Low-level Laser Therapy in the Acceleration of Fixed Orthodontic Tooth Movement: Protocol for a Systematic Review and Network Meta-analysis

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Protocol

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Abstract

Background: Orthodontic treatment is a long-term therapy with time-related adverse effects. Low-level laser therapy (LLLT) has been used in the clinic as an intervention to accelerate orthodontic tooth movement (OTM) and prevent adverse effects. Previous systematic reviews have evaluated the effectiveness of LLLT in the acceleration of OTM. However, it remains unclear which treatment parameters are appropriate for LLLT. This review will evaluate the efficacy of LLLT on the acceleration of fixed OTM and the prevention of adverse effects.

Methods: Several electronic databases will be searched. Grey literature also will be retrieved. Parallel or clustered randomised controlled trials that evaluated the effectiveness of different LLLTs on the acceleration of fixed OTM will be included. Two researchers will independently screen all titles, abstracts, and full-text articles retrieval, as well as data extraction. The risk bias of each study will be appraised using the Cochrane Risk of Bias tool (RoB 2.0). The primary outcome will be the efficacy of LLLT on the acceleration of fixed OTM (e.g., canine movement distance, orthodontic treatment duration). Secondary outcomes will be the effectiveness of LLLT to reduce orthodontic adverse effects such as pain and root resorption. The mean difference (MD) and relative risk (RR) with corresponding 95% confidence intervals (CI) will be chosen as effective measures for continuous and binary outcomes, respectively. When feasible, both fixed and random-effects pairwise meta-analyses and frequentist network meta-analyses will be conducted.

Discussion: This network meta-analysis will compare the efficacy of LLLT on the acceleration of fixed OTM as well as whether LLLT can prevent adverse effects of this orthodontic treatment. By integrating the current evidence from direct and indirect comparisons and ranking all included interventions, our findings have the potential to help clinicians achieve more effective treatment goals.

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Background

Rationale

For aesthetics reasons, low-cost orthodontic treatment has become increasingly popular. However, orthodontic treatment requires a protracted period, usually two years or more [1]. Long-term therapy is a concern for patients who seek professional treatment [2]. In addition, patients have difficulty maintaining oral hygiene during long-term fixed orthodontic treatments, which can lead to adverse effects such as white spot lesions and caries [3, 4]. Researchers think there is a positive correlation between orthodontic treatment duration and root resorption [5, 6]. Therefore, it is essential to accelerate orthodontic tooth movement (OTM) and shorten therapeutic duration to reduce orthodontic adverse effects and achieve satisfactory results.

Many interventions have been used to accelerate OTM, including the local injection or systemic medications, such as hormones and growth factors, which can result in acceleration of tooth movement by altering bone remodeling [7–9]. Also, researchers have tried different surgical methods to accelerate OTM, such as corticotomy, periodontally accelerated osteogenic orthodontics (PAOO), and piezocision [10, 11, 12]. However, none of these methods is ideal and some may have adverse effects. The evidence that medications can accelerate OTM is not robust because the results were based on animal studies rather than human studies [13]. Invasive techniques accelerating OTM by surgical methods are expensive and have inevitable postoperative reactions such as pain, bleeding and swelling.

Low-level laser therapy (LLLT) has gained attention in orthodontics because it is less expensive, non-invasive, and is rarely accompanied by adverse effects. LLLT, a type of photobiomodulation therapy, is based on the principle of the Arndt–Schulz law which states, “a low dose of any substance or drug has a stimulating effect, whereas a higher dose has an inhibitory effect”. It has been demonstrated that LLLT can accelerate OTM by enhancing bone remodeling, collagen synthesis and revascularization through a variety of mechanisms, such as stimulating the proliferation and differentiation of osteoblasts, osteoclasts, fibroblasts, and periodontal ligament cells [14–16]. Furthermore, LLLT can prevent or alleviate several orthodontic adverse effects, such as root resorption and pain [16, 17]. Previous randomised clinical trials (RCTs) have explored the efficacy of LLLT on the acceleration of OTM with conflicting results because of different study designs, types of laser used, and laser treatment parameters.

