SUPPLEMENTAL MATERIAL

Figure S6. Summary of Network Meta-Analysis: Pain Free Walking Ability Sensitivity Analysis (r 0.1 and 0.9). H: High-Pain, L: Low-Pain, C: Control. Effects were considered trivial at <0.2, small at 0.2-0.5, moderate at 0.5-0.8, and large at >0.8.

PRISMA Checklist

Expanded Methods. Search Strategy

The search used a mix of keyword synonyms and thesaurus terms, following the structure: intermittent claudication AND exercise AND walking assessment AND RCT filter (where filter available). This search strategy was tested using a list of 21 relevant RCTs identified by the lead author. The full MEDLINE strategy is reported below.

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to January 21st 2021>

Search Strategy:

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1 (peripheral adj3 ("arter* disease*" or "arter* disorder*" or arteriopath* or "occlusive disease*")).tw. (16504)

2 "limb* threat*".tw. (1478)

3 PVD.tw. (2425)

4 PAOD.tw. (761)

5 (peripheral adj3 ("vascul* disorder*" or "vascul* disease*")).tw. (10131)

6 atherosclero*.tw. (146228)

7 arteriosclero*.tw. (15527)

8 ((limb* or leg* or foot or feet* or peripheral or "lower extremit*") adj3 (occlus* or reocclus* or "re-occlus*" or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter* or calcificat* or restrict* or narrow* or block* or insufficien* or sclerosis or isch?em*)).tw. (41474)

9 ((arter* or vascular) adj3 (occlus* or reocclus* or "re-occlus*" or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter* or calcificat* or restrict* or narrow* or block* or insufficien* or sclerosis)).tw. (136575)

10 ((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) adj3 (occlus* or reocclus* or "re-occlus*" or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).tw. (10513)

11 claudicat*.tw. (10299)

12 "angina cruris".mp. (4)

13 "angiosclerotica intermittens".mp. (1)

14 "claudicatio intermittens".mp. (260)

15 dysbasia.mp. (54)

16 "intermittent claudicatio".mp. (4)

17 Intermittent Claudication/ (7854)

18 exp Peripheral Vascular Diseases/ (52604)

19 arterial occlusive diseases/ (27112)

20 arteriosclerosis/ (56562)

21 arteriolosclerosis/ (157)

22 arteriosclerosis obliterans/ (3996)

23 exp atherosclerosis/ (42109)

24 Ischemia/ (49422)

25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (448091)

26 walk*.tw. (113677)

27 movement.tw. (223985)

28 (physical adj3 (exertion or endurance or function or therap* or conditioning or activit* or ability or fitness or program* or train*)).tw. (164974)

29 exercis*.tw. (285706)

30 ((train* or conditioning) adj3 (circuit or intervention* or protocol* or program* or activit* or regim* or resist* or cardio*)).tw. (81849)

31 aerobic.tw. (82079)

32 resist*.tw. (1010407)

33 rehab*.tw. (162168)

34 (fitness adj3 (train* or intervention* or protocol* or program* or therap* or activit* or regim* or centre* or center*)).tw. (5872)

35 run*.tw. (185808)

36 treadmill*.tw. (31937)

37 swim*.tw. (39004)

38 danc*.tw. (6985)

39 cycling.tw. (59049)

40 physiotherap*.tw. (24701)

41 kinesiotherap*.tw. (199)

42 ergometry.tw. (3779)

43 sport*.tw. (72023)

44 "plantar flexion".tw. (2927)

45 (weight adj2 lift*).tw. (1506)

46 squat*.tw. (6283)

47 lunge*.tw. (1170)

48 "knee bend*".tw. (383)

49 ((calf or heel) adj2 raise*).tw. (329)

50 endurance.tw. (29054)

51 stretch*.tw. (73352)

52 exp Exercise/ (189788)

53 exp Exercise Therapy/ (49249)

54 physical exertion/ (56148)

55 exp physical fitness/ (29074)

56 exp Sports/ (179285)

57 exp Exercise Movement Techniques/ (7983)

58 Locomotion/ (24993)

59 Fitness Centers/ (546)

60 Physical Therapy Modalities/ (36185)

61 Physical Therapists/ (1725)

62 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (2402499)

63 (walk* adj3 (distance or abilit* or confiden* or duration or rate or time or capacit* or perform* or economy or speed or score* or maxim*)).tw. (27985)

64 "peak walking time".tw. (70)

65 PWT.tw. (554)

66 "maximal walking time".tw. (46)

67 ("6-minute walk*" adj2 (distance or test)).tw. (4570)

68 6MWT.tw. (2703)

69 6MWD.tw. (1558)

70 "pain-free walking time".tw. (60)

71 PFWT.tw. (14)

72 PFWD.tw. (73)

73 "ambulatory function*".tw. (389)

74 "Walking Impairment Questionnaire".tw. (184)

75 WIQ.tw. (133)

76 "maximal treadmill exercise time".tw. (9)

77 "functional capacit*".tw. (13871)

78 (claudicat* adj2 (time* or distance*)).tw. (542)

79 Walk Test/ (1276)

80 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 (44869)

81 randomized controlled trial.pt. (501068)

82 controlled clinical trial.pt. (93557)

83 randomized.ab. (470703)

84 placebo.ab. (205250)

85 drug therapy.fs. (2184138)

86 randomly.ab. (327794)

87 trial.ab. (495459)

88 groups.ab. (2013608)

89 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 (4642707)

