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A Systematic review and Network Meta-Analysis of Minimally Invasive Intervention Use in Pain Management

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Abstract: Background: Chronic, non-cancer pain represents a serious public health and economic issue affecting approximately 20% of the global population. Chronic pain can affect many aspects of patient's lives, including mental health, employment, and relationships. Current medical management is largely focussed on investigating and managing acute pain. Patients and clinicians are now increasingly aware of the potential benefits of combined treatments or complex interventions in alleviating chronic pain. These approaches include both physical interventions, such as exercise or yoga, as well as psychological support including cognitive behavioural therapy (CBT) and talking therapies. **Methods:** This study used network meta-analyses to explore the prevalence of complex interventions in pain management, and the effects of these interventions on quality of life, using outcome measures including intensity of chronic pain, assessment of functional disability and participant's psychological state. **Results:** Psychological interventions were associated with improvements in pain intensity and depression. Exercise and manipulation technique-based treatments provided a statistically significant reduction in pain intensity. This effect was enhanced when exercise and CBT were combined. Mensendieck somatocognitive therapy (MSCT) plus standard gynaecological treatment (STGT) treatments appeared to have a better effect on chronic pain than multimodal exercise plus CBT treatment. Combined MSCT and STGT treatment, and multimodal exercise plus CBT treatments, reduced pain intensity, whilst MSCT+STGT treatments had a slightly better effect than exercise plus CBT treatment. **Conclusions:** Complex interventions have become more popular with patients as the risks associated with other interventions including surgery and pharmacological management have become better understood. These interventions can have a significant positive effect both on the physical and psychological health of patients. The analysis presented in this study suggests that further work is warranted in this area and that additional studies are required, both in more geographically diverse locations, and with larger cohorts.

Keywords: chronic pain; non-pharmaceutical pain management; interventions

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Introduction

Chronic non-cancer pain impacts approximately 20% of the global population with a significant physical and mental health impact on the patient and their family [1]. The incidence of chronic pain may increase with advancing age, biological gender and lifestyle [2]. The focus of medical management is predominantly aimed at investigating and managing acute painful conditions. A lack of adequate resource allocations for managing chronic long-term painful conditions appropriately has resulted in chronic pain becoming a serious public health issue posing a large economic burden to healthcare and social care [3]. The delay in addressing the effects of chronic pain can result in mental health issues, breakdown of relationships, fatigue, lack of motivation, and affect patient's ability to remain in employment, or to return to work following sick leave. Failure to manage chronic pain appropriately therefore impacts both social well-being and economic productivity of populations.

Patients and clinicians now have a better understanding of both the management of long-term conditions including chronic pain, and the limitations of surgical and pharmacological interventions. As an example, spinal surgeries for managing chronic back and neck pain may lead to persistent pain and disabilities which could be attributed to the index condition or the treatment [1]. Pharmacological treatment options including NSAIDs, neuropathic pain medications and weak and strong opioids are no longer recommended for long term use due to their adverse side-effect profile; some patients find it difficult to tolerate these treatments, even at lower doses. The liberal use of opioids for managing chronic non-cancer pain in the western world has created an addiction problem for public health systems of epidemic proportions [4].

The importance of addressing psychological well-being and social care for effective management is being widely accepted and there is increasing awareness of establishing care delivery through community services incorporating exercise therapy, health coaching and social prescribing. Additionally, there is increasing recognition of the utility of psychology services, and patients are being offered support not only through pain clinics, but also through community-based services where they can even self-refer for assessment and support [1]. Patients can now be offered counselling, talking therapy, cognitive behavioural therapy (CBT), mindfulness and eye movement desensitization and reprocessing (EMDR). Psychology services can help to alleviate patients discomfort and stress, as well as equipping patients with self-management strategies to deal with their chronic pain.

Timely access to medical care and potential cost implications, as well as reluctance to take medications, can result in patients seeking advice and treatment from non-medical practitioners. This may also be rooted in cultural beliefs and availability of services. Physiotherapist sessions including manipulations, and exercise therapies including Pilates and other core-strengthening exercises and "alignment and adjustment treatments" by chiropractors and osteopaths are often sought by patients before seeking a conventional clinician. In Europe and the Americas and further east, yoga, tai chi, qi gong, massage, acupuncture, aromatherapy, reflexology and reiki practitioners are involved in managing pain and pain-related issues [3]. Practices such as yoga, tai chi, qi gong, massage, acupuncture, aromatherapy, reflexology and reiki, have now gained popularity across the globe in recent years, and some therapies like acupuncture are funded through healthcare systems. Anecdotally, small case series or individual patients claim significant benefit from some of these treatments, but there is paucity of evidence from reliable clinical trials or real-world data. Some of these treatments have been accessed by patients as part of early intervention and management even during the acute stage of their pain and there are significant variations in practice and how the treatments are delivered depending on the practitioner and remunerations.

Multidisciplinary management of pain employs the use of both psychological and physical therapies as a part of a multi-modal analgesic strategy. Studies have shown the benefit of using cognitive behavioural therapy with pharmacological management or exercise, rehabilitation and pain management programmes with pain interventional procedures and neuromodulation [5]. For the purpose of this study, complex interventions are defined as two or more clinical or non-clinical

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interventions used to treat non-cancer pain. The aim of this study was to demonstrate the prevalence of complex interventions used for the purpose of pain management.

Methods

We developed a systematic methodology and published this in PROSPERO (CRD42021235384) with the aim to demonstrate the prevalence of combined minimally invasive interventions used for the purpose of pain management. For the purpose of this study, two or more clinical or non-clinical interventions used to treat non-cancer pain was defined as complex interventions.

Eligibility criteria

The search strategy included key words of *chronic pain, complex interventions, non-opioids, acute pain, pain management*, rehabilitation, physiotherapy, non-clinical interventions, cognitive behavioural therapy, CBT, *back pain and analgesics*. We used multiple databases of PubMed, Science direct, ProQuest, Web of science, Ovid Psych INFO, PROSPERO, EBSCOhost, MEDLINE, ClinicalTrials.gov and EMBASE. All randomised clinical trials, epidemiology and mixed-methods studies peer reviewed and published in English between the 1st January 1990 and 31st April 2022 were included. All commentaries, editorials, opinions and grey literature were excluded from the final sample pool.

Data extraction

Data were extracted from the eligible studies using a study specific excel extraction template which included age, sex, outcome, outcomes measures, intervention and type used, geographical location and statistical details such as mean, median, standard deviation and confidence intervals. The final data pool was examined by two independent investigators before the statistical analysis was completed. All disputes around study eligibility were discussed and agreed with the Chief Investigator.

Outcome measures

Outcome measures included intensity of chronic pain, assessment of functional disability, and participants' psychological state during treatment. For pain intensity, a variety of methods were used, including visual analogue scale (VAS), numeric rating scale (NRS), Graded Chronic Pain Scale (GCPS), Brief Pain Inventory (BPI), Neck Pain Index (NPI, only used for chronic neck pain). For all measurements of pain intensity, a larger value indicated a worse condition of chronic pain. Assessment of functional disability of pain was differentiated according to types of pain. Neck-related disability was assessed by Neck Disability Index (NDI) and a modified version of NDI, while functional disability of low back pain and other types of pain was assessed by Roland Disability Questionnaire (also called Roland Morris Disability Questionnaire, RDQ or RMQ), Oswestry Disability Questionnaire (also called Oswestry Disability Index, ODQ or ODI) and a modified version of ODQ. A higher value of neck pain and low back pain represented poor physical function and greater disability. Psychological state of participants included several measurements, including depression and anxiety. Considering the impact of the number of studies on the results of network meta-analysis, depression was selected as a measurement of effectiveness on chronic pain, which was assessed by Patient Reported Outcomes Institute Measurement System (PROMIS), Beck Depression Inventory (BDI), Centre for Epidemiological Studies Depression Scale (CES-D) and Hospitality Anxiety and Depression Scale (HADS). A higher score indicated greater severity of depression.

Statistical analysis plan

Currently a variety of interventions are used to assess chronic pain with a large number of variables. In order to answer the research question comprehensively, all the data gathered was reported using a pairwise meta-analysis (PMA) and network meta-analysis (NMA) were performed. The NMA pooled standardized mean difference (SMD) with a 95% confidence interval (CI) to report

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the effectiveness of interventions for each study. The PMA combined the result of two or more studies which were used to compare the effectiveness of two or more interventions [6]. NMA was used to report indirect comparisons of the interventions in instances where there was more than two and all the comparisons of studies formed one or more networks.

SMD was used instead of mean difference (MD) to calculate the dimensionless effect measure as there were a number of pain variables. The dimensionless effect measure was defined as the mean difference divided by a standard deviation based either on a single treatment group or both treatment groups, reported as

$$\hat{g}_k = (1 - \frac{3}{4n_k - 9})\frac{\hat{\mu}_{1k} - \hat{\mu}_{2k}}{\sqrt{((n_{1k}-1){s_{1k}}^2 + (n_{2k}-1){s_{2k}}^2)/(n_k - 2)}}$$

where $n_{ik}, i = 1, 2$ denoted the number of patients in the experimental treatment i, s_{ik} $i = 1, 2$ denoted standard deviation of response in the experimental treatment i, $\hat{\mu}_{ik}$, $i = 1, 2$ denoted the mean response in the treatment i and $n_k = n_{1k} + n_{2k}$.

Statistical significance effect would be concluded based on the hypothesis test of network SMD.

Statistical heterogeneity was reported using the Cochrane's Q test and I^2 statistic, and statistically significant heterogeneity was considered present at I^2 larger than 50% and p value of Cochrane's Q smaller than 0.05. In comparison, there is no heterogeneity if I^2 is less than or equal to 50% with a large p-value indicates weak heterogeneity [7]. In the presence of high heterogeneity, the random effects model was employed whilst the fixed effects model was used in the presence of weak or no heterogeneity [8]. Publication bias was evaluated with funnel plots if a network included over 10 studies [9], and the funnel plot asymmetry was tested using Egger's test. A p-value larger than 0.05 of Egger's test was considered as the lack of significant publication bias [10].

Results

Of the 168 systematically included studies (Table 1), 46 were selected for the meta-analysis. Of the 46 studies, 14 were about exercise related interventions such as yoga, qigong, pilates and exercise whilst 12 were about acupuncture related intervention; 14 reported cognitive behavioral therapy (CBT) related interventions, and 6 indicated sports massage related interventions.

Table 1. Characteristics of the studies included in systematic review.