Several systematic reviews (SRs) and meta-analyses have provided conflicting results about whether LLLT can accelerate OTM [18–20], and the current evidence for efficacy is insufficient. Due to the limitations of traditional meta-analysis, most existing evidence comes from head-to-head comparisons of LLLT with an untreated control group, limiting the possibility to compare distinct active interventions. Further, the effectiveness of different types of LLLT still is unclear. As a novel methodology, network meta-analysis (NMA) is able to synthesize data from both direct and indirect comparisons of different interventions and estimate the respective probabilities of treatment efficacy [21–24]. Until now, no NMA has been performed to investigate the efficacy of LLLT on the acceleration of OTM. We propose to conduct a systematic review and network meta-analysis to evaluate the efficacy of LLLT with different parameters on the acceleration of OTM in humans to provide a basis for clinical decision-making.

Objectives

The primary objective of this systematic review and network meta-analysis is to evaluate the efficacy of LLLT on the acceleration of fixed OTM. The secondary goal is to explore whether LLLT will reduce orthodontic adverse effects, such as pain and root resorption.

Methods

This review protocol will be conducted under the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and the PRISMA Extension Statement for Reporting

Systematic Reviews incorporating Network Meta-analyses [25, 26]. Detailed PRISMA-P is provided in **Additional file 1**.

Eligibility criteria

Patients

We will only include healthy patients who received fixed orthodontic treatment, regardless of age, sex, ethnicity, country, and socio-economic status. Patients will be excluded if they were influenced by diseases, such as periodontal disease, or cleft lip and palate, or by anti-inflammatory medications that may interfere with alveolar bone metabolism. In addition, patients who achieved tooth movement using a removable appliance or clear alignment will be excluded.

Intervention

We will include any kind of low-level laser therapy used as monotherapy for accelerating orthodontic tooth movement regardless of the type of laser, wavelength, energy density, power output, laser treatment intervals and length of follow-up. If studies included interventions using both LLLT and non-laser therapy, only the outcomes data for LLLT will be included. Utilization of non-laser interventions, whether combined with laser therapy or not, will be excluded.

Comparison

LLLT monotherapy will be compared to sham and non-laser treated groups.

Outcomes

Included studies must evaluate the effects of LLLT or comparisons with other treatment modalities on the speed of canine tooth movement and treatment duration without any restriction on the duration of follow-up. Any adverse effects reduced by LLLT will be recorded. All outcomes are defined in detail in the section “Outcomes and prioritisation.”

Study type

Only parallel or split-mouth design RCTs will be included. Non-randomised studies, case reports, non-clinical studies and reviews will be excluded.

Search methods for identification of studies

Language

Studies written in English or Chinese will be included. Other language articles will be included if full-text translation is available. We will provide an appendix table of articles that could not be included due to language, but which may be relevant to our research.

Electronic searches

The following electronic databases will be searched systematically to identify all relevant published studies: Cochrane Library (on cochranelibrary-wiley.com), PubMed(via http://pubmed.gov), Embase(via https://www.embase.com), China National Knowledge Infrastructure (CNKI) (https://www.cnki.net/), WanFang(http://www.wanfangdata.com.cn), VIP(http://www.cqvip.com) and Google Scholar OpenGrey and ProQuest Dissertations will be searched to include grey literature. Ongoing trials will be found in the US National Institutes of Health Ongoing Trials Register(via http://clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform(via apps.who.int/trialsearch). Finally, a manual search will be performed to screen relevant RCTs in the reference lists of relevant systematic and narrative reviews.

