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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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Complete List of Authors:	<p>Leite, Renata; Sao Paulo State University Julio de Mesquita Filho Botucatu Campus Faculty of Medicine, Department of Internal Medicine Banzato , Luísa ; Sao Paulo State University Julio de Mesquita Filho Botucatu Campus Faculty of Medicine, Department of Internal Medicine Galendi, Julia; Sao Paulo State University Julio de Mesquita Filho Botucatu Campus Institute of Biosciences, Department of Internal Medicine</p> <p>Bolfi, Fernanda; Sao Paulo State University Julio de Mesquita Filho Botucatu Campus Faculty of Medicine, Department of Internal Medicine Mendes, Adriana; Sao Paulo State University Julio de Mesquita Filho Botucatu Campus Faculty of Medicine, Department of Internal Medicine Veroniki, Areti-Angeliki; University of Ioannina, Hygiene and Epidemiology</p> <p>Thabane, Lehana ; McMaster University, Clinical Epidemiology & Biostatistics</p> <p>Nunes-Nogueira, Vania; Sao Paulo State University Julio de Mesquita Filho Botucatu Campus Faculty of Medicine, ; Botucatu Medical School</p>
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3 **Effectiveness of non-pharmacological strategies in management of type 2 diabetes**
4 **in primary care: a protocol for a systematic review and network meta-analysis**
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7 Renata Giacomini Oliveira Ferreira Leite ⁽¹⁾, Luísa Rocco Banzato ⁽¹⁾, Júlia Simões Corrêa
8 Galendi ⁽¹⁾, Adriana Lúcia Mendes ⁽¹⁾, Fernanda Bolfi⁽¹⁾, Areti Angeliki Veroniki^(2,3,4,5),
9 Lehana Thabane ^(6,7), Vania dos Santos Nunes–Nogueira ⁽¹⁾
10
11

- 12
13 1. Department of Internal Medicine – São Paulo State University/UNESP, Medical School,
14 Sao Paulo, Brazil.
15
16 2. Department of Primary Education, School of Education, University of Ioannina,
17 Ioannina, Greece.
18
19 3. Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's
20 Hospital, Toronto, Ontario, Canada.
21
22 4. Institute of Reproductive and Developmental Biology, Department of Surgery & Cancer,
23 Faculty of Medicine, Imperial College, London, United Kingdom
24
25 5. Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto,
26 ON, Canada
27
28 6. Department of Health Research Methods, Evidence, and Impact, McMaster University,
29 Hamilton, ON, Canada
30
31 7. Departments of Pediatrics and Anesthesia, McMaster University, Hamilton, ON, Canada

32 E-mail address
33

34
35 Leite RGOF: renataocchiuto@ig.com.br

36 Banzato LR: lubanzato@gmail.com

37 Galendi JSC: jsimoescorrea@gmail.com

38 Mendes AL: mendes.adrianalucia@gmail.com

39 Bolfi F: febolfi@gmail.com

40 Veroniki AA: averonik@cc.uoi.gr

41 Thabane L: ThabanL@mcmaster.ca
42

43
44
45
46 Corresponding Author:

47 Vania dos Santos Nunes Nogueira

48 Departamento de Clínica Médica – FMB – UNESP

49 Avenida Professor Mário Rubens Guimarães Montenegro s/n, Bairro UNESP, Campus Botucatu,
50 Botucatu-SP 18618-687, Brazil

51 Phone: (55 14) 3880 11 71

52 Fax: (55 14) 3880 16 67

53 E-mail: vania.nunes-nogueira@unesp.br

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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

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3 NMA we will follow the GRADE (Grading of Recommendations Assessment,
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5 Development and Evaluation) approach.
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9 **Ethics Dissemination:** As no primary data collection will be undertaken, no formal
10
11 ethical assessment is required. We plan to present the results of this systematic review in
12
13 a peer-reviewed scientific journal, conferences and the popular press.
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16 **Registration Number:** Our systematic review protocol has been registered with the
17
18 International Prospective Register of Systematic Reviews (PROSPERO) on
19
20 _____2019 (registration number _____).
21

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23 **Key words:** diabetes mellitus type 2, primary health care, systematic review, network
24
25 meta-analysis.
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28 29 **Strengths and limitations of this study:** 30

- 31
32 • This is the first NMA in the field, and our results can help health managers to
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34 implement non-pharmacological strategies in diabetes management in primary
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36 care.
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39 • We will apply the GRADE approach to evaluate our confidence in an overall
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41 treatment ranking from the NMA.
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44 • Bias due to deviations from intended interventions and due to missing outcome
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46 data may be the main limitations of the study.
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49 • As the primary outcome selected is a surrogate endpoint, the quality of evidence
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51 according to GRADE approach will be probably low.
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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

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3 infarction (95% confidence interval (CI) 8% to 21%) and 21% for deaths related to
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5 diabetes (95% CI 15% to 27%).⁵
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9 Despite the increasing number of drugs available and various guidelines on the
10 management of T2DM, an expressive number of patients continue with the disease
11 uncontrolled. In a multicenter, cross-sectional, epidemiological, questionnaire-based
12 study conducted in nine Latin American countries, 56.8% of patients T2DM had poor
13 glycaemic control (HbA1c $\geq 7\%$).⁷ The highest prevalence of unsuccessful treatment was
14 in Peru, where only 7.5% achieved metabolic and blood pressure levels as recommended
15 by the American Diabetes Association (ADA).⁸ In the United States, according to a survey
16 performed between 1998 and 2002, only 42.3% of adults had HbA1c levels less than 7%,
17 and 14% had HbA1c 10% or more.⁹
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30 It is believed that this discrepancy between the large number of tools to treat these
31 patients and the low frequency of diabetes control is due to knowledge gaps, attitudes and
32 practices related to diabetes by patients and physicians who treat these individuals.¹⁰
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38 Therefore, in order to increase the percentage of diabetic patients with the disease
39 controlled and thereby reduce the number of deaths and morbidities related to this disease,
40 it has been studied the effectiveness of new strategies to help patients to control their
41 disease. These measures are complementary to the pharmacological treatment, and its
42 main objective is for patients to recognize the importance of self-management and full
43 involvement to treat their condition.^{10 11}
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52 The Innovative Care for Chronic Conditions framework advocated by the IDF has
53 divided these interventions in the treatment of diabetes into three spheres: macro (policy
54 and funding), meso (health and community organization) and micro (patient and
55 family).¹¹
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3 In the micro sphere, studies in T2DM have shown that programs focused on
4 counseling, therapy compliance, explanation of possible adverse events, patient
5 empowerment are associated with better glycemic and quality-of-life controls, and,
6 consequently, lower follow-up costs.¹⁰⁻¹³
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13 Although several systematic reviews have evaluated the effectiveness of these
14 strategies in the management of T2DM,^{8,14} no NMAs were found that compared multiple
15 interventions simultaneously in a single model.
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21 The objective of this review is to evaluate the comparative effectiveness of non-
22 pharmacological strategies in the management of T2DM in primary care or community
23 settings. We aim to asses all types of non-pharmacological interventions targeting a
24 greater commitment from patients in the control of T2DM.
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31 **METHODS AND DESIGN**

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34 This systematic review and network NMA protocol has been registered with the
35 International Prospective Register of Systematic Reviews (PROSPERO) database
36 (registration number:), and it was developed following the Preferred Reporting Items for
37 Systematic Reviews and Meta-Analyses for protocols (PRISMA-P).¹⁵
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44 **Patient and Public Involvement**