90 exp animals/ not humans.sh. (4675019)

91 89 not 90 (4022973)

92 25 and 62 and 80 and 91 (1475)

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Table S1. Summary of included studies

	Study Design	Sample Size	Inclusion Criteria	Exclusion Criteria	Follow-up period	Primary Outcomes	Secondary Outcomes
Brenner et al 2020[40]	RCT	33	18 years or older, diagnosed with stable PAD, expressing symptoms of IC, and having an ABPI ≤ 0.9.	Unable to read or write English; resided in a nursing home; were already involved in an exercise program; were wheelchair dependent; had angina, congestive heart failure, chronic obstructive pulmonary disease, severe arthritis, or limb amputation; had noncompressible arteries (ABPI > 1.2); or were cognitively impaired.	12 weeks	Maximal walking	Heart rate, blood pressure, heart rate variability.

Gardner et al 2011[30]	RCT	92	A history of any type of exertional leg pain, ambulation during a graded treadmill test limited by leg pain consistent with intermittent claudication, and an ABPI ≤0.90 at rest or an ABPI ≤0.73 after exercise.	Absence of PAD (ABPI >0.90 at rest and ABPI >0.73 after exercise); inability to obtain an ABPI measure because of non-compressible vessels; asymptomatic PAD determined from the medical history and verified during the graded treadmill test; use of cilostazol and pentoxifylline initiated within 3 months before investigation; exercise tolerance limited by factors other than leg pain; active cancer, renal disease, or liver disease.	12 weeks	Maximal and pain free walking	Daily ambulatory activity measures, peak oxygen uptake, walking economy, fractional utilisation, walking impairment questionnaire, physical function.

Mika et al 2006[41]	RCT	55	Claudication symptoms, defined as calf, thigh, or buttocks pain that limited walking duration and was relieved by rest, were stable for the 3 months before enrolment. Peripheral arterial disease was confirmed by an ABPI <0.9 at rest and 0.75 after exercise	Patients taking b-adrenergic–blocking drugs, pentoxifylline or other hemorheologically active drugs; patients affected by impaired cardiac or lung function, diabetes mellitus, cancer, kidney and liver disease, or arthritis that limited walking; patients who were unable to walk on the treadmill at a speed of at least 3.2 km/h.	12 weeks	Maximal and pain free walking	Changes in erythrocyte deformability
Gardner et al 2012[33]	RCT	142	Patients with claudication secondary to vascular insufficiency; a history of claudication, defined as reporting leg pain upon	Absence of PAD (ABPI >0.90 at rest and <20% decrease after exercise); asymptomatic PAD determined from the medical history and verified during the	6 months	Maximal and pain free walking	Peak oxygen uptake, ischemic window, walking

exertion; ambulation during a graded treadmill test limited by claudication; an ABPI ≤0.90 at rest or a 20% decrease in ABI after exercise.	graded treadmill test; rest pain PAD; inability to obtain an ABI measure due to noncompressible vessels (i.e., systolic blood pressure could be heard as the sphygmomanometer was inflated to the maximal value of 300mmHg); use of cilostazol and pentoxifylline ≤3 months of the investigation; lower extremity revascularization ≤3 months before the investigation; exercise tolerance limited by any disease process other than PAD, such as angina, dyspnoea, or evidence of myocardial ischemia	impairment questionnaire, daily physical activity, calf blood flow

				or rhythm changes from a 12-lead electrocardiogram; uncontrolled hypertension, uncontrolled diabetes, active cancer, renal insufficiency, or abnormal liver function; non-compliance with baseline testing.			
Hiatt et al 1990[34]	RCT	19	Patients with intermittent claudication that limited daily work or leisure-time activities were evaluated for the study. In all cases, claudication was due to PAD, defined as an ankle-to-arm systolic blood	Leg pain at rest, ischemic ulceration, gangrene, or a resting ankle blood pressure less than 50 mm Hg; patients who were unable to walk on the treadmill at a speed of at least 2 mph or whose exercise capacity was limited by symptoms of angina,	12 weeks	Maximal walking	Peak oxygen consumption, heart rate, systolic blood pressure, respiratory exchange ratio, ventilation,

			pressure ratio less than 0.95 at rest or less than 0.85 after exercise.	congestive heart failure, chronic obstructive pulmonary disease, or arthritis; diabetics because glycaemic control may affect the response to a conditioning program, and these patients often have a severe and distal distribution of arterial occlusive disease; patients taking 3-adrenergic-blocking drugs or pentoxifylline.			ABPI, calf blood flow, blood assay, community-based walking ability, perceived claudication pain.
Crowther et al 2008[35]	RCT	21	Patients with symptoms of IC Entry criteria included an appropriate history of intermittent claudication, imaging confirmation of	Inability to attend the program; selection for surgical or endovascular intervention, patient preference, and requirement for mobility aids,	12 weeks	Maximal and pain free walking	Lower limb mobility, physical activity levels and peak

			PAD on lower limb duplex or computed tomographic angiograph, and ability and willingness to attend regular supervised exercise	obvious gait abnormalities (e.g., circumduction) or medical conditions that influence gait (e.g., orthopaedic conditions and neurological impairment).			physiological responses to exercise.
Gardner et al 2001[23]	RCT	52	Positive Rose questionnaire for intermittent claudication; age ≥60; an ABPI <0.97 at rest; evidence of functional limitation due to intermittent claudication during the screening treadmill test.	Fontaine stage I PAD (ambulation not limited by claudication); Fontaine stage III PAD (pain at rest); exercise tolerance limited by factors other than claudication (e.g., severe coronary artery disease, poorly controlled hypertension, pulmonary disease, hemiparetic gait, severe	6 months	Maximal and pain free walking	Ambulatory function, peripheral circulation, perceived quality of life and daily physical activity.