Search strategy

The search strategy will be designed according to the PICOS acronym (patient, intervention, comparison, outcomes, study type). Retrieval will be comprised of subject headings and free terms related to 'orthodontic', 'low-level laser therapy', 'tooth movement' or 'randomised controlled trial' (a proposed Embase search strategy is shown in **Additional file 2**).

Publication date will not be restricted. The search strategies will be peer-reviewed by an information specialist according to the 2015 Guideline Statement for the Peer Review of Electronic Search Strategies (PRESS) [27, 28] (**Additional file 3**).

Study records

Study selection

All records identified in the databases or through manual retrieval will be aggregated in the reference management software EndNote® X9 and duplicate articles will be removed.

First, the titles and abstracts from the search records of all specified databases will be screened, according to eligibility criteria. Thereafter, the full-text of articles will be obtained for any articles that potentially meet eligibility criteria. If necessary, authors of full-text studies will be contacted to seek more information to judge eligibility. Articles excluded by full-text screening will be listed with reasons in an appendix. Two authors will independently screen each article. Reviewers will not be blinded as there is evidence that the blinding of reviewers has little impact on the meta-analysis [29]. All discrepancies will be addressed by consensus or by a third assessor. The entire screening process will be presented in a PRISMA flow diagram (Fig. 1).

Data management

Two reviewers will extract data independently from each study using Microsoft Excel 2019 with a standardized form based on the Cochrane Consumers and Communication Review Group's data

extraction template [30] and the DECiMAL guide [31]. Authors will be contacted when any necessary information is missing or unclear. We will initially contact the corresponding author via email, with one additional email as reminder should there be no reply within two weeks. Thereafter, the other author will be contacted. All disagreements will be addressed by discussion and re-review of the article or consultation with a third reviewer. .

Multiple reports of the same study will be merged. Dichotomous data will be extracted from 2 × 2 tables and means and standard deviations for continuous data will be extracted from effect estimates, confidence intervals, and other forms of data. If outcome results were not provided directly and it is feasible, we will impute the data. From each study, the following data/information will be extracted [30-32]:

–Study characteristics (author name, year of publication, study design, number of groups, sample size, orthodontic treatment duration, withdrawals), randomisation (parallel or split-mouth design)

–Participant characteristics (age, sex, number of participants)

–Intervention and comparator details (type of laser, wavelength, energy density, power output, laser treatment intervals, length of follow-up)

–Outcome (primary and secondary outcomes). We will extract data at the group level and not use summary effects.

Outcomes and prioritization

The primary outcome used to reflect the speed of OTM will be mean difference (MD) of the distance of canine retraction measured in millimeters. Any evaluation method of the canine distalisation will be included (e.g., dental casts, three-dimensional models) [33-35]. Because the amount of canine retraction will increase with time, synthesising different durations of follow-up may not be appropriate. We will evaluate data by month as most studies set follow-up time points monthly [33-35].

The secondary outcome will be the effectiveness of LLLT in reducing orthodontic adverse effects such as pain and root resorption.

Both fixed and random effects models of the NMA will be conducted to synthesise all evidence for each outcome. The choice will depend on whether heterogeneity is significant [36]. Many studies use a split-mouth design in which each patient may receive more than one intervention. Data from treatment arms within these trials are no longer independent, so correlations between dependent arms must be considered statistically. Ignoring these correlations may lead to incorrect conclusions. So, we will apply novel statistical approaches to adjust weights for the dependent arms within split-mouth design trials [37].

A comprehensive ranking of all treatments (ranking probabilities, the surface under the cumulative ranking curve (SUCRA), and mean ranks) will be calculated for each outcome [38]. The estimated relative ranking of interventions will be generated based on primary outcomes. Only when we do not perform the NMA and SUCRA on the primary outcome shall we refer to the NMA and SUCRA results of the secondary outcome.

