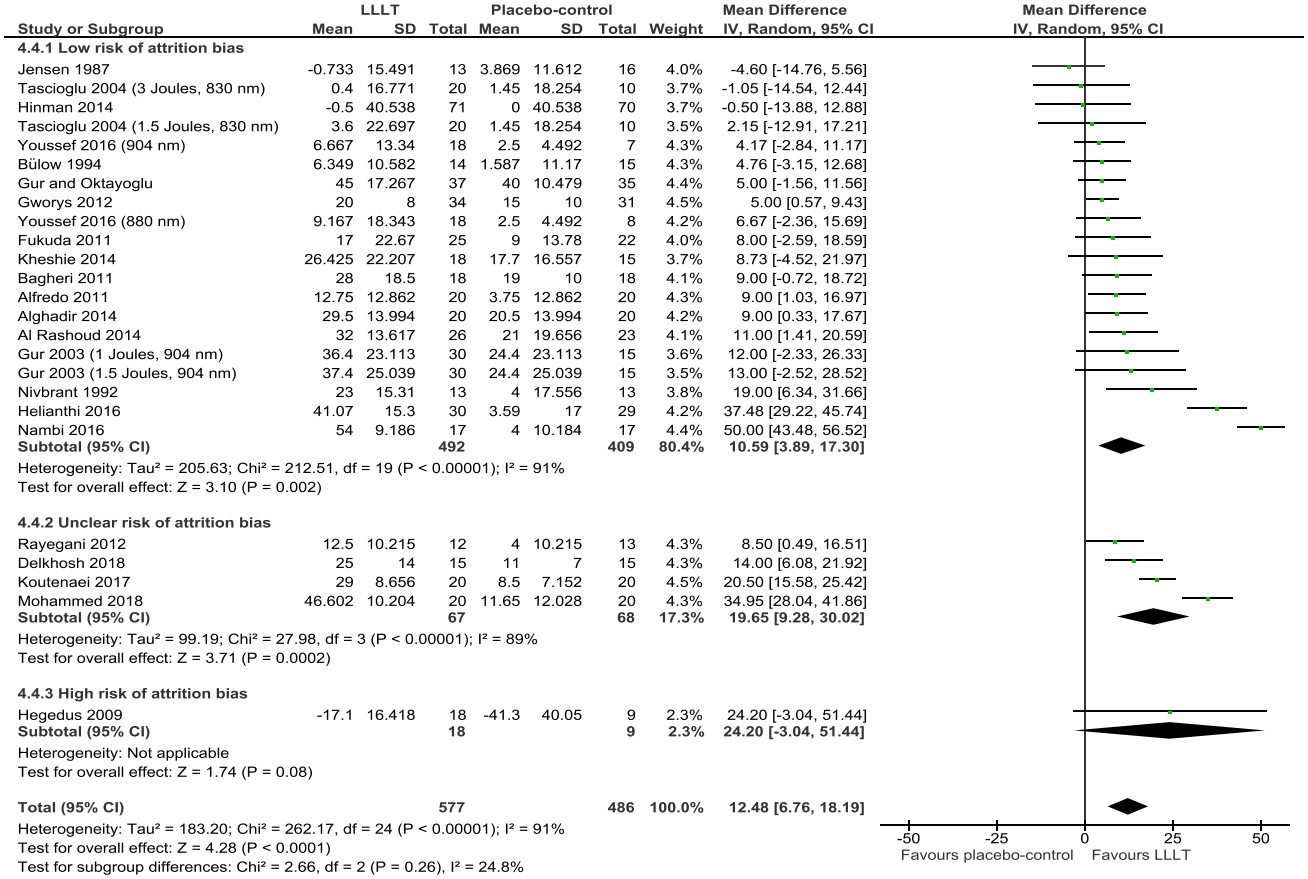

Figure 11 | Pain results - risk of attrition bias (incomplete outcome data)

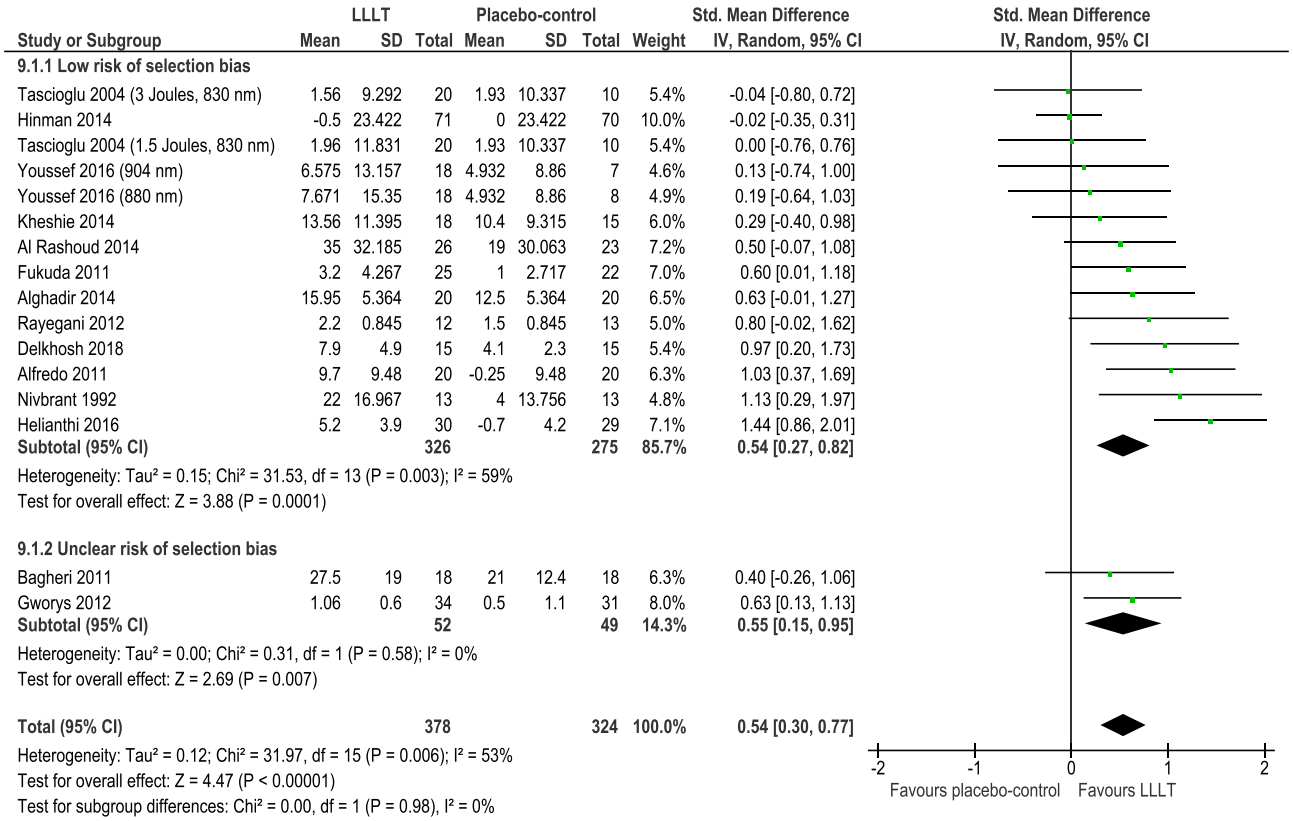

Figure 12 | Disability results - risk of selection bias (random sequence generation)

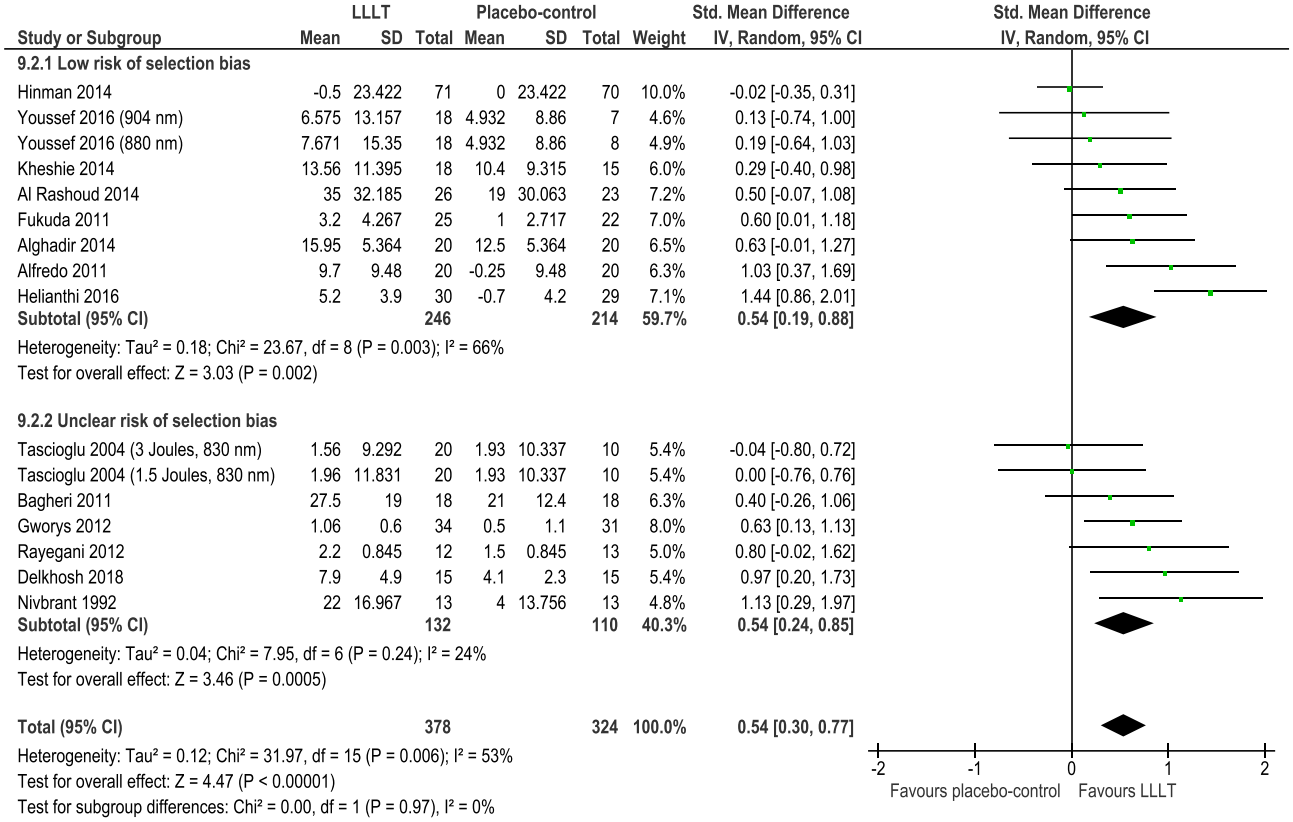

Figure 13 | Disability results - risk of selection bias (allocation concealment)

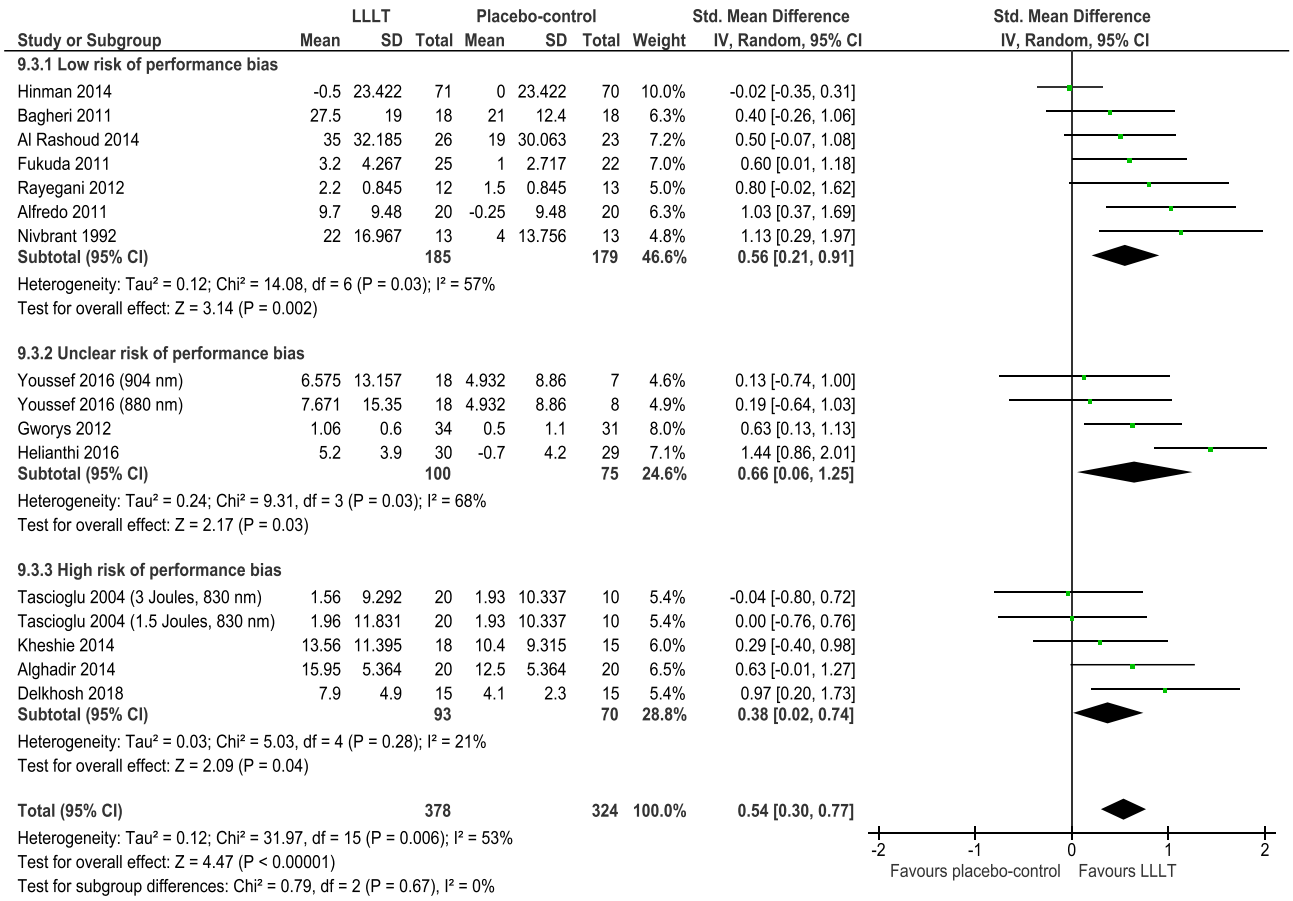

Figure 14 | Disability results - risk of performance bias (blinding of therapist)

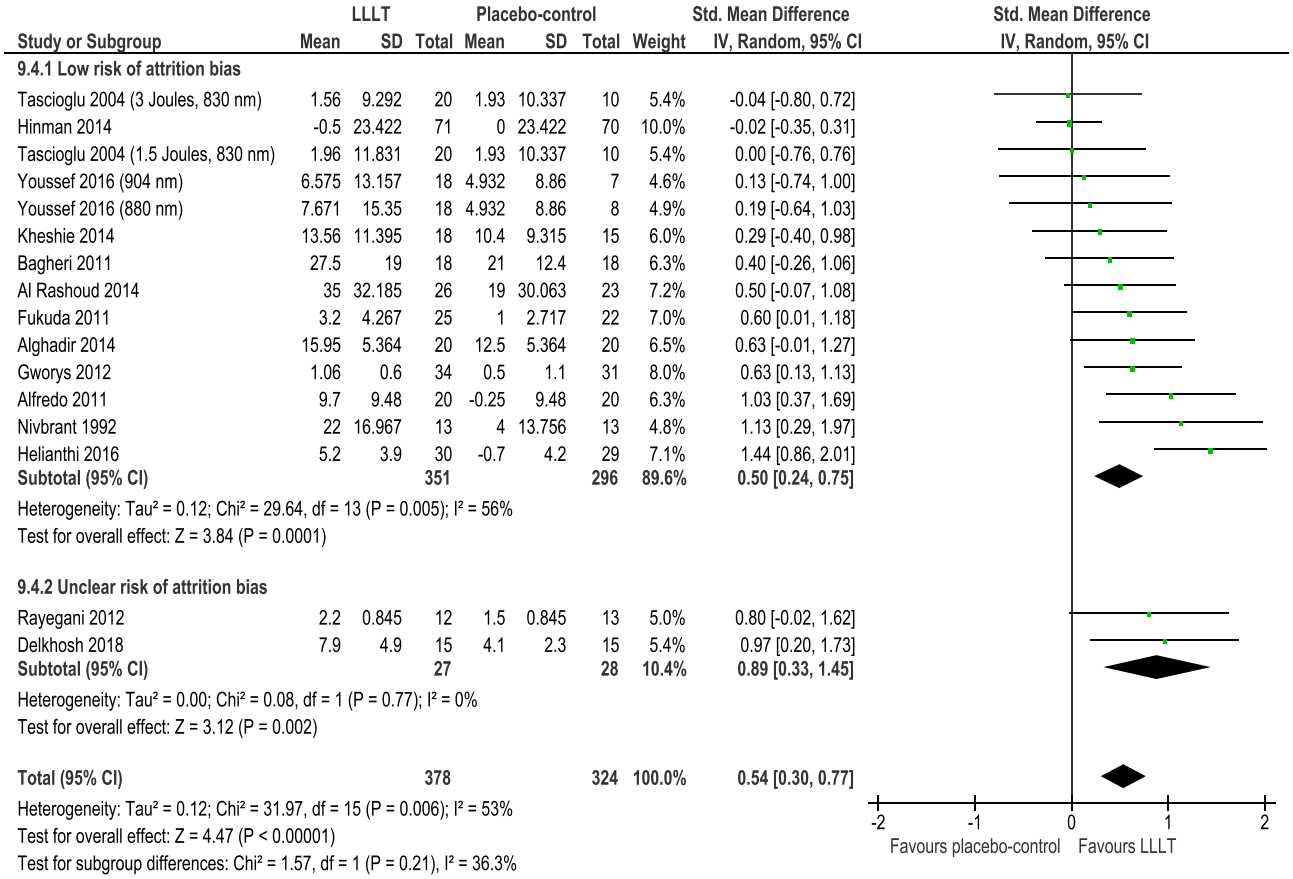

Figure 15 | Disability results - risk of attrition bias (incomplete outcome data)

Support for risk of bias judgments and funding of the included trials

Al Rashoud et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"... a randomization list was produced using software-generated randomised numbers to the randomisation depended on random blocks of 10."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	Low risk	Quote: *"Neither investigator nor the patient knew whether a placebo or active treatment was being administered to only the research assistant had the identifying code to determine which treatment was given."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"Forty-nine patients with knee osteoarthritis were assigned at random into two groups: Active laser group (n = 26) and placebo laser group (n = 23)", "... 49 completed the study ..."*. Our comment: Probably true.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (International Standard Randomised Controlled Trials Number: ISRCTN24010862).

Funding – quote: *"The project was funded by general administration for medical services of Ministry of Interior, Security Forces Hospital; Riyadh, Saudi Arabia."*.

Alfredo et al. 2011

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed by using sealed, randomly filled envelopes describing the treatment group. Patients and the physiotherapist responsible for the evaluation were unaware of randomization results"*. Our comment: Probably done. It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Allocation concealment	Low risk	Quote: *"Patients and the physiotherapist responsible for the randomization were unaware of the randomization results"*. Our comment: Probably true.
Blinding of participants and personnel	Low risk	Quote: "*All patients were treated by the same physiotherapist who had not taken part in the evaluations"*. *"The laser equipment had two identical pens, one for the active treatment and one for the placebo treatment (sealed)"*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"All participants were evaluated by the same blinded physiotherapist"* Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 13% of the included participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Reported in adherence to a protocol (Clinical Trials number: CT01306435).

Funding - quote: *"This study was supported financially by: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) – Foundation of Research Support of São Paulo State and Coordenação de Aperfeic¸oamentode Pessoalde Ni´vel Superior (CAPES) – Coordination for the Improvement of Higher Level – or Education – Personnel. Biostatistics Support Group, Department of Dentistic, School of Odontology, University of São Paulo, São Paulo, Brazil."*.

Alghadir et al. 2013

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed using sealed, randomly filled envelopes"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	High risk	Quote: *"The treatment parameters were identical, but without switching on the machine"*. Our comment: Probably done. The study is described as single-blinded. The experimental group was treated with invisible laser. The physiotherapists treating the participants were not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"(...) all of them completed the study period."*. Our comment: Probably true.
Selective reporting	Low risk	Our comment: Reported as stated in the protocol.

Funding – quote: *"The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project NO RGP-VPP-209."*.

Bagheri et al. 2010

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Quote (translated from Farsi): *"The random distribution of people was done in such a way that the number of male and female patients is the same in both groups"*. Our comment: Not enough information to make a qualified judgment.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Low risk	Quote (translated from Farsi): *"The presence of active or inactive lasers was not known"*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded. The experimental group was treated with invisible laser.
Incomplete data	Low risk	Our comment: 10% of the participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Sponsored by the Semnan University of Science.

Bülow et al. 1994

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized, but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Low risk	Quote: *"The nurse in charge of the randomization key selected the laser or placebo-laser before each treatment"* and *"The blinded settings for patient and physician were maintained"*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcomes of interest described in the method section is missing in the result section.

Funding – quote: *"The study was sponsored by Henny and Helge Holgersen's Foundation and the Bodil Petersen Foundation."*.

Delkhosh et al. 2018

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"… volunteers are randomly allocated to three groups by lottery."*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	High risk	Quotes: *"The patients were randomly assigned to three groups: 1-standard treatment with placebo laser…"* and *"Not blinded"*. Our comment: The investigators claimed the trial was placebo-controlled which is probably true as the participants were treated with invisible laser. Therefore, it seems likely that the investigators statement regarding lack of blinding refers to the therapist.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (Iranian Registry of Clinical Trials number: IRCT201502224549N8).

Funding – quote: *"Vice chancellor for research, Semnan University of Medical Sciences."*.

Fukuda et al. 2011

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"This distribution was made by a secretary who was not involved in the treatment or evaluation, through a draw of sealed opaque envelopes. The envelopes were taken directly to the therapist without the patient having access to the result."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"(...) two identical pens, of which one was active (laser) and the other was sealed (placebo). These were labelled A and B by the project secretary, and only this person knew the true identification of the pens."*. Our comment to the quote: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Physical Therapy Sector, Irmandade da Santa Casa de Misericórdia de São Paulo (ISCMSP), São Paulo, São Paulo, Brazil.

Gur & Oktayoglu

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Patients were randomly assigned to three treatment groups by one of the non-treating authors by drawing 1 of 120 envelopes."*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were sequentially numbered, opaque, and sealed.
Blinding of participants and personnel	High risk	Quote: *"The study was conducted in a double-blind fashion. Subjects and physician were unaware of the code for active or placebo laser until the data analysis was completed but therapist was aware of the code for active or placebo laser."*. Our comment: Probably true. The experimental group was treated with invisible laser. The participants were probably blinded, but the therapist was not.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 7.5% of the participants allocated to the laser group were not evaluated. 12.5% of the participants allocated to the control group were not evaluated. These numbers are unlikely to introduce a relevant bias. Reasons for dropout across groups are similar.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Gur et al. 2003

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Patients were randomly assigned to three treatment groups by one of the non-treating authors by drawing of 1 of 90 envelopes"*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were sequentially numbered, opaque, and sealed.
Blinding of participants and personnel	High risk	Quote: *"The study was conducted in a double-blind fashion. Subjects and physician were unaware of the code for active or placebo laser until the data analysis was completed but therapist was aware of the code for active or placebo laser."*. Our comment: Probably true. The experimental group was treated with invisible laser. The participants were probably blinded, but the therapist was not.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Gworys et al. 2012

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized, but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: *"(...) a placebo group where laser therapy procedures were simulated without actual irradiation."*. Our comment: Probably done. The experimental group was treated with invisible laser. The participants were probably blinded, but there is too little information to judge whether the therapists were blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"laser the therapy sessions were performed once a day, 5 days a week over 2 weeks. Each patient attended 10 sessions."*. Our comment: All participants probably attended to all 10 sessions. The outcomes were assessed immediately after the 10 sessions. Thus, there were probably no dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Hegedus et al. 2009

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was ensured by having patients randomly choose sealed envelopes from a bowl"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. Our comment: Probably true. All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	High risk	Our comment: 50% of the participants in the control group were not evaluated while 100% of the participants in the laser group were evaluated. These numbers are likely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"The authors wish to thank Dr. Gábor Deák for the Doppler examinations and András Tóth for taking the numerous thermographic images."*.

