Supplementary Online Content

Tedesco D, Gori D, Desai KR, et al. Drug-free interventions to reduce pain or opioid consumption after total knee arthroplasty: a systematic review and meta-analysis. *JAMA Surg*. Published online August 16, 2017. doi:10.1001/jamasurg.2017.2872

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Risk of Bias Summary from Randomized Controlled Trials for Non-pharmacological Postoperative Pain Management after Total Knee Arthroplasty.

Study	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Blinding
Adravanti et al. (2013)	Low	High	Unclear	High	Low	High
Albrecht et al. (2008)	Unclear	Unclear	Low	Unclear	Unclear	High
Beauprè et al. (2001)	Unclear	Unclear	Low	Unclear	Low	High
Bennett et al. (2005)	Low	Low	Low	High	Low	High
Borckardt et al. (2013)	Low	Low	Low	Unclear	Low	High
Bruun-Olsen et al. (2009)	High	Low	Low	Low	Unclear	High
Calatayud et al. (2016)	Low	Low	Low	Low	Unclear	High
Chen et al. (2013)	High	High	Unclear	Unclear	Low	High
Chen et al. (2015)	Unclear	Unclear	Low	Unclear	Unclear	High
Colwell et al. (1992)	Unclear	Unclear	Low	High	Low	High
Denis et al. (2006)	Low	Low	Low	Low	Low	High
Gibbons et al. (2001)	Unclear	Unclear	Low	High	Low	High

Gstoettner et al. (2011)	Low	Low	Unclear	Low	Low	High
Harms et al. (1991)	Unclear	Unclear	Unclear	High	Low	High
Ivey et al. (1994)	Low	Low	Unclear	Unclear	Unclear	Low
Kim et al. (2009)	Low	Unclear	Unclear	Low	Unclear	High
Kullenberg et al. (2006)	Unclear	Unclear	Low	High	Low	High
Lenssen et al. (2003)	Low	Low	Low	Low	Low	High
Lenssen et al. (2008)	Low	Low	Low	High	Low	High
Levy et al. (1993)	Unclear	Unclear	Unclear	High	Low	Unclear
MacDonald et al. (2000)	Low	Low	Unclear	High	Low	High
Maniar et al. (2012)	High	Low	Unclear	Low	High	High
May et al. (1999)	Unclear	Low	Low	High	Low	High
McKay et al. (2012)	Unclear	High	Low	Unclear	Low	High
Mclnnes et al. (1992)	High	Low	Low	Low	Unclear	High
Mikashima et al. (2012)	Low	Low	Low	Unclear	Unclear	Unclear
Montgomery et al. (1996)	High	Unclear	Low	Unclear	Low	High
Moretti et al. (2012)	Low	Low	High	High	Unclear	High

Morsi E. (2002)	High	High	Low	High	Low	High
Pope et al. (1997)	Unclear	Unclear	Low	Unclear	Unclear	High
Radkowski et al. (2007)	Low	Unclear	Low	High	Low	Low
Sahin et al. (2006)	High	Unclear	Low	Low	Unclear	High
Smith et al. (2002)	High	Unclear	Low	Unclear	Unclear	High
Su et al. (2012)	Unclear	Unclear	Low	Unclear	Low	High
Thienpont et al. (2014)	Low	Low	Low	Low	Unclear	Unclear
Tsang et al. (2007)	Low	Low	Low	High	Unclear	Unclear
Tzeng et al. (2015)	Unclear	Low	Unclear	Unclear	Low	High
Walker et al. (1991)	Unclear	Unclear	Low	Unclear	Low	Unclear
Webb et al. (1998)	Unclear	Unclear	Low	Unclear	Low	Unclear

eTable 2. GRADE of Evidence Assessment for Non-pharmacological Postoperative Pain Management after Total Knee Arthroplasty.

Study Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Pain relief – VAS						
CPM	Very Serious	Not Serious	Not Serious	Serious	Not Serious	⊕ Very Low
Cryotherapy	Very Serious	Serious	Not Serious	Not Serious	Serious	⊕ Very Low
Electrotherapy	Very Serious	Serious	Not Serious	Not Serious	Serious	⊕ Very Low
Acupuncture	Serious	Serious	Not Serious	Not Serious	Not Serious	⊕⊕ Low
Pain relief – WOMAC						
CPM	Very Serious	Not Serious	Not Serious	Not Serious	Not Serious	⊕⊕ Low
Preoperative exercise	Serious	Serious	Not Serious	Not Serious	Not Serious	⊕⊕ Low
Opioid consumption						
CPM	Serious	Serious	Not Serious	Serious	Not Serious	⊕ Very Low
Cryotherapy	Serious	Serious	Not Serious	Not Serious	Serious	⊕ Very Low
Electrotherapy	Serious	Not Serious	Not Serious	Not Serious	Not Serious	⊕⊕⊕ Moderate

Acupuncture	Serious	Serious	Not Serious	Not Serious	Not Serious	⊕⊕ Low
NSAID consumption						
Cryotherapy	Very Serious	Serious	Not Serious	Serious	Not Serious	⊕ Very Low
Time to first PCA						
Acupuncture	Serious	Not Serious	Not Serious	Not Serious	Not Serious	⊕⊕⊕ Moderate

eTable 3. Summary of Key Review Findings for Non-pharmacological Postoperative Pain Management after Total Knee Arthroplasty.

Study	Duration of intervention	Outcome measure timepoints	Primary outcome measure	Secondary outcome measure	Main findings/Conclusion	Conflict of interest/funding disclosure
Continuous passive motion (CPM)						
Beauprè et al. (2001)	3 days postoperatively (PO)	3 and 6 months PO	Knee extension and flexion	WOMAC (Pain, Stiffness, Function), SF36	Self-reported pain, function, or overall quality of life was not different at either of the postoperative measurement times.	Study funded by a grant from the Health Services Research and Innovation Fund, Canada.
Bennett et al. (2005)	6 days PO	3 months, 1 year PO	Range of Motion (ROM)	Length of stay (LOS), Pain, Wound healing, Perceived Health Status Measure SF-12	Statistically significant differences in mean pain scores between groups. The differences are not clinically significant (≤1 point on a 10-point scale).	Funds received in partial or total support of the research material described in this article from the Alfred Grant, Australia.

Brunn-Olsen et al. (2009)	6 to 12–14 weeks PO	14 weeks, 9 months PO	Pain (VAS scale)	ROM	CPM was not found to have an additional short-time effect compared with physiotherapy. After three months pain relief was obtained.	A grant for the study was received from the Norwegian Foundation of Postgraduate Physiotherapists. Conflict of interest not stated.
Chen et al. (2013)	3 days PO	2 weeks, 6 weeks, 3month, 6 month PO	ROM	Pain	No significant difference	Project funded by the National Health Research Institute, Taiwan.
Colwell et al. (1992)	3 days PO	1, 2 and 3 days PO	ROM	Analgesia use	CPM reduces opioid consumption and LOS.	Not stated.
Denis et al. (2006)	9 days PO	Discharge	ROM (flexion, extension, Timed up and go test - TUG)	WOMAC (Pain, Stiffness, Function)	The results do not support the addition of CPM applications to conventional physical therapy. CPM did not show to further reduce knee impairments or disability or the length of the hospital stay.	Not stated.
Harms et al. (1991)	6hr/day for 1 week PO	Discharge	Pain (VAS scale)	ROM, LOS	No significant differences found in VAS scores	Not stated.

Kim et al. (2009)	20 minutes/day, from day 2 to day 14 PO	Flexion contracture and maximum flexion: day 7 after TKA, day 14. 6 weeks, 3 months and 6 months. Level of pain during ROM exercise: day 7 and day 14.	Flexion contracture, maximum flexion	AKS knee score, AKS function score, WOMAC pain, WOMAC stiffness, WOMAC function	Regular passive ROM exercise does not offer additional clinical benefits to the patients after TKA	Not stated.
Lenssen et al. (2003)	4 days PO	4days	Pain (VAS scale)	ROM	No significant differences found in VAS scores	Not stated.
Lenssen et al. (2008)	4 hours/day for 4 days PO	17 day, 6 weeks, 3 months	Function and pain (WOMAC scale), ROM	Medication Use, Satisfaction	No significant differences found in WOMAC scores	The authors declare that they have no competing interests.
MacDonald et al. (2000)	6 weeks PO	6, 12, 26 weeks, and 1 year PO	Function (KSS scale)	ROM, Pain	No significant differences found in VAS scores	Not stated
Maniar et al. (2012)	Day 1 and 3 PO	3, 5, 14±2, 42±5, 90±10	Pain-VAS, ROM, TUG, swelling and wound healing	WOMAC, SF-12	No significant differences found in VAS scores	The Conflict of Interest disclosure related to this article available at doi:10.1016/j.arth.2011.04.009.
May et al. (1999)	1 week PO	1 month	ROM, VAS,	LOS	No differences at	Not stated.

			KSS		VAS outcome	
McInnes et al. (1992)	Starting within 24 hours from surgery	7 days, 6 weeks	Cost	Pain (VAS scale), swelling, ROM	No significant differences found in VAS scores	Study supported by National Institutes of Health.
Montgomery et al. (1996)	3 hours 3 times daily, 7 days a week	1, 3, 5 days PO	Pain (VAS scale)	Mid-patellar effusion, Knee flection, ROM	Postoperative pain levels and LOS similar in the two groups.	Not stated.
Pope et al. (1997)	1 week PO	Up to 1 year PO	ROM	Blood loss, analgesia use	Clinical disadvantages in the short term in CPM groups with no worthwhile improvement in the range of movement or function.	No benefits in any form received from a commercial party.
Sahin et al. (2006)	1 week PO	2 weeks, 6 weeks, 6 months PO	ROM, Pain (VAS scale)	Swelling, KSS score	No significant differences found in VAS scores in CPM groups	Not stated.
Walker et al. (1991)	From day 3 PO until discharge	1 month, 12 months.	Manipulatio, adverse events	ROM, pain (VAS scale), LOS	CPM showed a significant reduction in analgesia consumption	Supported by a grant from the National Institutes of Health, General Clinical Research Center Branch. Division of Research Resources.
Preoperative exercise						

Calatayud et al. (2016)	3 days/week for 8 weeks before surgery	8 weeks before surgery (T1), after 8 weeks of training (T2), 1 month after TKA (T3) and finally 3 months after TKA (T4)	WOMAC functional and pain scale	SF-36 scale, pain VAS scale, TUG	The present study supports the use of preoperative training in end-stage OA patients to improve early postoperative outcomes.	The authors did not receive financial support for this study, and there are no known conflicts of interest associated with this publication that could have influenced its outcome.
Gstoettner et al. (2011)	1 day/week for 6 weeks before surgery.	6 weeks pre-operatively; 6 weeks PO	Balance, gait speed, and function	WOMAC pain and stiffness subscales, KSS scale	There was a significant improvement in KSS, WOMAC pain and stiffness within both groups after TKA. No difference in clinical outcome was observed between the two groups.	Not stated.
McKay et al. (2012)	3 days/week for 6 weeks before surgery	Baseline testing 6 weeks (±3 days) before surgery. Before TKA, at 6 and 12 weeks after TKA,	Isometric quadriceps strength.	Mobility, pain, self-reported function, health-related quality of life, and arthritis self-	Reduction of pain within the groups, but there is not a direct comparison between them. Perceived functional ability shows an inverse relationship to pain,	Not stated.

		participants completed the questionnaire battery and physical testing.		efficacy.	but no information on significance.	
Cryotherapy						
Albrecht et al. (2008)	2 days PO	1 week PO	VAS Scale	Blood loss, ROM, Adverse effects	Significant reduction in VAS for CT group	Not stated.
Gibbons et al. (2001)	6 hours/day throughout the hospital stay	Blood loss: during the procedure. Amount of morphine received: over the 48 h The amount of oral analgesia: up to the 10-day stage. Pain scores recorded on alternate days after a period of physiotherapy at the end	Blood loss	ROM, pain scores, analgesia, LOS, complications	No difference was found between the 2 groups except for less blood loss in the surgical drains in the cold compression group.	Not stated.

		of the afternoon. The range of movement: 10 days after TKA.				
Ivey et al. (1994)	72 hours PO	Number of attempts: every hour PO Amount of morphine: daily	Pain	Number of Patient-controlled analgesia (PCA) attempts	Different temperature did not show any significant differences in pain improvement after surgery, and in the amount of injected morphine.	Not stated.
Kullenberg et al. (2006)	3 days PO	Up to 3 weeks PO	ROM	Pain, LOS, Hemoglobin loss	Cold compression therapy improves control of pain and might lead to improvement in ROM and reduce the length of hospital stay.	No benefits or funds were received in support of the study.
Levy et al. (1993)	4 days PO	Up to 2 weeks PO	Blood loss	Pain, ROM	Significant lower blood loss and morphine consumption in the intervention group; Significant	Not stated.

					improvement in ROM at 7 and 14 days from surgery.	
Morsi E. (2002)	2 weeks PO	Up to 6 weeks after discharge	Analgesic consumption	Pain score, ROM	Continuous-flow cold therapy is advantageous after TKA. It showed to provide better results in all the areas compared.	Not stated.
Radkowski et al. (2007)	Postsurgical period until discharge	2 weeks PO	Adverse events	Pain, Analgesia, Blood loss, ROM	Postoperative narcotic consumption, postoperative drainage, self-reported knee function, and range of motion were not affected by the different cryotherapy temperatures.	Not stated.
Smith et al. (2002)	Treatment 1 for 24 hours after surgery; treatment 2 for 6 hours; and then cryo-pad	Day 1-3 PO	Function, swelling	Pain, Analgesia	Not significant differences in pain improvement	Not stated.

