Supplementary material for the article entitled: Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials

Table of content

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 versus 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 versus 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 randomisation
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

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

Stausholm MB, *et al. BMJ Open* 2019; 9:e031142. doi: 10.1136/bmjopen-2019-031142

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).

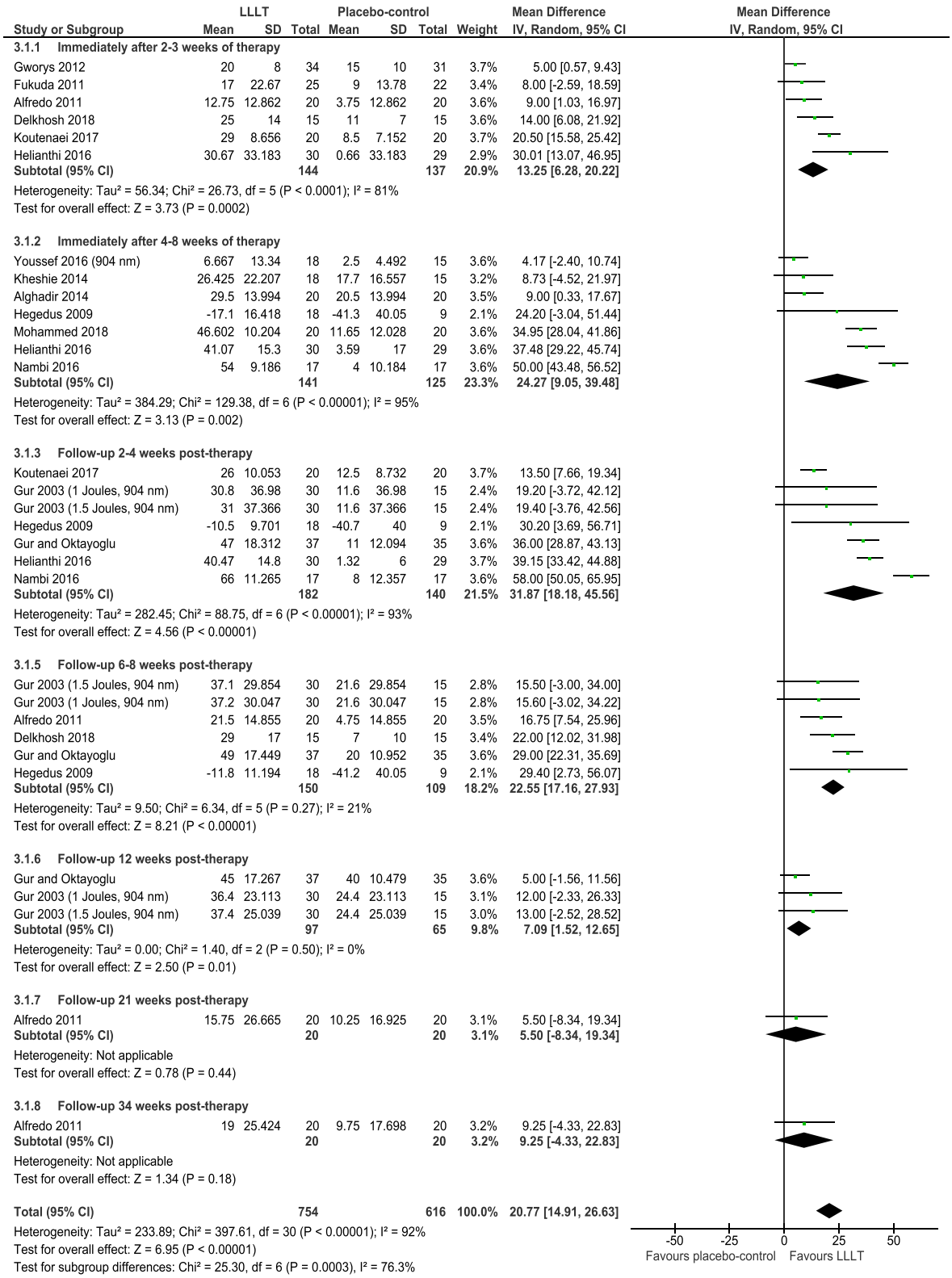

Figure 1 Pain time-effect profile (recommended low-level laser therapy doses versus placebo-control)

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 (figures 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 on a Visual Analogue Scale (VAS) (figures 4-5) and disability from 0.57 to 0.48 Standardised Mean Difference (SMD) (figures 6-7).

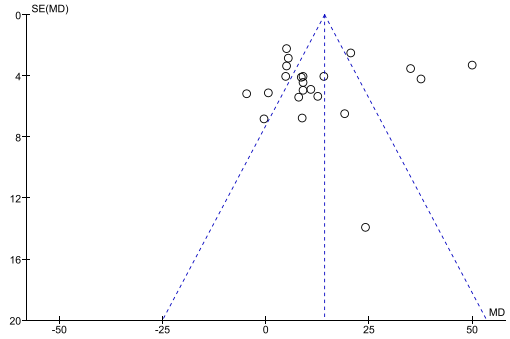

Figure 2 Funnel plot (pain)

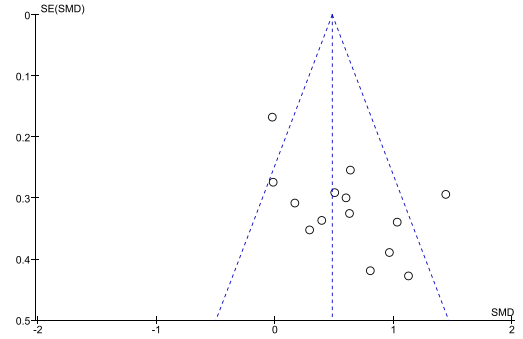

Figure 3 Funnel plot (disability)

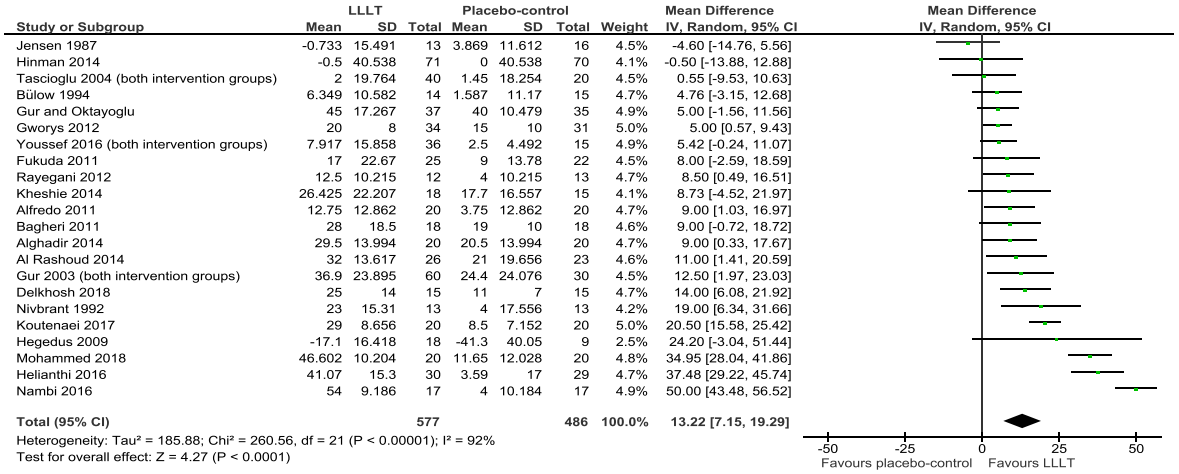

Figure 4 Random effects model (pain)