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

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3 The intervention must have been performed at primary care (or in community
4 settings), with minimum period of three months.
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8 An evaluation with a nutritionist, nurse, physical trainer, psychologist or educator
9 in diabetes, which provides a general orientation regarding lifestyle changes will be
10 considered conventional treatment if the patients are not provided with subsequent
11 follow-up.
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18 **Type of outcomes**

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

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

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

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3 For each selected trial, two reviewers will use an extraction form to record the
4 year of publication, number of patients included, duration of follow-up, information
5 regarding the inclusion and exclusion criteria, type of intervention (frequency,
6 descriptions, durations), baseline data (average age, gender, weight, BMI and WC,
7 glycemic control prior to the study, duration of T2DM, medications in use), and all
8 reported outcome measures (in all time points). To ensure consistency between reviewers,
9 we will perform a calibration exercise before beginning the review. In the case of
10 duplicate publications or more reports from the primary trial, data extraction will be
11 optimized using the best information available for all the items in the same trial.
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23 24 **Assessment of bias risk in included studies**

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

48 49 **Dealing with missing data**

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53 The authors of the original studies will be contacted, if necessary, to provide
54 missing information for each study included. We will use the data available in published
55 articles provided by their authors or registration platforms. If available, we will
56 preferentially use the data from intention-to-treat analysis. If numerical outcome data are
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3 missing and they cannot be obtained from the authors, we will calculate them, when
4 possible, from other available statistics, such as p values.²⁹ If an outcome value is
5 reported without a measure of variance, standard deviations (SDs) will be imputed
6 according to the method suggested by Furukawa et al.³⁰
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13 **Assessment of transitivity across treatment comparisons**

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

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43 We will perform an NMA for each outcome to compare multiple interventions
44 simultaneously in a single model.
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49 We will preferentially pool the direct evidence, however, in the absence of direct
50 comparisons, the effect estimate will be provided by indirect comparisons.
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55 Considering the expected between-study heterogeneity, we will use a random-
56 effects (RE) model for each intervention comparison.
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3 We will pool the data of each outcome using a Bayesian RE model separately.
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5 For dichotomous data, effect estimates will be calculated using odds ratio (OR) with a
6
7 95% credible interval (CrIs). The continuous data will be expressed as means and SDs
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9 for each study, and the mean difference or standardized mean difference (if different
10
11 metrics are used across studies) will be calculated with their respective 95% CrIs. For
12
13 count outcomes, we will calculate the rate ratio with a 95% CrI. For multi-arm studies,
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15 we plan to use data from all reported comparisons using the approach suggested by
16
17 Rucker et al by reducing the relevant weighting scheme.³²
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22 The intervention effect estimates will be presented along with their corresponding
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24 95% CrIs, and we will obtain the treatment hierarchy using the surface under the
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26 cumulative ranking (SUCRA) curve, with its 95% CrI, and the rank-heat plot.^{33 34}It is
27
28 expected that the best treatment will have high SUCRA values while the worst will have
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30 low values. For each comparison, we will present the direct, indirect, and network
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32 estimates.
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36 **Assessment of statistical heterogeneity**

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40 For direct evidence, we will assess heterogeneity by estimating the magnitude of
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42 the between-study variance using the empirical distribution as estimated by Turner et al.
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44 ³⁵ and Rhodes et al. ³⁶, and by using the I^2 statistic to quantify the percentage of variability
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46 that is due to true differences between studies rather than sampling error. ^{37 38}. We will
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48 interpret the I^2 according to thresholds set forth by the Cochrane Collaboration ²⁹, and it
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50 will be used as a criterion for pooling or not the results and for performing additional
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52 subgroup analyses. For count outcomes, we will use a minimally informative prior
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54 distribution (\sim Uniform(0,2)).³⁹
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3 If enough studies are available, we will perform subgroup analysis using the same
4 potential treatment effect modifiers described above. Our a priori hypothesis will be
5 individuals with longer time of T2DM, taking insulin, with a poorly controlled diabetes
6 at baseline (an uninterrupted HbA1c >8.0% for ≥ 1 year despite standard care) and with
7 more chronic diabetes complications subgroups may show less improvement in the
8 primary and secondary outcomes. We will also perform a network meta-regression
9 whenever possible (i.e., when at least 10 studies are available) using the random-effects
10 model to evaluate the impact of these potential effect modifiers (patient characteristic,
11 study quality, intervention type, follow up time, adherence).
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25 In the combination of direct and indirect estimates, violation of the transitivity
26 assumption (described above) will also lead to inconsistency. We will assess loop
27 inconsistency (disagreement between direct and indirect estimates) using the loop-
28 specific method, and design inconsistency (disagreement between studies that inform the
29 same treatment comparison but include a different number of treatment arms) using the
30 design-by-treatment model based on a χ^2 test.⁴⁰⁻⁴³
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38 **Sensitivity analysis**

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41 If sufficient studies are available, we will conduct a sensitivity analysis to assess
42 the robustness of results.^{35 36} We will assess the effect of excluding studies with high
43 risk of selection and attrition bias, and studies with imputed data.
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49 **Assessment of publication biases**

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52 For each treatment comparison, if more than 10 studies are included in the meta-
53 analysis, we will use the funnel plot to investigate the presence of publication bias.²⁹ In
54 such cases, we will also perform the Begg's rank correlation⁴⁴ and Egger's regression
55 tests⁴⁵.
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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

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3 inconsistency (measured by the difference of point estimates and the extent of overlap of
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5 CrIs and of direct and indirect effect estimates).
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10 **DISCUSSION**

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14 The continuously increasing prevalence of T2DM together the unsatisfactory
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16 glycemic control by some individuals justify the search for new and effective strategies
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18 for the prevention and control of this metabolic disease.
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21 Since inadequate glycemic control in DM is most often related to poor adherence
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23 to lifestyle changes and to the proposed treatment, initiatives have emerged to promote a
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25 better acceptance / understanding of the disease and its treatment by the patients. With
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27 this is expected that individuals have a more active participation in the control of his
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29 disease, and thus to achieve higher rates of glycemic control and fewer complications
30
31 associated with this dysglycemia.
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36 Since there are several different strategies for this purpose, we aim to answer the
37
38 following question: what is the effectiveness of non-pharmacological strategies in the
39
40 primary health care in promote in patients with T2DM a greater commitment of this
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42 condition and consequently a better control of their disease? The answer to this
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44 question may assist health managers in implementing these actions in primary care
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46 settings.
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51 To the best of our knowledge to date, there is no systematic review and NMA
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53 considering the direct and indirect effect of non-pharmacological interventions targeting
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55 a greater commitment from patients in the control of T2DM.
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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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Competing interests' statement:

There are no competing interests.