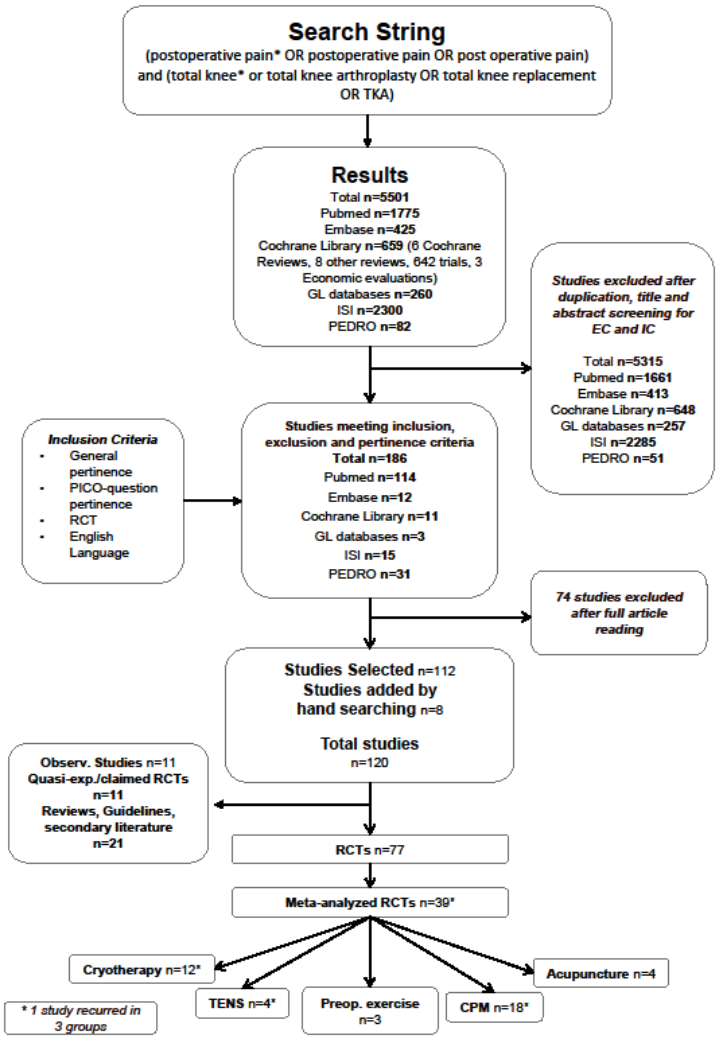
Su et al. (2012)	Inpatient stay: 2 hours on plus 1 hour off for a minimum of 4 cycles per day. After discharge: 1 hour on plus 30 minutes off for a minimum of 4 cycles per day.	Pre-operative, 2 weeks, 6 weeks PO	ROM and function	Pain (VAS scale) and morphine consumption	No improvement in ROM and pain perception. Significant decrease in pain medication consumption and higher satisfaction.	Not stated.
Thienpont et al. (2014)	Postsurgical period	Day 2, 6 weeks PO	Pain (VAS scale), and analgesics consumption.	ROM, swelling, and blood loss.	Advanced cryotherapy with a continuous cooling for a prolonged period did not provide an earlier recovery.	The authors report no conflict of interest. All conflict of interest forms are on file with the publication.
Webb et al. (1998)	48 hours PO	Pre-operative, 5 days, 6 weeks, 3 months PO	Blood loss	Pain scores, pain medication consumption, and ROM	Cryo/cuff showed improvement in postoperative blood loss and pain but did not influence swelling and return to motion	Not stated

Walker et al. (1991)	From day 3 PO until discharge	Discharge, 3 months	Manipulatio, adverse events	ROM, pain (VAS scale), LOS	Cryotherapy showed a significant reduction in analgesia request.	Supported by a grant from the National Institutes of Health, General Clinical Research Center Branch. Division of Research Resources.
Electrotherapy						
Adravanti et al. (2013)	2 months PO	1 month, 2 months, 6 months, 3 years PO	Pain (VAS scale)	KSS function score, SF36 score, Knee swelling	PEMFs showed significant differences in pain improvement and in functional scores in all timepoints.	One of the authors is employee of the device manufacturer.
Borckardt et al. (2013)	80 minutes/day in postoperative period	48 hours PO	Opioid Consumptio n	Pain (BPI and VAS scales)	TENS may be able to reduce post-TKA opioid requirements.	Not stated.
Moretti et al. (2012)	Treatment began within seven days from TKA, and consisted of 4-hour sessions/day for 60 days PO	Pre-operatively, and at 1, 2, 6, 12 months PO	Pain (VAS scale)	Knee Society Score; SF-36; Joint swelling score; Functional score	PEMFs showed significant differences in pain improvement and in functional scores in all timepoints.	Two of the authors are employees of the device manufacturer.
Walker et al. (1991)	From day 3 PO until discharge	3 day PO, discharge	Manipulatio, adverse events	ROM, pain (VAS scale), LOS	TENS did not show a significant difference in analgesia consumption.	Supported by a grant from the National Institutes of Health, General Clinical Research Center Branch. Division of Research

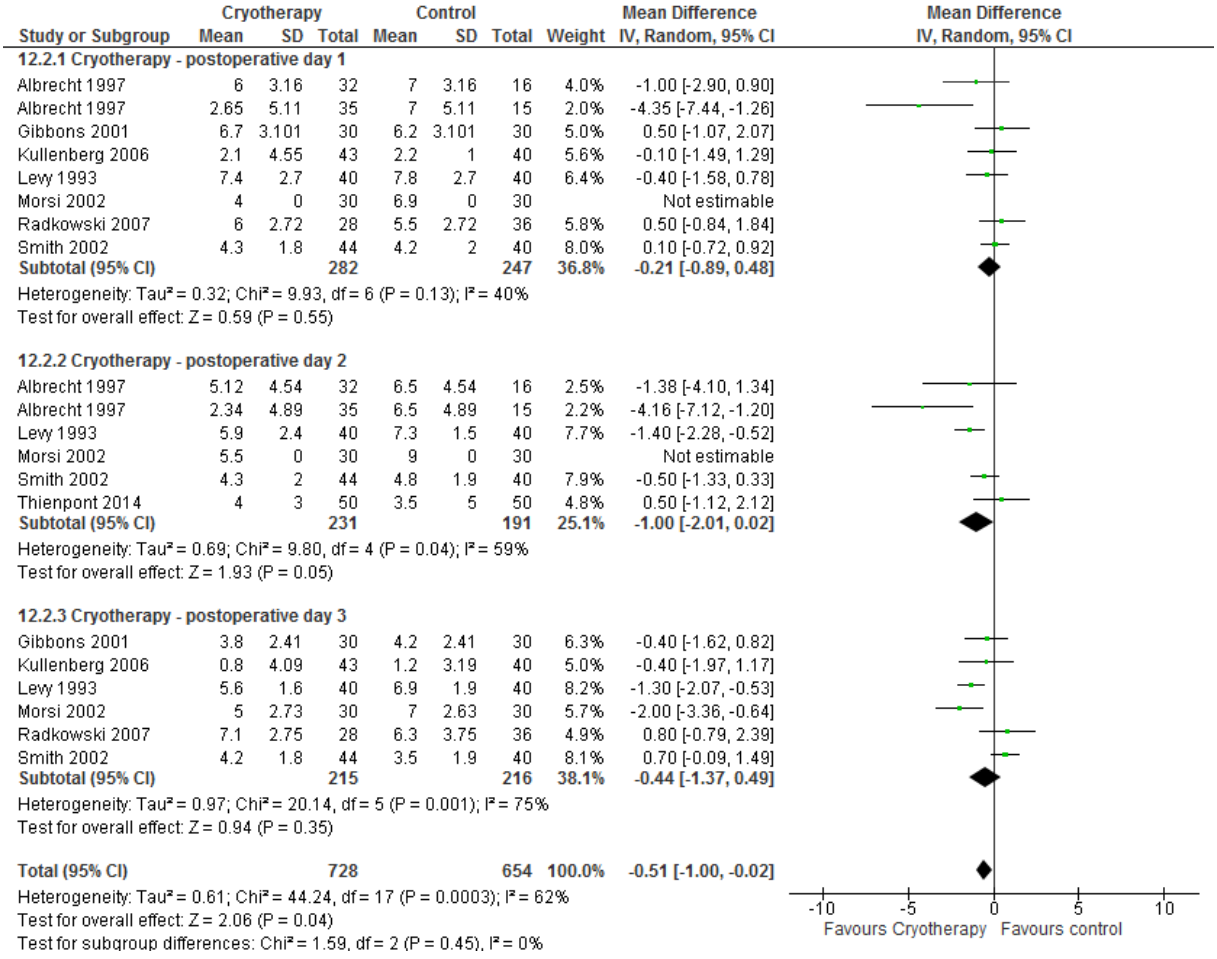
						Resources.
Acupuncture						
Chen et al. (2015)	20 minutes/day in the postoperative period	2, 4, 8, 12, 24, 36, 48 hours PO	Opioid consumption	Time to the first PCA request; pain intensity	Acupuncture showed significant pain improvement and opioid consumption.	The authors declare that they have no competing interests.
Mikashima et al. (2012)	3 times/week from day 7 until day 21 PO	6, 14, 21 days PO	VAS pain score	Swelling; time to achieve preoperative ROM	Acupuncture showed significant improvement in pain, reduction of swelling around the knee and early recovery of ROM.	Not stated.
Tsang et al. (2007)	Postsurgical period	4-8, 11-15 days PO	Pain at rest and at maximum after exercise (VAS scale).	ROM, TUG.	Acupuncture did not show significant improvement in pain, reduction of swelling around the knee and early recovery of ROM.	The authors declare that they have no competing interests.

Tzeng et al. (2015)	48 hours PO	48 hours PO	Time for first PCA request	N/A	Acupuncture showed significant longer time to the first demand for Patient-controlled Analgesia.	Supported by China Medical University under the Aim for Top University Plan of the Ministry of Education, Taiwan and by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence. The authors declare that they have no competing interests.

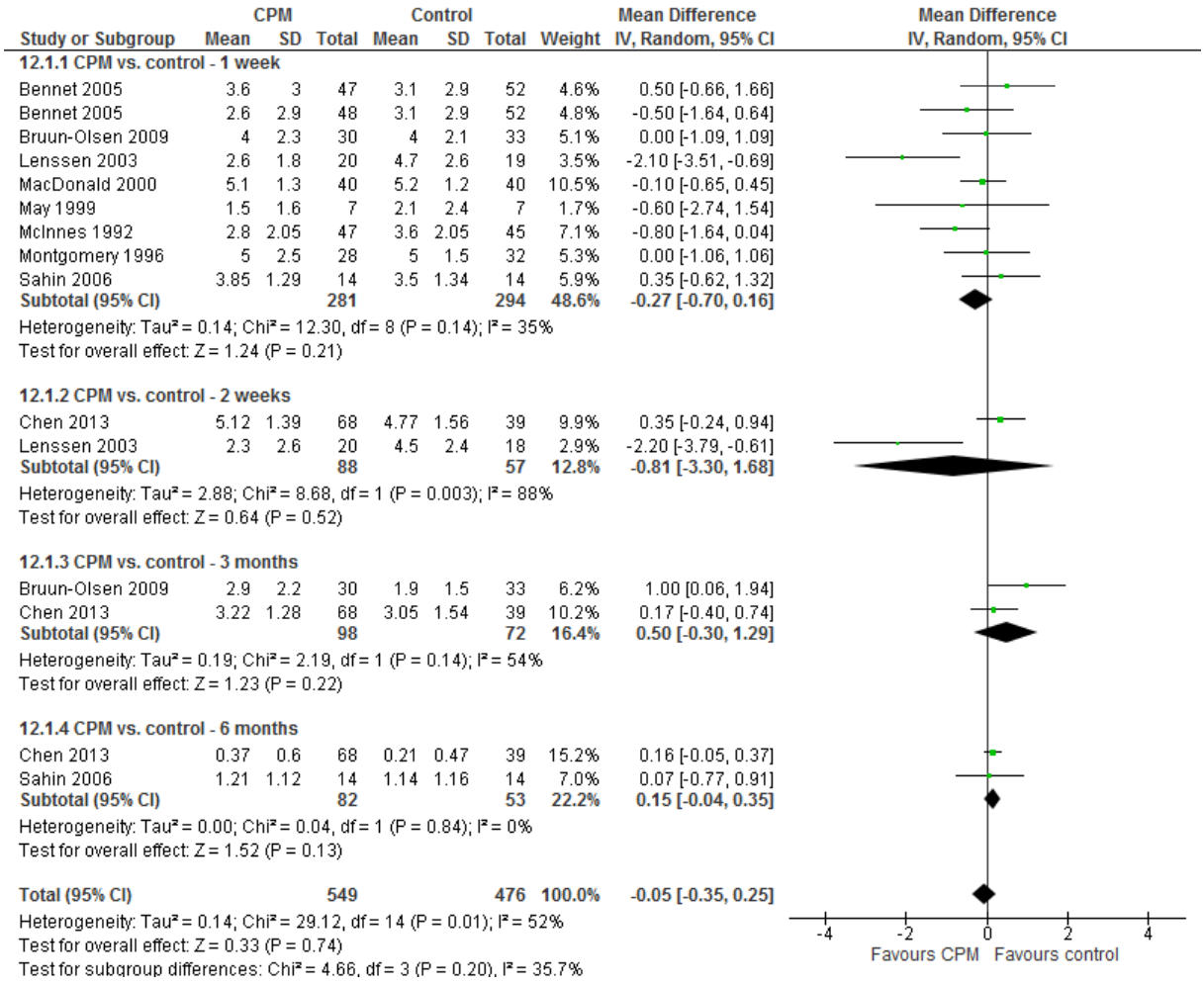
eFigure 1. PRISMA Flowchart Depicting the Search Strategy.