Helianti et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"a randomization list was created using a computer-generated table containing random numbers."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	Unclear risk	Quote: *"Both investigator and participants did not know whether laser acupuncture active treatment or placebo treatment was being administered. Only the researcher and her assistant had the code to determine which treatment was given. Both groups used the same laser device and the same study site. Participant blinding was optimized by using eye mask and headset (...)"*. Our comment: The experimental group was treated with invisible laser. The investigator and participants were probably blinded, but it is unclear who administered the therapy and if this person was blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 4.8% of the participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding sources: Not stated.

Hinman et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"An investigator (K.N.) accessed the computerized randomization to reveal allocation."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Participant codes for randomized laser treatment groups were pre-programmed into the laser machines by an independent biomechanical engineer to permit blinding of acupuncturist and participants in these groups."*. Our comment: Probably true.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 8.45% and 17.14% had dropped out from the experimental and placebo group at week 12, respectively. Intention to treat analysis was used and this analysis and the results did not differ from the per-protocol analysis.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (Australian New Zealand Clinical Trials Registry Number: ACTRN12609001001280).

Funding – quote: *"Funding/Support: This trial was funded by the National Health and Medical Research Council (project 566783). Drs Hinman and Bennell are both funded in part by Australian Research Council Future Fellowships (FT130100175 and FT0991413, respectively). Dr McCrory is funded in part by a National Health and Medical Research Council Practitioner Fellowship (1026383). Dr Pirotta is funded in part by a National Health and Medical Research Council Career Development Fellowship (1050830). Dr Williamson was funded in part by a National Health and Medical Research Council grant (1004233). Role of the Funder/Sponsor: The study sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; reparation, review, or approval of the manuscript; and decision to submit the manuscript for publication."*.

Jensen et al. 1987

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: (Translated from Danish) *"Two coded laser devices of the same appearance was utilized in the trial. One of the devices was inactive and served as control. The other was active with infrared laser."*. Our comment: The experimental group was treated with invisible laser. The participants were probably blinded, but it is unknown whether the therapists were blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are assessed and reported by the participants. The experimental group was treated with invisible laser.
Incomplete data	Low risk	Our comment: 1 participant was not evaluated.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Kheshie et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed simply by assigning a specific identification number for each patient. These numbers were randomized into three groups using the SPSS program"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	High risk	Our comment: The study is described as single-blinded and the participants were probably blinded. Thus, the therapist was not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 15% and 0% dropped out of the placebo and experimental group, respectively. These numbers are unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"This research received a grant from the Institute of Scientific Research and Revival of Islamic Heritage at Umm Al-Qura University, Makkah, Saudi Arabia."*.

Koutenaei et al. 2017

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"…were assigned randomly (using random blocks) …"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: The use of random blocks was probably sufficient.
Blinding of participants and personnel	Low risk	Quote: *"The placebo group also lasted for 70 seconds in these places, but the laser had no output"*. Our comment: Both participants and therapists were probably blinded because they described the study as double-blinded and treated the intervention group with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"The study was supported by the Department of Physiotherapy at the University of Social Welfare and Rehabilitation Sciences."*.

Mohammed et al. 2017

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	High risk	Quote: *"(…) placebo laser (laser probe is directed to the same acupoints while the device is off).".* Our comment: Probably done. The experimental group was treated with invisible laser. The study is described as single-blinded and the participants were probably blinded. As there was no description of a blinding procedure of the therapist, we assume that this person was not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: Not stated. The authors state: *"The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication."*.

Nambi et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Thirty-four subjects were randomized into two groups (active and placebo) by an investigator who is not involved in assessment, diagnosis or treatment. Randomization was performed by using sealed randomly filled envelopes from a bowl containing an equal number of slips with either number 1 or 2"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Subjects and the physiotherapist responsible for the evaluation were unaware of randomization results.". "super pulsed laser with (…) or with a placebo probe (…) of the same appearance and display."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"All subjects were evaluated by the same blinded physiotherapist"*. Our comment: Probably done. All outcomes of interest are assessed and reported by the participants who were probably blinded.
Incomplete data	Low risk	Quote: *"The required sample for the study was 17 subjects per group". "All 34 subjects completed the study with the 8-week follow-up evaluation.".* Our comment: Probably true.
Selective reporting	Low risk	Our comment: No outcomes of interest described in the method section was missing in the result section.

Funding - quote: *"Authors are grateful to the Deanship of scientific Research, Prince Sattam Bin Abdul Aziz University, Al-Kharj, Saudi Arabia for the financial support to carry out this project no 2015/01/4375. Research funding program: Specialized Research Grant program (Health)."*.

Nivbrant et al. 1992

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Our comment: Randomization was performed by drawing of randomly filled envelopes describing the treatment group.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were sequentially numbered, opaque and sealed.
Blinding of participants and personnel	Low risk	Quote (translated from Swedish): *"The placebo emitter was visually identical to the active laser. A practitioner otherwise not involved in the trial treated the participants with laser. The practitioner was unaware of which was the active and inactive laser."*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor (detection bias)	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 13% in each group were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Rayegani et al. 2012

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Randomization was ensured by having patients randomly choose sealed envelopes from a bowl.
Allocation concealment	Unclear risk	Our comment: It is unclear whether the envelopes were opaque.
Blinding of participants and personnel	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. *"The placebo group was treated with an ineffective probe (power 0 mW) and with the same method."*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Tascioglu et al. 2004

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Sixty patients, who fulfilled the entry criteria, were admitted to the study and they were randomly divided into three groups using numbered envelopes"*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether the envelopes were sealed and opaque.
Blinding of participants and personnel	High risk	Our comment: The study is described as single-blinded and the participants were probably blinded. Thus, the therapist was probably not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are assessed and reported by the participants who were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Youssef et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"They were assigned randomly to three groups by a blinded and independent research assistant who opened sealed envelopes that contained a computer-generated randomization card according to the recruitment diagram."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: *"(...) in the placebo group, procedure was identical but without emission of energy. The laser equipment had two identical pens, one for the active treatment and one for the placebo treatment (sealed)."*. Our comment: Probably done. The experimental group was treated with invisible laser. The participants were probably blinded, but there was no information regarding blinding of therapists.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	1 participant was not evaluated.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

LLLT with and without exercise therapy

Subgroup analyses were performed to assess the impact of exercise therapy on the effect of LLLT in a treatment package (results are from immediately after the end of therapy, primarily). LLLT was significantly superior to the placebo-control both with and without exercise therapy (figure 16-17). The levels of statistical heterogeneity were unaltered in the pain analyses (figure 16), and slightly lowered in the disability analysis (figure 17).

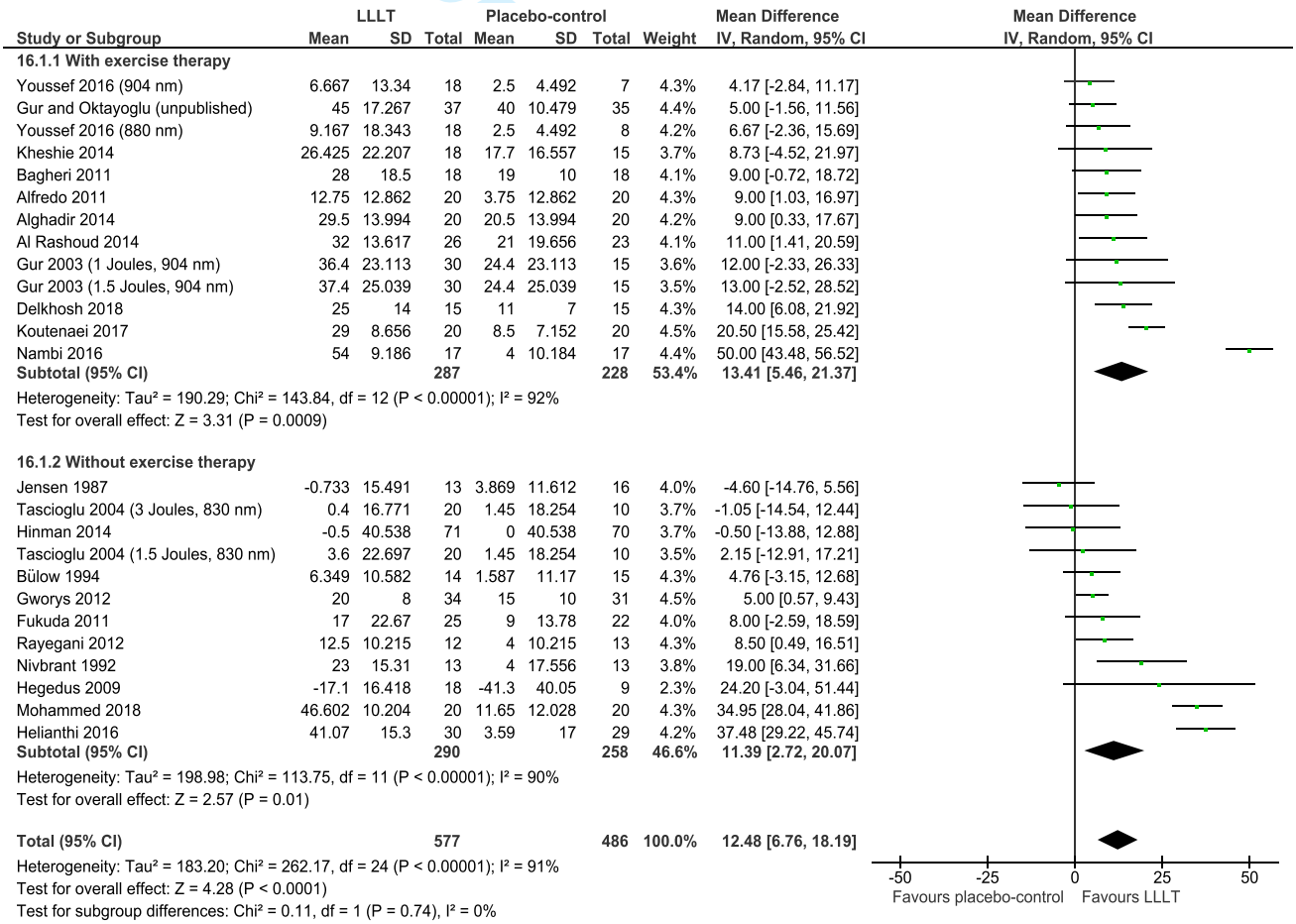

Figure 16 | LLLT with and without exercise therapy (pain)

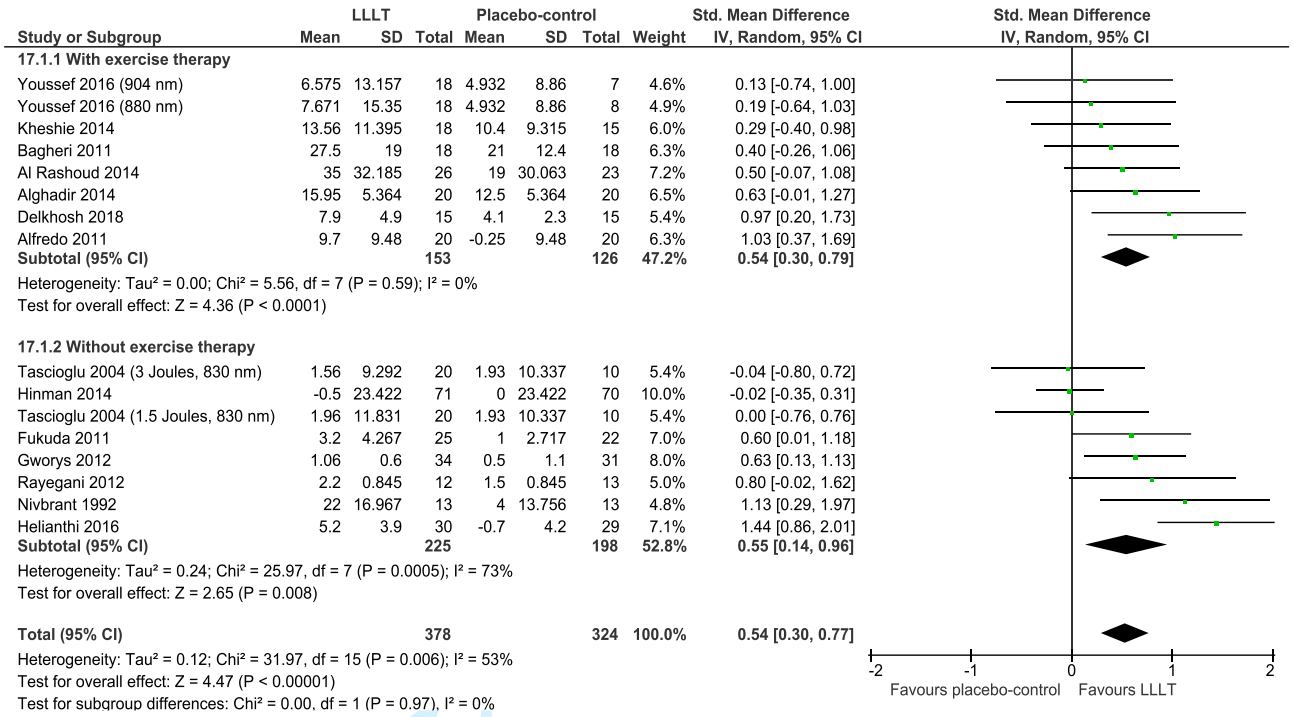

Figure 17 | LLLT with and without exercise therapy (disability)

Mean Difference vs Standardized Mean Difference

The levels of statistical heterogeneity changed only negligible when we switched from the Mean Difference (MD) method to the Standardized Mean Difference (SMD) method (figure 18-21). The trial by Hegedus et al. was omitted from these analyses as they solely reported final scores, and it is inappropriate to mix final scores with change scores in SMD analyses (figure 18-19).

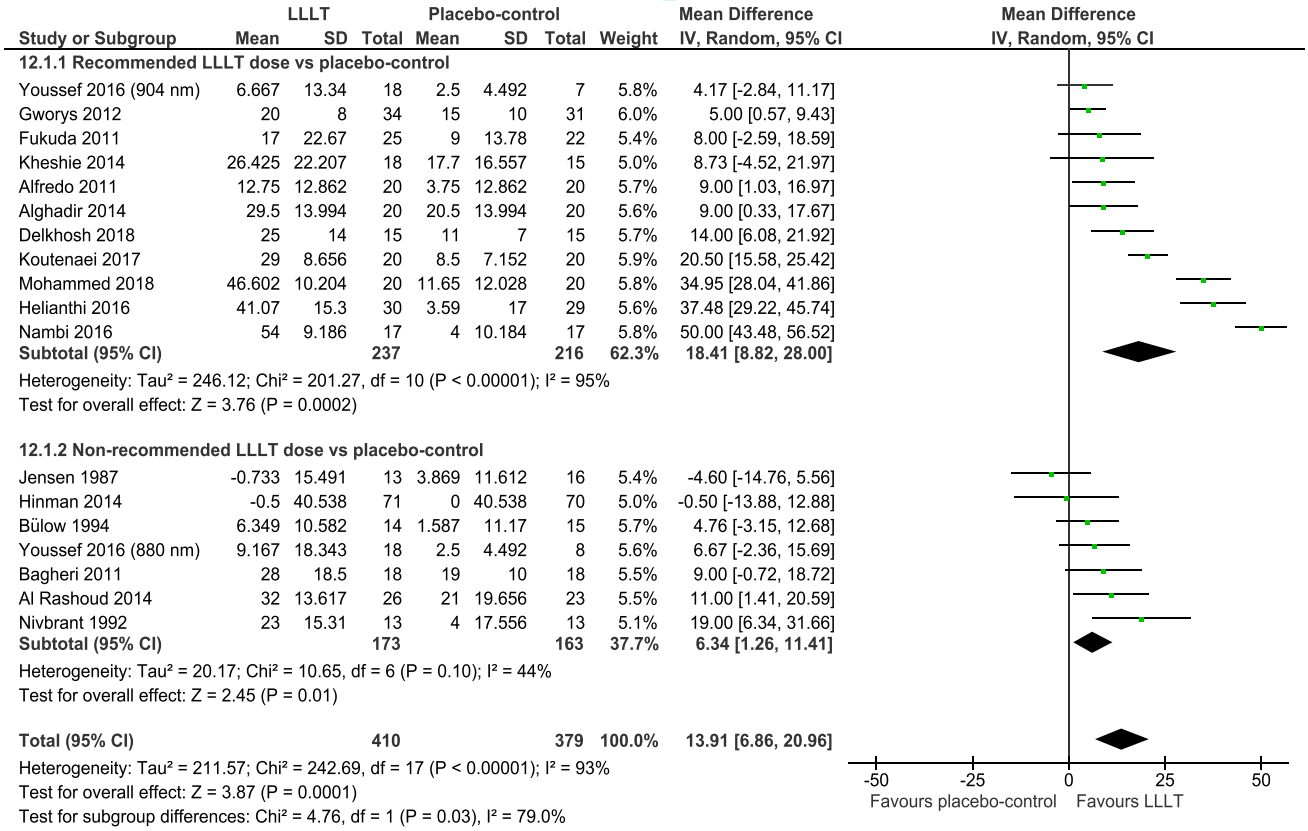

Figure 18 | Mean Difference (pain results from immediately after the end of therapy)

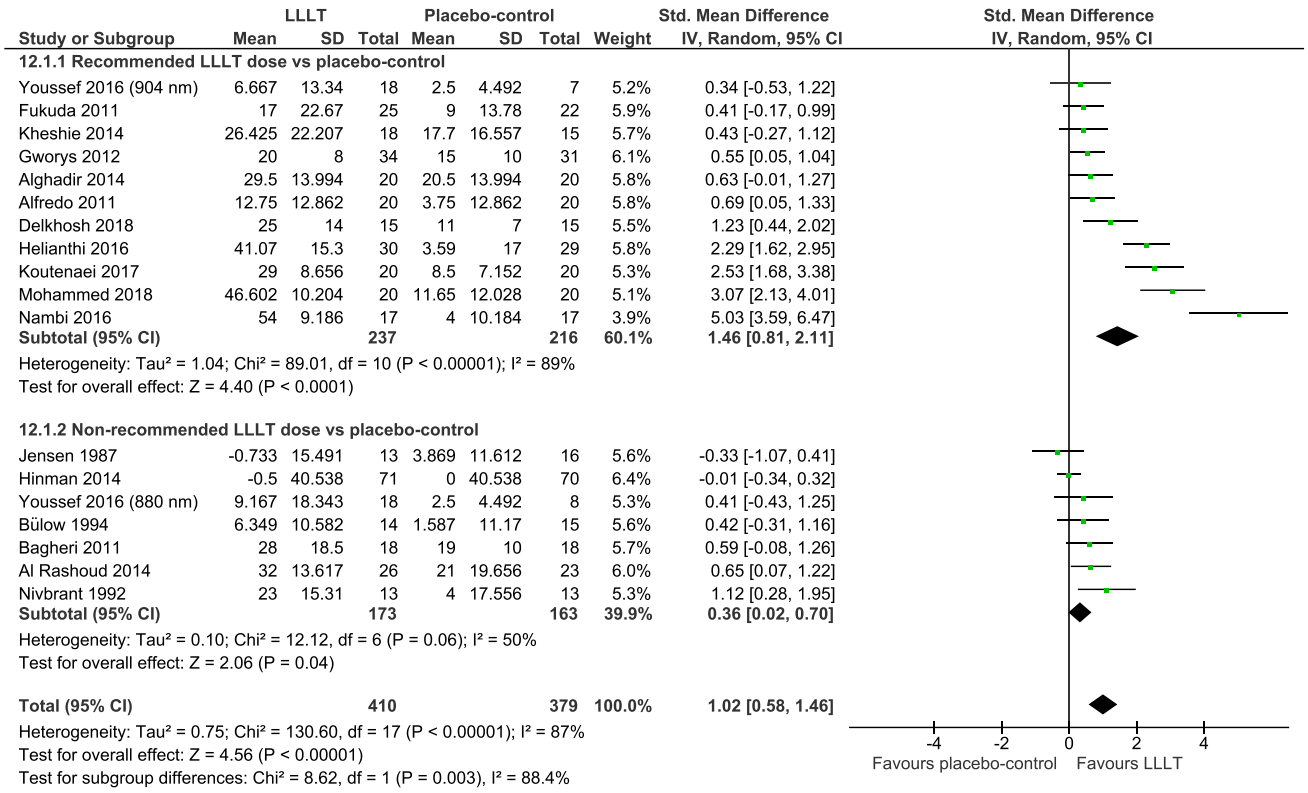

Figure 19 | Standardized Mean Difference (pain results from immediately after the end of therapy)

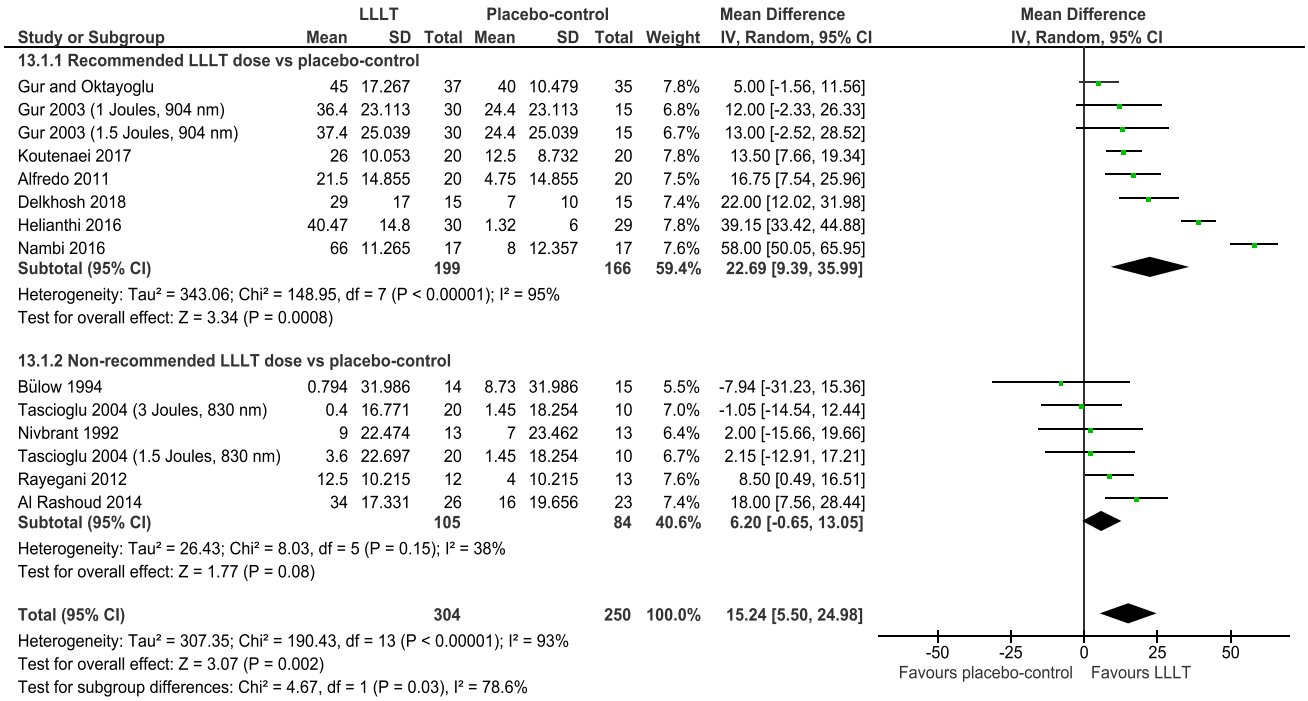

Figure 20 | Mean Difference (pain results from 2-12-weeks follow-ups)

