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Effectiveness of non-pharmacological strategies in management of type 2 diabetes in primary care: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction: Despite the increasing number of drugs and various guidelines on the management of type 2 diabetes (T2DM), many patients continue with the disease uncontrolled. There are several non-pharmacological treatments available for managing T2DM, but many them have never been compared directly to determine the best strategies. **Objective:** This study will evaluate the comparative effectiveness of non-pharmacological strategies in the management of T2DM in primary care or community settings. **Methods and Analysis**: We will perform a systematic review and network meta-analysis (NMA), and will include randomized controlled trials if one of the following interventions were applied in adult patients with T2DM: nutritional therapy, physical activity, psychological interventions, social interventions, multidisciplinary lifestyle interventions, diabetes self-management education and support (DSMES), technology-enabled DSMES, interventions delivered only either by pharmacists or by nurses, self-blood glucose monitoring in non-insulin-treated T2DM, health coaching, benchmarking, and conventional management of T2DM. The primary outcome will be glycemic control (glycated hemoglobin (HbA1c) (%)), and the secondary outcomes will be weight loss, quality of life, patient satisfaction, frequency of cardiovascular events and deaths, number of patients in each group with HbA1c <7, adverse events, medication adherence. Four general and adaptive search strategies have been created for Embase, Medline, Latin American and Caribbean Health Sciences Literature (LILACS) and Cochrane Central Register of Controlled Trials (CENTRAL). Four reviewers will assess studies for their eligibility and their risk of bias in pairs and independently, as well as will extract data from included studies. We will conduct an NMA using a Bayesian hierarchical model, and will obtain the treatment hierarchy using the surface under the cumulative ranking (SUCRA) curve. To determine our confidence in an overall treatment ranking from the

NMA we will follow the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Ethics Dissemination: As no primary data collection will be undertaken, no formal ethical assessment is required. We plan to present the results of this systematic review in a peer-reviewed scientific journal, conferences and the popular press.

Registration Number: Our systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) on _____2019 (registration number_____).

Key words: diabetes mellitus type 2, primary health care, systematic review, network meta-analysis.

Strengths and limitations of this study:

- This is the first NMA in the field, and our results can help health managers to implement non-pharmacological strategies in diabetes management in primary care.
- We will apply the GRADE approach to evaluate our confidence in an overall treatment ranking from the NMA.
- Bias due to deviations from intended interventions and due to missing outcome data may be the main limitations of the study.
- As the primary outcome selected is a surrogate endpoint, the quality of evidence according to GRADE approach will be probably low.

INTRODUCTION

Diabetes mellitus (DM) is an important challenge in public health, not only due to their high morbidity and mortality but also to the direct and indirect expenses associated with their treatment.[1] In addition, the number of individuals with this dysglycaemia is continuously increasing along with the high prevalence of obesity.

In 2015, the International Diabetes Federation (IDF) estimated that 8.8% (uncertainty interval: 7.2 to 11.4) of the world population aged between 20 and 79 (including 415 million people) lived with diabetes and 5.0 million deaths were attributable to diabetes.[2] For 2040, the IDF has estimated that 642 million adult people (uncertainty interval: 521 to 829 million) will have diabetes (global estimate prevalence of 10.4%).[2]

Type 2 diabetes (T2DM) accounts for 90 to 95% of all cases of diabetes, and usually affects individuals from the fourth decade of life, although in some countries there is an increase in its incidence in children and young people.[3]

The most relevant risk factor for complications related to T2DM is inadequate glycaemic control.[4] Prospective studies have evidenced an association between degree of hyperglycemia and increased risk of micro and macrovascular complications in patients with T2DM.[5]

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that in patients with T2DM an intensive blood glucose control, a median HbA1C level of 7.0% in comparison with a median level of 7.9%, was associated with a significant reduction in the incidence of microvascular complications.[6] In addition, each 1% reduction in updated mean HbA1c was associated with reductions in risk of 14% for myocardial

infarction (95% confidence interval (CI) 8% to 21%) and 21% for deaths related to diabetes (95% CI 15% to 27%). [5]

Despite the increasing number of drugs available and various guidelines on the management of T2DM, an expressive number of patients continue with the disease uncontrolled. In a multicenter, cross-sectional, epidemiological, questionnaire-based study conducted in nine Latin American countries, 56.8% of patients T2DM had poor glycaemic control (HbA1c ≥7%).[7] The highest prevalence of unsuccessful treatment was in Peru, were only 7.5% achieved metabolic and blood pressure levels as recommended by the American Diabetes Association (ADA).[8] In the United State, according to a survey performed between 1998 and 2002, only 42.3% of adults had HbA1c levels less than 7%, and 14% had HbA1c 10% or more. [9]

It is believed that this discrepancy between the large number of tools to treat these patients and the low frequency of diabetes control is due to knowledge gaps, attitudes and practices related to diabetes by patients and physicians who treat these individuals.[10]

Therefore, in order to increase the percentage of diabetic patients with the disease controlled and thereby reduce the number of deaths and morbidities related to this disease, it has been studied the effectiveness of new strategies to help patients to control their disease. These measures are complementary to the pharmacological treatment, and its main objective is for patients to recognize the importance of self-management and full involvement to treat their condition.[10 11]

The Innovative Care for Chronic Conditions framework advocated by the IDF has divided these interventions in the treatment of diabetes into three spheres: macro (policy and funding), meso (health and community organization) and micro (patient and family).[11]

In the micro sphere, studies in T2DM have shown that programs focused on counseling, therapy compliance, explanation of possible adverse events, patient empowerment are associated with better glycemic and quality-of-life controls, and, consequently, lower follow-up costs.[10-13].