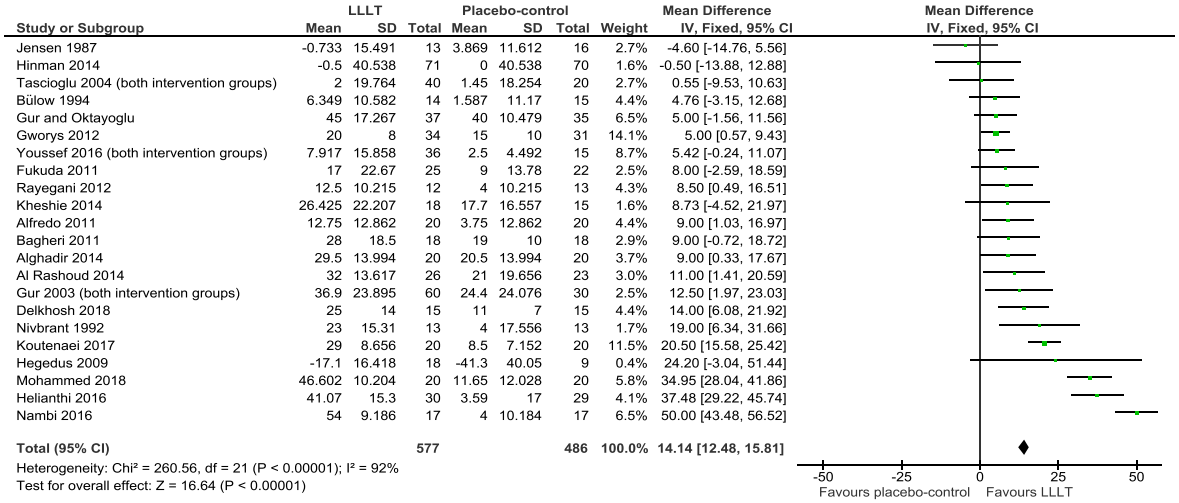

Figure 5 Fixed effects model (pain)

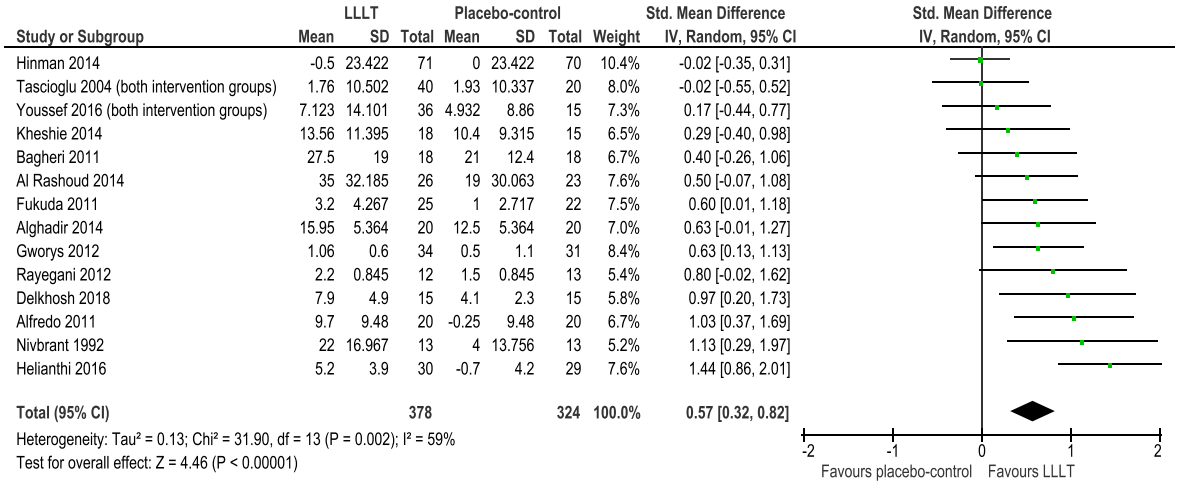

Figure 6 Random effects model (disability)

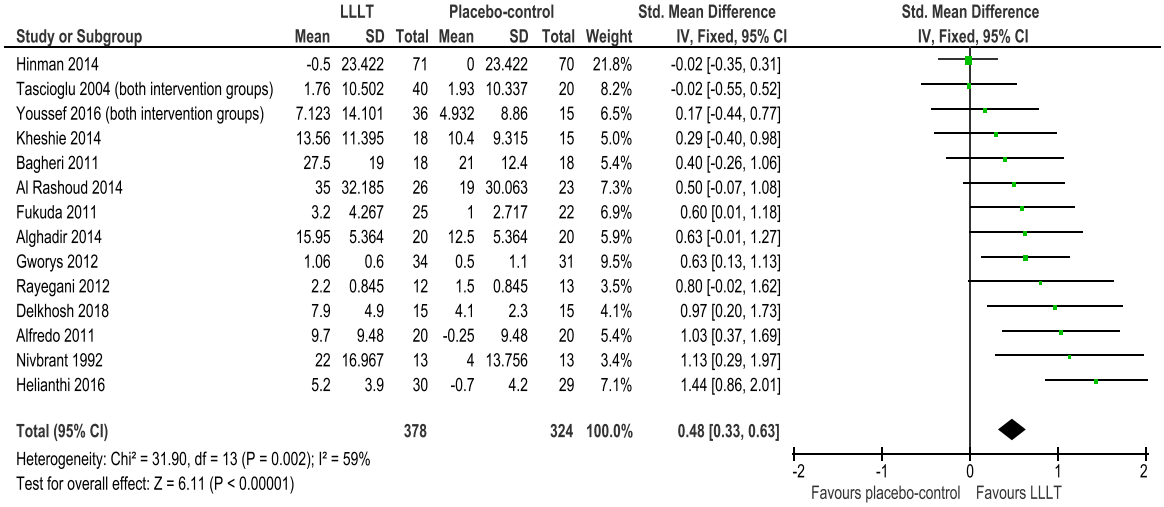

Figure 7 Fixed effects model (disability)

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 (figures 8-15).

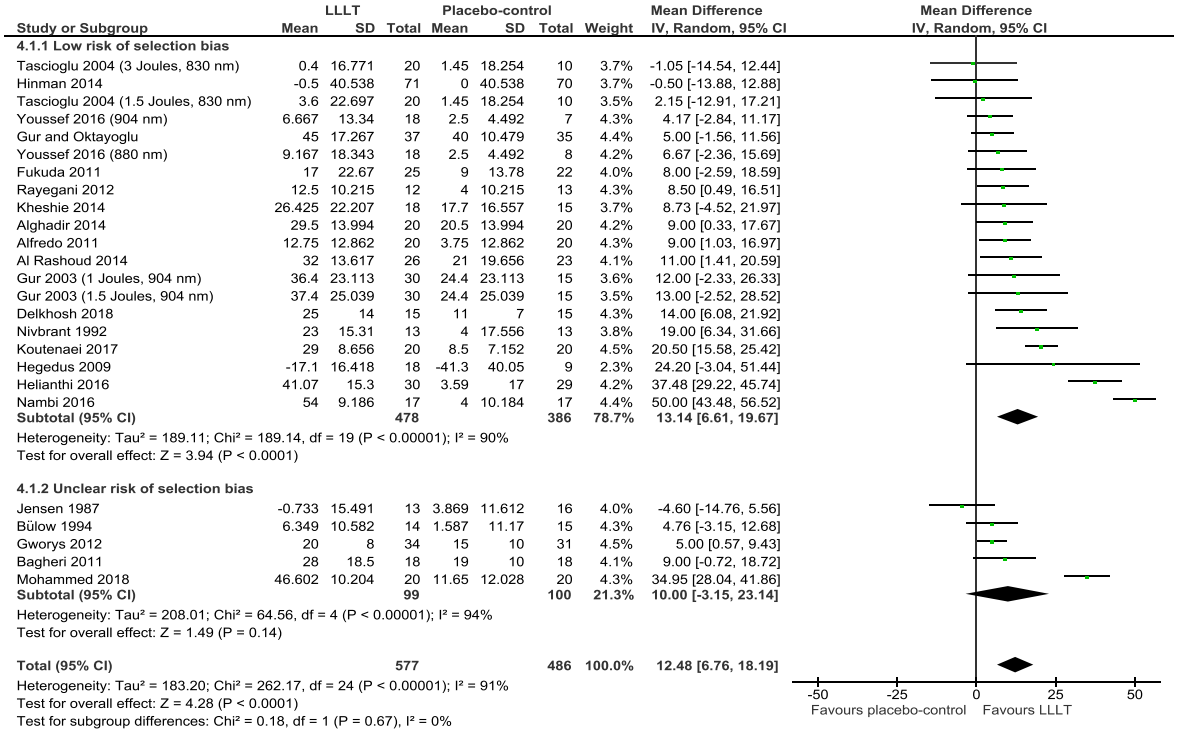

Figure 8 Pain results - risk of selection bias (random sequence generation)

