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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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4 **1 The effects of physical activity interventions on glycosylated haemoglobin A1c in**  
5 **2 the general population: a protocol for a systematic review and meta-analysis.**  
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3 25 **ABSTRACT**  
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6 **Introduction:** Epidemiological evidence suggests that physical activity has a positive  
7 effect of reducing glycosylated haemoglobin A1c (HbA1c) levels not only in diabetics,  
8 but also in healthy adults. Moreover, a positive association of HbA1c levels with  
9 cardiovascular disease and mortality in non-diabetic populations has recently been  
10 reported. This is a protocol for a systematic review and meta-analysis aiming to  
11 estimate the effects of physical activity on glycaemic control measured by HbA1c levels  
12 in general and non-diabetic populations; and to determine which type of physical  
13 activity has a greater influence on glycaemic control.  
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20 **Methods and analysis:** The search will be conducted using MEDLINE, EMBASE,  
21 Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic  
22 Reviews and Web of Science databases from inception to mid-2017. Randomised  
23 controlled trials, non-randomized experimental studies and controlled pre–post studies  
24 written in English, Portuguese or Spanish will be included. The Cochrane  
25 Collaboration’s tool and The Quality Assessment Tool for Quantitative Studies will be  
26 used to assess the risk of bias for the studies included in the systematic review.  
27 Standardised pre–post intervention mean differences of HbA1c with 95% confidence  
28 intervals will be calculated as primary outcome. Subgroup analyses will be performed  
29 based on the type of physical activity intervention, the type of population included in  
30 the studies and the age of the participants.  
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39 **Ethics and dissemination:** This systematic review will synthesise evidence on the  
40 association of physical activity and HbA1c levels in general and non-diabetic  
41 populations. The results will be disseminated by publication in a peer-reviewed journal.  
42 Ethics approval will not be required because the data used for this systematic review  
43 will be obtained from published studies and there will be no concerns about privacy.  
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48 **Trial registration number:** PROSPERO CRD42016050991.  
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51 **Key words:** HbA1c, physical activity, meta-analysis  
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## 54 **Strengths and limitations of this study**

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

## 66 **INTRODUCTION**

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

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

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3 84 type 2 diabetes.<sup>10</sup> Additionally, evidence has suggested that structured physical activity  
4 85 could substantially reduce the incidence of type 2 diabetes.<sup>11-14</sup>  
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7 86 Thus, physical activity is widely perceived to be beneficial for preventing type 2  
8 87 diabetes and for controlling glycaemic levels in patients with type 2 diabetes, but  
9 88 evidence supporting a positive effect in the control of glycaemic levels in healthy  
10 89 people is rather weak.<sup>15</sup> Therefore, considering the increasing incidence of type 2  
11 90 diabetes in industrialized countries, determining the effect of physical activity  
12 91 interventions to control HbA1c levels in non-diabetic populations is an important public  
13 92 health issue.  
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20 93 The purpose of this protocol is to provide the methodology for a review of intervention  
21 94 studies addressing the effectiveness of physical activity interventions in reducing  
22 95 HbA1c levels in general and non-diabetic populations.  
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## 25 96 **OBJECTIVE**

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28 97 This systematic review and meta-analysis protocol presents an objective and clear  
29 98 procedure for the extraction of information from experimental studies (randomised  
30 99 controlled trials [RCTs], non-randomized experimental studies and controlled pre-post  
31 100 studies), in which data on changes in HbA1c levels have been reported as an outcome,  
32 101 in order to: i) estimate the effects of physical activity on glycaemic control measured by  
33 102 HbA1c levels in the general population and in non-diabetic populations; and ii)  
34 103 determine which type of physical activity (based on qualitative or quantitative  
35 104 characteristics) has a greater positive influence on glycaemic control.  
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## 42 105 **METHODS AND ANALYSIS**

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45 106 This systematic review and meta-analysis protocol is based on the Preferred Reporting  
46 107 Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)<sup>16</sup> and the  
47 108 Cochrane Collaboration Handbook.<sup>17</sup> This protocol has been previously registered in  
48 109 PROSPERO (registration number: CRD42016050991).  
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5 113 **Inclusion/exclusion criteria for study selection**6  
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8 114 *Type of studies*9  
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11 115 Randomised controlled trials, non-randomized experimental studies and controlled pre-  
12 116 post studies written in English, French, Portuguese or Spanish.13  
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15 117 *Type of participants*16  
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18 118 Studies assessing the effect, in general and non-diabetic populations, of physical activity  
19 119 interventions on glycaemic control measured by HbA1c levels will be selected. Studies  
20 120 will be selected regardless of the age of the participants included. Studies will be  
21 121 excluded when they include: i) exclusively subjects who have been diagnosed with  
22 122 diabetes; and ii) more than 8.5% of diabetics in the sample (diabetes global prevalence  
23 123 according to WHO)<sup>18</sup> and/or when the prevalence of diabetes in the sample is unknown.  
24 124 When more than one study provides data referring to the same sample, we will choose  
25 125 the one presenting the most detailed results or providing the largest sample size.26  
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28 126 *Type of interventions*29  
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32 127 Studies reporting any type of intervention consisting mainly of physical activity,  
33 128 understood as repeated bouts of exercise over time involving multiple sessions during a  
34 129 number of weeks, will be eligible for inclusion. Studies comparing different types of  
35 130 physical activity interventions or examining a specific physical activity intervention  
36 131 with or without a control group will be eligible for inclusion. Also, studies consisting of  
37 132 advice on physical activity will be included. Nevertheless, studies combining physical  
38 133 activity with other health interventions, such as nutritional interventions, will be  
39 134 excluded when data concerning the effectiveness of physical activity programmes on  
40 135 glycaemic control measured by HbA1c levels cannot be extracted separately.41  
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43 136 *Type of outcome assessment*44  
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46 137 Studies in which glycaemic control is an outcome measured using any of the different  
47 138 methods certified by the National Glycohemoglobin Standardization Program (NGSP)

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3 139 for testing HbA1c will be included. Studies will be included regardless of the unit in  
4 140 which HbA1c levels were measured, for instance percentage (%) or mmol/mol.