REFERENCES

1. Diabetes SBd. Diretrizes da Sociedade Brasileira de Diabetes In: Farmacêutica SPA, ed., 2017-2018.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice* 2017;128:40-50. doi: 10.1016/j.diabres.2017.03.024 [published Online First: 2017/04/25]
3. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes care* 2019;42(Suppl 1):S13-S28. doi: 10.2337/dc19-S002 [published Online First: 2018/12/19]

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- 3
4. Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. *Diabetes* 2017;66(2):241-55. doi: 10.2337/db16-0806 [published Online First: 2016/12/17]
5. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ (Clinical research ed)* 2000;321(7258):405-12. doi: 10.1136/bmj.321.7258.405 [published Online First: 2000/08/11]
6. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(9131):837-53. [published Online First: 1998/09/22]
7. Lopez Stewart G, Tambascia M, Rosas Guzman J, et al. Control of type 2 diabetes mellitus among general practitioners in private practice in nine countries of Latin America. *Rev Panam Salud Publica* 2007;22(1):12-20. doi: 10.1590/s1020-49892007000600002 [published Online First: 2007/10/13]
8. Huayanay-Espinoza IE, Guerra-Castanon F, Lazo-Porrás M, et al. Metabolic control in patients with type 2 diabetes mellitus in a public hospital in Peru: a cross-sectional study in a low-middle income country. *PeerJ* 2016;4:e2577. doi: 10.7717/peerj.2577 [published Online First: 2016/10/21]
9. Saaddine JB, Cadwell B, Gregg EW, et al. Improvements in diabetes processes of care and intermediate outcomes: United States, 1988-2002. *Ann Intern Med* 2006;144(7):465-74. [published Online First: 2006/04/06]
10. Jacob S, Serrano-Gil M. Engaging and empowering patients to manage their type 2 diabetes, Part II: Initiatives for success. *Advances in therapy* 2010;27(10):665-80. doi: 10.1007/s12325-010-0071-0 [published Online First: 2010/09/17]
11. Serrano-Gil M, Jacob S. Engaging and empowering patients to manage their type 2 diabetes, Part I: a knowledge, attitude, and practice gap? *Advances in therapy* 2010;27(6):321-33. doi: 10.1007/s12325-010-0034-5 [published Online First: 2010/06/17]
12. American Diabetes A. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. *Clin Diabetes* 2017;35(1):5-26. doi: 10.2337/cd16-0067 [published Online First: 2017/02/02]
13. Chapman A, Liu S, Merkouris S, et al. Psychological Interventions for the Management of Glycemic and Psychological Outcomes of Type 2 Diabetes Mellitus in China: A Systematic Review and Meta-Analyses of Randomized Controlled Trials. *Frontiers in public health* 2015;3:252. doi: 10.3389/fpubh.2015.00252 [published Online First: 2015/12/05]
14. Loveman E, Frampton GK, Clegg AJ. The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review. *Health technology assessment (Winchester, England)* 2008;12(9):1-116, iii. [published Online First: 2008/04/15]
15. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;350:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]
16. Effective Practice and Organisation of Care (EPOC). EPOC Taxonomy 2015 [Available from: <https://epoc.cochrane.org/epoc-taxonomy> accessed 04 July 2019.
17. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes care* 2018;41(12):2669-701. doi: 10.2337/dci18-0033 [published Online First: 2018/10/07]
18. Chew BH, Vos RC, Metzendorf MI, et al. Psychological interventions for diabetes-related distress in adults with type 2 diabetes mellitus. *The Cochrane database of systematic*

- 1
2
3 *reviews* 2017;9:CD011469. doi: 10.1002/14651858.CD011469.pub2 [published Online
4 First: 2017/09/28]
- 5 19. Spencer-Bonilla G, Ponce OJ, Rodriguez-Gutierrez R, et al. A systematic review and meta-
6 analysis of trials of social network interventions in type 2 diabetes. *BMJ Open*
7 2017;7(8):e016506. doi: 10.1136/bmjopen-2017-016506 [published Online First:
8 2017/08/23]
- 9 20. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an Intensive Lifestyle Intervention
10 on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial.
11 *JAMA* 2017;318(7):637-46. doi: 10.1001/jama.2017.10169 [published Online First:
12 2017/08/16]
- 13 21. Chatterjee S, Davies MJ, Heller S, et al. Diabetes structured self-management education
14 programmes: a narrative review and current innovations. *Lancet Diabetes Endocrinol*
15 2018;6(2):130-42. doi: 10.1016/S2213-8587(17)30239-5 [published Online First:
16 2017/10/04]
- 17 22. Greenwood DA, Gee PM, Fatkin KJ, et al. A Systematic Review of Reviews Evaluating
18 Technology-Enabled Diabetes Self-Management Education and Support. *J Diabetes Sci*
19 *Technol* 2017;11(5):1015-27. doi: 10.1177/1932296817713506 [published Online First:
20 2017/06/01]
- 21 23. Aubert RE, Herman WH, Waters J, et al. Nurse case management to improve glycemic
22 control in diabetic patients in a health maintenance organization. A randomized,
23 controlled trial. *Ann Intern Med* 1998;129(8):605-12. doi: 10.7326/0003-4819-129-8-
24 199810150-00004 [published Online First: 1998/10/24]
- 25 24. Azami G, Soh KL, Sazlina SG, et al. Effect of a Nurse-Led Diabetes Self-Management
26 Education Program on Glycosylated Hemoglobin among Adults with Type 2 Diabetes. *J*
27 *Diabetes Res* 2018;2018:4930157. doi: 10.1155/2018/4930157 [published Online First:
28 2018/09/19]
- 29 25. Zhu H, Zhu Y, Leung SW. Is self-monitoring of blood glucose effective in improving
30 glycaemic control in type 2 diabetes without insulin treatment: a meta-analysis of
31 randomised controlled trials. *BMJ Open* 2016;6(9):e010524. doi: 10.1136/bmjopen-
32 2015-010524 [published Online First: 2016/09/04]
- 33 26. Willard-Grace R, Chen EH, Hessler D, et al. Health coaching by medical assistants to
34 improve control of diabetes, hypertension, and hyperlipidemia in low-income patients:
35 a randomized controlled trial. *Ann Fam Med* 2015;13(2):130-8. doi: 10.1370/afm.1768
36 [published Online First: 2015/03/11]
- 37 27. Hermans MP, Elisaf M, Michel G, et al. Benchmarking is associated with improved quality of
38 care in type 2 diabetes: the OPTIMISE randomized, controlled trial. *Diabetes care*
39 2013;36(11):3388-95. doi: 10.2337/dc12-1853 [published Online First: 2013/07/13]
- 40 28. Higgins JPT SJ, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S., editor. *A*
41 *revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J,*
42 *Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic*
43 *Reviews* 2016.
- 44 29. Collaboration TC. Cochrane Handbook for Systematic Reviews of Interventions Version
45 5.1.0 [updated March 2011], 2011.
- 46 30. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-
47 analyses can provide accurate results. *J Clin Epidemiol* 2006;59(1):7-10. doi:
48 10.1016/j.jclinepi.2005.06.006 [published Online First: 2005/12/20]
- 49 31. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis
50 demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;62(8):857-
51 64. doi: 10.1016/j.jclinepi.2008.10.001 [published Online First: 2009/01/23]
- 52 32. Rucker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches
53 to multi-arm studies in network meta-analysis. *Stat Med* 2014;33(25):4353-69. doi:
54 10.1002/sim.6236 [published Online First: 2014/06/20]
- 55
56
57
58
59
60