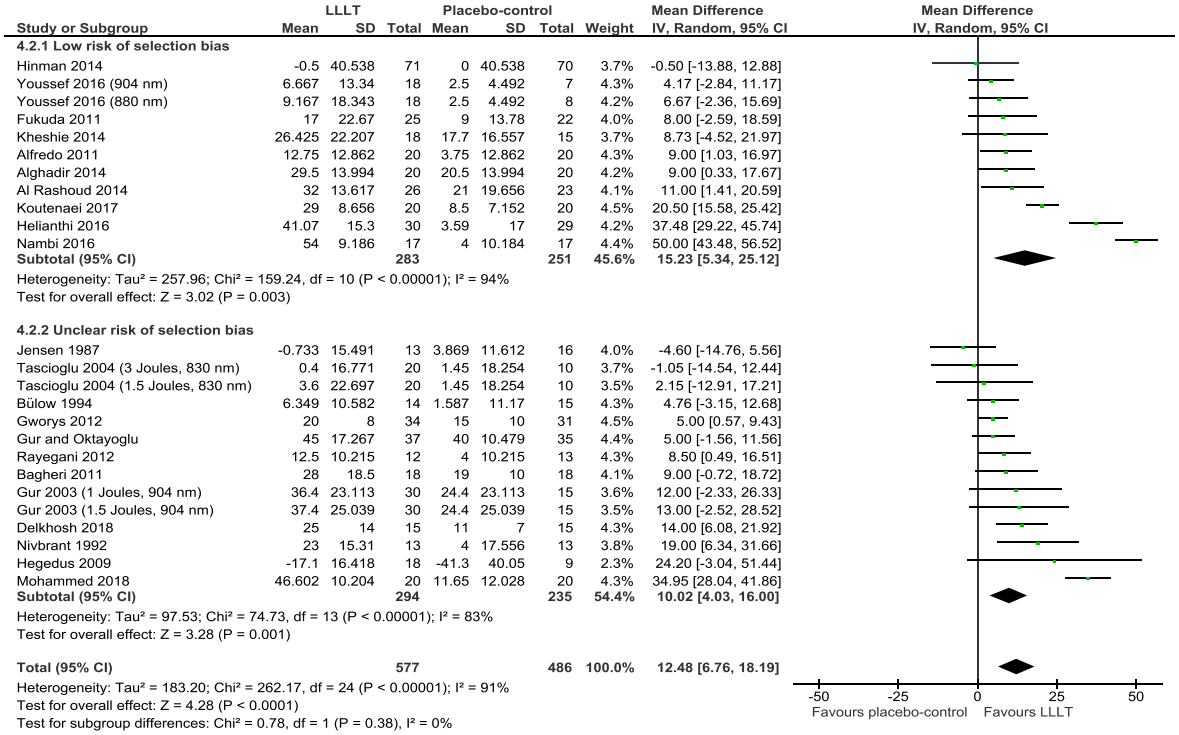

Figure 9 Pain results - risk of selection bias (allocation concealment)

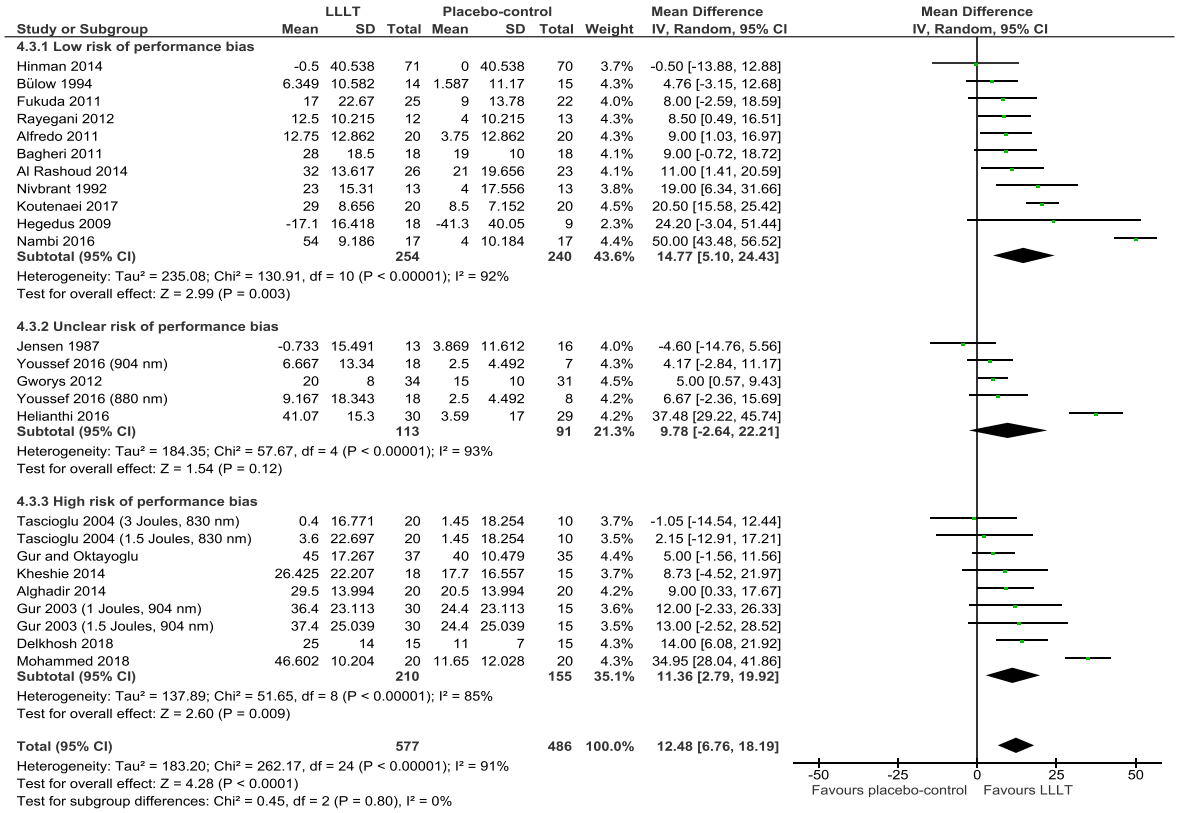

Figure 10 Pain results - risk of performance bias (blinding of therapist)

