BMJ Open

Comparative efficacy and acceptability of different exercise patterns for reducing cardiovascular events in pre-diabetes: protocol for a systematic review and network meta-analysis of randomised controlled trials

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To cite: Zhong Y, Lan M, Chen H, *et al*. Comparative efficacy and acceptability of different exercise patterns for reducing cardiovascular events in pre-diabetes: protocol for a systematic review and network meta-analysis of randomised controlled trials. *BMJ Open* 2024;**14**:e075783. doi:10.1136/bmjopen-2023-075783

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-075783).

Received 24 May 2023
Accepted 26 March 2024

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ABSTRACT

Introduction Exercise has been used to reverse dysglycaemic states in patients with pre-diabetes. Systematic reviews show that exercise is an effective way to reduce the incidence of diabetes, but there is conflicting evidence for reducing the occurrence of cardiovascular events. Therefore, we present a systematic review and network meta-analysis protocol designed to compare the effectiveness of different forms of exercise in reducing cardiovascular events and their tolerability in different populations.

Methods and analysis We will include all randomised controlled trials and compare one exercise intervention to another. We will compare the following exercise patterns: standard endurance training, strength training, high-intensity interval training, mind-body exercise, and mixed strength and aerobic training. The primary outcomes are the occurrence of major cardiovascular events and the rate of patient attrition during the intervention. We will search major English and Chinese databases as well as trial registry websites for published and unpublished studies. All reference selection and data extraction will be conducted by at least two independent reviewers. We will conduct a random effects model to combine effect sizes and use the surface under the cumulative ranking curve and the mean ranks to rank the effectiveness of interventions. All data will be fitted at WinBUGS in a Bayesian framework and correlation graphs will be plotted using StataSE 14. We will also use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to evaluate the quality of evidence for the study results.

Ethics and dissemination This study does not involve a population-based intervention, and therefore, does not require ethical approval. We will publish the findings of this systematic review in a peer-reviewed scientific journal, and the dataset will be made available free of charge. The completed review will be disseminated electronically in print and on social media, where appropriate.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We will conduct a random-effects network meta-analysis to synthesise all available evidence (either published or unpublished) for each prespecified outcome and obtain a comprehensive ranking of all treatments.
⇒ We will use subgroup analysis to evaluate the population for which the intervention is applicable and we will explore whether treatment effects are robust in network meta-regression.
⇒ There was considerable heterogeneity among studies, such as the intensity and frequency of exercise and the duration of follow-up, which may affect the transferability of evidence.
⇒ Limitations will be addressed through rigorous intervention predefinition and subgroup analysis, and the quality of evidence for network estimates of the primary outcome will be assessed using the GRADE framework.

PROSPERO registration number CRD42023422737.

BACKGROUND

Pre-diabetes is a high-risk state for developing diabetes, including impaire fasting glucose(IFG) and/or impaired glucose tolerance (IGT). 5%–10% of people with pre-diabetes will develop diabetes every year.[1] The global prevalence of pre-diabetes is expected to reach 730 million by 2045.[2] Pre-diabetes is associated with nephropathy, neuropathy, retinopathy, cardiovascular disease (CVD) and death.[1 3–7] Pre-diabetes is an independent risk factor for CVD.[8] Meta-studies have shown that pre-diabetes increases the risk of cardiovascular events and all-cause mortality.[9 10] In particular, compared with patients with

abnormal fasting glucose, patients with IGT are at increased risk of coronary heart disease (CHD), stroke and all-cause mortality.

Exercise has several health benefits, including lowering blood pressure, improving insulin sensitivity, the lipoprotein profile, C reactive protein, and other CHD biomarkers, and helping with weight management.[11] Additionally, it can lower the chance of having a stroke, type 2 diabetes, CHD and several types of cancer. The Daqing study[12] showed that lifestyle interventions (eg, healthy diet and exercises) in people with IGT delayed the onset of type 2 diabetes, reduced the incidence of cardiovascular events, microvascular complications, cardiovascular and all-cause mortality, and increased life expectancy.