## 141 **Search methods for the identification of studies**

### 142 *Electronic search*

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

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

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

## 155 **Data collection and analysis**

### 156 *Selection of studies*

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



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3 166 Two authors will independently extract information from the included studies regarding  
4 167 the main study characteristics: author, year of publication, country, study design,  
5 168 number and age of participants, population characteristics (healthy or with any specific  
6 169 disease), prevalence of diabetes, methods certified by the NGSP used for HbA1c  
7 170 testing, HbA1c mean values before the intervention, and type and characteristics of the  
8 171 physical activity intervention (Table 2). In order to avoid double counting of patients  
9 172 because they have been included in more than one report by the same author or working  
10 173 group, the recruitment periods will be evaluated. When necessary, corresponding  
11 174 authors of the potentially included studies will be contacted to obtain any missing  
12 175 information.

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21 176 Any disagreements will be resolved by discussion to reach a consensus.

### 22 23 177 *Assessment of risk of bias in the included studies*

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26 178 Two researchers will independently conduct a quality assessment according to the  
27 179 Cochrane Collaboration Handbook recommendations.<sup>17</sup> Any disagreements will be  
28 180 resolved by discussion and a third reviewer will solve the disagreements if consensus is  
29 181 not reached.

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33 182 Methodological quality of the RCTs will be assessed using The Cochrane  
34 183 Collaboration's tool for assessing risk of bias.<sup>19</sup> This tool evaluates the risk of bias  
35 184 according to six domains: selection bias, performance bias, detection bias, attrition bias,  
36 185 reporting bias and other bias.

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41 186 The Quality Assessment Tool for Quantitative Studies<sup>20</sup> is proposed to assess the  
42 187 quality of pre-post studies and non-RCTs. This tool evaluates seven domains: selection  
43 188 bias, study design, confounders, blinding, data collection method, withdrawals and  
44 189 drop-outs.

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49 190 In both quality assessment tools, each domain could be considered as strong, moderate  
50 191 or weak, and studies could be classified as low risk of bias (with no weak ratings),  
51 192 moderate risk of bias (with one weak rating) and high risk of bias (with two or more  
52 193 weak ratings). The agreement rate between reviewers will be reported by calculating  
53 194 kappa statistics.

### 54 55 56 57 58 195 *Data synthesis*



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3 196 The researchers will create ad hoc tables to summarise the characteristics of the  
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5 197 included studies and any important questions related to the aim of this systematic  
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7 198 review. The reviewers will determine whether a meta-analysis is possible after data  
8  
9 199 extraction. At least five observations addressing the same specific outcome will be  
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11 200 required to conduct a meta-analysis; where a meta-analysis is not feasible, we will  
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13 201 undertake a narrative synthesis. Studies providing insufficient data to perform the  
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15 202 analyses will be omitted from data syntheses.

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17 203 If a meta-analysis is possible, STATA 14 software will be used to combine the pooled  
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19 204 mean differences with 95% confidence intervals (CI). A fixed-effects model will be  
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21 205 used if there is no evidence of heterogeneity; otherwise, a random-effects model will be  
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23 206 used. Study heterogeneity will be assessed with an  $I^2$  statistic.  $I^2$  values are considered  
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25 207 as: might not be important (0% to 40%); may represent moderate heterogeneity (30% to  
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27 208 60%); may represent substantial heterogeneity (50% to 90%) and considerable  
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29 209 heterogeneity (75% to 100%), the corresponding p-values will also be taken into  
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31 210 account.<sup>17</sup>

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33 211 Data from intention-to-treat analyses will be considered whenever available in RCTs.  
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35 212 The HbA1c pre-post intervention mean difference will be the primary indicator of the  
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37 213 intervention outcome. Standardised mean differences (standard deviation (SD)) will be  
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39 214 calculated for HbA1c levels. For example, when the standard error (SE) is provided, the  
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41 215 SD will be calculated according to the following formula:  $SD = SE \times \sqrt{n}$ . Finally,  
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43 216 publication bias will be assessed using a contour-enhanced funnel plot of each effect  
44  
45 217 size against the standard error. Funnel plot asymmetry will be visually evaluated, as  
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47 218 well as with the method proposed by Egger,<sup>21</sup> and a significant publication bias will be  
48  
49 219 considered to be present if the p-value is less than 0.10.<sup>22</sup> The trim-and-fill computation  
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51 220 will be used to assess the effect of publication bias on the interpretation of results.<sup>23</sup>

### 221 *Subgroup analysis and meta-regression*

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53 222 Subgroup analyses and meta-regression will be performed based on the type of physical  
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55 223 activity intervention (leisure-time physical activity, physical activity programme or  
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57 224 physical activity counselling), type of population included in the studies (general  
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59 225 population and non-diabetic population), type of studies design (RCT, non-RCT and  
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226 controlled pre-post studies), age of participants (children and/or adolescents, young

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3 227 adults aged 18–35 years, middle-aged adults aged 36–55 years or older adults aged  
4 228 above 55 years), because these are the potential major factors causing heterogeneity.  
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6 229 Furthermore, the methodological quality of studies included will be considered for  
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8 230 additional subgroup analyses.  
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### 11 232 *Sensitivity analysis*

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15 233 Sensitivity analyses will be conducted excluding studies from the analysis one by one.  
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17 234 These will be performed to prove that the findings from the meta-analysis do not  
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19 235 depend on arbitrary or unclear decisions.  
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## 21 236 **DISCUSSION**

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24 237 An association between physical activity interventions and glycaemic control measured  
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26 238 by HbA1c levels has been reported by recent systematic reviews and meta-analyses in  
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28 239 both type 2<sup>24-28</sup> and type 1 diabetic populations.<sup>29,30</sup> One meta-analysis<sup>28</sup> reported no  
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30 240 significant benefits of glycaemic control in non-diabetic populations, but included only  
31  
32 241 three intervention studies divided in two subgroups (healthy and chronic disease). No  
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34 242 previous systematic review or meta-analysis has included studies in the general  
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36 243 population or in non-diabetics. Therefore, the aim of this protocol is to present a clear  
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38 244 and reliable methodology to estimate the effects of physical activity on glycaemic  
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40 245 control measured by HbA1c levels in general and non-diabetic populations.