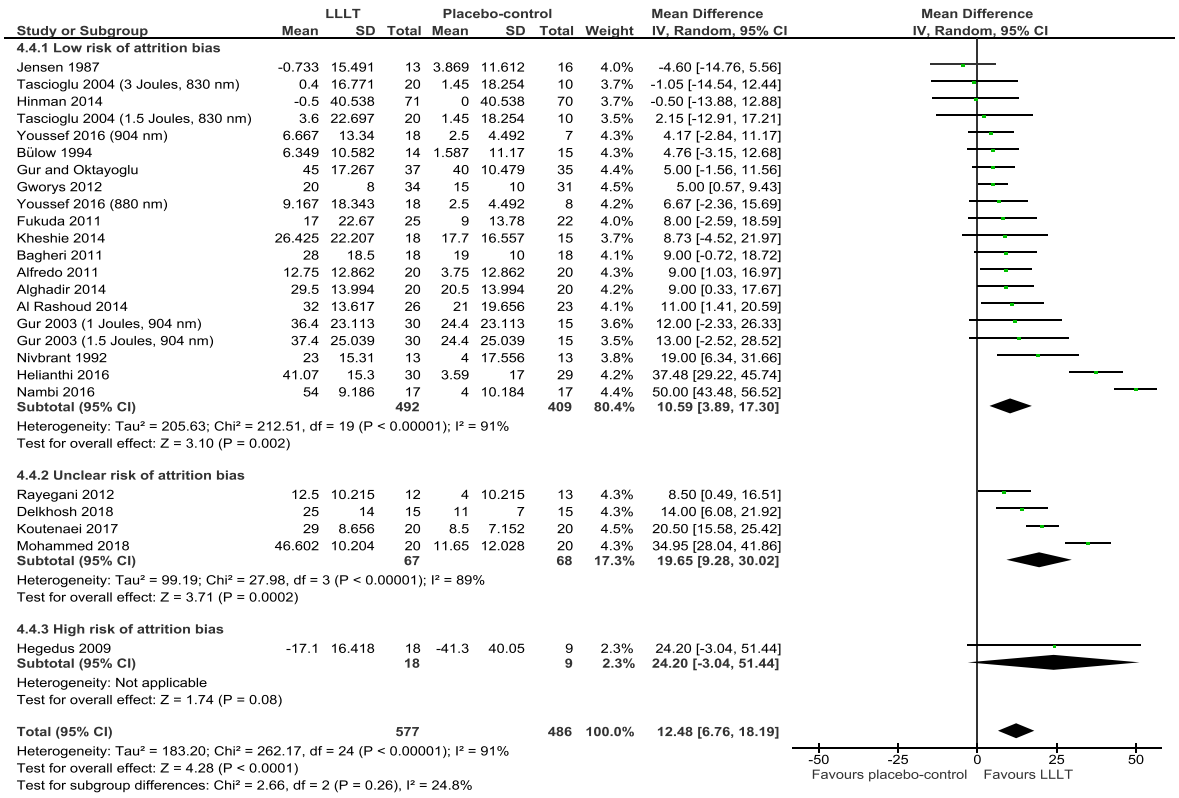

Figure 11 Pain results - risk of attrition bias (incomplete outcome data)

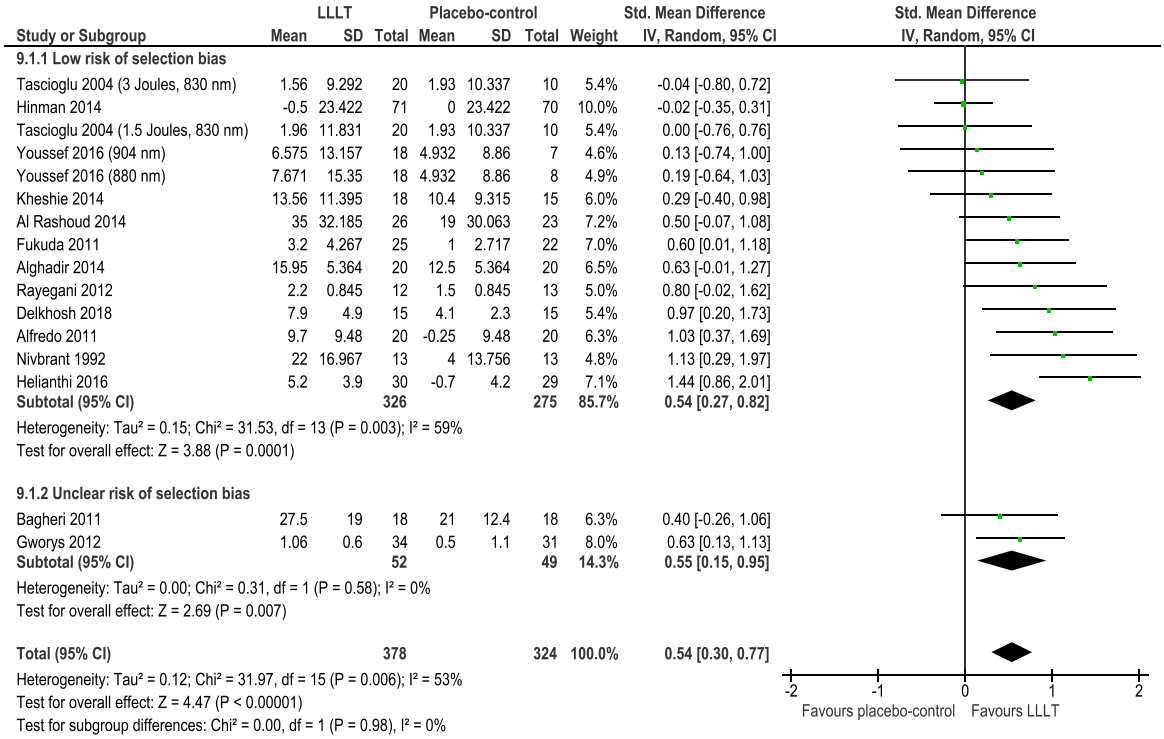

Figure 12 Disability results - risk of selection bias (random sequence generation)

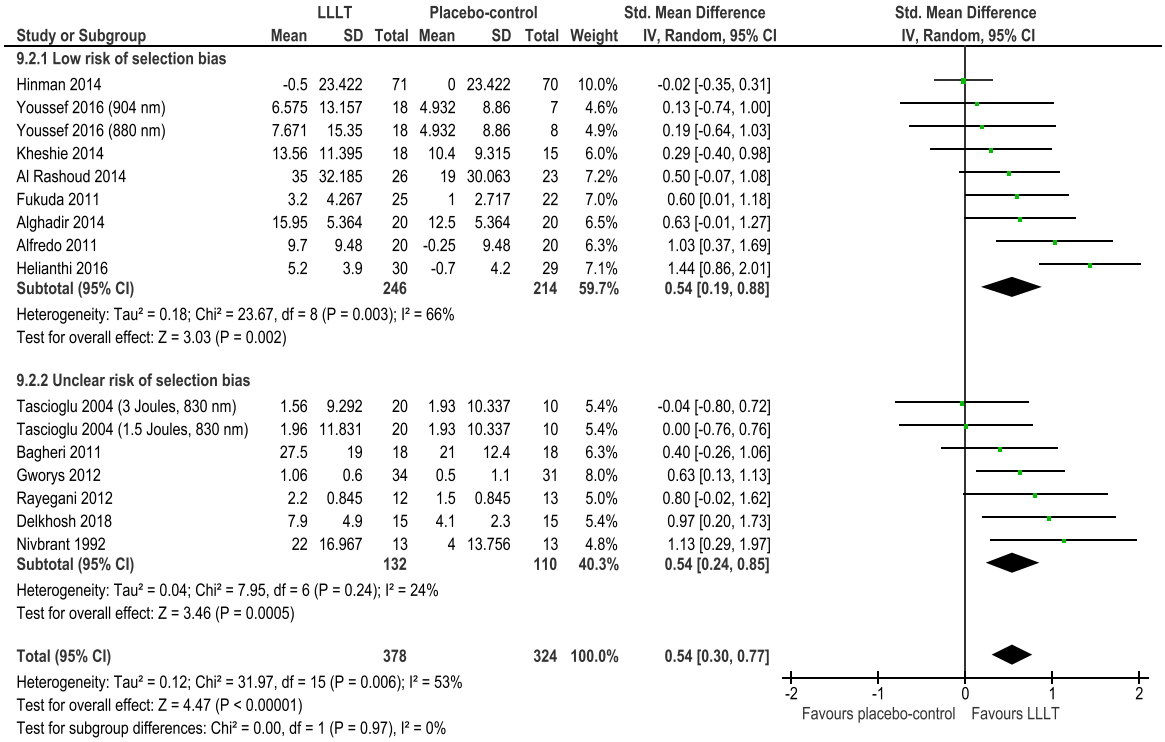

Figure 13 Disability results - risk of selection bias (allocation concealment)

