Effectiveness of stress management and relaxation interventions for the management of hypertension and pre-hypertension: a systematic review and network meta-analysis (Protocol)

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Plain English summary

What is the problem?

High blood pressure (or “hypertension”) is a common condition that affects around 1 in 3 adults worldwide. It is known to be a risk factor for many serious diseases, including heart attacks, strokes, kidney disease and dementia. Lowering blood pressure helps reduce the risk of these diseases. Therefore, it is important that people with high blood pressure are offered advice or treatment to help lower their blood pressure.

Standard treatment for high blood pressure includes taking tablets. However, there are also a lot of ways to reduce blood pressure that do not involve taking medicines. These include things like weight loss, reducing the amount of salt consumed, changing your diet (such as eating more fruit and vegetables), stopping smoking or reducing alcohol intake. In some countries, people who have raised blood pressure over a long period of time may be told they are at risk of developing hypertension. This is often called ‘pre-hypertension’.

Blood pressure has often been linked to stress levels, and many people think that reducing stress can help to lower blood pressure. There are many ways to tackle stress, but some examples are meditation, yoga, mindfulness, and tai chi. At present it is unclear which, if any, of the different approaches to managing stress work to reduce blood pressure in people diagnosed with hypertension or pre-hypertension.

What are we trying to find out?

We will bring together the available evidence on stress reduction and relaxation therapies for people with high blood pressure, and for people at risk of developing high blood pressure. We will compare the different types of stress reduction methods and relaxation therapies to see if any of these are able to lower blood pressure, and to identify which are the best approaches.

Background

Hypertension is a major risk factor for cardiovascular, cerebrovascular and peripheral arterial disease, as well as dementia and chronic kidney disease. Worldwide, hypertension is thought to affect more than 30% of adults aged 30-79 years - approximately 1.28 billion people[1]. The Global Burden of Disease study identified hypertension as the leading risk factor for attributable deaths in women worldwide, and the second highest risk factor in men (after tobacco smoking)[1]. However, relatively small changes in blood pressure are associated with better health outcomes – a reduction in systolic blood pressure of only 5mmHg is associated with a 10% decrease in major cardiovascular events[2]. As such, hypertension is an attractive target for interventions to prevent cardiovascular morbidity and mortality. Strategies to prevent and treat hypertension are therefore of great importance to maximize health outcomes.

Medication is typically recommended at the time of diagnosis of hypertension[3]. However, adherence to prescribed medication is often poor. Estimates of adherence range from 62% to 75% in high income countries and are even lower in low- and middle-income countries[4]. Non-pharmacological interventions may therefore provide an important method to supplement blood pressure reduction alongside conventional pharmacological therapies. Indeed, alternatives to medication, such as lifestyle and behavioural changes, have long been recognized as an important adjunct in blood pressure control and are first-line recommendations for treatment by many international guidelines[5-9]. Non-pharmacological alternatives include the provision of lifestyle and dietary advice, including a recommendation for reducing salt intake, stopping smoking, taking exercise and adopting a healthy diet[9]. Current international guidance defines a threshold of ≥140/90mmHg for the diagnosis of hypertension[10]. However, blood pressure measurements of 120-139/80-89mmHg may also represent a risk to later cardiovascular health[11], and indicate an increased chance of progression to hypertension[12]. Therefore, many countries use these lower thresholds to define 'pre-hypertension' or 'high-normal blood pressure', and advise lifestyle or behavioural changes at this stage[10, 13].

Prevention of deaths due to non-communicable disease - including cardiovascular disease - is a key concern for the World Health Organization (WHO). One of the nine WHO global targets to prevent and control non-communicable diseases from 2013-2020 was a 25% relative reduction in the prevalence of raised blood pressure[14]. The current general programme of work for the WHO includes broader targets, but one of these is a particular focus on the prevention of non-communicable diseases - including hypertension[15]. In a 2021 report, WHO highlighted the growing global disparities in hypertension diagnosis and treatment. Of the 1.28 billion people thought to have hypertension, approximately two-thirds are based in low- or middle-income countries (LMIC)[1]. However, those living in LMIC are also less likely to have their hypertension diagnosed and/ or receive medication to sufficiently control their condition than people living in high income countries (e.g. 70% of people with hypertension living in Canada receive treatment compared to 20% of men living in sub-Saharan Africa)[1].

There are also well-documented health inequalities and inequities relating to hypertension prevalence and treatment outcomes within high income countries, such as the UK. For example, people living in economically disadvantaged communities in England are 30% more likely than the least-deprived to have high blood pressure[16]. Hypertension is more common in British people with black Caribbean or African backgrounds[17, 18] and their hypertension is more likely to be poorly controlled[19], compared with those of other ethnicities.