Current forms of exercise interventions for diabetes prevention include aerobic exercise, resistance exercise, high-intensity interval training (HIIT) and traditional Chinese exercise.[13 14] However, conclusions on the optimal form of exercise are inconsistent.[14 15] A multicentre randomised trial noted[16] that the combination of moderate-intensity aerobic and resistance training for 24 months reduced the 10-year risk of CVD in patients with pre-diabetes. It is believed that vigorous-intensity exercise is associated with greater risk reductions for CVD and all-cause mortality compared with moderate-intensity activity of similar energy expended.[11] Ma *et al* noted[17] that the Chinese traditional exercise Baduanjin was comparable to moderate-intensity aerobic exercise in reducing cardiovascular complications in patients with pre-diabetes. Also, recommendations for the optimal duration of exercise for different exercise forms are not clear.[13 17]

Previous systematic evaluations have only evaluated the association of exercise with the reduction of diabetes risk,[14 15] and fewer systematic reviews have reviewed the reduction of the risk of developing CVD. Second, the risk of cardiovascular events in patients with IGT is inconsistent with that in patients with IFG,[9 10] and a review of the indications for different forms of exercise is needed. In addition, the risk of CVD in patients with pre-diabetes differs by ethnicity,[9] requiring individualised recommendations for forms of exercise.[18] Therefore, this systematic review and network meta-analysis aimed at comparing the effectiveness of different forms of exercise interventions in preventing the development of CVD in patients with pre-diabetes and their tolerability among different populations, to better guide clinical practice. We used the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist when writing our report.[19]

METHODS AND ANALYSIS

Criteria for considering studies for this review

Types of studies

All reports of randomised controlled trials (RCTs) comparing one mode of exercise to another or no exercise intervention will be included. The duration of the intervention should be at least 4 weeks. Only studies with a single exercise intervention will be included; therefore, RCTs combined with dietary therapy or pharmacological therapy will be excluded. Conference proceedings, case reports, quasi-experimental studies, study protocols, reviews, systematic evaluations and meta-analyses will be excluded. Studies with incomplete data information, studies with no reported data or studies in which the specific incidence of relative risk (RR) values with 95% confidence intervals (CIs) or indices could not be calculated will be excluded. For duplicate publications, we will include only the most informative reports with the most complete data, and the rest will be excluded. Studies with randomisation failure (eg, incorporate patient preferences, no randomisation process and only baseline comparability) and significant differences in baseline data between groups will be excluded.

Types of participants

Patients aged 18 years or older, of both sexes, with a diagnosis of pre-diabetes, will be included according to the diagnostic criteria of the World Health Organization (WHO).[20] Patients with a diagnosis of diabetes in the study, including children and elderly (≥80 years) and pregnant women, will be excluded.

Types of interventions

We grouped exercise patterns into several named exercise categories: standard endurance training, strength training, HIIT, mind-body exercise, and mixed strength and aerobic training. See online supplemental table 1 for more details.

Considering the dose–response correlation between exercise volume and health outcomes, if the study refers to exercise intensity, it will be classified as follows according to Garber[11]: light: the percentages of heart rate reserve (%HRR) or oxygen uptake reserve ($\%VO_2R$) 30%–40%; moderate: %HRR or $\%VO_2R$ 40%–60%; vigorous: %HRR or $\%VO_2R$ 60%–90%; near maximal: %HRR or $\%VO_2R$>90 percent. If the study does not mention %HRR or $\%VO_2R$, we will classify them as moderate-intensity exercise and vigorous-intensity exercise according to MacIntosh *et al*[21] as follows: moderate-intensity exercise, such as walking briskly, dancing, playing doubles tennis, or raking the yard, slow and swimming, and vigorous-intensity such as jogging, running, carrying heavy groceries or other loads upstairs, shovelling snow, or participating in a strenuous fitness class, and fast swimming.

Considering that researchers often compare high-intensity interval exercise with moderate-intensity continuous training (MICT),[22 23] we will also search for MICT in order not to omit some important literature. Figure 1 shows a comparison network of eligible interventions.