Although several systematic reviews have evaluated the effectiveness of these strategies in the management of T2DM, [8,14] no NMAs were found that compared multiple interventions simultaneously in a single model.

The objective of this review is to evaluate the comparative effectiveness of non-pharmacological strategies in the management of T2DM in primary care or community settings. We aim to asses all types of non-pharmacological interventions targeting a greater commitment from patients in the control of T2DM.

METHODS AND DESIGN

This systematic review and network NMA protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number:), and it was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for protocols (PRISMA-P).[15]

Patient and Public Involvement

We will not directly include patient-level data in this study, but the protocol development, priority of the research question, choice of outcome measures, and type of intervention were informed by discussions with members of the Brazilian Health Ministry which identified this research as being a priority area for managing patients with T2DM in primary health care.

Eligibility Criteria

We will include randomized controlled trials (RCTs) if one or more interventions (described below) were applied in adult patients, over 18 years of age, with a diagnosis of T2DM according to ADA [12]. Comparator will be considered a conventional management of T2DM (drug treatment associated with a general orientation regarding lifestyle changes provided by a general practitioner) or another intervention.

Definitions of interventions

We will consider as intervention all non-pharmacological and patient-mediated strategies [16] that are complementary to the drug treatment of T2DM, and whose main objective was to promote in diabetic patients a greater commitment to this condition and consequently a better control of their disease.

Based on our previous search in the literature, the interventions may be (1) nutritional therapy (dietary quality or energy restriction), [17] (2) physical activity program (running, walking, bicycling, swimming, resistance training, yoga, Tai chi, many others), [17] (3) psychological interventions (emotion-focused or cognition-focused),[18] (4) social network interventions (friends, families and peers),[19] (5) multidisciplinary lifestyle interventions (an intervention that combines at least two of the following modalities: physical activity, nutrition therapy, social or psychological support),[20] (6) diabetes self-management education and support (DSMES),[21] (7) technology-enabled DSMES (mobile phones, secure messaging, web-based information), [22](8) interventions delivered only or mainly by pharmacists (DSMES and/or pharmacy management), [23] (9) interventions delivered only or mainly by nurses (DSMES and/or pharmacy management), [24] (10) self-blood glucose monitoring in non-insulin-treated T2DM, [25] (11) health coaching, [26], (12) benchmarking. [27]

The intervention must have been performed at primary care (or in community settings), with minimum period of three months.

An evaluation with a nutritionist, nurse, physical trainer, psychologist or educator in diabetes, which provides a general orientation regarding lifestyle changes will be considered conventional treatment if the patients are not provided with subsequent follow-up.

Type of outcomes

The primary outcome will be glycemic control (HbA1c (%)). The secondary outcomes will be weight loss (measured by weight or waist circumference, or body mass index (BMI)), quality of life, patient satisfaction, frequency of cardiovascular events and deaths, number of patients in each group with HbA1c <7, adverse events related to non-pharmacological strategies, medication adherence.

Time of outcome evaluation

The outcomes will be evaluated at 6, 12, and more than 12 months. For trials with outcomes within these time-points we will consider the closest time-point, and for those who had more than one time of outcome evaluation, we will consider the longest time-point.

Exclusion Criteria

We will exclude trials conducted in other scenarios than primary care or community sittings, trials whose aim was to compare the effectiveness of pharmacological treatments, trials in which the intervention was any type of surgery to lose weight, trials with follow-up inferior to six months and trials that included predominantly participants with secondary diabetes, type 1 DM, or gestational diabetes.

Data sources and search strategy

Four search strategies will be created and will be adapted to electronic health databases: Embase (by Elsevier, 1980-2019), Medline (by PubMed, 1966-2019), LILACS (by Virtual Health Library, 1982-2019) and Controlled Clinical Trials of the Cochrane Collaboration (CENTRAL - Cochrane). The terms and synonyms of T2DM and primary health care will be used. There will be no language or year restriction. We will use the validated RCT filters created by the Cochrane Collaboration for Medline and Embase. A draft Medline search strategy is included in Appendix 1.

The following databases will also be searched for eligible studies: Trip database, SCOPUS, Web of Science, CINAHL, Australasian Medical Index, Chinese Biomedical Literature Database. We will also search for studies on ClinicalTrials.gov, and the gray literature, through conferences, abstracts published and dissertations.

References of relevant primary or secondary studies will be searched in order to identify additional eligible studies. We will use the Endnote software to download all references and remove duplicates. The initial screening of abstracts and titles will be performed using the software Rayyan QCRI.

Study selection

Four reviewers independently will perform in pairs the assessment of titles and abstracts (RGOFL, LRB, JSCG, VSNN), and the studies potentially eligible for the inclusion in the review will be selected for full reading and subsequently assessed for adequacy to the eligibility criteria. In case of disagreement, there will be a consensus meeting before the final decision.

Data extraction

For each selected trial, two reviewers will use an extraction form to record the year of publication, number of patients included, duration of follow-up, information regarding the inclusion and exclusion criteria, type of intervention (frequency, descriptions, durations), baseline data (average age, gender, weight, BMI and WC, glycemic control prior to the study, duration of T2DM, medications in use), and all reported outcome measures (in all time points). To ensure consistency between reviewers, we will perform a calibration exercise before beginning the review. In the case of duplicate publications or more reports from the primary trial, data extraction will be optimized using the best information available for all the items in the same trial.