41 246 There are some sources of heterogeneity that will be controlled in this systematic review  
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43 247 and meta-analysis. Those sources of variability will be determined by analysing the  
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45 248 design (type of study, type of intervention and control group, sample size, and length of  
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47 249 intervention) and the sample characteristics (type of population, age range and gender  
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49 250 distribution) of the included studies.

50 251 As different study designs will be considered for inclusion, we will use two quality  
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52 252 assessment tools: The Cochrane Collaboration's tool for assessing risk of bias<sup>19</sup> and  
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54 253 Quality Assessment Tool for Quantitative Studies.<sup>20</sup> Both tools are rigorously  
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56 254 developed, evidence-based, valid, reliable and easy to use.<sup>31</sup>  
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3 255 Random-effects meta-regression will be used to evaluate whether the relationship  
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5 256 between physical activity and glycaemic levels could differ according to certain sample  
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7 257 characteristics and whether those characteristics could be considered major sources of  
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9 258 heterogeneity.<sup>32</sup> Additionally, subgroup analyses in this meta-analysis will be designed  
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11 259 to control for heterogeneity between the studies. To determine the level of  
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13 260 heterogeneity, we will use the definition suggested by the Cochrane Collaboration  
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15 261 Handbook.<sup>17</sup>

16  
17 262 Potential limitations of this research may be publication bias, information bias, poor  
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19 263 statistical analyses, and inadequate reporting of methods and findings of the primary  
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21 264 studies.<sup>22</sup> However, it is important to summarise the information available on this issue.  
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23 265 To overcome these limitations, we will follow the recommendations included in the  
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25 266 PRISMA<sup>33</sup> and the Cochrane Collaboration Handbook.<sup>17</sup>

26  
27 267 Numerous meta-analyses synthesizing the effects of physical activity on glycaemic  
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29 268 control measured by HbA1c levels in diabetic populations have already been conducted.  
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31 269 However, there is no meta-analysis in the general population and/or non-diabetic  
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33 270 populations relating physical activity with glycaemic control measured by HbA1c  
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35 271 levels, despite the increasing number of intervention studies on this association.  
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37 272 Therefore, it seems necessary to conduct a systematic review that could provide a global  
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39 273 overview of the current literature and could also improve future research on this topic.  
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41 274 This protocol provides a clear and structured procedure for maximising the extraction  
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43 275 and summarising of relevant information on the association of physical activity and  
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45 276 HbA1c levels.

46  
47 277 **Authors' contributions:** VMV and ICR designed the study. VMV was the principal  
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49 278 investigator and guarantor. ICR and VMV were the main coordinators of the study. BP,  
50  
51 279 CAB, and VMV conducted the study. ICR, BP, EA and CAB gave statistical and  
52  
53 280 epidemiological support. ICR wrote the article with the support of EA and BP. All  
54  
55 281 authors revised and approved the final version of the manuscript.

56  
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58  
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60  
284 **Competing interests:** None

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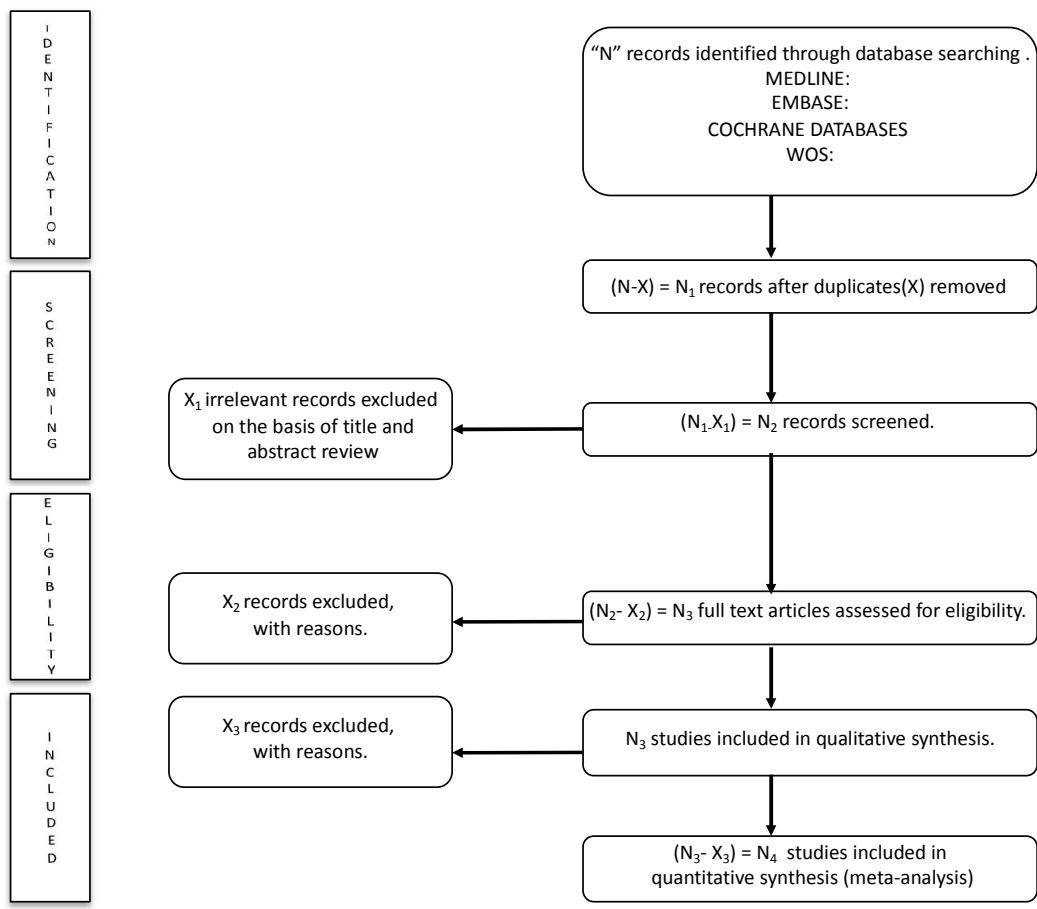
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Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.