Outcome measures

Primary outcomes

- The occurrence of cardiovascular events which is defined as cardiovascular death or major cardiovascular events (for studies ≥1 year), including myocardial infarction, stroke, transient ischaemic attack, coronary interventions (including stent thrombosis),

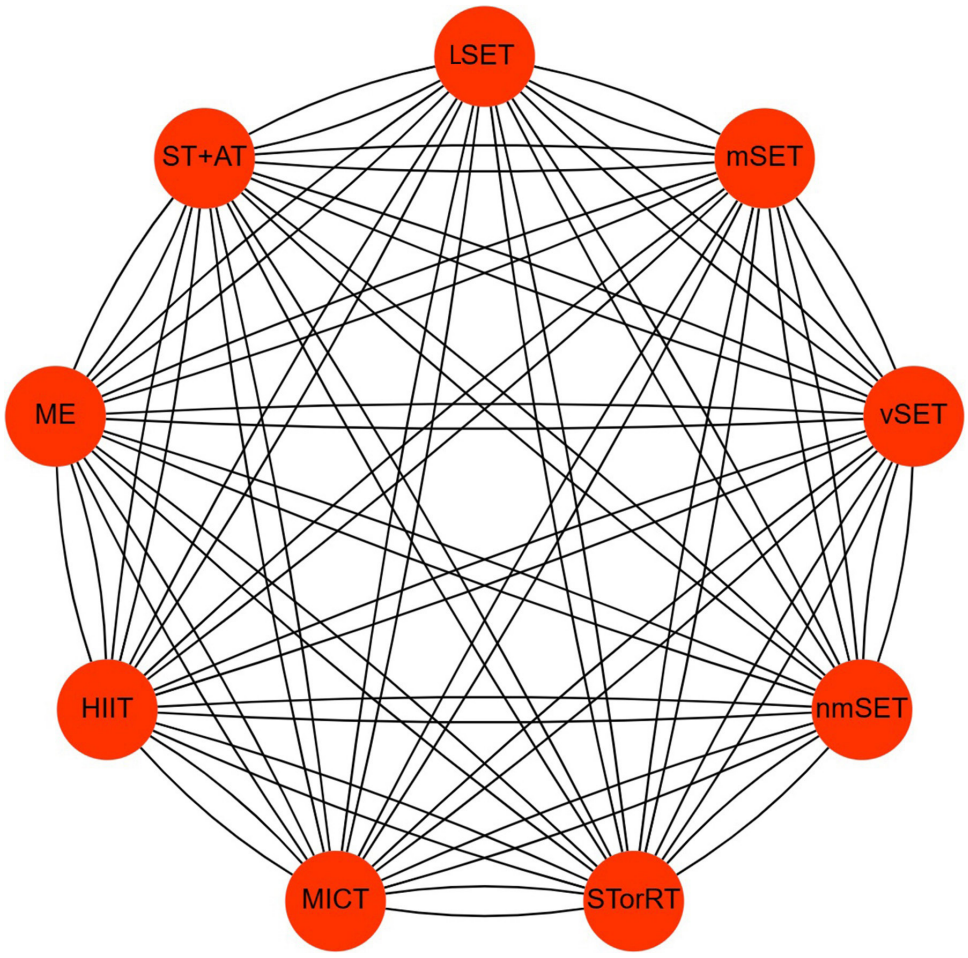

Figure 1 Network diagram of all possible pairwise comparisons. HIIT, high-intensity interval training; LSET, light-intensity standard endurance training; ME, mind-body exercise; MICT, moderate-intensity continuous training; mSET, moderate-intensity standard endurance training; nmSET, near maximal-intensity standard endurance training; ST+AT, mixed strength and aerobic training; STorRT, strength training or resistance training; vSET, vigorous-intensity standard endurance training.

peripheral vascular interventions, hospitalisation for unstable angina and acute heart failure, according to cardiovascular endpoints developed by American College of Cardiology.[24]

- Tolerability of treatment.

The proportion of patients who leave the study early due to any events. (for studies ≥4 weeks).

Secondary outcomes

Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, Hemoglobin A1c(HbA1c) levels, fasting glucose, body mass index and waist circumference (for studies ≥3 months).

Search strategy and study selection

We will search in Medline, Cochrane Library, Ovid, Embase, Web of Science, PubMed, China National Knowledge Infrastructure(CNKI), VIP, SinoMed and Wanfang databases from the date of their inception to 1 June 2023. Searches will also be performed on ClinicalTrials.gov and www.chictr.org.cn. Before publication, updated articles will be retrieved again and data will be updated. The languages of the publication are Chinese and English. The search is conducted in Chinese and English. Two reviewers will search and review studies independently and discrepancies will be discussed and judged by a third reviewer. Specific search strategies are described in online supplemental material.