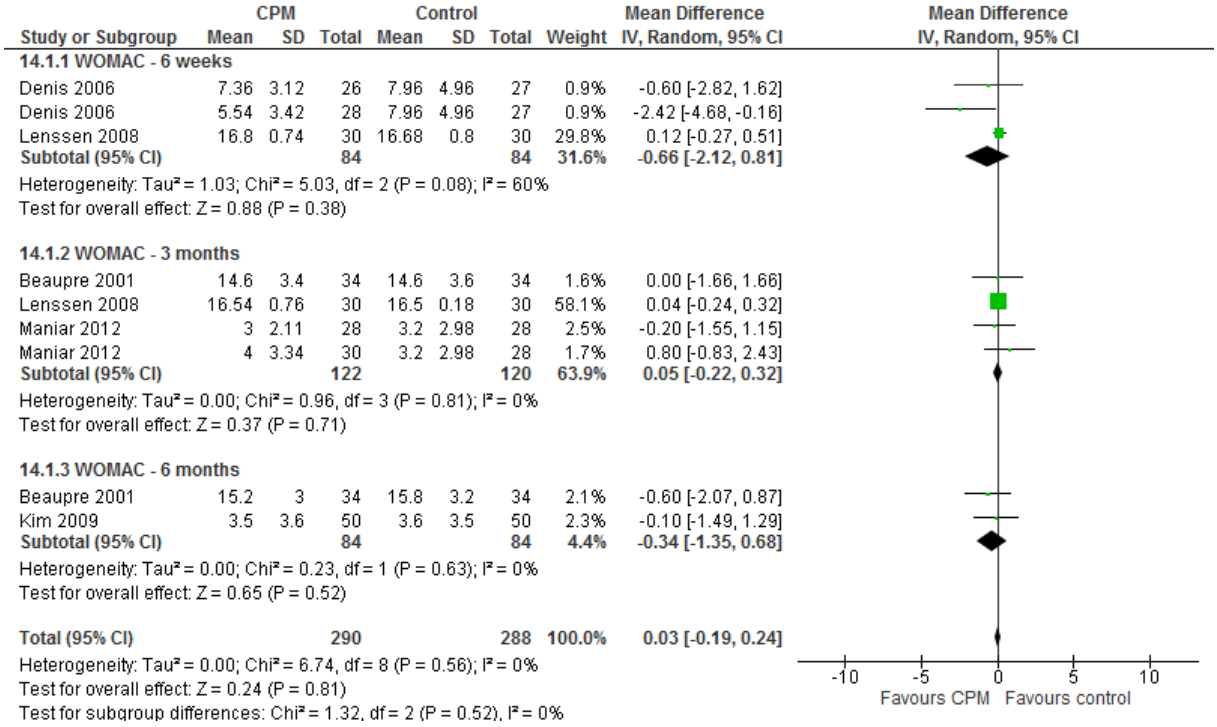
eFigure 2. Pain relief: Cryotherapy



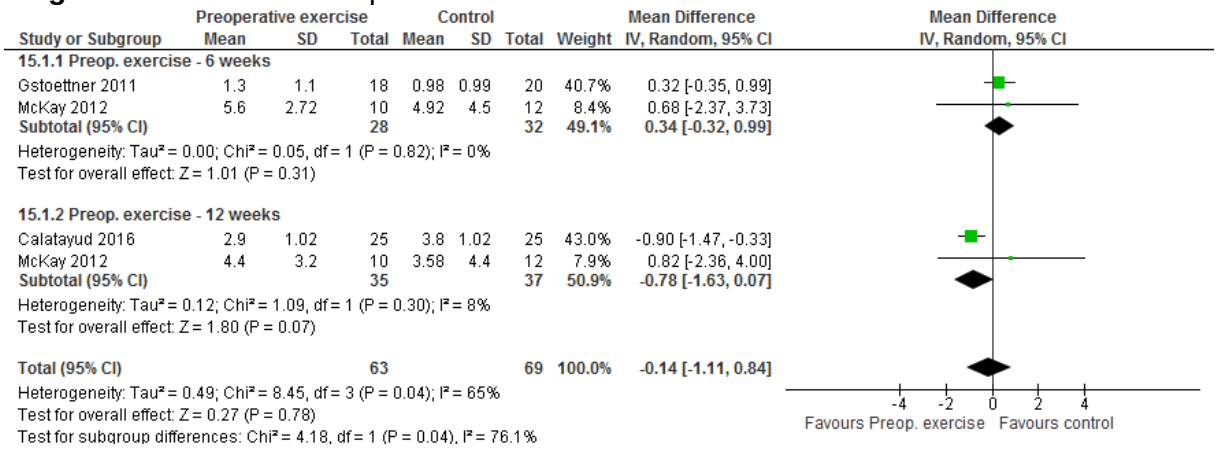
eFigure 3. Pain relief: Continuous Passive Motion (CPM)



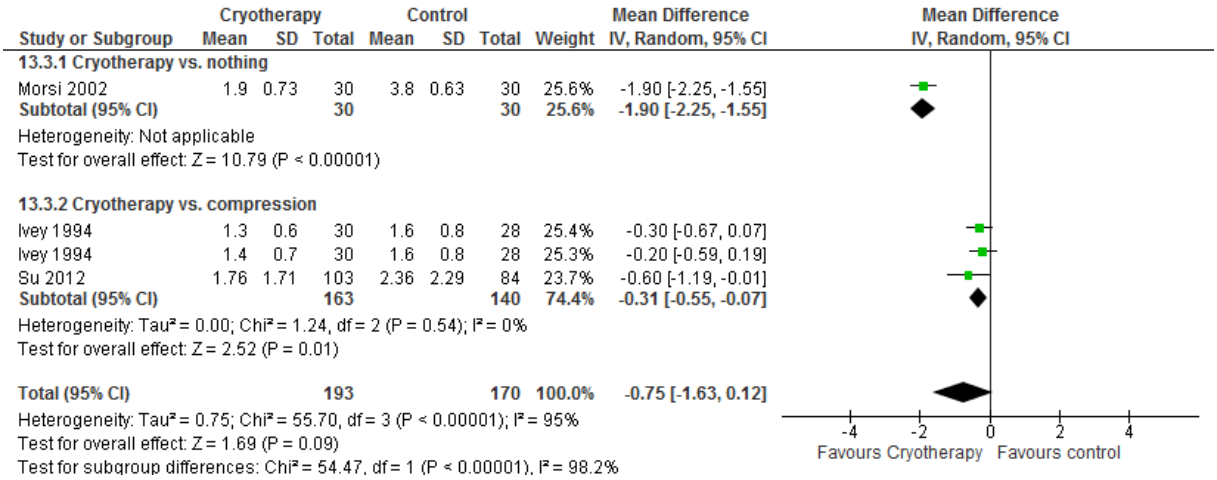
eFigure 4. Pain relief: Continuous Passive Motion (CPM)



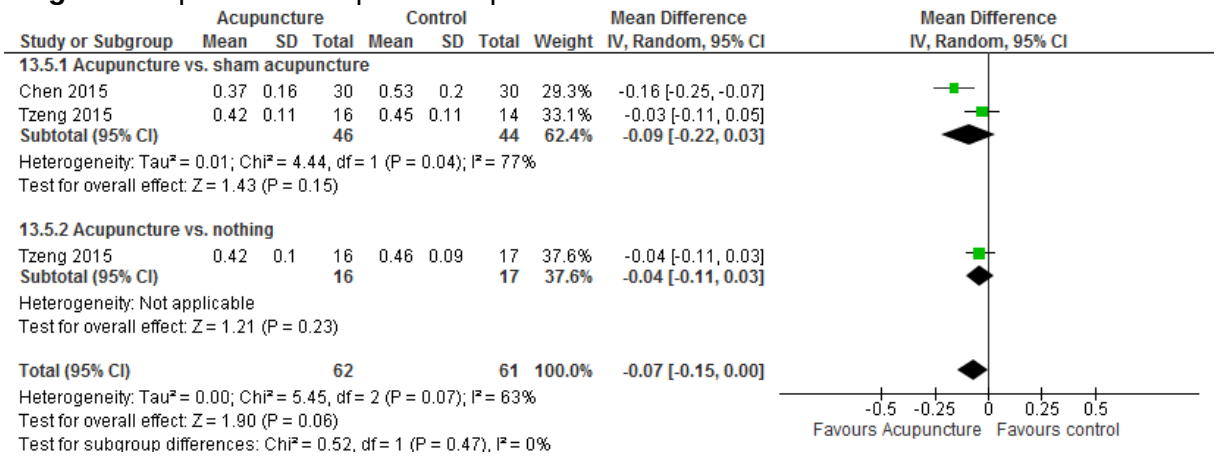
eFigure 5. Pain relief: Preoperative Exercise



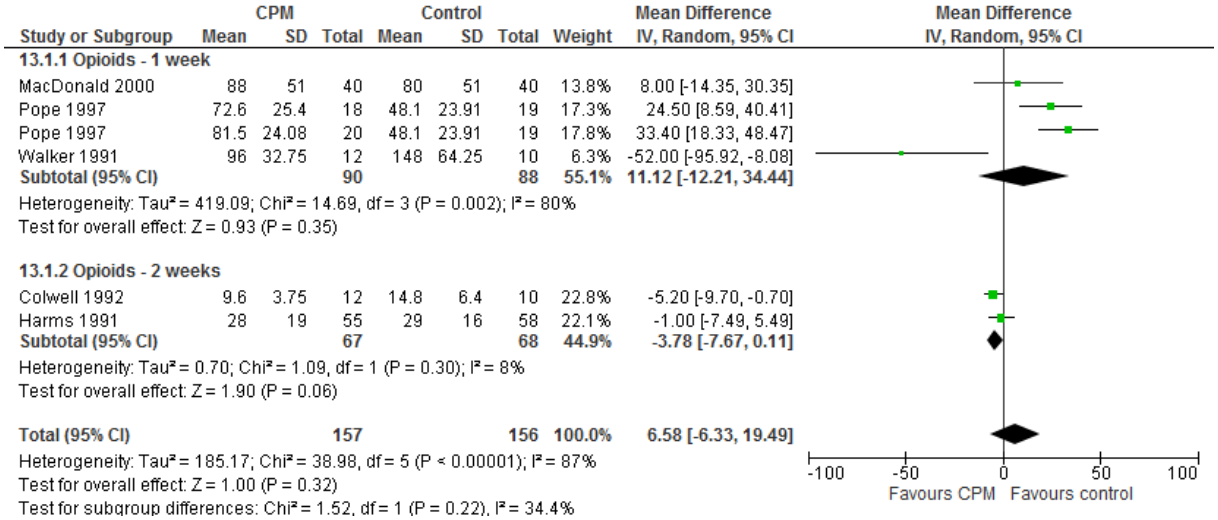
eFigure 6. NSAID Consumption: Cryotherapy



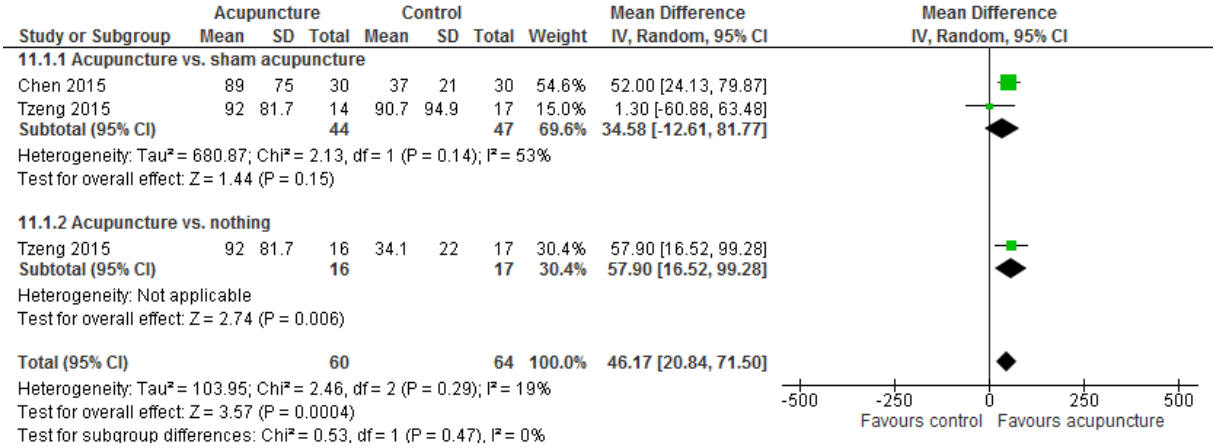
eFigure 7. Opioid consumption: Acupuncture



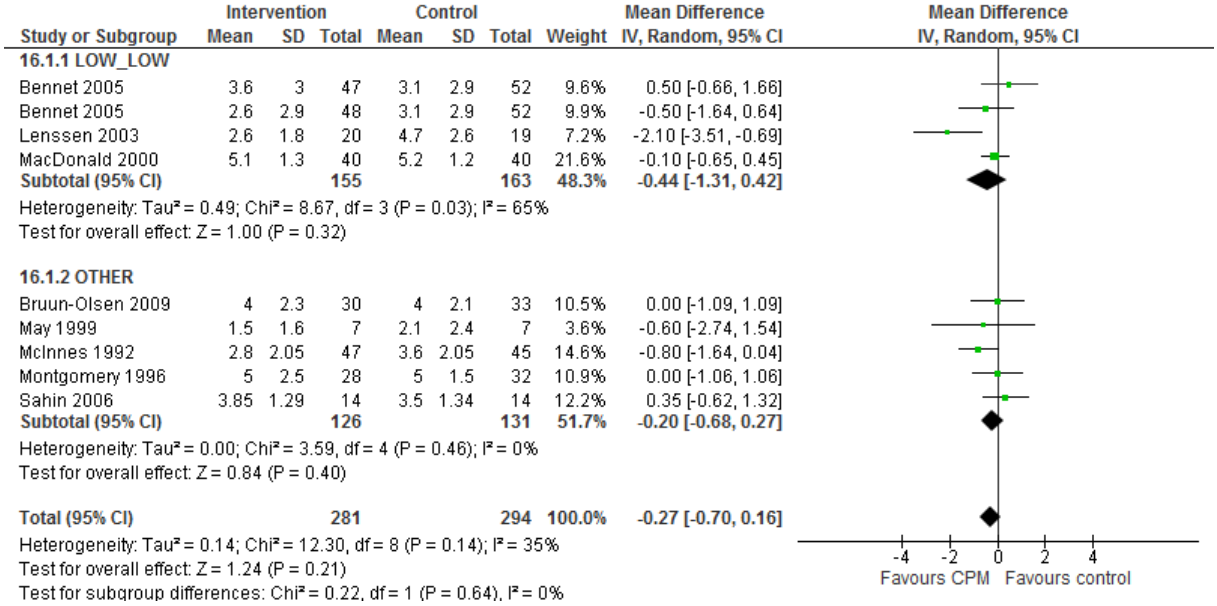
eFigure 8. Opioid consumption: Continuous Passive Motion (CPM)