- 1
2
3 33. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for
4 presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J*
5 *Clin Epidemiol* 2011;64(2):163-71. doi: 10.1016/j.jclinepi.2010.03.016 [published
6 Online First: 2010/08/07]
7
8 34. Veroniki AA, Straus SE, Fyraridis A, et al. The rank-heat plot is a novel way to present the
9 results from a network meta-analysis including multiple outcomes. *J Clin Epidemiol*
10 2016;76:193-9. doi: 10.1016/j.jclinepi.2016.02.016 [published Online First:
11 2016/03/05]
12
13 35. Turner RM, Davey J, Clarke MJ, et al. Predicting the extent of heterogeneity in meta-
14 analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J*
15 *Epidemiol* 2012;41(3):818-27. doi: 10.1093/ije/dys041 [published Online First:
16 2012/03/31]
17
18 36. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent
19 of heterogeneity in meta-analyses of continuous outcome data. *J Clin Epidemiol*
20 2015;68(1):52-60. doi: 10.1016/j.jclinepi.2014.08.012 [published Online First:
21 2014/10/12]
22
23 37. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*
24 2002;21(11):1539-58. doi: 10.1002/sim.1186 [published Online First: 2002/07/12]
25
26 38. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*
27 (*Clinical research ed*) 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557
28 [published Online First: 2003/09/06]
29
30 39. Lambert PC, Sutton AJ, Burton PR, et al. How vague is vague? A simulation study of the
31 impact of the use of vague prior distributions in MCMC using WinBUGS. *Stat Med*
32 2005;24(15):2401-28. doi: 10.1002/sim.2112 [published Online First: 2005/07/15]
33
34 40. White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-
35 analysis: model estimation using multivariate meta-regression. *Res Synth Methods*
36 2012;3(2):111-25. doi: 10.1002/jrsm.1045 [published Online First: 2012/06/01]
37
38 41. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-
39 analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3(2):98-
40 110. doi: 10.1002/jrsm.1044 [published Online First: 2012/06/01]
41
42 42. Veroniki AA, Mavridis D, Higgins JP, et al. Characteristics of a loop of evidence that affect
43 detection and estimation of inconsistency: a simulation study. *BMC Med Res Methodol*
44 2014;14:106. doi: 10.1186/1471-2288-14-106 [published Online First: 2014/09/23]
45
46 43. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of
47 interventions. *Int J Epidemiol* 2013;42(1):332-45. doi: 10.1093/ije/dys222 [published
48 Online First: 2013/03/20]
49
50 44. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication
51 bias. *Biometrics* 1994;50(4):1088-101. [published Online First: 1994/12/01]
52
53 45. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple,
54 graphical test. *BMJ (Clinical research ed)* 1997;315(7109):629-34. doi:
55 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]
56
57 46. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a
58 network meta-analysis. *PLoS One* 2014;9(7):e99682. doi:
59 10.1371/journal.pone.0099682 [published Online First: 2014/07/06]
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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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			Page
		Reporting Item	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

1		#2	If registered, provide the name of the registry (such as	3
2			PROSPERO) and registration number	
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6	Contact	#3a	Provide name, institutional affiliation, e-mail address of all	1
7			protocol authors; provide physical mailing address of	
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20			completed or published protocol, identify as such and list	
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29	Sources	#5a	Indicate sources of financial or other support for the review	16
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36	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or	n/a
37	funder		institution(s), if any, in developing the protocol	
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41	Rationale	#6	Describe the rationale for the review in the context of what is	4
42			already known	
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46	Objectives	#7	Provide an explicit statement of the question(s) the review	6-8
47			will address with reference to participants, interventions,	
48			comparators, and outcomes (PICO)	
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54	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	6-8
55			design, setting, time frame) and report characteristics (such	
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1			as years considered, language, publication status) to be	
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3			used as criteria for eligibility for the review	
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6	Information	#9	Describe all intended information sources (such as	9
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10			registers or other grey literature sources) with planned dates	
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15	Search strategy	#10	Present draft of search strategy to be used for at least one	Supp.
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17			electronic database, including planned limits, such that it	Data
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23	Study records -	#11a	Describe the mechanism(s) that will be used to manage	9-10
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25	data management		records and data throughout the review	
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28	Study records -	#11b	State the process that will be used for selecting studies	10
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30	selection process		(such as two independent reviewers) through each phase of	
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32			the review (that is, screening, eligibility and inclusion in	
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34			meta-analysis)	
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38	Study records -	#11c	Describe planned method of extracting data from reports	10
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40	data collection		(such as piloting forms, done independently, in duplicate),	
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42	process		any processes for obtaining and confirming data from	
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48	Data items	#12	List and define all variables for which data will be sought	10
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50			(such as PICO items, funding sources), any pre-planned	
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1	Outcomes and	#13	List and define all outcomes for which data will be sought,	8
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3	prioritization		including prioritization of main and additional outcomes, with	
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8	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	10
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10	individual studies		individual studies, including whether this will be done at the	
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12			outcome or study level, or both; state how this information	
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14			will be used in data synthesis	
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16	Data synthesis	#15a	Describe criteria under which study data will be	11-13
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18			quantitatively synthesised	
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20		#15b	If data are appropriate for quantitative synthesis, describe	11-13
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22			planned summary measures, methods of handling data and	
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24			methods of combining data from studies, including any	
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26			planned exploration of consistency (such as I ² , Kendall's τ)	
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28		#15c	Describe any proposed additional analyses (such as	13
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30			sensitivity or subgroup analyses, meta-regression)	
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32		#15d	If quantitative synthesis is not appropriate, describe the type	N/A
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34			of summary planned	
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36	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	13
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38			publication bias across studies, selective reporting within	
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40			studies)	
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42	Confidence in	#17	Describe how the strength of the body of evidence will be	14
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44	cumulative		assessed (such as GRADE)	
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BMJ Open

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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Secondary Subject Heading:	Evidence based practice
Keywords:	diabetes mellitus type 2, primary health care, systematic review, network meta-analysis.

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Manuscripts

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3 **Effectiveness of non-pharmacological strategies in the management of type 2**
4 **diabetes in primary care: a protocol for a systematic review and network meta-**
5 **analysis**
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9 Renata Giacomini Oliveira Ferreira Leite¹, Luísa Rocco Banzato¹, Júlia Simões Corrêa
10 Galendi¹, Adriana Lúcia Mendes¹, Fernanda Bolfi¹, Areti Angeliki Veroniki^{2,3,4},
11 Lehana Thabane^{6,7}, Vania dos Santos Nunes–Nogueira¹
12
13

14 ¹Department of Internal Medicine – São Paulo State University/UNESP, Medical School,
15 Sao Paulo, Brazil
16

17 ²Department of Primary Education, School of Education, University of Ioannina,
18 Ioannina, Greece
19

20 ³Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's
21 Hospital, Unity Health Toronto, Toronto, Ontario, Canada
22

23 ⁴Institute of Reproductive and Developmental Biology, Department of Surgery & Cancer,
24 Faculty of Medicine, Imperial College, London, United Kingdom
25

26 ⁶Department of Health Research Methods, Evidence, and Impact, McMaster University,
27 Hamilton, ON, Canada
28

29 ⁷Departments of Pediatrics and Anesthesia, McMaster University, Hamilton, ON, Canada
30
31

32 E-mail address

33 Leite RGOF: renataocchiuto@ig.com.br

34 Banzato LR: lubanzato@gmail.com

35 Galendi JSC: jsimoescorrea@gmail.com

36 Mendes AL: mendes.adrianalucia@gmail.com

37 Bolfi F: febolfi@gmail.com

38 Veroniki A: averoniki@uoi.gr

39 Thabane L: ThabanL@mcmaster.ca
40
41
42
43
44

45 **Corresponding Author:**

46 Vania dos Santos Nunes Nogueira

47 Departamento de Clínica Médica – FMB – UNESP

48 Avenida Professor Mário Rubens Guimarães Montenegro s/n, Bairro UNESP, Campus Botucatu,
49 Botucatu-SP 18618-687, Brazil
50

