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The effects of physical activity interventions on glycosylated haemoglobin A1c in the general population: a protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction: Epidemiological evidence suggests that physical activity has a positive effect of reducing glycosylated haemoglobin A1c (HbA1c) levels not only in diabetics, but also in healthy adults. Moreover, a positive association of HbA1c levels with cardiovascular disease and mortality in non-diabetic populations has recently been reported. This is a protocol for a systematic review and meta-analysis aiming to estimate the effects of physical activity on glycaemic control measured by HbA1c levels in general and non-diabetic populations; and to determine which type of physical activity has a greater influence on glycaemic control.

Methods and analysis: The search will be conducted using MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Web of Science databases from inception to mid-2017. Randomised controlled trials, non-randomized experimental studies and controlled pre–post studies written in English, Portuguese or Spanish will be included. The Cochrane Collaboration's tool and The Quality Assessment Tool for Quantitative Studies will be used to assess the risk of bias for the studies included in the systematic review. Standardised pre–post intervention mean differences of HbA1c with 95% confidence intervals will be calculated as primary outcome. Subgroup analyses will be performed based on the type of physical activity intervention, the type of population included in the studies and the age of the participants.

Ethics and dissemination: This systematic review will synthesise evidence on the association of physical activity and HbA1c levels in general and non-diabetic populations. The results will be disseminated by publication in a peer-reviewed journal. Ethics approval will not be required because the data used for this systematic review will be obtained from published studies and there will be no concerns about privacy.

Trial registration number: PROSPERO CRD42016050991.

Key words: HbA1c, physical activity, meta-analysis

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Strengths and limitations of this study

- This study presents a comprehensive methodology for analysing the effect of physical activity interventions on glycaemic control measured using HbA1c levels in general and non-diabetic populations.
- Two researchers will independently perform study selection, data extraction and quality assessment.
- The assessment of risk of bias of the selected studies and heterogeneity among studies included, with particular reference to study design and sample characteristics, is a featured point in this evidence review.
- The differences among physical activity interventions could be a source of variable quality and heterogeneity among studies, and may limit the quality of the evidence of this meta-analysis.

INTRODUCTION

Currently, guidelines from the American Diabetes Association (ADA)[1] and the World Health Organization (WHO)[2] propose glycosylated haemoglobin A1c (HbA1c) levels greater than 6.5% for the diagnosis of diabetes. Also, recent meta-analyses have reported an increase for all-cause mortality with HbA1c levels around 5.7% in non-diabetic and around 7.5% in diabetic populations.[3,4] HbA1c is a biochemical test useful to identify people with subclinical diabetes at the onset of clinical symptoms. Since micro vascular complications of diabetes are present in the early stages of the disease, controlling HbA1c levels should not be restricted to the diabetic population.

Substantial evidence supports that physical activity reduces the risk of dying prematurely because of its positive influence on a variety of health conditions, such as cardiovascular disease, diabetes and other disorders of metabolism, as well as neurological diseases, sarcopenia, osteoporosis and cancer.[6,7] In the case of diabetes, up to 46% of the incidence could be reduced by engaging in physical activity programs[8]; moreover, these programs have revealed improvements in glycaemic control and metabolic profile among both diabetic and non-diabetic populations.[9] One meta-analysis concluded that structured physical activity such as aerobic exercise, resistance training, or the combination of both may be associated with HbA1c reduction in patients with

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type 2 diabetes.[10] Additionally, evidence has suggested that structured physical activity could substantially reduce the incidence of type 2 diabetes.[11-14]

Thus, physical activity is widely perceived to be beneficial for preventing type 2 diabetes and for controlling glycaemic levels in patients with type 2 diabetes, but evidence supporting a positive effect in the control of glycaemic levels in healthy people is rather weak.[15] Therefore, considering the increasing incidence of type 2 diabetes in industrialized countries, determining the effect of physical activity interventions to control HbA1c levels in non-diabetic populations is an important public health issue.

The purpose of this protocol is to provide the methodology for a review of intervention studies addressing the effectiveness of physical activity interventions in reducing HbA1c levels in general and non-diabetic populations.

OBJECTIVE

This systematic review and meta-analysis protocol presents an objective and clear procedure for the extraction of information from experimental studies (randomised controlled trials [RCTs], non-randomized experimental studies and controlled pre–post studies), in which data on changes in HbA1c levels have been reported as an outcome, in order to: i) estimate the effects of physical activity on glycaemic control measured by HbA1c levels in the general population and in non-diabetic populations; and ii) determine which type of physical activity (based on qualitative or quantitative characteristics) has a greater positive influence on glycaemic control.

METHODS AND ANALYSIS

This systematic review and meta-analysis protocol is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[16] and the Cochrane Collaboration Handbook.[17] This protocol has been previously registered in PROSPERO (registration number: CRD42016050991).

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Inclusion/exclusion criteria for study selection

Type of studies

Randomised controlled trials, non-randomized experimental studies and controlled pre–post studies written in English, French, Portuguese or Spanish.

Type of participants

Studies assessing the effect, in general and non-diabetic populations, of physical activity interventions on glycaemic control measured by HbA1c levels will be selected. Studies will be selected regardless of the age of the participants included. Studies will be excluded when they include: i) exclusively subjects who have been diagnosed with diabetes; and ii) more than 8.5% of diabetics in the sample (diabetes global prevalence according to WHO)[18] and/or when the prevalence of diabetes in the sample is unknown. When more than one study provides data referring to the same sample, we will choose the one presenting the most detailed results or providing the largest sample size.

Type of interventions

Studies reporting any type of intervention consisting mainly of physical activity, understood as repeated bouts of exercise over time involving multiple sessions during a number of weeks, will be eligible for inclusion. Studies comparing different types of physical activity interventions or examining a specific physical activity intervention with or without a control group will be eligible for inclusion. Also, studies consisting of advice on physical activity will be included. Nevertheless, studies combining physical activity with other health interventions, such as nutritional interventions, will be excluded when data concerning the effectiveness of physical activity programmes on glycaemic control measured by HbA1c levels cannot be extracted separately.

Type of outcome assessment

Studies in which glycaemic control is an outcome measured using any of the different methods certified by the National Glycohemoglobin Standardization Program (NGSP)

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for testing HbA1c will be included. Studies will be included regardless of the unit in which HbA1c levels were measured, for instance percentage (%) or mmol/mol.

Search methods for the identification of studies

Electronic search

The literature search will be conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Web of Science databases from inception to 31st June, 2017. The searches will be re-done just before the final analyses, in order to search for further potential studies. Study records will be managed using the Mendeley reference manager.

The following search terms will be combined by Boolean operators for conducting the literature search: “physical activity”, “physical fitness”, “physical exercise”, exercise, “intense exercise”, “exercise training”, “glycemic control”, “metabolic outcomes”, “HbA1c”, “haemoglobin level”, “glycated haemoglobin”, “randomised control trial”, RCT, “quasi-experimental study”, non-RCT and “controlled pre–post study” (Table 1).

Previous reviews and meta-analyses, and relevant references cited in the selected studies will be screened as supplemental sources.

Data collection and analysis

Selection of studies

The title and abstract of retrieved articles will be independently evaluated by two reviewers in order to identify eligible studies according to the inclusion criteria. Then, full manuscripts of the identified studies will be examined. Finally, the two reviewers will review the included and excluded studies in order to verify the reasons for inclusion/exclusion (Figure 1). Abstracts not providing enough information regarding the inclusion/exclusion criteria will be selected for full-text evaluation. The reviewers will not be blinded to the authors, institutions or manuscript journals of the reviewed papers. Disagreements will be solved by consensus; when disagreements persist after discussion, a third reviewer will be required.