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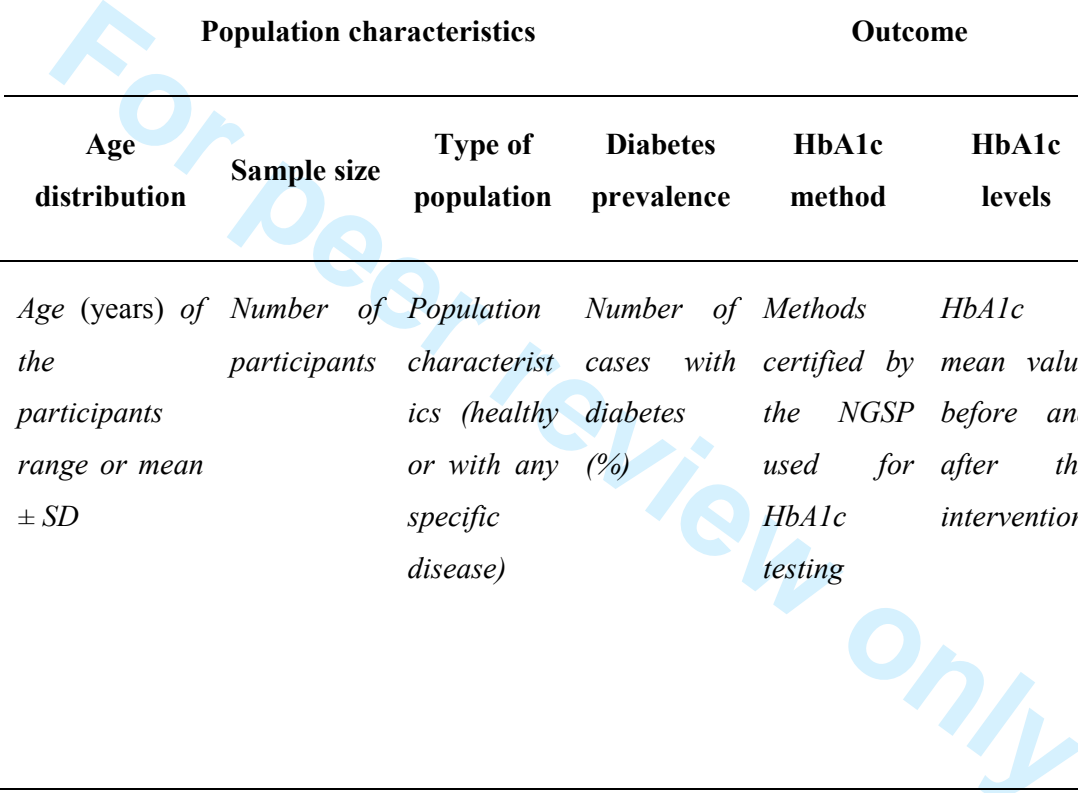
BMJ Open: first published as 10.1136/bmjopen-2016-015801 on 20 July 2017. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

**Table 1.** Search strategy for MEDLINE.

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

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

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Reference	Country	Study Design	Population characteristics				Outcome		Intervention characteristics	
			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 $\pm$ SD	Number of participants	Population characteristics (healthy or with any specific disease)	Number of diabetes cases with (%)	Methods certified by the NGSP used for HbA1c testing	HbA1c mean value before and after the intervention	Type of physical activity (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.

**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
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

**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 $\tau$ )	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.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

**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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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-015801.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Mar-2017
Complete List of Authors:	Cavero-Redondo, Iván; Universidad de Castilla-La Mancha, Health and Social Research Center Peleteiro, Barbara; University of Porto, EPIUnit - Institute of Public Health Álvarez-Bueno, Celia; Universidad de Castilla-La Mancha, Health and Social Research Center Garrido-Miguel, Miriam; Universidad de Castilla-La Mancha, Health and Social Research Center Artero, Enrique Martinez-Vizcaino, Vicente; Universidad de Castilla-La Mancha, Centro de Estudios Sociosanitarios
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Sports and exercise medicine
Keywords:	HbA1c, physical activity, meta-analysis

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4 1 **The effects of physical activity interventions on glycated haemoglobin A1c in non-**  
5 **diabetic population: a protocol for a systematic review and meta-analysis.**  
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8 3 Cavero-Redondo I,<sup>1</sup> Peleteiro B,<sup>2,3</sup> Alvarez-Bueno C,<sup>1\*</sup> Garrido-Miguel M,<sup>1</sup> Artero EG,<sup>4</sup>  
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## 26 ABSTRACT

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

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

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

53 **Trial registration number:** PROSPERO CRD42016050991.

54 **Key words:** HbA1c, physical activity, meta-analysis

55 **Strengths and limitations of this study**

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3 56 - This study presents a comprehensive methodology for analysing the effect of  
4 57 physical activity interventions on glycaemic control measured using HbA1c  
5 58 levels in general and non-diabetic populations.  
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9 59 - Two researchers will independently perform study selection, data extraction and  
10 60 quality assessment.  
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13 61 - The assessment of risk of bias of the selected studies and heterogeneity among  
14 62 studies included, with particular reference to study design and sample  
15 63 characteristics, is a featured point in this evidence review.  
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19 64 - The differences among physical activity interventions could be a source of  
20 65 variable quality and heterogeneity among studies, and may limit the quality of  
21 66 the evidence of this meta-analysis.  
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## 25 67 INTRODUCTION