Two key priorities within NHS England's long-term plan are that of prevention of disease and tackling health inequalities[20]. There is widespread international consensus that the promotion of lifestyle and behavioural modification plays a key role both in the prevention and treatment of hypertension[9, 10, 21]. A recent systematic review of international guidelines found broad agreement across ten clinical guidelines for smoking cessation, dietary sodium restriction, increased potassium intake, regular physical activity and dietary advice (including increased consumption of fresh fruit, vegetables and whole grains, reduction of red meat intake, increasing fish intake, and lowering of saturated and trans-fat intake)[8]. However, there are still areas of uncertainty. Although most guidelines recommend enquiring about psychological stress for people with hypertension, few provide recommendations on the use of techniques designed to alleviate this stress[8].

The mechanisms through which stress reduction and management may decrease blood pressure depend on the class of intervention. For example, relaxation interventions may work by modifying reactions to stress and acting on physiological mechanisms involved in the regulation of blood pressure, as the same neuroendocrine systems mediate stress responses. Psychotherapeutic interventions, such as cognitive behavioural therapy (CBT), may work via better regulation of negative emotions or improving coping strategies, which in turn reduce physiological arousal and sympathetic activity[22, 23].

A recent priority setting partnership from the James Lind Alliance identified lifestyle interventions – and particularly stress management strategies – as a key issue for patients and healthcare providers alike[24]. The top two research priorities identified were "What healthy lifestyle habits or combination of habits can reduce or eliminate the need for antihypertensive agents?" and "Does treating stress influence blood pressure and what is the optimal therapy?". In the UK, the National Institute of Health and Care Excellence (NICE) has prioritized relaxation therapies as an area for future research, with a research recommendation in the latest hypertension guideline ("What is the clinical and cost effectiveness of relaxation therapies for managing primary hypertension in adults in terms of reducing cardiovascular events and improving quality of life?)[9].

The identification of effective stress management and reduction interventions is therefore a key priority for people with hypertension or pre-hypertension to prevent the condition progressing further. In this review we will compare a variety of stress management and reduction interventions using network meta-analysis, a statistical technique that allows the simultaneous analysis of studies making different comparisons from an eligible set of possible interventions.

Aims and Objectives

To assess the comparative effectiveness of non-pharmacological stress management and relaxation interventions for improving outcomes for people with a diagnosis of hypertension or pre-hypertension.

Eligibility criteria

Population

For the purposes of this review we will follow the definition of hypertension provided by the International Society of Hypertension[10], and which is identical to the definition used by the World Health Organization[3] and NICE[9].

We will include studies of adults (≥18 years) with:

- primary (essential) hypertension; either with a clinical diagnosis of hypertension, or with office-measured blood pressure ≥140/90mmHg or ambulatory/home measured BP of ≥135/85mmHg[10].
- pre-hypertension or high-normal blood pressure or hypertension diagnosed at a lower threshold; either with a clinical diagnosis of pre-hypertension, or with blood pressure ≥120/80mmHg, but less than 140/90mmHg[25]

We will include studies where participants are taking medication for hypertension, as well as those where participants are on no additional treatment.

We will exclude studies of children or adolescents (<18 years), people with secondary hypertension, people who are pregnant or post-partum, and people with a hypertensive emergency (blood pressure ≥180/120mmHg).

Interventions and comparators

We will include studies examining non-pharmacological stress reduction, stress management or relaxation interventions for which a demonstrable mechanism of action has been proposed for the effect of the intervention on stress (hereafter referred to as 'stress management' interventions). The following stress management interventions are of interest to the review:

- Accessing outdoor green or blue space e.g. 'forest bathing' or horticultural therapy;
- Animal-assisted therapies;
- Autogenic training;
- Biofeedback;
- Breathing control and guided breathing;
- Massage therapy;
- Meditation and mindfulness-based strategies e.g. mindfulness-based stress reduction;
- Meditative movement-based strategies e.g. Qigong, Tai chi, Yoga;
- Music therapy;
- Progressive muscle relaxation;
- Psychotherapeutic and counselling strategies, e.g. cognitive behavioural therapy (CBT).

This list excludes interventions that are not used specifically to manage or reduce stress, or to promote relaxation, e.g. acupuncture, reflexology, moxibustion, dietary and nutritional supplement interventions. Exercise or physical activity-based interventions are not of interest where they can be categorized as being of moderate to vigorous intensity and/or where the intervention focus is improving general cardiovascular health (rather than for relaxation purposes).

We will include studies in which any of the intervention arms is one of our stress management interventions of interest or a combination of them. Specifically, we will include studies comparing stress management interventions with each other, with a control group or with another eligible active comparator intervention (as defined below).