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Two authors will independently extract information from the included studies regarding the main study characteristics: author, year of publication, country, study design, number and age of participants, population characteristics (healthy or with any specific disease), prevalence of diabetes, methods certified by the NGSP used for HbA1c testing, HbA1c mean values before the intervention, and type and characteristics of the physical activity intervention (Table 2). In order to avoid double counting of patients because they have been included in more than one report by the same author or working group, the recruitment periods will be evaluated. When necessary, corresponding authors of the potentially included studies will be contacted to obtain any missing information.

Any disagreements will be resolved by discussion to reach a consensus.

Assessment of risk of bias in the included studies

Two researchers will independently conduct a quality assessment according to the Cochrane Collaboration Handbook recomendations.[17] Any disagreements will be resolved by discussion and a third reviewer will solve the disagreements if consensus is not reached.

Methodological quality of the RCTs will be assessed using The Cochrane Collaboration's tool for assessing risk of bias.[19] This tool evaluates the risk of bias according to six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.

The Quality Assessment Tool for Quantitative Studies[20] is proposed to assess the quality of pre–post studies and non-RCTs. This tool evaluates seven domains: selection bias, study design, confounders, blinding, data collection method, withdrawals and drop-outs.

In both quality assessment tools, each domain could be considered as strong, moderate or weak, and studies could be classified as low risk of bias (with no weak ratings), moderate risk of bias (with one weak rating) and high risk of bias (with two or more weak ratings). The agreement rate between reviewers will be reported by calculating kappa statistics.

Data synthesis

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The researchers will create ad hoc tables to summarise the characteristics of the included studies and any important questions related to the aim of this systematic review. The reviewers will determine whether a meta-analysis is possible after data extraction. At least five observations addressing the same specific outcome will be required to conduct a meta-analysis; where a meta-analysis is not feasible, we will undertake a narrative synthesis. Studies providing insufficient data to perform the analyses will be omitted from data syntheses.

If a meta-analysis is possible, STATA 14 software will be used to combine the pooled mean differences with 95% confidence intervals (CI). A fixed-effects model will be used if there is no evidence of heterogeneity; otherwise, a random-effects model will be used. Study heterogeneity will be assessed with an I^2 statistic. I^2 values are considered as: might not be important (0% to 40%); may represent moderate heterogeneity (30% to 60%); may represent substantial heterogeneity (50% to 90%) and considerable heterogeneity (75% to 100%), the corresponding p-values will also be taken into account.[17]

Data from intention-to-treat analyses will be considered whenever available in RCTs. The HbA1c pre–post intervention mean difference will be the primary indicator of the intervention outcome. Standardised mean differences (standard deviation (SD)) will be calculated for HbA1c levels. For example, when the standard error (SE) is provided, the SD will be calculated according to the following formula: $SD = SE \times \sqrt{n}$. Finally, publication bias will be assessed using a contour-enhanced funnel plot of each effect size against the standard error. Funnel plot asymmetry will be visually evaluated, as well as with the method proposed by Egger,[21] and a significant publication bias will be considered to be present if the p-value is less than 0.10.[22] The trim-and-fill computation will be used to assess the effect of publication bias on the interpretation of results.[23]

Subgroup analysis and meta-regression

Subgroup analyses and meta-regression will be performed based on the type of physical activity intervention (leisure-time physical activity, physical activity programme or physical activity counselling), type of population included in the studies (general population and non-diabetic population), type of studies design (RCT, non-RCT and controlled pre–post studies), age of participants (children and/or adolescents, young

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adults aged 18–35 years, middle-aged adults aged 36–55 years or older adults aged above 55 years), because these are the potential major factors causing heterogeneity. Furthermore, the methodological quality of studies included will be considered for additional subgroup analyses.

Sensitivity analysis

Sensitivity analyses will be conducted excluding studies from the analysis one by one. These will be performed to prove that the findings from the meta-analysis do not depend on arbitrary or unclear decisions.

DISCUSSION

An association between physical activity interventions and glycaemic control measured by HbA1c levels has been reported by recent systematic reviews and meta-analyses in both type 2[24-28] and type 1 diabetic populations.[29,30] One meta-analysis[28] reported no significant benefits of glycaemic control in non-diabetic populations, but included only three intervention studies divided in two subgroups (healthy and chronic disease). No previous systematic review or meta-analysis has included studies in the general population or in non-diabetics. Therefore, the aim of this protocol is to present a clear and reliable methodology to estimate the effects of physical activity on glycaemic control measured by HbA1c levels in general and non-diabetic populations.

There are some sources of heterogeneity that will be controlled in this systematic review and meta-analysis. Those sources of variability will be determined by analysing the design (type of study, type of intervention and control group, sample size, and length of intervention) and the sample characteristics (type of population, age range and gender distribution) of the included studies.

As different study designs will be considered for inclusion, we will use two quality assessment tools: The Cochrane Collaboration's tool for assessing risk of bias[19] and Quality Assessment Tool for Quantitative Studies.[20] Both tools are rigorously developed, evidence-based, valid, reliable and easy to use.[31]

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Random-effects meta-regression will be used to evaluate whether the relationship between physical activity and glycaemic levels could differ according to certain sample characteristics and whether those characteristics could be considered major sources of heterogeneity.[32] Additionally, subgroup analyses in this meta-analysis will be designed to control for heterogeneity between the studies. To determine the level of heterogeneity, we will use the definition suggested by the Cochrane Collaboration Handbook.[17]

Potential limitations of this research may be publication bias, information bias, poor statistical analyses, and inadequate reporting of methods and findings of the primary studies.[22] However, it is important to summarise the information available on this issue. To overcome these limitations, we will follow the recommendations included in the PRISMA[33] and the Cochrane Collaboration Handbook.[17]

Numerous meta-analyses synthesizing the effects of physical activity on glycaemic control measured by HbA1c levels in diabetic populations have already been conducted. However, there is no meta-analysis in the general population and/or non-diabetic populations relating physical activity with glycaemic control measured by HbA1c levels, despite the increasing number of intervention studies on this association. Therefore, it seems necessary to conduct a systematic review that could provide a global overview of the current literature and could also improve future research on this topic. This protocol provides a clear and structured procedure for maximising the extraction and summarising of relevant information on the association of physical activity and HbA1c levels.

Authors' contributions: VMV and ICR designed the study. VMV was the principal investigator and guarantor. ICR and VMV were the main coordinators of the study. BP, CAB, and VMV conducted the study. ICR, BP, EA and CAB gave statistical and epidemiological support. ICR wrote the article with the support of EA and BP. All authors revised and approved the final version of the manuscript.

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Competing interests: None

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Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.