51 Phone: (55 14) 3880 11 71. Fax: (55 14) 3880 16 67

52 E-mail: vania.nunes-nogueira@unesp.br

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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

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3 hierarchy will be obtained using the surface under the cumulative ranking curve. To
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5 determine our confidence in an overall treatment ranking from the NMA, we will follow
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7 the Grading of Recommendations Assessment, Development and Evaluation (GRADE)
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9 approach.
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13 **Ethics and Dissemination:** As no primary data collection will be undertaken, no formal
14
15 ethical assessment is required. We plan to present the results of this systematic review in
16
17 a peer-reviewed scientific journal, conferences, and the popular press.
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20 **Prospero Registration Number:** Our systematic review protocol has been registered
21
22 with the International Prospective Register of Systematic Reviews on October 30, 2019
23
24 (registration number CRD42019127856).
25

26 **Key words:** diabetes mellitus type 2, primary health care, systematic review, network
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28 meta-analysis.
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31 **Strengths and limitations of this study:**
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- 33 • Network meta-analysis (NMA) allows the simultaneous comparison of multiple
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35 treatment alternatives in a single model.
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- 38 • NMA improves precision of treatment effect estimates, ranks treatments
39
40 according to their effectiveness, and can assess the impact of observed treatment
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42 effects in the evidence network.
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- 45 • A potential limitation of this study can be missing outcome data, which may bias
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47 our findings. In such a case, valid imputation methods will be applied and
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49 robustness of results will be explored.
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- 52 • Intransitivity in indirect comparisons may be another potential limitation, which
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54 can impact the validity of our NMA results. In case of intransitivity, reasons for
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56 this will be explored.
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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] $\geq 7\%$).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,

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3 consequently, lower follow-up costs.⁶⁻⁹ A systematic review of the effects of group-based,
4 patient-centered training on clinical, lifestyle, and psychosocial outcomes in patients with
5 T2DM showed significant reductions in HbA1c in favor of group-based interventions.¹⁰
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7 Similarly, other strategies with similar objectives have also been reported in the
8 management of T2DM, such as psychological¹¹ and social interventions.¹²
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15 However, despite the evidence of effectiveness of these non-pharmacological
16 strategies in T2DM metabolic control, in primary healthcare settings, some RCTs have
17 not achieved similar results.¹³⁻¹⁵ In a pragmatic clustered randomized controlled trial
18 conducted in public community health centers in Cape Town involving 1,570 adults with
19 T2DM, a group diabetes education program did not show greater improvement in
20 glycemia control compared with usual care.¹⁶
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30 Since there are several different non-pharmacological strategies for the
31 management of T2DM and with contradictory results in some healthcare settings, we aim
32 to answer the following questions: In primary care, are the non-pharmacological
33 strategies effective in the glyceic control of adults with T2DM? Which of these
34 strategies have the best glyceic control?
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42 Hence, the objective of this study is to evaluate the comparative effects of non-
43 pharmacological strategies in the management of T2DM in primary care or community
44 settings.
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50 **METHODS AND DESIGN**

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53 A systematic review and network meta-analysis (NMA) for the assessment of the
54 effectiveness of all non-pharmacological strategies available for T2DM in diabetes
55 control will be performed.
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3 NMA combines direct and indirect evidence; therefore, the relative effectiveness
4 of two non-pharmacological strategies can be estimated even if studies that directly
5 compared them did not exist.
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10 Denoting nutritional therapy, social support, and usual care as non-
11 pharmacological strategies A, B, and C, respectively, an indirect comparison (AB) can be
12 obtained by subtracting the meta-analytic estimates of all studies of nutritional therapy
13 versus usual care (AC) from the estimate of all studies of social support versus usual care
14 (BC).¹⁷
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23 Traditional meta-analyses are limited to the comparisons of two groups, failing
24 to generate a complete picture of the effectiveness of non-pharmacological treatments for
25 T2DM. In the current review, since there are more than 10 strategies of interest and for
26 most there are no trials involving a direct comparison, the NMA was selected a substitute
27 of the traditional meta-analysis.
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35 The protocol of this review has been registered with the International Prospective
36 Register of Systematic Reviews (PROSPERO) database (registration number:
37 CRD42019127856), and it was developed following the Preferred Reporting Items for
38 Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P).¹⁸
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45 **Patient and Public Involvement**

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48 We will not directly include patient-level data in this study, but the protocol
49 development, priority of the research question, choice of outcome measures, and type of
50 intervention have been informed through discussions with the members of the Brazilian
51 Health Ministry and a group of patients with T2DM during follow-up in a tertiary
52 Brazilian healthcare; both identified this study as a priority area for managing patients
53 with T2DM in primary healthcare.
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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 strategies¹⁹ 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

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3 education and support (DSMES),²² (7) technology-enabled DSMES (mobile phones,
4 secure messaging, web-based information),²³(8) interventions delivered only or mainly
5 by pharmacists (DSMES and/or pharmacy management),²⁴ (9) interventions delivered
6 only or mainly by nurses (DSMES and/or pharmacy management),²⁵ (10) self-blood
7 glucose monitoring in non-insulin-treated T2DM,²⁶ (11) health coaching,²⁷ and (12)
8 benchmarking.²⁸
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12 The intervention must have been performed at the primary care (or in community
13 settings), with a minimum follow-up period of 6 months.
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16 17 18 **Comparison (C)**

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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 protocol²⁹ 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).

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

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3 circumference [WC], or body mass index [BMI]), quality of life, patient satisfaction,
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5 frequency of cardiovascular events and deaths, number of patients in each group with
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7 HbA1c <7, adverse events related to non-pharmacological strategies, and medication
8
9 adherence.
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13 **Time-frame of outcome evaluation (T)**

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16 We will include only studies with follow up greater than 6 months. The outcomes
17
18 will be evaluated at 6 to 12 months and greater than 12 months. For trials that had more
19
20 than one time of outcome evaluation, we will consider the longest time point.
21
22

23 **Exclusion Criteria**

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26 We will exclude trials that were conducted in settings other than the primary care
27
28 or community settings, trials whose aim was to compare the effectiveness of
29
30 pharmacological treatments, trials in which the intervention was any type of surgery to
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32 lose weight, trials with follow-up period less than 6 months, and trials that included
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34 predominantly participants with type 1 DM, gestational diabetes, or diabetes secondary
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36 to medication or a chronic disease.
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41 **Data sources and search strategy**

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45 Search strategies have been created and adapted to the following electronic health
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47 databases: Embase (by Elsevier, 1980–2019), Medline (by PubMed, 1966–2019), Latin
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49 American and Caribbean Health Sciences Literature (by Virtual Health Library, 1982–
50
51 2019), and Controlled Clinical Trials of the Cochrane Collaboration (Cochrane Central
52
53 Register of Controlled Trials). We have used the following index terms and their
54
55 synonyms: Diabetes Mellitus, Type 2; Primary Health Care; and Community Health
56
57 Planning. Language or year restrictions will not be considered in this study. We have used
58
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1
2
3 the validated RCT filters created by the Cochrane Collaboration for Medline and Embase.
4
5 A draft Medline search strategy is included in Appendix 1.
6
7

8 The following databases will also be searched for eligible studies: Trip database,
9
10 Scopus, Web of Science, CINAHL, Australasian Medical Index, and Chinese Biomedical
11
12 Literature Database. We will also search for studies on ClinicalTrials.gov and the gray
13
14 literature through conferences, published abstracts, and dissertations.
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18 References of relevant primary or secondary studies will be searched to identify
19
20 additional eligible studies. We will use the Endnote software to download all references
21
22 and remove duplicates. The initial screening of abstracts and titles will be performed
23
24 using the software Rayyan QCRI.³⁰
25
26