Study ID	Authors	Year	Study Type	Sample Size	Country	Mean	Meta-analysis inclusion Y/N
1	Gardiner et al.	2019	Single-blind RCT	159	USA	50.5	N
2	Malfliet et al.	2018	2-center, Triple-blind RCT	120	Belgium	37.5	N
3	Gkolias et al.	2019	Double-blind RCT	21	Greece	58.76	N
4	Turner et al.	2021	Cohort study	328	USA	53.17	N
5	Lehinger et al.	2020	RCT	103	USA	45.33	N
6	Gkolias et al.	2019	Double-blind RCT	21	Greece	58.76	N
7	Loose et al.	2021	Single-blind RCT	99	Germany	51.7	N
8	Miller-Matero et al.	2021	RCT	60	USA	61.9	N
9	Yarns et al.	2020	RCT	53	USA	73.5	Y
10	Muthulingam et al.	2021	Double-blind RCT	38	Denmark	56.6	N
11	Regina Wing Shan et al.	2021	RCT	72	China	70.3	N
12	Kohns et al.	2020	RCT	104	USA	44.35	N
13	Hooten et al.	2018	RCT	100	USA	39	N
14	Damush et al.	2015	RCT	250	USA	55.1	N
15	Turner et al.	2018	RCT	111	USA	56.5	N
16	Lee et al.	2018	Two-arm, Assessor-blind RCT	36	Korea	51.125	Y
17	Koyuncu et al.	2016	RCT	60	Turkey	52.7	Y
18	Cederbom et al.	2019	RCT	105	Norway	85	N

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19	Reneman et al.	2018	Single-blind, two armed RCT	201	Germany	43.8	N
20	Nygaard et al.	2020	RCT	62	Norway	38.1	N
21	Kisling et al.	2021	RCT	381	Germany	11.4	N
22	Öte Karaca et al.	2016	RCT	50	Turkey	43.7	Y
23	Matthias et al.	2020	RCT	215	USA	58.6	N
24	Heathcote et al.	2018	RCT	66	UK	13.48	N
25	Hüppe et al.	2019	RCT	552	Germany	53.5	N
26	Stahlschmidt et al.	2018	RCT	107	Germany	13.8	N
27	Dogan et al.	2021	RCT	419	Germany	14.3	N
28	Heapy et al.	2016	RCT	230	USA	57.9	N
29	Carty et al.	2019	RCT	62	USA	46.03	N
30	Ziadni et al.	2021	RCT	104	USA	48.6	N
31	Bourke et al.	2014	RCT	641	UK	38.5	N
32	Gardiner et al.	2016	RCT	159	USA	50.5	N
33	Mehlsen et al.	2017	RCT	500	Denmark	54.2	N
34	Corrêa et al.	2016	RCT	150	Brazil	51.2	N
35	Cederbom et al.	2014	RCT	23	Sweden.	84.5	N
36	Smith et al.	2019	RCT	80	Australia	45	N
37	Monticone et al.	2016	RCT	170	Italy	53.8	Y
38	Baker et al.	2018	RCT	39	Australia	43.3	Y
39	Karlsson et al.	2014	RCT	57	Sweden.	44	N
40	Lauche et al.	2013	RCT	200	Germany	51.4	Y
41	Lluch et al.	2014	RCT	23	Spain	38.9	N
42	Brage et al.	2015	Single-blind RCT	200	Denmark	42.14	N
43	Meeus et al.	2014	Double-blind RCT	70	Belgium	54.25	N
44	Chelimsky et al.	2013	RCT	31	USA	53.4	N
45	Lauche et al.	2016	RCT	114	Germany	49.4	Y
46	Beinert et al.	2018	RCT	29	Germany	45.5	N
47	Fernández-Carnero et al.	2018	RCT	54	Spain	20.91	N
48	Guillory et al.	2015	RCT	68	USA	48.59	N
49	Jeitler et al.	2014	RCT	89	Germany	49.7	N
50	Lane et al.	2017	RCT	316	USA	range: 18–75	N
51	Van Oosterwijck et al.	2013	Double-blind RCT	30	Belgium	45.8	N
52	Löffler et al.	2017	Double-blind RCT	20	Germany	44.8	N
53	Kroenke et al.	2014	Double-blind RCT	250	USA	55.2	N
54	Weeks et al.	2015	RCT	20	USA	60.2	N
55	Buhrman et al.	2015	RCT	52	Sweden	50.69	N
56	Weiner et al.	2019	RCT	55	USA	69.1	N
57	Sahin et al.	2011	RCT	146	Turkey	47.25	Y
58	Ang et al.	2010	RCT	250	USA	55.5	N
59	Makino et al.	2013	RCT	39	Japan	-	N
60	Vanti et al.	2019	RCT	64	Italy	48.3	N
61	Plews-Ogan et al.	2005	RCT	30	USA	46.5	N
62	Holmberg et al.	2014	A qualitative interview study	20	Germany	76	N
63	Cook et al.	2015	RCT	179	USA	47.1	Y
64	Chen et al.	2019	RCT	204	USA	55 (median)	Y
65	de Araujo Cazotti et al.	2018	RCT	64	Brazil	48.8	Y
66	Lauche et al.	2012	RCT	40	Germany	49.2	N
67	Murtezani et al.	2011	RCT	101	Kosovo	50.6	N
68	Rutledge et al.	2018	RCT	61	USA	62.5	Y
69	Hechler et al.	2013	RCT	120	Germany	14	N
70	Hinman et al.	2012	RCT	282	Australia	64.3	N

71	Flack et al.	2018	RCT	104	Germany	14.3	N
72	Blödt et al.	2015	RCT	127	Germany	46.7	Y
73	Lauche et al.	2015	RCT	72	Germany	39.9	N
74	Zhang et al.	2015	RCT	80	China	45	Y
75	Galindez-Ibarbengoetxea et al.	2017	Single-blind RCT	27	Spain	33.29	Y
76	Haugstad et al.	2008	RCT	20	Norway	-	Y
77	Kumar et al.	2016	RCT	64	Germany	54.8	Y
78	Sherman et al.	2014	RCT	228	USA	46.75	Y
79	Thorn et al.	2011	RCT	83	USA	50.2	Y
80	Fink et al.	2002	RCT	45	Austria	52.5	N
81	Kabay et al.	2009	RCT	89	Turkey	37.7	N
82	Gur et al.	2003	RCT	75	Turkey	35.7	Y
83	Racine et al.	2020	RCT	69	Canada	51.12	N
84	Turner et al.	2006	RCT	158	USA	37.3	Y
85	Michalsen et al.	2016	RCT	68	Germany	55	N
86	Trapp et al.	2015	RCT	30	Germany	45.53	N
87	Lee et al.	2019	RCT	25	Malaysia	65.63	N
88	Rothman et al.	2013	RCT	182	Sweden	-	N
89	Durmus et al.	2013	Single-blind RCT	41	Germany	54.9	N
90	Teut et al.	2016	RCT	176	Germany	73	Y
91	Elder et al.	2017	RCT	138	USA	48.7	N
92	Walach et al.	2003	RCT	19	Germany	39.4	N
93	Durmus et al.	2013	Single-blind RCT	60	Turkey	48.7	N
94	Heutink et al.	2014	RCT	31	The Netherlands	56.5	N
95	Karst et al.	2000	Double-blind RCT	39	Germany	49	Y
96	Koldaş Doğan et al.	2016	Double-blind RCT	49	turkey	52.14	N
97	Berry et al.	2015	RCT	85	Canada	50.4	N
98	Lauche et al.	2013	RCT	61	Germany	54.16	Y
99	Yeh et al.	2015	RCT	61	USA	60.97	N
100	Magalhães et al.	2015	RCT	66	Brazil	46.6	N
101	Haugstad et al.	2006	RCT	20	Norway	32.3	Y
102	Cho et al.	2013	Assessor-blinded RCT	45	Korea	38.8	Y
103	Sayilir & Yildizgoren	2017	A randomised, follow-up study	55	Turkey	51.1	N
104	Braun et al.	2011	RCT	48	Germany.	58.5	N
105	Lin et al.	2013	RCT	63	China	39.9	N
106	Ferrell et al.	1997	RCT	29	USA	73	N
107	Zhang et al.	2013	RCT	206	China	45.8	N
108	Sköld et al.	2013	RCT	152	Sweden	39.4	N
109	Bello et al.	2015	RCT	80	Ghana	45	N
110	Hinman et al.	2014	RCT	2882	Australia	63.5	N
111	Witt et al.	2006	A Multicentre RCT plus a Non-randomized Cohort.	3451	Germany	49.8	N
112	Lluch et al.	2013	n experimental study	35	India	42	N
113	Monticone et al.	2016	RCT	150	Italy	53.2	Y
114	Palermo et al.	2020	RCT	143	USA	14.5	N
115	He et al.	2005	RCT	24	Norway	47	N
116	Itoh et al.	2004	RCT	35	Japan	71.9	Y
117	Koldaş Doğan et al.	2008	RCT	55	Turkey	40.2	Y
118	Civelek et al.	2012	RCT	100	turkey	51.8	N
119	Özkul et al.	2015	RCT	24	Turkey	32.33	N
120	Salo et al.	2012	RCT	101	Finland	41	N
121	Williams et al.	2018	RCT	159	Australia	56.7	N
122	Turner & Jensen	1993	RCT	102	USA	42	Y

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123	García-Pérez-Juana et al.	2018	RCT	54	Spain	37	N
124	Ólason et al.	2017	RCT	115	Iceland	37.32	Y
125	Ebadi et al.	2017	RCT	30	Iran	44.26	N
126	Fuentes et al.	2014	Double-blind RCT	117	Canada	30	N
127	Linden et al.	2014	RCT	103	Germany	50	Y
128	Licciardone et al.	2013	Double-blind RCT	455	USA	41	N
129	Falla et al.	2013	RCT	46	Denmark	39.1	N
130	Heapy et al.	2017	RCT	125	USA	57.9	Y
131	Sanei et al.	2020	RCT	52	Iran	37.25	N
132	Kääpä et al.	2006	RCT	120	Finland.	46	N
133	Monticone et al.	2014	RCT	20	Italy	58.9	Y
134	Di Cesare et al.	2011	RCT	62	Italy	52.5	Y
135	Yan et al.	2020	RCT	20	China	53.65	Y
136	Von Korff et al.	2005	RCT	240	USA	49.7	N
137	Defrin et al.	2005	RCT	22	Israel.	44.5	N
138	Cramer et al.	2013	RCT	36	Germany	47.8	N
139	Cruz-Díaz et al.	2015	RCT	97	Spain	71.14	N
140	Häkkinen et al.	2007	RCT	125	Finland	42.5	N
141	Monticone et al.	2018	RCT	30	Italy	48.6	N
142	Uluğ et al.	2018	RCT	56	Turkey	39.7	Y
143	Sertpoyraz et al.	2009	RCT	40	Turkey	38.75	Y
144	Rizzo et al.	2018	RCT	100	Brazil	51.7	N
145	S. Lee & B. Lee	2009	RCT	63	USA	39.8	N
146	Garcia et al.	2020	Double-blind RCT	188	USA	51.5	N
147	Almeida Silva et al.	2021	RCT	90	Brazil	30	Y
148	Loizidis et al.	2020	RCT	25	Greece	44	N
149	Nabeta & Kawakita	2002	RCT	34	Japan	34.2	Y
150	Gilmore et al.	2019	RCT	28	USA	46.5	N
151	Poleshuck et al.	2014	RCT	61	USA	36.7	N
152	Zhang et al.	2014	RCT	54	China	22.29	N
153	Cho et al.	2013	RCT	130	Korea	42.06	Y
154	Zhu & Polus	2002	Single-blind RCT	29	Australia	50	Y
155	Gur et al.	2004	Double-blind RCT	60	Turkey	31.72	N
156	Liang et al.	2011	Single-blind RCT	190	China	36.72	Y
157	Andrade Ortega et al.	2014	RCT	149	Spain	44.2	N
158	Ylinen et al.	2006	RCT	180	Finland.	46	N
159	Cruz-Díaz et al.	2015	Single-blind RCT	101	Spain	71.05	Y
160	Ylinen et al.	2003	RCT	180	Finland	45.7	N
161	Morone et al.	2008	RCT	25	USA	74.1	N
162	Vibe Fersum et al.	2019	RCT	121'	Norway	43	Y
163	Meissner et al.	2016	RCT	60	Germany	35.6	N
164	Harris et al.	2017	RCT	214	Norway	44.8	N
165	Narouei et al.	2020	Single-blind RCT	32	Iran	32.18	N
166	Ghasabmahaleh et al.	2020	RCT	44	Iran	44.3	N
167	Thomas et al.	2020	RCT	162	USA	25	N
168	Lauche et al.	2016	RCT	81	Germany	65.9	N

Network Meta-analysis

The study sample was categorised into four networks of exercise-related, acupuncture-related, CBT-related and massage-related interventions. Effect of interventions within each network was compared directly and indirectly using a NMA method.