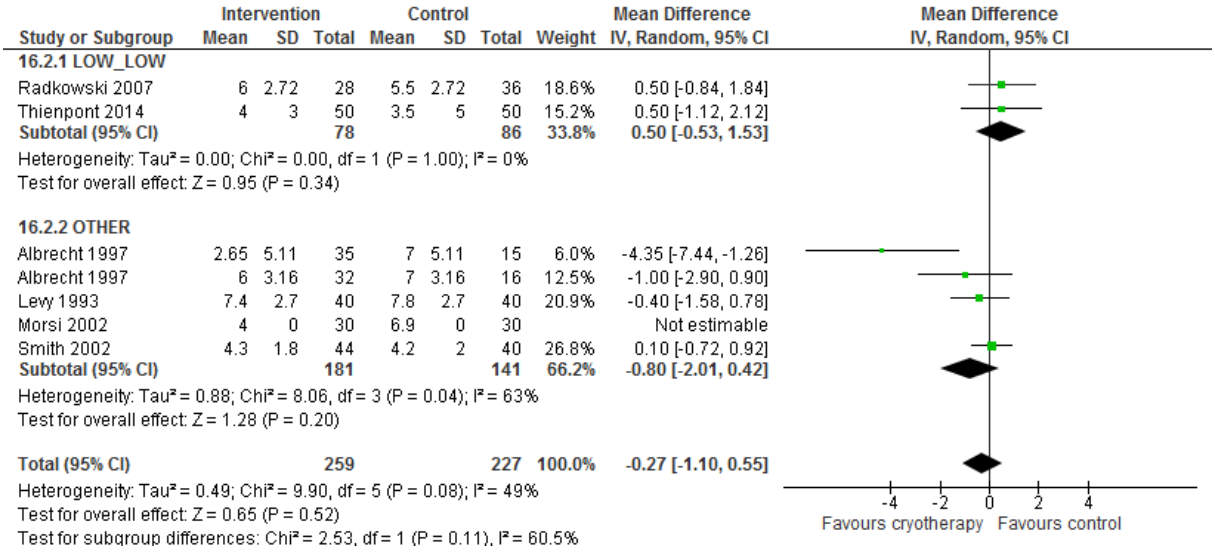
eFigure 9. Acupuncture



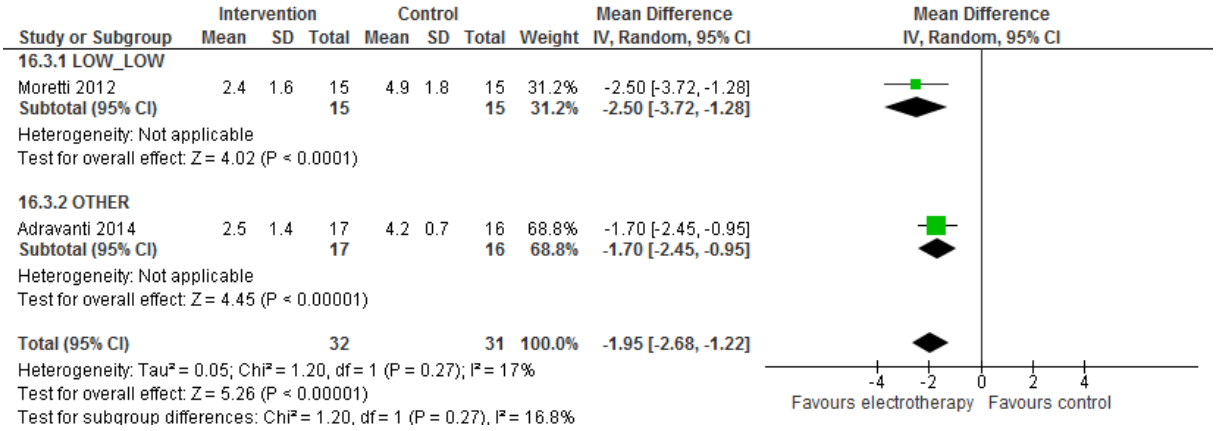
eFigure 10: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



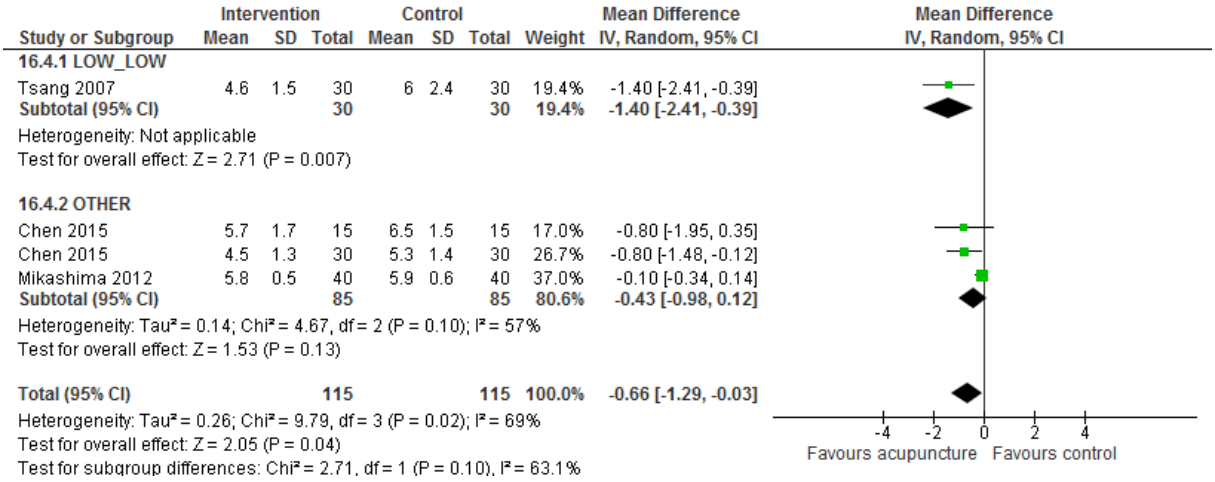
eFigure 11: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



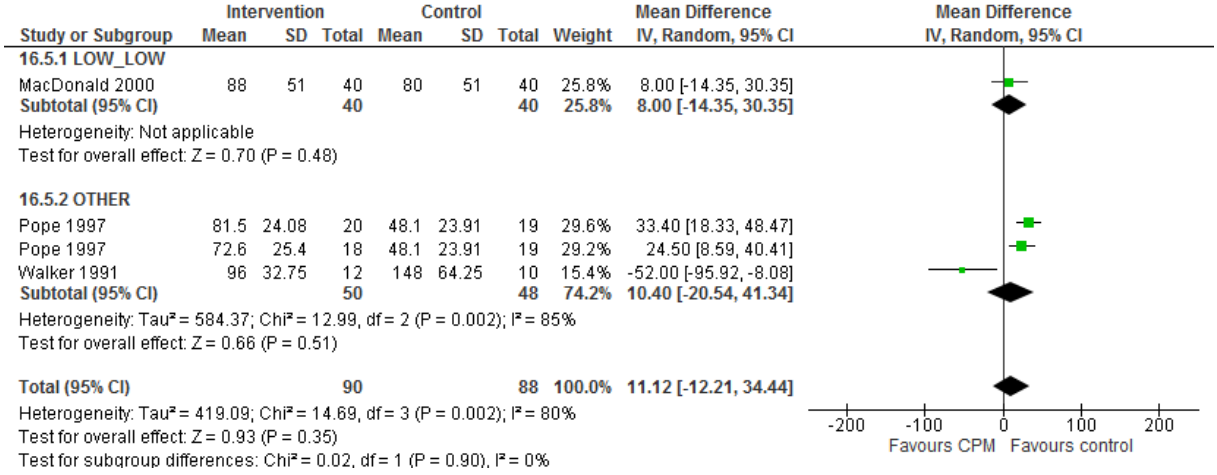
eFigure 12: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



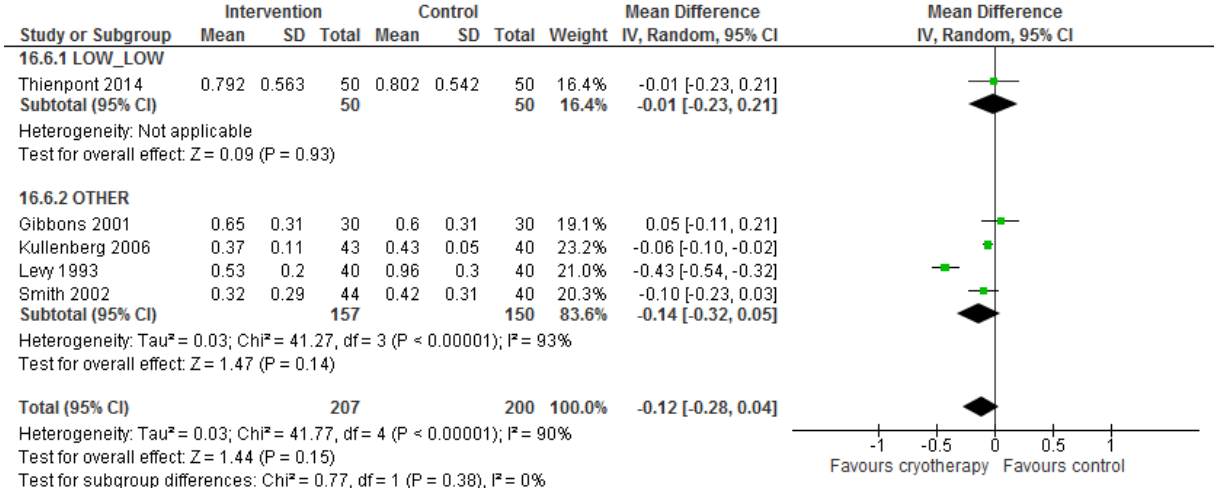
eFigure 13: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



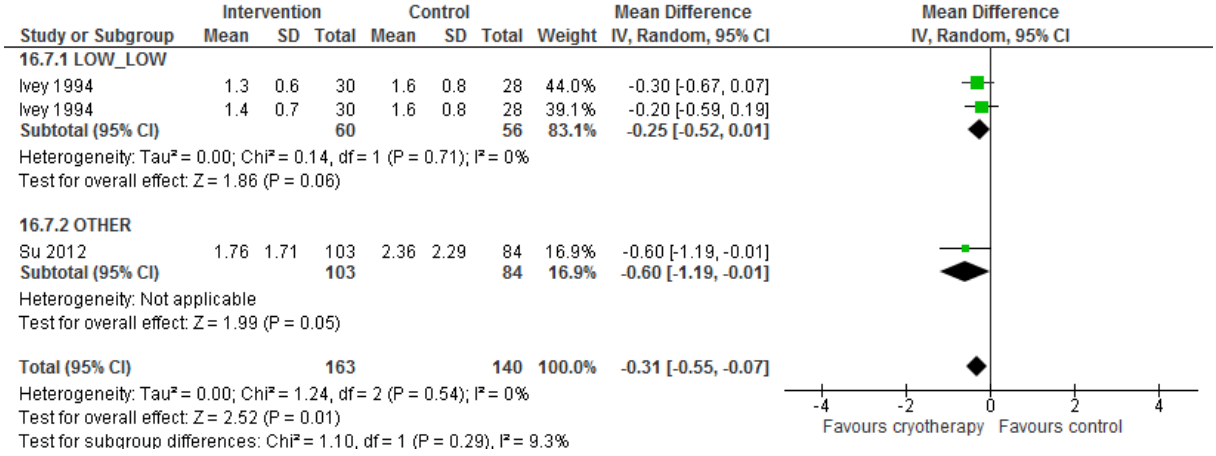
eFigure 14: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



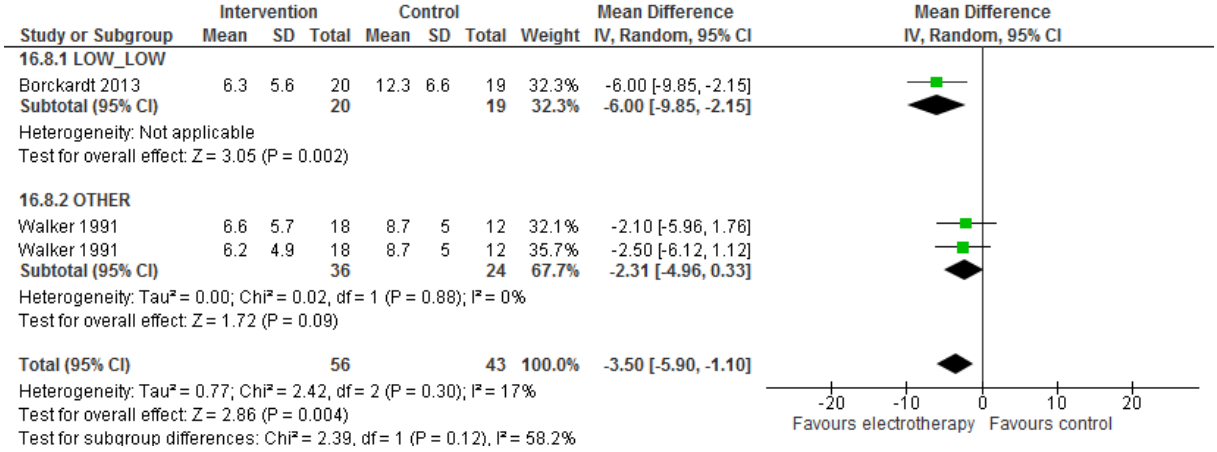
eFigure 15: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