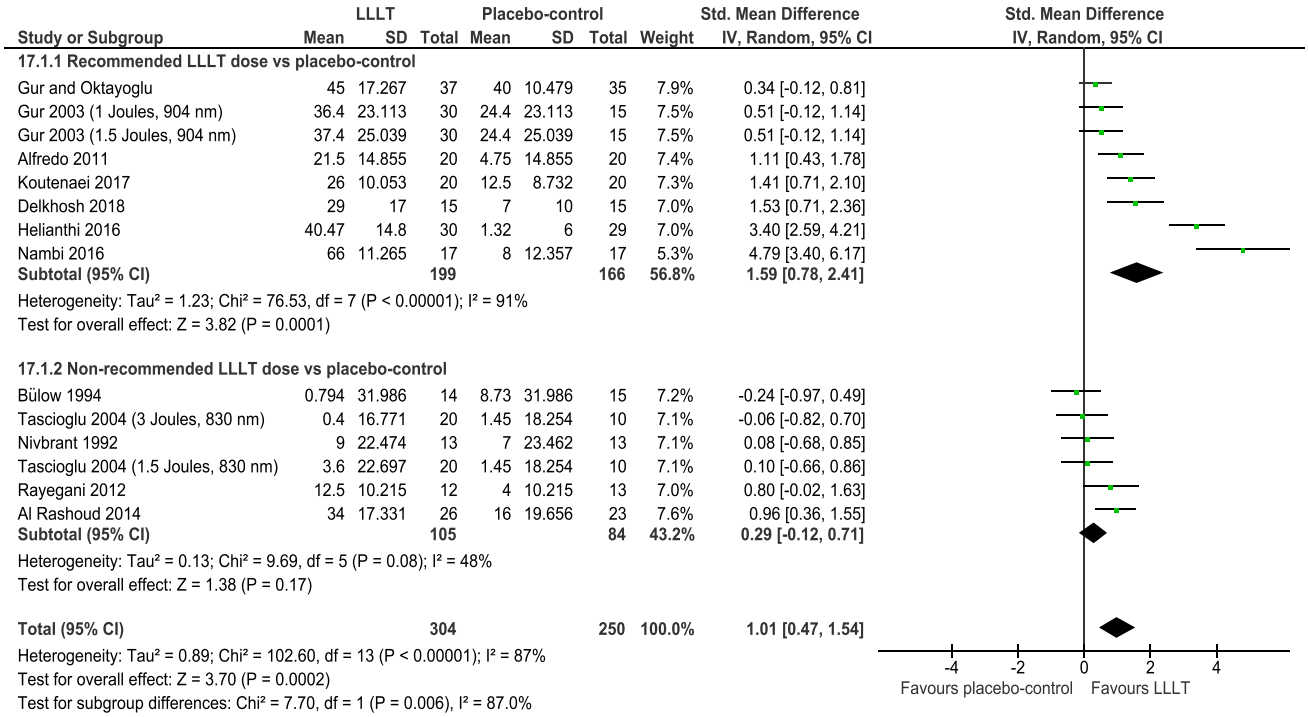

Figure 21 | Standardized Mean Difference (pain results from 2-12-weeks follow-ups)

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PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3 + PROSPERO protocol
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3 + PROSPERO protocol
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 3 + PROSPERO protocol
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 3 + PROSPERO protocol
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4 + PROSPERO protocol
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5-8 (table 1-2) + PROSPERO protocol
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 3-4 + PROSPERO protocol + supplementary material
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4 + PROSPERO protocol
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4 + supplementary material + PROSPERO protocol

PRISMA checklist (continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4 + 9 + supplementary material
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 9 + supplementary material
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 4-5 + supplementary material (table of excluded articles)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5-8 (table 1-2)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 9 (figure 6) + supplementary material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	figure 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 8-9 + figure 2-5 + supplementary material
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9 + supplementary material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 9 + supplementary material
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11 + PROSPERO protocol

BMJ Open

Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials

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Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials

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Abstract
Objectives Low-Level Laser Therapy (LLLT) is not recommended in major knee osteoarthritis (KOA) treatment guidelines. We investigated whether a LLLT dose-response relationship exists in KOA.
Design Systematic review and meta-analysis.
Data sources Eligible articles were identified through PubMed, Embase, CINAHL, PEDro and CENTRAL on the 18th February 2019, reference lists, a book, citations and experts in the field.
Eligibility criteria for selecting studies We solely included randomized placebo-controlled trials involving participants with KOA according to the American College of Rheumatology and/or Kellgren/Lawrence criteria, in which LLLT was applied to participants' knee(s). There were no language restrictions.
Data extraction and synthesis The included trials were synthesised with random effects meta-analyses and subgrouped by dose using the World Association for Laser Therapy treatment recommendations. Cochrane's risk of bias tool was used.
Results 22 trials (N = 1063) were meta-analysed. Risk of bias was insignificant. Overall, pain was significantly reduced by LLLT compared to placebo at the end of therapy (14.23 mm VAS [95% CI: 7.31 to 21.14]) and during follow-ups 2-12 weeks later (15.92 mm VAS [95% CI: 6.47 to 25.37]). The subgroup analysis revealed that pain was significantly reduced by the recommended LLLT doses compared to placebo at the end of therapy (18.71 mm [95% CI: 9.42 to 27.99]) and during follow-ups 2-12 weeks after the end of therapy (23.23 mm VAS [95% CI: 10.60 to 35.86]). The pain reduction from the recommended LLLT doses peaked during follow-ups 2-4 weeks after the end of therapy (31.87 mm VAS significantly beyond placebo [95% CI: 18.18 to 45.56]). Disability was also statistically significantly reduced by LLLT. No adverse events were reported.
Conclusion LLLT reduces pain and disability in KOA at 4-8 Joules with 785-860 nm wavelength and at 1-3 Joules with 904 nm wavelength per treatment spot.
PROSPERO registration number CRD42016035587.

Keywords Phototherapy; Laser therapy; Knee osteoarthritis; Systematic review; Meta-analysis

Strengths and limitations of this study

- The review was conducted in conformance with a detailed a priori published protocol, which included e.g. laser dose subgroup criteria.
- No language restrictions were applied; four (18%) of the included trials were reported in non-English language.
- A series of meta-analyses were conducted to estimate the effect of Low-Level Laser Therapy on pain over time.
- Three persons each independently extracted the outcome data from the included trial articles to ensure high reproducibility of the meta-analyses.
- The review lacks quality of life analyses, a detailed disability time-effect analysis and direct comparisons between Low-Level Laser Therapy and other interventions.

Introduction

Approximately 13% of women and 10% of men in the population aged ≥ 60 years suffer from knee osteoarthritis (KOA) in the USA.[1] KOA is a degenerative inflammatory disease affecting the entire joint and is characterised by progressive loss of cartilage and associated with pain, disability and reduced quality of life (QoL).[1] Increased inflammatory activity is associated with higher pain intensity and more rapid KOA disease progression.[1 2]

Some of the conservative intervention options for KOA are exercise therapy, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and anti-inflammatory Low-Level Laser Therapy (LLLT). There is evidence that exercise therapy reduces pain and disability and improves QoL in persons with KOA.[3 4] NSAIDs are recommended in most KOA clinical treatment guidelines and is probably the most frequently prescribed therapy category for osteoarthritis, despite intake of these drugs is associated with negative side effects[5], which is problematic, especially since the disease requires long-term treatment. Furthermore, a recently published network meta-analysis indicates that the pain relieving effect of NSAIDs in KOA beyond placebo is small to moderate (depending on drug type).[6] Likewise, in the first systematic review on this topic, the pain relieving effect of NSAIDs was estimated to be only 10.1 mm on the 0-100 mm Visual Analogue Scale (VAS) better than placebo.[7]

LLLT is a non-invasive treatment modality[8 9], which has been reported to induce anti-inflammatory effects.[9-14] LLLT was compared to NSAID in rats with KOA by Tomazoni et al. in a laboratory; NSAID (10 mg diclofenac/knee/session) and LLLT (830 nm wavelength, 6 Joules/knee/session) reduced similar levels of inflammatory cells and metalloproteinase (MP-3 and MP-13). In addition, LLLT reduced the expression of pro-inflammatory cytokines (interleukin-1β and -6 and tumour necrosis factor α), myeloperoxidase and prostaglandin E_2 significantly more than NSAID did.[10 11]

LLLT has been applied to rabbits with KOA three times per week for eight weeks in a placebo-controlled experiment by Wang et al. At the end of treatment week six, they found that LLLT had significantly reduced pain and synovitis and the production of interleukin-1β, inducible nitric oxide synthase and MP-3 and slowed down loss of Metallopeptidase Inhibitor 1. Two weeks later, LLLT had significantly reduced MP-1 and MP-13 and slowed down loss of collagen II, aggrecan and transforming growth factor beta, and the previous changes were sustained.[12] These findings indicate that the effects of LLLT increase over time.

Pallotta et al. conducted a study on LLLT in rats with acute knee inflammation, which demonstrated that even though LLLT (810 nm) significantly enhanced cyclooxygenase (COX-1 and -2) expression it significantly reduced several other inflammatory makers, i.e., leukocyte infiltration, myeloperoxidase, interleukin-1 and -6 and especially prostaglandin E_2. Pallotta et al. hypothesised that the increase in COX levels by LLLT was involved in a production of inflammatory mediators related to the resolution of the inflammatory process.[14]

LLLT is not recommended in major osteoarthritis treatment guidelines. LLLT for KOA was mentioned in the European League Against Rheumatism (EULAR) osteoarthritis guidelines (2018) but not recommended[15], and in the Osteoarthritis Research Society International (OARSI) guidelines (2018), it was stressed that LLLT should not be considered a core intervention in the management of KOA.[16]

This may be partly due to conflicting results of two recently published systematic reviews on the current topic (Huang et al. 2015 and Rayegani et al. 2017).[8 17] The conflicting results may arise from omission of relevant trials[8 17-23] and unresolved LLLT dose-related issues. Only Huang et al. conducted a LLLT dose-response relationship investigation in KOA, i.e., by subgrouping the trials by laser dose, but they did not consider that World Association for Laser Therapy (WALT) recommends applying four times the laser dose with continuous irradiation compared to super-pulsed irradiation.[17 22 24-26] Thus, it was unknown whether LLLT is effective in KOA, and we saw a need for a new systematic review.

The objectives of the current review were to estimate the effectiveness of LLLT in KOA regarding knee pain, disability and QoL, and we only considered randomized placebo-controlled clinical trials (RCTs) for inclusion to minimize risk of bias.

Methods

This review was conducted in adherence to a PROSPERO protocol (number CRD42016035587) and is reported in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis statement 2009.[27]

Literature search and selection of studies

Any identified study was included if it was a placebo-controlled RCT involving participants with KOA according to the American College of Rheumatology tool and/or a radiographic inspection with the Kellgren/Lawrence (K/L) criteria, in which LLLT was applied to participants' knee(s) and self-reported pain, disability and/or QoL was reported. There were no language restrictions.

We updated a search for eligible articles indexed in PubMed, Embase, CINAHL, PEDro and CENTRAL on the 18th February 2019. The database search strings contained synonyms for LLLT and KOA, and keywords were added when optional. The PubMed search string is available in the supplementary material. The search was continued by reading reference lists of all the eligible trial and relevant review articles[8 17 28], citations[29-33] and a laser book[34] and involving experts in the field.

Two reviewers (MBS and JMB) each independently selected the trial articles. Both reviewers scrutinised the titles/abstracts of all the publications identified in the search, and any accessible full-text article was retrieved if it was judged potential eligible by at least one reviewer. Both reviewers evaluated the full texts of all potentially eligible retrieved articles and made an independent decision to include or exclude each article, with close attention to the inclusion criteria. When selection disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Any retrieved article not fulfilling the inclusion criteria was omitted and listed with reason for exclusion.

Risk of bias analysis

Two reviewers (MBS and JJ) each independently evaluated all included trials for risk of bias at the outcome level, using the Cochrane Collaboration's risk of bias tool.[35] When risk of bias disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Likelihood of publication bias was assessed with graphical funnel plots.[35]

Data-extraction and meta-analysis

Three reviewers (MBS, JMB and KVF) each independently extracted the data for meta-analysis. Two of the reviewers (MBS and KVF) each independently collected the other trial characteristics. The data-extraction forms were subsequently compared, and data disagreements were resolved by consensus-based discussions. Summary data were extracted, unless published individual participant data were available.[21] The results from the included trials for statistical analysis were selected from outcome scales in adherence to hierarchies published by Juhl et al.[36]

Pain intensity was the primary outcome. As pain reported with continuous, numeric and categorical/Likert scales highly correlates with pain measured using the VAS, the scores of all pain scales were transformed to 0-100%, corresponding to 0-100 mm VAS.[37] The pain results were combined with the Mean Difference (MD) method, primarily using change scores, i.e., when only final scores could be obtained from a trial, change and final scores were mixed in the analysis, since the MD method allows for this without introducing bias.[35]

Self-reported disability results were synthesized using the Standardized Mean Difference (SMD) method using change scores solely. The SMD was adjusted to Hedges' *g* and interpreted as follows: SMDs of 0.2, ~ 0.5, and > 0.8 represent a small, moderate and large effect, respectively.[35]

Lack of QoL data prohibited an analysis of this outcome.

Random effects meta-analyses were conducted, and impact from heterogeneity (inconsistency) on the analyses was examined using I^2 statistics. An I^2 value of 0% indicates no inconsistency, and an I^2 value of 100% indicates maximal inconsistency[35]; the values were categorised as low (25%), moderate (50%) and high (75%).[38]

Standard deviations (SD) for analysis were extracted or estimated from other variance data in a pre-specified prioritised order: (1) SD, (2) standard error, (3) 95% confidence interval, (4) P-value, (5) interquartile range, (6) median of correlations, (7) visually from graph or (8) other methods.[35]

The trials were subgrouped by adherence and non-adherence to the WALT recommendations for laser dose per treatment spot, as pre-specified. WALT recommends irradiating the knee joint line/synovia with the following doses per treatment spot: ≥ 4 Joules using 5-500 mW mean power 780-860 nm wavelength laser and/or ≥ 1 Joules using 5-500 mW mean power (> 1000 mW peak power) 904 nm wavelength laser.[24 25]

The main meta-analyses were conducted using two pre-specified time points of assessment, i.e., immediately after the end of LLLT and last time point of assessment 1-12 weeks after the end of LLLT (follow-up).

MBS performed the meta-analyses, under supervision of JMB, using the software programs Excel 2016 (Microsoft) and Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

Results

In total, 2735 publications were identified in the search, of which 22 trial articles were judged eligible and included in the review (N = 1089) (figure 1 and table 1-2) with data for meta-analysis (N = 1063). Four included trials were not reported in the English language[19 21 23 39] and one included trial was unpublished (Gur and Oktayoglu). Excluded articles initially judged potentially eligible were listed with reasons for omission (supplementary material).

Figure 1 | Flow chart illustrating the trial identification process
LLLT = Low-Level Laser Therapy.

At the group level, the mean age of the participants was 60.25 (50.11-69) years (data from 19 trials), the mean percentage of women was 69.63 (0-100) (data from 17 trials), the mean BMI of the participants was 29.55 (25.8-38) (data from 14 trials), the mean of median K/L grades was 2.37 (data from 13 trials) and the mean baseline pain was 63.61 mm VAS (35.25-92) (data from 22 trials). LLLT was used as an adjunct to exercise therapy in eleven trials. The mean duration of the treatment periods was 3.53 weeks with the recommended LLLT doses and 3.89 weeks with the non-recommended LLLT doses (table 1-2). Non-recommended LLLT doses were applied in nine of the trials. That is, Al Rashoud et al.[31], Bülow et al.[20], Tascioglu et al.[40] and Bagheri et al.[23] applied too few (< 4) Joules per treatment spot with 830 nm wavelength, Jensen et al.[21], Nivbrant et al.[19] and Hinman et al.[41] applied too few (< 1) Joules per treatment spot with 904 nm wavelength and Youssef et al.[42] (one group) and Rayegani et al.[43] used continuous laser with too long of a wavelength (880 nm) (table 2). No adverse event was reported by any of the trial authors. None of the authors stated receiving funding from the laser industry (supplementary material).

Table 1 | Characteristics of the included trials

First author	Intervention group at baseline	Control group at baseline	Intervention vs control programme	Outcome scales, week of reassessment
Al Rashoud 2014[31]	N: 26 Women: 62% Age: 52 years BMI: 38 VAS pain: 64 mm K/L: -	N: 23 Women: 65% Age: 56 years BMI: 37.1 VAS pain: 59 mm K/L: -	3 weeks of exercise therapy, advice and LLLT vs 3 weeks of exercise therapy, advice and sham LLLT	Pain: VAS (movement) Disability: SKFS QoL: - Week of assessment: 2, **3**, **9**, 29
Alfredo 2011/2018[29] [44]	N: 24 Women: 75% Age: 61.15 years BMI: 30.16 VAS pain: 53.2 mm K/L: 3	N: 22 Women: 80% Age: 62.25 years BMI: 29.21 VAS pain: 35.4 mm K/L: 2	3 weeks of LLLT followed by 8 weeks of exercise therapy vs 3 weeks of sham LLLT followed by 8 weeks of exercise therapy	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, **11**, 24, 37
Alghadir 2014[32]	N: 20 Women: 50% Age: 55.2 years BMI: 32.34 VAS pain: 74.5 mm K/L: 2	N: 20 Women: 40% Age: 57 years BMI: 33.09 VAS pain: 75.5 mm K/L: 2	4 weeks of exercise therapy, heat packs and LLLT vs 4 weeks of exercise therapy, heat packs and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **4**
Bagheri 2011[23]	N: 18 Women: 83.13% Age: 58.32 years BMI: 28.87 VAS pain: 67 mm K/L: -	N: 18 Women: 83.13% Age: 56.14 years BMI: 27.66 VAS pain: 59 mm K/L: -	5 weeks of exercise therapy, therapeutic ultrasound, TENS and LLLT vs 5 weeks of exercise therapy, therapeutic ultrasound, TENS and sham LLLT	Pain: WOMAC (VAS) 0-100 Disability: WOMAC QoL: - Week of assessment: **5**
Bülow 1994[20]	N: 14 Women: - Age: - BMI: - VAS pain: 65.08 mm K/L: -	N: 15 Women: - Age: - BMI: - VAS pain: 56.35 mm K/L: -	3 weeks of LLLT vs 3 weeks of sham LLLT	Pain: 0-121 Likert scale (movement/rest) Disability: - QoL: - Week of assessment: **3**, **6**
Delkhosh 2018[39]	N: 15 Women: 100% Age: 55.9 years BMI: 26.5 VAS pain: 57 mm K/L: -	N: 15 Women: 100% Age: 58.3 years BMI: 27.8 VAS pain: 45 mm K/L: -	2 weeks of exercise therapy, therapeutic ultrasound, TENS and LLLT vs 2 weeks of exercise therapy, therapeutic ultrasound, TENS and sham LLLT	Pain: VAS Disability: WOMAC QoL: - Week of assessment: **2**, **8**
Fukuda 2011[30]	N: 25 Women: 80% Age: 63 years BMI: 30 VAS pain: 61 mm K/L: 2	N: 22 Women: 64% Age: 63 years BMI: 30 VAS pain: 62 mm K/L: 2	3 weeks of LLLT vs 3 weeks of sham LLLT	Pain: VNSP (movement) Disability: Lequesne QoL: - Week of assessment: **3**
Gur 2003[33] (1.5 Joules)	N: 30 Women: 83.3% Age: 58.64 years BMI: 31.17 VAS pain: 73.2 mm	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**

	K/L: 2	K/L: 2		
Gur 2003[33] (1 Joules)	N: 30 Women: 76.7% Age: 59.8 years BMI: 28.49 VAS pain: 74.4 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**
Gur and Oktayoglu	N: 40 Women: 75% Age: 58.2 years BMI: 29.11 VAS pain: 88 mm K/L: 3	N: 40 Women: 72.5% Age: 58.26 years BMI: 30.11 VAS pain: 92 mm K/L: 3	14 weeks of exercise and 2 weeks of LLLT vs 14 weeks of exercise and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: 6, 10, **14**
Gworys 2012[18]	N: 34 Women: - Age: 57.6 BMI: - VAS pain: 54 mm K/L: -	N: 31 Women: - Age: 67.7 BMI: - VAS pain: - K/L: -	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: VAS Disability: Lequesne QoL: - Week of assessment: **2**
Hegedus 2009[45]	N: 18 Women: - Age: - BMI: - VAS pain: 57.5 mm K/L: 2	N: 17 Women: - Age: - BMI: - VAS pain: 56.2 mm K/L: 2	4 weeks of LLLT vs 4 weeks of sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**, 6, **12**
Helianthi 2016[46]	N: 30 Women: 60% Age: 69 years BMI: 25.8 VAS pain: 60.2 mm K/L: 3	N: 29 Women: 82.8% Age: 68 years BMI: 26.3 VAS pain: 54.1 mm K/L: 3	5 weeks of LLLT vs 5 weeks of sham LLLT	Pain: VAS (movement) Disability: Lequesne QoL: - Week of assessment: 2, **5**, **7**
Hinman 2014[41]	N: 71 Women: 39% Age: 63.4 years BMI: 30.7 VAS pain: 41.5 mm K/L: -	N: 70 Women: 56% Age: 63.8 years BMI: 28.8 VAS pain: 43 mm K/L: -	12 weeks of LLLT vs 12 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: AQoL-6D Week of assessment: **12**, 52
Jensen 1987[21]	N: 13 Women: - Age: - BMI: - VAS pain: 67 mm K/L: -	N: 16 Women: - Age: - BMI: - VAS pain: 72.6 mm K/L: -	1 week of LLLT vs 1 week of sham LLLT	Pain: 0-21 (movement) Disability: - QoL: - Week of assessment: **1**
Kheshie 2014[47]	N: 18 Women: 0% Age: 56.56 years BMI: 28.62 VAS pain: 76.8 mm K/L: 2.5	N: 15 Women: 0% Age: 55.6 years BMI: 28.51 VAS pain: 78.7 mm K/L: 2.5	6 weeks of exercise and LLLT vs 6 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **6**
Koutenaei 2017[48]	N: 20 Women: 85% Age: 52.3 years BMI: 28.4 VAS pain: 74 mm K/L: 3	N: 20 Women: 80% Age: 53 years BMI: 28.6 VAS pain: 65.5 mm K/L: 3	2 weeks of exercise and LLLT vs 2 weeks of exercise and sham LLLT	Pain: VAS (movement) Disability: - QoL: - Week of assessment: **2**, **4**
Mohammed 2018[49]	N: 20 Women: 85% Age: 55.25 years BMI: ≥ 25 VAS pain: 70 mm K/L: 2	N: 20 Women: 85% Age: 50.11 years BMI: ≥ 25 VAS pain: 80 mm K/L: 2	4 weeks of LLLT vs 4 weeks of sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**
Nambi 2016[50]	N: 17 Women: - Age: 58 BMI: 26.9 VAS pain: 78 mm K/L: 3.1	N: 17 Women: - Age: 60 BMI: 28.3 VAS pain: 76 mm K/L: 3.2	4 weeks of exercise, kinesio tape and LLLT vs 4 weeks of exercise, kinesio tape and sham LLLT	Pain: VAS Disability: - QoL: - Week of assessment: **4**, **8**
Nivbrant 1992[19]	N: 15 Women: 69.2% Age: 69 years BMI: - VAS pain: 67 mm	N: 15 Women: 84.6% Age: 66 years BMI: - VAS pain: 58 mm	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: VAS (movement) Disability: Walking disability QoL: - Week of assessment: **2**, 3, **6**

	K/L: -	K/L: -		
Rayegani 2012[43]	N: 12 Women: 83.3% Age: 61.7 years BMI: - VAS pain: 63 mm K/L: < 4	N: 13 Women: 92.3% Age: 61.2 years BMI: - VAS pain: 52 mm K/L: < 4	2 weeks of LLLT vs 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: 6, **14**
Tascioglu 2004[40] (3 Joules)	N: 20 Women: 70% Age: 62.86 years BMI: 27.56 VAS pain: 68 mm K/L: 2	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	10 days of LLLT vs 10 days of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, 26
Tascioglu 2004[40] (1.5 Joules)	N: 20 Women: 75% Age: 59.92 years BMI: 28.63 VAS pain: 65.72 mm K/L: 2.5	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	10 days of LLLT vs 10 days of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **3**, 26
Youssef 2016[42] (904 nm)	N: 18 Women: 66.7% Age: 67.5 BMI: < 40 VAS pain: 51.67 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: < 40 VAS pain: 50 mm K/L: 2	8 weeks of exercise and LLLT vs 8 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **8**
Youssef 2016[42] (880 nm)	N: 18 Women: 61.1% Age: 67.3 BMI: < 40 VAS pain: 52.50 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: < 40 VAS pain: 50 mm K/L: 2	8 weeks of exercise and LLLT vs 8 weeks of exercise and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: - Week of assessment: **8**

The values for age and BMI are means and the values for K/L grade are medians. Baseline VAS scores have been extracted or estimated as described in the method section. Week of assessment in bold denotes time point used for the main meta-analyses.