Assessment of bias risk in included studies

For each selected trial, the risk of bias will be assessed according to the criteria described in the revised Cochrane risk-of-bias tool for randomized trials (RoB 2 tool),[28] which considers for each outcome evaluated five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, (5) bias in selection of the reported result. Each of the items will be evaluated by two reviewers as having low risk of bias, some concerns, and high risk of bias. In case of disagreement, there will be a discussion between the reviewers before the final classification.

Data synthesis

Dealing with missing data

The authors of the original studies will be contacted, if necessary, to provide missing information for each study included. We will use the data available in published articles provided by their authors or registration platforms. If available, we will preferentially use the data from intention-to-treat analysis. If numerical outcome data are

missing and they cannot be obtained from the authors, we will calculate them, when possible, from other available statistics, such as p values. [29] If an outcome value is reported without a measure of variance, standard deviations (SDs) will be imputed according to the method suggested by Furukawa et al. [30]

Assessment of transitivity across treatment comparisons

The transitivity across treatment comparisons will be assessed using boxplots, and we are proposing seven a priori hypotheses to explain variability between studies as possible effect modifiers: (1) patient characteristics (average patient age, gender distribution, disease severity, time of diabetes diagnosis, presence of diabetes chronic complications), (2) type of pharmacological treatment of T2DM, (3) study methodology quality (low risk of bias compared with high risk of bias), sample size (large versus small studies), (4) duration of follow-up (6-12 months, more than 12 months), (5) frequency of sessions/visits with participants, (6) medication adherence, (7) adherence to a healthier lifestyle. Conventional management of T2DM will be assessed for their similarity across treatment comparisons. [31]

Methods for direct and indirect or mixed treatment comparisons

We will perform an NMA for each outcome to compare multiple interventions simultaneously in a single model.

We will preferentially pool the direct evidence, however, in the absence of direct comparisons, the effect estimate will be provided by indirect comparisons.

Considering the expected between-study heterogeneity, we will use a random-effects (RE) model for each intervention comparison.

We will pool the data of each outcome using a Bayesian RE model separately. For dichotomous data, effect estimates will be calculated using odds ratio (OR) with a 95% credible interval (CrIs). The continuous data will be expressed as means and SDs for each study, and the mean difference or standardized mean difference (if different metrics are used across studies) will be calculated with their respective 95% CrIs. For count outcomes, we will calculate the rate ratio with a 95% Crl. For multi-arm studies, we plan to use data from all reported comparisons using the approach suggested by Rucker et al by reducing the relevant weighting scheme.[32]

The intervention effect estimates will be presented along with their corresponding 95% Crls, and we will obtain the treatment hierarchy using the surface under the cumulative ranking (SUCRA) curve, with its 95% Crl, and the rank-heat plot. [33] [34]It is expected that the best treatment will have high SUCRA values while the worst will have low values. For each comparison, we will present the direct, indirect, and network estimates.

Assessment of statistical heterogeneity

For direct evidence, we will assess heterogeneity by estimating the magnitude of the between-study variance using the empirical distribution as estimated by Turner et al. [35] and Rhodes et al. [36], and by using the I^2 statistic to quantify the percentage of variability that is due to true differences between studies rather than sampling error. [37] [38]. We will interpret the I^2 according to thresholds set forth by the Cochrane Collaboration [29], and it will be used as a criterion for pooling or not the results and for performing additional subgroup analyses. For count outcomes, we will use a minimally informative prior distribution ($\sim$ Uniform(0,2)).[39]

If enough studies are available, we will perform subgroup analysis using the same potential treatment effect modifiers described above. Our a priori hypothesis will be individuals with longer time of T2DM, taking insulin, with a poorly controlled diabetes at baseline (an uninterrupted HbA1c >8.0% for ≥*1* year despite standard care) and with more chronic diabetes complications subgroups may show less improvement in the primary and secondary outcomes. We will also perform a network meta-regression whenever possible (i.e., when at least 10 studies are available) using the random-effects model to evaluate the impact of these potential effect modifiers (patient characteristic, study quality, intervention type, follow up time, adherence).

In the combination of direct and indirect estimates, violation of the transitivity assumption (described above) will also lead to inconsistency. We will assess loop inconsistency (disagreement between direct and indirect estimates) using the loop-specific method, and design inconsistency (disagreement between studies that inform the same treatment comparison but include a different number of treatment arms) using the design-by-treatment model based on a chi^2 test. [40-43] .

Sensitivity analysis

If sufficient studies are available, we will conduct a sensitivity analysis to assess the robustness of results. [35 36]. We will assess the effect of excluding studies with high risk of selection and attrition bias, and studies with imputed data.

Assessment of publication biases

For each treatment comparison , if more than 10 studies are included in the meta-analysis, we will use the funnel plot to investigate the presence of publication bias. [29] In such cases, we will also perform the Begg's rank correlation [44] and Egger's regression tests [45].

Quality of evidence

To determine our confidence in an overall treatment ranking from the NMA we will follow the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, with some modifications as described below in order to reflect specific issues from NMA.[46] This process will be performed in pairs and independently (RGOFL, LRB, JSCG, VSNN).

Based on the five categories (risk of bias, imprecision, inconsistency and publication bias) the certainty of evidence of effect estimates obtained by direct comparisons will be rated as high, moderate, low, or very low.

For indirect comparisons, the quality of evidence in estimates will be rated following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. We will focus our assessments on quality of indirect evidence on the dominant first-order loop (loops with a single common comparator connecting the two interventions of the comparison of interest). The quality of evidence rating for indirect comparisons will be the lower of the ratings of quality for the two direct estimates that contribute to the first order loop of the indirect comparison. For instance, if one of the direct comparisons will be rated as low and the other will be rated as moderate evidence, we will rate the quality of indirect evidence as low [45]. We will rate down the quality of the indirect comparison one further level for violation of the transitivity assumption (similarity of trials in terms of population, intervention (type and dosing frequency), settings, and trial methodology) [45].