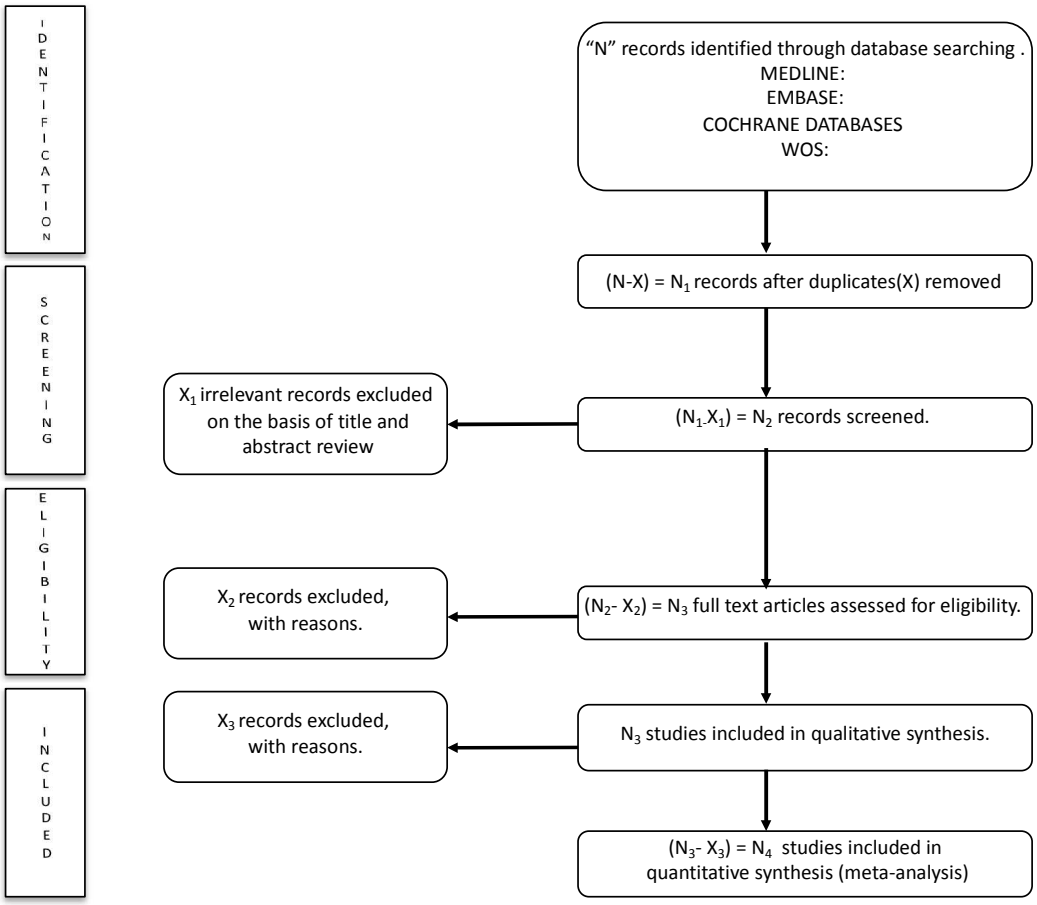

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Table 1. Search strategy for MEDLINE.

"physical activity" OR "physical fitness" OR "physical exercise" OR exercise OR "intense exercise" OR "exercise training"	AND	"glycemic control" OR "metabolic outcomes" OR HbA1c OR "haemoglobin level" OR "glycated haemoglobin"	AND	"randomised control trial" OR RCT OR "quasi-experimental study" OR non-RCT OR "controlled pre–post study"

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Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

			Population characteristics				Outcome		Intervention characteristics	
Reference	**Country**	**Study Design**	**Age distribution**	**Sample size**	**Type of population**	**Diabetes prevalence**	**HbA1c method**	**HbA1c levels**	**Physical activity intervention**	**Physical activity characteristics**
Author information and year of publication	*Country*	*Design of the study*	*Age* (years) *of the participants range or mean ± SD*	*Number of participants*	*Population characteristics (healthy or with any specific disease)*	*Number of cases with diabetes (%)*	*Methods certified by the NGSP used for HbA1c testing*	*HbA1c mean value before and after the intervention*	*Type of physical activity intervention (leisure-time physical activity, physical activity programme or physical activity counselling)*	*Definition of physical activity intervention (duration of intervention, number of sessions and duration of each session)*

HbA1c: Glycosilated haemoglobin A1c; SD: Standard deviation; NGSP: National Glycohemoglobin Standardization Program.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1; line 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2; line 50
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1; line 3-22
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 10; line 270-274
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 10; line 275-276
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4; line 67-94
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4; line 96-103
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5; line 112-139
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other	Page 6; line

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

		grey literature sources) with planned dates of coverage	140-153
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6; line 155-164
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6-7; line 165-174
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6-7; line 165-174
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	Page 6-7; line 165-174 Table 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7; line 175-190
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7-8; line 191-198
	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)	Page 8; line 199-215
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 8-9; line 216-230
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 7-8; line 194-197
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8; line 212-215
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The effects of physical activity interventions on glycated haemoglobin A1c in non-diabetic population: a protocol for a systematic review and meta-analysis.

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The effects of physical activity interventions on glycated haemoglobin A1c in non-diabetic population: a protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction: Epidemiological evidence suggests that physical activity has a positive effect on reducing glycated haemoglobin A1c (HbA1c) levels not only in diabetics, but also in healthy subjects. Moreover, a positive association of HbA1c levels with cardiovascular disease and mortality in non-diabetic populations has recently been reported. This is a protocol for a systematic review and meta-analysis aiming to estimate the effects of physical activity on glycaemic control measured by HbA1c levels in non-diabetic populations; and to determine which type of physical activity has a greater influence on glycaemic control.

Methods and analysis: The search will be conducted using MEDLINE, EMBASE, the Cochrane Library and Web of Science databases from inception to mid-2017. Randomised controlled trials, non-randomised experimental studies and controlled pre–post studies written in English, Portuguese, French or Spanish will be included. The Cochrane Collaboration's tool and The Quality Assessment Tool for Quantitative Studies will be used to assess the risk of bias for studies included in the systematic review. Standardised pre–post intervention mean differences of HbA1c will be calculated as the primary outcome. Subgroup analyses will be performed based on the characteristics of physical activity intervention and population included in the studies.

Ethics and dissemination: This systematic review will synthesise evidence on the association of physical activity and HbA1c in non-diabetic populations. This study is important from the clinical and public health point because it will estimate the effect of physical activity on the glycemic control, and it will also examine which is the type of physical activity that should be recommended for preventing type 2 diabetes and its complications. The results will be disseminated by publication in a peer-reviewed journal. Ethical approval will not be required because the data used for this systematic review will be obtained from published studies and there will be no concerns about privacy.

Trial registration number: PROSPERO CRD42016050991.

Key words: HbA1c, physical activity, meta-analysis

Strengths and limitations of this study

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- This study presents a comprehensive methodology for analysing the effect of physical activity interventions on glycaemic control measured using HbA1c levels in general and non-diabetic populations.

- Two researchers will independently perform study selection, data extraction and quality assessment.

- The assessment of risk of bias of the selected studies and heterogeneity among studies included, with particular reference to study design and sample characteristics, is a featured point in this evidence review.

- The differences among physical activity interventions could be a source of variable quality and heterogeneity among studies, and may limit the quality of the evidence of this meta-analysis.

INTRODUCTION

Currently, guidelines from the American Diabetes Association (ADA)[1] and the World Health Organization (WHO)[2] propose glycated haemoglobin A1c (HbA1c) levels greater than 6.5% (48.0 mmol/mol) for the diagnosis of diabetes. Also, recent meta-analyses have reported an increase for all-cause mortality with HbA1c levels around 5.7% (39.0 mmol/mol) in non-diabetic and around 7.5% (58.0 mmol/mol) in diabetic populations.[3,4] HbA1c is a biochemical test useful to identify people with subclinical diabetes at the onset of clinical symptoms.[5] Since micro vascular complications of diabetes are present in the early stages of the disease, controlling HbA1c levels should not be restricted to the diabetic population.