AQoL-6D = Assessment of Quality of Life 6 Dimensions; BMI = Body Mass Index; DIQ = Disability Index Questionnaire; K/L = Kellgren/Lawrence; LLLT = Low-Level Laser Therapy; NRS = Numeric Rating Scale; QoL = Quality of life; SKFS = Saudi Knee Function Scale; TENS = Transcutaneous Electrical Nerve Stimulation; VAS = Visual Analogue Scale; VNPS = Visual Numerical Pain Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2 | Laser therapy characteristics of the included trials

First author	Treated area	Wave-length (nm)	Joules per treatment spot	Mean output (mW)	Seconds per treated spot	Number of spots treated	Sessions/ sessions per week
Al Rashoud 2014[31]*	Knee joint line (medial and lateral) and acupoints (SP9, SP10, ST36)	830	1.2	30	40	5	9/3
Alfredo 2011, 2018[29] [44]	Knee joint line (medial and lateral)	904	3	60	50	9	9/3
Alghadir 2014[32]	Knee condyles, joint line (medial and lateral) and popliteal fossa	850	6	100	60	8	8/2
Bagheri 2011[23]*	Knee joint line	830	3	30	100	10	10/5
Bülow 1994[20]*	Painful spots in 0-10 cm radius of the knee joint line	830	1.5-4.5	25	60-180	5-15	9/3
Delkhosh 2018[39]	Knee joint	830	5	30	167	5	10/5
Fukuda 2011[30]	Front knee capsule	904	3	60	50	9	9/3
Gur 2003[33] (1.5 Joules)	Antero-lateral and antero-medial portal of the knee	904	1.5	10	150	2	10/2
Gur 2003[33] (1 Joules)	Antero-lateral and antero-medial portal of the knee	904	1	11.2	90	2	10/2
Gur and Oktayoglu	Antero-lateral and antero-medial portal of the knee	904	1.5	10	150	2	10/2
Gworys 2012[18]	Knee joint line, patellofemoral joint and popliteal fossa	810	8	400	20	12	10/2
Hegedus 2009[45]	Knee joint line, popliteal fossa and condyles	830	6	50	120	8	8/2
Helianthi 2016[46]	Knee joint line (lateral) and acupoints (ST36, SP9, GB34, EX-LE-4)	785	4	50	80	5	10/2

Hinman 2014[41]*	Acupoints (locations not stated)	904	0.2	10	20	6	8-12/0.67-1
Jensen 1987[21]*	Knee joint line (medial and lateral), apex and basis of patellae	904	0.054	0.3	180	4	5/5
Kheshie 2014[47]#	Front knee	830	-	160	-	-	12/2
Koutenaei 2017[48]	Front knee, popliteal fossa and femur condyles in the popliteal cavity	810	7	100	70	8	10/5
Mohammed 2018[49]	Knee joint line (lateral) and acupoints (ST36, Sp10, GB, ashi)	808	5.4	90	60	7	12/3
Nambi 2016[50]	Knee joint line, condyles and popliteal fossa	904	1.5	25	60	8	12/4
Nivbrant 1992[19]*	Knee joint line (medial and lateral) and acupoints (ST34, SP10, X32)	904	0.72	4	180	7	6/3
Rayegani 2012[43]*	Knee joint line and popliteal fossa	880	6	50	120	8	10/5
Tascioglu 2004[40] (3 Joules)*	Painful spots on the knee	830	3	50	60	5	10/5
Tascioglu 2004[40] (1.5 Joules)*	Painful spots on the knee	830	1.5	50	30	5	10/5
Youssef 2016[42] (904 nm)	Knee joint line (medial and lateral)	904	3	60	50	9	16/2
Youssef 2016[42] (880 nm)*	Knee joint line (medial and lateral), epicondyles and popliteal fossa	880	6	50	120	8	16/2

* Non-recommended Low-Level Laser Therapy dose; # 1250 Joules per session.

Overall, pain was significantly reduced by LLLT compared to the placebo-control at the end of therapy (14.23 mm VAS [95% CI: 7.31 to 21.14]; I^2 = 93%; N = 816) (figure 2) and during follow-ups 2-12 weeks later (15.92 mm VAS [95% CI: 6.47 to 25.37]; I^2 = 93%; N = 581) (figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the recommended LLLT doses compared to placebo at the end of therapy (18.71 mm [95% CI: 9.42 to 27.99]; I^2 = 95%; N = 480) (figure 2) and during follow-ups 2-12 weeks later (23.23 mm VAS [95% CI: 10.60 to 35.86]; I^2 = 95%; N = 392) (figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the non-recommended LLLT doses compared to placebo at the end of therapy (6.34 mm VAS [95% CI: 1.26 to 11.41]; I^2 = 44%; N = 336) (figure 2), but the difference during follow-ups 2-12 weeks later was not significant (6.20 mm VAS [95% CI: -0.65 to 13.05]; I^2 = 38%; N = 189) (figure 3). The between-subgroup differences (recommended versus non-recommended doses) in pain results were significantly in favour of the recommended LLLT doses regarding both time points (P = 0.02 and 0.02) (figure 2-3).

Overall, disability was significantly reduced by LLLT compared to placebo at the end of therapy (SMD = 0.59 [95% CI: 0.33 to 0.86]; I^2 = 57%; N = 617) (figure 4) and during follow-ups 2-12 weeks later (SMD = 0.66 [95% CI: 0.23 to 1.09]; I^2 = 67%; N = 289) (figure 5). The dose subgroup analyses demonstrated that disability was significantly reduced by the recommended LLLT doses compared to placebo at the end of therapy (SMD = 0.75 [95% CI: 0.46 to 1.03]; I^2 = 34%; N = 339) (figure 4) and during follow-ups 2-8 weeks later (SMD = 1.31 [95% CI: 0.92 to 1.69]; I^2 = 0%; N = 129) (figure 5). The dose subgroup analyses demonstrated that disability was neither significantly reduced by the non-recommended LLLT doses compared to placebo at the end of therapy (SMD = 0.36 [95% CI: -0.02 to 0.73]; I^2 = 49%; N = 278) (figure 4) nor during follow-ups 2-12 weeks later (SMD = 0.26 [95% CI: -0.06 to 0.58]; I^2 = 0%; N = 160) (figure 5). The between-subgroup differences in disability results were in favour of the recommended LLLT doses over the non-recommended LLLT doses but only significantly regarding one of two time points (P = 0.11 and < 0.0001) (figure 4-5).

No QoL meta-analysis was performed because this outcome was only assessed in a single trial, i.e., by Hinman et al. who applied a non-recommended LLLT dose and reported insignificant results.[41]

The funnel plots indicated that there was no publication bias (supplementary material). We additionally checked for small study bias by reducing the statistical weight of the smallest studies

through a change from random to fixed effects models and this led to similar mean effect estimates, indicating that there was no small study bias (supplementary material).[35]
Methodological quality of the included trials was judged adequate (low risk of bias), unclear (unclear risk of bias) and inadequate (high risk of bias) in 75%, 19% and 6% instances, respectively. Risk of detection bias and reporting bias appeared low in all the trials. There was a lack of information regarding random sequence generation in five trials, allocation concealment in twelve trials, blinding of therapist in four trials and incomplete outcome data in four trials. Therapist blinding was inadequate in seven trials and there was an inadequate handling of data in a single trial (figure 6). However, risk of bias subgroup-analyses conducted post hoc revealed that there was no statistically significant interaction between the effect estimates and risk of bias, and the analyses did not display a drop in statistical heterogeneity (supplementary material). Support for our risk of bias judgments is available (supplementary material).
Neither did the levels of statistical heterogeneity change when we switched from the MD to the SMD method post hoc (supplementary material).
Post hoc analyses demonstrated that LLLT was significantly superior to placebo both with exercise therapy ($P = 0.0009$ for pain and $P < 0.0001$ for disability) and without exercise therapy ($P = 0.01$ for pain and $P = 0.008$ for disability) as co-intervention (supplementary material).
Post hoc analyses were performed to more precisely estimate the pain time-effect profile for the recommended LLLT doses by imputing the results of the trials with these doses in subgroups with narrower time intervals. Pain was significantly reduced by the recommended LLLT doses compared to placebo immediately after therapy week 2-3 and 4-8 and at follow-ups 2-4, 6-8 and 12 weeks later; the peak point was 2-4 weeks after the end of therapy (31.87 mm VAS beyond placebo [95% CI: 18.18 to 45.56]; $I^2 = 93\%$; $N = 322$). The 21- and 34-weeks follow-up pain results were not statistically significant (figure 7 and supplementary material). The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high ($I^2 = 95\%$) (figure 2-3) but the mean statistical heterogeneity of the six subgroups covering the same time period was only moderate ($I^2 = 58\%$) (figure 7 and supplementary material).

Figure 2 | Pain results from immediately after the end of therapy

Figure 3 | Pain results from follow-ups 2-12 weeks after the end of therapy

Figure 4 | Disability results from immediately after the end of therapy

Figure 5 | Disability results from follow-ups 2-12 weeks after the end of therapy

Figure 6 | Risk of bias plot of the included trials
The trials are ranked by mean pain effect estimates, i.e., more laser positive results in the bottom of the figure; the plot is based on the results from the main pain analyses (immediately after the end of therapy, primarily). Support for our judgements and risk of bias statistical analyses are available (supplementary material).

Figure 7 | Pain time-effect profile (recommended LLLT doses versus placebo-control)
Values on the y-axis are mm VAS pain results. Positive VAS score indicates the recommended LLLT doses are superior to the placebo-control. The related forest plot is available (supplementary material).
LLLT = Low-Level Laser Therapy; VAS = Visual Analogue Scale.
** The recommended LLLT doses are highly statistically significantly superior to placebo ($P \leq 0.01$).

Discussion

Our meta-analyses showed that pain and disability were significantly reduced by LLLT compared to placebo. We sub-grouped the included trials according to the WALT recommendations (2010)

for laser dose per treatment spot, and this revealed a significant dose-response relationship. Our principal finding is that the recommended LLLT doses offers clinically relevant pain relief in KOA. The non-recommended LLLT doses provided no or little positive effect.

The absolute Minimally Clinically Important Improvement (MCII) of pain in KOA has been estimated to be 19.9, 17 and 9 units on a 0-100 scale in 2005, 2012 and 2015, respectively.[51-53] It is important to note that the MCII of pain is a within-subject improvement and depends on baseline pain intensity.[51-53] The pain reduction from the recommended LLLT doses was significantly superior to placebo even at follow-ups 12 weeks after the end of therapy, and the difference was greater than 20 mm VAS from the final 4-8 weeks of therapy through follow-ups 6-8 weeks after the end of therapy. Interestingly, the pain reduction from the recommended LLLT doses peaked at follow-ups 2-4 weeks after the end of therapy (31.87 mm VAS highly significantly beyond placebo).

Disability was also significantly reduced by the recommended LLLT doses compared to placebo, i.e., to a moderate extent at the end of therapy (SMD = 0.75) and to a large extent during follow-ups 2-8 weeks later (SMD = 1.31). More trials with disability assessments are needed to precisely estimate the effect of LLLT on this outcome during follow-up.

Furthermore, our analyses demonstrated that LLLT is effective in KOA both with and without exercise therapy as co-intervention. Strength training was seemingly only used as an adjunct to LLLT in two of the included trials[47 50], and thus more trials with this combination of treatments are needed.

Risk of bias of the included trials appeared insignificant and could not explain the statistical heterogeneity (supplementary material). We find it plausible that some of the statistical heterogeneity of the overall analyses is associated with the dose subgroup criteria (wavelength specific laser doses per treatment spot) since the mean levels of statistical heterogeneity of the subgroup analyses were consistently lower than the overall levels. It is unknown to us whether other differences in the LLLT protocols impacted the results.

The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high, and some of it can be explained by the pooling of results from various time points of assessment given the pain reduction increased and subsequent decreased with time; the pain reduction time profile showed a drop in statistical heterogeneity to a moderate level.

According to WALT, the osteoarthritic knee should be laser irradiated to reduce inflammation and promote tissue repair.[24 25 54] One of the discrepancies from our review and previously published reviews of the same topic is that we omitted the RCT by Yurtkuran et al.[8 17 28 55], as they solely applied laser to an acupoint located distally from the knee joint (spleen 9).

In line with our findings and the WALT dose recommendations, Joensen et al. (2012) observed that the percentage of laser penetrating rat skin at 810 and 904 nm wavelength was 20% and 38-58%, respectively. That is, to deliver the same dose beneath the skin, 2.4 times the energy on the skin surface is required with an 810 nm laser compared to a 904 nm laser device. This may be due to the different wavelengths and/or because 904 nm laser is super-pulsed (pulse peak power ≥ 10000 mW typically), whereas shorter wavelength laser is delivered continuously or with less intense pulsation.[26] The estimated median dose applied with the recommended LLLT was six and three Joules per treatment spot with 785-860 and 904 nm wavelength laser, respectively. Most of the trial authors reported LLLT parameters in detail but did not state whether the laser devices were calibrated. Therefore, in the LLLT trials with non-significant effect estimates, equipment failure cannot be ruled out.

It is important to note that no adverse events were reported by any of the trial authors and the dropout rate was minor, indicating that LLLT is harmless.

Our clinical findings that the effect of LLLT progresses over time is in line with in vivo results of Wang et al.[12] The positive effect from LLLT seems to last longer than those of widely recommended painkiller drugs.[56] The effect of using the NSAID tiaprofenic acid, for example, is probably gone within a week, unless the treatment is continued.[56] Future trials should investigate whether booster sessions of LLLT can prolong the positive effect. Comparative cost-effectiveness analyses of LLLT and NSAIDs would also be of great interest.

Strengths and limitations of this study

In contrast to previous reviews on the current topic, our review was conducted in conformance with an a priori published protocol[8 17 28], which included a detailed plan for statistical analysis (e.g. laser dose subgroup criteria). Furthermore, this is the first review on this topic without language restrictions[8 17 28], and this expansion proved important since four (18%) of the included trials were reported in non-English language.[19 21 23 39]

We conducted a series of meta-analyses illustrating the effect of LLLT on pain over time. To ensure high reproducibility of the meta-analyses, three persons each independently extracted the outcome data from the included trial articles.

This review is not without limitations. It lacks QoL analyses, a detailed disability time-effect analysis and direct comparisons between LLLT and other interventions.

Conclusions

LLLT reduces pain and disability in KOA at 4-8 Joules with 785-860 nm wavelength and at 1-3 Joules with 904 nm wavelength per treatment spot.

Contributors: MBS, JMB and HL wrote the PROSPERO protocol. MBS and JMB selected the trials, with the involvement of IFN when necessary. MBS and JJ judged the risk of bias, with the involvement of IFN when necessary. MBS and IFN did the translations. MBS, JMB and KVF extracted the data. MBS performed the analyses, under supervision of JMB. All the authors participated in interpreting of the results. MBS drafted the first version of the manuscript, and subsequently revised it, based on comments by RABLM, HS and all the other authors. All the authors read and accepted the final version of the manuscript.

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Ethical approval: Not required.

Data sharing: The dataset for meta-analysis is available from the corresponding author upon reasonable request. The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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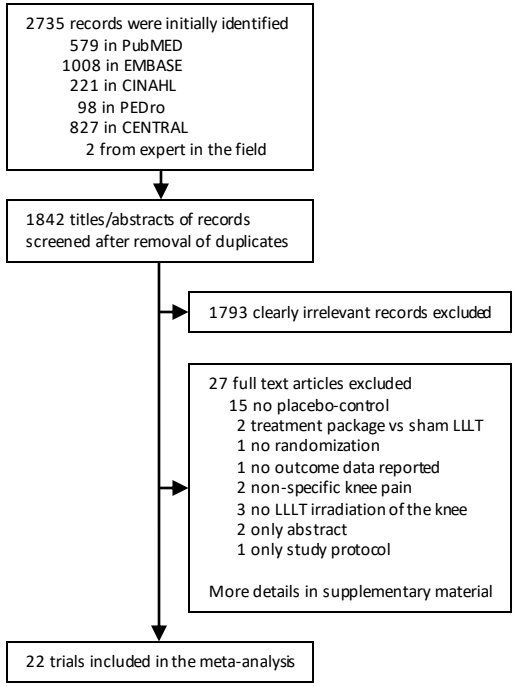
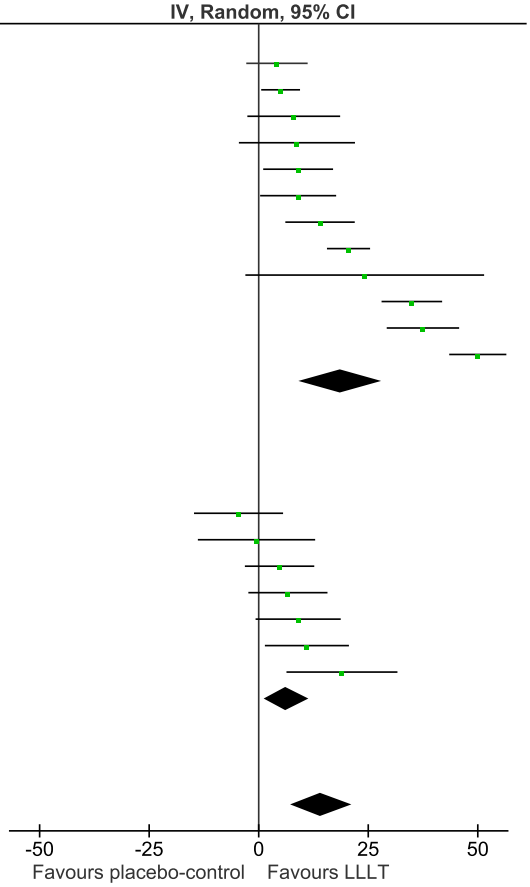
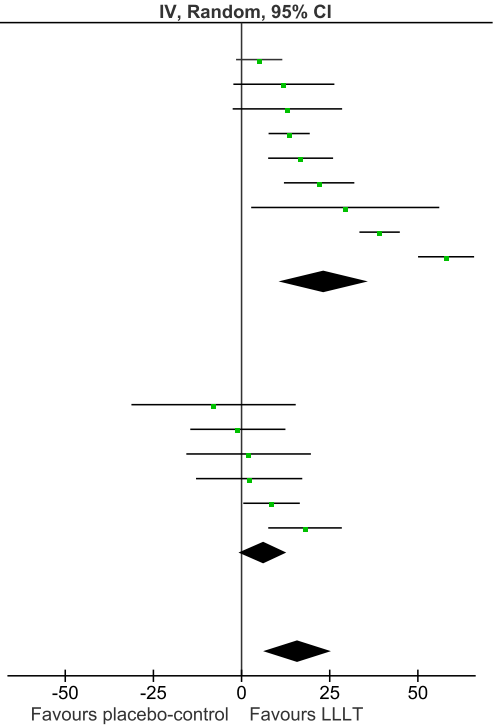

2735 records were initially identified
579 in PubMED
1008 in EMBASE
221 in CINAHL
98 in PEDro
827 in CENTRAL
2 from expert in the field
1842 titles/abstracts of records screened after removal of duplicates
1793 clearly irrelevant records excluded
27 full text articles excluded
15 no placebo-control
2 treatment package vs sham LLLT
1 no randomization
1 no outcome data reported
2 non-specific knee pain
3 no LLLT irradiation of the knee
2 only abstract
1 only study protocol
More details in supplementary material
22 trials included in the meta-analysis

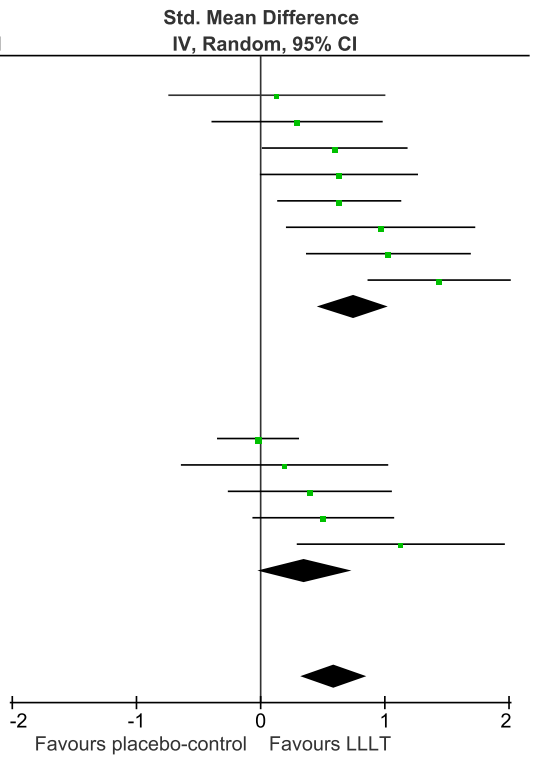
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Recommended LLLT dose vs placebo-control								
Youssef 2016 (904 nm)	6.667	13.34	18	2.5	4.492	7	5.6%	4.17 [-2.84, 11.17]
Gworys 2012	20	8	34	15	10	31	5.8%	5.00 [0.57, 9.43]
Fukuda 2011	17	22.67	25	9	13.78	22	5.2%	8.00 [-2.59, 18.59]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	4.9%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	5.5%	9.00 [1.03, 16.97]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	5.4%	9.00 [0.33, 17.67]
Delkhosh 2018	25	14	15	11	7	15	5.5%	14.00 [6.08, 21.92]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	5.8%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	3.1%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	5.6%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	5.5%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	5.6%	50.00 [43.48, 56.52]
Subtotal (95% CI)			**255**			**225**	**63.4%**	**18.71 [9.42, 27.99]**
Heterogeneity: Tau² = 243.24; Chi² = 201.44, df = 11 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.95 (P < 0.0001)								
1.1.2 Non-recommended LLLT dose vs placebo-control								
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	5.3%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	4.9%	-0.50 [-13.88, 12.88]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	5.5%	4.76 [-3.15, 12.68]
Youssef 2016 (880 nm)	9.167	18.343	18	2.5	4.492	8	5.4%	6.67 [-2.36, 15.69]
Bagheri 2011	28	18.5	18	19	10	18	5.3%	9.00 [-0.72, 18.72]
Al Rashoud 2014	32	13.617	26	21	19.656	23	5.3%	11.00 [1.41, 20.59]
Nivbrant 1992	23	15.31	13	4	17.556	13	4.9%	19.00 [6.34, 31.66]
Subtotal (95% CI)			**173**			**163**	**36.6%**	**6.34 [1.26, 11.41]**
Heterogeneity: Tau² = 20.17; Chi² = 10.65, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 2.45 (P = 0.01)								
Total (95% CI)			**428**			**388**	**100.0%**	**14.23 [7.31, 21.14]**
Heterogeneity: Tau² = 209.90; Chi² = 243.08, df = 18 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 4.03 (P < 0.0001)								
Test for subgroup differences: Chi² = 5.25, df = 1 (P = 0.02), I² = 80.9%								