Geometry and feasibility of the network

We will explicitly describe the node-making process [39, 40]. The network of treatments will be judged based on the characteristics of the available studies and presented and evaluated graphically. We will evaluate the following: (1) if the network is disconnected; (2) if there are sufficient comparisons in the network with available direct data; (3) if there is a large number of comparisons in a single study; and (4) if any key intervention is missing. Next, the feasibility of the network meta-analysis will be assessed by checking: (1) transitivity (i.e., the comparable distribution of effect modifiers across comparisons), which will be examined using panels or percentages to visually inspect potential treatment effect modifiers [41]; (2) consistency between direct and indirect estimates of the effects, which will be examined using the node-splitting method [42], and globally (i.e., evaluating the network as a whole) using the design-by-treatment interaction model [43]; and (3) the extent of variability that can be attributed to heterogeneity and inconsistency rather than sampling error, by calculating the I^2 statistic [44].

We will include both two-arm trials and multi-arm trials, and those using different types of laser (i.e., CO2 laser and Ga-Al-As laser). Lasers with similar energy density will be analysed together and considered as the same treatment for all outcomes as no published literature has reported that the type of laser influences the OTM. Previous studies have shown that LLLT increases the rate of OTM in a dose-sensitive manner, so the energy density of the laser is the most important parameter that influences the OTM [45, 46]. We plan to divide data into groups according to energy density, such as a minor group (group1: 10J/cm^2/point), a medium group (group2: 20J/cm^2/point), and a high group (group3: ≥20J/cm^2/point). We will not distinguish sham and non-laser treatment groups but will merge them for global analysis of each outcome.

Risk of bias in individual studies

Two reviewers will independently assess the risk of bias for each study according to version 2 of the Cochrane risk-of-bias tool (RoB2) for randomized trials in section 8.2 of the Cochrane Handbook for Systematic Reviews of Interventions and in section 3.5 of Chaimani's study [47, 48]. All disagreements will be addressed by discussion or by a third reviewer. We will assess the following domains as 'low', 'unclear', or 'high' risk of bias:

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data

- Bias in measurement of the outcome
- Bias in selection of the reported result

We will report these assessments in a 'Risk of bias' table for each study and will provide detailed reasons for judgments of each domain in additional materials. The overall risk-of-bias judgement for the primary outcome will be summarised following Table 8.2.b in the Cochrane Handbook for Systematic Reviews of Interventions [47].

- Low risk of bias (the trial is judged to be at low risk of bias for all domains for this result).
- Some concerns (the trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain).
- High risk of bias (the trial is judged to be at high risk of bias in at least one domain for this result or the trial is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result).

Statistical analysis

The contrast-level NMA model will be employed by multivariate meta-analysis (commands network meta and mvmeta) in software STATA (version 16, Stata Corp, College Station, TX, USA) within a frequentist framework [24, 48, 49]. In the NMA, the between-study variance will be estimated by the restricted maximum likelihood method [50]. We intend to perform both traditional pairwise meta-analyses and NMA. If NMA is not appropriate due to significant global inconsistency or other conditions, only pairwise meta-analyses will be conducted. If a pairwise meta-analysis is also impossible, outcomes will be summarized narratively. All the outcomes of continuous and dichotomous data will be presented as MDs and RRs with 95% CIs.

An assumed network plot is presented to show the maximum number of interventions that can be compared (Fig. 2). The rank of each intervention among all interventions of each outcome will be assessed using plots of the treatment rank probabilities.

Unit of analysis

The participants will be the unit of analysis of the NMA. If both split-mouth design studies and randomised studies are included in the same analysis, we will calculate the effective sample sizes of cluster-randomised trials under the guidance of section 23.1 of the Cochrane Handbook for Systematic Reviews of Interventions [47, 51].

Dealing with missing data

We will try to contact the authors of studies if any potentially useful data are unclear or missing. Graphical software will be applied to obtain data which are presented only in figures. We will refer to the

suggestions in section 10.12 of the Cochrane Handbook for Systematic Reviews of Interventions when missing data are unavailable [47].