Data extraction

The EndNote V.X9 file management software will be applied. First, the retrieved articles will be imported into the software for preliminary screening to eliminate duplicate documents. Second, two reviewers will screen the abstracts and titles of the retrieved literature back-to-back according to the inclusion criteria, exclude literature that does not meet the criteria and then cross-check the screening results. Differences will be resolved through discussion and consultation. If agreement cannot be reached, a third reviewer should step in to make the final decision. Finally, the full text of the qualified study will be available, and the reviewer will review the full text again and exclude literature that does not meet the criteria. Two reviewers will read each article independently, assess

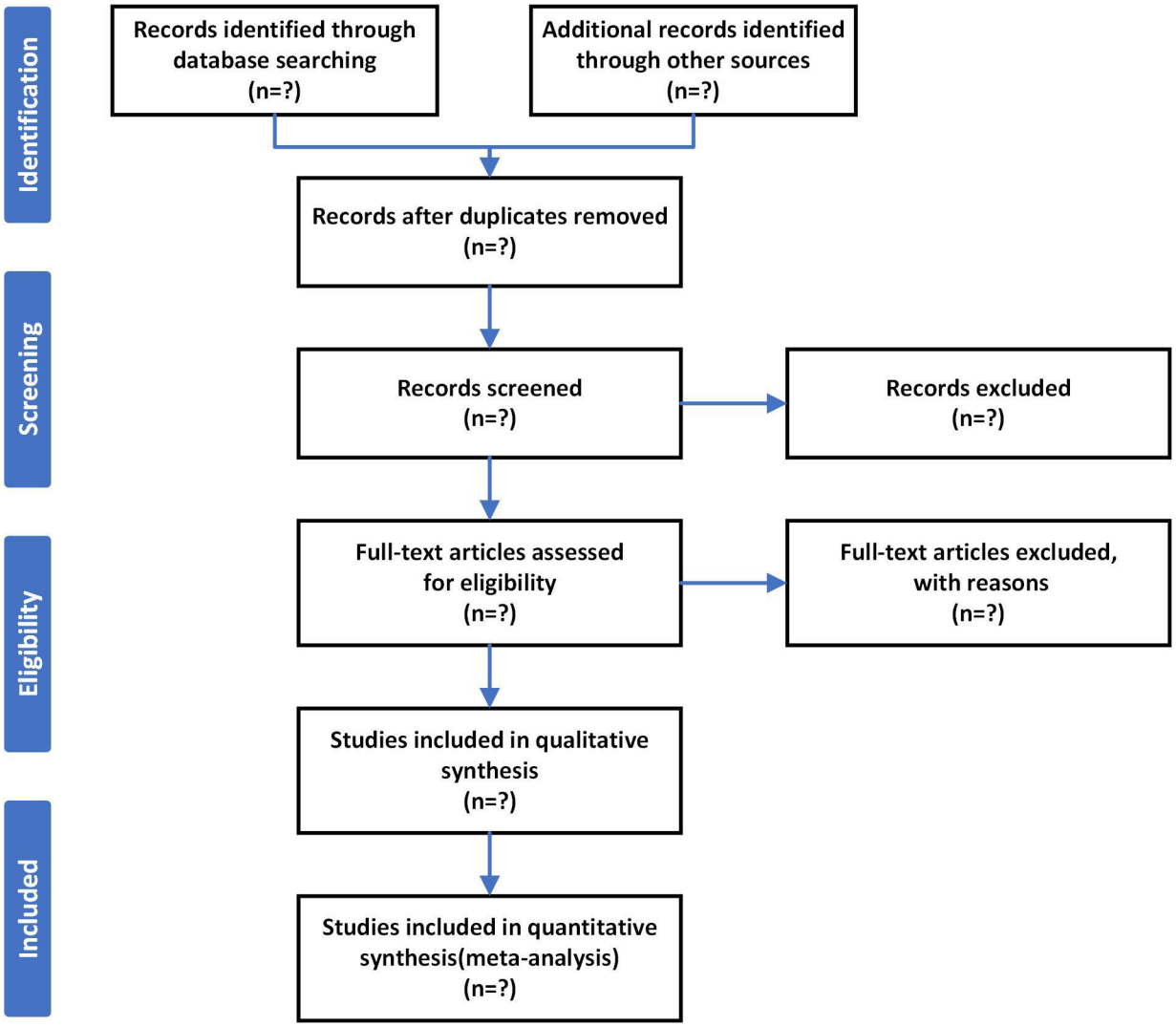

Figure 2 Flow chart for research retrieval and inclusion.

the integrity of the data and give a quality rating. The flow chart (figure 2) outlines the inclusion steps and exclusion reasons for full-text retrieval.