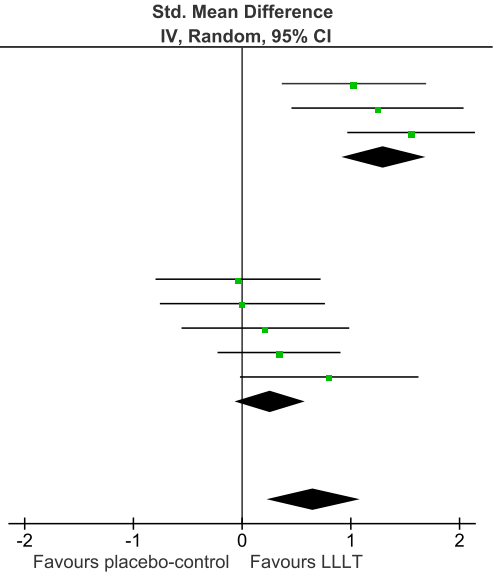
Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Recommended LLLT dose vs placebo-control								
Gur and Oktayoglu	45	17.267	37	40	10.479	35	7.4%	5.00 [-1.56, 11.56]
Gur 2003 (1 Joules, 904 nm)	36.4	23.113	30	24.4	23.113	15	6.5%	12.00 [-2.33, 26.33]
Gur 2003 (1.5 Joules, 904 nm)	37.4	25.039	30	24.4	25.039	15	6.4%	13.00 [-2.52, 28.52]
Koutenaei 2017	26	10.053	20	12.5	8.732	20	7.4%	13.50 [7.66, 19.34]
Alfredo 2011	21.5	14.855	20	4.75	14.855	20	7.1%	16.75 [7.54, 25.96]
Delkhosh 2018	29	17	15	7	10	15	7.1%	22.00 [12.02, 31.98]
Hegedus 2009	-11.8	11.194	18	-41.2	40.05	9	4.8%	29.40 [2.73, 56.07]
Helianthi 2016	40.47	14.8	30	1.32	6	29	7.5%	39.15 [33.42, 44.88]
Nambi 2016	66	11.265	17	8	12.357	17	7.3%	58.00 [50.05, 65.95]
Subtotal (95% CI)			**217**			**175**	**61.4%**	**23.23 [10.60, 35.86]**
Heterogeneity: Tau² = 335.90; Chi² = 149.09, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.60 (P = 0.0003)								
2.1.2 Non-recommended LLLT dose vs placebo-control								
Bülow 1994	0.794	31.986	14	8.73	31.986	15	5.2%	-7.94 [-31.23, 15.36]
Tascioglu 2004 (3 Joules, 830 nm)	0.4	16.771	20	1.45	18.254	10	6.6%	-1.05 [-14.54, 12.44]
Nivbrant 1992	9	22.474	13	7	23.462	13	6.0%	2.00 [-15.66, 19.66]
Tascioglu 2004 (1.5 Joules, 830 nm)	3.6	22.697	20	1.45	18.254	10	6.4%	2.15 [-12.91, 17.21]
Rayegani 2012	12.5	10.215	12	4	10.215	13	7.3%	8.50 [0.49, 16.51]
Al Rashoud 2014	34	17.331	26	16	19.656	23	7.0%	18.00 [7.56, 28.44]
Subtotal (95% CI)			**105**			**84**	**38.6%**	**6.20 [-0.65, 13.05]**
Heterogeneity: Tau² = 26.43; Chi² = 8.03, df = 5 (P = 0.15); I² = 38%								
Test for overall effect: Z = 1.77 (P = 0.08)								
Total (95% CI)			**322**			**259**	**100.0%**	**15.92 [6.47, 25.37]**
Heterogeneity: Tau² = 303.25; Chi² = 190.87, df = 14 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 3.30 (P = 0.0010)								
Test for subgroup differences: Chi² = 5.40, df = 1 (P = 0.02), I² = 81.5%								

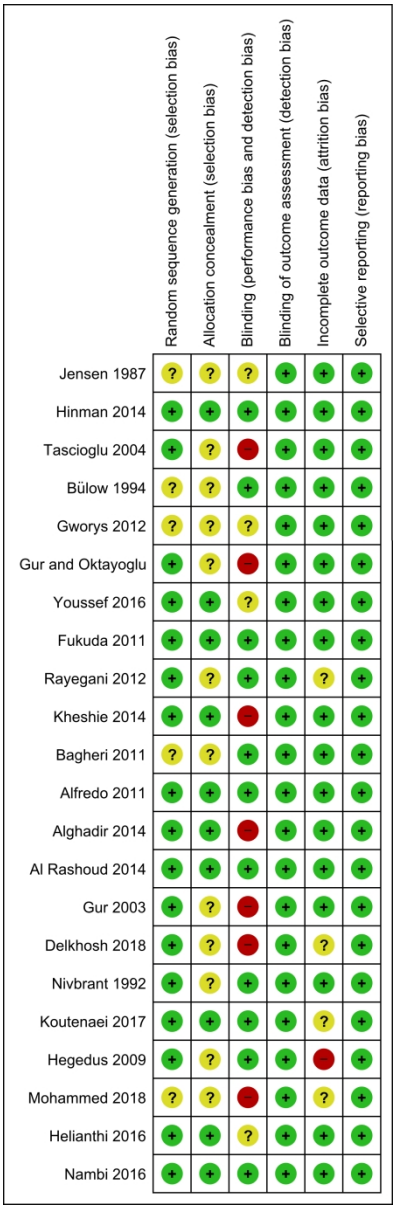


Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Random, 95% CI
7.1.1 Recommended LLLT dose vs placebo-control								
Youssef 2016 (904 nm)	6.575	13.157	18	4.932	8.86	7	5.5%	0.13 [-0.74, 1.00]
Kheshie 2014	13.56	11.395	18	10.4	9.315	15	7.2%	0.29 [-0.40, 0.98]
Fukuda 2011	3.2	4.267	25	1	2.717	22	8.3%	0.60 [0.01, 1.18]
Alghadir 2014	15.95	5.364	20	12.5	5.364	20	7.8%	0.63 [-0.01, 1.27]
Gworys 2012	1.06	0.6	34	0.5	1.1	31	9.4%	0.63 [0.13, 1.13]
Delkhosh 2018	7.9	4.9	15	4.1	2.3	15	6.5%	0.97 [0.20, 1.73]
Alfredo 2011	9.7	9.48	20	-0.25	9.48	20	7.5%	1.03 [0.37, 1.69]
Helianthi 2016	5.2	3.9	30	-0.7	4.2	29	8.5%	1.44 [0.86, 2.01]
Subtotal (95% CI)			**180**			**159**	**60.7%**	**0.75 [0.46, 1.03]**
Heterogeneity: Tau² = 0.06; Chi² = 10.67, df = 7 (P = 0.15); I² = 34%								
Test for overall effect: Z = 5.19 (P < 0.00001)								
7.1.2 Non-recommended LLLT dose vs placebo-control								
Hinman 2014	-0.5	23.422	71	0	23.422	70	11.7%	-0.02 [-0.35, 0.31]
Youssef 2016 (880 nm)	7.671	15.35	18	4.932	8.86	8	5.8%	0.19 [-0.64, 1.03]
Bagheri 2011	27.5	19	18	21	12.4	18	7.5%	0.40 [-0.26, 1.06]
Al Rashoud 2014	35	32.185	26	19	30.063	23	8.5%	0.50 [-0.07, 1.08]
Nivbrant 1992	22	16.967	13	4	13.756	13	5.8%	1.13 [0.29, 1.97]
Subtotal (95% CI)			**146**			**132**	**39.3%**	**0.36 [-0.02, 0.73]**
Heterogeneity: Tau² = 0.09; Chi² = 7.78, df = 4 (P = 0.10); I² = 49%								
Test for overall effect: Z = 1.86 (P = 0.06)								
Total (95% CI)			**326**			**291**	**100.0%**	**0.59 [0.33, 0.86]**
Heterogeneity: Tau² = 0.13; Chi² = 27.92, df = 12 (P = 0.006); I² = 57%								
Test for overall effect: Z = 4.44 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.62, df = 1 (P = 0.11), I² = 61.8%								



Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Random, 95% CI
8.1.1 Recommended LLLT dose vs placebo-control								
Alfredo 2011	14.35	10.052	20	3.8	10.052	20	13.1%	1.03 [0.36, 1.69]
Delkhosh 2018	8.5	4.6	15	3.1	3.8	15	11.6%	1.25 [0.45, 2.04]
Helianthi 2016	5.3	4.5	30	-1.2	3.7	29	14.1%	1.55 [0.97, 2.14]
Subtotal (95% CI)			**65**			**64**	**38.7%**	**1.31 [0.92, 1.69]**
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0%								
Test for overall effect: Z = 6.65 (P < 0.00001)								
8.1.2 Non-recommended LLLT dose vs placebo-control								
Tascioglu 2004 (3 Joules, 830 nm)	1.56	9.292	20	1.93	10.337	10	12.0%	-0.04 [-0.80, 0.72]
Tascioglu 2004 (1.5 Joules, 830 nm)	1.96	11.831	20	1.93	10.337	10	12.0%	0.00 [-0.76, 0.76]
Nivbrant 1992	12	17.329	13	8	18.815	13	11.8%	0.21 [-0.56, 0.99]
Al Rashoud 2014	31	33.423	26	20	30.063	23	14.3%	0.34 [-0.23, 0.90]
Rayegani 2012	2.2	0.845	12	1.5	0.845	13	11.2%	0.80 [-0.02, 1.62]
Subtotal (95% CI)			**91**			**69**	**61.3%**	**0.26 [-0.06, 0.58]**
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 4 (P = 0.59); I² = 0%								
Test for overall effect: Z = 1.60 (P = 0.11)								
Total (95% CI)			**156**			**133**	**100.0%**	**0.66 [0.23, 1.09]**
Heterogeneity: Tau² = 0.25; Chi² = 20.90, df = 7 (P = 0.004); I² = 67%								
Test for overall effect: Z = 2.99 (P = 0.003)								
Test for subgroup differences: Chi² = 16.73, df = 1 (P < 0.0001), I² = 94.0%								




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias and detection bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Jensen 1987
Hinman 2014
Tascioglu 2004
Bülow 1994
Gworys 2012
Gur and Oktayoglu
Youssef 2016
Fukuda 2011
Rayegani 2012
Kheshie 2014
Bagheri 2011
Alfredo 2011
Alghadir 2014
Al Rashoud 2014
Gur 2003
Delkhosh 2018
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Hegedus 2009
Mohammed 2018
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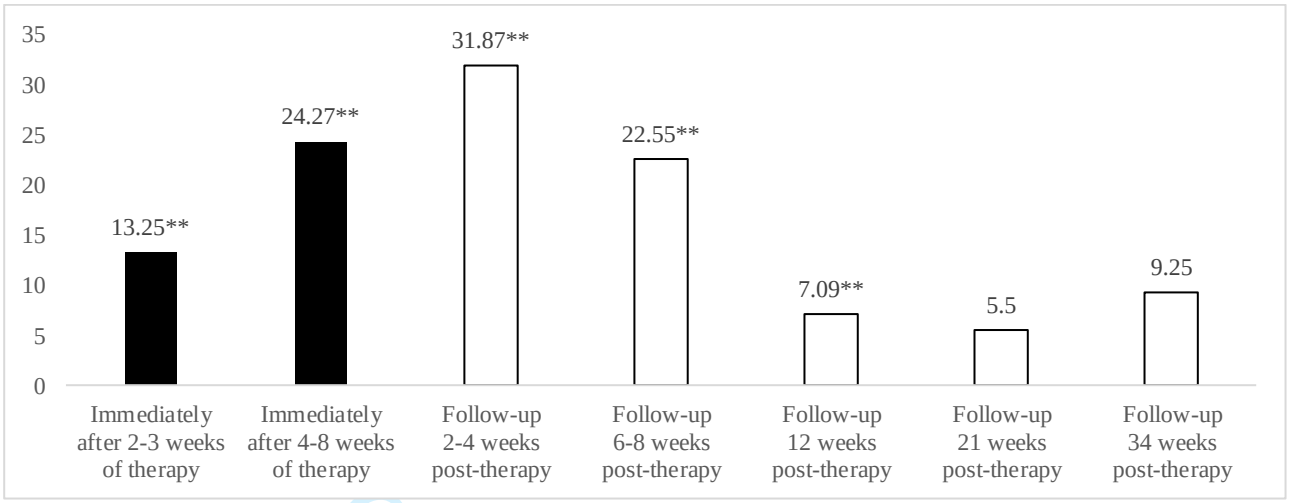
Nambi 2016



Supplementary material for the article by Stausholm et al. entitled *Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials*

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PubMed database search string

The PubMed database search string was: ("Osteoarthritis, Knee"[Mesh] OR "Knee Joint"[Mesh] OR "Knee"[Mesh] OR "Osteoarthritis"[Mesh] OR Knee[Title/Abstract] OR Knees[Title/Abstract] OR Osteoarthr*[Title/Abstract]) AND ("Low-Level Light Therapy"[Mesh] OR LLLT[Title/Abstract] OR "low level"[Title/Abstract] OR "low power"[Title/Abstract] OR laser therap*[Title/Abstract] OR "laser acupuncture"[Title/Abstract] OR "narrow band"[Title/Abstract] OR "HeNe"[Title/Abstract] OR "632 nm"[Title/Abstract] OR "Ga-Al-As"[Title/Abstract] OR "820 nm"[Title/Abstract] OR "830 nm"[Title/Abstract] OR "850 nm"[Title/Abstract] OR "GaAs"[Title/Abstract] OR "904 nm"[Title/Abstract])

Excluded articles

Table 1 | Excluded articles initially judged potentially eligible

First author	Reason for exclusion
Alayat 2017[1]	HILT, not LLLT
Ciechanowska 2008[2]	No placebo-control
Coelho[3]	Only study protocol
de Matos 20184[4]	No placebo-control
de Meneses[5]	Full-text not available (emailed)
de Paula 2018[6]	NBLT + LLLT vs sham LLLT alone
Giavelli 1998[7]	No placebo-control
Götte 1995[8]	No outcome data reported
Kujawa 2004[9]	No placebo-control
Leal-Junior 2014[10]	Non-specific knee pain
Lepilina 1990[11]	No placebo-control
Marquina 2012[12]	Non-specific knee pain
Montes-Molina 2009[13]	No placebo-control
Nakamura 2014[14]	No placebo-control
Paolillo 2018[15]	No placebo-control
Pinfildi[16]	Full-text not available (emailed)
Ren 2010[17]	No placebo-control
Shen 2009[18]	LLLT + moxibustion vs sham LLLT alone
Soleimanpour 2014[19]	No placebo-control
Stelian 1992[20]	NBLT, not laser
Trelles 1991[21]	No placebo-control
Wang 2013[22]	No randomization
Yavuz 2013[23]	No placebo-control
Yurtkuran 2006[24]	Irradiated acupoint spleen 9, not the knee joint
Yuvarani 2018[25]	No placebo-control
Zhao 2010[26]	No placebo-control
Zou 2017[27]	No placebo-control

NBLT = narrow-band light therapy; LLLT = Low-Level Laser Therapy; HILT = High Intensity Laser Therapy.

Pain time-effect profile of Low-Level Laser Therapy

Analyses were performed to estimate the pain time-effect profile of the recommended Low-Level Laser Therapy doses by imputing the results of the trials with these doses in subgroups with narrower time intervals (figure 1).

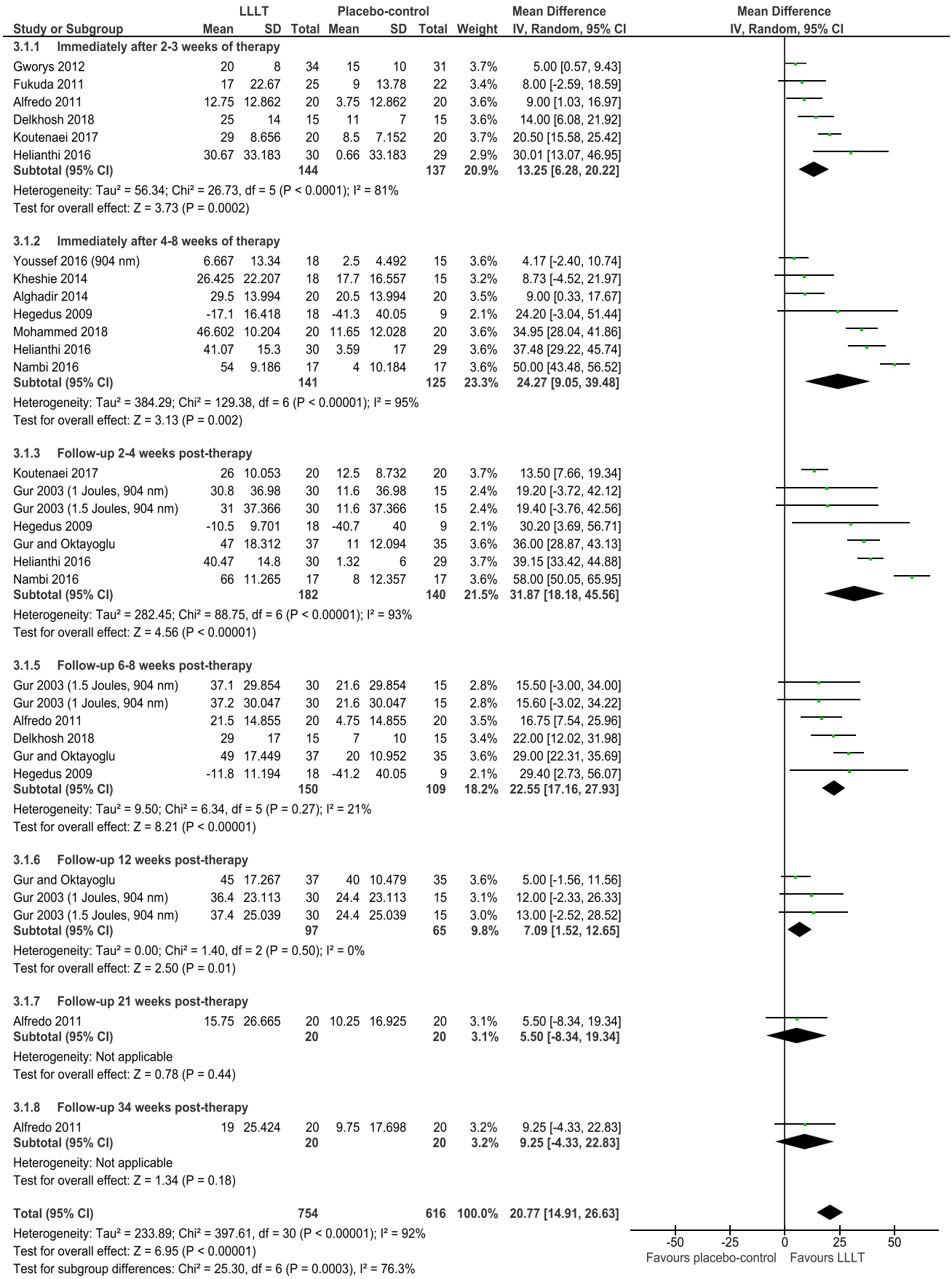

Figure 1 | Pain time-effect profile (recommended Low-Level Laser Therapy doses vs placebo-control)

Publication and small study bias assessment

Funnel plots were performed using the results from the main analyses (immediately after the end of therapy, primarily). There were no clear indications of publication bias (figure 2-3). Moreover, a subsequent change from random to fixed effects models only caused a slight change in point effect estimates: Pain results from 13.22 to 14.14 mm VAS (figure 4-5) and disability from 0.57 to 0.48 (SMD) (figure 6-7).

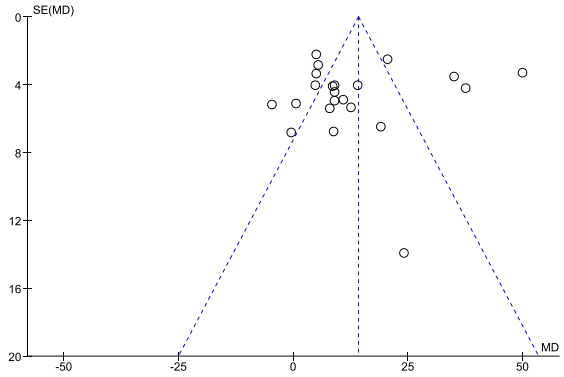

Figure 2 | Funnel plot (pain)

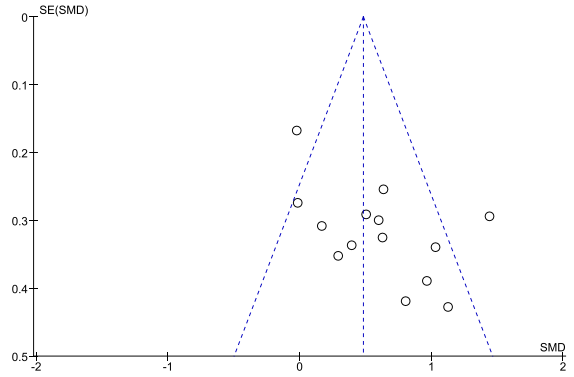

Figure 3 | Funnel plot (disability)

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	4.5%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	4.1%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (both intervention groups)	2	19.764	40	1.45	18.254	20	4.5%	0.55 [-9.53, 10.63]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.7%	4.76 [-3.15, 12.68]
Gur and Oktayoglu	45	17.267	37	40	10.479	35	4.9%	5.00 [-1.56, 11.56]
Gworys 2012	20	8	34	15	10	31	5.0%	5.00 [0.57, 9.43]
Youssef 2016 (both intervention groups)	7.917	15.858	36	2.5	4.492	15	4.9%	5.42 [-0.24, 11.07]
Fukuda 2011	17	22.67	25	9	13.78	22	4.5%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.7%	8.50 [0.49, 16.51]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	4.1%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.7%	9.00 [1.03, 16.97]
Bagheri 2011	28	18.5	18	19	10	18	4.6%	9.00 [-0.72, 18.72]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	4.7%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	4.6%	11.00 [1.41, 20.59]
Gur 2003 (both intervention groups)	36.9	23.895	60	24.4	24.076	30	4.5%	12.50 [1.97, 23.03]
Delkhosh 2018	25	14	15	11	7	15	4.7%	14.00 [6.08, 21.92]
Nivbrant 1992	23	15.31	13	4	17.556	13	4.2%	19.00 [6.34, 31.66]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	5.0%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	2.5%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	4.8%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.7%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	4.9%	50.00 [43.48, 56.52]
Total (95% CI)			**577**			**486**	**100.0%**	**13.22 [7.15, 19.29]**

Heterogeneity: Tau² = 185.88; Chi² = 260.56, df = 21 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.27 (P < 0.0001)

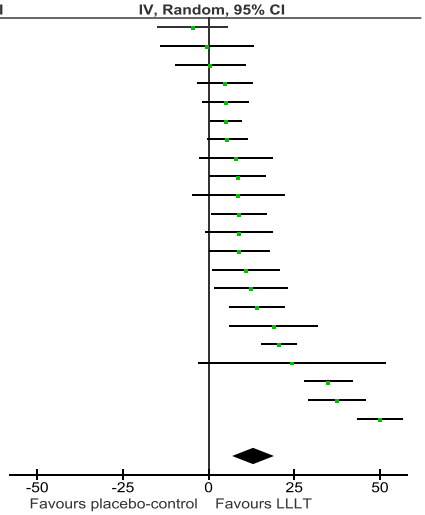

Figure 4 | Random effects model (pain)

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Fixed, 95% CI
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	2.7%	-4.60 [-14.76, 5.56]
Hinman 2014	-0.5	40.538	71	0	40.538	70	1.6%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (both intervention groups)	2	19.764	40	1.45	18.254	20	2.7%	0.55 [-9.53, 10.63]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.4%	4.76 [-3.15, 12.68]
Gur and Oktayoglu	45	17.267	37	40	10.479	35	6.5%	5.00 [-1.56, 11.56]
Gworys 2012	20	8	34	15	10	31	14.1%	5.00 [0.57, 9.43]
Youssef 2016 (both intervention groups)	7.917	15.858	36	2.5	4.492	15	8.7%	5.42 [-0.24, 11.07]
Fukuda 2011	17	22.67	25	9	13.78	22	2.5%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.3%	8.50 [0.49, 16.51]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	1.6%	8.73 [-4.52, 21.97]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.4%	9.00 [1.03, 16.97]
Bagheri 2011	28	18.5	18	19	10	18	2.9%	9.00 [-0.72, 18.72]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	3.7%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	3.0%	11.00 [1.41, 20.59]
Gur 2003 (both intervention groups)	36.9	23.895	60	24.4	24.076	30	2.5%	12.50 [1.97, 23.03]
Delkhosh 2018	25	14	15	11	7	15	4.4%	14.00 [6.08, 21.92]
Nivbrant 1992	23	15.31	13	4	17.556	13	1.7%	19.00 [6.34, 31.66]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	11.5%	20.50 [15.58, 25.42]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	0.4%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	5.8%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.1%	37.48 [29.22, 45.74]
Nambi 2016	54	9.186	17	4	10.184	17	6.5%	50.00 [43.48, 56.52]
Total (95% CI)			**577**			**486**	**100.0%**	**14.14 [12.48, 15.81]**