We specify the following controls as of interest to the review as main comparators for the stress management interventions:

- No intervention;
- Sham control;
- Waiting list;
- Standard care.

The combined list of stress management interventions and these control comparators form the 'decision set' for the review, that is those in which we have primary interest[26, 27].

In addition, the following further comparators are eligible:

- Self-monitoring of blood pressure;
- Anti-hypertensive medication (classes of such interventions include ACE inhibitors, angiotensin-II receptor blockers, beta blockers, calcium channel blockers, centrally acting alpha agonists and diuretics; any pharmacological treatment not classified as an antihypertensive will be excluded);
- Physical activity and exercise strategies of moderate to vigorous intensity;
- Specific dietary interventions, such as the Dietary Approaches to Stop Hypertension (DASH) diet or a Mediterranean diet;
- General lifestyle advice, including recommendations for weight loss, smoking cessation and/or dietary modification e.g. salt reduction.

These form a 'supplementary set' of interventions to complement the decision set. Network meta-analysis allows the simultaneous analysis of a body of coherent evidence relating to multiple interventions, through the use of indirect comparisons. The comparison of interventions within the decision set may be strengthened by including further indirect evidence from such a supplementary set of interventions, forming a more extensive network of comparisons[26, 27].

We will not include studies that compare only control and/or supplementary interventions (e.g. exercise compared with dietary interventions, or anti-hypertensive medication compared with no intervention).

Study design

We will include randomized controlled trials (RCTs) only, including cross-over trials and cluster RCTs.

To be eligible for inclusion, studies must have a minimum period of 4 weeks from baseline to outcome measurement. No maximum study/ intervention length will be applied.

Outcomes of interest

We will consider the following outcomes in the review:

Primary outcomes

- Systolic blood pressure
- Diastolic blood pressure

Secondary outcomes

- Mortality
- Cerebrovascular disease (including ischaemic or haemorrhagic stroke, transient ischaemic attack)
- Ischaemic heart disease (including myocardial infarction and angina)

Other outcomes

- Heart failure
- Vascular procedures (e.g. coronary stent procedures, carotid artery surgery, lower limb revascularization)
- Economic outcomes such as costs, net-monetary benefit, return on investment, ICERs, QALYs, utilities and health-related quality of life (as measured by a validated instrument (e.g. EQ-5D))

For the purposes of analysis, outcomes will be grouped into short-term (up to 3 months [12 weeks]), medium-term (between 3 and 12 months), or long-term (over 12 months).

Study identification

To identify potentially eligible studies, we will search the following databases using relevant subject headings (controlled vocabularies), text-words and search syntax, appropriate to each resource:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2023, current issue) in the Cochrane Library;
- MEDLINE (Ovid) 1946 onwards (Appendix 1);
- AMED (Ovid) (Allied and Complementary Medicine; 1985 onwards);
- CINAHL (EBSCOHost) (Cumulative Index to Nursing and Allied Health Literature; 1982 onwards);
- PsycINFO (Ovid) all years.

Records from Embase will be identified via CENTRAL (Cochrane Library)[28]. From a scoping exercise, we do not anticipate finding many additional records unique to this database.

To help identify further published or unpublished research, we will scan the reference lists of included studies and any relevant systematic reviews.

We will not apply any date restrictions to the search but will limit to reports published in English. We will exclude pre-prints, conference abstracts, dissertations and theses and ongoing trial protocols. We will check for any relevant retraction statements or errata of included studies.

Review strategy

Two reviewers will independently screen titles and abstracts of studies identified by the database searches. We plan to use software tools e.g. Rayyan or EPPI-Reviewer to support the screening process. We will obtain full copies of all reports considered potentially relevant and two reviewers will independently assess these for inclusion. Any disagreements will be resolved by consensus or discussion with a third reviewer.

We will collect the following data:

- Country and setting of study;
- Inclusion/exclusion criteria;
- Any criteria used for the diagnosis of hypertension/pre-hypertension;
- Features of the participants, including co-morbidities (such as diabetes, previous cardiovascular disease, chronic kidney disease), the proportion receiving antihypertensives, and PROGRESS+ characteristics[29, 30];
- Details of the intervention, including intervention components, frequency of use, duration of intervention, mode and format of delivery, intervention facilitator and setting, adherence/fidelity to the intervention. We will use the TIDieR checklist[31] to guide our extraction of intervention and control details;
- Details of the comparator, including a description of ‘usual care’, if provided, or details of any sham treatment;
- Details of outcome measurement, including the protocol, setting, device(s) used, and person doing the measurement for the primary outcomes, and time points for all outcomes;
- Arm-level outcome data will be extracted following guidance in the Cochrane Handbook for continuous and dichotomous data[32]. However, where arm level data are not

available, we will extract study level summary effect estimates or other statistical values that may be used to approximate summary effect estimates.