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28 68 Currently, guidelines from the American Diabetes Association (ADA)<sup>1</sup> and the World  
29 69 Health Organization (WHO)<sup>2</sup> propose glycated haemoglobin A1c (HbA1c) levels  
30 70 greater than 6.5% (48.0 mmol/mol) for the diagnosis of diabetes. Also, recent meta-  
31 71 analyses have reported an increase for all-cause mortality with HbA1c levels around  
32 72 5.7% (39.0 mmol/mol) in non-diabetic and around 7.5% (58.0 mmol/mol) in diabetic  
33 73 populations.<sup>3,4</sup> HbA1c is a biochemical test useful to identify people with subclinical  
34 74 diabetes at the onset of clinical symptoms.<sup>5</sup> Since micro vascular complications of  
35 75 diabetes are present in the early stages of the disease, controlling HbA1c levels should  
36 76 not be restricted to the diabetic population.  
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44 77 Substantial evidence supports that physical activity reduces the risk of dying  
45 78 prematurely because of its positive influence on a variety of health conditions, such as  
46 79 cardiovascular disease, diabetes and other disorders of metabolism, as well as  
47 80 neurological diseases, sarcopenia, osteoporosis and cancer.<sup>6,7</sup> The Surgeon General's  
48 81 Report on Physical Activity and Health<sup>8</sup> underscores the pivotal role physical activity  
49 82 plays in health promotion and disease prevention. It recommends that individuals  
50 83 should accumulate 30 min of moderate physical activity on most days of the week.  
51 84 Research suggests that more than 60% of adults do not achieve the recommended  
52 85 amount of physical activity and 25% of adults are not physically active at all. Among  
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3 86 young people, almost 50% do not regularly practice vigorous physical activity. A  
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5 87 previous meta-analysis showed that higher levels of physical activity (3000-4000 MET  
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7 88 minutes/week) were significantly associated with lower risk for breast cancer, colon  
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9 89 cancer, diabetes, ischemic heart disease and ischemic stroke events.<sup>9</sup> In the case of  
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11 90 diabetes, up to 46% of the incidence could be reduced by engaging in physical activity  
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13 91 programs;<sup>10</sup> moreover, these programs have revealed improvements in glycaemic  
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15 92 control and metabolic profile among both diabetic and non-diabetic populations.<sup>11</sup> One  
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17 93 meta-analysis concluded that structured physical activity such as aerobic exercise,  
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19 94 resistance training or the combination of both may be associated with HbA1c reduction  
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21 95 in patients with type 2 diabetes. This study showed that aerobic exercise, resistance  
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23 96 training and both combined were associated with HbA1c reductions of 0.73%, 0.57%  
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25 97 and 0.51%, respectively. Also, structured exercise lasting more than 150 minutes per  
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27 98 week was associated with HbA1c reductions of 0.89%.<sup>12</sup> Additionally, evidence has  
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29 99 suggested that structured physical activity could substantially reduce the incidence of  
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31 100 type 2 diabetes.<sup>13-16</sup>

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33 101 In most industrialized countries, there is an alarming increase of the incidence of type 2  
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35 102 diabetes in children and adolescents with low levels of physical activity. This growing  
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37 103 incidence parallels the childhood obesity pandemic.<sup>17</sup> A previous meta-analysis has  
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39 104 proven the effectiveness of a high intensity physical activity intervention on reducing  
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41 105 adiposity, and also on mitigating the risk of type 2 diabetes and its cardiovascular  
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43 106 complications in adulthood.<sup>18</sup>

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45 107 Thus, physical activity is widely perceived to be beneficial for preventing type 2  
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47 108 diabetes and for controlling glycaemic levels in patients with type 2 diabetes, but  
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49 109 evidence supporting a positive effect in the control of glycaemic levels in healthy  
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51 110 people is rather weak.<sup>19</sup> Therefore, considering the increasing incidence of type 2  
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53 111 diabetes in industrialized countries, determining the effect of physical activity  
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55 112 interventions to control HbA1c levels in non-diabetic populations is an important public  
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57 113 health issue.

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59 114 The purpose of this protocol is to provide the methodology for a review of intervention  
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115 studies addressing the effectiveness of physical activity interventions in reducing  
116 HbA1c levels in general and non-diabetic populations.

**117 OBJECTIVE**

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

**126 METHODS AND ANALYSIS**

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

**131 Inclusion/exclusion criteria for study selection***132 Type of studies*

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

*135 Type of participants*

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

*142 Type of interventions*

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

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3 145 repeated bouts of exercise over time involving more than two sessions/week with a  
4 146 duration of at least 3 weeks, will be eligible for inclusion. Studies comparing different  
5 147 types of physical activity interventions or examining a specific physical activity  
6 148 intervention with or without a control group will be eligible for inclusion. Also, studies  
7 149 consisting of advice on physical activity will be included. Nevertheless, studies  
8 150 combining physical activity with other health interventions, such as nutritional  
9 151 interventions, will be excluded when data concerning the effectiveness of physical  
10 152 activity programmes on glycaemic control measured by HbA1c levels cannot be  
11 153 extracted separately.

#### 154 *Type of outcome assessment*

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

#### 160 **Search methods for the identification of studies**

##### 161 *Electronic search*

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

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

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



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3 174 **Data collection and analysis**  
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5 175 *Selection of studies*  
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8 176 The title and abstract of retrieved articles will be independently evaluated by two  
9 177 reviewers in order to identify eligible studies according to the inclusion criteria. Then,  
10 178 full manuscripts of the identified studies will be examined. Finally, the two reviewers  
11 179 will review the included and excluded studies in order to verify the reasons for  
12 180 inclusion/exclusion (Figure 1). Abstracts not providing enough information regarding  
13 181 the inclusion/exclusion criteria will be selected for full-text evaluation. The reviewers  
14 182 will not be blinded to the authors, institutions or journals of the reviewed papers.  
15 183 Disagreements will be solved by consensus; when disagreements persist after  
16 184 discussion, a third reviewer will be required.  
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24 185 Two authors will independently extract information from the included studies regarding  
25 186 the main study characteristics: author, year of publication, country, study design,  
26 187 number and age of participants, population characteristics (healthy or with any specific  
27 188 disease), prevalence of diabetes, methods certified by the NGSP and standardised by the  
28 189 IFCC used for HbA1c testing, HbA1c mean values before the intervention, and type and  
29 190 characteristics of the physical activity intervention (Table 2). In order to avoid double  
30 191 counting of patients because they have been included in more than one report by the  
31 192 same author or working group, the recruitment periods will be evaluated. When  
32 193 necessary, corresponding authors of the potentially included studies will be contacted to  
33 194 obtain any missing information.  
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42 195 Any disagreements will be resolved by discussion to reach a consensus.  
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44 196 *Assessment of risk of bias in the included studies*  
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47 197 Two researchers will independently conduct a quality assessment according to the  
48 198 Cochrane Collaboration Handbook recommendations.<sup>21</sup> Any disagreements will be  
49 199 resolved by discussion and a third reviewer will solve disagreements if consensus is not  
50 200 reached.  
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54 201 The methodological quality of the RCTs will be assessed using The Cochrane  
55 202 Collaboration's tool for assessing risk of bias.<sup>22</sup> This tool evaluates the risk of bias  
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203 according to six domains: selection bias, performance bias, detection bias, attrition bias,  
204 reporting bias and other bias.