				arthritis, or orthopaedic conditions); poorly controlled diabetes mellitus; or other active major medical problems including cancer, renal or liver disease, anaemia, substance abuse, or dementia.			
Mika et al 2011[42]	RCT	61	Patients with peripheral obstructive arterial disease and intermittent claudication. Fontaine stage II (claudication without rest pain, gangrene, or ulceration), aged 50–70 years, have been recruited for this	History of angina pectoris, recent myocardial infarction or vascular surgery within the previous year, impaired cardiac or lung function, diabetes mellitus, cancer, or kidney and liver disease; patients with arthritis who were unable to walk on the treadmill at a speed	12 weeks	Maximal and pain free walking	Blood analyses for haematocrit, fibrinogen, triglycerides, and cholesterol: total, high-density

			study from the vascular outpatient clinic All included patients had stable claudication distance and were able to walk no less than 150 m without pain. The PAD was diagnosed clinically and confirmed by the presence of an ankle brachial blood pressure index of <0.9 at rest and 0.75 after exercise.	of at least 3.2 km/h; women in menopausal status and those taking oestrogen.			lipoprotein (HDL) and low-density lipoprotein (LDL)
Hodges et al 2008[36]	RCT	28	Peripheral atherosclerotic disease was confirmed in all subjects by an ABI	Inability to complete the familiarisation test; poorly controlled hypertension; poorly	12 weeks	Maximal walking	Peak oxygen consumption, peak cardiac

			<0.9 at rest using a hand held Doppler. Symptomatic intermittent claudication was evaluated using the Edinburgh Walking Questionnaire.	controlled diabetes; severe coronary artery disease (angina at rest); valvular heart disease and debilitating pulmonary disease.			output, peak cardiac power, peak heart rate, respiratory exchange ratio, rating of perceived exertion
Mays et al 2015[37]	RCT	20	Patients were included if they were 40 years of age, had received peripheral endovascular therapy four to six weeks prior to baseline testing or presented with stable IC symptoms and had not	Lower extremity amputation(s) that interfered with walking on a treadmill; critical limb ischemia; PAD of non-atherosclerotic nature; primarily limited in walking by comorbidities other than IC; exhibited severe cardiac ischemia as documented on non-	14 weeks	Maximal and pain free walking	Walking impairment questionnaire

			previously received revascularization within the four to six week window. For those with IC, patients were included if their ABI was 0.90.	invasive testing; had a previous myocardial infarction, transient ischemic attack or stroke three months prior to screening; were treated with pentoxifylline or cilostazol for the treatment of IC (one-month washout period allowed).			
Leicht et al 2011[38]	RCT	17	Patients with IC, PAD was confirmed based on the absence of lower limb peripheral pulses, lower limb artery stenosis, or occlusion on duplex or computed tomographic	Not specified.	12 months	Maximal and pain free walking	Heart rate variability, peak aerobic capacity

			angiography, and ABPI 0.9.				
Mika et al 2005[44]	RCT	80	The diagnosis of peripheral arterial occlusive disease was confirmed by Doppler ultrasound and an ABPI of 0.9 at rest that decreased to 0.75 after exercise. Patients were recruited for this study if their walking distance to the onset of claudication pain as measured on the treadmill (speed, 3.2 km/hr; inclination, 12 degrees)	Angina pectoris; recent myocardial infarction; vascular surgery within the previous year; impaired cardiac or lung function; diabetes mellitus; cancer; kidney or liver disease; arthritis that limited walking; or other conditions presenting contraindications to the proposed exercise regimen; patients taking adrenergic–blocking drugs or pentoxifylline and other hemorheologically active drugs.	12 weeks	Pain free walking	Leukocyte count, neutrophil count, and microalbuminuria

			was between 50 and 200 m and claudication was stable over a 3-mo period before enrolment.				
Novakovic et al 2019[43]	RCT	19	Established diagnosis of PAD and Fontaine II symptoms	Unstable cardiovascular disease or recent cardiovascular events (<3 months before inclusion); acute illness or recent non-cardiovascular diseases requiring hospitalization (<3 months before inclusion); emergency or unplanned specialist management; permanent atrial fibrillation; unstable or poorly controlled dysrhythmias;	12 weeks	Maximal and pain free walking	Flow-mediated vasodilation and pulse wave velocity, heart rate variability, quality of life, N-terminal pro-B-type natriuretic peptide and fibrinogen levels.

				pregnancy; and intellectual development disorder.			
Hiatt et al 1994[39]	RCT	18	Intermittent claudication, defined pain in the calf, thigh, buttocks that as or limited walking ability and that relieved by within 10 rest was minutes. PAD was confirmed by an ankle/arm systolic blood ratio of <0.94 at rest that decreased <0.73 after exercise.	Leg pain at rest, ischemic ulceration, or gangrene; unable to walk on the treadmill at a speed of at least 2 mph or whose exercise capacity was limited by symptoms of angina, congestive heart failure, chronic obstructive pulmonary disease, or arthritis; diabetics; undergone vascular surgery or angioplasty within the previous year.	12 weeks	Maximal and pain free walking	Peak oxygen consumption, heart rate, respiratory exchange ratio, lactate.