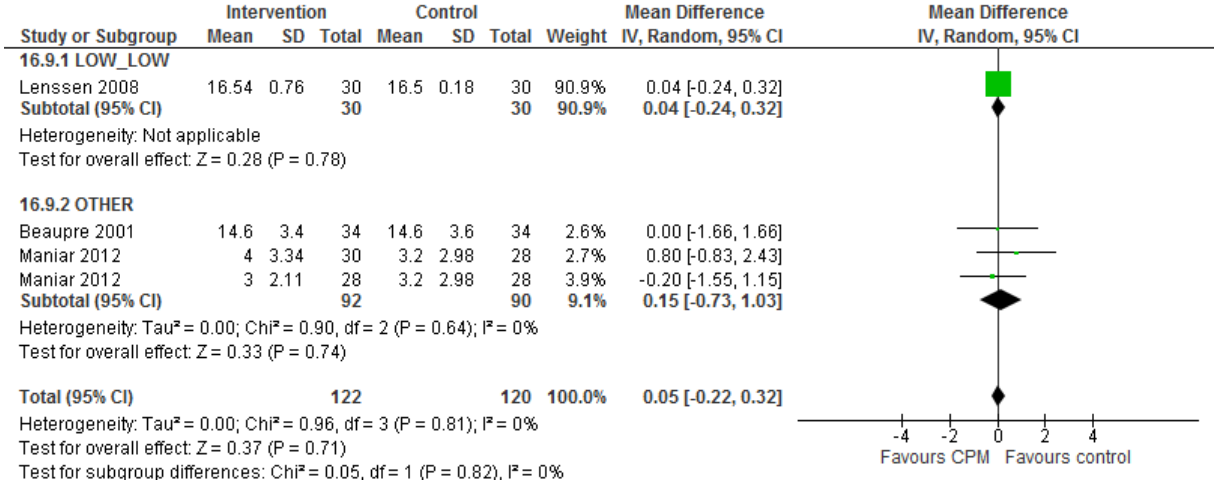
eFigure 16: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



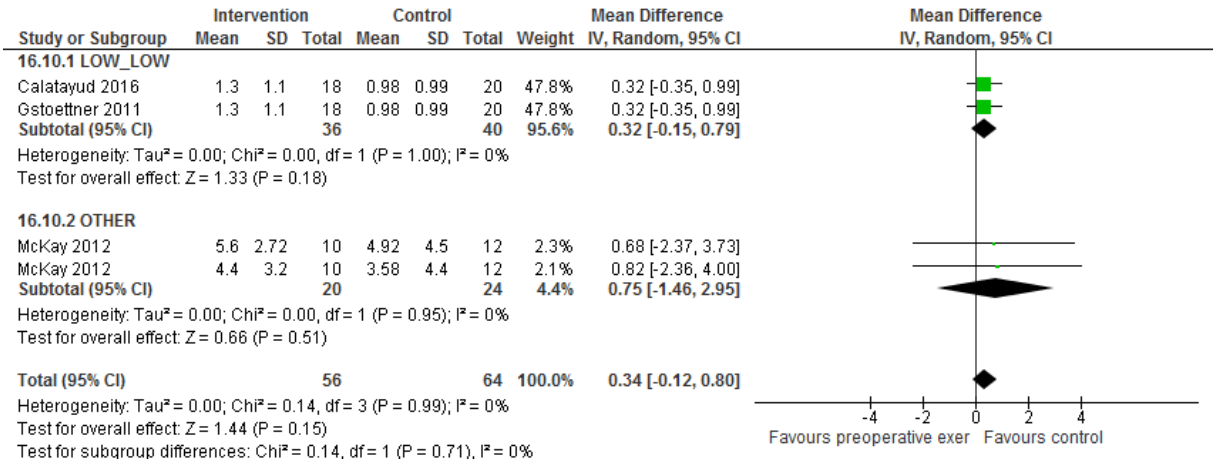
eFigure 17: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



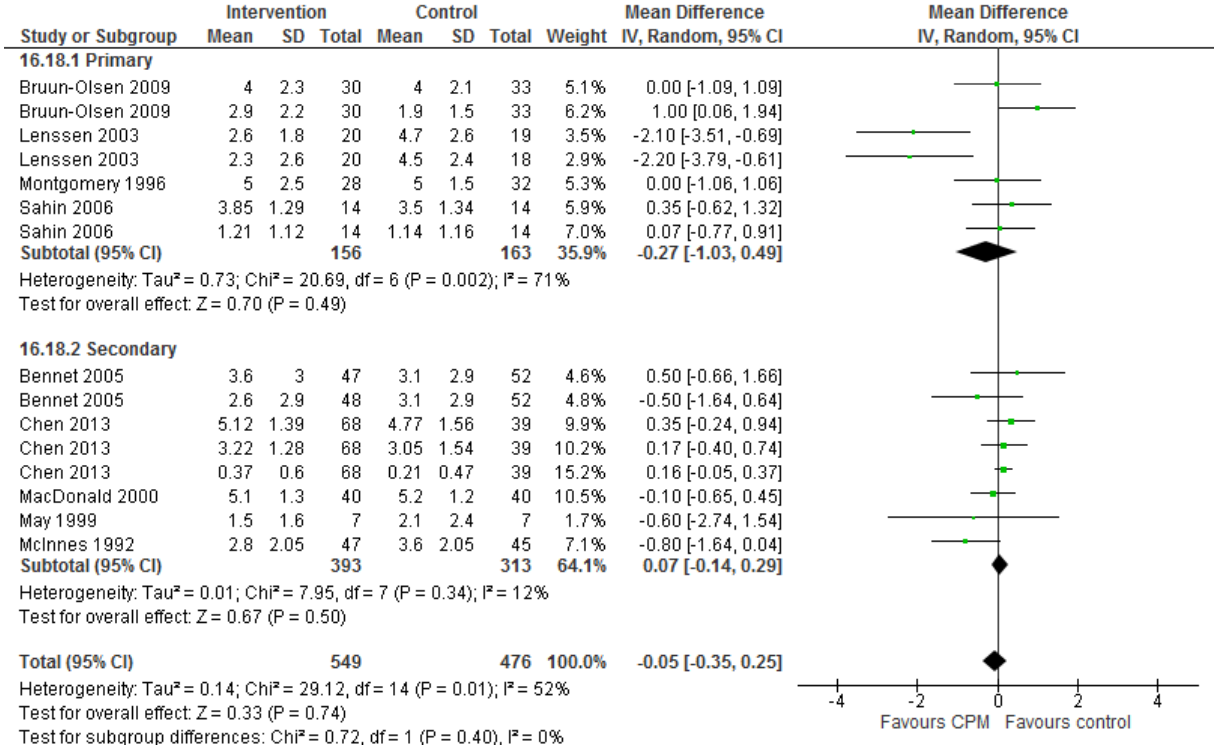
eFigure 18: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



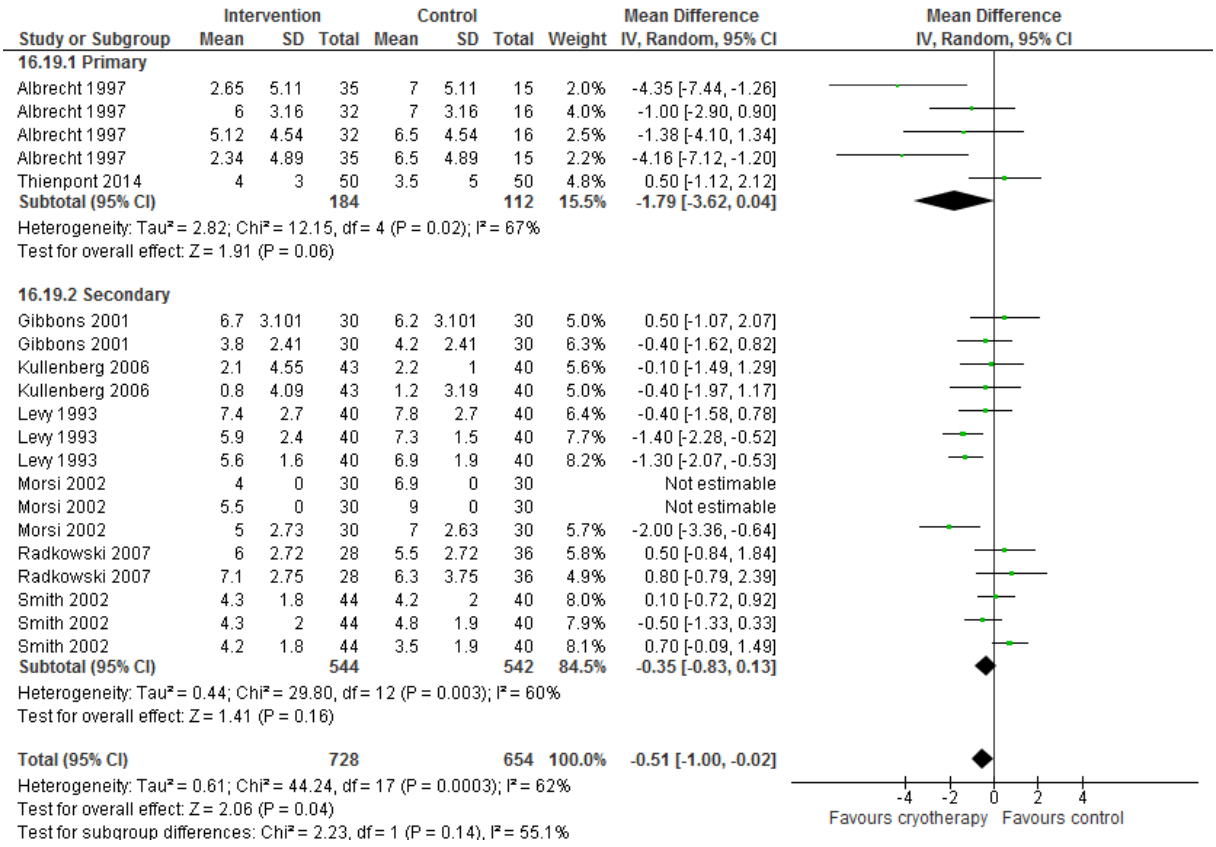
eFigure 19: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation



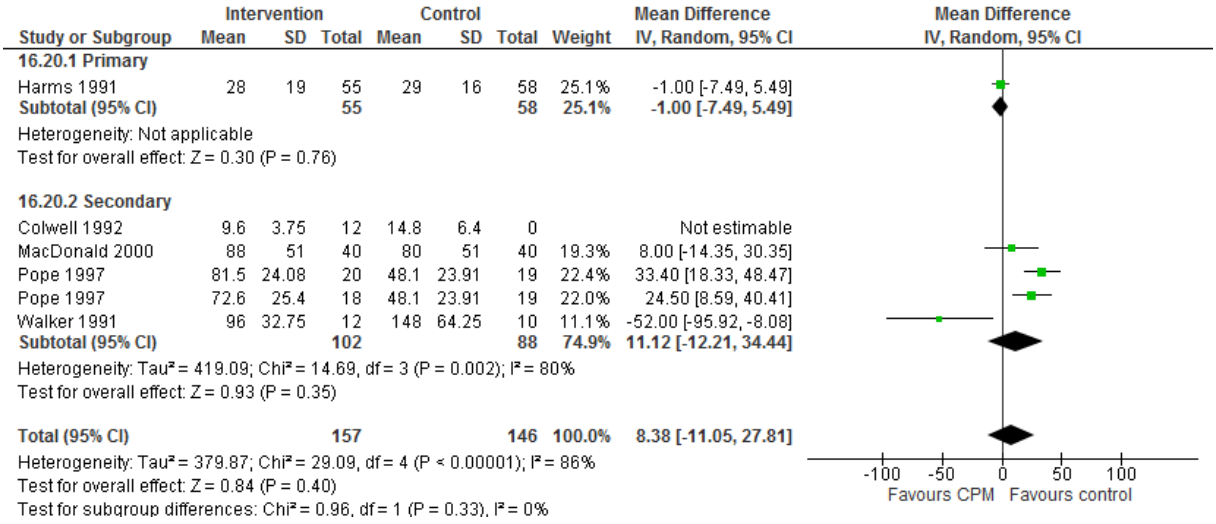
eFigure 20: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)



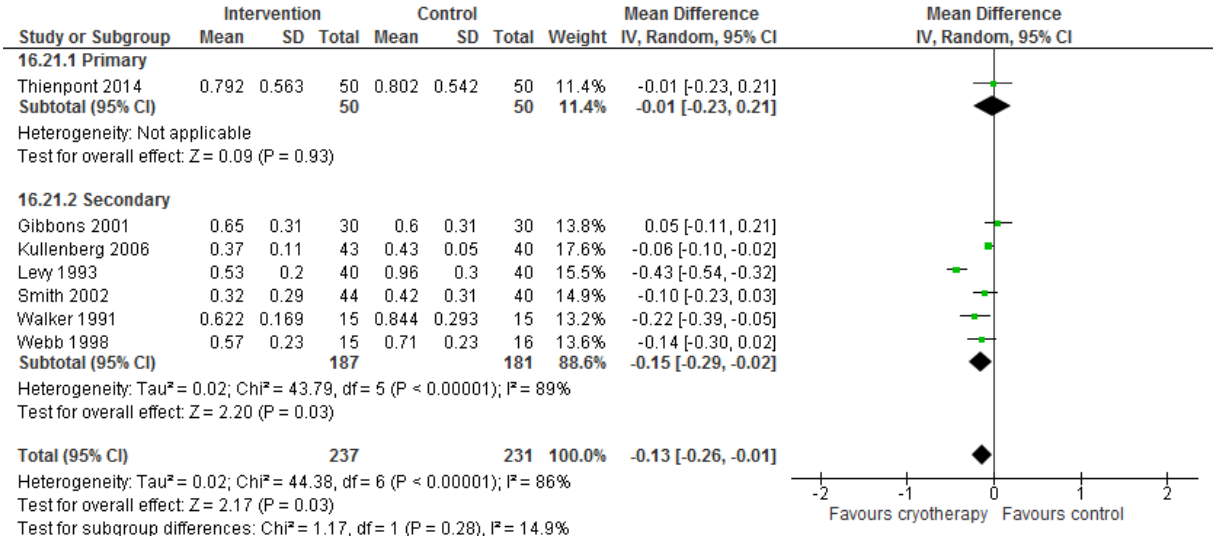
eFigure 21: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)