We will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidences are present. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have

inconsistency (measured by the difference of point estimates and the extent of overlap of CrIs and of direct and indirect effect estimates).

DISCUSSION

The continuously increasing prevalence of T2DM together the unsatisfactory glycemic control by some individuals justify the search for new and effective strategies for the prevention and control of this metabolic disease.

Since inadequate glycemic control in DM is most often related to poor adherence to lifestyle changes and to the proposed treatment, initiatives have emerged to promote a better acceptance / understanding of the disease and its treatment by the patients. With this is expected that individuals have a more active participation in the control of his disease, and thus to achieve higher rates of glycemic control and fewer complications associated with this dysglycemia.

Since there are several different strategies for this purpose, we aim to answer the following question: what is the effectiveness of non-pharmacological strategies in the primary health care in promote in patients with T2DM a greater commitment of this condition and consequently a better control of their disease? The answer to this question may assist health managers in implementing these actions in primary care settings.

To the best of our knowledge to date, there is no systematic review and NMA considering the direct and indirect effect of non-pharmacological interventions targeting a greater commitment from patients in the control of T2DM.

ETHICS DISSEMINATION

As no primary data collection will be undertaken, no formal ethical assessment is required by our institution. We plan to present the findings of this systematic review in a peer-reviewed scientific journal. We also intend to present it, including preliminary findings, at the appropriate conferences.

Authors' contributions:

VSNN, LT and AAV conceptualized and design the study. LT, RGOFL, AAV and VSNN draft the manuscript protocol. VSNN, RGOFL, LRB, ALM, JSCG, AAV and LT critically revised the protocol and manuscript submitted. All authors read and approved the final manuscript.

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There are no competing interests.

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APPENDIX 1

#1 "Diabetes Mellitus, Type 2"[Mesh] OR (Diabetes Mellitus, Noninsulin-Dependent) OR (Diabetes Mellitus, Ketosis Resistant) OR (Ketosis-Resistant Diabetes Mellitus) OR (Diabetes Mellitus, Non Insulin Dependent) OR (Diabetes Mellitus, Non-Insulin-Dependent) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Diabetes Mellitus, Stable) OR (Stable Diabetes Mellitus) OR (Diabetes Mellitus, Type II) OR(NIDDM) OR (Diabetes Mellitus, Noninsulin Dependent) OR (Diabetes Mellitus, Maturity-Onset) OR (Diabetes Mellitus, Maturity Onset) OR (Maturity-Onset Diabetes Mellitus) OR (Maturity Onset Diabetes Mellitus) OR (MODY) OR (Diabetes Mellitus, Slow-Onset) OR (Diabetes Mellitus, Slow Onset) OR (Slow-Onset Diabetes Mellitus) OR (Type 2 Diabetes Mellitus) OR (Noninsulin-Dependent Diabetes Mellitus) OR (Noninsulin Dependent Diabetes Mellitus) OR (Maturity-Onset Diabetes) OR (Diabetes, Maturity-Onset) OR (Maturity Onset Diabetes) OR (Type 2 Diabetes) OR (Diabetes, Type 2) OR (Diabetes Mellitus, Adult-Onset) OR (Adult-Onset Diabetes Mellitus) OR (Diabetes Mellitus, Adult Onset)

#2 "Primary Health Care"[Mesh] OR (Care, Primary Health) OR (Health Care, Primary) OR (Primary Healthcare) OR (Healthcare, Primary) OR (Primary Care) OR (Care, Primary) or "Physicians, Primary Care"[Mesh] OR (Physician, Primary Care) OR (Primary Care Physician) OR (Primary Care Physicians) OR (Healthy Primary Care) OR "Primary Care Nursing"[Mesh] OR (Care Nursing, Primary) OR (Nursing, Primary Care)

#3 "Community Health Planning"[Mesh] OR (Community Health Plannings) OR (Health Planning, Community) OR (Health Plannings, Community) OR (Planning, Community Health) OR (Plannings, Community Health) OR (Population-Based Planning) OR (Planning, Population-Based) OR (Plannings, Population-Based) OR (Population Based Planning) OR (Population-Based Plannings) OR (Community Health Systems) OR (Community Health System) OR (Health System, Community) OR (Health Systems, Community) OR (System, Community Health) OR (Systems, Community Health)

#4* randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])

#1 AND #2 AND #3 AND #4

* Direct link to PubMed with **sensitivity- and precision-maximizing version**(2008 revision). [1] Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from **www.cochrane-handbook.org**

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-8
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	6-8

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp. Data
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-13
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

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Effectiveness of non-pharmacological strategies in the management of type 2 diabetes in primary care: a protocol for a systematic review and network meta-analysis

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Effectiveness of non-pharmacological strategies in the management of type 2 diabetes in primary care: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction: Despite the increasing number of drugs and various guidelines on the management of type 2 diabetes mellitus (T2DM), several patients continue with the disease uncontrolled. There are several non-pharmacological treatments available for managing T2DM, but various of them have never been compared directly to determine the best strategies.

Objective: This study will evaluate the comparative effects of non-pharmacological strategies in the management of T2DM in primary care or community settings.