27 28 **Study selection**

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30 Four reviewers independently will perform in pairs the assessment of titles and
31
32 abstracts (RGOFL, LRB, JSCG, VSNN), and the studies potentially eligible for inclusion
33
34 in the review will be selected for full reading and subsequently assessed for adequacy to
35
36 the proposed PICOT In case of disagreement, a consensus meeting before the final
37
38 decision will be held.
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42 43 **Data extraction**

44
45 For each selected trial, the same four reviewers will use in pairs and independently
46
47 an extraction form to record the year of publication, number of patients included, duration
48
49 of follow-up, information regarding the inclusion and exclusion criteria, type of
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51 intervention (frequency, descriptions, durations), baseline data (average age, gender,
52
53 weight, BMI and WC, glycemic control prior to the study, duration of T2DM, medications
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55 in use), and all reported outcome measures (in all time points). To ensure consistency
56
57 between the reviewers, we will perform a calibration exercise before beginning the
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3 review. In the case of duplicate publications or more reports from the primary trial, data
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5 extraction will be optimized using the best information available for all the items in the
6
7 same trial.
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10 **Assessment of bias risk in the included studies**

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14 For each selected trial, the risk of bias will be assessed according to the criteria
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16 described in the revised Cochrane risk-of-bias tool for randomized trials (RoB 2 tool),³¹
17
18 which considers the following five domains for each outcome evaluated: (1) bias arising
19
20 from the randomization process, (2) bias due to deviations from intended interventions,
21
22 (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and
23
24 (5) bias in the selection of the reported result. Each of the items will be evaluated by two
25
26 reviewers as having low risk of bias, some concerns, and high risk of bias. In case of
27
28 disagreement, a discussion between the reviewers before the final classification will be
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30 held.
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35 **Data synthesis**

36 **Dealing with missing data**

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41 The authors of the original studies will be contacted, if necessary, to provide
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43 missing information for each study included. We will use the data available in published
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45 articles provided by their authors or registration platforms. If available, we will
46
47 preferentially use the data from intention-to-treat analysis. If numerical outcome data are
48
49 missing and they cannot be obtained from the authors, we will calculate them, when
50
51 possible, from other available statistics, such as p values.³² If an outcome value is reported
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53 without a measure of variance, standard deviations (SDs) will be imputed according to
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55 the method suggested by Furukawa et al.³³
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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

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2
3 across studies) will be calculated with their respective 95% CrIs. For count outcomes, we
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5 will calculate the rate ratio with a 95% CrI. For multi-arm studies, we plan to use data
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7 from all reported comparisons using the approach suggested by Rucker et al. by reducing
8
9 the relevant weighting scheme.³⁵
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11

12
13 The intervention effect estimates will be presented along with their corresponding
14
15 95% CrIs, and we will obtain the treatment hierarchy using the surface under the
16
17 cumulative ranking (SUCRA) curve, with its 95% CrI, and the rank-heat plot.^{36 37} It is
18
19 expected that the best treatment will have high SUCRA values while the worst will have
20
21 low values. For each comparison, we will present the direct, indirect, and network
22
23 estimates.
24
25

26 27 **Assessment of statistical heterogeneity**

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29
30 For direct evidence, we will assess heterogeneity by estimating the magnitude of
31
32 the between-study variance using the empirical distribution as estimated by Turner et al.³⁸
33
34 and Rhodes et al.³⁹ and by using the I^2 statistic to quantify the percentage of variability
35
36 due to true differences between studies rather than sampling error.^{40 41} We will interpret
37
38 the I^2 according to thresholds set forth by the Cochrane Collaboration³², and it will be
39
40 used as a criterion for pooling or not the results and for performing additional subgroup
41
42 analyses. For count outcomes, we will use a minimally informative prior distribution (\sim
43
44 Uniform[0,2]).⁴²
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50 If enough studies are available, we will perform subgroup analysis using the same
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52 potential treatment effect modifiers described above. Our a priori hypothesis is as follows:
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54 individuals with greater than 10 years of T2DM, taking insulin, with a poorly controlled
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56 diabetes at baseline (an uninterrupted HbA1c >8.0% for ≥ 1 year despite standard care),
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58 and with more than one of the macro or micro chronic diabetes complications, the
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3 subgroups analysis may show less improvement in the primary and secondary outcomes.
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5 We will also perform a network meta-regression whenever possible (i.e., when at least 10
6
7 studies are available) using the RE model to evaluate the impact of these potential effect
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9 modifiers (patient characteristic, study quality, intervention type, follow-up time,
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11 adherence).

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15 With the combination of direct and indirect estimates, violation of the transitivity
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17 assumption (described above) will also lead to inconsistency. We will assess loop
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19 inconsistency (disagreement between direct and indirect estimates) using the loop-
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21 specific method and design inconsistency (disagreement between studies that inform the
22
23 same treatment comparison but include a different number of treatment arms) using the
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25 design-by-treatment model based on a chi-squared test.⁴³⁻⁴⁶

26 27 28 29 **Sensitivity analysis**

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

39 40 41 42 **Assessment of publication biases**

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45 For each treatment comparison, if more than 10 studies are included in the meta-
46
47 analysis, we will use the funnel plot to investigate the presence of publication bias.³² In
48
49 such cases, we will also perform the Begg's rank correlation⁴⁷ and Egger's regression
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51 tests.⁴⁸

52 53 54 55 **Quality of evidence**

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

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

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

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

DISCUSSION

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

Since inadequate glycaemic 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 glycaemic 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:

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3 VSNN, LT, and AAV conceptualized and design the study. LT, RGOFL, AAV,
4 and VSNN drafted the manuscript protocol. VSNN, RGOFL, LRB, ALM, JSCG, FB,
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6
7 AAV, and LT critically revised the protocol and manuscript submitted. All authors read
8
9
10 and approved the final manuscript.
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12

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17
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19
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21 2020 (No. 754936).
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24 **Competing interests' statement:**

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26
27 There are no competing interests.
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30 **REFERENCES**

- 31
32
33 1. Lopez Stewart G, Tambascia M, Rosas Guzman J, et al. Control of type 2 diabetes mellitus
34 among general practitioners in private practice in nine countries of Latin America. *Rev*
35 *Panam Salud Publica* 2007;22(1):12-20. doi: 10.1590/s1020-49892007000600002
36 [published Online First: 2007/10/13]
37
38 2. Saaddine JB, Cadwell B, Gregg EW, et al. Improvements in diabetes processes of care and
39 intermediate outcomes: United States, 1988-2002. *Ann Intern Med* 2006;144(7):465-
40 74. [published Online First: 2006/04/06]
41
42 3. Franz MJ, MacLeod J. Success of nutrition-therapy interventions in persons with type 2
43 diabetes: challenges and future directions. *Diabetes Metab Syndr Obes* 2018;11:265-
44 70. doi: 10.2147/DMSO.S141952 [published Online First: 2018/06/22]
45
46 4. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention
47 with remission of type 2 diabetes. *JAMA* 2012;308(23):2489-96. doi:
48 10.1001/jama.2012.67929 [published Online First: 2013/01/05]
49
50 5. Franz MJ, Boucher JL, Rutten-Ramos S, et al. Lifestyle weight-loss intervention outcomes in
51 overweight and obese adults with type 2 diabetes: a systematic review and meta-
52 analysis of randomized clinical trials. *J Acad Nutr Diet* 2015;115(9):1447-63. doi:
53 10.1016/j.jand.2015.02.031 [published Online First: 2015/05/04]
54
55 6. American Diabetes A. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care
56 Providers. *Clin Diabetes* 2017;35(1):5-26. doi: 10.2337/cd16-0067 [published Online
57 First: 2017/02/02]
58
59 7. Jacob S, Serrano-Gil M. Engaging and empowering patients to manage their type 2 diabetes,
60 Part II: Initiatives for success. *Advances in therapy* 2010;27(10):665-80. doi:
10.1007/s12325-010-0071-0 [published Online First: 2010/09/17]