MWA: Maximal Walking Ability, PFWA: Pain-Free Walking Ability; ABPI: Ankle-Brachial Index; RCT: Randomised controlled trial; PAD: Peripheral Artery Disease; IC: Intermittent Claudication

Table S2. Summary demographics

	Sample Size Control Group n(male/female)	Sample Size Exercise Group n(male/female)	Control Group Age in Years (Mean ± SD)	Exercise Group Age in Years (Mean ± SD)
Brenner et al 2020[40]	15(9/6)	18(12/6)	63.67 ± 8.47	68.56 ± 6.87
Gardner et al 2011[30]	30(N/A)	62*(N/A)	65± 10	65 ± 11 (home-based), 66 ± 12 (supervised)
Mika et al 2006[41]	28(25/3)	27(23/4)	58 ± 9	60 ± 7
Gardner et al 2012[33]	36(30/6)	106(91/15)	68 ± 8	68 ± 8
Hiatt et al 1990[34]	9(9/0)	10(10/0)	59 ± 12	61 ± 13
Crowther et al 2008[35]	11(5/6)	10(5/5)	67.1 ± 6.8	71.3 ± 8.5
Gardner et al 2001[23]	24(22/2)	28(25/3)	70 ± 1	71 ± 1
Mika et al 2011[42]	31(26/5)	30(27/3)	62.1 ± 6.9	63.5 ± 7.2
Hodges et al 2008[36]	14(N/A)	14(N/A)	Not Available	Not Available
Mays et al 2015[37]	10(8/2)	10 MWA(8/2), 9 PFWA	63.1 ± 6.7	67.6 ± 11.8
Leicht et al 2011[38]	9(5/4)	8(4/4)	65.0 ± 8.7	68.3 ± 6.1
Mika et al 2005[44]	39(31/8)	41(35/6)	60.9 ± 5.4	61.4 ± 6.5

Novakovic et al 2019[43]	8(6/2)	11(9/2)	62.0 ± 8.3	65.6 ± 11
Hiatt et al 1994[39]	8(8/0)	10(10/0)	67 ± 5	67 ± 7

** Combined High-Pain Arms, MWA: Maximal Walking Ability, PFWA: Pain-Free Walking Ability, N/A: Not available*

Table S3. Characteristics of the included studies

Study	Control activity	Sample Size (Mean age ± SD) Control group	Training modality	Claudication pain level during exercise	Sample Size (Mean age ± SD) Exercise group	Exercise frequency and volume	Intervention length	Treadmill test	Walking outcome	Supervision of exercise	Overall Risk of Bias
Brenner et al 2020[40]	Usual level of activity	15 (63.67 ± 8.47)	Overground walking	Low	18 (68.56 ± 6.87)	5x·week patients walked to minimal claudication pain	12 weeks	G-S	MWD	None	High
Gardner et al 2011[30]	Verbal advice to walk	30 (65± 10)	A: Treadmill Walking	High	A: 33 (66 ± 12) B: 29 (65 ± 11)	A: 3x·week, progressing up to 45 mins	12 weeks	G-S	MWT and PFWT	A: All B: None	Some concerns

			* B: Overground walking*			B: 3x.week, progressing up to 40 mins					
Mika et al 2006[41]	Usual activity level	28 (58 ± 9)	Treadmill walking	Low	27 (60 ± 7)	3x·week 60 mins·day	12 weeks	G-S	MWT and PFWT	All	High
Gardner et al 2012[33]	Verbal advice to walk	36 (68 ± 8)	Treadmill walking	High	106 (68 ± 8)	3x·week progressing up to 40 mins	6 months	G-S	MWT and PFWT	All	Some concerns
Hiatt et al 1990[34]	Usual activity level	9 (59 ± 12)	Treadmill walking	High	10 (61 ± 13)	3x·week 15 mins progressing	12 weeks	G-S	MWT	All	High

						up to 60 mins·day					
Crowther et al 2008[35]	Usual medical care	11 (67.1 ± 6.8)	Treadmill walking	High	10 (71.3 ± 8.5)	3x·week 25 mins progressing up to 40 mins	12 months	G-S	MWT and PFWT	All	High
Gardner et al 2001[23]	Usual medical care	24 (70 ± 1)	Treadmill walking	High	28 (71 ± 1)	3x·week 15 mins progressing up to 40 mins	6 months	G-S	MWD and PFWD	All	High
Mika et al 2011[42]	Usual level of activity	31 (62.1 ± 6.9)	Treadmill walking	Low	30 (63.5 ± 7.2)	3x·week 30 mins progressing	12 weeks	G-S	MWT and PFWT	All	High

						up to 55 mins					
Hodges et al 2008[36]	Verbal advice to walk	14 (not available)	Treadmill walking	High	14 (not available)	2x·week 30 mins	12 weeks	G-S	MWT	All	Some concerns
Mays et al 2015[37]	Verbal advice to exercise	10 (63.1 ± 6.7)	Combined treadmill and overground walking	High	10 MWT, 9 PFWT (67.6 ± 11.8)	3x·week 35 mins progressing up to 50 mins	14 weeks	G-S	MWT and PFWT	Initial 2 weeks	High
Leicht et al 2011[38]	Conservative medical	9 (65.0 ± 8.7)	Treadmill walking	High	8 (68.3 ± 6.1)	3x·week 25 mins progressing	12 months	G-S	MWD and PFWD	All	Some concerns

	treatment					up to 40 mins					
Mika et al 2005[44]	Usual level of activity	39 (60.9 ± 5.4)	Treadmill walking	Low	41 (61.4 ± 6.5)	3x·week patients walked to 85% pain free walking distance	12 weeks	Constant speed of 3.2km·hr, 12-degree inclination angle	PFWD	All	High
Novakovic et al 2019[43]	Usual level of activity	8 (62.0 ± 8.3)	Treadmill walking with cycling	Low	11 (65.6 ± 11)	2-3x·week 60 minutes	12 weeks	Constant speed of 3.2 km/h and an inclination of 12.5%.	MWD and PFWD	All	High