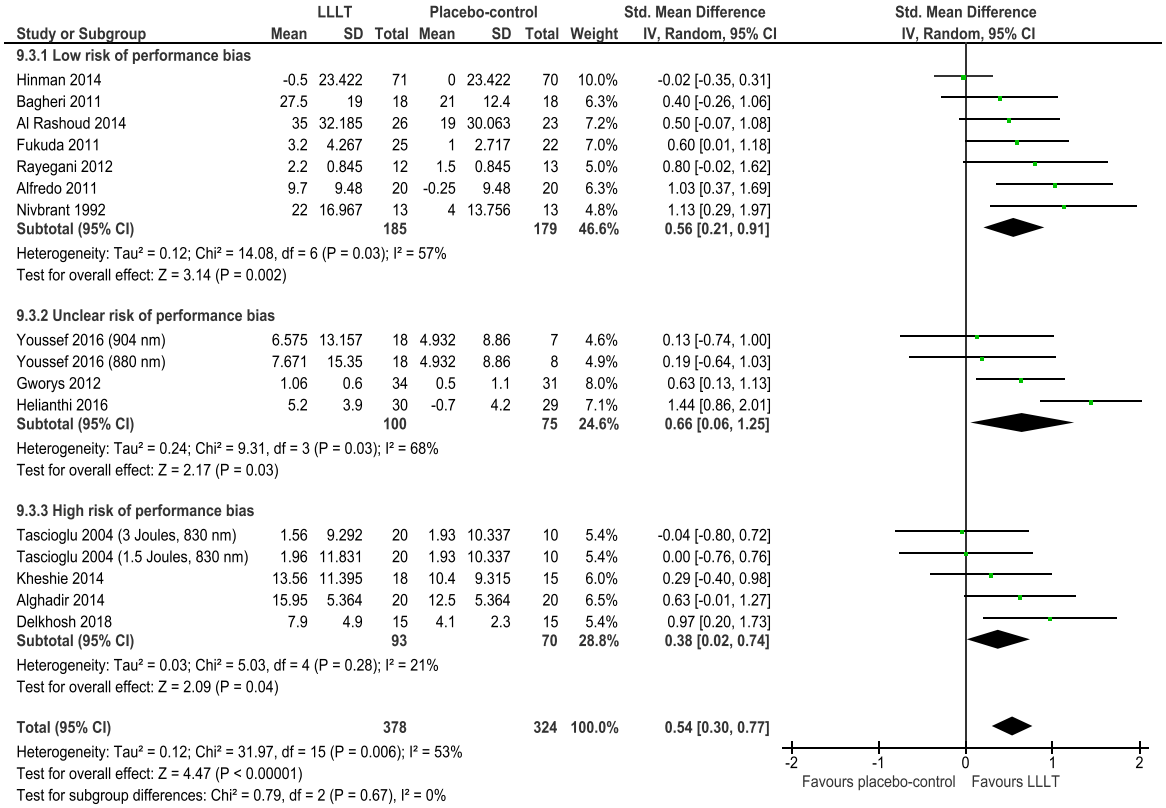

Figure 14 Disability results - risk of performance bias (blinding of therapist)

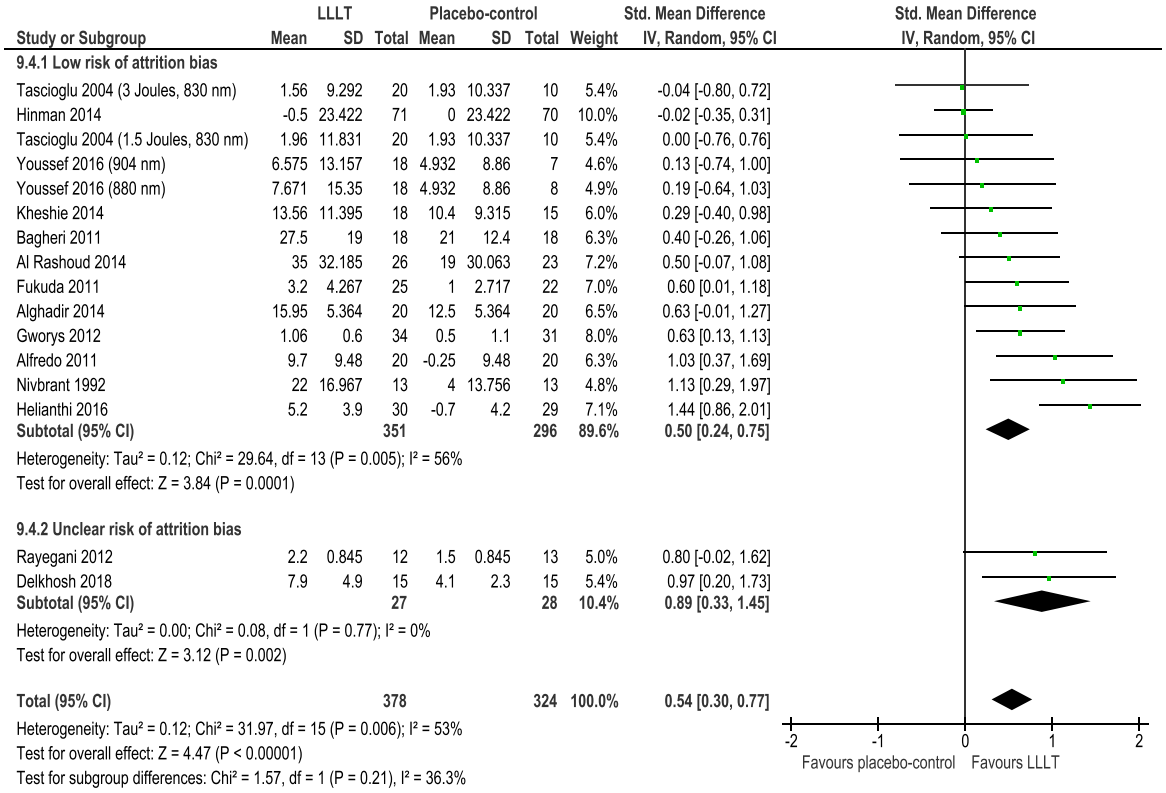

Figure 15 Disability results - risk of attrition bias (incomplete outcome data)

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 randomisation 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."*.

Stausholm MB, *et al. BMJ Open* 2019; 9:e031142. doi: 10.1136/bmjopen-2019-031142

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 randomised, but there is no description of the randomisation 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 randomised, but there is no description of the randomisation 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 randomisation 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.

Stausholm MB, *et al. BMJ Open* 2019; 9:e031142. doi: 10.1136/bmjopen-2019-031142

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 randomised but there is no description of the randomisation 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 randomisation 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 randomised but there is no description of the randomisation 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: Randomisation 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	Randomisation 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.

Exercise therapy as cointervention

Low-level laser therapy was significantly superior to placebo both with and without exercise therapy as cointervention (results are from immediately after the end of therapy, primarily) (figures 16-17). The levels of statistical heterogeneity were unaltered in the pain analysis (figure 16) and slightly lowered in the disability analysis (figure 17).