Structured data extraction tables will be designed and used to ensure the consistency of information and assessment for each study. The extracted information will include study characteristics (eg, lead author, year of publication and journal), participant characteristics (eg, pre-diabetes diagnostic criteria, age, sex, region, ethnicity), intervention details (eg, type of exercise, intensity, frequency, duration and monitoring) and the aforementioned outcome measures (see figure 3 for more details). Two reviewers will determine if the data are correctly entered into the final data set.

Dichotomous outcomes

RR value will be used as the effect value. When only odds ratio(OR) values were given in the study, RR=OR/[(1−pRef)+(pRef*OR)] will be used to transform it into no RR value, Where pRef indicates the incidence of the outcome of interest in the control group, and then the effect value will be combined.[25]

Continuous outcomes

Standardized mean difference(SMD) will be used as the effect value. Mean, standard deviation(SD) and randomised patient numbers for each study group will be extracted. If the mean and its SD are not recorded, the author will be asked to provide the data. When standard error (SE), t-statistics or p values are reported, these will be converted to SD. When only the median is given in the study, the Box-Cox method will be used to convert it to the mean.[26]

Missing outcome data

The occurrence of prediabetic cardiovascular events was the result of long-term follow-up.[9] Therefore, for the dichotomous outcome, that is, the occurrence of cardiovascular events, we will treat different missing values based on the study follow-up time: (1) For studies with a follow-up time of <3 years, we will apply the impute missing=no event (0) scenario (Imputed case analysis-0,I-CA-0), assuming that all missing participants did not experience this event in both the experimental and control groups. (2) For studies with follow-up time >3 years, we