Heterogeneity: Chi² = 260.56, df = 21 (P < 0.00001); I² = 92%
Test for overall effect: Z = 16.64 (P < 0.00001)

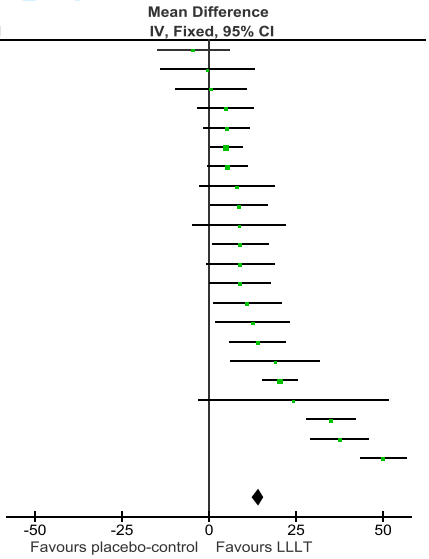

Figure 5 | Fixed effects model (pain)

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hinman 2014	-0.5	23.422	71	0	23.422	70	10.4%	-0.02 [-0.35, 0.31]
Tascioglu 2004 (both intervention groups)	1.76	10.502	40	1.93	10.337	20	8.0%	-0.02 [-0.55, 0.52]
Youssef 2016 (both intervention groups)	7.123	14.101	36	4.932	8.86	15	7.3%	0.17 [-0.44, 0.77]
Kheshie 2014	13.56	11.395	18	10.4	9.315	15	6.5%	0.29 [-0.40, 0.98]
Bagheri 2011	27.5	19	18	21	12.4	18	6.7%	0.40 [-0.26, 1.06]
Al Rashoud 2014	35	32.185	26	19	30.063	23	7.6%	0.50 [-0.07, 1.08]
Fukuda 2011	3.2	4.267	25	1	2.717	22	7.5%	0.60 [0.01, 1.18]
Alghadir 2014	15.95	5.364	20	12.5	5.364	20	7.0%	0.63 [-0.01, 1.27]
Gworys 2012	1.06	0.6	34	0.5	1.1	31	8.4%	0.63 [0.13, 1.13]
Rayegani 2012	2.2	0.845	12	1.5	0.845	13	5.4%	0.80 [-0.02, 1.62]
Delkhosh 2018	7.9	4.9	15	4.1	2.3	15	5.8%	0.97 [0.20, 1.73]
Alfredo 2011	9.7	9.48	20	-0.25	9.48	20	6.7%	1.03 [0.37, 1.69]
Nivbrant 1992	22	16.967	13	4	13.756	13	5.2%	1.13 [0.29, 1.97]
Helianthi 2016	5.2	3.9	30	-0.7	4.2	29	7.6%	1.44 [0.86, 2.01]
Total (95% CI)			**378**			**324**	**100.0%**	**0.57 [0.32, 0.82]**

Heterogeneity: Tau² = 0.13; Chi² = 31.90, df = 13 (P = 0.002); I² = 59%
Test for overall effect: Z = 4.46 (P < 0.00001)

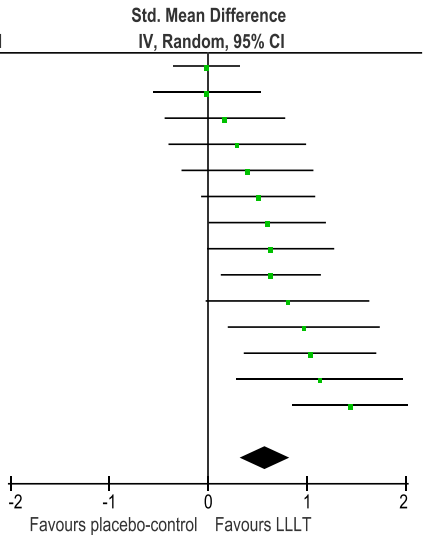

Figure 6 | Random effects model (disability)

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Hinman 2014	-0.5	23.422	71	0	23.422	70	21.8%	-0.02 [-0.35, 0.31]
Tascioglu 2004 (both intervention groups)	1.76	10.502	40	1.93	10.337	20	8.2%	-0.02 [-0.55, 0.52]
Youssef 2016 (both intervention groups)	7.123	14.101	36	4.932	8.86	15	6.5%	0.17 [-0.44, 0.77]
Kheshie 2014	13.56	11.395	18	10.4	9.315	15	5.0%	0.29 [-0.40, 0.98]
Bagheri 2011	27.5	19	18	21	12.4	18	5.4%	0.40 [-0.26, 1.06]
Al Rashoud 2014	35	32.185	26	19	30.063	23	7.3%	0.50 [-0.07, 1.08]
Fukuda 2011	3.2	4.267	25	1	2.717	22	6.9%	0.60 [0.01, 1.18]
Alghadir 2014	15.95	5.364	20	12.5	5.364	20	5.9%	0.63 [-0.01, 1.27]
Gworys 2012	1.06	0.6	34	0.5	1.1	31	9.5%	0.63 [0.13, 1.13]
Rayegani 2012	2.2	0.845	12	1.5	0.845	13	3.5%	0.80 [-0.02, 1.62]
Delkhosh 2018	7.9	4.9	15	4.1	2.3	15	4.1%	0.97 [0.20, 1.73]
Alfredo 2011	9.7	9.48	20	-0.25	9.48	20	5.4%	1.03 [0.37, 1.69]
Nivbrant 1992	22	16.967	13	4	13.756	13	3.4%	1.13 [0.29, 1.97]
Helianthi 2016	5.2	3.9	30	-0.7	4.2	29	7.1%	1.44 [0.86, 2.01]
Total (95% CI)			**378**			**324**	**100.0%**	**0.48 [0.33, 0.63]**

Heterogeneity: Chi² = 31.90, df = 13 (P = 0.002); I² = 59%
Test for overall effect: Z = 6.11 (P < 0.00001)

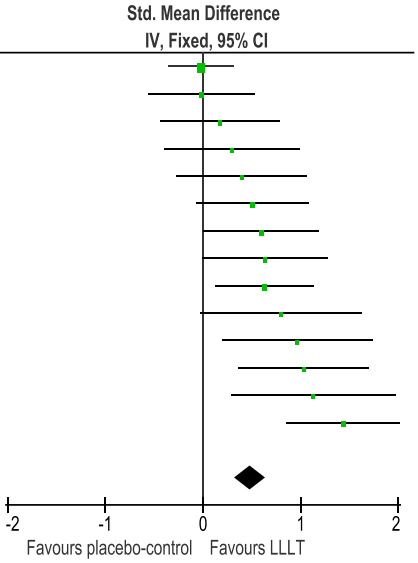

Figure 7 | Fixed effects model (disability)

Risk of bias impact analysis

Risk of bias impact analyses were performed using the results from the main analyses (immediately after the end of therapy, primarily). The mean statistical heterogeneity of the subgroup analyses were similar to the overall levels (figure 8-15).

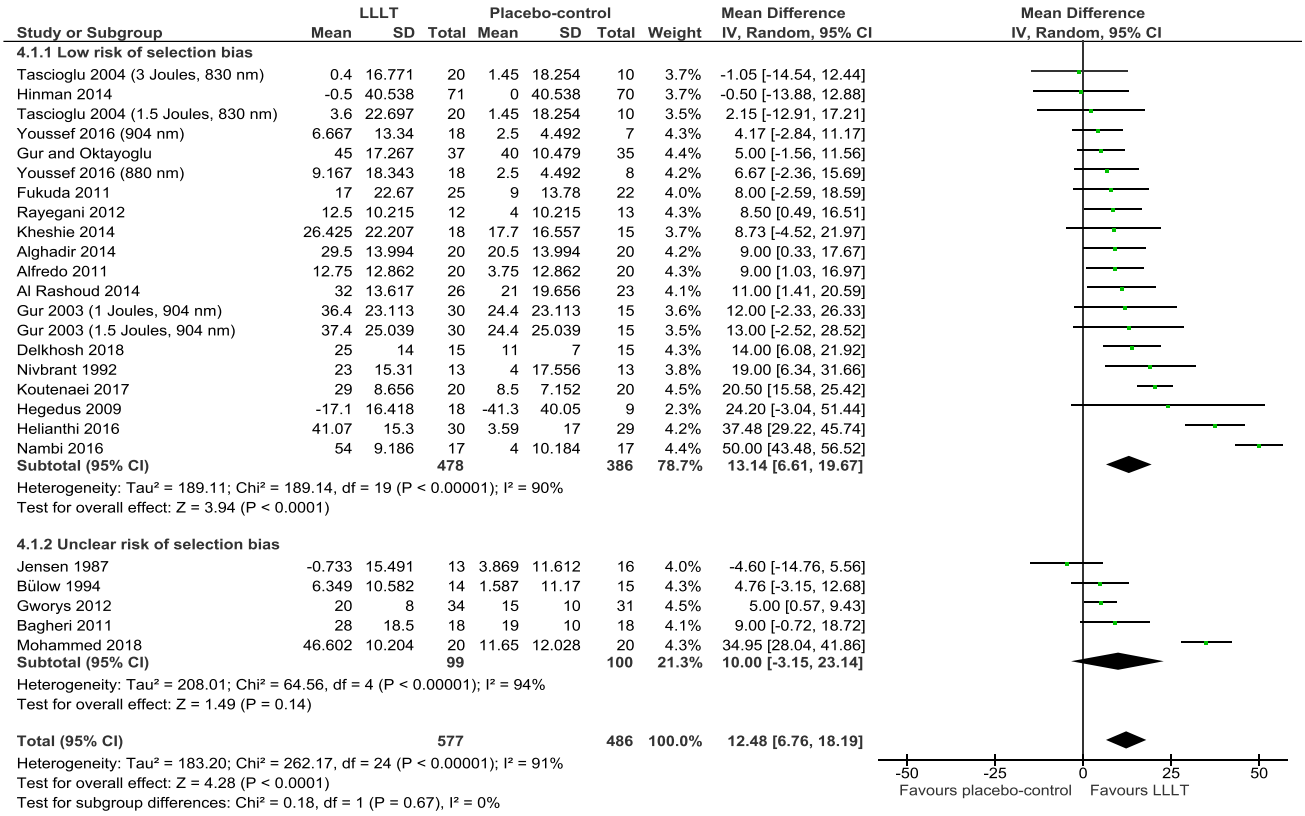

Figure 8 | Pain results - risk of selection bias (random sequence generation)

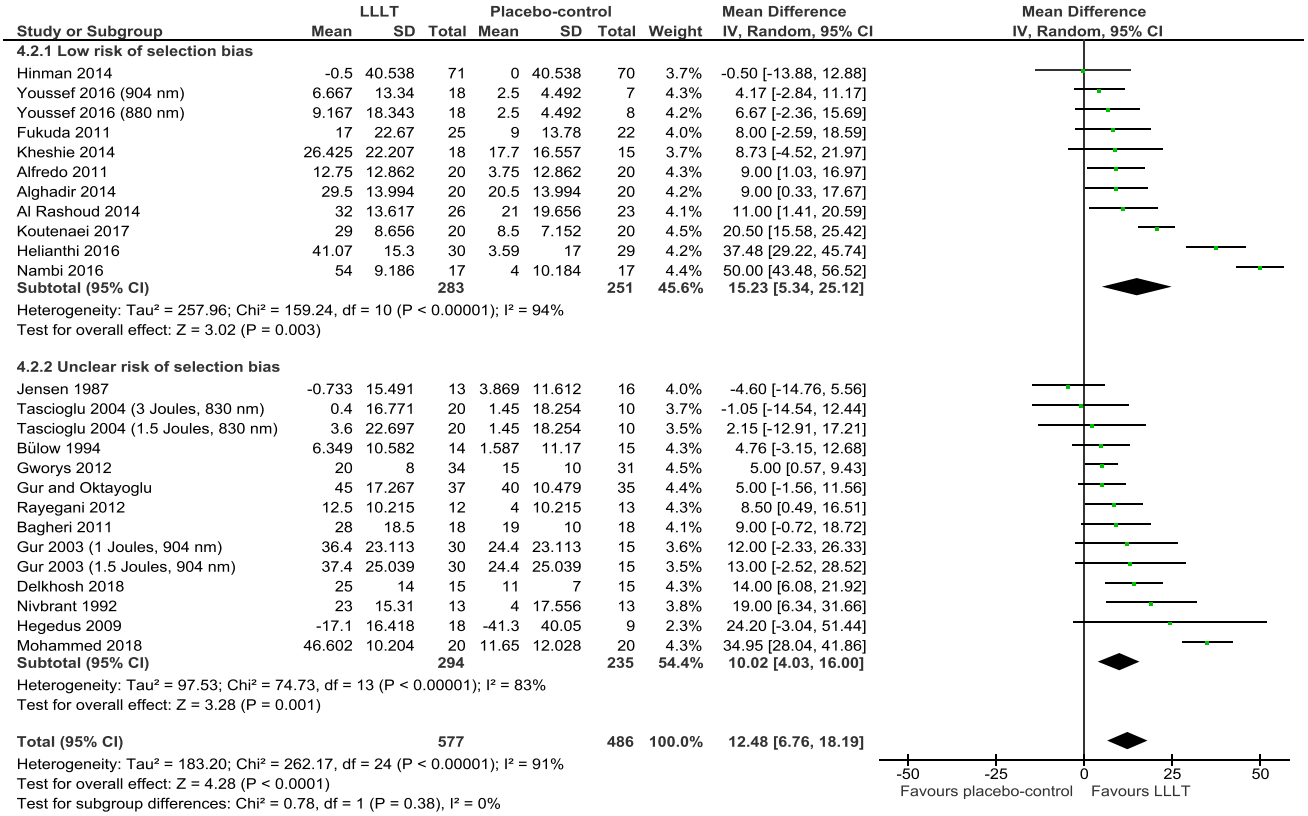

Figure 9 | Pain results - risk of selection bias (allocation concealment)

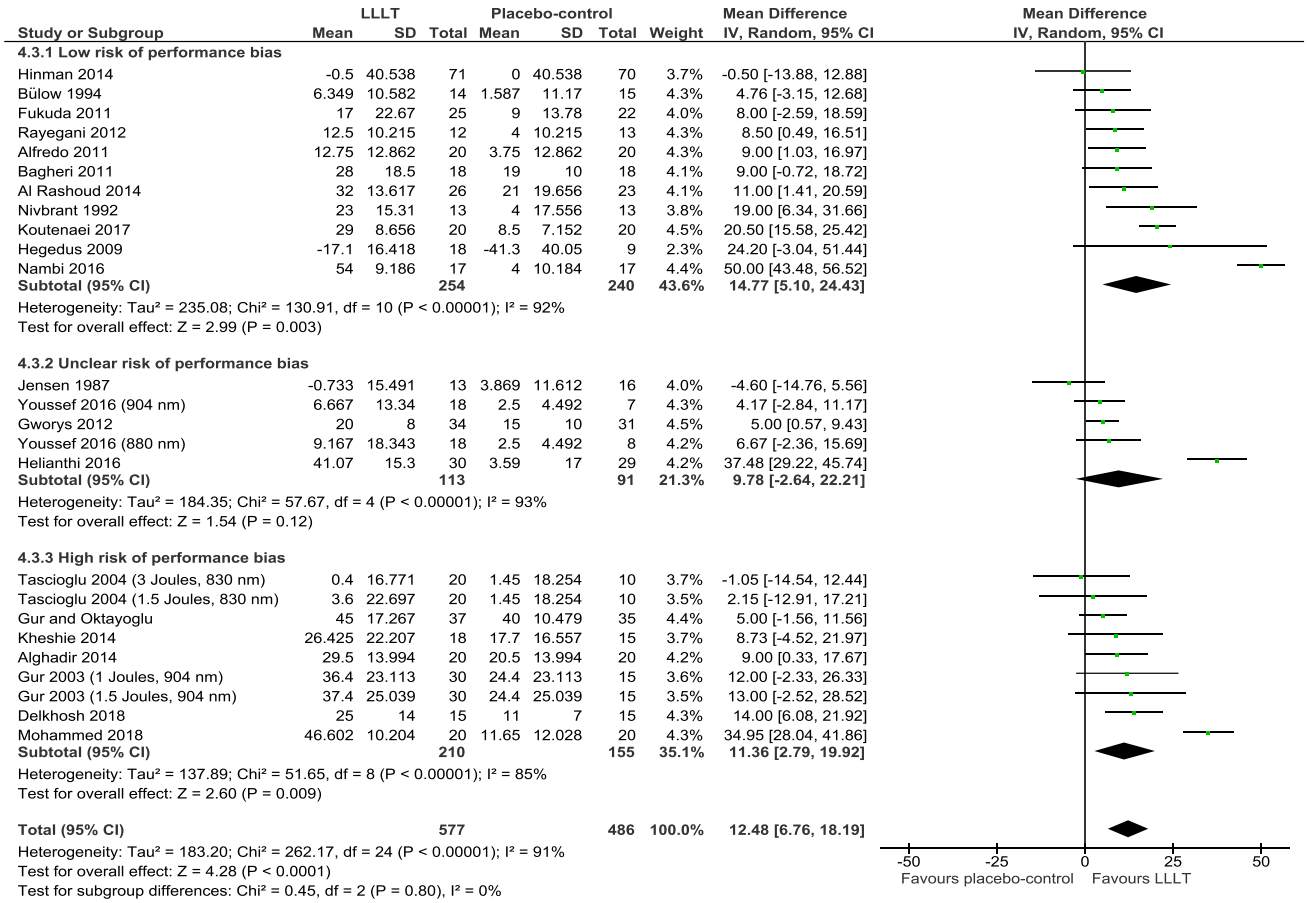

Figure 10 | Pain results - risk of performance bias (blinding of therapist)

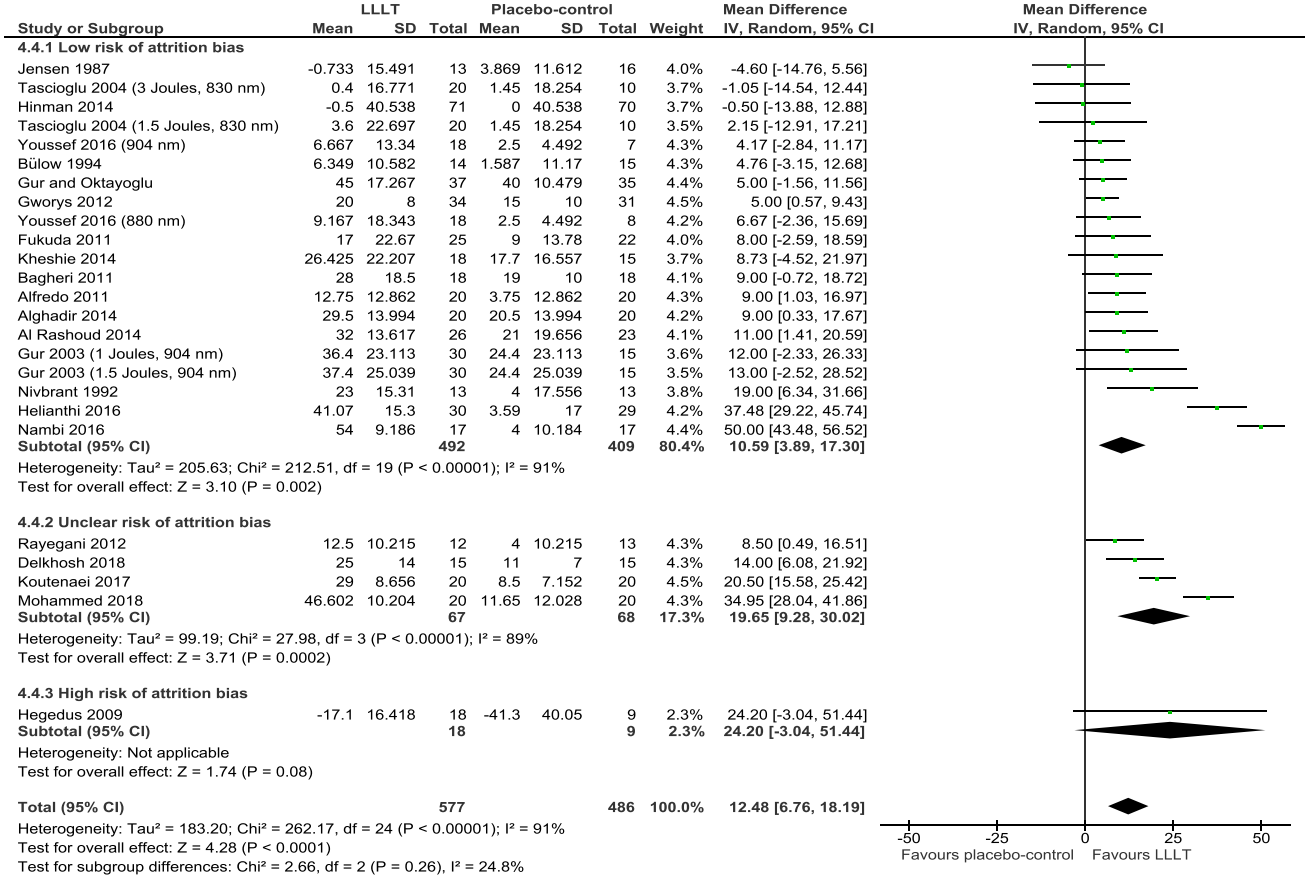

Figure 11 | Pain results - risk of attrition bias (incomplete outcome data)

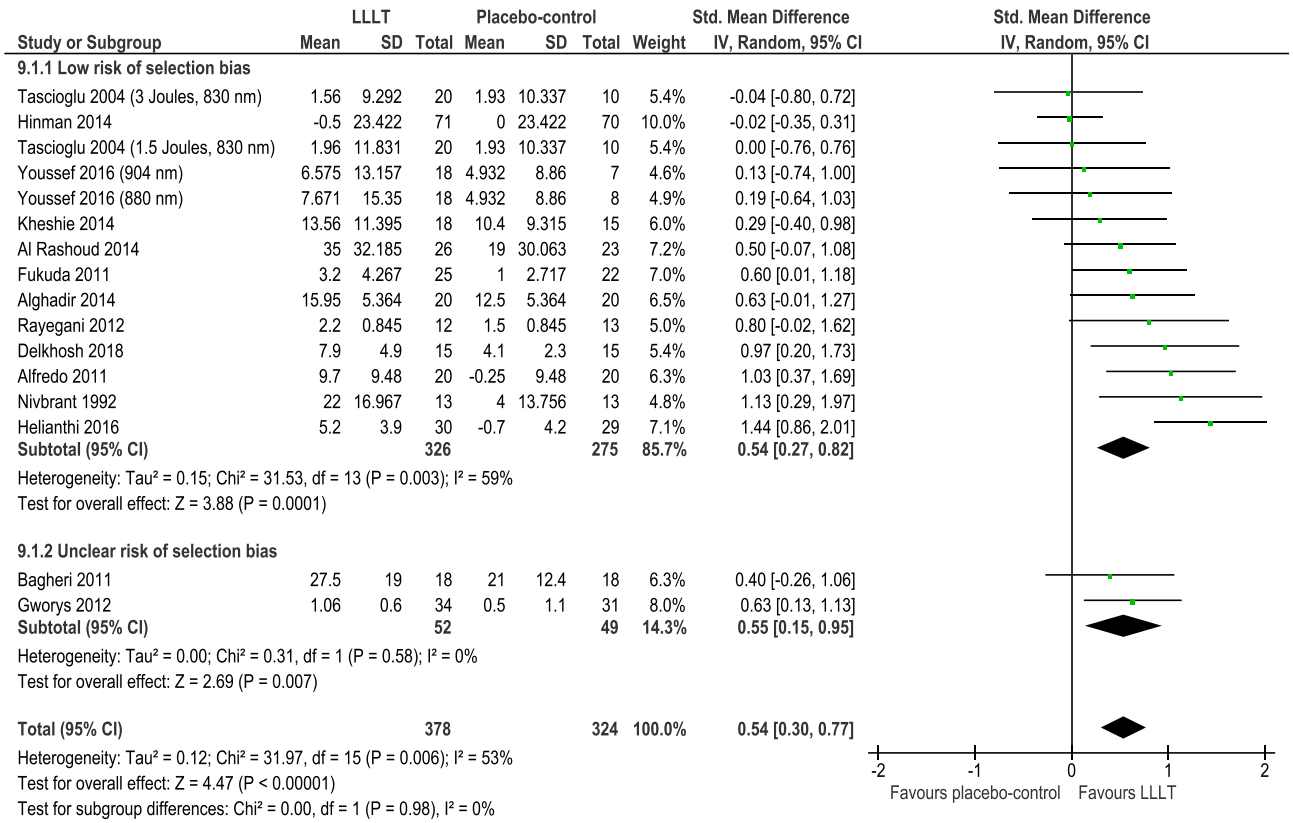

Figure 12 | Disability results - risk of selection bias (random sequence generation)