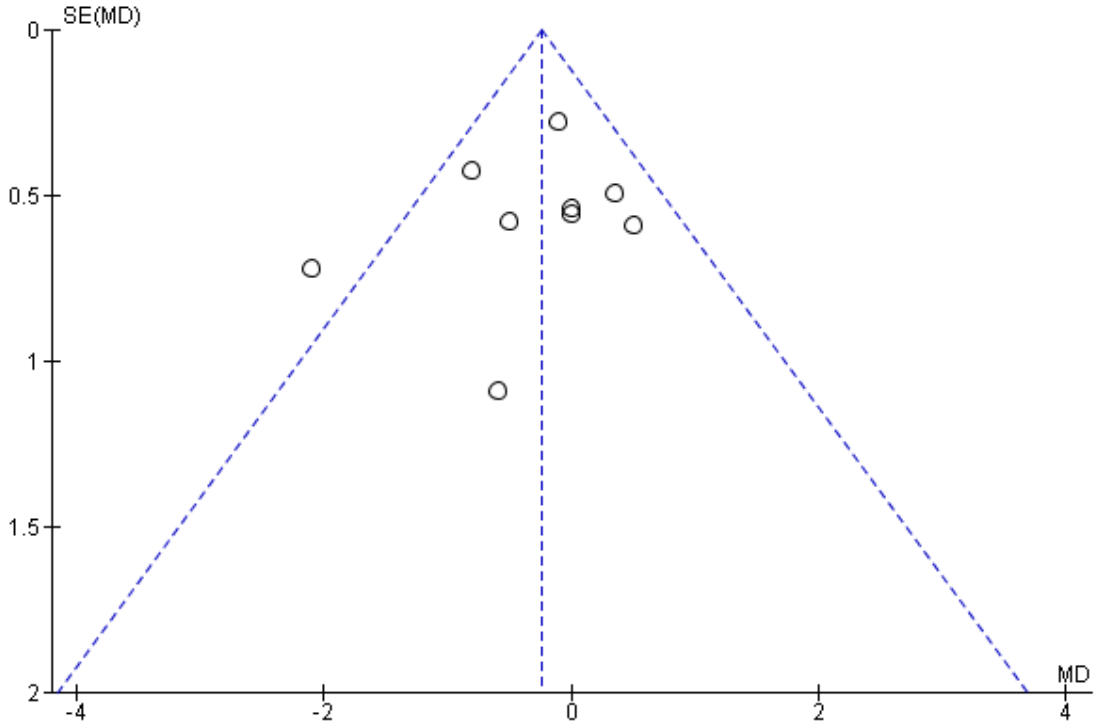
eFigure 22: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)



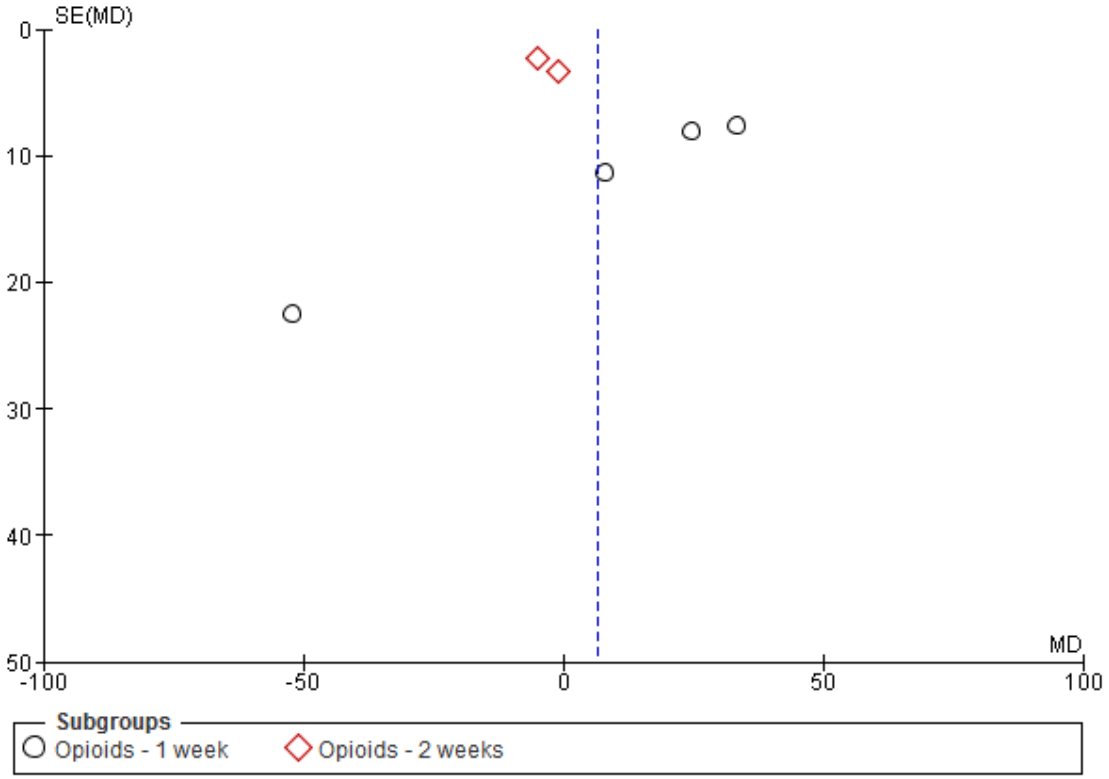
eFigure 23: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)



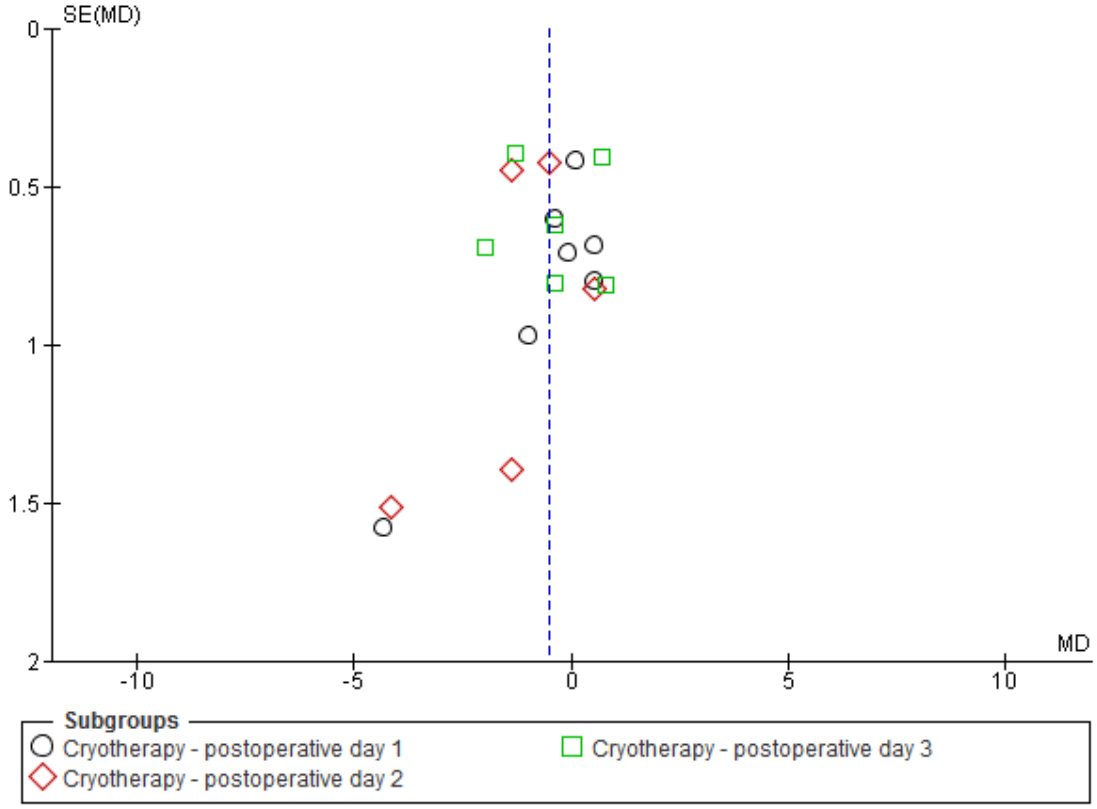
eFigure 24: Funnel Plot of Comparison for CPM Trials Measured in Terms of Reported Points in the VAS Scale at 1 Week



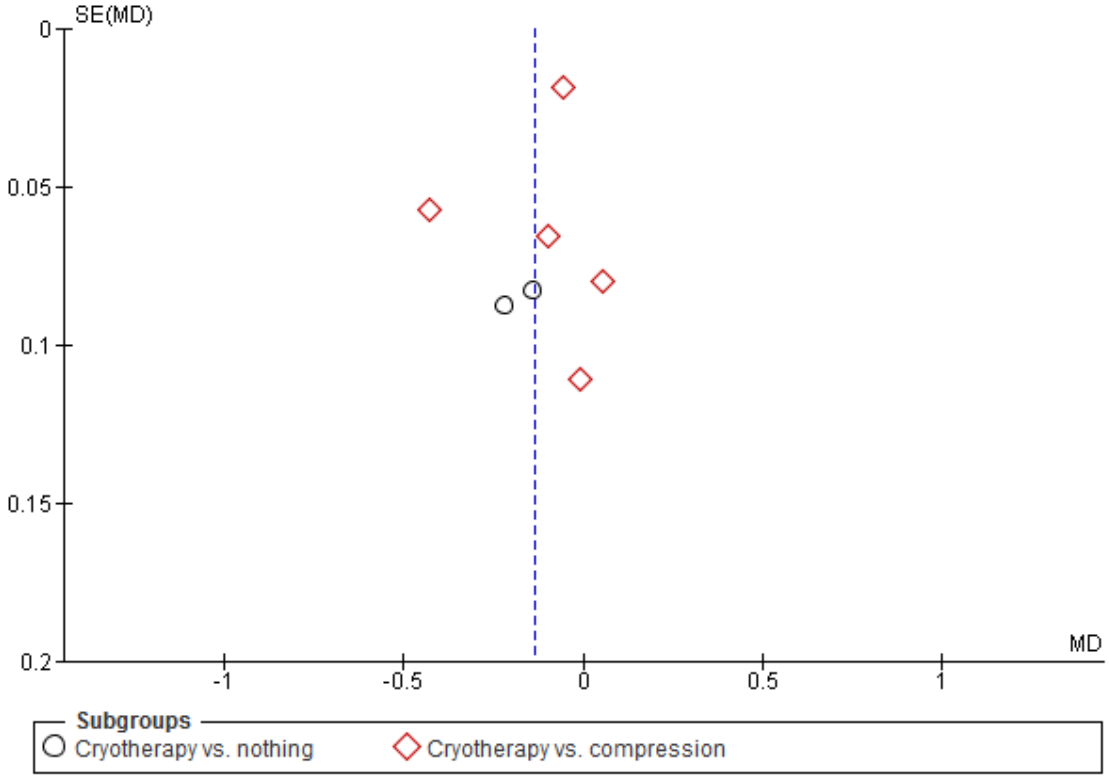
eFigure 25: Funnel Plot of Comparison for CPM Trials Measured in Terms of Opioid Consumption (mg/kg/48 Hours of Morphine Equivalent)



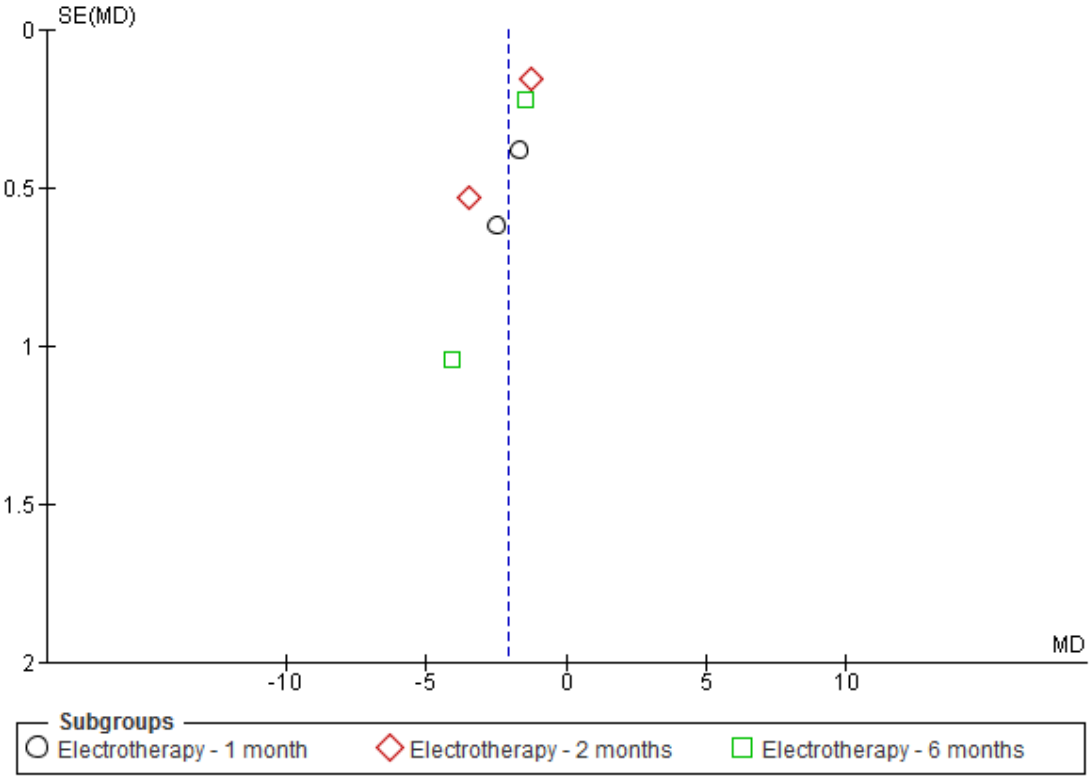
eFigure 26: Funnel Plot of Comparison for Cryotherapy Trials Measured in Terms of Reported Points in the VAS Scale