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Effectiveness of exercise-related interventions on chronic low back pain and neck pain

Exercise-related interventions included exercise, home exercise, aerobic exercise, physical therapy, isokinetic exercise, qigong, yoga, tai chi and pilates. The primary outcome reported among these studies was pain intensity, assessed by VAS and the secondary outcome was disability, assessed by RDQ or ODQ or Modified ODQ for people with low back pain and NDI for people with neck pain.

Comparisons of pain intensity under exercise-related interventions

Based on the meta-analysis findings, the network of exercise-related interventions were separated into two sub-nets. The first subnet (Figure 1) included 8 studies with 594 observations, 6 treatments and 12 pairwise comparisons.

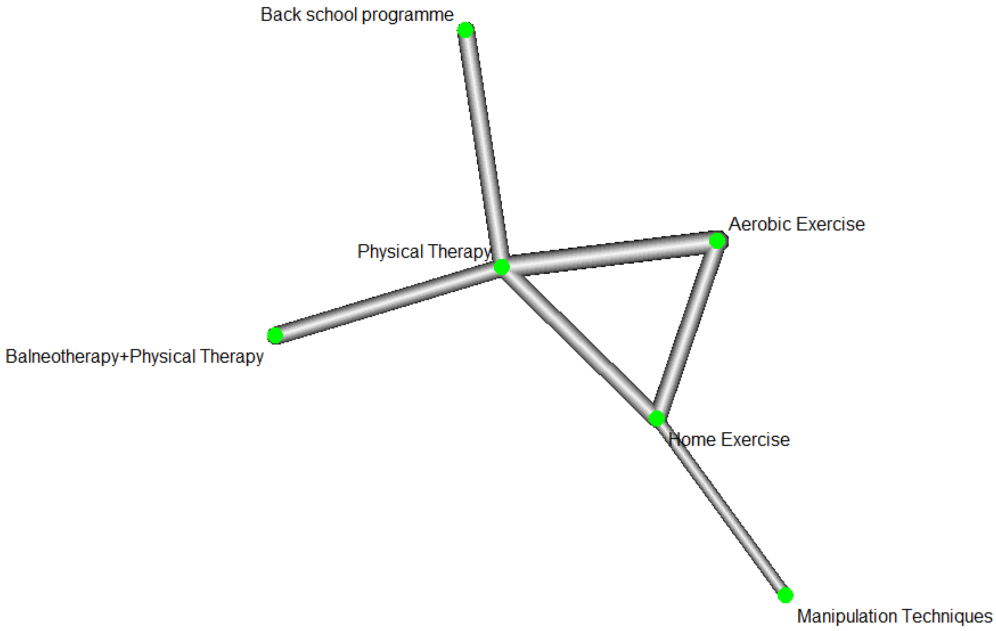

Figure 1. Network plot of pain intensity under exercise-related treatments in the first subnet.

The first sub-net (Figure 2) forest plot showed 93.6% of I^2 (95% CI of I^2: [88.7%, 96.4%], Q=77.74, p-value <0.0001) indicating a significant statistical heterogeneity. According to the point estimate and 95% CI, 3 comparisons showed statistically significant effect on chronic pain.

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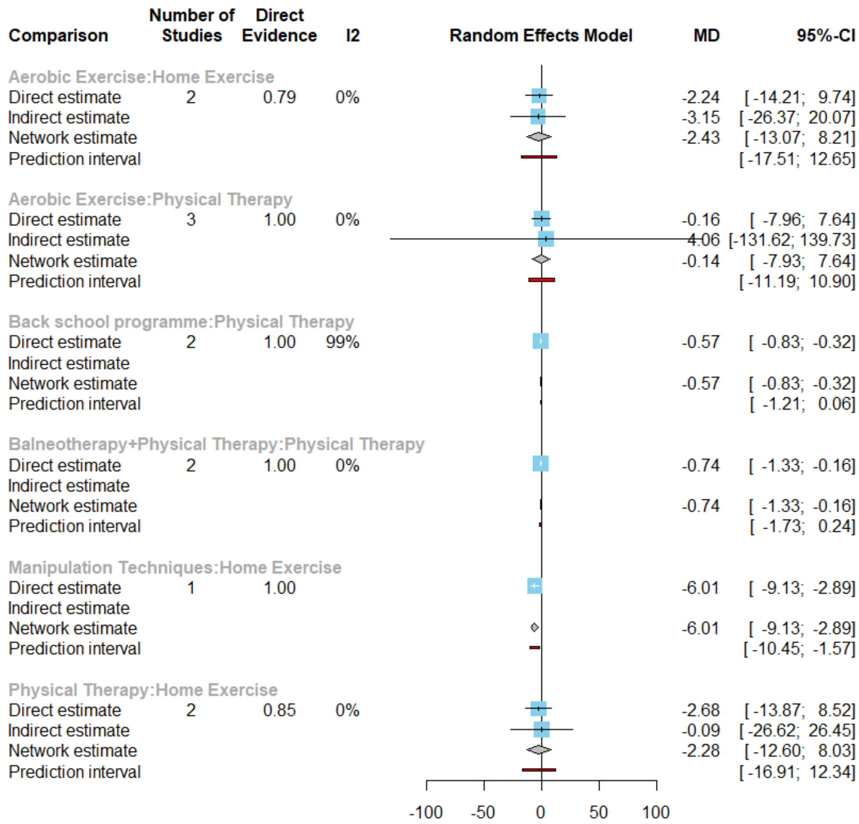

Figure 2. Forest plot of pain intensity under all direct comparisons of exercise-related treatments in the first subnet.

The direct and indirect mean differences of all the treatments within the subnet compared with home exercise treatment (Figure 3).

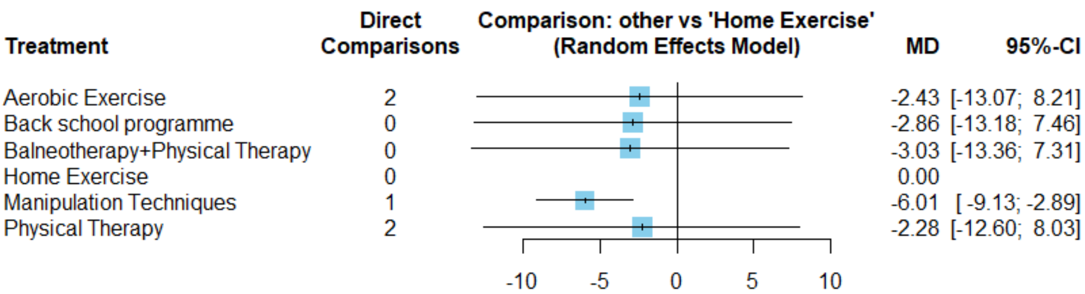

Figure 3. Forest plot of all exercise-related treatments compared with control treatment in the first subnet.

The second sub-net of exercise-related treatments (Figure 4) included 13 studies with 1250 observations, 10 treatments and 23 pairwise comparisons. In this network, the control treatment meant no additional intervention or usual activities and therapies without any new therapeutic regimen for symptom management.

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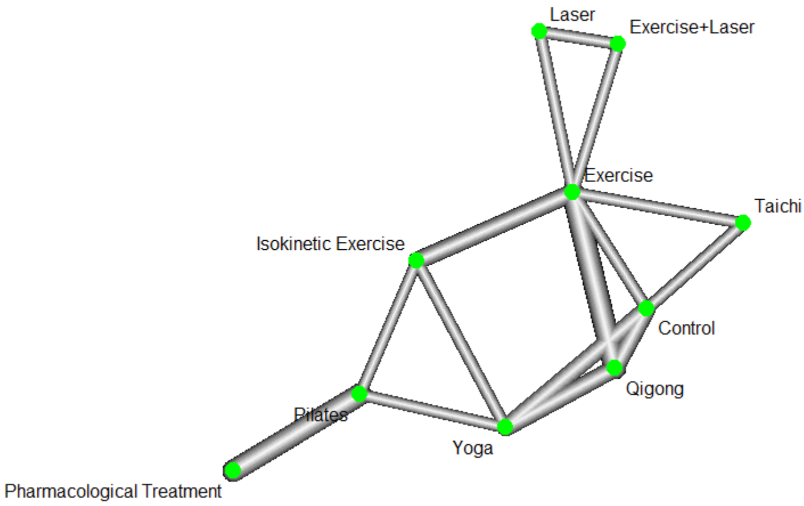

Figure 4. Network plot of pain intensity under exercise-related treatments in the second subnet.

The second sub-net indicated 97.5% of I^2 (95% CI: [96.6%, 98.2%], Q=204.54, p-value <0.0001) with a significant statistical heterogeneity (Figure 5). The significant difference between treatment comparisons were shown within the network with exercise, qigong and the control treatment.