Hiatt et al 1994[39]	Usual level of activity	8 (67 ± 5)	Treadmill walking	High	10 (67 ± 7)	3x·week 60 minutes	12 weeks	Initial workload of 2 mph, 0% grade for 3 minutes, increased 3.5% in grade every 3 minutes[3] [9]	MWT and PFWT	All	High

*G-S: Gardner-Skinner treadmill protocol, MWT: maximal walking time, PFWT: pain free walking time, MWD: maximal walking distance, PFWD: pain free walking distance, * combined as single high pain group in analysis*

Table S4. Cochrane Risk of Bias 2.0 (Intention to treat)

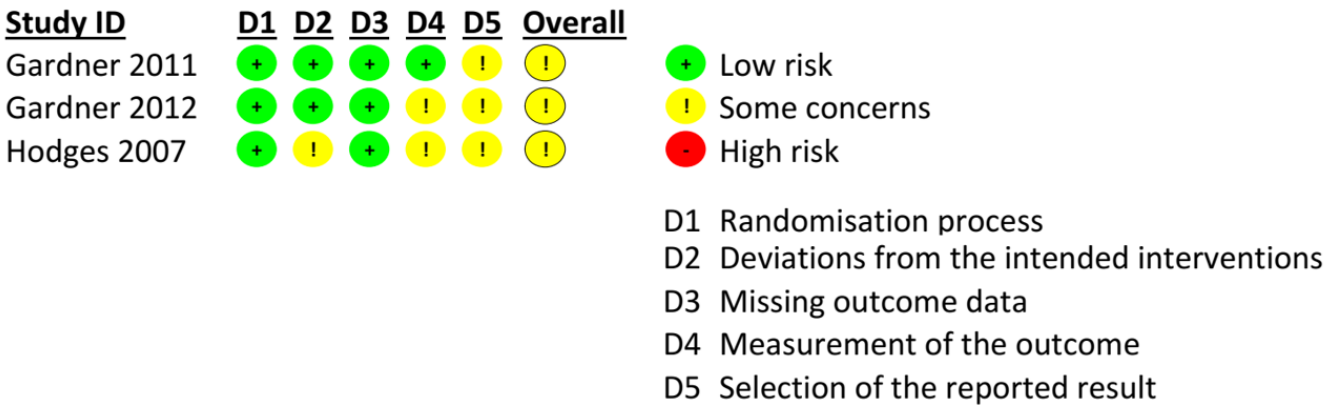
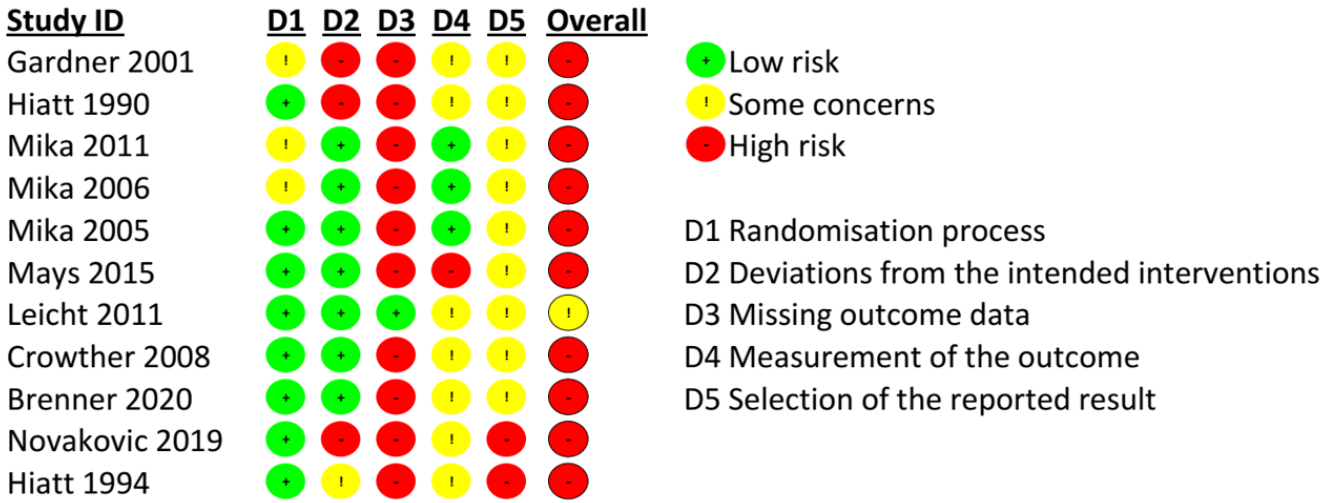


Table S5. Cochrane Risk of Bias 2.0 (Per Protocol)