Substantial evidence supports that physical activity reduces the risk of dying prematurely because of its positive influence on a variety of health conditions, such as cardiovascular disease, diabetes and other disorders of metabolism, as well as neurological diseases, sarcopenia, osteoporosis and cancer.[6,7] The Surgeon General's Report on Physical Activity and Health[8] underscores the pivotal role physical activity plays in health promotion and disease prevention. It recommends that individuals should accumulate 30 min of moderate physical activity on most days of the week. Research suggests that more than 60% of adults do not achieve the recommended amount of physical activity and 25% of adults are not physically active at all. Among

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young people, almost 50% do not regularly practice vigorous physical activity. A previous meta-analysis showed that higher levels of physical activity (3000-4000 MET minutes/week) were significantly associated with lower risk for breast cancer, colon cancer, diabetes, ischemic heart disease and ischemic stroke events.[9] In the case of diabetes, up to 46% of the incidence could be reduced by engaging in physical activity programs;[10] moreover, these programs have revealed improvements in glycaemic control and metabolic profile among both diabetic and non-diabetic populations.[11] One meta-analysis concluded that structured physical activity such as aerobic exercise, resistance training or the combination of both may be associated with HbA1c reduction in patients with type 2 diabetes. This study showed that aerobic exercise, resistance training and both combined were associated with HbA1c reductions of 0.73%, 0.57% and 0.51%, respectively. Also, structured exercise lasting more than 150 minutes per week was associated with HbA1c reductions of 0.89%.[12] Additionally, evidence has suggested that structured physical activity could substantially reduce the incidence of type 2 diabetes.[13-16]

In most industrialized countries, there is an alarming increase of the incidence of type 2 diabetes in children and adolescents with low levels of physical activity. This growing incidence parallels the childhood obesity pandemic.[17] A previous meta-analysis has proven the effectiveness of a high intensity physical activity intervention on reducing adiposity, and also on mitigating the risk of type 2 diabetes and its cardiovascular complications in adulthood.[18]

Thus, physical activity is widely perceived to be beneficial for preventing type 2 diabetes and for controlling glycaemic levels in patients with type 2 diabetes, but evidence supporting a positive effect in the control of glycaemic levels in healthy people is rather weak.[19] Therefore, considering the increasing incidence of type 2 diabetes in industrialized countries, determining the effect of physical activity interventions to control HbA1c levels in non-diabetic populations is an important public health issue.

The purpose of this protocol is to provide the methodology for a review of intervention studies addressing the effectiveness of physical activity interventions in reducing HbA1c levels in general and non-diabetic populations.

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OBJECTIVE

This systematic review and meta-analysis protocol presents an objective and clear procedure for the extraction of information from experimental studies (randomised controlled trials [RCTs], non-randomised experimental studies and controlled pre–post studies), in which data on changes in HbA1c levels are reported as an outcome, in order to: i) estimate the effects of physical activity on glycaemic control measured by HbA1c levels in non-diabetic populations; and ii) determine which type of physical activity (based on qualitative or quantitative characteristics) has a greater positive influence on glycaemic control.

METHODS AND ANALYSIS

This systematic review and meta-analysis protocol is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[20] and the Cochrane Collaboration Handbook.[21] This protocol has been previously registered in PROSPERO (registration number: CRD42016050991).

Inclusion/exclusion criteria for study selection

Type of studies

Randomised controlled trials, non-randomised experimental studies and controlled pre–post studies written in English, French, Portuguese, French or Spanish.

Type of participants

Studies assessing the effect, in general and non-diabetic populations, of physical activity interventions on glycaemic control measured by HbA1c levels will be selected. Studies will be selected regardless of the age of the participants included. Studies will be excluded when they include exclusively subjects who have been diagnosed with diabetes. When more than one study provides data referring to the same sample, we will choose the one presenting the most detailed results or providing the largest sample size.

Type of interventions

Studies reporting any type of intervention consisting mainly of physical activity (endurance, resistance or alternative exercise [such as yoga or pilates]), understood as

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repeated bouts of exercise over time involving more than two sessions/week with a duration of at least 3 weeks, will be eligible for inclusion. Studies comparing different types of physical activity interventions or examining a specific physical activity intervention with or without a control group will be eligible for inclusion. Also, studies consisting of advice on physical activity will be included. Nevertheless, studies combining physical activity with other health interventions, such as nutritional interventions, will be excluded when data concerning the effectiveness of physical activity programmes on glycaemic control measured by HbA1c levels cannot be extracted separately.

Type of outcome assessment

Studies in which glycaemic control is an outcome measured using any of the different methods certified by the National Glycohemoglobin Standardization Program (NGSP) and standardised by the International Federation of Clinical Chemistry Working Group (IFCC) for testing HbA1c will be included. Studies will be included regardless of the unit in which HbA1c levels were measured, for instance percentage (%) or mmol/mol.

Search methods for the identification of studies

Electronic search

The literature search will be conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Web of Science databases from inception to June 31st, 2017. The searches will be re-done just before the final analyses, in order to search for further potential studies. Study records will be managed using the Mendeley reference manager.

The following search terms will be combined by Boolean operators for conducting the literature search: “physical activity”, “physical fitness”, “physical exercise”, exercise, “intense exercise”, “exercise training”, “glycemic control”, “metabolic outcomes”, “HbA1c”, “haemoglobin level”, “glycated haemoglobin”, “randomised control trial”, RCT, “quasi-experimental study”, non-RCT and “controlled pre–post study” (Table 1).

Previous reviews and meta-analyses, and relevant references cited in the selected studies will be screened.

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Data collection and analysis

Selection of studies

The title and abstract of retrieved articles will be independently evaluated by two reviewers in order to identify eligible studies according to the inclusion criteria. Then, full manuscripts of the identified studies will be examined. Finally, the two reviewers will review the included and excluded studies in order to verify the reasons for inclusion/exclusion (Figure 1). Abstracts not providing enough information regarding the inclusion/exclusion criteria will be selected for full-text evaluation. The reviewers will not be blinded to the authors, institutions or journals of the reviewed papers. Disagreements will be solved by consensus; when disagreements persist after discussion, a third reviewer will be required.

Two authors will independently extract information from the included studies regarding the main study characteristics: author, year of publication, country, study design, number and age of participants, population characteristics (healthy or with any specific disease), prevalence of diabetes, methods certified by the NGSP and standardised by the IFCC used for HbA1c testing, HbA1c mean values before the intervention, and type and characteristics of the physical activity intervention (Table 2). In order to avoid double counting of patients because they have been included in more than one report by the same author or working group, the recruitment periods will be evaluated. When necessary, corresponding authors of the potentially included studies will be contacted to obtain any missing information.

Any disagreements will be resolved by discussion to reach a consensus.

Assessment of risk of bias in the included studies

Two researchers will independently conduct a quality assessment according to the Cochrane Collaboration Handbook recomendations.[21] Any disagreements will be resolved by discussion and a third reviewer will solve disagreements if consensus is not reached.

The methodological quality of the RCTs will be assessed using The Cochrane Collaboration's tool for assessing risk of bias.[22] This tool evaluates the risk of bias

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according to six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.

The Quality Assessment Tool for Quantitative Studies[23] assesses the quality of pre–post studies and non-RCTs. This tool evaluates seven domains: selection bias, study design, confounders, blinding, data collection method, withdrawals and drop-outs.

In both quality assessment tools, each domain will be considered as strong, moderate or weak, and studies will be classified as low risk of bias (with no weak ratings), moderate risk of bias (with one weak rating) and high risk of bias (with two or more weak ratings). The agreement rate between reviewers will be reported by calculating kappa statistics.

Data synthesis

The researchers will create ad hoc tables to summarise the characteristics of the included studies and any important questions related to the aim of this systematic review. The reviewers will determine whether a meta-analysis is possible after data extraction. At least five observations addressing the same specific outcome will be required to conduct a meta-analysis; where a meta-analysis is not feasible, we will undertake a narrative synthesis. Studies providing insufficient data to perform the analyses will be omitted from data syntheses.