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8. Serrano-Gil M, Jacob S. Engaging and empowering patients to manage their type 2 diabetes, Part I: a knowledge, attitude, and practice gap? *Advances in therapy* 2010;27(6):321-33. doi: 10.1007/s12325-010-0034-5 [published Online First: 2010/06/17]
9. Chapman A, Liu S, Merkouris S, et al. Psychological Interventions for the Management of Glycemic and Psychological Outcomes of Type 2 Diabetes Mellitus in China: A Systematic Review and Meta-Analyses of Randomized Controlled Trials. *Frontiers in public health* 2015;3:252. doi: 10.3389/fpubh.2015.00252 [published Online First: 2015/12/05]
10. Odgers-Jewell K, Ball LE, Kelly JT, et al. Effectiveness of group-based self-management education for individuals with Type 2 diabetes: a systematic review with meta-analyses and meta-regression. *Diabetic medicine : a journal of the British Diabetic Association* 2017;34(8):1027-39. doi: 10.1111/dme.13340 [published Online First: 2017/02/23]
11. Chew BH, Vos RC, Metzendorf MI, et al. Psychological interventions for diabetes-related distress in adults with type 2 diabetes mellitus. *The Cochrane database of systematic reviews* 2017;9:CD011469. doi: 10.1002/14651858.CD011469.pub2 [published Online First: 2017/09/28]
12. Spencer-Bonilla G, Ponce OJ, Rodriguez-Gutierrez R, et al. A systematic review and meta-analysis of trials of social network interventions in type 2 diabetes. *BMJ Open* 2017;7(8):e016506. doi: 10.1136/bmjopen-2017-016506 [published Online First: 2017/08/23]
13. Browning C, Chapman A, Yang H, et al. Management of type 2 diabetes in China: the Happy Life Club, a pragmatic cluster randomised controlled trial using health coaches. *BMJ open* 2016;6(3):e009319. doi: 10.1136/bmjopen-2015-009319
14. Liss DT, Finch EA, Cooper A, et al. One-year effects of a group-based lifestyle intervention in adults with type 2 diabetes: a randomized encouragement trial. *Diabetes research and clinical practice* 2018;140:36-44. doi: 10.1016/j.diabres.2018.03.030
15. Edelman D, Dolor RJ, Coffman CJ, et al. Nurse-led behavioral management of diabetes and hypertension in community practices: a randomized trial. *Journal of general internal medicine* 2015;30(5):626-33. doi: 10.1007/s11606-014-3154-9
16. Mash RJ, Rhode H, Zwarenstein M, et al. Effectiveness of a group diabetes education programme in under-served communities in South Africa: a pragmatic cluster randomized controlled trial. *Diabetic medicine* 2014;31(8):987-93. doi: 10.1111/dme.12475
17. Cipriani A, Higgins JP, Geddes JR, et al. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013;159(2):130-7. doi: 10.7326/0003-4819-159-2-201307160-00008 [published Online First: 2013/07/17]
18. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;350:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]
19. Effective Practice and Organisation of Care (EPOC). EPOC Taxonomy 2015 [Available from: <https://epoc.cochrane.org/epoc-taxonomy> accessed 04 July 2019.
20. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes care* 2018;41(12):2669-701. doi: 10.2337/dci18-0033 [published Online First: 2018/10/07]
21. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *JAMA* 2017;318(7):637-46. doi: 10.1001/jama.2017.10169 [published Online First: 2017/08/16]
22. Chatterjee S, Davies MJ, Heller S, et al. Diabetes structured self-management education programmes: a narrative review and current innovations. *Lancet Diabetes Endocrinol*

- 2018;6(2):130-42. doi: 10.1016/S2213-8587(17)30239-5 [published Online First: 2017/10/04]
23. Greenwood DA, Gee PM, Fatkin KJ, et al. A Systematic Review of Reviews Evaluating Technology-Enabled Diabetes Self-Management Education and Support. *J Diabetes Sci Technol* 2017;11(5):1015-27. doi: 10.1177/1932296817713506 [published Online First: 2017/06/01]
24. Aubert RE, Herman WH, Waters J, et al. Nurse case management to improve glycemic control in diabetic patients in a health maintenance organization. A randomized, controlled trial. *Ann Intern Med* 1998;129(8):605-12. doi: 10.7326/0003-4819-129-8-199810150-00004 [published Online First: 1998/10/24]
25. Azami G, Soh KL, Sazlina SG, et al. Effect of a Nurse-Led Diabetes Self-Management Education Program on Glycosylated Hemoglobin among Adults with Type 2 Diabetes. *J Diabetes Res* 2018;2018:4930157. doi: 10.1155/2018/4930157 [published Online First: 2018/09/19]
26. Zhu H, Zhu Y, Leung SW. Is self-monitoring of blood glucose effective in improving glycaemic control in type 2 diabetes without insulin treatment: a meta-analysis of randomised controlled trials. *BMJ Open* 2016;6(9):e010524. doi: 10.1136/bmjopen-2015-010524 [published Online First: 2016/09/04]
27. Willard-Grace R, Chen EH, Hessler D, et al. Health coaching by medical assistants to improve control of diabetes, hypertension, and hyperlipidemia in low-income patients: a randomized controlled trial. *Ann Fam Med* 2015;13(2):130-8. doi: 10.1370/afm.1768 [published Online First: 2015/03/11]
28. Hermans MP, Elisaf M, Michel G, et al. Benchmarking is associated with improved quality of care in type 2 diabetes: the OPTIMISE randomized, controlled trial. *Diabetes care* 2013;36(11):3388-95. doi: 10.2337/dc12-1853 [published Online First: 2013/07/13]
29. Simoes Correa Galendi J, Leite R, Mendes AL, et al. Effectiveness of strategies for nutritional therapy for patients with type 2 diabetes and/or hypertension in primary care: protocol of a systematic review of randomised controlled trials. *BMJ Open* 2019;9(9):e030450. doi: 10.1136/bmjopen-2019-030450 [published Online First: 2019/09/07]
30. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First: 2016/12/07]
31. Higgins JPT SJ, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S., editor. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). *Cochrane Methods. Cochrane Database of Systematic Reviews* 2016.
32. Collaboration TC. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011], 2011.
33. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59(1):7-10. doi: 10.1016/j.jclinepi.2005.06.006 [published Online First: 2005/12/20]
34. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;62(8):857-64. doi: 10.1016/j.jclinepi.2008.10.001 [published Online First: 2009/01/23]
35. Rucker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. *Stat Med* 2014;33(25):4353-69. doi: 10.1002/sim.6236 [published Online First: 2014/06/20]
36. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64(2):163-71. doi: 10.1016/j.jclinepi.2010.03.016 [published Online First: 2010/08/07]