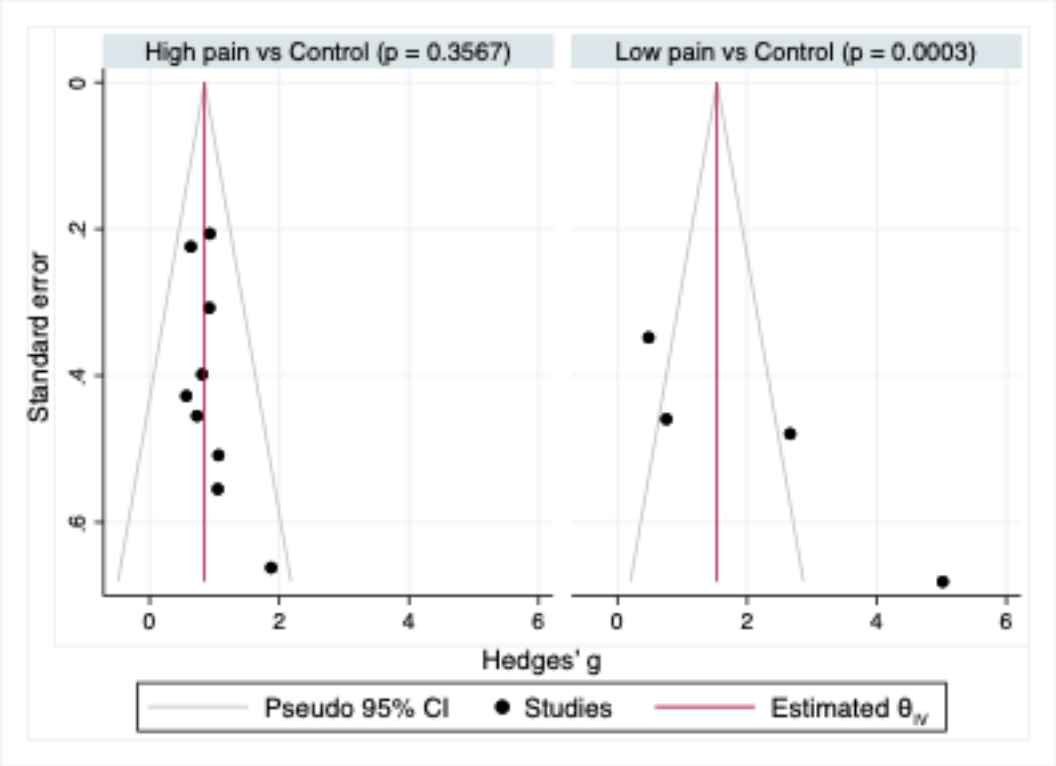


Figure S1. Funnel Plots High-Pain vs. Control and Low-Pain vs. Control (r 0.5) Maximal Walking Ability. P values are estimated using Egger's test for small-study effect.

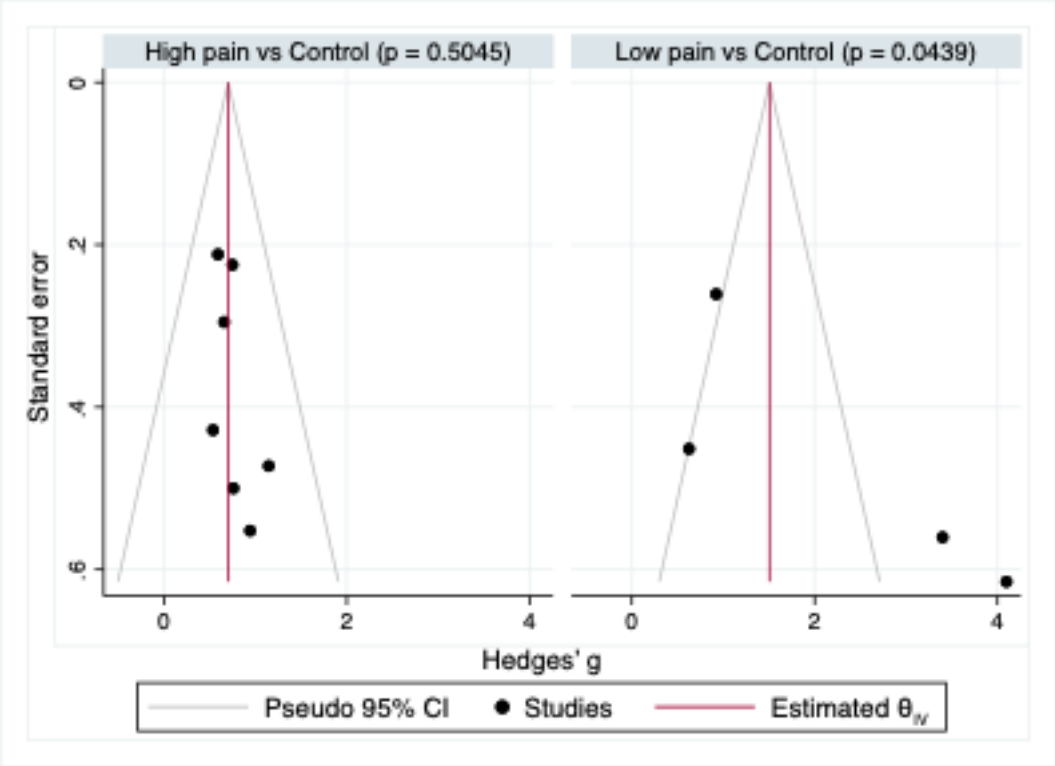


Figure S2. Funnel Plots High-Pain vs. Control and Low-Pain vs. Control (r 0.5) Pain Free Walking Ability. P values are estimated using Egger's test for small-study effect.