Methods and Analysis: We will perform a systematic review and network meta-analysis (NMA), and will include randomized controlled trials if one of the following interventions were applied in adult patients with T2DM: nutritional therapy, physical activity, psychological interventions, social interventions, multidisciplinary lifestyle interventions, diabetes self-management education and support (DSMES), technology-enabled DSMES, interventions delivered only either by pharmacists or by nurses, self-blood glucose monitoring in non-insulin-treated T2DM, health coaching, benchmarking, and usual care. The primary outcome will be glycemic control (glycated hemoglobin [HbA1c] [%]), and the secondary outcomes will be weight loss, quality of life, patient satisfaction, frequency of cardiovascular events and deaths, number of patients in each group with HbA1c <7, adverse events, and medication adherence. We have developed search strategies for Embase, Medline, Latin American and Caribbean Health Sciences Literature, Cochrane Central Register of Controlled Trials, Trip database, Scopus, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Australasian Medical Index, and Chinese Biomedical Literature Database. Four reviewers will assess the studies for their eligibility and their risk of bias in pairs and independently. An NMA will be performed using a Bayesian hierarchical model, and the treatment

hierarchy will be obtained using the surface under the cumulative ranking curve. To determine our confidence in an overall treatment ranking from the NMA, we will follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Ethics and Dissemination: As no primary data collection will be undertaken, no formal ethical assessment is required. We plan to present the results of this systematic review in a peer-reviewed scientific journal, conferences, and the popular press.

Prospero Registration Number: Our systematic review protocol has been registered with the International Prospective Register of Systematic Reviews on October 30, 2019 (registration number CRD42019127856).

Key words: diabetes mellitus type 2, primary health care, systematic review, network meta-analysis.

Strengths and limitations of this study:

- Network meta-analysis (NMA) allows the simultaneous comparison of multiple treatment alternatives in a single model.
- NMA improves precision of treatment effect estimates, ranks treatments according to their effectiveness, and can assess the impact of observed treatment effects in the evidence network.
- A potential limitation of this study can be missing outcome data, which may bias our findings. In such a case, valid imputation methods will be applied and robustness of results will be explored.
- Intransitivity in indirect comparisons may be another potential limitation, which can impact the validity of our NMA results. In case of intransitivity, reasons for this will be explored.

INTRODUCTION

Despite the increasing number of drugs available and various guidelines on the management of type 2 diabetes mellitus (T2DM), an expressive number of patients continue with the disease uncontrolled. In a multicenter, cross-sectional, epidemiological, questionnaire-based study conducted in nine Latin American countries, 56.8% of patients with T2DM had poor glycemic control (hemoglobin A1c [HbA1c] ≥7%).[1] In the United State, according to a survey performed between 1998 and 2002, only 42.3% of adults had HbA1c levels less than 7%, and 14% had HbA1c levels greater than 10%.[2]

Therefore, to increase the percentage of diabetic patients with the disease controlled and thereby reduce the number of deaths and morbidities related to this disease, non-pharmacological strategies that are complementary to the drug treatment have been studied in the management of T2DM.

Randomized clinical trials (RCTs) have shown that medical nutritional therapy and physical activity, considered as non-pharmacological treatments of T2DM, effectively improve glycemic control and other metabolic outcomes in patients with T2DM.[3] [4] Additionally, a systematic review of lifestyle weight loss interventions in overweight and obese adults with T2DM showed that a weight loss of >5% is considered necessary for its beneficial effects on HbA1c, lipids, and blood pressure, and to achieve this level of weight loss, intense interventions, including energy restriction, regular physical activity, and frequent contact with healthcare professionals, are required.[5]

Meanwhile, other non-pharmacological strategies have been introduced in diabetes treatment. Some studies in T2DM have shown that programs focused on counseling, therapy compliance, explanation of possible adverse events, and patient empowerment are associated with better glycemic and quality-of-life controls and,

consequently, lower follow-up costs.[6-9] A systematic review of the effects of group-based, patient-centered training on clinical, lifestyle, and psychosocial outcomes in patients with T2DM showed significant reductions in HbA1c in favor of group-based interventions.[10] Similarly, other strategies with similar objectives have also been reported in the management of T2DM, such as psychological[11] and social interventions.[12]

However, despite the evidence of effectiveness of these non-pharmacological strategies in T2DM metabolic control, in primary healthcare settings, some RCTs have not achieved similar results.[13-15] In a pragmatic clustered randomized controlled trial conducted in public community health centers in Cape Town involving 1,570 adults with T2DM, a group diabetes education program did not show greater improvement in glycemia control compared with usual care.[16]

Since there are several different non-pharmacological strategies for the management of T2DM and with contradictory results in some healthcare settings, we aim to answer the following questions: In primary care, are the non-pharmacological strategies effective in the glycemic control of adults with T2DM? Which of these strategies have the best glycemic control?

Hence, the objective of this study is to evaluate the comparative effects of non-pharmacological strategies in the management of T2DM in primary care or community settings.

METHODS AND DESIGN

A systematic review and network meta-analysis (NMA) for the assessment of the effectiveness of all non-pharmacological strategies available for T2DM in diabetes control will be performed.

NMA combines direct and indirect evidence; therefore, the relative effectiveness of two non-pharmacological strategies can be estimated even if studies that directly compared them did not exist.

Denoting nutritional therapy, social support, and usual care as non-pharmacological strategies A, B, and C, respectively, an indirect comparison (AB) can be obtained by subtracting the meta-analytic estimates of all studies of nutritional therapy versus usual care (AC) from the estimate of all studies of social support versus usual care (BC).[17]

Traditional meta-analyses are limited to the comparisons of two groups, failing to generate a complete picture of the effectiveness of non-pharmacological treatments for T2DM. In the current review, since there are more than 10 strategies of interest and for most there are no trials involving a direct comparison, the NMA was selected a substitute of the traditional meta-analysis.