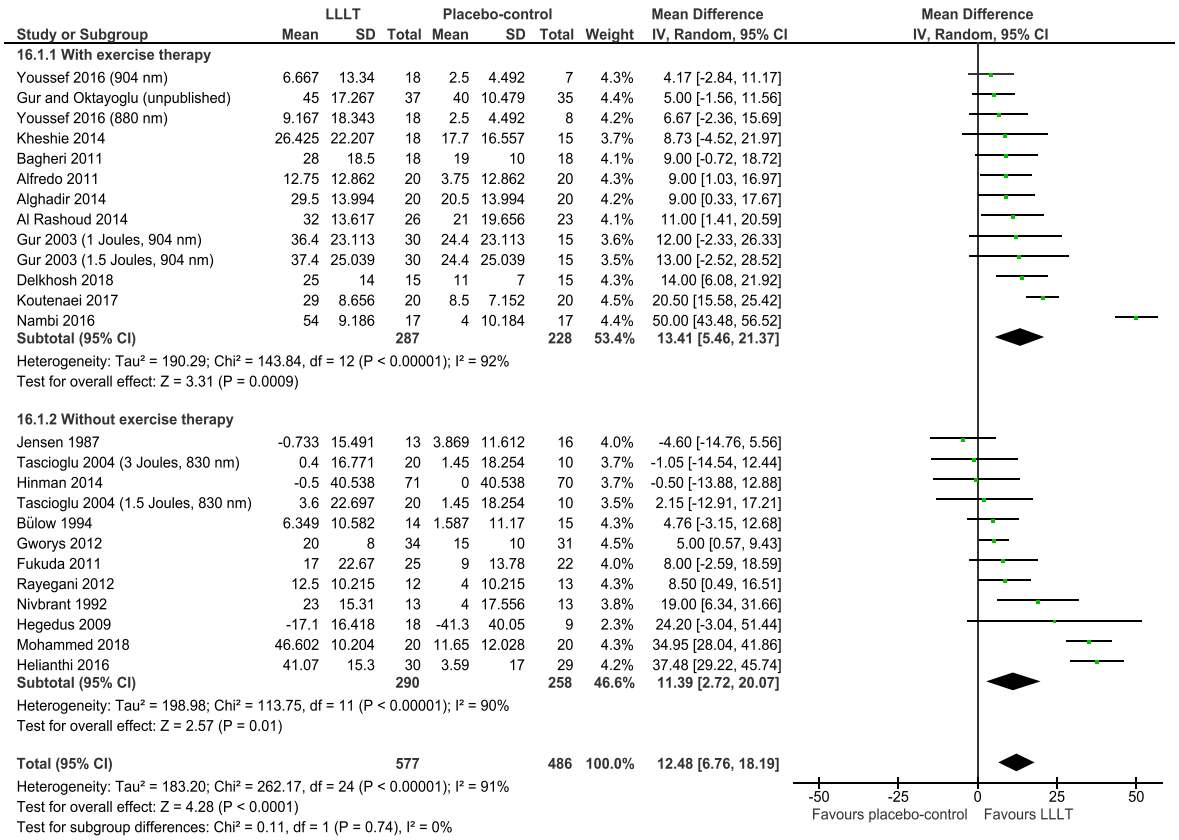

Figure 16 Results with and without exercise therapy as cointervention (pain)

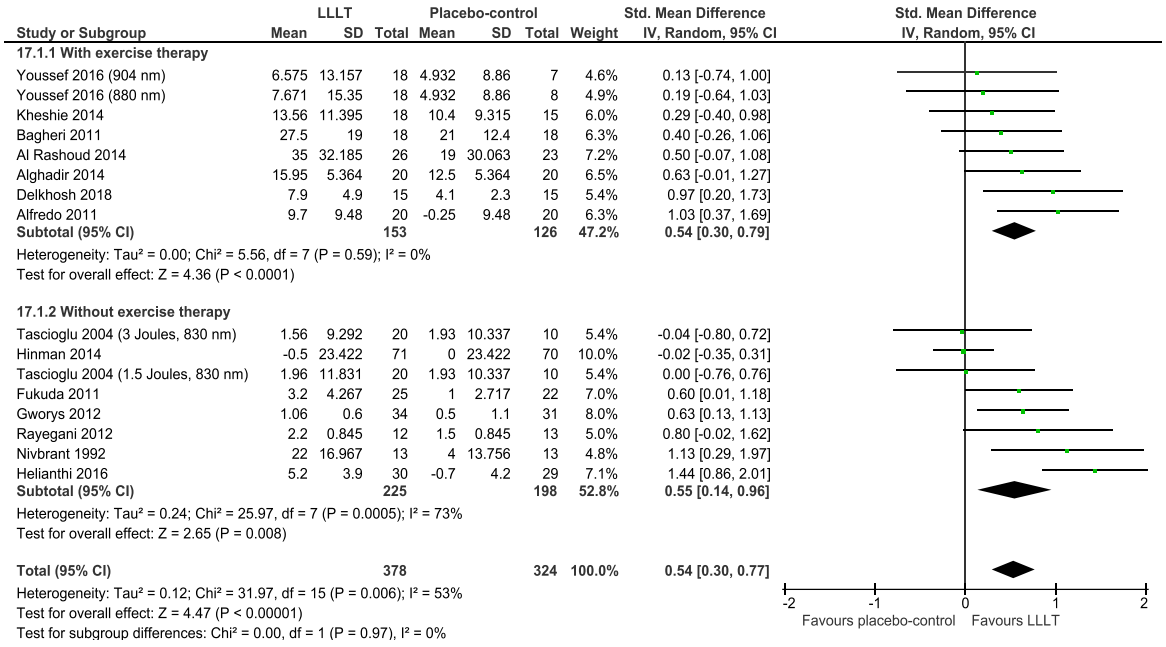

Figure 17 Results with and without exercise therapy as cointervention (disability)

Mean Difference versus Standardised Mean Difference

The levels of statistical heterogeneity changed only negligible when we switched from the Mean Difference (MD) method to the SMD method (figures 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 (figures 18-19).

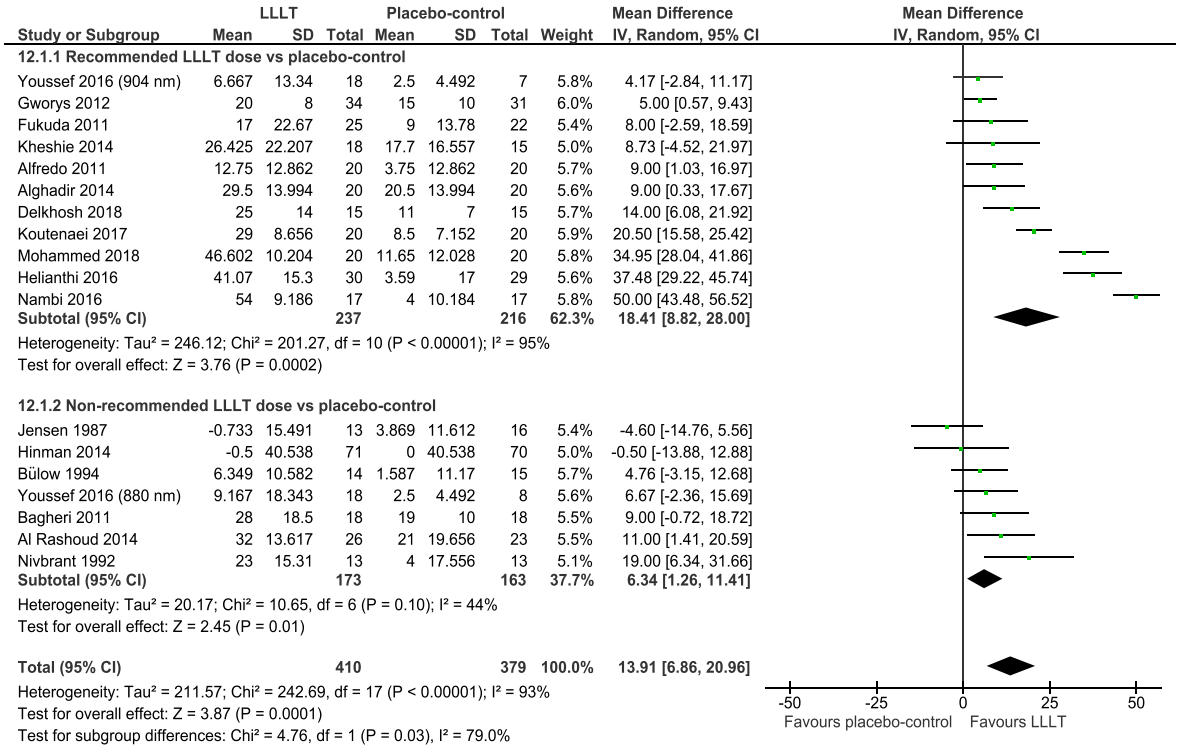

Figure 18 Mean Difference (pain results from immediately after the end of therapy)