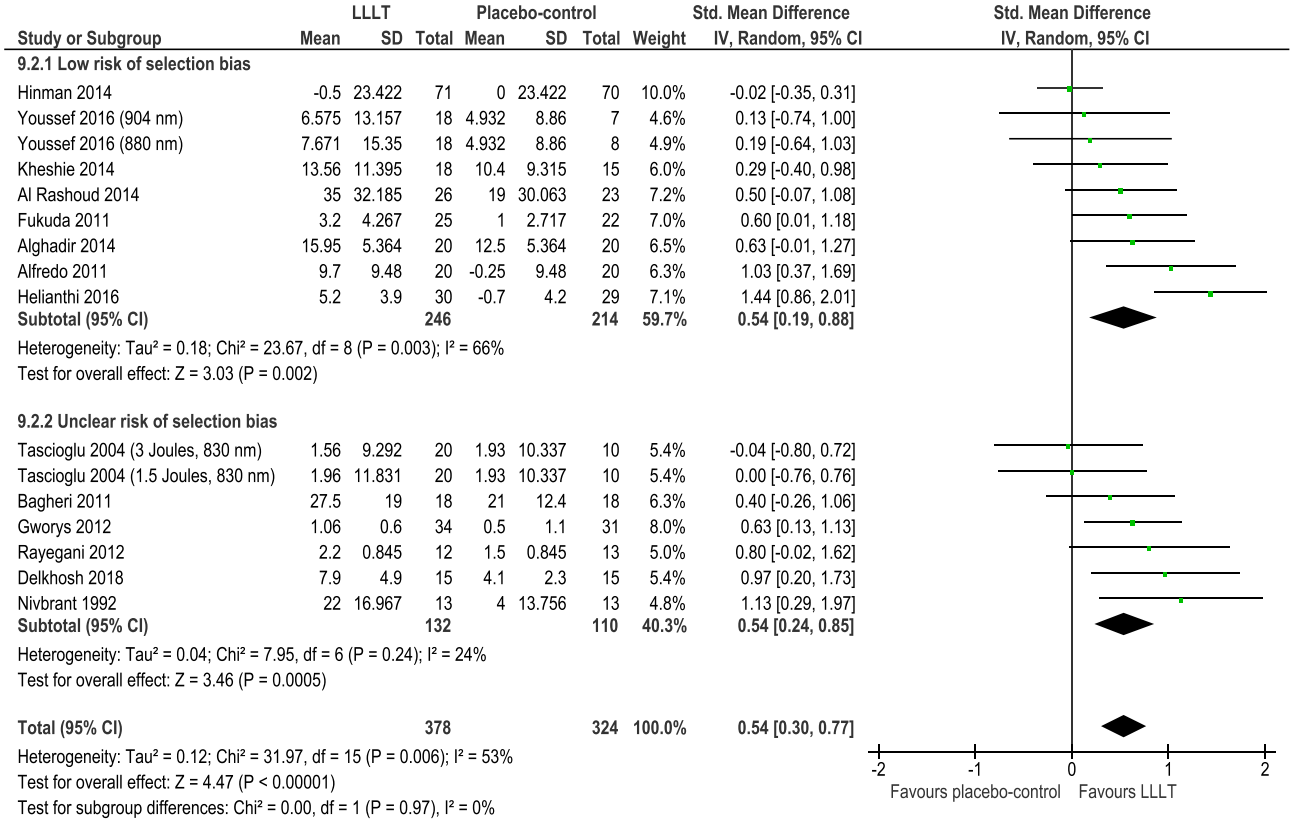

Figure 13 | Disability results - risk of selection bias (allocation concealment)

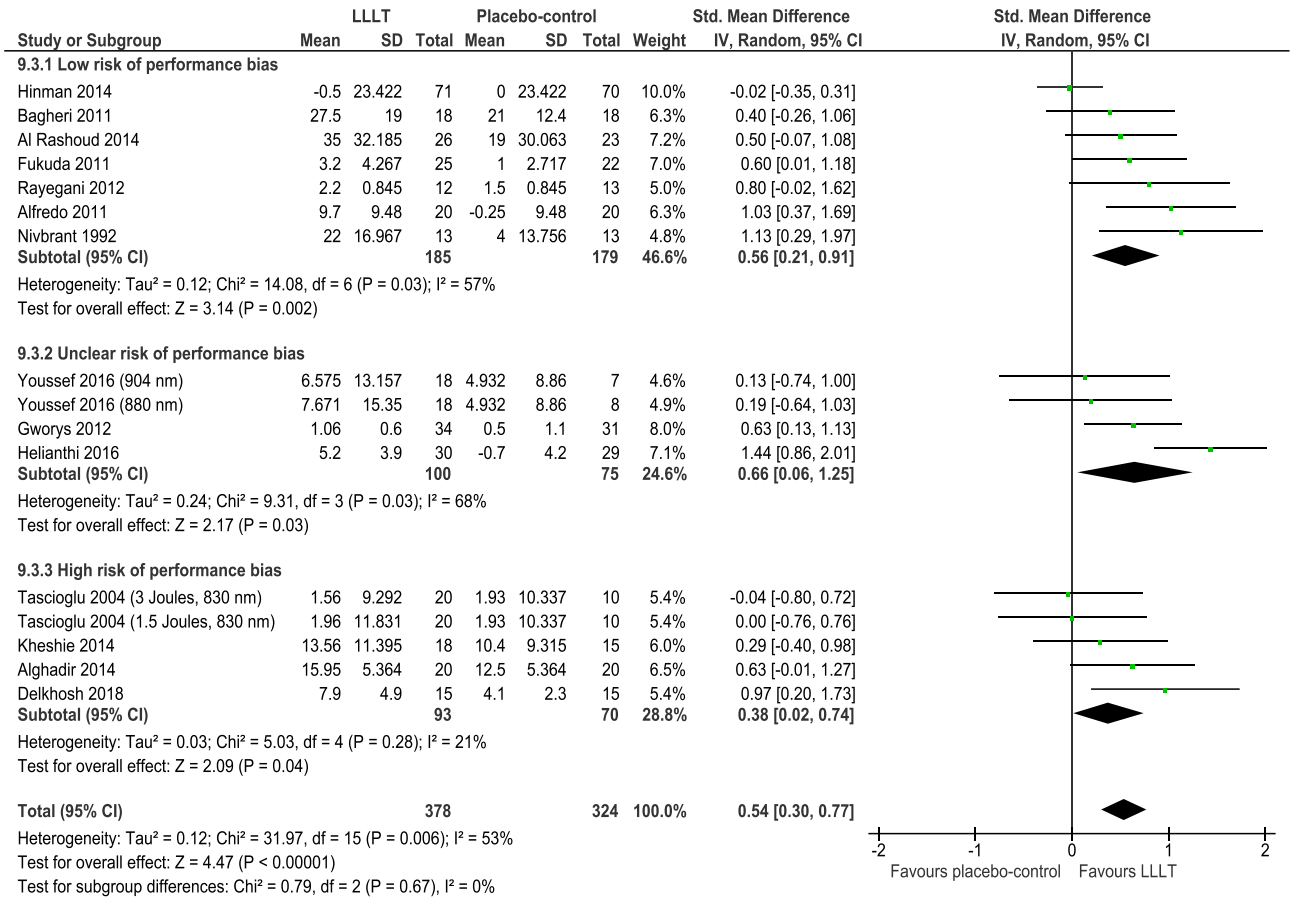

Figure 14 | Disability results - risk of performance bias (blinding of therapist)

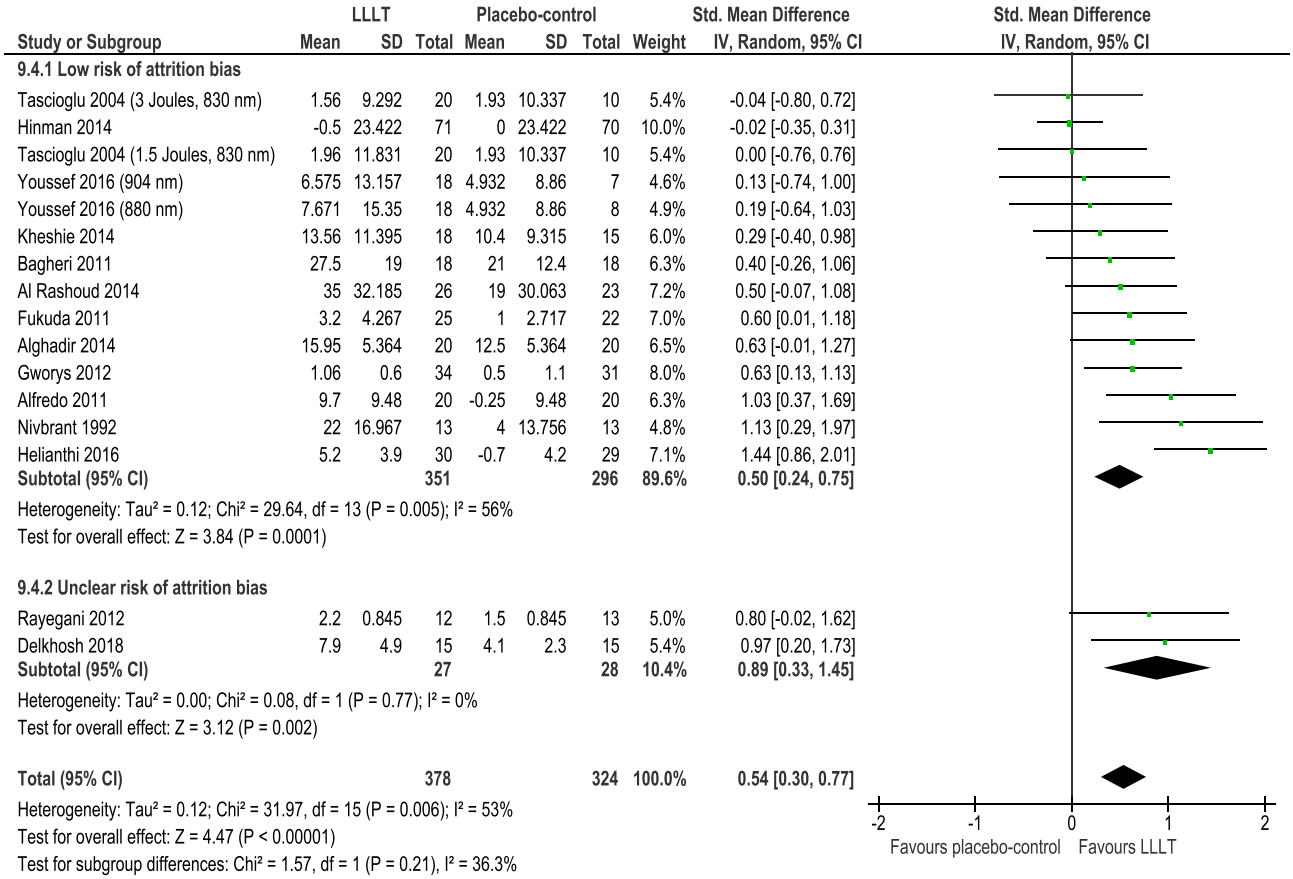

Figure 15 | Disability results - risk of attrition bias (incomplete outcome data)

Support for risk of bias judgments and funding of the included trials

Al Rashoud et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"... a randomization list was produced using software-generated randomised numbers to the randomisation depended on random blocks of 10."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	Low risk	Quote: *"Neither investigator nor the patient knew whether a placebo or active treatment was being administered to only the research assistant had the identifying code to determine which treatment was given."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"Forty-nine patients with knee osteoarthritis were assigned at random into two groups: Active laser group (n = 26) and placebo laser group (n = 23)", "... 49 completed the study ..."*. Our comment: Probably true.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (International Standard Randomised Controlled Trials Number: ISRCTN24010862).

Funding – quote: *"The project was funded by general administration for medical services of Ministry of Interior, Security Forces Hospital; Riyadh, Saudi Arabia."*.

Alfredo et al. 2011

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed by using sealed, randomly filled envelopes describing the treatment group. Patients and the physiotherapist responsible for the evaluation were unaware of randomization results"*. Our comment: Probably done. It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Allocation concealment	Low risk	Quote: *"Patients and the physiotherapist responsible for the randomization were unaware of the randomization results"*. Our comment: Probably true.
Blinding of participants and personnel	Low risk	Quote: "*All patients were treated by the same physiotherapist who had not taken part in the evaluations". "The laser equipment had two identical pens, one for the active treatment and one for the placebo treatment (sealed)".* Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"All participants were evaluated by the same blinded physiotherapist"* Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 13% of the included participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Reported in adherence to a protocol (Clinical Trials number: CT01306435).

Funding - quote: *"This study was supported financially by: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) – Foundation of Research Support of São Paulo State and Coordenação de Aperfeic, oamentode Pessoalde Nı´vel Superior (CAPES) – Coordination for the Improvement of Higher Level – or Education – Personnel. Biostatistics Support Group, Department of Dentistic, School of Odontology, University of São Paulo, São Paulo, Brazil."*.

Alghadir et al. 2013

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed using sealed, randomly filled envelopes"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	High risk	Quote: *"The treatment parameters were identical, but without switching on the machine"*. Our comment: Probably done. The study is described as single-blinded. The experimental group was treated with invisible laser. The physiotherapists treating the participants were not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"(...) all of them completed the study period."*. Our comment: Probably true.
Selective reporting	Low risk	Our comment: Reported as stated in the protocol.

Funding – quote: *"The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project NO RGP-VPP-209."*.

Bagheri et al. 2010

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Quote (translated from Farsi): *"The random distribution of people was done in such a way that the number of male and female patients is the same in both groups"*. Our comment: Not enough information to make a qualified judgment.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Low risk	Quote (translated from Farsi): *"The presence of active or inactive lasers was not known"*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded. The experimental group was treated with invisible laser.
Incomplete data	Low risk	Our comment: 10% of the participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Sponsored by the Semnan University of Science.

Bülow et al. 1994

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized, but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Low risk	Quote: *"The nurse in charge of the randomization key selected the laser or placebo-laser before each treatment"* and *"The blinded settings for patient and physician were maintained"*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcomes of interest described in the method section is missing in the result section.

Funding – quote: *"The study was sponsored by Henny and Helge Holgersen's Foundation and the Bodil Petersen Foundation."*.

Delkhosh et al. 2018

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"… volunteers are randomly allocated to three groups by lottery."*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	High risk	Quotes: *"The patients were randomly assigned to three groups: 1-standard treatment with placebo laser…"* and *"Not blinded"*. Our comment: The investigators claimed the trial was placebo-controlled which is probably true as the participants were treated with invisible laser. Therefore, it seems likely that the investigators statement regarding lack of blinding refers to the therapist.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (Iranian Registry of Clinical Trials number: IRCT201502224549N8).

Funding – quote: *"Vice chancellor for research, Semnan University of Medical Sciences."*.

Fukuda et al. 2011

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"This distribution was made by a secretary who was not involved in the treatment or evaluation, through a draw of sealed opaque envelopes. The envelopes were taken directly to the therapist without the patient having access to the result."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could easily predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"(...) two identical pens, of which one was active (laser) and the other was sealed (placebo). These were labelled A and B by the project secretary, and only this person knew the true identification of the pens."*. Our comment to the quote: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Physical Therapy Sector, Irmandade da Santa Casa de Misericórdia de São Paulo (ISCMSP), São Paulo, São Paulo, Brazil.

Gur & Oktayoglu

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Patients were randomly assigned to three treatment groups by one of the non-treating authors by drawing 1 of 120 envelopes."*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were opaque and sealed.
Blinding of participants and personnel	High risk	Quote: *"The study was conducted in a double-blind fashion. Subjects and physician were unaware of the code for active or placebo laser until the data analysis was completed but therapist was aware of the code for active or placebo laser."*. Our comment: Probably true. The experimental group was treated with invisible laser. The participants were probably blinded, but the therapist was not.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 7.5% of the participants allocated to the laser group were not evaluated. 12.5% of the participants allocated to the control group were not evaluated. These numbers are unlikely to introduce a relevant bias. Reasons for dropout across groups are similar.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Gur et al. 2003

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Patients were randomly assigned to three treatment groups by one of the non-treating authors by drawing of 1 of 90 envelopes"*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were opaque and sealed.
Blinding of participants and personnel	High risk	Quote: *"The study was conducted in a double-blind fashion. Subjects and physician were unaware of the code for active or placebo laser until the data analysis was completed but therapist was aware of the code for active or placebo laser."*. Our comment: Probably true. The experimental group was treated with invisible laser. The participants were probably blinded, but the therapist was not.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Gworys et al. 2012

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized, but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: *"(…) a placebo group where laser therapy procedures were simulated without actual irradiation."*. Our comment: Probably done. The experimental group was treated with invisible laser. The participants were probably blinded, but there is too little information to judge whether the therapists were blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Quote: *"laser the therapy sessions were performed once a day, 5 days a week over 2 weeks. Each patient attended 10 sessions."*. Our comment: All participants probably attended to all 10 sessions. The outcomes were assessed immediately after the 10 sessions. Thus, there were probably no dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Hegedus et al. 2009

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was ensured by having patients randomly choose sealed envelopes from a bowl"*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were opaque.
Blinding of participants and personnel	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. Our comment: Probably true. All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	High risk	Our comment: 50% of the participants in the control group were not evaluated while 100% of the participants in the laser group were evaluated. These numbers are likely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"The authors wish to thank Dr. Gábor Deák for the Doppler examinations and András Tóth for taking the numerous thermographic images."*.

Helianti et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"a randomization list was created using a computer-generated table containing random numbers."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	Unclear risk	Quote*: "Both investigator and participants did not know whether laser acupuncture active treatment or placebo treatment was being administered. Only the researcher and her assistant had the code to determine which treatment was given. Both groups used the same laser device and the same study site. Participant blinding was optimized by using eye mask and headset (…)"*. Our comment: The experimental group was treated with invisible laser. The investigator and participants were probably blinded, but it is unclear who administered the therapy and if this person was blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 4.8% of the participants were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding sources: Not stated.

Hinman et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"An investigator (K.N.) accessed the computerized randomization to reveal allocation."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Participant codes for randomized laser treatment groups were pre-programmed into the laser machines by an independent biomechanical engineer to permit blinding of acupuncturist and participants in these groups."*. Our comment: Probably true.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 8.45% and 17.14% had dropped out from the experimental and placebo group at week 12, respectively. Intention to treat analysis was used and this analysis and the results did not differ from the per-protocol analysis.
Selective reporting	Low risk	Our comment: Reported in adherence to a protocol (Australian New Zealand Clinical Trials Registry Number: ACTRN12609001001280).

Funding – quote: *"Funding/Support: This trial was funded by the National Health and Medical Research Council (project 566783). Drs Hinman and Bennell are both funded in part by Australian Research Council Future Fellowships (FT130100175 and FT0991413, respectively). Dr McCrory is funded in part by a National Health and Medical Research Council Practitioner Fellowship (1026383). Dr Pirotta is funded in part by a National Health and Medical Research Council Career Development Fellowship (1050830). Dr Williamson was funded in part by a National Health and Medical Research Council grant (1004233). Role of the Funder/Sponsor: The study sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; reparation, review, or approval of the manuscript; and decision to submit the manuscript for publication."*.

Jensen et al. 1987

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: (Translated from Danish) *"Two coded laser devices of the same appearance was utilized in the trial. One of the devices was inactive and served as control. The other was active with infrared laser."*. Our comment: The experimental group was treated with invisible laser. The participants were probably blinded, but it is unknown whether the therapists were blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are assessed and reported by the participants. The experimental group was treated with invisible laser.
Incomplete data	Low risk	Our comment: 1 participant was not evaluated.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Kheshie et al. 2014

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Randomization was performed simply by assigning a specific identification number for each patient. These numbers were randomized into three groups using the SPSS program"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Investigators are unable to predict the allocation made by a computer-based randomization program.
Blinding of participants and personnel	High risk	Our comment: The study is described as single-blinded and the participants were probably blinded. Thus, the therapist was not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 15% and 0% dropped out of the placebo and experimental group, respectively. These numbers are unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"This research received a grant from the Institute of Scientific Research and Revival of Islamic Heritage at Umm Al-Qura University, Makkah, Saudi Arabia."*.

Koutenaei et al. 2017

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"…were assigned randomly (using random blocks) …"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: The use of random blocks was probably sufficient.
Blinding of participants and personnel	Low risk	Quote: *"The placebo group also lasted for 70 seconds in these places, but the laser had no output"*. Our comment: Both participants and therapists were probably blinded because they described the study as double-blinded and treated the intervention group with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: *"The study was supported by the Department of Physiotherapy at the University of Social Welfare and Rehabilitation Sciences."*.

Mohammed et al. 2017

Type of bias	Judgment	Support for judgment
Random sequence generation	Unclear risk	Our comment: The authors state that the study is randomized but there is no description of the randomization method.
Allocation concealment	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	High risk	Quote: *"(…) placebo laser (laser probe is directed to the same acupoints while the device is off).".* Our comment: Probably done. The experimental group was treated with invisible laser. The study is described as single-blinded and the participants were probably blinded. As there was no description of a blinding procedure of the therapist, we assume that this person was not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding – quote: Not stated. The authors state: *"The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication."*.

Nambi et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Thirty-four subjects were randomized into two groups (active and placebo) by an investigator who is not involved in assessment, diagnosis or treatment. Randomization was performed by using sealed randomly filled envelopes from a bowl containing an equal number of slips with either number 1 or 2"*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: It seems unlikely that the investigators could predict the group allocation due to the sequence generation.
Blinding of participants and personnel	Low risk	Quote: *"Subjects and the physiotherapist responsible for the evaluation were unaware of randomization results.". "super pulsed laser with (…) or with a placebo probe (…) of the same appearance and display."*. Our comment: Probably true. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Quote: *"All subjects were evaluated by the same blinded physiotherapist"*. Our comment: Probably done. All outcomes of interest are assessed and reported by the participants who were probably blinded.
Incomplete data	Low risk	Quote: *"The required sample for the study was 17 subjects per group". "All 34 subjects completed the study with the 8-week follow-up evaluation.".* Our comment: Probably true.
Selective reporting	Low risk	Our comment: No outcomes of interest described in the method section was missing in the result section.