Data will be extracted using a standardized data extraction form in Microsoft Excel. Data extraction will be piloted on a small sample of papers and adapted as necessary. Data will be extracted by one reviewer and checked in detail by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Risk of bias assessment

Risk of bias in results for primary and secondary outcomes will be conducted independently by two reviewers using the risk-of-bias 2 tool (RoB 2) for randomized trials[33]. Any discrepancies will be resolved through consensus, or by recourse to a third reviewer, if necessary.

Synthesis methods

Synthesis of effectiveness evidence:

Standard pairwise meta-analyses will be conducted for the primary and secondary outcomes. Separate analyses are planned for people with pre-hypertension and people with existing hypertension. Statistical heterogeneity is anticipated, and random-effects analyses are planned in the first instance. However, fixed-effect models will also be performed for reference. Interventions will be broadly categorized, and we anticipate final groupings will be similar to the list of stress management interventions in the 'interventions' section of this protocol. However, final intervention classifications will be generated via discussion with public contributors, stakeholders and clinicians.

Where interventions form a connected network, we will also conduct a network meta-analysis (NMA) to allow the simultaneous comparison of all interventions in a single analysis. This will form our primary analysis. Primary analyses will include the interventions in the supplemental set if inclusion of these creates additional indirect comparisons among the interventions in the decision set (otherwise they are uninformative). An example of a network diagram is shown in appendix 2, based on systematic reviews identified during scoping. All analyses will follow NICE TSD[34] and Cochrane guidance[26]. Inconsistency/ incoherence will be assessed using a range of approaches, including loop-specific and global approaches. Where there is evidence of inconsistency, we will first check for, and correct, any data extraction errors. We will then explore potential reasons for the inconsistency using network meta-regression techniques, including potential effect modifiers as covariates. Where inconsistency cannot be explained, pairwise analyses will be reported. All analyses will be implemented within a Bayesian framework. Goodness of fit and model comparison metrics will be used as a basis for final model selection. In the first instance, separate NMAs will be conducted for the primary and secondary outcomes. However, these outcomes are not independent and, where reported data allow, we plan to conduct multivariate analyses that allow for the joint synthesis of multiple endpoints[35].

The primary analysis will exclude studies assessed to be at high risk of bias. We plan to conduct sensitivity analyses (i) including studies considered to be at high risk of bias and (ii) restricting the analysis to studies in which *all* participants met the specific blood pressure thresholds outlined in the eligibility criteria.

We may conduct additional analyses that extend the network to include additional second-order indirect comparisons between interventions in the supplemental set (for example, diet versus anti-hypertensives, or medication versus exercise). We will do these if there are comparisons of our stress management interventions of interests with supplementary interventions that fail to contribute to indirect evidence, but which would become informative (as part of four-way 'loops' in

the network) if additional evidence comparing supplemental interventions is added to the network. To conduct these analyses, we would identify and include the results of robust meta-analyses from well-conducted systematic reviews, rather than data from primary studies.

Evidence for other outcomes will not be analysed statistically but will be summarized descriptively.

Subgroup analyses

Potential study level effect modifiers that we plan to explore in subgroup analyses are:

- Severity of hypertension[10]: ≥140/90 but <160/100 [grade 1] versus ≥160/100mmHg [grade 2];
- Pharmacological treatment for hypertension: use of concurrent medication vs no medication;
- Country level economic resource: studies conducted in low and low-middle income countries vs high income countries;
- Age (≥75 years versus less than 75 years)

Where reported data are insufficient for formal subgroup analysis, study level subgroup characteristics and results will be summarized in narrative or tabular form.

Where study authors present data relating to PROGRESS+ characteristics this will be extracted and reported in tables, alongside summary estimates of effect. However, we will not conduct formal subgroup analyses.

Certainty in the evidence

We will assess the certainty of the evidence using CINeMA[36].

Study Within A Review (SWAR)

Systematic reviews with network meta-analyses are often considered to be more time-consuming and resource intensive to conduct than those with standard, pairwise meta-analyses[37, 38]. We plan to conduct a SWAR to identify the resource implications and length of time it takes to carry out the reviewing activities associated with this systematic review and NMA. We will submit an outline proposal to the SWAR repository hosted by the Northern Ireland Network for Trials Methodology Research, at Queen's University, Belfast.