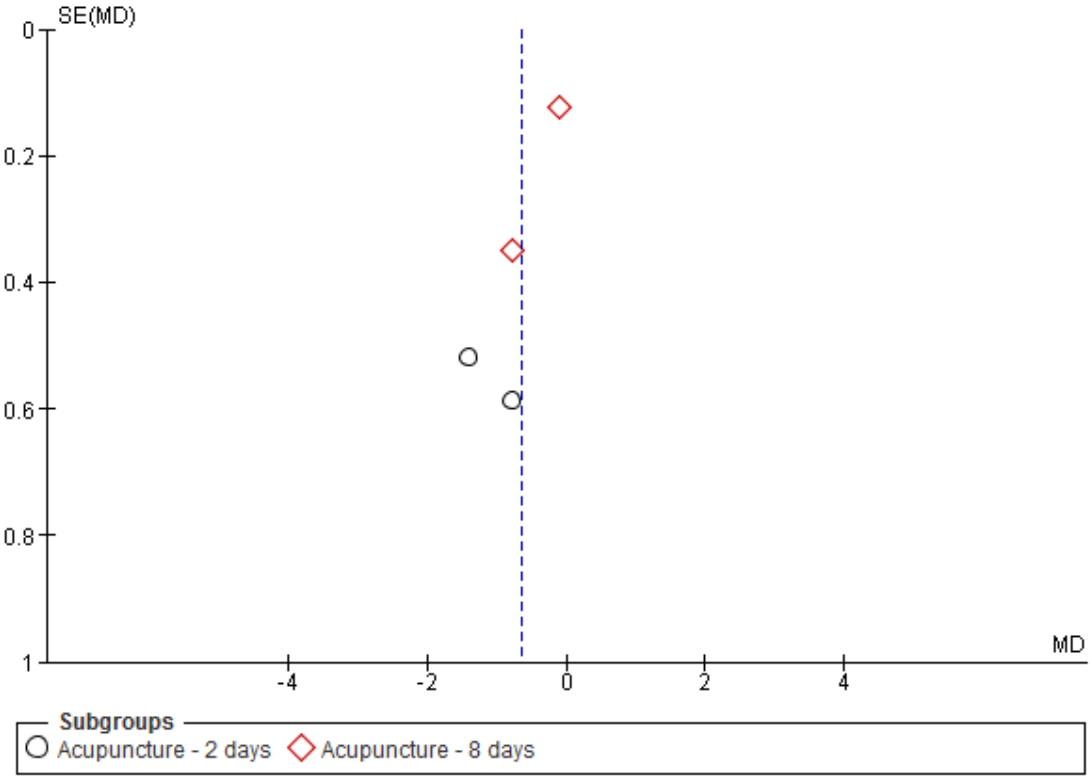
eFigure 27: Funnel Plot of Comparison for Cryotherapy Trials Measured in Terms of Opioid Consumption (mg/kg/48 Hours of Morphine Equivalent)



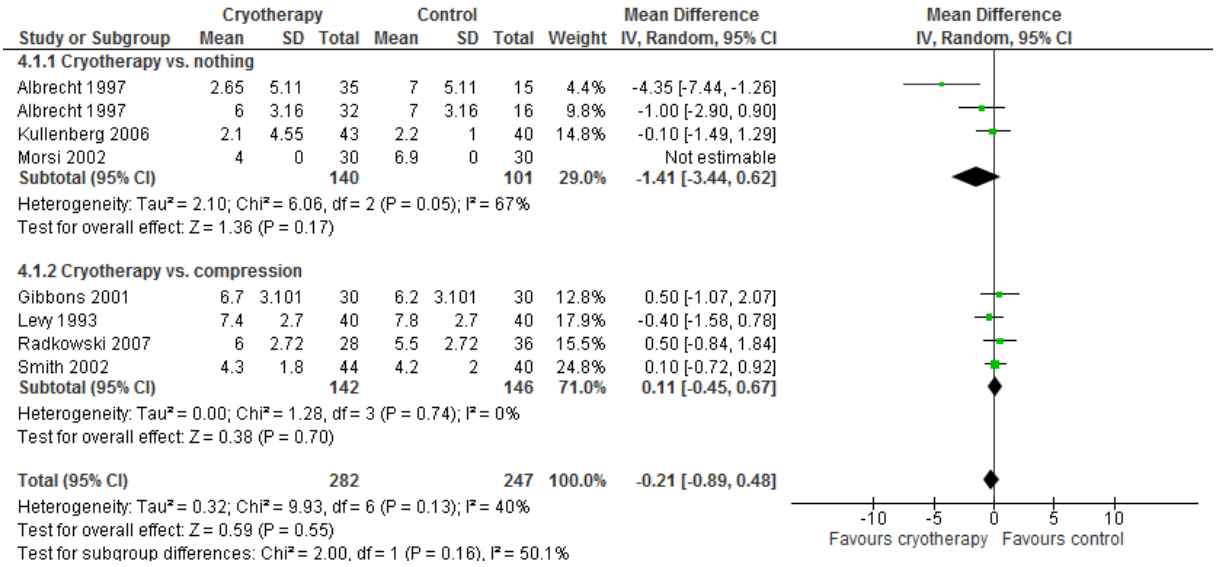
eFigure 28: Funnel Plot of Comparison for Electrotherapy Trials Measured in Terms of Reported Points in the VAS Scale at 1 Week



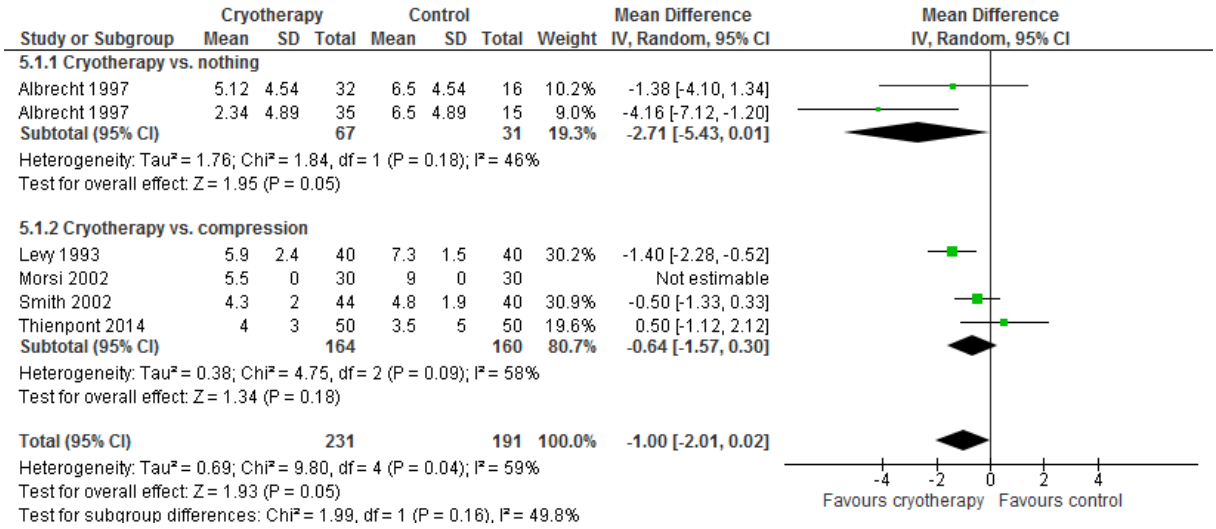
eFigure 29: Funnel Plot of Comparison For Acupuncture Trials Measured in Terms of Reported Points in the VAS Scale at 1 Week



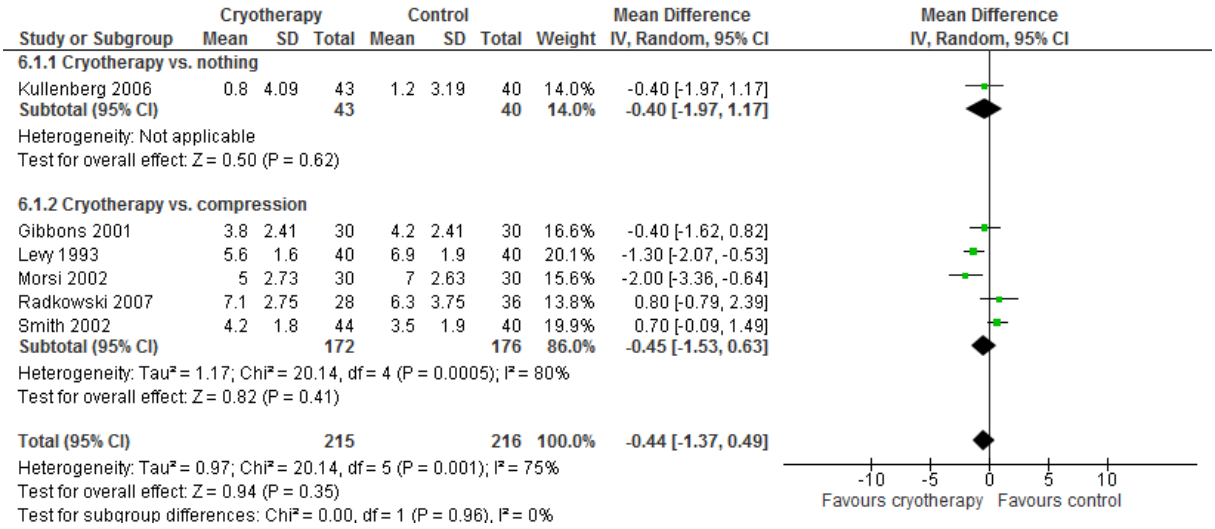
eFigure 30: Subgroup Sensitivity Analysis Comparing Studies by Type of Control.



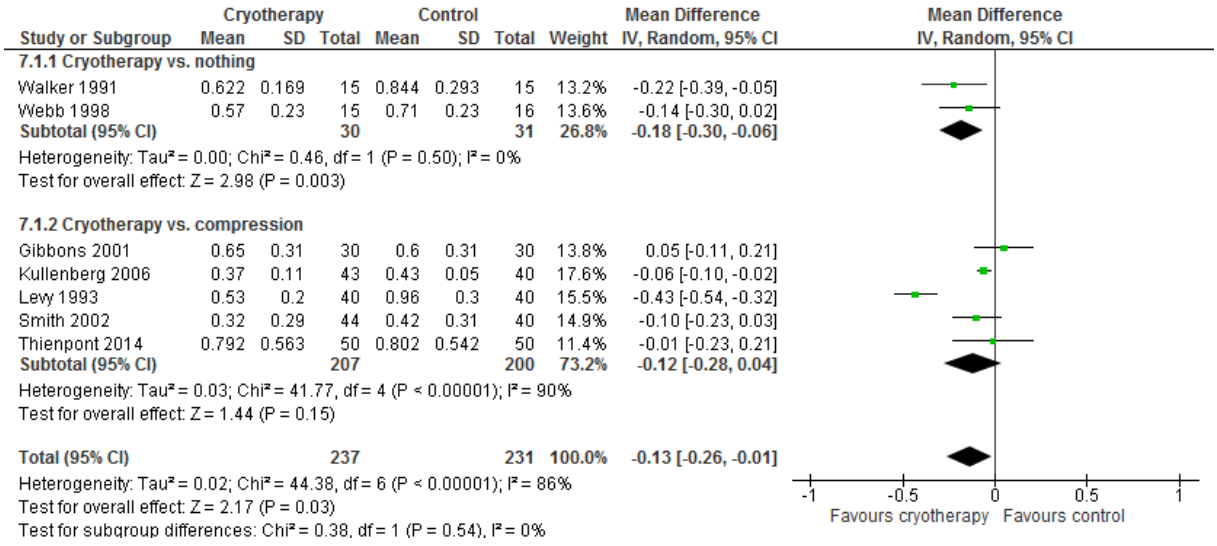
eFigure 31: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



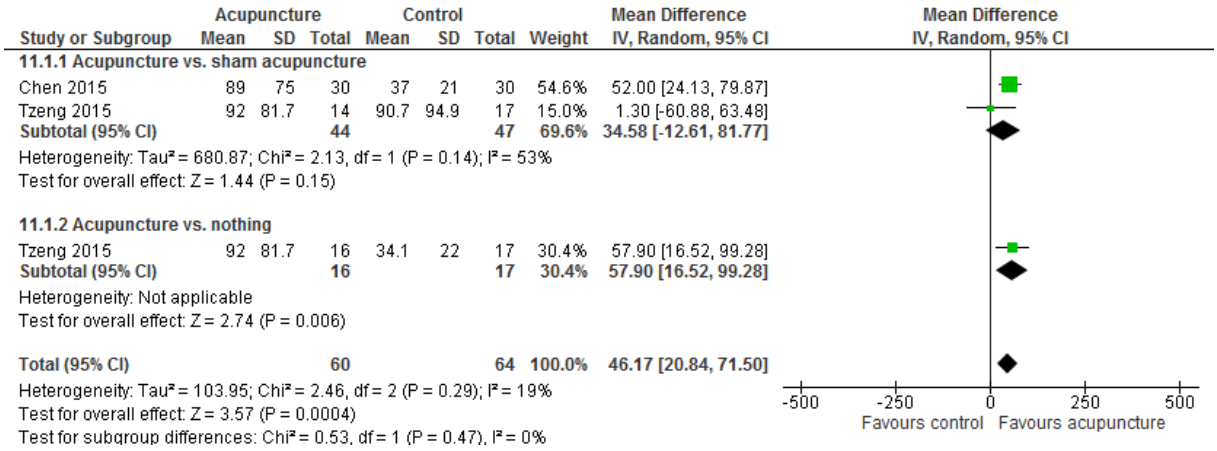
eFigure 32: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