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

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

### 213 *Data synthesis*

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

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

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

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

### 238 *Subgroup analysis and meta-regression*

239 Subgroup analyses and meta-regression will be conducted by age of participants  
240 (children and/or adolescents, young adults aged 18–35 years, middle-aged adults aged  
241 36–55 years or older adults aged above 55 years), type of physical activity intervention  
242 (leisure-time physical activity, active commuting, physical activity programme or  
243 physical activity counselling), type of exercise (endurance, resistance or alternative  
244 exercises), length of physical activity intervention (above or below 12 weeks), physical  
245 activity duration per week (above or below 150 minutes), type of study design (RCT,  
246 non-RCT and controlled pre–post studies), because these may be the potential major  
247 factors to cause heterogeneity. Furthermore, the methodological quality of studies  
248 included will be considered for additional subgroup analyses.

### 249 *Sensitivity analysis*

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

## 253 **ETHICS AND DISSEMINATION**

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

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3 263 There are some sources of heterogeneity that will be controlled in this systematic review  
4 264 and meta-analysis. Sources of variability will be determined by analysing the design  
5 265 (type of study, type of intervention and control group, sample size, and length of  
6 266 intervention) and the sample characteristics (type of population, age range and gender  
7 267 distribution) of the studies included.

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11 268 As different study designs will be considered for inclusion, we will use two quality  
12 269 assessment tools: the Cochrane Collaboration's tool for assessing risk of bias<sup>22</sup> and the  
13 270 Quality Assessment Tool for Quantitative Studies.<sup>23</sup> Both tools were rigorously  
14 271 developed, and are evidence-based, valid, reliable and easy to use.<sup>34</sup>

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20 272 Random-effects meta-regression will be used to evaluate whether the relationship  
21 273 between physical activity and glycaemic levels could differ according to certain sample  
22 274 characteristics and whether those characteristics could be considered major sources of  
23 275 heterogeneity.<sup>35</sup> Additionally, subgroup analyses in this meta-analysis will be conducted  
24 276 to control for heterogeneity between the studies. To determine the level of  
25 277 heterogeneity, we will use the definition suggested by the Cochrane Collaboration  
26 278 Handbook.<sup>21</sup>

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32 279 Therefore, some aspects of physical activity that currently seem to be controversial will  
33 280 be deeply studied in this meta-analysis, such as the effect that each type of physical  
34 281 activity could produce on glycemic control measured by HbA1c in non-diabetic  
35 282 populations. The evidence of the effect of each type of physical activity might help to  
36 283 establish physical activity programs tailored to the characteristics of each subject and  
37 284 the aimed objectives. Moreover, whether physical activity counseling interventions that  
38 285 involve written advice by a health professional are capable of increasing the daily  
39 286 amount of time that patients spend on physical exercise-related activities should be  
40 287 clarified.<sup>36</sup> Finally, another important issue to take into account in this meta-analysis  
41 288 will be whether complying with The Surgeon General's Report on Physical Activity and  
42 289 Health recommendations has beneficial effects on glycemic control in non-diabetic  
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53 291 Potential limitations of this research may be publication bias, information bias, poor  
54 292 statistical analyses, and inadequate reporting of methods and findings of the studies  
55 293 included.<sup>25</sup> However, it is important to summarise the information available on this

294 issue. To overcome these limitations, we will follow the recommendations included in  
295 the PRISMA<sup>37</sup> and the Cochrane Collaboration Handbook.<sup>21</sup>

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

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

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319 **Competing interests:** None

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**Table 1.** Search strategy for MEDLINE.

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

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

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

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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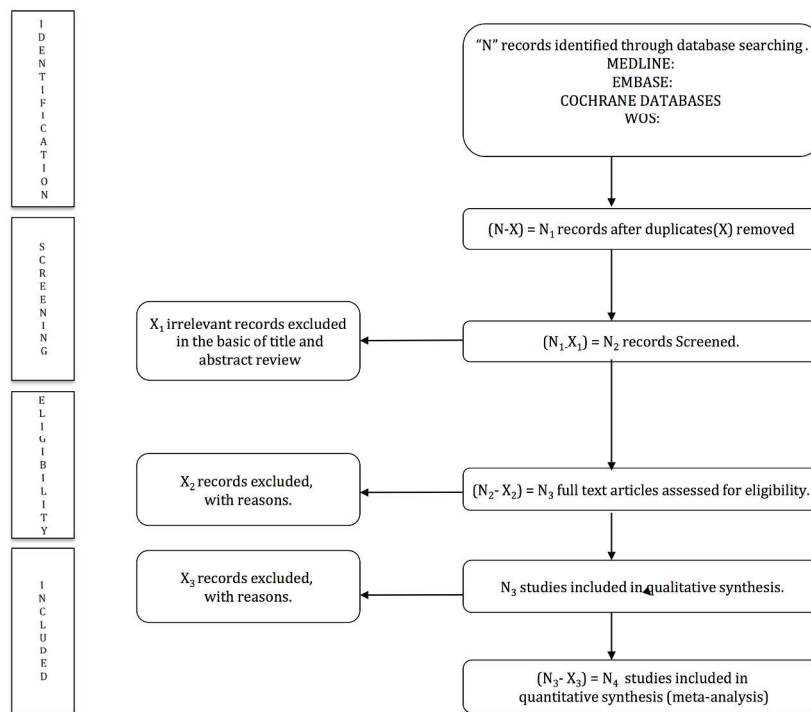


Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.