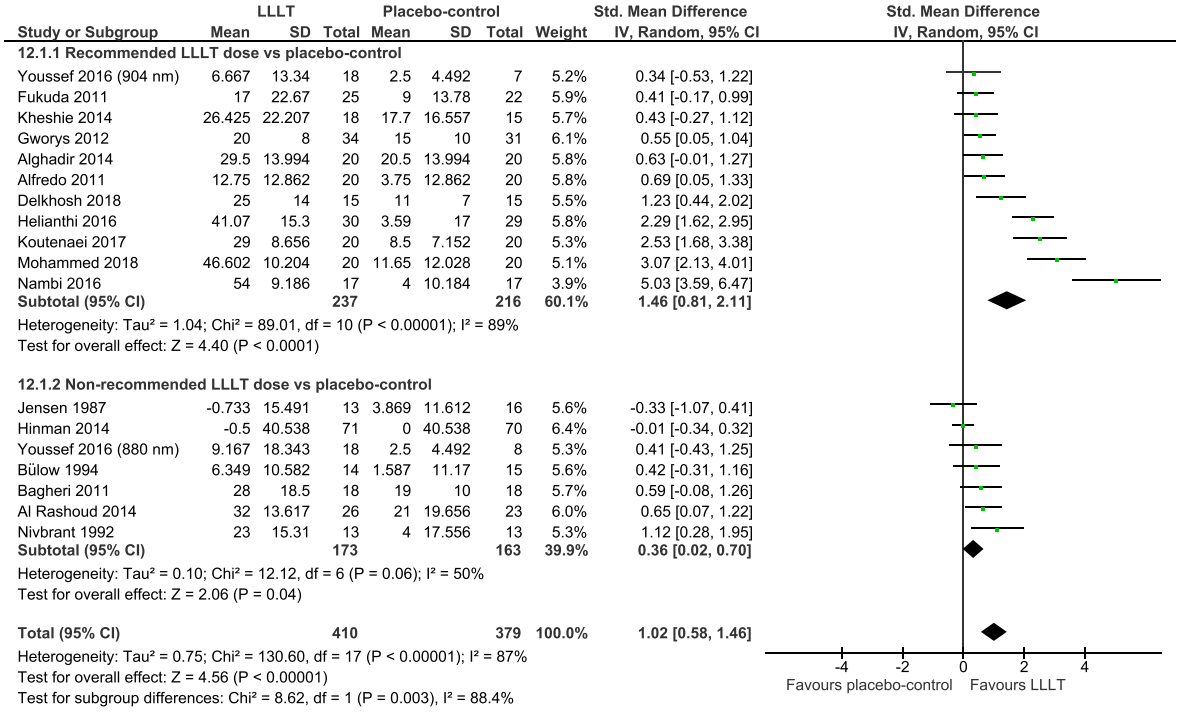

Figure 19 Standardised Mean Difference (pain results from immediately after the end of therapy)

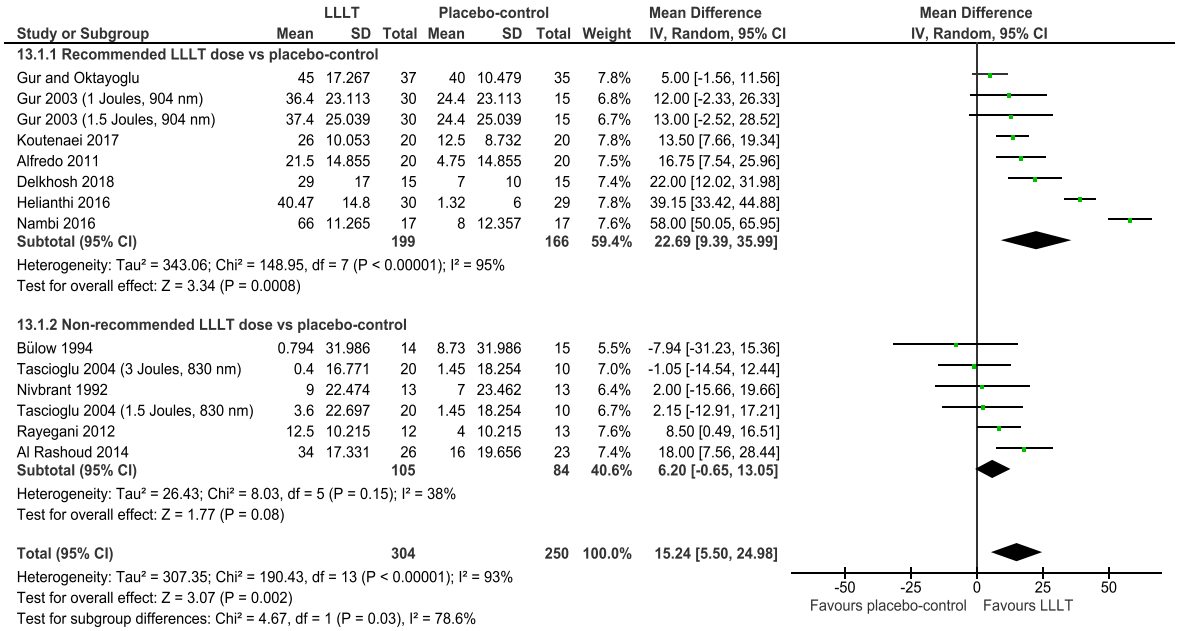

Figure 20 Mean Difference (pain results from 1-12-weeks follow-ups)

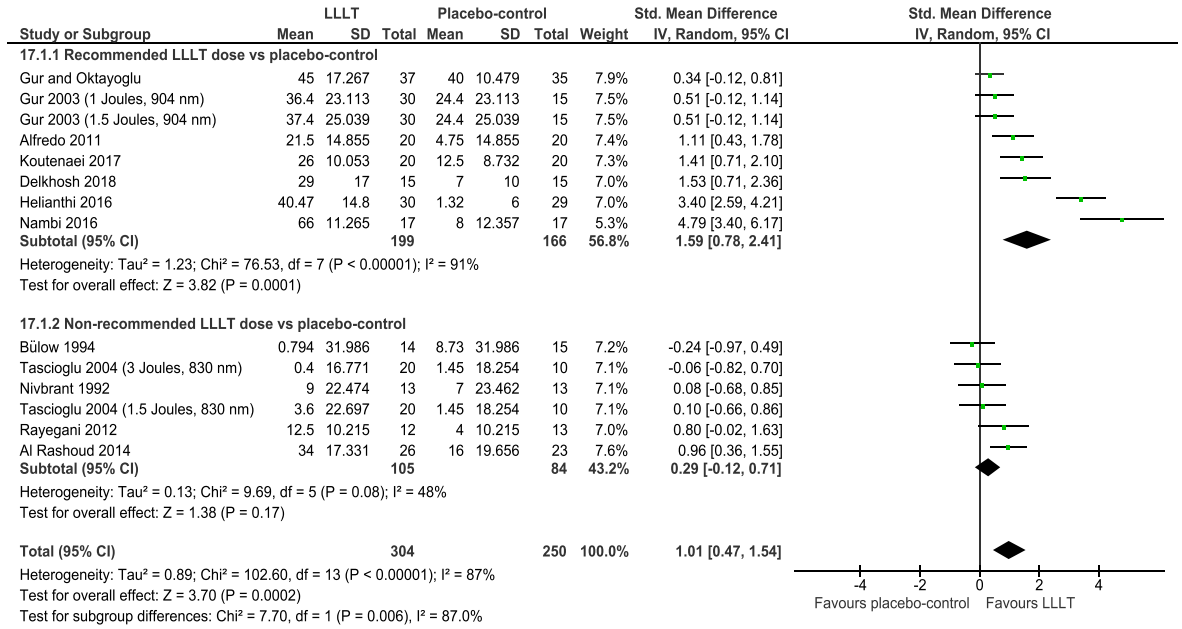

Figure 21 Standardised Mean Difference (pain results from 1-12-weeks follow-ups)