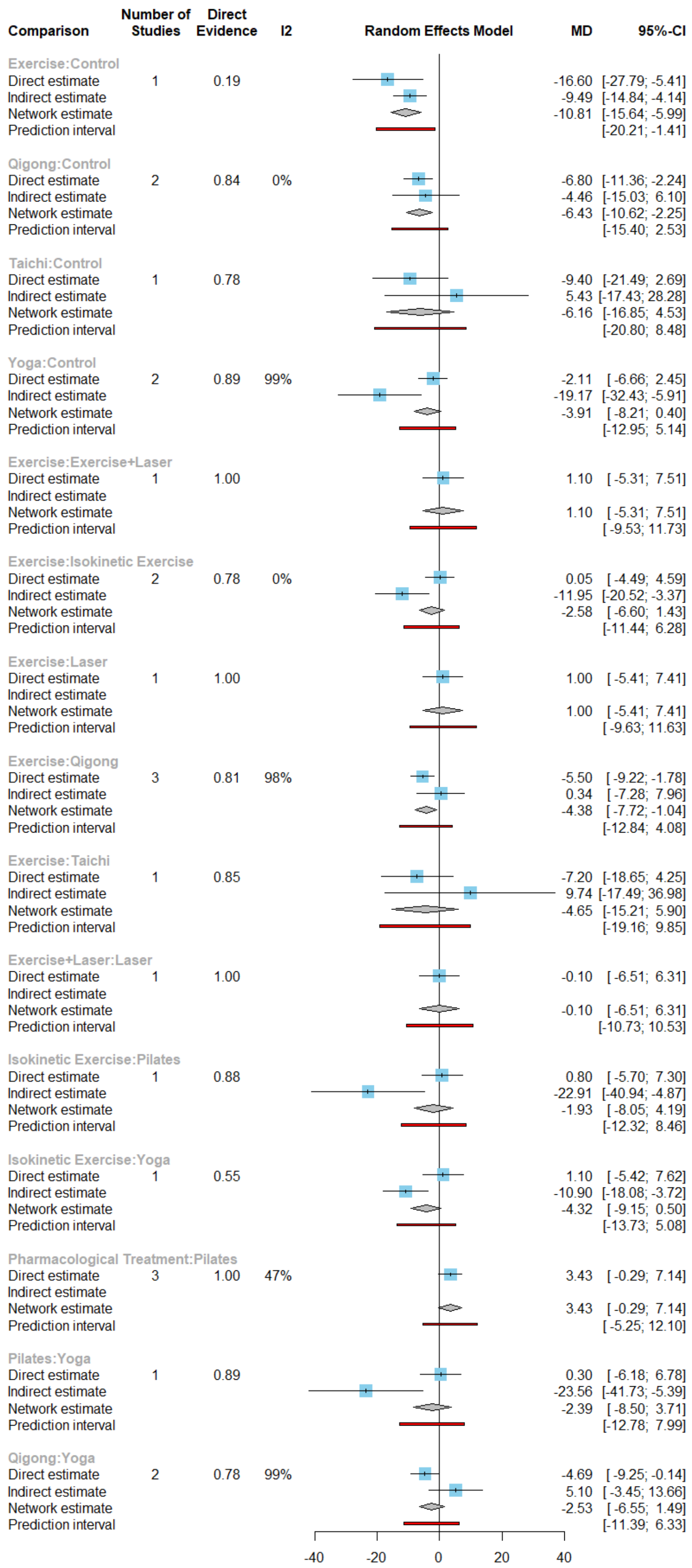

Figure 5. Forest plot of pain intensity under all direct comparisons of exercise-related treatments in the second subnet.

The mean differences of all treatments in the second sub-net directly compared with exercise treatment (Figure 6) showed in pain intensity as indicated by the statistical significance [Table 2]. Pilates, pharmacological and yoga interventions could not provide direct comparisons to exercise treatment, did not provide direct evidence to support a statistically significant effect on chronic low back pain and neck pain.

Table 2. Moved to supplementary material.

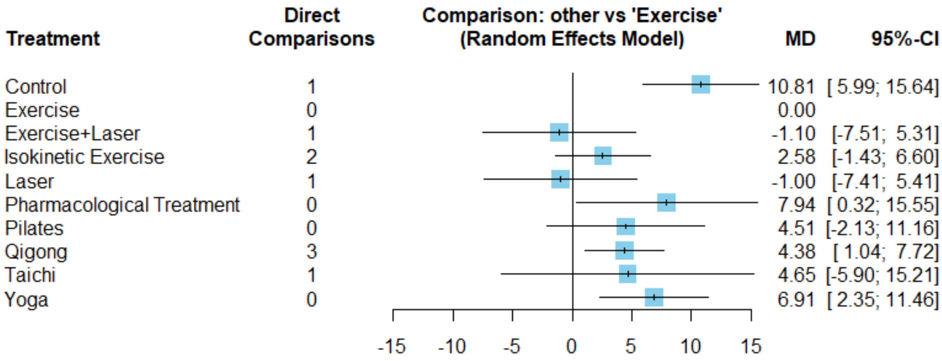

Figure 6. Forest plot of pain intensity under all exercise-related treatments compared with control treatment in the second subnet.

Comparisons of pain disability under exercise-related interventions

The network of pain disability with exercise-related interventions included two sub-nets. The first subnet was shown (Figure 7) 8 studies with 724 observations, 6 treatments and 12 pairwise comparisons.

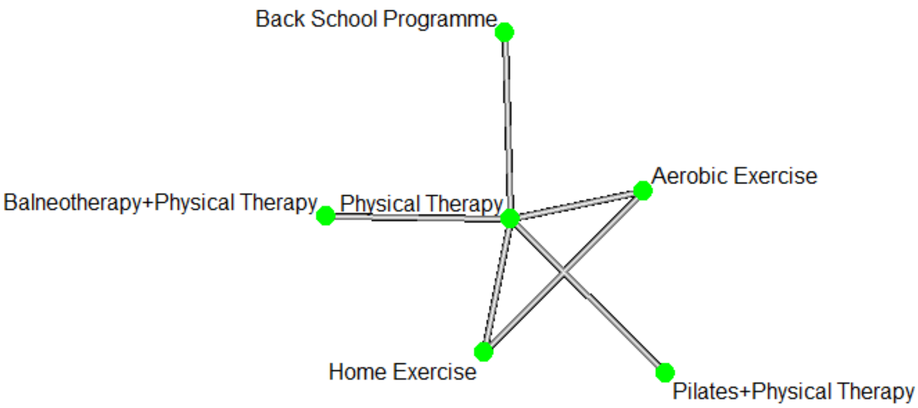

Figure 7. Network plot pain disability under exercise-related treatments in the first subnet.

The direct comparisons of the first sub-net (Figure 8) was 93.4% of I^2 (95% CI of I^2: [88.3%, 96.3%], Q= 75.86, p-value <0.0001) indicating a significant statistical heterogeneity. The direct comparisons showed (Figure 8), 4 comparisons that had significant differences in pain disability.

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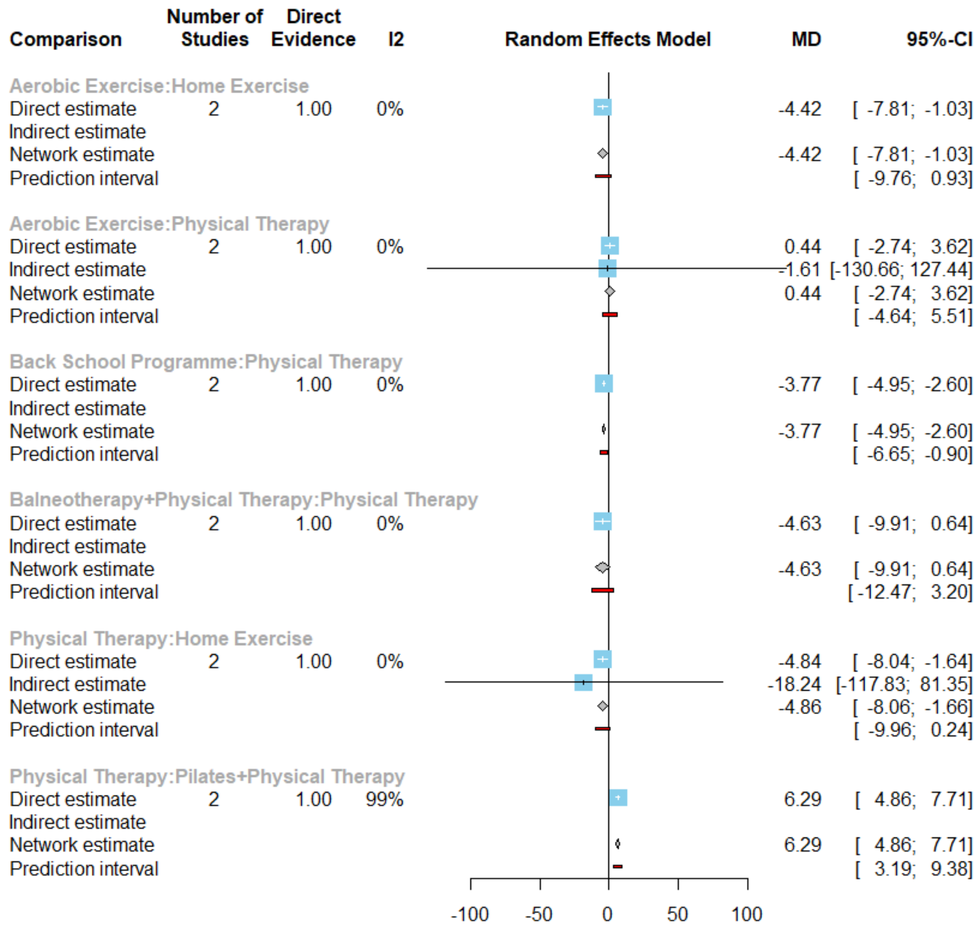

Figure 8. Forest plot of pain disability in the studies of exercise-related treatments in the first subnet.

The second sub-net measuring pain disability based on exercise related interventions (Figure 10) included 15 studies with 1329 observations, 9 treatments and 19 pairwise comparisons. The control treatment for this network meant usual activities and therapies without any new therapeutic regimen for symptom management.

Figure 1 Forest plot of pain disability under all exercise-related treatments compared with control treatment in the first subnet.

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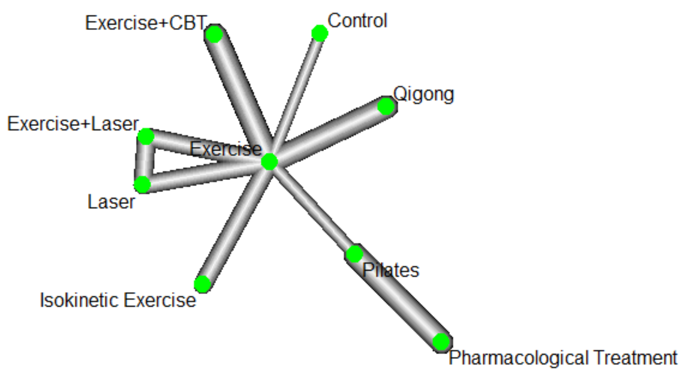

Figure 10. Network plot of pain disability under exercise-related treatments in the second subnet.

The direct comparisons of the second sub-net identified 90% of I^2 (95% CI of I^2: [83.8%; 93.9%], Q=90.36, p-value <0.0001) indicating a significant statistical heterogeneity (Figure 11). Of the direct comparisons identified, 4 had a statistically significant difference of pain disability (Figure 11).