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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
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

**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 $\tau$ )	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.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*



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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\***

For peer review only

# BMJ Open

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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Sports and exercise medicine
Keywords:	HbA1c, physical activity, meta-analysis

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4 1 **The effects of physical activity interventions on glycated haemoglobin A1c in non-**  
5 **diabetic population: a protocol for a systematic review and meta-analysis.**  
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8 3 Cavero-Redondo I,<sup>1</sup> Peleteiro B,<sup>2,3</sup> Alvarez-Bueno C,<sup>1\*</sup> Garrido-Miguel M,<sup>1</sup> Artero EG,<sup>4</sup>  
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## 26 ABSTRACT

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

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

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

53 **Trial registration number:** PROSPERO CRD42016050991.

54 **Key words:** HbA1c, physical activity, meta-analysis

55 **Strengths and limitations of this study**

- 1  
2  
3 56 - This study presents a comprehensive methodology for analysing the effect of  
4 57 physical activity interventions on glycaemic control measured using HbA1c  
5 58 levels in general and non-diabetic populations.  
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9 59 - Two researchers will independently perform study selection, data extraction and  
10 60 quality assessment.  
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13 61 - The assessment of risk of bias of the selected studies and heterogeneity among  
14 62 studies included, with particular reference to study design and sample  
15 63 characteristics, is a featured point in this evidence review.  
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19 64 - The differences among physical activity interventions could be a source of  
20 65 variable quality and heterogeneity among studies, and may limit the quality of  
21 66 the evidence of this meta-analysis.  
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## 25 67 INTRODUCTION

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28 68 Currently, guidelines from the American Diabetes Association (ADA)<sup>1</sup> and the World  
29 69 Health Organization (WHO)<sup>2</sup> propose glycated haemoglobin A1c (HbA1c) levels  
30 70 greater than 6.5% (48.0 mmol/mol) for the diagnosis of diabetes. Also, recent meta-  
31 71 analyses have reported an increase for all-cause mortality with HbA1c levels around  
32 72 5.7% (39.0 mmol/mol) in non-diabetic and around 7.5% (58.0 mmol/mol) in diabetic  
33 73 populations.<sup>3,4</sup> HbA1c is a biochemical test useful to identify people with subclinical  
34 74 diabetes at the onset of clinical symptoms.<sup>5</sup> Since micro vascular complications of  
35 75 diabetes are present in the early stages of the disease, controlling HbA1c levels should  
36 76 not be restricted to the diabetic population.  
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44 77 Substantial evidence supports that physical activity reduces the risk of dying  
45 78 prematurely because of its positive influence on a variety of health conditions, such as  
46 79 cardiovascular disease, diabetes and other disorders of metabolism, as well as  
47 80 neurological diseases, sarcopenia, osteoporosis and cancer.<sup>6,7</sup> The Surgeon General's  
48 81 Report on Physical Activity and Health<sup>8</sup> underscores the pivotal role physical activity  
49 82 plays in health promotion and disease prevention. It recommends that individuals  
50 83 should accumulate 30 min of moderate physical activity on most days of the week.  
51 84 Research suggests that more than 60% of adults do not achieve the recommended  
52 85 amount of physical activity and 25% of adults are not physically active at all. Among  
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3 86 young people, almost 50% do not regularly practice vigorous physical activity. A  
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5 87 previous meta-analysis showed that higher levels of physical activity (3000-4000 MET  
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7 88 minutes/week) were significantly associated with lower risk for breast cancer, colon  
8  
9 89 cancer, diabetes, ischemic heart disease and ischemic stroke events.<sup>9</sup> In the case of  
10  
11 90 diabetes, up to 46% of the incidence could be reduced by engaging in physical activity  
12  
13 91 programs;<sup>10</sup> moreover, these programs have revealed improvements in glycaemic  
14  
15 92 control and metabolic profile among both diabetic and non-diabetic populations.<sup>11</sup> One  
16  
17 93 meta-analysis concluded that structured physical activity such as aerobic exercise,  
18  
19 94 resistance training or the combination of both may be associated with HbA1c reduction  
20  
21 95 in patients with type 2 diabetes. This study showed that aerobic exercise, resistance  
22  
23 96 training and both combined were associated with HbA1c reductions of 0.73%, 0.57%  
24  
25 97 and 0.51%, respectively. Also, structured exercise lasting more than 150 minutes per  
26  
27 98 week was associated with HbA1c reductions of 0.89%.<sup>12</sup> Additionally, evidence has  
28  
29 99 suggested that structured physical activity could substantially reduce the incidence of  
30  
31 100 type 2 diabetes.<sup>13-16</sup>

32  
33 101 In most industrialized countries, there is an alarming increase of the incidence of type 2  
34  
35 102 diabetes in children and adolescents with low levels of physical activity. This growing  
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37 103 incidence parallels the childhood obesity pandemic.<sup>17</sup> A previous meta-analysis has  
38  
39 104 proven the effectiveness of a high intensity physical activity intervention on reducing  
40  
41 105 adiposity, and also on mitigating the risk of type 2 diabetes and its cardiovascular  
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43 106 complications in adulthood.<sup>18</sup>

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45 107 Thus, physical activity is widely perceived to be beneficial for preventing type 2  
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47 108 diabetes and for controlling glycaemic levels in patients with type 2 diabetes, but  
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49 109 evidence supporting a positive effect in the control of glycaemic levels in healthy  
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51 110 people is rather weak.<sup>19</sup> Therefore, considering the increasing incidence of type 2  
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53 111 diabetes in industrialized countries, determining the effect of physical activity  
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55 112 interventions to control HbA1c levels in non-diabetic populations is an important public  
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57 113 health issue.

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59 114 The purpose of this protocol is to provide the methodology for a review of intervention  
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115 studies addressing the effectiveness of physical activity interventions in reducing  
116 HbA1c levels in general and non-diabetic populations.

**117 OBJECTIVE**

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

**126 METHODS AND ANALYSIS**

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

**131 Inclusion/exclusion criteria for study selection***132 Type of studies*

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

*135 Type of participants*

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

*142 Type of interventions*

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



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3 145 repeated bouts of exercise over time involving more than two sessions/week with a  
4 146 duration of at least 3 weeks, will be eligible for inclusion. Studies comparing different  
5 147 types of physical activity interventions or examining a specific physical activity  
6 148 intervention with or without a control group will be eligible for inclusion. Also, studies  
7 149 consisting of advice on physical activity will be included. Nevertheless, studies  
8 150 combining physical activity with other health interventions, such as nutritional  
9 151 interventions, will be excluded when data concerning the effectiveness of physical  
10 152 activity programmes on glycaemic control measured by HbA1c levels cannot be  
11 153 extracted separately.