If a meta-analysis is possible, STATA 14 software will be used to combine the pooled mean differences with 95% confidence intervals (CI). A fixed-effects model will be used if there is no evidence of heterogeneity; otherwise, a random-effects model will be used. Study heterogeneity will be assessed with the I^2 statistic. I^2 values will be considered as: might not be important (0% to 40%); may represent moderate heterogeneity (30% to 60%); may represent substantial heterogeneity (50% to 90%) and considerable heterogeneity (75% to 100%), the corresponding p-values will also be taken into account.[21]

Data from intention-to-treat analyses will be considered whenever available in RCTs. The HbA1c pre–post intervention mean difference will be the primary indicator of the intervention outcome. Standardised mean differences (standard deviation [SD]) will be calculated for HbA1c levels. Finally, publication bias will be assessed using a contour-

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enhanced funnel plot of each effect size against the standard error. Funnel plot asymmetry will be visually evaluated, as well as with the method proposed by Egger,[24] and significant publication bias will be considered to be present if the p-value is less than 0.10.[25] The trim-and-fill computation will be used to assess the effect of publication bias on the interpretation of results.[26]

Subgroup analysis and meta-regression

Subgroup analyses and meta-regression will be conducted by age of participants (children and/or adolescents, young adults aged 18–35 years, middle-aged adults aged 36–55 years or older adults aged above 55 years), type of physical activity intervention (leisure-time physical activity, active commuting, physical activity programme or physical activity counselling), type of exercise (endurance, resistance or alternative exercises), length of physical activity intervention (above or below 12 weeks), physical activity duration per week (above or below 150 minutes), type of study design (RCT, non-RCT and controlled pre–post studies), because these may be the potential major factors to cause heterogeneity. Furthermore, the methodological quality of studies included will be considered for additional subgroup analyses.

Sensitivity analysis

Sensitivity analyses will be conducted excluding studies from the analysis one by one. These will be performed to prove that the findings from the meta-analysis do not depend on arbitrary or unclear decisions.

ETHICS AND DISSEMINATION

An association between physical activity interventions and glycaemic control measured by HbA1c levels has been reported by recent systematic reviews and meta-analyses in both type 2[27-31] and type 1 diabetic populations.[32,33] One meta-analysis[31] reported no significant benefits of glycaemic control in non-diabetic populations, but included only three intervention studies divided in two subgroups (healthy and chronic disease). No previous systematic review or meta-analysis has included studies in non-diabetics. Therefore, the aim of this protocol is to present a clear and reliable methodology to estimate the effects of physical activity on glycaemic control measured by HbA1c levels in general and non-diabetic populations.

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There are some sources of heterogeneity that will be controlled in this systematic review and meta-analysis. Sources of variability will be determined by analysing the design (type of study, type of intervention and control group, sample size, and length of intervention) and the sample characteristics (type of population, age range and gender distribution) of the studies included.

As different study designs will be considered for inclusion, we will use two quality assessment tools: the Cochrane Collaboration's tool for assessing risk of bias[22] and the Quality Assessment Tool for Quantitative Studies.[23] Both tools were rigorously developed, and are evidence-based, valid, reliable and easy to use.[34]

Random-effects meta-regression will be used to evaluate whether the relationship between physical activity and glycaemic levels could differ according to certain sample characteristics and whether those characteristics could be considered major sources of heterogeneity.[35] Additionally, subgroup analyses in this meta-analysis will be conducted to control for heterogeneity between the studies. To determine the level of heterogeneity, we will use the definition suggested by the Cochrane Collaboration Handbook.[21]

Therefore, some aspects of physical activity that currently seem to be controversial will be deeply studied in this meta-analysis, such as the effect that each type of physical activity could produce on glycemic control measured by HbA1c in non-diabetic populations. The evidence of the effect of each type of physical activity might help to establish physical activity programs tailored to the characteristics of each subject and the aimed objectives. Moreover, whether physical activity counseling interventions that involve written advice by a health professional are capable of increasing the daily amount of time that patients spend on physical exercise-related activities should be clarified.[36] Finally, another important issue to take into account in this meta-analysis will be whether complying with The Surgeon General's Report on Physical Activity and Health recommendations has beneficial effects on glycemic control in non-diabetic populations.

Potential limitations of this research may be publication bias, information bias, poor statistical analyses, and inadequate reporting of methods and findings of the studies included.[25] However, it is important to summarise the information available on this

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issue. To overcome these limitations, we will follow the recommendations included in the PRISMA[37] and the Cochrane Collaboration Handbook.[21]

Numerous meta-analyses synthesizing the effects of physical activity on glycaemic control measured by HbA1c levels in diabetic populations have already been conducted. However, there is no meta-analysis in non-diabetic populations relating physical activity with glycaemic control measured by HbA1c levels, despite the increasing number of intervention studies on this association. Therefore, it seems necessary to conduct a systematic review that may provide a global overview of the current literature and could also improve future research on this topic. This protocol provides a clear and structured procedure for maximising the extraction, and summarising of relevant information on the association of physical activity and HbA1c levels. This study will have important clinical and public health implications, because it could provide support to recommend physical exercise in non-diabetic subjects as this may be useful for preventing type 2 diabetes and its complications. According to the findings of this systematic review and meta-analysis, suggestions for future research will be made, and recommendations for evidence-based physical activity interventions for glycaemic control and prevention of diabetes mellitus in healthy subjects will be implemented.

Authors' contributions: VMV and ICR designed the study. VMV was the principal investigator and guarantor. ICR and VMV were the main coordinators of the study. BP, CAB and VMV conducted the study. ICR, BP, EA and CAB gave statistical and epidemiological support. ICR wrote the article with the support of EA and BP. All authors revised and approved the final version of the manuscript.

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Competing interests: None

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Table 1. Search strategy for MEDLINE.

"physical activity" OR "physical fitness" OR "physical exercise" OR exercise OR "intense exercise" OR "exercise training"	AND	"glycemic control" OR "metabolic outcomes" OR HbA1c OR "haemoglobin level" OR "glycated haemoglobin"	AND	"randomised control trial" OR RCT OR "quasi-experimental study" OR non-RCT OR "controlled pre–post study"

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Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

			Population characteristics				Outcome		Intervention characteristics	
Reference	**Country**	**Study Design**	**Age distribution**	**Sample size**	**Type of population**	**Diabetes prevalence**	**HbA1c method**	**HbA1c levels**	**Physical activity intervention**	**Physical activity characteristics**
Author information and year of publication	*Country*	*Design of the study*	*Age* (years) *of the participants range or mean ± SD*	*Number of participants*	*Population characteristics (healthy or with any specific disease)*	*Number of cases with diabetes (%)*	*Methods certified by the NGSP and standardised by IFCC used for HbA1c testing*	*HbA1c mean value before and after the intervention*	*Type of physical activity intervention (leisure-time physical activity, physical activity programme or physical activity counselling)*	*Definition of physical activity intervention (duration of intervention, number of sessions and duration of each session)*

HbA1c: Glycated haemoglobin A1c; SD: Standard deviation; NGSP: National Glycohemoglobin Standardization Program; IFCC: International Federation of Clinical Chemistry.

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FIGURE CAPTIONS

Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.