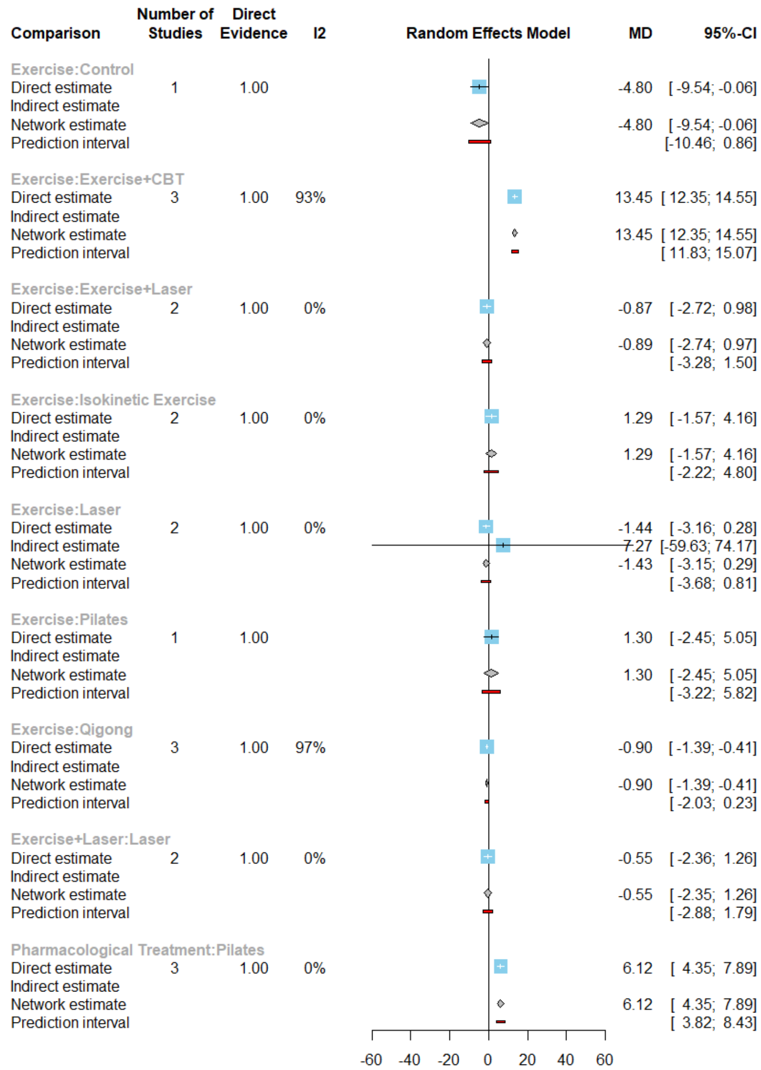

Figure 11. Forest plot of direct comparisons of pain disability under exercise-related treatments in the second subnet.

Figure 12 summarized mean differences of pain disability under all treatments in the second subnet directly and indirectly compared with exercise treatment. Among treatments with direct comparisons to exercise treatment, control treatment and qigong treatment provided a statistically significant increase in pain disability, while exercise plus CBT showed a statistically significant decrease (as Table 2). The number of direct comparison with exercise treatment of pharmacological treatment was 0, indicating no direct evidence of statistically significant effect.

Moved to supplementary material.

Effectiveness of acupuncture related interventions on chronic pain

A total of 36 studies, 2352 observations, 8 treatments and 58 pairwise comparisons were identified (Figure 13). Interventions related to acupuncture included acupuncture with non-steroidal anti-inflammatory drugs (NSAIDs), only NSAID treatment, superficial treatment on trigger points (S-TrP), deep treatment on trigger points (D-TrP), sham acupuncture and thread-embedding acupuncture. Primary outcome was pain intensity, which was assessed by VAS.

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The control treatment for this network was conventional orthopaedic therapy including physical exercise, heat, or cold therapy, routine care, placebo acupuncture and trigger point mesotherapy.

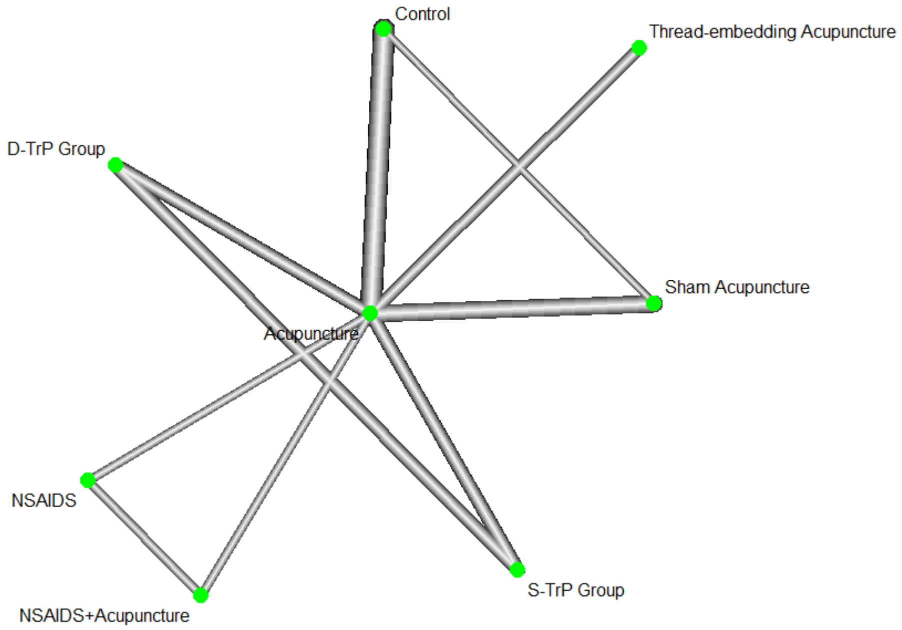

Figure 13. Network plot of acupuncture-related treatments.

Based on the random effect model of all direct comparisons of acupuncture related interventions, I^2 was 92.6% (95% CI of I^2: [90.8%, 94.0%], Q= 547.07, p-value<0.0001) indicating significant statistical heterogeneity. The direct comparisons (Figure 14) showed 4 comparisons had significant difference of pain intensity.

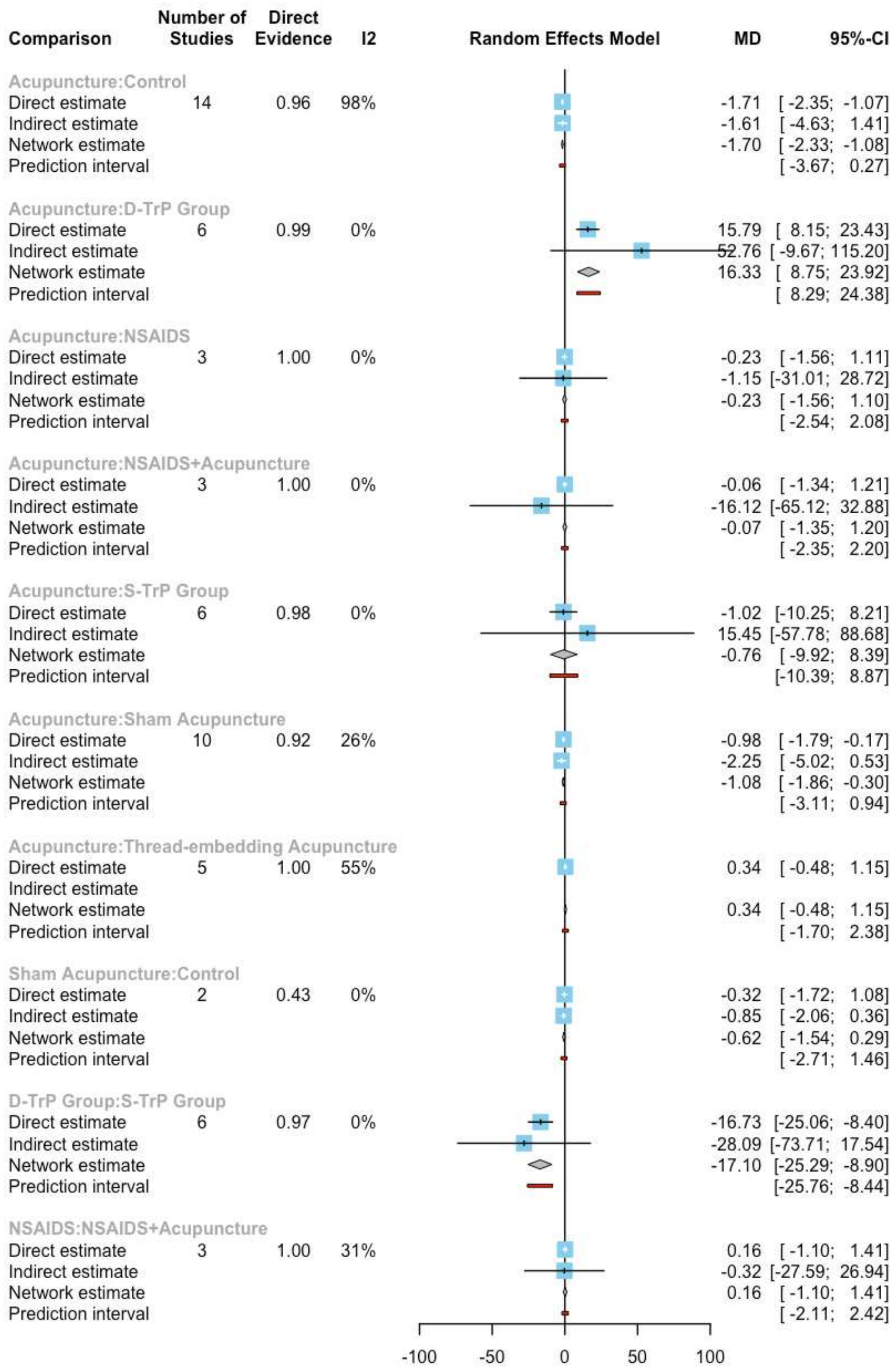

Figure 14. Forest plot of direct comparisons in the studies of acupuncture-related treatments.

Figure 15 summarized mean differences of all treatments in the acupuncture related network directly and indirectly compared with control treatment.

Moved to supplementary material.

Effectiveness of cognitive behavioral related interventions on chronic pain

Interventions related to CBT included brief cognitive interventions (BCI), CBT, cognitive functional therapy (CFT), cognitive plus relaxation (CR), emotional awareness and expression therapy (EAET), education (EDU), interactive voice response–based CBT (IVR CBT), mensendieck somatocognitive therapy (MSCT) plus standard gynaecological treatment (STGT), multimodal

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exercises plus CBT (MT-EX), physical exercise (PE) and relaxation. Primary outcome was pain intensity, which was assessed by VAS, NRS, GCPS and BPI. Secondary outcome was depression, assessed by BDI, CES-D, HADS and PROMIS.

The control treatments were general physiotherapy, standard rehabilitation pain treatment, standard gynaecological treatments, general orthopaedic treatments, and routine care.

Comparisons of pain intensity under CBT-related interventions

The network of CBT-related interventions including 23 studies with 1801 observations, 11 treatments and 32 pairwise comparisons (Figure 16).