The protocol of this review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42019127856), and it was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P).[18]

Patient and Public Involvement

We will not directly include patient-level data in this study, but the protocol development, priority of the research question, choice of outcome measures, and type of intervention have been informed through discussions with the members of the Brazilian Health Ministry and a group of patients with T2DM during follow-up in a tertiary Brazilian healthcare; both identified this study as a priority area for managing patients with T2DM in primary healthcare.

Eligibility Criteria

RCTs meeting the "PICOT" structure described below will be included in this study.

Participants (P)

Adult patients, over 18 years old, diagnosed with T2DM according to the American Diabetes Association (fasting glycemia greater than or equal to 126 mg/dL, glycemia greater than 200 mg/dL associated with classic DM symptoms, glycemia 2 hours after overload with 75 grams of glucose greater than or equal to 200 mg/dL, HbA1c greater than or equal to 6.5%) will be included in the study.[6]

Definitions of interventions (I)

All non-pharmacological and patient-mediated strategies[19] aimed at promoting better control of the disease for diabetic patients will be considered as interventions. The strategies can be implemented as either standalone or adjunct to the pharmacotherapy of T2DM. Regarding adjunct treatment, both groups must have received similar drug treatment.

Based on our previous search in the literature, the interventions may be (1) nutritional therapy (dietary quality or energy restriction),[20] (2) physical activity program (running, walking, bicycling, swimming, resistance training, yoga, Tai chi),[20] (3) psychological interventions (emotion-focused or cognition-focused),[11] (4) social network interventions (friends, families, and peers),[12] (5) multidisciplinary lifestyle interventions (an intervention that combines at least two of the following modalities: physical activity, nutritional therapy, social or psychological support),[21] (6) diabetes self-management

education and support (DSMES),[22] (7) technology-enabled DSMES (mobile phones, secure messaging, web-based information), [23](8) interventions delivered only or mainly by pharmacists (DSMES and/or pharmacy management), [24] (9) interventions delivered only or mainly by nurses (DSMES and/or pharmacy management),[25] (10) self-blood glucose monitoring in non-insulin-treated T2DM,[26] (11) health coaching,[27] and (12) benchmarking.[28]

The intervention must have been performed at the primary care (or in community settings), with a minimum follow-up period of 6 months.

Comparison (C)

Comparator will be considered an usual care of T2DM (drug treatment associated with a general orientation regarding lifestyle changes provided by a general practitioner) or another intervention described above. An episodic evaluation with a nutritionist, nurse, physical trainer or educator in diabetes, which provides a general orientation regarding changes in lifestyle, will be considered usual care if the patients are not provided with subsequent follow-up.

This protocol differs from our previous published protocol[29] because in the current systematic review, we will consider all non-pharmacological strategies for T2DM in primary care. Additionally, here, we will perform direct and indirect comparisons of all strategies. In the previous protocol, only nutritional therapy has been evaluated in direct comparisons (only nutritional therapy versus usual care).

Type of outcomes (O)

The primary outcome will be glycemic control (HbA1c [%]). The secondary outcomes will be anthropometric measurements (measured by weight or waist

circumference [WC], or body mass index [BMI]), quality of life, patient satisfaction, frequency of cardiovascular events and deaths, number of patients in each group with HbA1c <7, adverse events related to non-pharmacological strategies, and medication adherence.

Time-frame of outcome evaluation (T)

We will include only studies with follow up greater than 6 months. The outcomes will be evaluated at 6 to 12 months and greater than 12 months. For trials that had more than one time of outcome evaluation, we will consider the longest time point.

Exclusion Criteria

We will exclude trials that were conducted in settings other than the primary care or community settings, trials whose aim was to compare the effectiveness of pharmacological treatments, trials in which the intervention was any type of surgery to lose weight, trials with follow-up period less than 6 months, and trials that included predominantly participants with type 1 DM, gestational diabetes, or diabetes secondary to medication or a chronic disease.

Data sources and search strategy

Search strategies have been created and adapted to the following electronic health databases: Embase (by Elsevier, 1980–2019), Medline (by PubMed, 1966–2019), Latin American and Caribbean Health Sciences Literature (by Virtual Health Library, 1982–2019), and Controlled Clinical Trials of the Cochrane Collaboration (Cochrane Central Register of Controlled Trials). We have used the following index terms and their synonyms: Diabetes Mellitus, Type 2; Primary Health Care; and Community Health Planning. Language or year restrictions will not be considered in this study. We have used

the validated RCT filters created by the Cochrane Collaboration for Medline and Embase. A draft Medline search strategy is included in Appendix 1.

The following databases will also be searched for eligible studies: Trip database, Scopus, Web of Science, CINAHL, Australasian Medical Index, and Chinese Biomedical Literature Database. We will also search for studies on ClinicalTrials.gov and the gray literature through conferences, published abstracts, and dissertations.

References of relevant primary or secondary studies will be searched to identify additional eligible studies. We will use the Endnote software to download all references and remove duplicates. The initial screening of abstracts and titles will be performed using the software Rayyan QCRI.[30]

Study selection

Four reviewers independently will perform in pairs the assessment of titles and abstracts (RGOFL, LRB, JSCG, VSNN), and the studies potentially eligible for inclusion in the review will be selected for full reading and subsequently assessed for adequacy to the proposed PICOT In case of disagreement, a consensus meeting before the final decision will be held.