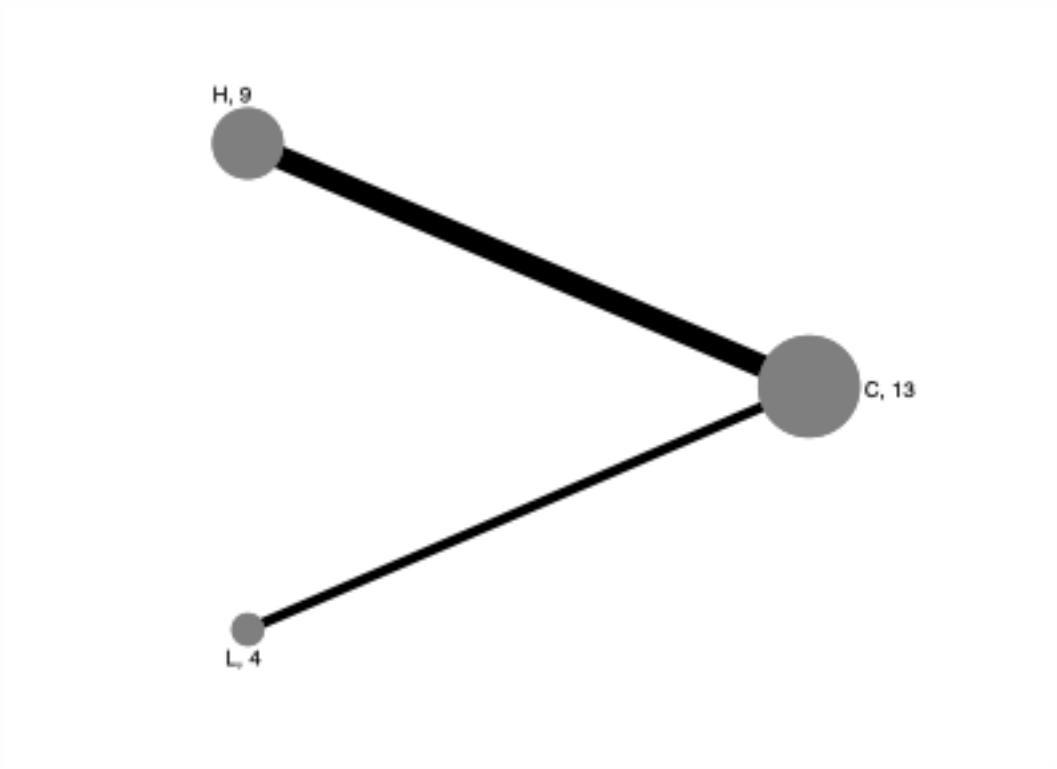


Figure S3. Network plot for 9 high-pain exercise arms (H, 9) and 4 low-pain exercise arms (L, 4) vs. 13 control arms (C, 13) maximal walking ability. Thickness of lines between nodes and size of the nodes based on the number of studies in each comparison and treatment, respectively.

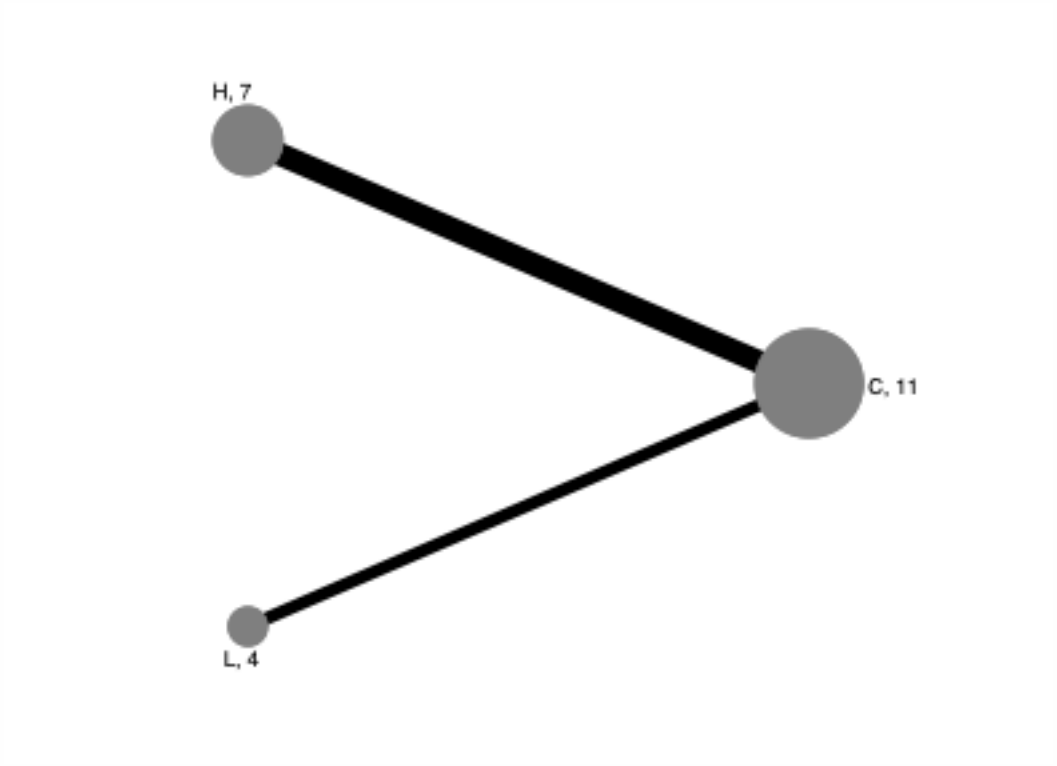


Figure S4. Network plot for 7 high-pain exercise arms (H, 7), 4 low-pain exercise arms (L, 4) vs. 11 control arms (C, 11) pain free walking ability. Thickness of lines between nodes and size of the nodes based on the number of studies in each comparison and treatment, respectively.