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 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
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 - 57
 - 58
 - 59
 - 60
37. Veroniki AA, Straus SE, Fyraridis A, et al. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. *J Clin Epidemiol* 2016;76:193-9. doi: 10.1016/j.jclinepi.2016.02.016 [published Online First: 2016/03/05]
38. Turner RM, Davey J, Clarke MJ, et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41(3):818-27. doi: 10.1093/ije/dys041 [published Online First: 2012/03/31]
39. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *J Clin Epidemiol* 2015;68(1):52-60. doi: 10.1016/j.jclinepi.2014.08.012 [published Online First: 2014/10/12]
40. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58. doi: 10.1002/sim.1186 [published Online First: 2002/07/12]
41. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557 [published Online First: 2003/09/06]
42. Lambert PC, Sutton AJ, Burton PR, et al. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. *Stat Med* 2005;24(15):2401-28. doi: 10.1002/sim.2112 [published Online First: 2005/07/15]
43. White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3(2):111-25. doi: 10.1002/jrsm.1045 [published Online First: 2012/06/01]
44. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3(2):98-110. doi: 10.1002/jrsm.1044 [published Online First: 2012/06/01]
45. Veroniki AA, Mavridis D, Higgins JP, et al. Characteristics of a loop of evidence that affect detection and estimation of inconsistency: a simulation study. *BMC Med Res Methodol* 2014;14:106. doi: 10.1186/1471-2288-14-106 [published Online First: 2014/09/23]
46. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;42(1):332-45. doi: 10.1093/ije/dys222 [published Online First: 2013/03/20]
47. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088-101. [published Online First: 1994/12/01]
48. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]
49. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9(7):e99682. doi: 10.1371/journal.pone.0099682 [published Online First: 2014/07/06]
50. Loveman E, Frampton GK, Clegg AJ. The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review. *Health technology assessment (Winchester, England)* 2008;12(9):1-116, iii. [published Online First: 2008/04/15]

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SUPPLEMENTARY DATA APPENDIX 1

Search Strategy – PubMed (November 25, 2019)

10 #1 "Diabetes Mellitus, Type 2"[Mesh] OR (Diabetes Mellitus, Noninsulin-Dependent) OR
11 (Diabetes Mellitus, Ketosis Resistant) OR (Ketosis-Resistant Diabetes Mellitus) OR (Diabetes
12 Mellitus, Non Insulin Dependent) OR (Diabetes Mellitus, Non-Insulin-Dependent) OR (Non-
13 Insulin-Dependent Diabetes Mellitus) OR (Diabetes Mellitus, Stable) OR (Stable Diabetes
14 Mellitus) OR (Diabetes Mellitus, Type II) OR(NIDDM) OR (Diabetes Mellitus, Noninsulin
15 Dependent) OR (Diabetes Mellitus, Maturity-Onset) OR (Diabetes Mellitus, Maturity Onset)
16 OR (Maturity-Onset Diabetes Mellitus) OR (Maturity Onset Diabetes Mellitus) OR (MODY)
17 OR (Diabetes Mellitus, Slow-Onset) OR (Diabetes Mellitus, Slow Onset) OR (Slow-Onset
18 Diabetes Mellitus) OR (Type 2 Diabetes Mellitus) OR (Noninsulin-Dependent Diabetes
19 Mellitus) OR (Noninsulin Dependent Diabetes Mellitus) OR (Maturity-Onset Diabetes) OR
20 (Diabetes, Maturity-Onset) OR (Maturity Onset Diabetes) OR (Type 2 Diabetes) OR
21 (Diabetes, Type 2) OR (Diabetes Mellitus, Adult-Onset) OR (Adult-Onset Diabetes Mellitus)
22 OR (Diabetes Mellitus, Adult Onset)

23
24
25 #2 "Primary Health Care"[Mesh] OR (Care, Primary Health) OR (Health Care, Primary) OR
26 (Primary Healthcare) OR (Healthcare, Primary) OR (Primary Care) OR (Care, Primary) or
27 "Physicians, Primary Care"[Mesh] OR (Physician, Primary Care) OR (Primary Care Physician)
28 OR (Primary Care Physicians) OR (Healthy Primary Care) OR "Primary Care Nursing"[Mesh]
29 OR (Care Nursing, Primary) OR (Nursing, Primary Care)

30
31
32 #3 "Community Health Planning"[Mesh] OR (Community Health Plannings) OR (Health
33 Planning, Community) OR (Health Plannings, Community) OR (Planning, Community Health)
34 OR (Plannings, Community Health) OR (Population-Based Planning) OR (Planning,
35 Population-Based) OR (Plannings, Population-Based) OR (Population Based Planning) OR
36 (Population-Based Plannings) OR (Community Health Systems) OR (Community Health
37 System) OR (Health System, Community) OR (Health Systems, Community) OR (System,
38 Community Health) OR (Systems, Community Health)

39
40
41
42 #4* randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR
43 placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT
44 (animals[mh] NOT humans [mh])

45
46 #1 AND #2 AND #3 AND #4

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48
49 * Direct link to PubMed with **sensitivity- and precision-maximizing version**(2008
50 revision).¹ Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies.
51 In: Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of
52 Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration,
53 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.

Upload your completed checklist as an extra file when you submit to a journal.

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

1			changes; otherwise, state plan for documenting important	
2			protocol amendments	
3				
4	Sources	#5a	Indicate sources of financial or other support for the review	17
5				
6	Sponsor	#5b	Provide name for the review funder and / or sponsor	17
7				
8	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or	n/a
9	funder		institution(s), if any, in developing the protocol	
10				
11				
12	Rationale	#6	Describe the rationale for the review in the context of what is	4
13			already known	
14				
15				
16	Objectives	#7	Provide an explicit statement of the question(s) the review	7-9
17			will address with reference to participants, interventions,	
18			comparators, and outcomes (PICO)	
19				
20				
21	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	7-9
22			design, setting, time frame) and report characteristics (such	
23			as years considered, language, publication status) to be	
24			used as criteria for eligibility for the review	
25				
26				
27				
28	Information	#9	Describe all intended information sources (such as	9
29	sources		electronic databases, contact with study authors, trial	
30			registers or other grey literature sources) with planned dates	
31			of coverage	
32				
33				
34				
35	Search strategy	#10	Present draft of search strategy to be used for at least one	Supp.
36			electronic database, including planned limits, such that it	Data
37			could be repeated	
38				
39				
40	Study records -	#11a	Describe the mechanism(s) that will be used to manage	9-10
41	data management		records and data throughout the review	
42				
43				
44	Study records -	#11b	State the process that will be used for selecting studies	10
45	selection process		(such as two independent reviewers) through each phase of	
46			the review (that is, screening, eligibility and inclusion in	
47			meta-analysis)	
48				
49				
50				
51	Study records -	#11c	Describe planned method of extracting data from reports	10
52	data collection		(such as piloting forms, done independently, in duplicate),	
53	process		any processes for obtaining and confirming data from	
54			investigators	
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1	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
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6	Outcomes and	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
7	prioritization			
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10				
11	Risk of bias in	#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
12	individual studies			
13				
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18	Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-13
19				
20				
21				
22		#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 I ² , Kendall's τ)	11-13
23				
24				
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28				
29		#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
30				
31				
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33		#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
34				
35				
36	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
37				
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42	Confidence in	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14-15
43	cumulative			
44	evidence			
45				
46				

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