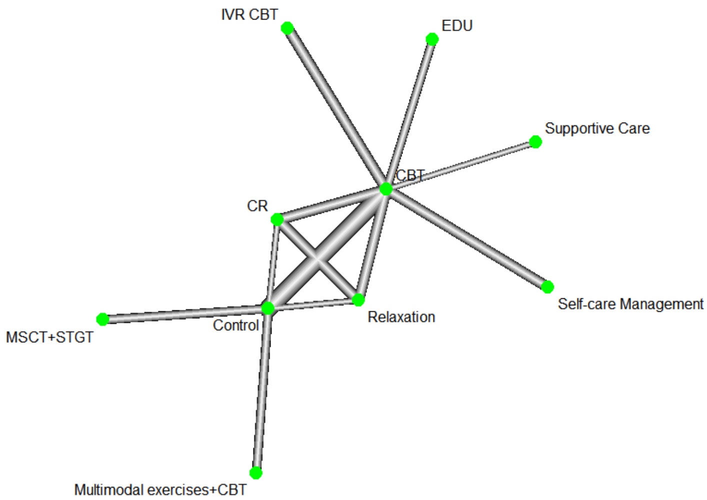

Figure 16. Network plot of pain intensity under CBT-related treatments.

Based on the random effect model of all direct comparisons of CBT-related interventions, the I^2 was 94.8% (95% CI of I^2: [93.1%, 96.1%], Q= 339.90, p-value<0.0001) indicating a significant statistical heterogeneity. The direct comparisons showed (Figure 17) 5 comparisons had significant difference of pain intensity.

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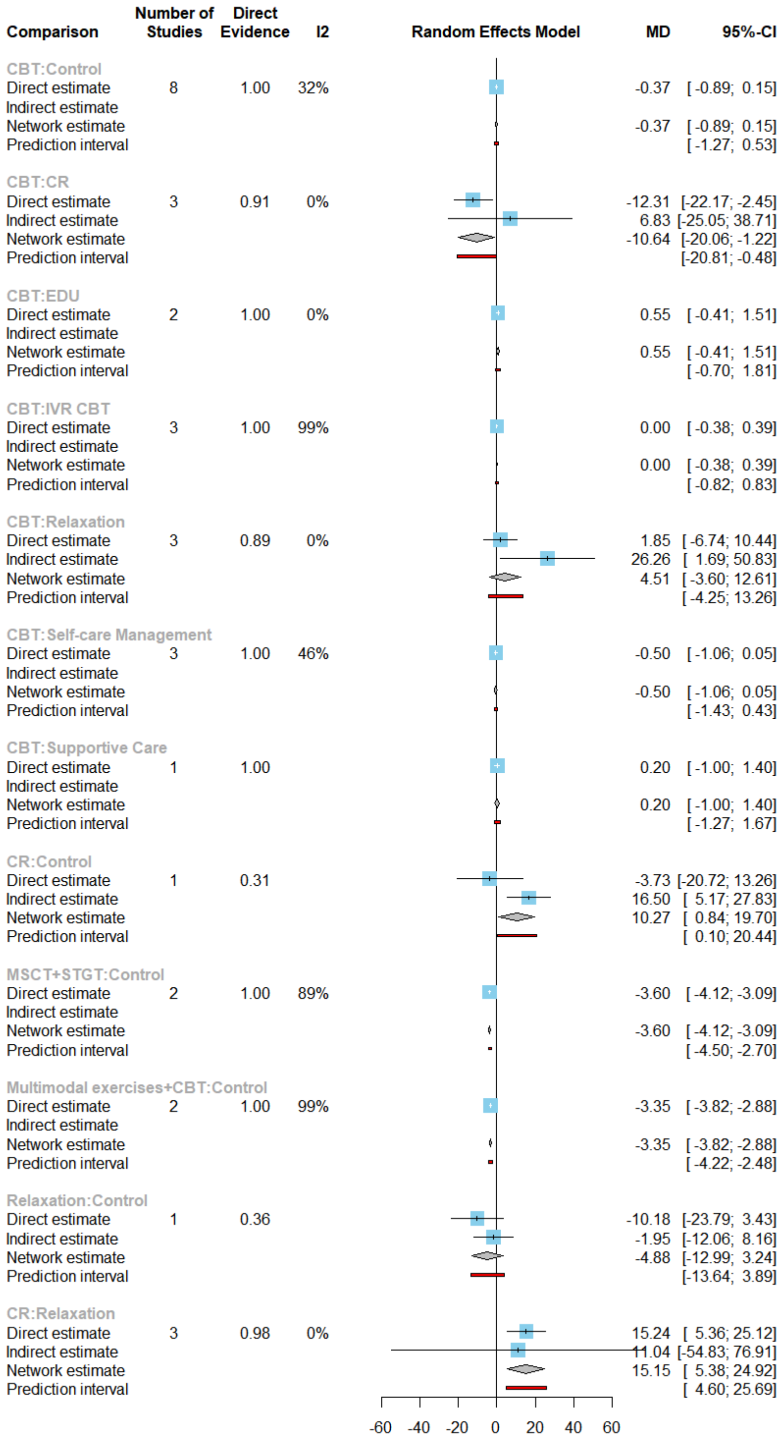

Figure 17. Forest plot of pain intensity under direct comparisons in the studies of CBT-related treatments.

Figure 18 summarized mean differences of pain intensity under all treatments in the CBT-related network directly and indirectly compared with control treatment.

Moved to supplementary material.

Comparisons of depression under CBT-related interventions

The network plot of depression included CBT-related treatments (Figure 19) including 19 studies with 1565 observations, 10 treatments and 30 pairwise comparisons.

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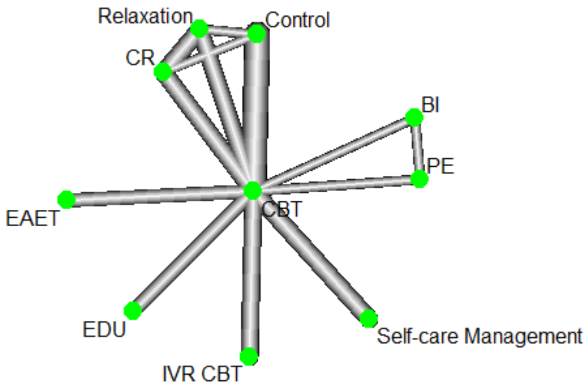

Figure 19. Network plot of depression under CBT-related treatments.

Based on the random effect model of all direct comparisons of CBT-related interventions, I^2 was 55.7% (95% CI of I^2: [22.3%, 74.7%], Q=33.02, p-value=0.0010) indicating a significant statistical heterogeneity. Based on all pooled direct comparisons (Figure 20) 3 comparisons had a statistically significant difference in depression.

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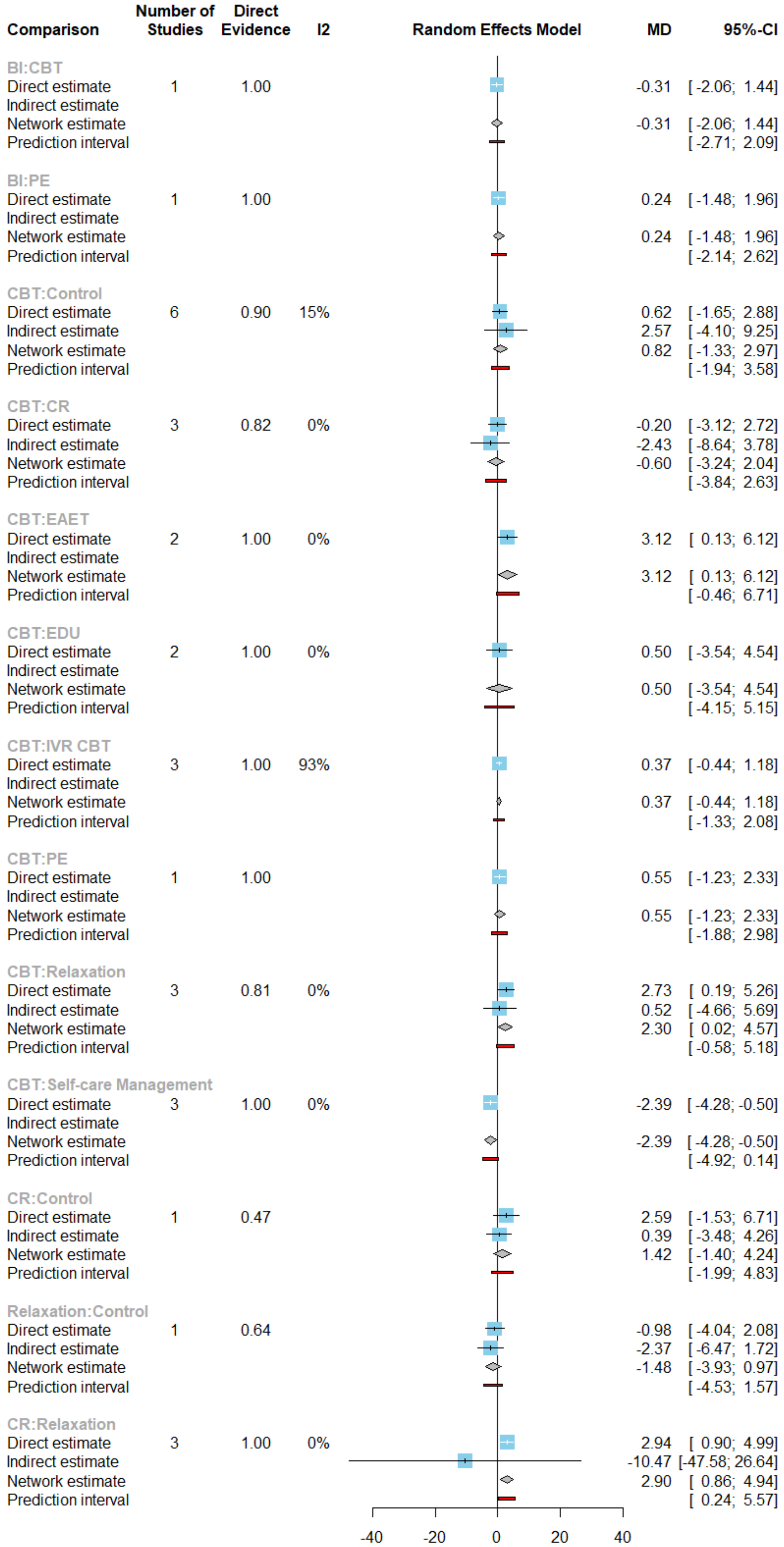

Figure 20. Forest plot of depression under direct comparisons of CBT-related treatments.

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Figure 21 summarized mean differences of all treatments in the CBT-related network directly and indirectly compared with control treatment.

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Effectiveness of massage related interventions on chronic pain

The network of massage included cupping massage and progressive muscle relaxation (PMR) based on a program with varied durations. The primary outcome was pain intensity, which was assessed by VAS, NRS or NPI. The secondary outcome was functional impairment and disability, which was assessed by NDI, RDQ or ODQ. The control treatment included no additional massage, sham cupping and standard medical care.