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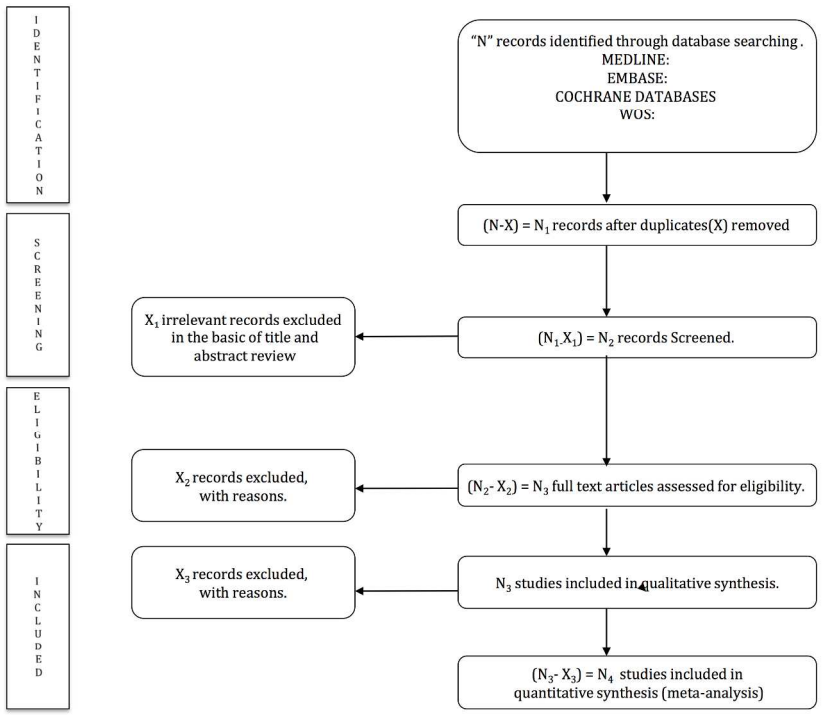

Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.

254x190mm (300 x 300 DPI)

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1; line 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2; line 50
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1; line 3-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 11; line 306-310
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 11; line 311-312
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4; line 67-113
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4-5; line 115-122
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5-6; line 129-156
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other	Page 6; line

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

		grey literature sources) with planned dates of coverage	159-170
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6-7; line 171-181
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7; line 182-192
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6-7; line 171-192
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	Page 7; line 182-192 Table 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7-8; line 193-208
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8-9; line 209-233
	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)	Page 8; line 217-224
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9; line 234-244
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 8; line 214-215-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8; line 229-233
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

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The effects of physical activity interventions on glycated haemoglobin A1c in non-diabetic populations: a protocol for a systematic review and meta-analysis.

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Keywords:	HbA1c, physical activity, meta-analysis

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The effects of physical activity interventions on glycated haemoglobin A1c in non-diabetic population: a protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction: Epidemiological evidence suggests that physical activity has a positive effect on reducing glycated haemoglobin A1c (HbA1c) levels not only in diabetics, but also in healthy subjects. Moreover, a positive association of HbA1c levels with cardiovascular disease and mortality in non-diabetic populations has recently been reported. This is a protocol for a systematic review and meta-analysis aiming to estimate the effects of physical activity on glycaemic control measured by HbA1c levels in non-diabetic populations; and to determine which type of physical activity has a greater influence on glycaemic control.

Methods and analysis: The search will be conducted using MEDLINE, EMBASE, the Cochrane Library and Web of Science databases from inception to mid-2017. Randomised controlled trials, non-randomised experimental studies and controlled pre–post studies written in English, Portuguese, French or Spanish will be included. The Cochrane Collaboration's tool and The Quality Assessment Tool for Quantitative Studies will be used to assess the risk of bias for studies included in the systematic review. Standardised pre–post intervention mean differences of HbA1c will be calculated as the primary outcome. Subgroup analyses will be performed based on the characteristics of physical activity intervention and population included in the studies.

Ethics and dissemination: This systematic review will synthesise evidence on the association of physical activity and HbA1c in non-diabetic populations. This study is important from the clinical and public health point because it will estimate the effect of physical activity on the glycemic control, and it will also examine which is the type of physical activity that should be recommended for preventing type 2 diabetes and its complications. The results will be disseminated by publication in a peer-reviewed journal. Ethical approval will not be required because the data used for this systematic review will be obtained from published studies and there will be no concerns about privacy.

Trial registration number: PROSPERO CRD42016050991.

Key words: HbA1c, physical activity, meta-analysis

Strengths and limitations of this study

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- This study presents a comprehensive methodology for analysing the effect of physical activity interventions on glycaemic control measured using HbA1c levels in general and non-diabetic populations.

- Two researchers will independently perform study selection, data extraction and quality assessment.

- The assessment of risk of bias of the selected studies and heterogeneity among studies included, with particular reference to study design and sample characteristics, is a featured point in this evidence review.

- The differences among physical activity interventions could be a source of variable quality and heterogeneity among studies, and may limit the quality of the evidence of this meta-analysis.

INTRODUCTION

Currently, guidelines from the American Diabetes Association (ADA)[1] and the World Health Organization (WHO)[2] propose glycated haemoglobin A1c (HbA1c) levels greater than 6.5% (48.0 mmol/mol) for the diagnosis of diabetes. Also, recent meta-analyses have reported an increase for all-cause mortality with HbA1c levels around 5.7% (39.0 mmol/mol) in non-diabetic and around 7.5% (58.0 mmol/mol) in diabetic populations.[3,4] HbA1c is a biochemical test useful to identify people with subclinical diabetes at the onset of clinical symptoms.[5] Since micro vascular complications of diabetes are present in the early stages of the disease, controlling HbA1c levels should not be restricted to the diabetic population.

Substantial evidence supports that physical activity reduces the risk of dying prematurely because of its positive influence on a variety of health conditions, such as cardiovascular disease, diabetes and other disorders of metabolism, as well as neurological diseases, sarcopenia, osteoporosis and cancer.[6,7] The Surgeon General's Report on Physical Activity and Health[8] underscores the pivotal role physical activity plays in health promotion and disease prevention. It recommends that individuals should accumulate 30 min of moderate physical activity on most days of the week. Research suggests that more than 60% of adults do not achieve the recommended amount of physical activity and 25% of adults are not physically active at all. Among

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young people, almost 50% do not regularly practice vigorous physical activity. A previous meta-analysis showed that higher levels of physical activity (3000-4000 MET minutes/week) were significantly associated with lower risk for breast cancer, colon cancer, diabetes, ischemic heart disease and ischemic stroke events.[9] In the case of diabetes, up to 46% of the incidence could be reduced by engaging in physical activity programs;[10] moreover, these programs have revealed improvements in glycaemic control and metabolic profile among both diabetic and non-diabetic populations.[11] One meta-analysis concluded that structured physical activity such as aerobic exercise, resistance training or the combination of both may be associated with HbA1c reduction in patients with type 2 diabetes. This study showed that aerobic exercise, resistance training and both combined were associated with HbA1c reductions of 0.73%, 0.57% and 0.51%, respectively. Also, structured exercise lasting more than 150 minutes per week was associated with HbA1c reductions of 0.89%.[12] Additionally, evidence has suggested that structured physical activity could substantially reduce the incidence of type 2 diabetes.[13-16]

In most industrialized countries, there is an alarming increase of the incidence of type 2 diabetes in children and adolescents with low levels of physical activity. This growing incidence parallels the childhood obesity pandemic.[17] A previous meta-analysis has proven the effectiveness of a high intensity physical activity intervention on reducing adiposity, and also on mitigating the risk of type 2 diabetes and its cardiovascular complications in adulthood.[18]

Thus, physical activity is widely perceived to be beneficial for preventing type 2 diabetes and for controlling glycaemic levels in patients with type 2 diabetes, but evidence supporting a positive effect in the control of glycaemic levels in healthy people is rather weak.[19] Therefore, considering the increasing incidence of type 2 diabetes in industrialized countries, determining the effect of physical activity interventions to control HbA1c levels in non-diabetic populations is an important public health issue.

The purpose of this protocol is to provide the methodology for a review of intervention studies addressing the effectiveness of physical activity interventions in reducing HbA1c levels in general and non-diabetic populations.

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OBJECTIVE

This systematic review and meta-analysis protocol presents an objective and clear procedure for the extraction of information from experimental studies (randomised controlled trials [RCTs], non-randomised experimental studies and controlled pre–post studies), in which data on changes in HbA1c levels are reported as an outcome, in order to: i) estimate the effects of physical activity on glycaemic control measured by HbA1c levels in non-diabetic populations; and ii) determine which type of physical activity (based on qualitative or quantitative characteristics) has a greater positive influence on glycaemic control.