Update 13-11-2023: the SWAR is registered as "SWAR 24: Time and resource implications of a systematic review with network meta-analysis". It is available from: https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWARStore/

Public and patient involvement

The development of this review protocol was informed by consultation with public and patient contributors with lived experience of hypertension. Contributor input was sought to inform inclusion of relaxation and stress management interventions and important outcomes for managing hypertension. The contributors considered relaxation/stress reduction interventions as supplementary therapies rather than alternatives to medication. No additional stress reduction or relaxation interventions were identified by the contributors. Anti-hypertensive medication was consistently highlighted as the primary component of usual care for hypertension, with an addition of lifestyle advice regarding exercise and diet, and these were included in the 'supplementary set' of

interventions in the current protocol. Lowering blood pressure (our primary outcome) was identified as the key measure of effectiveness of any treatments for hypertension. Other important outcomes included reducing the risk of stroke or myocardial infarction, and increasing life expectancy (secondary outcomes in the current protocol). The potential for relaxation/stress reduction approaches to have short-lived effects was raised. Contributors emphasized the importance of long-term outcome assessment, as well as reliability of the outcome measurement. Therefore, we considered short-, medium-, and long-term time-points of outcome assessment, with a minimum study duration of four weeks, to capture sustained rather than only transient effects of relaxation/stress management interventions. We did not restrict the settings of blood pressure measurement (since more reliable office-based or ambulatory measures are likely to be associated with shorter follow-up, and less reliable home-based self-measurements with longer follow-up).

Declaration of author interests

CC is a Committee Member for the NICE guideline Hypertension in adults: diagnosis and management (update).

None of the other authors have any competing interests to declare.

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Appendix 1

Example search strategy for MEDLINE.

Ovid MEDLINE(R) ALL <1946 to September 05, 2023>		
Population		
1	exp Hypertension/	318476
2	(hypertensi* or prehypertensi*).tw,kf.	517363
3	antihypertensi*.ti,kf.	16553
4	(antihypertensi* adj3 (effect* or outcome?)).ab.	9160
5	((elevated or high* or increased or borderline) adj3 (blood pressure or bloodpressure or BP)).tw,kf.	64153
6	((elevated or high* or increased or borderline) adj3 ((arterial or diastolic or systolic) adj3 pressur*)).tw,kf.	19862
7	((reduc* or lower*) adj3 (blood pressure or bloodpressure or BP)).tw,kf.	48343
8	((reduc* or lower*) adj3 ((arterial or diastolic or systolic) adj3 pressur*)).tw,kf.	14192
9	blood pressure.tw,kf,hw. and Cardiovascular Diseases/pc [Prevention & Control]	7307
10	or/1-9	641513
Intervention		
11	Relaxation/ or Muscle Relaxation/ or Relaxation Therapy/	20757
12	relaxation.ti,kf.	30249
13	((relaxation or relaxing) adj3 (activit* or acup* or app* or assist* or based or behavi* or breath* or control* or counsel* or effect* or exercis* or hobby or hobbies or hypno* or imag* or intervention* or instruction* or lifestyl* or meditat* or mediat* or mental* or mind* or music* or muscle* or muscular or program* or progressi* or psychotherap* or psycholog* or respons* or self or stress or study or teach* or technique* or therap* or train* or treat* or trial or video* or virtual*)).tw,kf.	41694
14	(music* or acoustic stimulat* or song? or singing or choir?).tw,kf.	40291
15	(physiological stress/ or exp chronic stress/ or exp mental stress/ or exp physically induced stress/) and therapy.fs.	1946
16	(stress* adj1 (manag* or recovery or prevent* or reduc*)).tw,kf.	23237
17	(stress adj3 coping).tw,kf.	8305
18	((NPI or nonpharma* or non-pharma*) adj (intervention* or trial)).tw,kf. and (stress or relax*).mp.	882
19	Breathing/ and therapy.fs.	4240
20	exp Breathing Exercise/	4221
21	(slow breathing or ((nostril? or paced or pursed* or rhythmic* or yog*) adj3 breathing)).tw,kf.	1545
22	(breath work* or breathwork* or holotropic breathing or buteyk* or pranayam*).tw,kf.	589
23	(breathing adj3 (activit* or app* or exercis* or intervention* or instruction* or meditat* or program* or progressi* or study or teach* or technique* or therap* or train* or trial)).tw,kf.	9015
24	(breathing control or guided breathing).tw,kf.	602
25	(forest bathing or shinrin yoku or shinrinyoku).tw,kf.	112
26	((inspiratory or respiratory) adj3 (activit* or app* or device? or exercis* or intervention* or instruction* or meditat* or program* or progressi* or study or teach* or technique* or therap* or train* or trial)).tw,kf.	38291