Data extraction

For each selected trial, the same four reviewers will use in pairs and independently an extraction form to record the year of publication, number of patients included, duration of follow-up, information regarding the inclusion and exclusion criteria, type of intervention (frequency, descriptions, durations), baseline data (average age, gender, weight, BMI and WC, glycemic control prior to the study, duration of T2DM, medications in use), and all reported outcome measures (in all time points). To ensure consistency between the reviewers, we will perform a calibration exercise before beginning the

review. In the case of duplicate publications or more reports from the primary trial, data extraction will be optimized using the best information available for all the items in the same trial.

Assessment of bias risk in the included studies

For each selected trial, the risk of bias will be assessed according to the criteria described in the revised Cochrane risk-of-bias tool for randomized trials (RoB 2 tool),[31] which considers the following five domains for each outcome evaluated: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. Each of the items will be evaluated by two reviewers as having low risk of bias, some concerns, and high risk of bias. In case of disagreement, a discussion between the reviewers before the final classification will be held.

Data synthesis

Dealing with missing data

The authors of the original studies will be contacted, if necessary, to provide missing information for each study included. We will use the data available in published articles provided by their authors or registration platforms. If available, we will preferentially use the data from intention-to-treat analysis. If numerical outcome data are missing and they cannot be obtained from the authors, we will calculate them, when possible, from other available statistics, such as p values.[32] If an outcome value is reported without a measure of variance, standard deviations (SDs) will be imputed according to the method suggested by Furukawa et al.[33]

Assessment of transitivity across treatment comparisons

The transitivity across treatment comparisons will be assessed using boxplots, and we are proposing the following seven a priori hypotheses to explain the variability between studies as possible effect modifiers: (1) patient characteristics (average patient age, gender distribution, disease severity, time of diabetes diagnosis, presence of diabetes chronic complications), (2) type of pharmacological treatment of T2DM, (3) study methodology quality (low risk of bias compared with high risk of bias), sample size (large versus small studies), (4) duration of follow-up (6–12 months, greater than 12 months), (5) frequency of sessions/visits with participants, and (6) adherence to a healthier lifestyle. Usual care of T2DM will be assessed for their similarity across treatment comparisons.[34]

Network meta-analysis

We will perform an NMA for each outcome to simultaneously compare multiple interventions in a single model using the Stata Statistical Software 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC).

We will preferentially pool the direct evidence; however, in the absence of direct comparisons, the effect estimate will be provided by indirect comparisons.

Considering the expected between-study heterogeneity, we will use a random effects (RE) model for each intervention comparison.

We will pool the data of each outcome using a Bayesian RE model separately. For dichotomous data, effect estimates will be calculated using odds ratio with a 95% credible interval (CrI). The continuous data will be expressed as means and SDs for each study, and the mean difference or standardized mean difference (if different metrics are used

across studies) will be calculated with their respective 95% CrIs. For count outcomes, we will calculate the rate ratio with a 95% CrI. For multi-arm studies, we plan to use data from all reported comparisons using the approach suggested by Rucker et al. by reducing the relevant weighting scheme.[35]

The intervention effect estimates will be presented along with their corresponding 95% CrIs, and we will obtain the treatment hierarchy using the surface under the cumulative ranking (SUCRA) curve, with its 95% CrI, and the rank-heat plot.[36 37] It is expected that the best treatment will have high SUCRA values while the worst will have low values. For each comparison, we will present the direct, indirect, and network estimates.

Assessment of statistical heterogeneity

For direct evidence, we will assess heterogeneity by estimating the magnitude of the between-study variance using the empirical distribution as estimated by Turner et al.[38] and Rhodes et al.[39] and by using the I^2 statistic to quantify the percentage of variability due to true differences between studies rather than sampling error.[40 41] We will interpret the I^2 according to thresholds set forth by the Cochrane Collaboration[32], and it will be used as a criterion for pooling or not the results and for performing additional subgroup analyses. For count outcomes, we will use a minimally informative prior distribution (~ Uniform[0,2]).[42]

If enough studies are available, we will perform subgroup analysis using the same potential treatment effect modifiers described above. Our a priori hypothesis is as follows: individuals with greater than 10 years of T2DM, taking insulin, with a poorly controlled diabetes at baseline (an uninterrupted HbA1c >8.0% for ≥*1* year despite standard care), and with more than one of the macro or micro chronic diabetes complications, the

subgroups analysis may show less improvement in the primary and secondary outcomes. We will also perform a network meta-regression whenever possible (i.e., when at least 10 studies are available) using the RE model to evaluate the impact of these potential effect modifiers (patient characteristic, study quality, intervention type, follow-up time, adherence).

With the combination of direct and indirect estimates, violation of the transitivity assumption (described above) will also lead to inconsistency. We will assess loop inconsistency (disagreement between direct and indirect estimates) using the loop-specific method and design inconsistency (disagreement between studies that inform the same treatment comparison but include a different number of treatment arms) using the design-by-treatment model based on a chi-squared test.[43-46]

Sensitivity analysis

If sufficient studies are available, we will conduct a sensitivity analysis to assess the robustness of results.[38 39] This analysis will be performed by comparison of studies with high risk of selection and attrition bias versus studies with low risk of bias in these domains and studies with data published versus studies with imputed data.

Assessment of publication biases

For each treatment comparison, if more than 10 studies are included in the meta-analysis, we will use the funnel plot to investigate the presence of publication bias.[32] In such cases, we will also perform the Begg's rank correlation [47] and Egger's regression tests.[48]

Quality of evidence

To determine our confidence in an overall treatment ranking from the NMA, we will follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, with some modifications as described below to reflect specific issues from NMA.[49] This process will be performed in pairs and independently (RGOFL, LRB, JSCG, VSNN).