Comparisons of pain intensity under massage-related interventions

The network plot of pain intensity based on massage-related treatments (Figure 22) included 11 studies with1106 observations, 8 treatments and 43 pairwise comparisons.

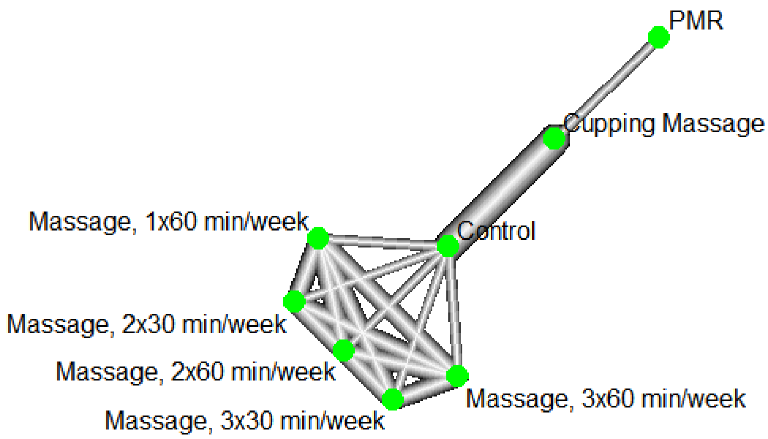

Figure 22. Network plot of pain intensity under massage-related treatments.

Based on the random effect model of all direct comparisons of massage related interventions, an I^2 of 92.8% (95% CI of I^2: [89.8%, 95.0%], Q=128.44, p-value<0.0001) was identified indicating significant statistical heterogeneity. Based on all the direct comparisons (Figure 23), 8 comparisons had significant difference of pain intensity.

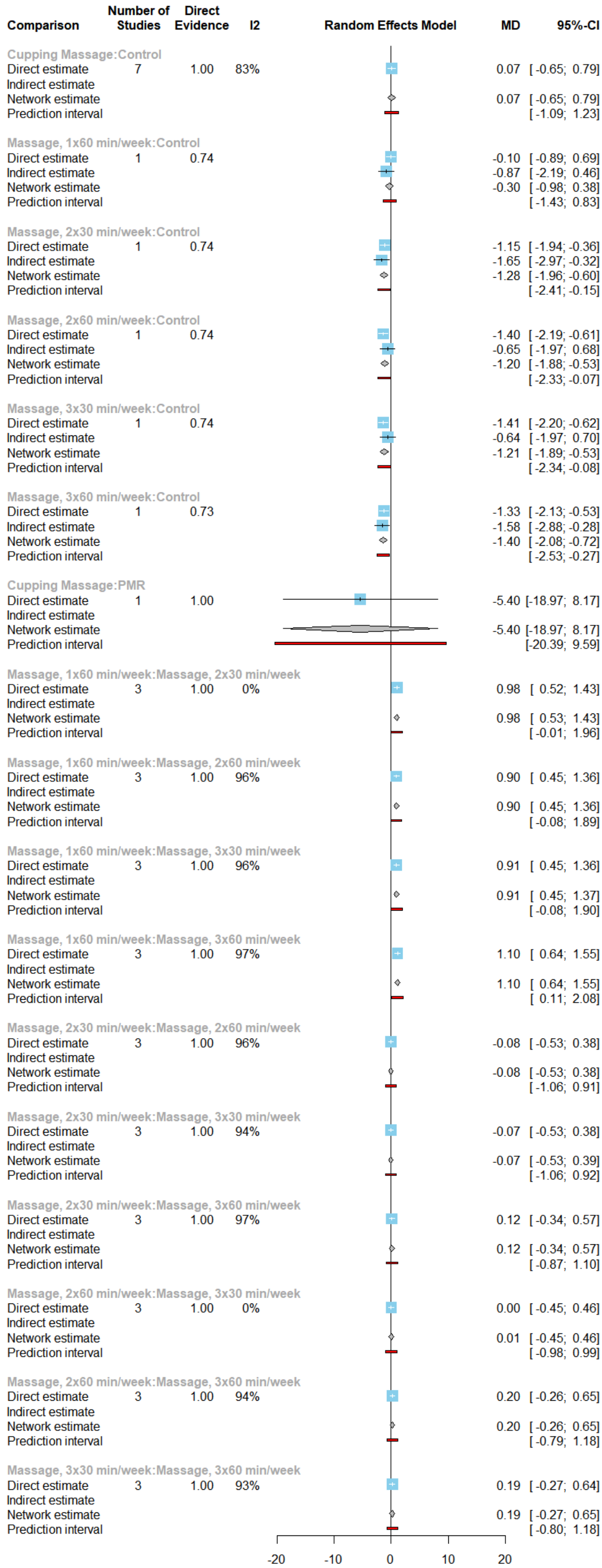

Figure 23. Forest plot of pain intensity under direct comparisons in the studies of massage-related treatments.

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Figure 24 summarized mean differences of all treatments in the massage related network directly and indirectly compared with control treatment.

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Comparisons of pain disability under massage-related interventions

The network plot of pain disability based on massage-related treatments was separated into two subnets. The first subnet only included two treatments of ayurvedic massage therapy and physical therapy. The pairwise meta-analysis included 2 studies, 2 pairwise comparisons, 128 observations and 2 treatments.

The second subnet comprised of a network plot of pain disability based on massage related treatments (Figure 25) using 9 studies, 926 observations, 9 treatments and 41 pairwise comparisons.

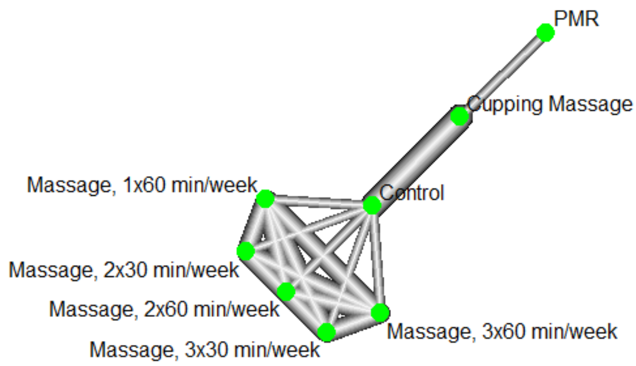

Figure 25. Network plot of pain disability under massage-related treatments.

Based on the random effect model of mean difference of pain disability under all direct comparisons of massage related interventions, an I^2 *of* 95.2% (95% CI of I^2: [93.3%, 96.6%], Q= 59.72, p-value<0.0001) was identified indicating a significant statistical heterogeneity. Besides, on the pooled direct comparisons (Figure 26), 8 comparisons had significant difference of pain disability.

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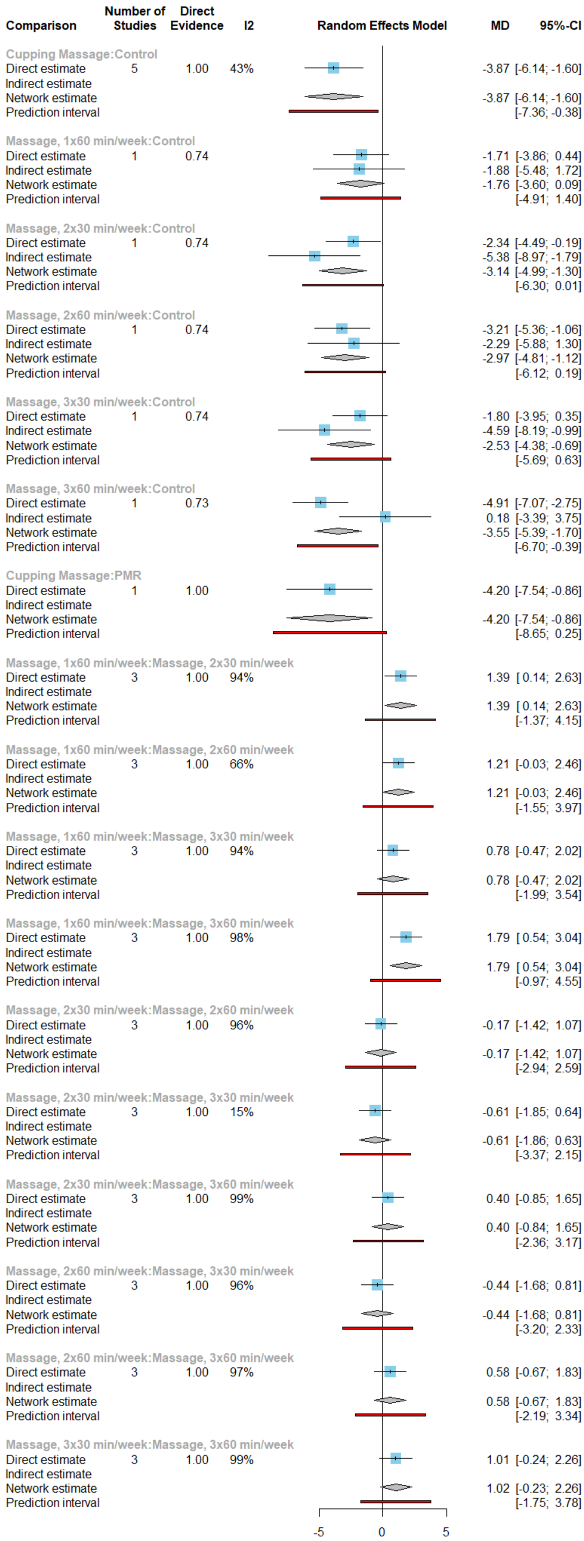

Figure 26. Forest plot of pain disability under direct comparisons in the studies of massage-related treatments.

Figure 27 summarized mean differences of pain disability under all treatments in the massage related network directly and indirectly compared with control treatment.

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Publication bias

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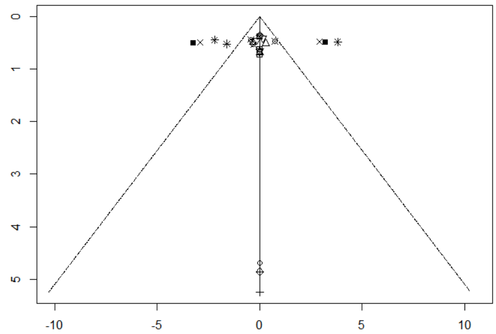
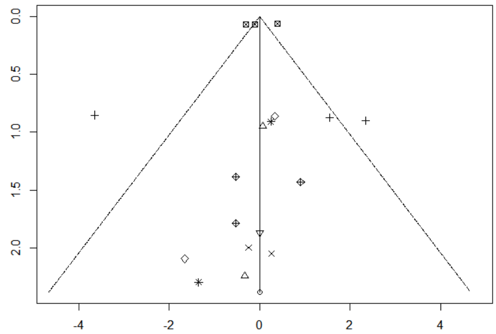
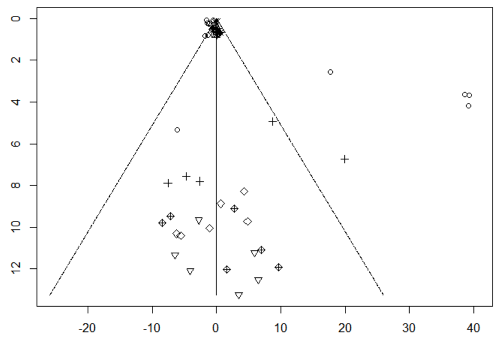
Publication bias of networks with more than ten studies was assessed using funnel plots (Figure 28 (a)-(g)). Besides, Egger's test was used as a statistical method to evaluate publication bias of network meta-analysis (result shown in Table 3).