Assessment of statistical heterogeneity

For the traditional pairwise comparisons, we will assess the statistical heterogeneity between studies using the I^2 statistic. An I^2 value of 0% to 40% is not a concern; 30 to 60% may represent moderate heterogeneity; 50 to 90% may represent substantial heterogeneity; and 75 to 100% represents considerable heterogeneity, per section 10.10 of the Cochrane Handbook for Systematic Reviews of Interventions [47]. In the NMA, we will assume that the standard heterogeneity variance (τ^2) is constant across the different comparisons based on frequentist models [52]. If substantial heterogeneity is confirmed, we will explore heterogeneity by subgroup analyses or meta-regression [47].

Assessment of transitivity and similarity

The assumptions of transitivity (or similarity) will be judged based on clinical and methodological characteristics. We will assume that intervention effects are transitive in this network meta-analysis, and we will investigate transitivity based on clinical characteristics, such as the similar condition of patients (age, male-female ratio), and similar kind of OTM (force, visit frequency) at baseline. All potential modifiers will be investigated and reported before the network meta-analysis is carried out.

Assessment of inconsistency

We will assess consistency between direct and indirect data using three approaches: loop, design-by-treatment interaction, and node/sidesplitting [42, 43, 53-57]. First, global consistency will be examined by assessing the network as a whole employing the design-by treatment interaction model [43]. Second, when there is a loop containing three or more interventions, the loop-specific method will be applied to examine local consistency [55, 57]. Third, we will use the node-splitting method to calculate the inconsistency of the model, which separates evidence based on a particular treatment contrast into direct and indirect evidence [58].

Assessment of reporting biases

If there are ten or more studies in a meta-analysis, we will investigate reporting biases using funnel plots. The asymmetry of funnel plot will be judged by visual evaluation and statistical tests. Different tests will be employed for continuous and dichotomous variables [57, 58]. If asymmetry is detected in any of these tests, we will perform further analyses to explore it.

Subgroup and sensitivity analysis

Intervention effects vary with different populations or intervention characteristics. To make our review results robust, we plan to conduct subgroup analyses for the primary outcome which may include subsets according to age (adolescents/adults), and frequency of intervention. If heterogeneity is still

substantial after subgroup meta-analyses, we will perform sensitivity analyses by excluding studies with high risk of bias.

Assessing the quality of the evidence

We will consult the literature on GRADE for network meta-analyses quality evaluation and use the GRADE approach to generate a 'Summary of Findings' table [59-60].

Discussion

Strengths and limitations

This review will assess the effectiveness of different low-level laser therapies (especially different energy density) in the acceleration of fixed orthodontic tooth movement. Although several pairwise meta-analyses have been published, it still unknown which is the most appropriate parameter for LLLT to achieve OTM acceleration. To the best of our knowledge, this will be the first comprehensive systematic review incorporating network meta-analysis by using direct and indirect evidence to explore this topic.

Our review will have many strengths including: (I) the retrieval of a broader range of electronic databases in combination with a manual search; (II) the predetermined systematic process of screening, data extraction, and quality judgement by 2–3 experienced independent assessors; (III) a transparent reporting of description of interventions for consistent node decision making. Potential limitations and challenges are: (I) language restriction to English and Chinese which may lead to language or cultural bias; (II) potential limitations of study methodology (clinical heterogeneity, poor quality in reporting); (III) limitations of review level (a lack of available treatment comparisons to build robust nodes, the network unable to cover all the interventions in all outcomes).

Amendments

Any important amendments (such as nodes decision, results reporting) made to the current protocol will be published as a supplement in the final manuscript. We will disseminate the results of the NMA: we will publish the findings in a scientific journal, present them at scientific conferences, and provide dissemination meetings with key stakeholders, including policymakers and healthcare providers.