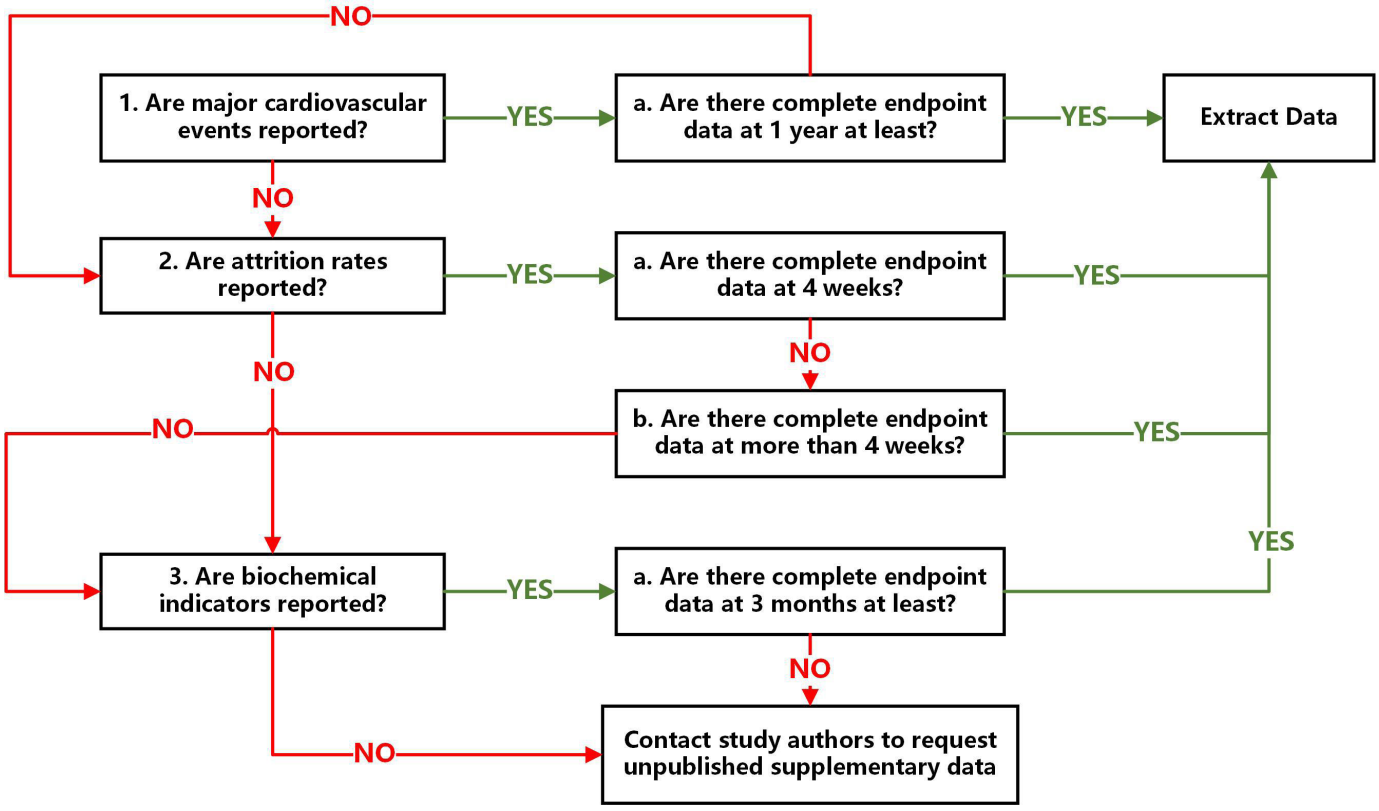

Figure 3 Decision-tree for data extraction.

will apply the impute missing=event (1) scenario (ICA-1), assuming that all missing participants experienced this event in both the experimental and control groups.[27] For continuity variables, missing data will be processed using the last observation carried forward[28] and filled in based on the last observation or baseline data.

Length of trial

It is believed that the occurrence of cardiovascular events depends on long-term follow-up.[12] Therefore, this systematic review will combine studies with long-term follow-up conditions (≥1 year) to determine the incidence of cardiovascular events, and if the studies have large variability in follow-up time, we will eliminate the direct combination or use subgroup analysis.

Risk of bias and quality appraisal

We will assess the risk of bias using the Cochrane Risk of Bias tool (2011).[29] The assessment will be conducted by two independent researchers. If the researchers disagree, the final rating will be made by consensus with the involvement (if necessary) of another member of the review group. We will assess the risk of bias in the following domains: generation of allocation sequence, allocation concealment, blinding of study personnel and participants, blinding of outcome assessor, attrition, selective outcome reporting and other domains, including sponsorship bias. If adequate details of the trial assignment, withholding and other characteristics are not provided, the trial author may be contacted for further information. The risk of bias can be divided into low bias risk, high bias risk or uncertain bias risk. The overall bias risk of the study should be evaluated according to the influence of the bias risk items on the outcome indicators.

We will also assess the quality of evidence with the GRADE approach extended to network meta-analysis.[30] The GRADE approach leads to judgements about the confidence with which an estimate of treatment effect for a particular outcome can be believed, using four levels: high, moderate, low and very low. The GRADE framework characterises the quality of evidence in terms of study limitations, inconsistency, indirectness, imprecision and publication bias. For each component, the quality of the evidence can be maintained or downgraded by up to two levels, subject to a maximum downgrade by three levels (to very low quality) across the five components.

Statistical synthesis of study data

Characteristics of included studies and information flow in the network

It is necessary to generate descriptive statistics of the trials, and study population characteristics in all eligible trials, describing the type of comparison and some important variables, either clinical or methodological (eg, year of publication, mean age difference of subjects, gender, sponsorship and clinical setting, and journal of publication).

The available evidence will be presented in the network plot. The size of the nodes will reflect the amount of

evidence accumulated for each treatment (total number of patients), the width of each edge will be proportional to the inverse of the variance of the summary effect for each direct treatment comparison and the colour of each edge will represent the risk of bias (low, moderate or high, as defined in the Risk of bias and quality appraisal section).