METHODS AND ANALYSIS

This systematic review and meta-analysis protocol is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[20] and the Cochrane Collaboration Handbook.[21] This protocol has been previously registered in PROSPERO (registration number: CRD42016050991).

Inclusion/exclusion criteria for study selection

Type of studies

Randomised controlled trials, non-randomised experimental studies and controlled pre–post studies written in English, French, Portuguese, French or Spanish.

Type of participants

Studies assessing the effect, in general and non-diabetic populations, of physical activity interventions on glycaemic control measured by HbA1c levels will be selected. Studies will be selected regardless of the age of the participants included. Studies will be excluded when they include exclusively subjects who have been diagnosed with diabetes. When more than one study provides data referring to the same sample, we will choose the one presenting the most detailed results or providing the largest sample size.

Type of interventions

Studies reporting any type of intervention consisting mainly of physical activity (endurance, resistance or alternative exercise [such as yoga or pilates]), understood as

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repeated bouts of exercise over time involving more than two sessions/week with a duration of at least 3 weeks, will be eligible for inclusion. Studies comparing different types of physical activity interventions or examining a specific physical activity intervention with or without a control group will be eligible for inclusion. Also, studies consisting of advice on physical activity will be included. Nevertheless, studies combining physical activity with other health interventions, such as nutritional interventions, will be excluded when data concerning the effectiveness of physical activity programmes on glycaemic control measured by HbA1c levels cannot be extracted separately.

Type of outcome assessment

Studies in which glycaemic control is an outcome measured using any of the different methods certified by the National Glycohemoglobin Standardization Program (NGSP) and standardised by the International Federation of Clinical Chemistry Working Group (IFCC) for testing HbA1c will be included. Studies will be included regardless of the unit in which HbA1c levels were measured, for instance percentage (%) or mmol/mol.

Search methods for the identification of studies

Electronic search

The literature search will be conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Web of Science databases from inception to June 31st, 2017. The searches will be re-done just before the final analyses, in order to search for further potential studies. Study records will be managed using the Mendeley reference manager.

The following search terms will be combined by Boolean operators for conducting the literature search: “physical activity”, “physical fitness”, “physical exercise”, exercise, “intense exercise”, “exercise training”, “glycemic control”, “metabolic outcomes”, “HbA1c”, “haemoglobin level”, “glycated haemoglobin”, “randomised control trial”, RCT, “quasi-experimental study”, non-RCT and “controlled pre–post study” (Table 1).

Previous reviews and meta-analyses, and relevant references cited in the selected studies will be screened.

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Data collection and analysis

Selection of studies

The title and abstract of retrieved articles will be independently evaluated by two reviewers in order to identify eligible studies according to the inclusion criteria. Then, full manuscripts of the identified studies will be examined. Finally, the two reviewers will review the included and excluded studies in order to verify the reasons for inclusion/exclusion (Figure 1). Abstracts not providing enough information regarding the inclusion/exclusion criteria will be selected for full-text evaluation. The reviewers will not be blinded to the authors, institutions or journals of the reviewed papers. Disagreements will be solved by consensus; when disagreements persist after discussion, a third reviewer will be required.

Two authors will independently extract information from the included studies regarding the main study characteristics: author, year of publication, country, study design, number and age of participants, population characteristics (healthy or with any specific disease), prevalence of diabetes, methods certified by the NGSP and standardised by the IFCC used for HbA1c testing, HbA1c mean values before the intervention, and type and characteristics of the physical activity intervention (Table 2). In order to avoid double counting of patients because they have been included in more than one report by the same author or working group, the recruitment periods will be evaluated. When necessary, corresponding authors of the potentially included studies will be contacted to obtain any missing information.

Any disagreements will be resolved by discussion to reach a consensus.

Assessment of risk of bias in the included studies

Two researchers will independently conduct a quality assessment according to the Cochrane Collaboration Handbook recomendations.[21] Any disagreements will be resolved by discussion and a third reviewer will solve disagreements if consensus is not reached.

The methodological quality of the RCTs will be assessed using The Cochrane Collaboration's tool for assessing risk of bias.[22] This tool evaluates the risk of bias

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according to six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.

The Quality Assessment Tool for Quantitative Studies[23] assesses the quality of pre–post studies and non-RCTs. This tool evaluates seven domains: selection bias, study design, confounders, blinding, data collection method, withdrawals and drop-outs.

In both quality assessment tools, each domain will be considered as strong, moderate or weak, and studies will be classified as low risk of bias (with no weak ratings), moderate risk of bias (with one weak rating) and high risk of bias (with two or more weak ratings). The agreement rate between reviewers will be reported by calculating kappa statistics.

Data synthesis

The researchers will create ad hoc tables to summarise the characteristics of the included studies and any important questions related to the aim of this systematic review. The reviewers will determine whether a meta-analysis is possible after data extraction. At least five observations addressing the same specific outcome will be required to conduct a meta-analysis; where a meta-analysis is not feasible, we will undertake a narrative synthesis. Studies providing insufficient data to perform the analyses will be omitted from data syntheses.

If a meta-analysis is possible, STATA 14 software will be used to combine the pooled mean differences with 95% confidence intervals (CI). A fixed-effects model will be used if there is no evidence of heterogeneity; otherwise, a random-effects model will be used. Study heterogeneity will be assessed with the I^2 statistic. I^2 values will be considered as: might not be important (0% to 40%); may represent moderate heterogeneity (30% to 60%); may represent substantial heterogeneity (50% to 90%) and considerable heterogeneity (75% to 100%), the corresponding p-values will also be taken into account.[21]

Data from intention-to-treat analyses will be considered whenever available in RCTs. The HbA1c pre–post intervention mean difference will be the primary indicator of the intervention outcome. Standardised mean differences (standard deviation [SD]) will be calculated for HbA1c levels. Finally, publication bias will be assessed using a contour-

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enhanced funnel plot of each effect size against the standard error. Funnel plot asymmetry will be visually evaluated, as well as with the method proposed by Egger,[24] and significant publication bias will be considered to be present if the p-value is less than 0.10.[25] The trim-and-fill computation will be used to assess the effect of publication bias on the interpretation of results.[26]

Subgroup analysis and meta-regression

Subgroup analyses and meta-regression will be conducted by age of participants (children and/or adolescents, young adults aged 18–35 years, middle-aged adults aged 36–55 years or older adults aged above 55 years), type of physical activity intervention (leisure-time physical activity, active commuting, physical activity programme or physical activity counselling), type of exercise (endurance, resistance or alternative exercises), length of physical activity intervention (above or below 12 weeks), physical activity duration per week (above or below 150 minutes), type of study design (RCT, non-RCT and controlled pre–post studies), because these may be the potential major factors to cause heterogeneity. Furthermore, the methodological quality of studies included will be considered for additional subgroup analyses.

Sensitivity analysis

Sensitivity analyses will be conducted excluding studies from the analysis one by one. These will be performed to prove that the findings from the meta-analysis do not depend on arbitrary or unclear decisions.

ETHICS AND DISSEMINATION

An association between physical activity interventions and glycaemic control measured by HbA1c levels has been reported by recent systematic reviews and meta-analyses in both type 2[27-31] and type 1 diabetic populations.[32,33] One meta-analysis[31] reported no significant benefits of glycaemic control in non-diabetic populations, but included only three intervention studies divided in two subgroups (healthy and chronic disease). No previous systematic review or meta-analysis has included studies in non-diabetics. Therefore, the aim of this protocol is to present a clear and reliable methodology to estimate the effects of physical activity on glycaemic control measured by HbA1c levels in general and non-diabetic populations.