Funding - quote: *"Authors are grateful to the Deanship of scientific Research, Prince Sattam Bin Abdul Aziz University, Al-Kharj, Saudi Arabia for the financial support to carry out this project no 2015/01/4375. Research funding program: Specialized Research Grant program (Health).".*

Nivbrant et al. 1992

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Our comment: Randomization was performed by drawing of randomly filled envelopes describing the treatment group.
Allocation concealment	Unclear risk	Our comment: It is unclear whether envelopes were sequentially numbered, opaque and sealed.
Blinding of participants and personnel	Low risk	Quote (translated from Swedish): *"The placebo emitter was visually identical to the active laser. A practitioner otherwise not involved in the trial treated the participants with laser. The practitioner was unaware of which was the active and inactive laser."*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor (detection bias)	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	Our comment: 13% in each group were not evaluated. This number is unlikely to introduce a relevant bias.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Rayegani et al. 2012

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Randomization was ensured by having patients randomly choose sealed envelopes from a bowl.
Allocation concealment	Unclear risk	Our comment: It is unclear whether the envelopes were opaque.
Blinding of participants and personnel	Low risk	Quote: *"Neither the patients nor the operator knew which was the active or placebo LLLT probe."*. *"The placebo group was treated with an ineffective probe (power 0 mW) and with the same method."*. Our comment: Probably done. The experimental group was treated with invisible laser.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Unclear risk	Our comment: Not enough information to make a qualified judgment.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Tascioglu et al. 2004

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"Sixty patients, who fulfilled the entry criteria, were admitted to the study and they were randomly divided into three groups using numbered envelopes"*. Our comment: Probably done.
Allocation concealment	Unclear risk	Our comment: It is unclear whether the envelopes were sealed and opaque.
Blinding of participants and personnel	High risk	Our comment: The study is described as single-blinded and the participants were probably blinded. Thus, the therapist was probably not blinded.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are assessed and reported by the participants who were probably blinded.
Incomplete data	Low risk	Our comment: No dropouts.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Youssef et al. 2016

Type of bias	Judgment	Support for judgment
Random sequence generation	Low risk	Quote: *"They were assigned randomly to three groups by a blinded and independent research assistant who opened sealed envelopes that contained a computer-generated randomization card according to the recruitment diagram."*. Our comment: Probably done.
Allocation concealment	Low risk	Our comment: Not enough information to make a qualified judgment.
Blinding of participants and personnel	Unclear risk	Quote: *"(...) in the placebo group, procedure was identical but without emission of energy. The laser equipment had two identical pens, one for the active treatment and one for the placebo treatment (sealed)."*. Our comment: Probably done. The experimental group was treated with invisible laser. The participants were probably blinded, but there was no information regarding blinding of therapists.
Blinding of assessor	Low risk	Our comment: All outcomes of interest are self-reported (participant-assessed) and the participants were probably blinded.
Incomplete data	Low risk	1 participant was not evaluated.
Selective reporting	Low risk	Our comment: No outcome of interest described in the method section is missing from the result section.

Funding: Not stated.

Low-Level Laser Therapy with and without exercise therapy

Subgroup analyses were performed to assess the impact of exercise therapy on the effect of Low-Level Laser Therapy in a treatment package (results are from immediately after the end of therapy, primarily). Low-Level Laser Therapy was significantly superior to the placebo-control both with and without exercise therapy (figure 16-17). The levels of statistical heterogeneity were unaltered in the pain analyses (figure 16), and slightly lowered in the disability analysis (figure 17).

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Placebo-control Mean	Placebo-control SD	Placebo-control Total	Weight	Mean Difference IV, Random, 95% CI
16.1.1 With exercise therapy								
Youssef 2016 (904 nm)	6.667	13.34	18	2.5	4.492	7	4.3%	4.17 [-2.84, 11.17]
Gur and Oktayoglu (unpublished)	45	17.267	37	40	10.479	35	4.4%	5.00 [-1.56, 11.56]
Youssef 2016 (880 nm)	9.167	18.343	18	2.5	4.492	8	4.2%	6.67 [-2.36, 15.69]
Kheshie 2014	26.425	22.207	18	17.7	16.557	15	3.7%	8.73 [-4.52, 21.97]
Bagheri 2011	28	18.5	18	19	10	18	4.1%	9.00 [-0.72, 18.72]
Alfredo 2011	12.75	12.862	20	3.75	12.862	20	4.3%	9.00 [1.03, 16.97]
Alghadir 2014	29.5	13.994	20	20.5	13.994	20	4.2%	9.00 [0.33, 17.67]
Al Rashoud 2014	32	13.617	26	21	19.656	23	4.1%	11.00 [1.41, 20.59]
Gur 2003 (1 Joules, 904 nm)	36.4	23.113	30	24.4	23.113	15	3.6%	12.00 [-2.33, 26.33]
Gur 2003 (1.5 Joules, 904 nm)	37.4	25.039	30	24.4	25.039	15	3.5%	13.00 [-2.52, 28.52]
Delkhosh 2018	25	14	15	11	7	15	4.3%	14.00 [6.08, 21.92]
Koutenaei 2017	29	8.656	20	8.5	7.152	20	4.5%	20.50 [15.58, 25.42]
Nambi 2016	54	9.186	17	4	10.184	17	4.4%	50.00 [43.48, 56.52]
Subtotal (95% CI)			**287**			**228**	**53.4%**	**13.41 [5.46, 21.37]**
Heterogeneity: Tau² = 190.29; Chi² = 143.84, df = 12 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 3.31 (P = 0.0009)								
16.1.2 Without exercise therapy								
Jensen 1987	-0.733	15.491	13	3.869	11.612	16	4.0%	-4.60 [-14.76, 5.56]
Tascioglu 2004 (3 Joules, 830 nm)	0.4	16.771	20	1.45	18.254	10	3.7%	-1.05 [-14.54, 12.44]
Hinman 2014	-0.5	40.538	71	0	40.538	70	3.7%	-0.50 [-13.88, 12.88]
Tascioglu 2004 (1.5 Joules, 830 nm)	3.6	22.697	20	1.45	18.254	10	3.5%	2.15 [-12.91, 17.21]
Bülow 1994	6.349	10.582	14	1.587	11.17	15	4.3%	4.76 [-3.15, 12.68]
Gworys 2012	20	8	34	15	10	31	4.5%	5.00 [0.57, 9.43]
Fukuda 2011	17	22.67	25	9	13.78	22	4.0%	8.00 [-2.59, 18.59]
Rayegani 2012	12.5	10.215	12	4	10.215	13	4.3%	8.50 [0.49, 16.51]
Nivbrant 1992	23	15.31	13	4	17.556	13	3.8%	19.00 [6.34, 31.66]
Hegedus 2009	-17.1	16.418	18	-41.3	40.05	9	2.3%	24.20 [-3.04, 51.44]
Mohammed 2018	46.602	10.204	20	11.65	12.028	20	4.3%	34.95 [28.04, 41.86]
Helianthi 2016	41.07	15.3	30	3.59	17	29	4.2%	37.48 [29.22, 45.74]
Subtotal (95% CI)			**290**			**258**	**46.6%**	**11.39 [2.72, 20.07]**
Heterogeneity: Tau² = 198.98; Chi² = 113.75, df = 11 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 2.57 (P = 0.01)								
Total (95% CI)			**577**			**486**	**100.0%**	**12.48 [6.76, 18.19]**
Heterogeneity: Tau² = 183.20; Chi² = 262.17, df = 24 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%								

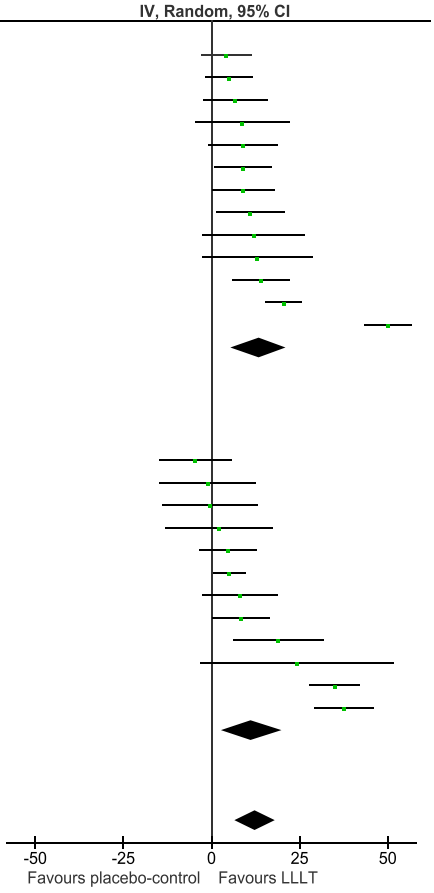

Figure 16 | Low-Level Laser Therapy with and without exercise therapy (pain)

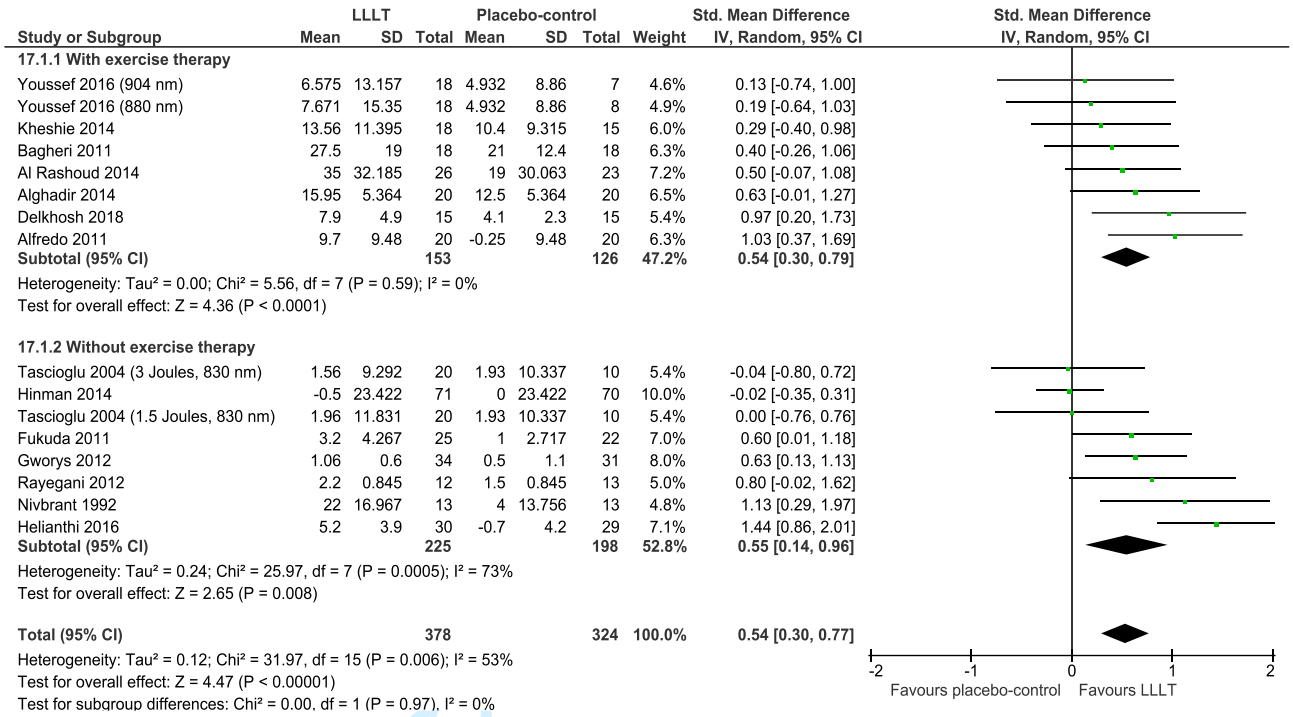

Figure 17 | Low-Level Laser Therapy with and without exercise therapy (disability)

Mean Difference vs Standardized Mean Difference

The levels of statistical heterogeneity changed only negligible when we switched from the Mean Difference (MD) method to the Standardized Mean Difference (SMD) method (figure 18-21). The trial by Hegedus et al. was omitted from these analyses as they solely reported final scores, and it is inappropriate to mix final scores with change scores in SMD analyses (figure 18-19).

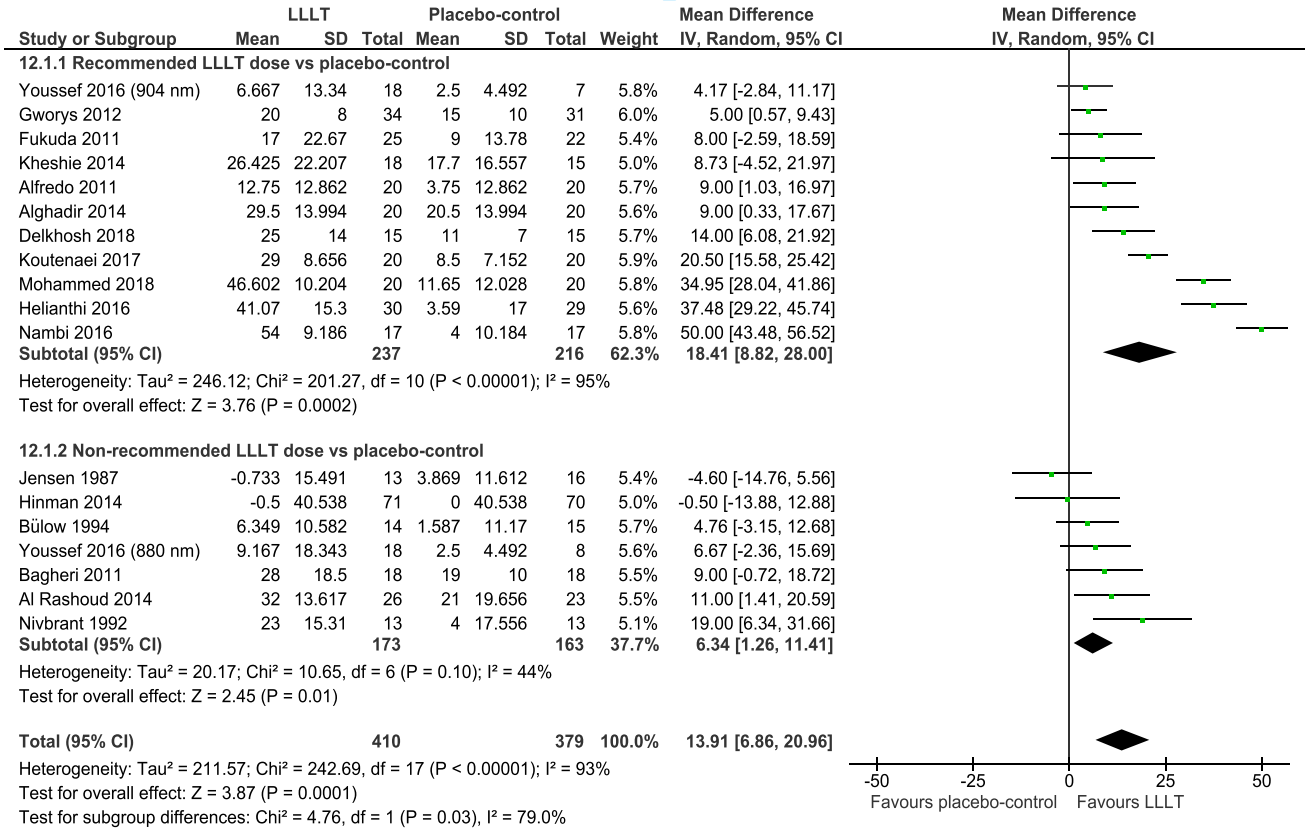

Figure 18 | Mean Difference (pain results from immediately after the end of therapy)

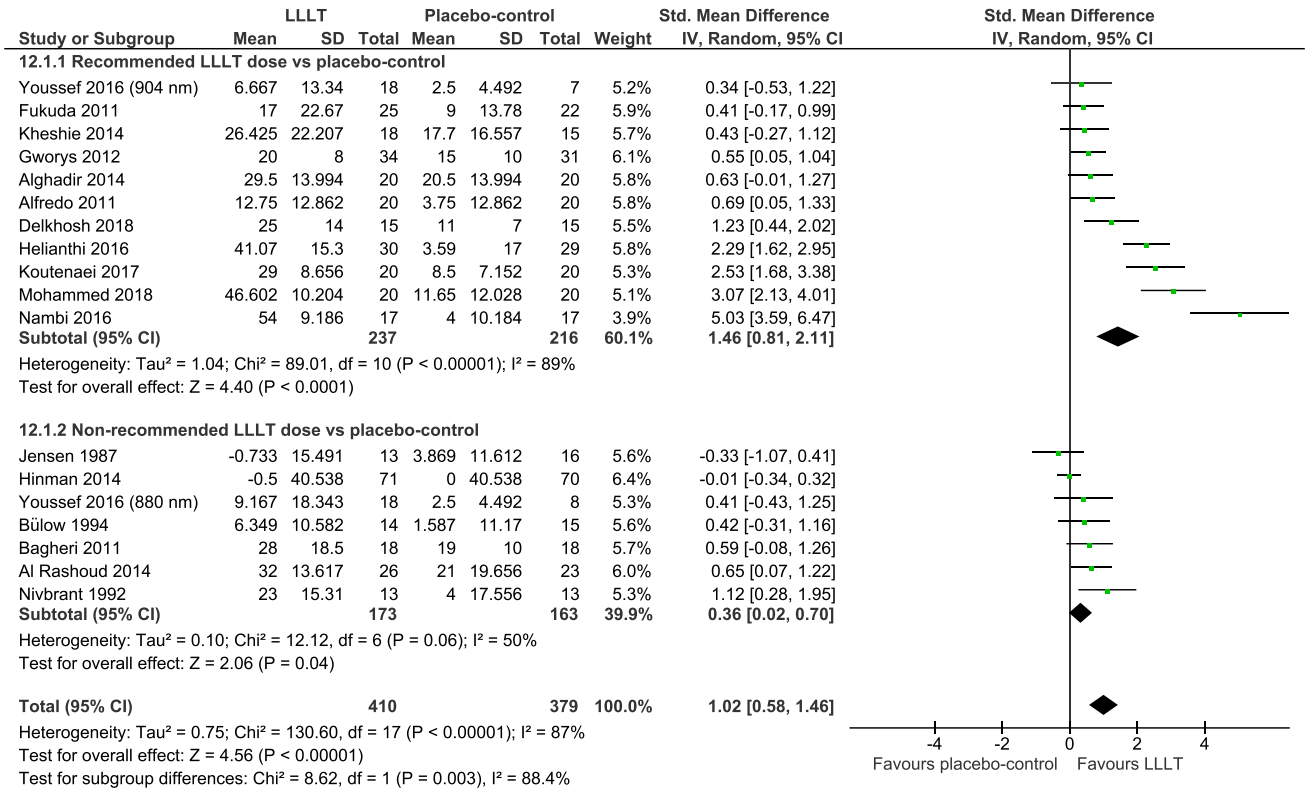

Figure 19 | Standardized Mean Difference (pain results from immediately after the end of therapy)

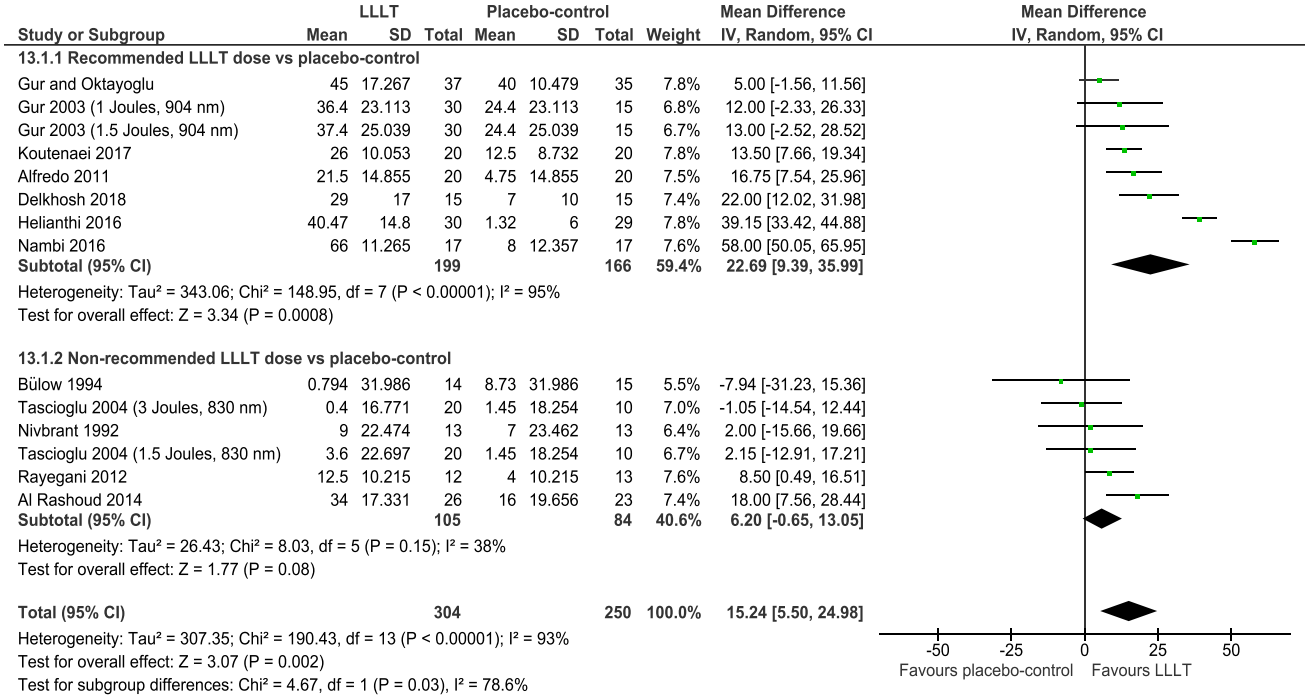

Figure 20 | Mean Difference (pain results from 2-12-weeks follow-ups)

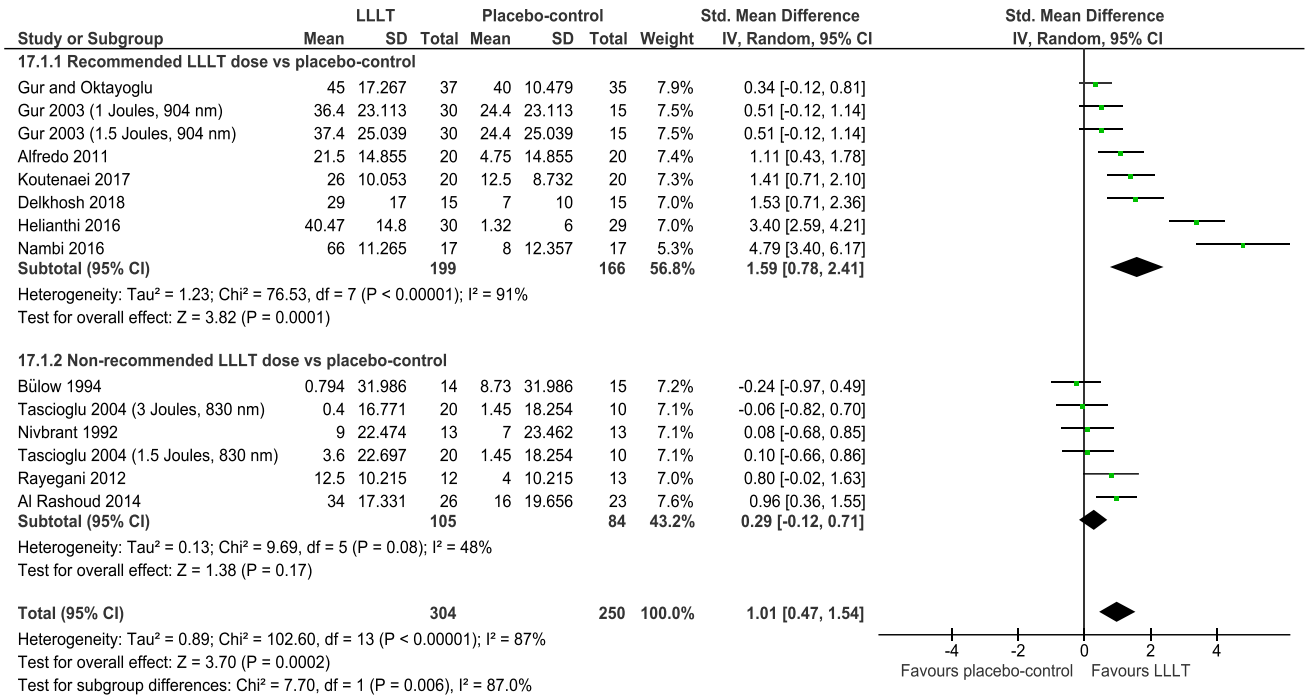

Figure 21 | Standardized Mean Difference (pain results from 2-12-weeks follow-ups)

References

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PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3 + PROSPERO protocol
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3 + PROSPERO protocol
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 3 + PROSPERO protocol
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 3 + PROSPERO protocol
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4 + PROSPERO protocol
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5-8 (table 1-2) + PROSPERO protocol
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 3-4 + PROSPERO protocol + supplementary material
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4 + PROSPERO protocol
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4 + supplementary material + PROSPERO protocol

PRISMA checklist (continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 3 + 9 + supplementary material
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 9 + supplementary material
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 4 + figure 1 + supplementary material
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5-8 (table 1-2)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 9 (figure 6) + supplementary material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	figure 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 8-9 + figure 2-5 + supplementary material
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9 + supplementary material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 9 + supplementary material
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11 + PROSPERO protocol