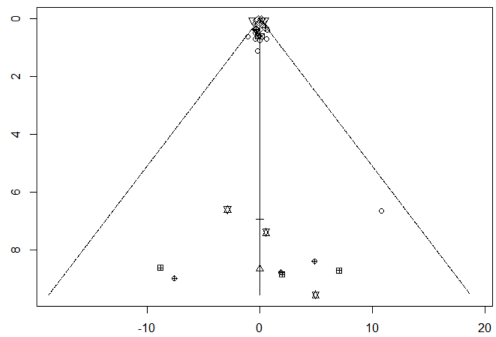
(a)



(b)



(c)



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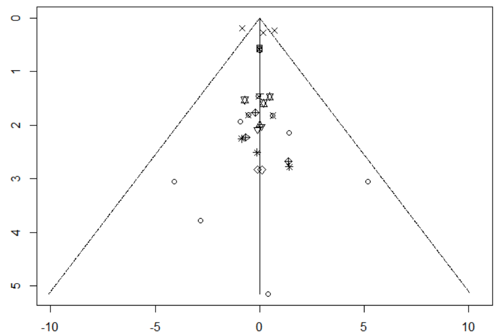
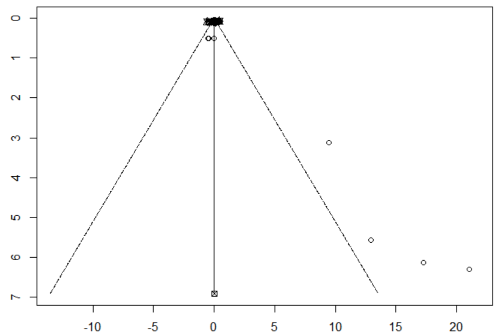


(e)



(f)

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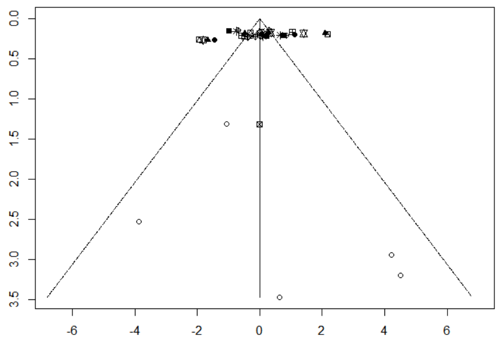

(g)

Figure 28. Funnel plots of mean difference centered at comparison-specific effect. (a) Pain intensity under exercise-related comparisons; (b) Pain disability under exercise-related comparisons; (c) Pain intensity under acupuncture-related comparisons; (d) Pain intensity under CBT-related comparisons; (e) Depression under CBT-related comparisons; (f) Pain intensity under massage-related comparisons; (g) Pain disability under massage-related comparisons.

Table 3. Results of Egger's Test.

Network	Measurements	p-value of Egger's Test
Exercise-related comparisons	pain intensity	0.9791
Exercise-related comparisons	pain disability	0.8671
Acupuncture-related comparisons	pain intensity	0.0082
CBT-related comparisons	pain intensity	0.8404
CBT-related comparisons	depression	0.6502
Massage-related comparisons	pain intensity	0.8347
Massage-related comparisons	pain disability	0.6890

According to the test of funnel plot asymmetry, only one network, the network with acupuncture related interventions (Figure 28(c)), had a p-value smaller than .05 and asymmetry of funnel plot, which indicated significant publication bias in this network. Other networks (Figure 28 (a), (b), (d)-(g)) did not show significant publication bias.

When focusing on the asymmetrical network, there were four points on the far-right side of the reference line, which represented the comparison of Acupuncture vs control treatment in the study No.74. Since the mean difference between two treatments seemed larger than other studies with the same comparison, the funnel plot showed these large mean differences as the dots on the right outside 95% CI (i.e., the dotted line on both sides of the reference line).

Discussion

This study explored 168 studies that evaluated non-clinical and clinical-interventions for pain management with a total sample size of 21,305. Most patients with long-term chronic pain conditions

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preferred clinically effective but minimally invasive interventions that had fewer side effects in comparison to pharmacological and medical device treatments. Our findings indicate that the minimally invasive and combined treatment approach may have improved the quality of life.

In clinical practice, routine therapeutic interactions such as physiotherapy or yoga or pilates was preferred by patients especially with lower back pain and could be cost-effective in comparison to pharmacological or medical device use to support patient recovery and simultaneously support their physical and psychological wellbeing. The potential for enhancing the benefits of pilates, yoga and various other forms of exercise therapy in combination with cognitive behavioural therapy could also assist other pain conditions such as Fibromyalgia based on our findings although larger sample sizes would be required along with longitudinal data to better assess the generalisability and applicability to a wider population.

Our analyses demonstrated that the findings were from differing geographical locations of Europe, Australia, India, Iran, Africa, south and north Americas. The variation in demographics and healthcare system practices could influence pain management outcomes. Of the 168 studies, 91 were from Europe which could have some parity with routine clinical practices although differences in phenotypic characteristics can widen the applicability of the findings.

Another key finding of our pooled sampled was small sample sizes with only one study having a statistically significant sample size of 3451 [11] and therefore the possibility of showing generalisability to a wider population. The smaller effect sizes within each study allowed the NMA to explore direct and indirect comparisons of the interventions by combining the observations reported by way of outcomes such as pain intensity, pain disability, psychological state and depression.

Psychological interventions such as CBT showed significance in improving pain intensity and depression and it is likely that combining CBT with exercise therapy, physical therapy or massage therapy could lead to better therapeutic outcomes; future clinical trials should be designed accordingly and this would also be aligned to real-world clinical practice.

The use of exercise and related treatments demonstrated statistically significant heterogeneity. The home exercise and manipulation technique-based treatments provided a statistically significant reduction in pain intensity. When exercise treatment was compared to a control and qigong treatment, there was a statistically significant increase in pain intensity and pain disability which could lead to increased apathy in continuing with the exercise programme. This would act as an advisory to better define exercise programs and to use other modalities including short-term pharmacological therapy or targeted nerve blocks for managing pain intensity for better outcomes. Based on this evidence, exercise could be considered as a better treatment for pain management as it improves function and mobility and could be part of a long-term management strategy. The generalisability of these findings would require statistically significant sample sizes to be used when conducting future studies with clear use of case definitions indicating the primary and secondary causes of pain. Direct comparisons of home exercise, physical therapy and aerobic exercise indicated a reduction in pain disability scores based on a of SMD of -4.86 and -4.42, respectively. Further reductions in pain disability were observed when exercise treatments were combined with CBT. The direct comparisons between routine care and acupuncture related treatments indicated a statistically significant reduction in pain intensity. Direct comparisons between routine care, cognitive plus relaxation, indicated an increase in pain intensity, whilst MSCT plus STGT, and multimodal exercise plus CBT treatment provided a statistically significant decrease in pain intensity. MSCT+STGT treatments appeared to have had a better effect in pain intensity among chronic pain populations than multimodal exercise plus CBT treatment. MSCT+STGT treatment, and multimodal exercise plus CBT treatments, reduced pain intensity, whilst MSCT+STGT treatments had a slightly better effect than multimodal exercise plus CBT treatment (with a SMD of -3.6 and -3.35, respectively).

Due to the lack of studies comparing exercise treatment with analgesics, there is no evidence to demonstrate the effectiveness and efficacy of the combined approach, although this is a preferred approach in clinical practice.

The Witt et al. [11] study is the largest RCT on acupuncture for managing neck pain; less than a third of the patients were randomised and the non-randomised group had more severe pain and disability at baseline but showed higher levels of improvement for both pain intensity and pain disability. By contrast, systematic review and NMA of 40 RCTs reviewed the comparative effectiveness of physical exercise interventions for chronic non-specific neck pain but showed no superiority for any specific type of physical exercise with only low-quality evidence for various exercise treatments [12].

Future clinical trials should look at comparing exercise with other modalities including local or systemic analgesia, acupuncture and CBT for better outcomes than exercise therapy alone.

Pain disability is a complex issue where there is limited knowledge available regarding the underlying mechanisms of common chronic pain conditions as lower back pain. For patients with demonstrable compression of a nerve root and spinal degeneration, chronic pain can be debilitating. Experience with pain is heterogeneous, hence, the degree of discomfort is not necessarily relational to the physical or physiological damage. The physiological factors may equally not have an impact on the transition from acute to chronic pain, to functional disability. Therefore, the physiological manifestations may inextricably intertwine with psychological factors. The pain disability findings from this study indicate key evidence to these phenomena where no treatments showed a statistical significance increase in depression. In clinical practice, management plans should have a combination of treatments to reduce pain intensity enabling active interventions like exercise or Pilates, thereby achieving a reduction in pain disability.

Pain disability is a complex issue where there is limited knowledge available with the underlying mechanisms of common chronic pain conditions as lower back pain. For patients with demonstratable compression of a nerve root and spinal degeneration, chronic pain can be debilitating. Experience with pain is heterogeneous hence, the degree of discomfort is not necessarily relational to the physical or physiological damage. The physiological factors may equally not have an impact on the transition from acute to chronic pain to functional disability. Therefore, the physiological manifestations may inextricably intertwine with psychological factors. The pain disability findings from this study indicate key evidence to this phenomena where no treatments showed a statistical significance increase in depression. Treatments such as treatment programs with combination of treatments such aligned to post massage could reduce pain intensity thereby reaching a reduction in pain disability.

Conclusion

The study shows combined interventions for non-cancer chronic pain management need further evidence, including longitudinal data. Future research should not be limited to the use of randomised controlled clinical trials or clinical studies, but real-world data that can demonstrate crucial information that could aid best clinical practices. Developing clinical and patient reported outcomes with aligned outcome measures could support the development of optimal evidence that can enhance precision clinical practice at a fraction of the current per patient cost. As the addition of psychological interventions alongside physical and exercise therapy showed improvements with mental health and wellbeing, these should be considered for better parameter selection. In conjunction with the findings, we recommend combining physical and psychological therapies alongside other routine treatments but with early diagnosis approaches to optimise clinical care offered to patients.

Author contributions: AS and GD developed the study protocol and embedded this within the POP project. GD and JQS designed and completed the study analysis. The data extraction was completed by HC and CD. All authors critically appraised and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Code availability: The authors will consider sharing the novel code created upon receipt of reasonable requests.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: All authors consented to publish this manuscript.

Availability of data and material: The authors will consider sharing the dataset gathered upon receipt of reasonable requests.

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