27	((breathing or inspiratory or respiratory) and (non-pharma* or nonpharma* or npi)).tw,kf.	1705
28	Mindfulness/ or Mindfulness meditation/ or Mindfulness-Based Cognitive Therapy/ or Mindfulness-Based Stress Reduction/	6348
29	(mindfulnes* or mindfullnes* or (mind? adj3 (therap* or train*)) or mind-body or mindbody).tw,kf.	17258
30	(MBSR or MBCT).tw,kf.	1557
31	exp Meditation/	3802
32	meditat*.tw,kf.	8530
33	exp Mind-Body Therapies/	47383
34	(kinesiotherap* or movement therap* or motion therap* or dance therap* or pilates or plyometrics or plyometric exercis* or static exercis* or stretching exercis* or qigong or qi gong or baduanjin or ba duan jin or chigung or chi gung or chikung or chi kung or tai chi or taichi or tai ji or taiji or taijiquan or yoga or yogic).tw,kf.	14984
35	(reiki or therapeutic touch or laying-on-of-hands or energy healing).tw,kf.	911
36	(hypnosis or hypnotism or hypnotherap* or hypno-therap* or hypnoanalysis or hypno-analysis or hypno* exercis* or mesmerism or autosuggestion or auto-suggestion or autogenic training).tw,kf.	10565
37	(guided imagery or (imagery and (therap* or psychotherap* or psychol*)) or reverie therap*).tw,kf.	3280
38	(biofeedback* or bio-feedback* or psycho* feedback* or myofeedback* or myo-feedback* or ((bogus or false) adj physiological adj (feedback* or feed-back*))).tw,kf.	8463
39	(neurofeedback* or neuro-feedback* or ((alpha or brainwave* or brain wave* or EEG or electroencephalo* or electro-encephalo* or electromyo* or electromyo*) adj feedback*)).tw,kf.	2450
40	(psychodrama or psycho* drama or drama therapy or role play* or laughter).tw,kf.	26551
41	massage/ or acupressure/	7744
42	(massag* or acupressure or (acupoint? adj2 stimulat*) or chihya or chih ya or shiatsu or shiatzu or zhiya or zhi ya or tuina or tui na).tw,kf.	15462
43	(reflexology* or ((foot or feet or hand?) adj1 massag*) or ((foot or reflex*) adj zone adj therap*)).tw,kf.	867
44	(aromatherap* or aroma* therap* or essential oils).tw,kf.	14208
45	exp Acupuncture Therapy/	29276
46	(acupuncture or electroacupuncture or moxabustion or moxibustion or auriculotherap*).tw,kf.	32576
47	cupping.ti,kf. or (cupping adj2 (dry or wet or fire or flash or manipulation or moving or suction or therap* or treat* or vacuum or hijama)).ab.	1015
48	(dry needling or (dry needl* adj (technique* or therap* or trigger)) or ((intramuscular or intra-muscular) adj stimulation)).tw,kf.	1011
49	exp complementary therapies/ or (complementary therap* or alternative medicine*).tw,kf.	253464
50	(naturopath* or nature therap*).tw,kf.	1443
51	((green adj (environment* or health* or infrastructur* or infra-structur* or space?)) or greenspace* or open space* or open air or outdoor? or countryside or rural environment* or natural environment or natural space? or wilderness or woods or (forest adj (environment* or setting*)) or parks or parkland* or park setting* or ((urban or town? or city or cities or innercit* or "access to") adj3 park) or garden* or horticultur*).tw,kf,hw. or forests.ti,kf,sh.	105736