Based on the five categories (risk of bias, imprecision, inconsistency, and publication bias) the certainty of evidence of effect estimates obtained by direct comparisons will be rated as high, moderate, low, or very low.

For indirect comparisons, the quality of evidence in estimates will be rated following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. We will focus our assessments on the quality of indirect evidence on the dominant first-order loop (loops with a single common comparator connecting the two interventions of the comparison of interest). The quality of evidence rating for indirect comparisons will be the lower ratings of quality for the two direct estimates that contribute to the first-order loop of the indirect comparison. For instance, if one of the direct comparisons is rated as low and the other is rated as moderate evidence, we will rate the quality of indirect evidence as low.[45] We will rate down the quality of the indirect comparison one further level for violation of the transitivity assumption (similarity of trials in terms of population, intervention [type and dosing frequency], settings, and trial methodology).[45]

We will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidences are present. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency (measured by the difference of point estimates and the extent of overlap of CrIs and of direct and indirect effect estimates).

DISCUSSION

With the consistent increase in the prevalence of T2DM together with the unsatisfactory glycemic control by some individuals, the search for new and effective strategies for the prevention and control of this metabolic disease is underway.

Since inadequate glycemic control in DM is most often related to poor adherence to lifestyle changes and to the proposed treatment, initiatives have emerged to promote a better acceptance/understanding of the disease and its treatment by the patients. With this, it is expected that individuals have a more active participation in the control of his, disease, thus achieving higher rates of glycemic control and fewer complications associated with this dysglycemia.

Although several systematic reviews have evaluated the effectiveness of these strategies in the management of T2DM,[8 50] to the best of our knowledge to date, there are no systematic reviews and NMA considering the direct and indirect effects of non-pharmacological interventions targeting a greater control of T2DM.

ETHICS AND DISSEMINATION

Since primary data collection will be undertaken, no formal ethical assessment is required by our institution. We plan to present the findings of this systematic review in a peer-reviewed scientific journal. We also intend to present it, including preliminary findings, at the appropriate conferences.

Authors' contributions:

VSNN, LT, and AAV conceptualized and design the study. LT, RGOFL, AAV, and VSNN drafted the manuscript protocol. VSNN, RGOFL, LRB, ALM, JSCG, FB, AAV, and LT critically revised the protocol and manuscript submitted. All authors read and approved the final manuscript.

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Competing interests' statement:

There are no competing interests.

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SUPPLEMENTARY DATA
APPENDIX 1

Search Strategy – PubMed (November 25, 2019)

#1 "Diabetes Mellitus, Type 2"[Mesh] OR (Diabetes Mellitus, Noninsulin-Dependent) OR (Diabetes Mellitus, Ketosis Resistant) OR (Ketosis-Resistant Diabetes Mellitus) OR (Diabetes Mellitus, Non Insulin Dependent) OR (Diabetes Mellitus, Non-Insulin-Dependent) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Diabetes Mellitus, Stable) OR (Stable Diabetes Mellitus) OR (Diabetes Mellitus, Type II) OR(NIDDM) OR (Diabetes Mellitus, Noninsulin Dependent) OR (Diabetes Mellitus, Maturity-Onset) OR (Diabetes Mellitus, Maturity Onset) OR (Maturity-Onset Diabetes Mellitus) OR (Maturity Onset Diabetes Mellitus) OR (MODY) OR (Diabetes Mellitus, Slow-Onset) OR (Diabetes Mellitus, Slow Onset) OR (Slow-Onset Diabetes Mellitus) OR (Type 2 Diabetes Mellitus) OR (Noninsulin-Dependent Diabetes Mellitus) OR (Noninsulin Dependent Diabetes Mellitus) OR (Maturity-Onset Diabetes) OR (Diabetes, Maturity-Onset) OR (Maturity Onset Diabetes) OR (Type 2 Diabetes) OR (Diabetes, Type 2) OR (Diabetes Mellitus, Adult-Onset) OR (Adult-Onset Diabetes Mellitus) OR (Diabetes Mellitus, Adult Onset)

#2 "Primary Health Care"[Mesh] OR (Care, Primary Health) OR (Health Care, Primary) OR (Primary Healthcare) OR (Healthcare, Primary) OR (Primary Care) OR (Care, Primary) or "Physicians, Primary Care"[Mesh] OR (Physician, Primary Care) OR (Primary Care Physician) OR (Primary Care Physicians) OR (Healthy Primary Care) OR "Primary Care Nursing"[Mesh] OR (Care Nursing, Primary) OR (Nursing, Primary Care)

#3 "Community Health Planning"[Mesh] OR (Community Health Plannings) OR (Health Planning, Community) OR (Health Plannings, Community) OR (Planning, Community Health) OR (Plannings, Community Health) OR (Population-Based Planning) OR (Planning, Population-Based) OR (Plannings, Population-Based) OR (Population Based Planning) OR (Population-Based Plannings) OR (Community Health Systems) OR (Community Health System) OR (Health System, Community) OR (Health Systems, Community) OR (System, Community Health) OR (Systems, Community Health)

#4* randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])

#1 AND #2 AND #3 AND #4

* Direct link to PubMed with **sensitivity- and precision-maximizing version**(2008 revision). [1] Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from **www.cochrane-handbook.org**

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	n/a

		changes; otherwise, state plan for documenting important protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	17
Sponsor	#5b	Provide name for the review funder and / or sponsor	17
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-9
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp. Data
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10

Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-13
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14-15