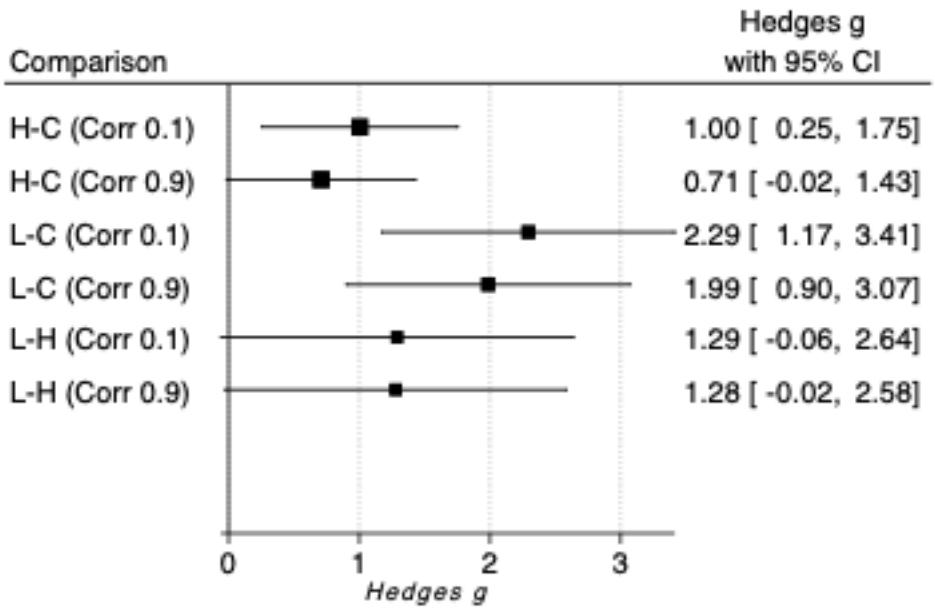


Figure S5. Summary of Network Meta-Analysis: Maximal Walking Ability Sensitivity Analysis (r 0.1 and 0.9). H: High-Pain, L: Low-Pain, C: Control. Effects were considered trivial at <0.2, small at 0.2-0.5, moderate at 0.5-0.8, and large at >0.8.

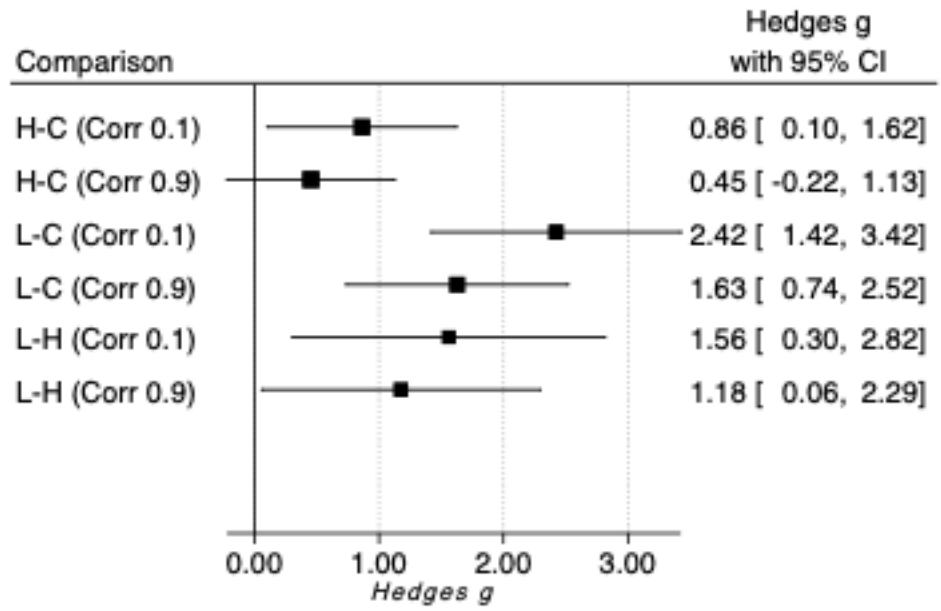


Figure S6. Summary of Network Meta-Analysis: Pain Free Walking Ability Sensitivity Analysis (r 0.1 and 0.9). H: High-Pain, L: Low-Pain, C: Control. Effects were considered trivial at <0.2, small at 0.2-0.5, moderate at 0.5-0.8, and large at >0.8.

PRISMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis[16]

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***Title Page***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**3**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**4**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**5**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**5-6**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**7**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Supplement**

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**5-6**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**6-8**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**7-8**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**7-8**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**7-8**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**7-8**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**7-8**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**N/A**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**7-8**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**7-8**
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**9**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Supplement**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**9**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1, 3 and 4**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**9-10**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**10-11**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**10-11**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**N/A**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**Supplemental table 1 and 2**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**11 and Supplement**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**12-14**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as*	**12-14**

		transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**14-15**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**16**