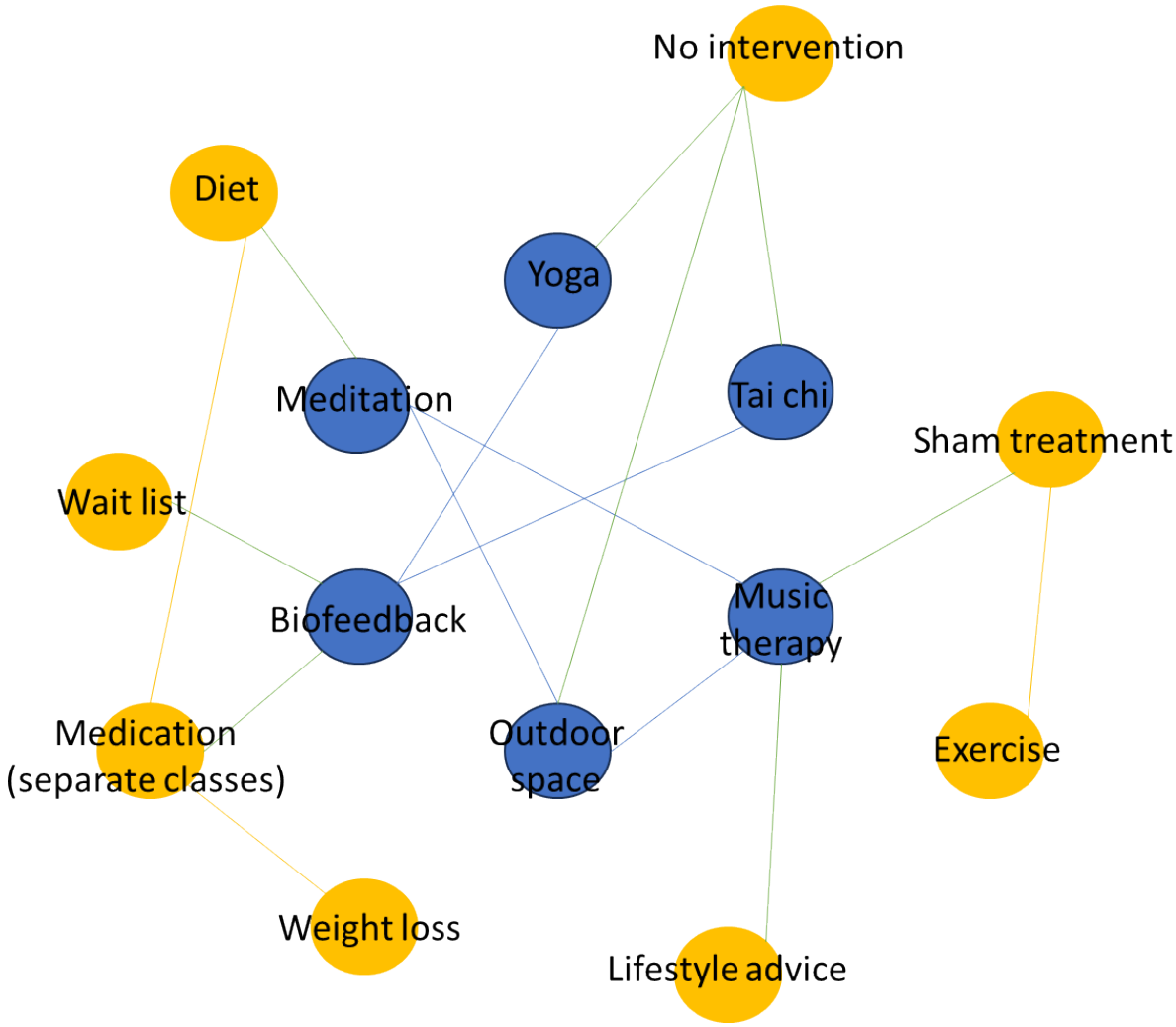
52	((blue adj (environment* or health* or infrastructure* or infra-structure* or space?)) or bluespace* or waterfront* or water-front* or waterway* or water-way* or waters or seaside* or sea-side* or beach or beaches or streams or canals or lakes or ponds or rivers or riparian or wetlands or wet-lands or marshes or running water? or fountains or ((outdoor* or out-door* or outside or out-side or open* or wild*) adj (pool? or bath* or water*))).tw,kf,hw.	198647
53	((blue or water or aquatic or green or nature or land* or outdoor* or out-door*) adj (based or activit* or hobby or hobbies or leisure or recreation*)).tw,kf,hw.	18705
54	exp Balneology/	12813
55	(balneo* or ammotherap* or ammo-therap* or ((mud or sand or steam or air) adj3 (bath* or therap*)) or sauna* or hotspring* or hot spring*).tw,kf.	8792
56	exp Hydrotherapy/	20936
57	(hydrotherap* or hydro-therap* or whirlpool bath* or (shiatsu adj1 water) or watsu).tw,kf.	1625
58	((water* adj3 immersi*) or baths or bathing).tw,kf.	23863
59	Hyperthermia, induced/	19470
60	(((thermal* or hypertherm* or hypertherm*) adj (induc* or intervention* or therap*)) or waon).tw,kf.	9491
61	exp Cognitive Behavioral Therapy/	36812
62	exp Psychotherapy, Group/	27826
63	(CBT* or CBGT*).tw,kf.	16068
64	((cogniti* or behavio*) adj3 (counsel* or intervention or management or psychotherap* or therap* or training or treatment or technique* or restructur* or defusion)).tw,kf.	104384
65	(rational emotive or (problem* adj2 (focus* or sol*)) or psychoeducat* or psycho-educat* or schema* or self-control* or self controlling).tw,kf.	101058
66	(((psychotherap* or therap*) adj3 (commitment or acceptance)) or ((self* or stress*) adj3 (control or analysis or direct* or esteem or help or instruct* or manage*))).tw,kf.	133303
67	(acceptance adj2 commitment adj2 (intervention or training or treatment or technique*)).tw,kf.	146
68	((attribution* or reattribution*) adj3 (therap* or psychotherap*)).tw,kf.	61
69	((anxiety adj2 manag*) or confidence building or coping skills or exposure therapy or exposure task? or sensitivity training or self talk).tw,kf.	9147
70	((controlling or overcoming) adj2 (anxiety or panic or fear)).tw,kf.	698
71	((thirdwave or third-wave) adj3 (cogniti* or behavi* or counsel* or intervention or psychotherap* or therap*)).tw,kf.	214
72	(compassion* adj3 (counsel* or intervention or psychotherap* or therap* or train*)).tw,kf.	861
73	(functional analy* adj3 (counsel* or intervention or psychotherap* or therap* or train*)).tw,kf.	162
74	((metacogniti* or meta-cogniti*) adj3 (counsel* or intervention or psychotherap* or therap* or train*)).tw,kf.	669
75	(dialectic* adj3 (counsel* or intervention or psychotherap* or therap* or train*)).tw,kf.	1322
76	((behavio* adj1 activat*) or BATD).ti,ab,kf.	3041
77	behavio*.mp. and (self adj (evaluat* or monitor*)).ti,ab,kf.	4949
78	((gain? or reapprais*) adj2 focus*).ti,ab,kf.	225