References

1 Alayat MSM, Aly THA, Elsayed AEM, Fadil ASM. Efficacy of pulsed Nd:YAG laser in the treatment of patients with knee osteoarthritis: A randomized controlled trial. *Lasers Med Sci* 2017; **32**: 503-11.

2 Ciechanowska K, Lukowicz M, Weber-Zimmermann M, Buszko K. Ocena skutecznosci terapii skojarzonej - Laseroterapii i terapii zimnem z kompresoterapia w leczeniu objawow gonartrozy. *Postepy Rehabilitacji* 2008.

3 Coelho, Leal-Junior E, Biasotto-Gonzalez D, et al. Effectiveness of phototherapy incorporated into an exercise program for osteoarthritis of the knee: Study protocol for a randomized controlled trial. *BMC* 2014; **15**.

4 de Matos Brunelli Braghin R, Cavalheiro Libardi E, Junqueira C, et al. The effect of low-level laser therapy and physical exercise on pain, stiffness, function, and spatiotemporal gait variables in subjects with bilateral knee osteoarthritis: A blind randomized clinical. *Disabil Rehabil: Epub ahead of print* 2018

5 de Meneses SR, Hunter DJ, Young Docko E, Pasqual Marques A. Effect of low-level laser therapy (904 nm) and static stretching in patients with knee osteoarthritis: A protocol of randomised controlled trial. *BMC Musculoskelet Disord* 2015; **16**.

6 de Paula Gomes CAF, Leal-Junior ECP, Dibai-Filho AV, et al. Incorporation of photobiomodulation therapy into a therapeutic exercise program for knee osteoarthritis: A placebo-controlled, randomized, clinical trial. *Lasers Surg Med* 2018; **8**: 819-28.

7 Giavelli S, Fava G, Castronuovo G, Spinoglio L, Galanti A. Laserterapia con bassa potenza nelle malattie osteoarticolari nel paziente geriatrico. *La Radiologia medica* 1998; **95**: 303-9.

8 Gotte S, Keyi W, Wirzbach E. Doppelblindstudie zur uberprufung der wirksamkeit und vertaraglichkeit einer niederenergetischen lasertherapie bei patienten mit aktivierter gonarthrose [German]. *Jatros Orthopadie* 1995; **12**: 30-4.

9 Kujawa J, Talar J, Gworys K, Gworys P, Pieszynski I, Janiszewski M. The analgesic effectiveness of laser therapy in patients with gonarthrosis: An evaluation. *Ortop Traumatol Rehabil* 2004; **6**: 356-66.

10 Leal-Junior ECP, Johnson DS, Saltmarche A, Demchak T. Adjunctive use of combination of super-pulsed laser and light-emitting diodes phototherapy on nonspecific knee pain: Double-blinded randomized placebo-controlled trial. *Lasers Med Sci* 2014; **29**: 1839-47.

11 Lepilina A, Nikulicheva I, Speranskii V. Lazeroterapiia pri revmatoidnom artrite i deformiruiushchem osteoartroze. *Sov Med* 1990: 82-4.

12 Marquina N, Dumoulin-White R, Mandel A, Lilge L. Laser therapy applications for osteoarthritis and chronic joint pain – A randomized placebo-controlled clinical trial. *Photonics Lasers Med* 2012; **1**: 299–307.

13 Montes-Molina R, Madronero-Agreda MA, Romojaro-Rodriguez AB, et al. Efficacy of interferential low-level laser therapy using two independent sources in the treatment of knee pain. *Photomed Laser Surg* 2009; **27**: 467-71.

14 Nakamura T, Ebihara S, Ohkuni I, et al. Low level laser therapy for chronic knee joint pain patients. *Laser Ther* 2014; **23**: 273-7.
15 Paolillo FR, Paolillo AR, João JP, et al. Ultrasound plus low-level laser therapy for knee osteoarthritis rehabilitation: A randomized, placebo-controlled trial. *Rheumatol int* 2018; **38**: 785-93. doi: 10.1007/s00296-018-4000-x
16 Pinfildi CE, Sardim AC, Yi LC, Prado RP. Neuromuscular training with phototerapy associated in patients knee osteoarthritis. *Arch Phys Med Rehabil* 2013; **94**: e59-e60.
17 Ren XM, Wang M, Shen XY, Wang LZ, Zhao L. Clinical observation on acupoint irradiation with combined laser or red light on patients with knee osteoarthritis of yang deficiency and cold coagulation type. *Zhongguo Zhen Jiu* 2010; **30**: 977-81.
18 Shen X, Zhao L, Ding G, et al. Effect of combined laser acupuncture on knee osteoarthritis: a pilot study. *Lasers med sci* 2009; **24**: 129-36.
19 Soleimanpour H, Gahramani K, Taheri R, et al. The effect of low-level laser therapy on knee osteoarthritis: Prospective, descriptive study. *Lasers med sci* 2014; **29**: 1695-700.
20 Stelian J, Gil I, Habot B, et al. Improvement of pain and disability in elderly patients with degenerative osteoarthritis of the knee treated with narrow-band light therapy. *J Am Geriatr Soc* 1992; **40**: 23-6.
21 Trelles MA, Rigau J, Sala P, Calderhead G, Ohshiro T. Infrared diode laser in low reactive-level laser therapy (LLLT) for knee osteoarthrosis. *Laser Therapy* 1991; **3**: 149-53.
22 Wang L, Wu F, Zhao L, et al. Patterns of traditional chinese medicine diagnosis in thermal laser acupuncture treatment of knee osteoarthritis. *Evidence-Based Complementary and Alternative Medicine* 2013.
23 Yavuz M, Ataoglu S, Ozsahin M, Baki A, Icmel C. Primer Diz Osteoartritinde İzokinetik Egzersiz, Lazer ve Diklofenak İyontoforezi Uygulamalarının Etkilerinin ve Etkinliklerinin Karşılaştırılması. *Düzce Medical Journal* 2013; **15**: 15-21.
24 Yurtkuran M, Alp A, Konur S, Ozçakir S, Bingol U. Laser acupuncture in knee osteoarthritis: A double-blind, randomized controlled study. *Photomed Laser Surg* 2007; **25**: 14-20.
25 Yuvarani G, Thonisha Xavier L, Mohan Kumar G, et al. To compare the effectiveness between LASER and neuromuscular electrical stimulation in knee osteoarthritis. *Biomedicine (India)* 2018;38:142-46.
26 Zhao L, Shen X, Cheng K, et al. Validating a nonacupoint sham control for laser treatment of knee osteoarthritis. *Photomed Laser Surg* 2010; **28**: 351-6.
27 Zou YC, Deng HY, Mao Z, Zhao C, Huang J, Liu G. Decreased synovial fluid ghrelin levels are linked with disease severity in primary knee osteoarthritis patients and are increased following laser therapy. *Clin Chim Acta* 2017; **470**: 64-9.