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There are some sources of heterogeneity that will be controlled in this systematic review and meta-analysis. Sources of variability will be determined by analysing the design (type of study, type of intervention and control group, sample size, and length of intervention) and the sample characteristics (type of population, age range and gender distribution) of the studies included.

As different study designs will be considered for inclusion, we will use two quality assessment tools: the Cochrane Collaboration's tool for assessing risk of bias[22] and the Quality Assessment Tool for Quantitative Studies.[23] Both tools were rigorously developed, and are evidence-based, valid, reliable and easy to use.[34]

Random-effects meta-regression will be used to evaluate whether the relationship between physical activity and glycaemic levels could differ according to certain sample characteristics and whether those characteristics could be considered major sources of heterogeneity.[35] Additionally, subgroup analyses in this meta-analysis will be conducted to control for heterogeneity between the studies. To determine the level of heterogeneity, we will use the definition suggested by the Cochrane Collaboration Handbook.[21]

Therefore, some aspects of physical activity that currently seem to be controversial will be deeply studied in this meta-analysis, such as the effect that each type of physical activity could produce on glycemic control measured by HbA1c in non-diabetic populations. The evidence of the effect of each type of physical activity might help to establish physical activity programs tailored to the characteristics of each subject and the aimed objectives. Moreover, whether physical activity counseling interventions that involve written advice by a health professional are capable of increasing the daily amount of time that patients spend on physical exercise-related activities should be clarified.[36] Finally, another important issue to take into account in this meta-analysis will be whether complying with The Surgeon General's Report on Physical Activity and Health recommendations has beneficial effects on glycemic control in non-diabetic populations.

If the study confirms the positive effects of physical activity on controlling or decreasing HbA1c levels in non-diabetic population, this would mean that promoting physical activity should be a useful strategy not only in the prevention of diabetes

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mellitus, but also its micro- and macrovascular complications such as retinopathy, nephropathy, arterial stiffness or cardiovascular diseases. Thus, synthesizing the evidence in the effectiveness of different types of physical activity on HbA1c levels might provide support for the inclusion of the physical activity in population-based prevention interventions in different population groups (i.e. children, adults, elderly ...). This study would also evidence the weaknesses of the available evidence supporting the relationship between HbA1c levels and glycaemic related disorders, therefore this study could suggest future research areas regarding these issues.

Potential limitations of this research may be publication bias, information bias, poor statistical analyses, and inadequate reporting of methods and findings of the studies included.[25] However, it is important to summarise the information available on this issue. To overcome these limitations, we will follow the recommendations included in the PRISMA[37] and the Cochrane Collaboration Handbook.[21]

Numerous meta-analyses synthesizing the effects of physical activity on glycaemic control measured by HbA1c levels in diabetic populations have already been conducted. However, there is no meta-analysis in non-diabetic populations relating physical activity with glycaemic control measured by HbA1c levels, despite the increasing number of intervention studies on this association. Therefore, it seems necessary to conduct a systematic review that may provide a global overview of the current literature and could also improve future research on this topic. This protocol provides a clear and structured procedure for maximising the extraction, and summarising of relevant information on the association of physical activity and HbA1c levels. This study will have important clinical and public health implications, because it could provide support to recommend physical exercise in non-diabetic subjects as this may be useful for preventing type 2 diabetes and its complications. According to the findings of this systematic review and meta-analysis, suggestions for future research will be made, and recommendations for evidence-based physical activity interventions for glycaemic control and prevention of diabetes mellitus in healthy subjects will be implemented.

Authors' contributions: VMV and ICR designed the study. VMV was the principal investigator and guarantor. ICR and VMV were the main coordinators of the study. BP, CAB and VMV conducted the study. ICR, BP, EA and CAB gave statistical and

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epidemiological support. ICR wrote the article with the support of EA and BP. All authors revised and approved the final version of the manuscript.

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Competing interests: None

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Table 1. Search strategy for MEDLINE.

"physical activity" OR "physical fitness" OR "physical exercise" OR exercise OR "intense exercise" OR "exercise training"	AND	"glycemic control" OR "metabolic outcomes" OR HbA1c OR "haemoglobin level" OR "glycated haemoglobin"	AND	"randomised control trial" OR RCT OR "quasi-experimental study" OR non-RCT OR "controlled pre–post study"

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Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

			Population characteristics				Outcome		Intervention characteristics	
Reference	**Country**	**Study Design**	**Age distribution**	**Sample size**	**Type of population**	**Diabetes prevalence**	**HbA1c method**	**HbA1c levels**	**Physical activity intervention**	**Physical activity characteristics**
Author information and year of publication	*Country*	*Design of the study*	*Age* (years) *of the participants range or mean ± SD*	*Number of participants*	*Population characteristics (healthy or with any specific disease)*	*Number of cases with diabetes (%)*	*Methods certified by the NGSP and standardised by IFCC used for HbA1c testing*	*HbA1c mean value before and after the intervention*	*Type of physical activity intervention (leisure-time physical activity, physical activity programme or physical activity counselling)*	*Definition of physical activity intervention (duration of intervention, number of sessions and duration of each session)*

HbA1c: Glycated haemoglobin A1c; SD: Standard deviation; NGSP: National Glycohemoglobin Standardization Program; IFCC: International Federation of Clinical Chemistry.

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FIGURE CAPTIONS

Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.

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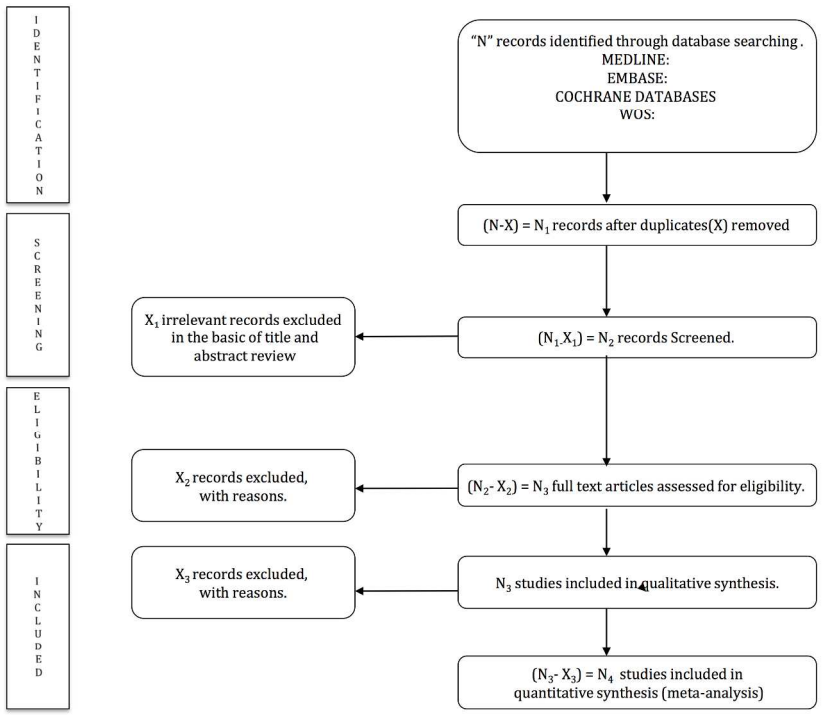

Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1; line 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2; line 50
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1; line 3-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 11; line 306-310
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 11; line 311-312
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4; line 67-113
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4-5; line 115-122
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5-6; line 129-156
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other	Page 6; line

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		grey literature sources) with planned dates of coverage	159-170
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6-7; line 171-181
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7; line 182-192
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6-7; line 171-192
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	Page 7; line 182-192 Table 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7-8; line 193-208
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8-9; line 209-233
	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)	Page 8; line 217-224
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9; line 234-244
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 8; line 214-215-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8; line 229-233
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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