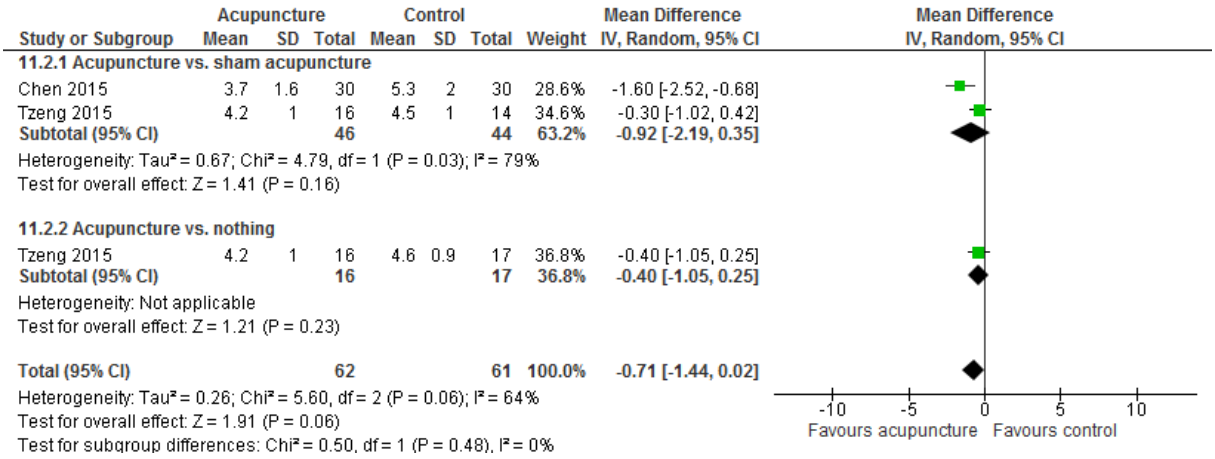
eFigure 33: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



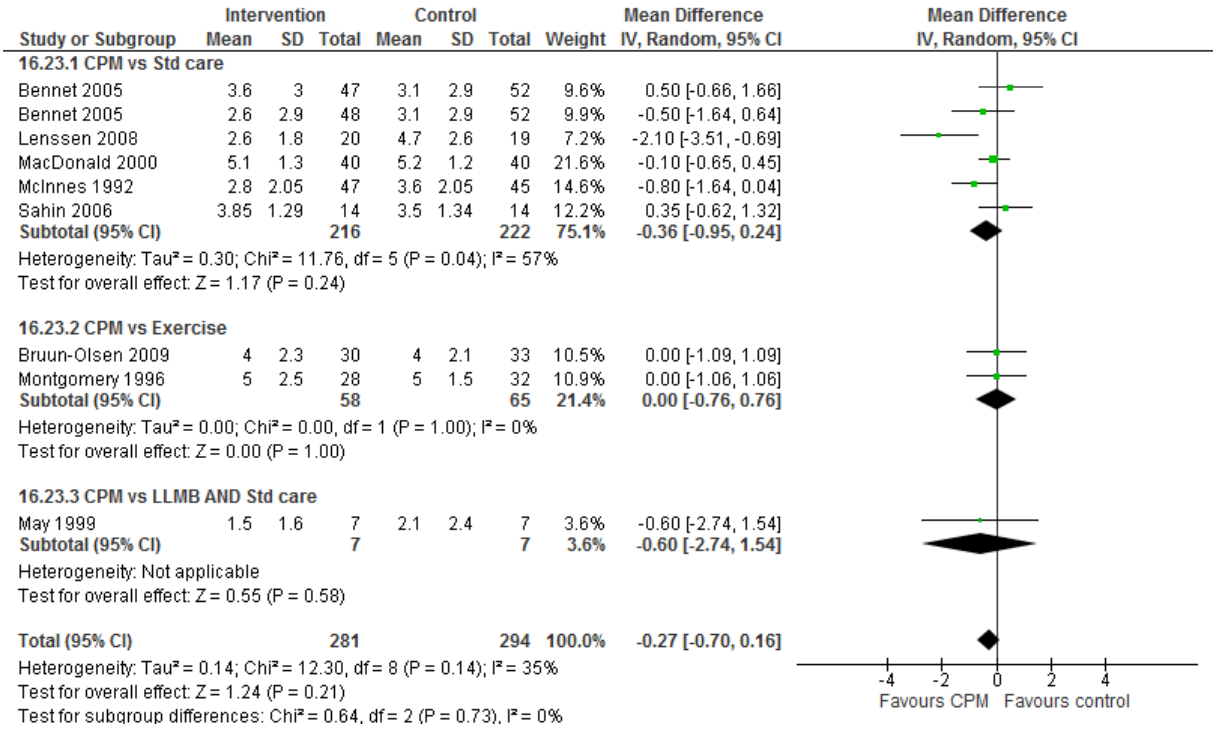
eFigure 34: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



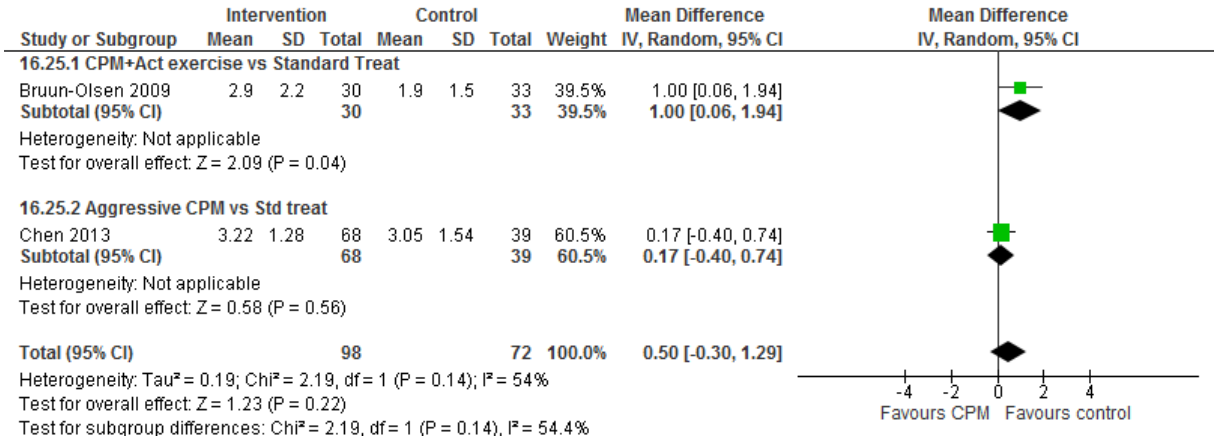
eFigure 35: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



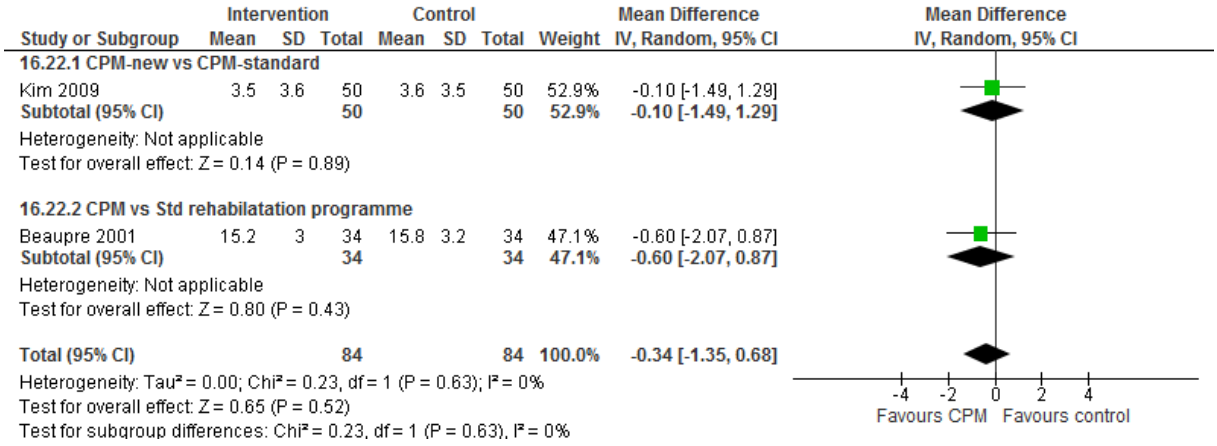
eFigure 36: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



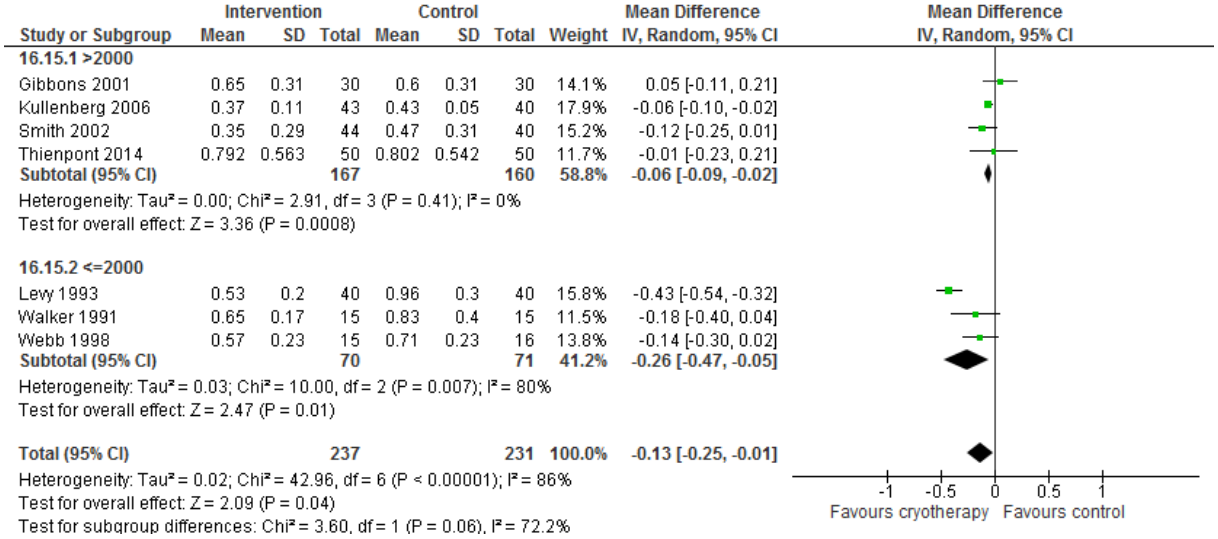
eFigure 37: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



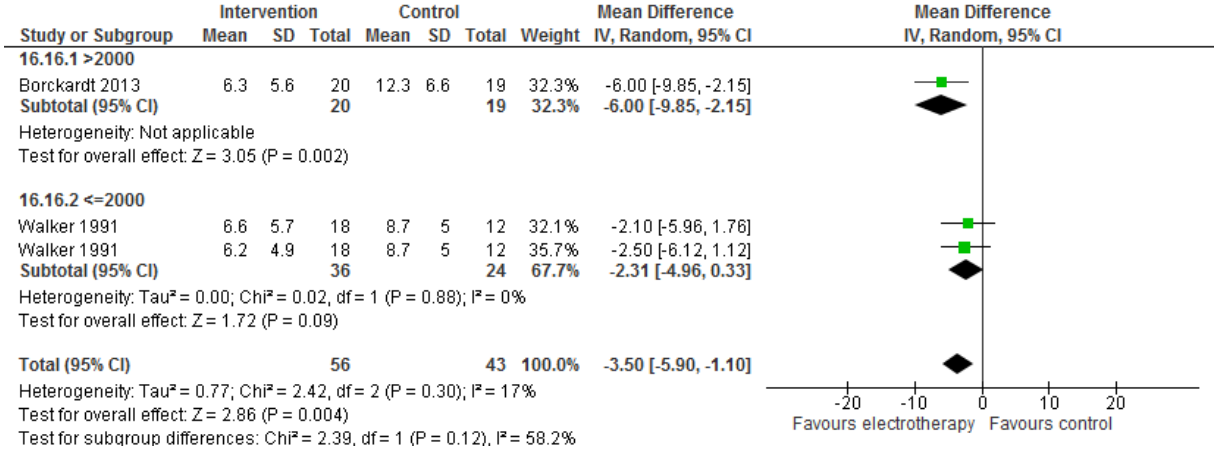
eFigure 38: Subgroup Sensitivity Analysis Comparing Studies by Type of Control



eFigure 39: Subgroup Sensitivity Analysis Comparing Studies by Time (Studies Divided If Published Prior or Comprising Year 2000 or From 2001 Onwards)



eFigure 40: Subgroup Sensitivity Analysis Comparing Studies by Time (Studies Divided If Published Prior or Comprising Year 2000 or From 2001 Onwards)



eFigure 41: Results of the Meta-regression for the Distribution of Age in the Groups (Treatment vs Control)

```
. metareg AGE Group, wsse ( SD)

Meta-regression                                         Number of obs  =      28
REML estimate of between-study variance                 tau2           =   .6622
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =  53.35%
With Knapp-Hartung modification
```

AGE	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Group	-1.365645	1.703033	-0.80	0.430	-4.86628	2.134991
_cons	68.7297	1.19114	57.70	0.000	66.28128	71.17813

eFigure 42: Results of the Meta-regression for the Distribution of Sex in the Groups (Treatment vs Control)

```
. metareg SEX Group1, wsse ( SD1)

Meta-regression                                         Number of obs  =      57
REML estimate of between-study variance                 tau2           =   213.6
% residual variation due to heterogeneity               I-squared_res  =  95.96%
Proportion of between-study variance explained          Adj R-squared  =  -1.26%
With Knapp-Hartung modification
```

SEX	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Group1	2.310076	4.002792	0.58	0.566	-5.711698	10.33185
_cons	68.4375	3.045668	22.47	0.000	62.33385	74.54115