79	(behavio* adj3 (contracting or modification or modify* or reinforce* or re-inforce*)).tw,kf.	13580
80	(positive affirmation* or ((positive or contingent) adj1 reinforc*) or (reinforc* adj3 (environment* or experience*))).tw,kf.	3972
81	((activit* adj2 schedul*) or ((pleas* or enjoyable or rewarding) adj (activit* or event?))).tw,kf.	1548
82	(operant conditioning or instrumental learning or positive interaction* or avoidant coping or environmental contingenc* or contigency management).tw,kf.	7197
83	psychotherapy.mp.	93497
84	((psychosocial* or psycho-social*) adj3 (activit* or app* or control* or counsel* or intervention* or program* or study or therap* or train* or treat* or trial)).tw,kf.	21852
85	Anger Management Therapy/	69
86	(anger adj3 (activit* or app* or behavi* or control* or counsel* or intervention* or instruction* or lifestyl* or management or managing or meditat* or mediat* or program* or psycho* or study or teach* or technique* or therap* or train* or treat* or trial or video* or virtual*)).tw,kf.	3051
87	self-control/ or emotional regulation/	5812
88	(emotion* adj3 regulat*).tw,kf.	18536
89	((positiv* adj3 (emoti* or psych*)) or (reduc* adj3 negative adj3 (emoti* or psych*)) or (reduc* adj3 hostil*) or qi therap*).tw,kf.	22253
90	exp Animal Assisted Therapy/	823
91	((pet or pets or (animal adj (assisted or facilitated))) adj3 therap*).tw,kf.	2343
92	((complex or factorial or multi component* or multicomponent* or multidimension* or multi dimension* or multifactor* or multi factor* or multifacet* or multi facet* or multilevel* or multi level* or multimodal* or multi modal* or multiparamet* or multi paramet* or multiecological or multi* ecological) adj (evidence or intervention* or trial)).tw,kf.	12746
93	or/11-92	1355533
94	10 and 93	18609
RCT Filter		
95	clinical trials as topic/	201200
96	controlled clinical trial.pt.	95418
97	randomized controlled trial.pt.	599338
98	random allocation/	106960
99	(randomi#ed or randomi#ation or randomi#ing).ti,ab,kf.	819417
100	(RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).tw,kf.	732162
101	trial.ti.	292155
102	(control* adj3 (arm or arms or group*)).ab.	682412
103	((control* or compar* or versus) and (trial or study or group* or arm or arms) and (waitlist* or wait* list* or attention* control* or treatment-as-usual or TAU or care-as-usual or CAU or ((conventional or routine or standard or usual) adj2 (care or therap* or treatment or control?)) or untreated group* or untreated control* or no-therap* or non-therap* or nontherap* or minim* therap* or no-contact or pseudotherap* or sham or receiv* nothing or no-	297886

	intervention or no-treatment* or non-treatment* or nontreatment* or (without adj2 (treatment or therap* or intervention)))).tw,kf,hw.	
104	or/95-103	2151146
105	exp animals/ not humans/	5152370
106	104 not 105	1851503
107	94 and 106	4129
108	limit 107 to english language	3744

Appendix 2

Figure to demonstrate an example of the anticipated network diagram for this NMA. Note this is a representation of the potential network, based on systematic reviews identified during preliminary scoping for the protocol. As such, not all potentially relevant interventions are included in this figure and the network is not considered final.



We will include trials that compare any two (or more) relaxation therapies (blue connecting lines), and trials that compare at least one relaxation therapy with a comparator (green connecting lines).

We will exclude studies that only compare supplementary interventions (e.g. diet versus no intervention, diet versus exercise: all yellow connecting lines in the diagram).