Model implementation

We will perform all analyses within WinBUGS and StataSE 14. Our study will synthesise evidence through Bayesian network meta-analysis in a random effect model, and Markov Chain Monte Carlo sampling will be performed by using WinBUGS. We will check convergence evaluating the mixing of two chains, after discarding the first 10 000 iterations. Analyses for statistical evaluation of the inconsistency and production of network graphs and result figures will be carried out in Stata using the network command[31] and mvmeta command.[32]

Pairwise meta-analyses

In network meta-analysis, we will use group-level data. The binomial likelihood will be used for dichotomous outcomes and the normal likelihood for continuous outcomes. For all direct comparisons, when two or more RCTs are available, we will perform a conventional pairwise meta-analysis using a DerSimonian and Laird random effects model.[33] For dichotomous outcome indicators, the effect value RR will be used for evaluation, and for continuous outcome indicators, the SMD will be used for evaluation. The forest graph will show the effect value and 95% Credible interval (CrI).

Assessment of the transitivity assumption

The assumption of transitivity that indirect comparison validly estimates the unobserved head-to-head comparison cannot be tested statistically, but its plausibility can be evaluated conceptually and epidemiologically.[34] We will ensure that the treatment protocols as nodes are similar in terms of intervention settings, such as the type, duration and frequency of exercise. Also, some effect modifiers, such as gender distribution and age distribution of the study population, will be fully considered to improve transitivity.

Assessment of statistical heterogeneity and inconsistency

To evaluate the presence of heterogeneity and inconsistency in the entire network, we will use the I^2 statistic and visual inspection of the forest plots to assess heterogeneity in direct comparisons. The assumption of consistency that the direct and indirect estimates are in agreement is a prerequisite to calculating a valid mixed estimate.[34] We will apply the 'node-splitting' method suggested by Dias *et al*.[35]

Exploring heterogeneity and inconsistency and sensitivity analyses

We will evaluate the presence of clinical and methodological heterogeneity through subgroup and sensitivity analyses. We will explore whether treatment effects for the two primary outcomes are robust in subgroup analyses and network meta-regression using the following characteristics: (1) different diagnostic criteria for pre-diabetes: The group with IFG, the group with IGT,and the group with both (IFG and IGT); (2) duration of intervention: short-term intervention (≤3 months), medium-term intervention (3 months to 1 year), long-term intervention (≥1 year); (3) ethnicity: Asians versus non-Asians; (4) follow-up duration: ≤3 years vs ≥3 years. We will conduct sensitivity analyses on (1) only studies with reported RR and SD rather than imputed; (2) only studies with low risk of bias (as defined in the Risk of bias and quality appraisal section) and (3) only head-to-head studies. When the heterogeneity of the study is high and the cause can not be found by subgroup analysis or meta-regression, we will abandon the integration and conduct a descriptive analysis of the study.

Selection bias

We will search trial registry websites to identify completed trials not published elsewhere to minimise or identify publication bias. For all direct comparisons informed by 10 studies or more, we will assess small study effects using Harbord's test,[36] and we will use the comparison-adjusted and contour-enhanced funnel plots to investigate whether results in imprecise trials differ from those in more precise trials.

Network meta-analyses

The Markov Chain Monte Carlo method based on the Bayesian framework will be used for calculation and statistics, and WinBUGS will be used for implementation. For all outcomes, the analysis will generate RRs with 95% CrI as the summary measure. To estimate ranking probabilities, we will use the surface under the cumulative ranking curve and the mean ranks. In general, the largest contribution to each network estimate is provided by the respective direct evidence, but when direct evidence is missing or imprecise, more information is obtained indirectly. Therefore, to understand which are the most influential comparisons in the network and how direct and indirect evidence influences the final pooled data, we will use a contribution matrix that describes the percentage contribution of each direct meta-analysis to the overall body of evidence. All graphs will be implemented in StataSE 14.

Patient and public involvement

None.

Ethics and dissemination

This study does not involve a population-based intervention, and therefore, does not require ethical approval. We will publish the findings of this systematic review in a peer-reviewed scientific journal, and the dataset will be made available free of charge. The completed review will be disseminated electronically in print and on social media, where appropriate.

Contributors YZhong designed the study and drafted the protocol, designed and will conduct the literature search with YZhang; YC and HC will conduct the literature exclusion and assist with data extraction and analysis, and YZhong and YC will draft the results and discussion section. ML provided input to the work on the manuscript, designed the analysis plan and will conduct the statistical analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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