Abbreviations

CI: confidence intervals;

LLLT: Low-level laser therapy;

MD: mean difference;

NMA: Network meta-analysis;

OTM: orthodontic tooth movement;

PAOO: periodontally accelerated osteogenic orthodontics;

PRISMA-P: The Preferred Reporting Items for Systematic Review and Meta-analysis Protocols;

RR: relative risk;

SUCRA: Surface under the cumulative ranking curve.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All the data generated or analyzed during the study will be included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

ZYG, LJZ, CF contributed equally to this study. ZYG, LJZ, CF and XZZ conceived the study. ZYG, LJZ, and CF developed search strategies. ZYG and CF wrote the first draft. XC, KFH, XW, SXL, JXZ and XZZ revised the draft.. All authors approve the publication of this protocol.

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Figures

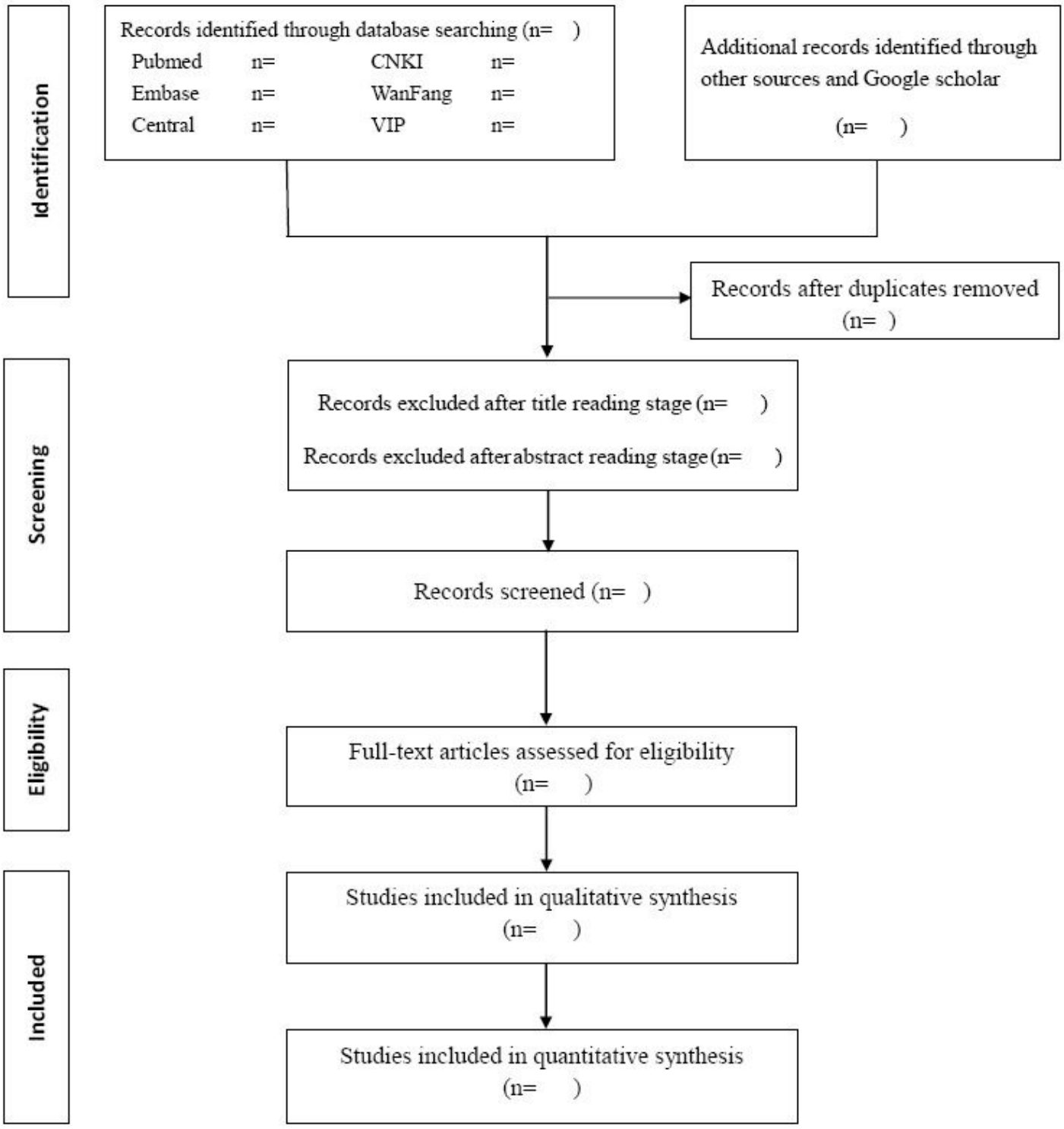

Figure 1

PRISMA flow program for study selection of this systematic review and network meta-analysis

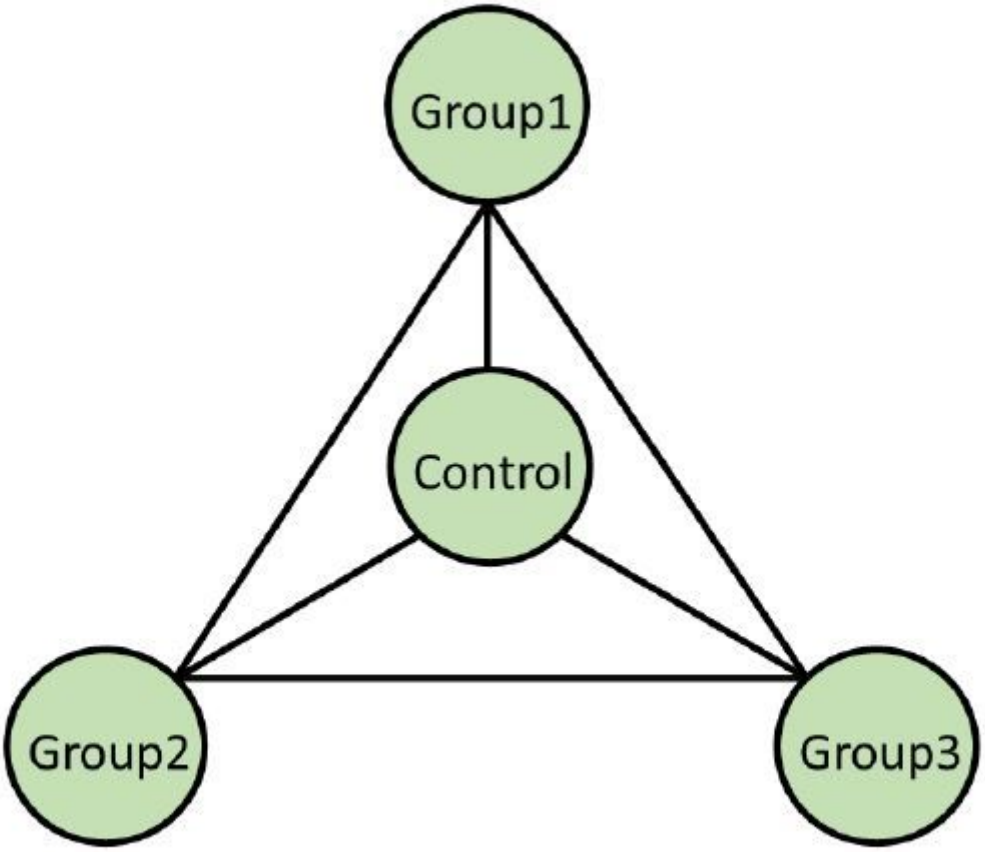

Figure 2

The network plot of all possible direct comparisons between the eligible interventions

Supplementary Files

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- Additionalfile1PRISMAPchecklist.pdf
- Additionalfile2Embasesearchstrategy.pdf
- Additionalfile3PRESS.pdf