#### 154 *Type of outcome assessment*

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

#### 160 **Search methods for the identification of studies**

##### 161 *Electronic search*

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

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

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

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3 174 **Data collection and analysis**  
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5 175 *Selection of studies*  
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8 176 The title and abstract of retrieved articles will be independently evaluated by two  
9 177 reviewers in order to identify eligible studies according to the inclusion criteria. Then,  
10 178 full manuscripts of the identified studies will be examined. Finally, the two reviewers  
11 179 will review the included and excluded studies in order to verify the reasons for  
12 180 inclusion/exclusion (Figure 1). Abstracts not providing enough information regarding  
13 181 the inclusion/exclusion criteria will be selected for full-text evaluation. The reviewers  
14 182 will not be blinded to the authors, institutions or journals of the reviewed papers.  
15 183 Disagreements will be solved by consensus; when disagreements persist after  
16 184 discussion, a third reviewer will be required.  
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24 185 Two authors will independently extract information from the included studies regarding  
25 186 the main study characteristics: author, year of publication, country, study design,  
26 187 number and age of participants, population characteristics (healthy or with any specific  
27 188 disease), prevalence of diabetes, methods certified by the NGSP and standardised by the  
28 189 IFCC used for HbA1c testing, HbA1c mean values before the intervention, and type and  
29 190 characteristics of the physical activity intervention (Table 2). In order to avoid double  
30 191 counting of patients because they have been included in more than one report by the  
31 192 same author or working group, the recruitment periods will be evaluated. When  
32 193 necessary, corresponding authors of the potentially included studies will be contacted to  
33 194 obtain any missing information.  
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42 195 Any disagreements will be resolved by discussion to reach a consensus.  
43

44 196 *Assessment of risk of bias in the included studies*  
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47 197 Two researchers will independently conduct a quality assessment according to the  
48 198 Cochrane Collaboration Handbook recommendations.<sup>21</sup> Any disagreements will be  
49 199 resolved by discussion and a third reviewer will solve disagreements if consensus is not  
50 200 reached.  
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54 201 The methodological quality of the RCTs will be assessed using The Cochrane  
55 202 Collaboration's tool for assessing risk of bias.<sup>22</sup> This tool evaluates the risk of bias  
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203 according to six domains: selection bias, performance bias, detection bias, attrition bias,  
204 reporting bias and other bias.

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

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

### 213 *Data synthesis*

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

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

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

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

### 238 *Subgroup analysis and meta-regression*

239 Subgroup analyses and meta-regression will be conducted by age of participants  
240 (children and/or adolescents, young adults aged 18–35 years, middle-aged adults aged  
241 36–55 years or older adults aged above 55 years), type of physical activity intervention  
242 (leisure-time physical activity, active commuting, physical activity programme or  
243 physical activity counselling), type of exercise (endurance, resistance or alternative  
244 exercises), length of physical activity intervention (above or below 12 weeks), physical  
245 activity duration per week (above or below 150 minutes), type of study design (RCT,  
246 non-RCT and controlled pre–post studies), because these may be the potential major  
247 factors to cause heterogeneity. Furthermore, the methodological quality of studies  
248 included will be considered for additional subgroup analyses.

### 249 *Sensitivity analysis*

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

## 253 **ETHICS AND DISSEMINATION**

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

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3 263 There are some sources of heterogeneity that will be controlled in this systematic review  
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5 264 and meta-analysis. Sources of variability will be determined by analysing the design  
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7 265 (type of study, type of intervention and control group, sample size, and length of  
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9 266 intervention) and the sample characteristics (type of population, age range and gender  
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11 267 distribution) of the studies included.

12  
13 268 As different study designs will be considered for inclusion, we will use two quality  
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15 269 assessment tools: the Cochrane Collaboration's tool for assessing risk of bias<sup>22</sup> and the  
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17 270 Quality Assessment Tool for Quantitative Studies.<sup>23</sup> Both tools were rigorously  
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19 271 developed, and are evidence-based, valid, reliable and easy to use.<sup>34</sup>

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21 272 Random-effects meta-regression will be used to evaluate whether the relationship  
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23 273 between physical activity and glycaemic levels could differ according to certain sample  
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25 274 characteristics and whether those characteristics could be considered major sources of  
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27 275 heterogeneity.<sup>35</sup> Additionally, subgroup analyses in this meta-analysis will be conducted  
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29 276 to control for heterogeneity between the studies. To determine the level of  
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31 277 heterogeneity, we will use the definition suggested by the Cochrane Collaboration  
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33 278 Handbook.<sup>21</sup>

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35 279 Therefore, some aspects of physical activity that currently seem to be controversial will  
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37 280 be deeply studied in this meta-analysis, such as the effect that each type of physical  
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39 281 activity could produce on glycemic control measured by HbA1c in non-diabetic  
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41 282 populations. The evidence of the effect of each type of physical activity might help to  
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43 283 establish physical activity programs tailored to the characteristics of each subject and  
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45 284 the aimed objectives. Moreover, whether physical activity counseling interventions that  
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47 285 involve written advice by a health professional are capable of increasing the daily  
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49 286 amount of time that patients spend on physical exercise-related activities should be  
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51 287 clarified.<sup>36</sup> Finally, another important issue to take into account in this meta-analysis  
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53 288 will be whether complying with The Surgeon General's Report on Physical Activity and  
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55 289 Health recommendations has beneficial effects on glycemic control in non-diabetic  
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57 290 populations.

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59 291 If the study confirms the positive effects of physical activity on controlling or  
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292 decreasing HbA1c levels in non-diabetic population, this would mean that promoting  
293 physical activity should be a useful strategy not only in the prevention of diabetes

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3 294 mellitus, but also its micro- and macrovascular complications such as retinopathy,  
4 295 nephropathy, arterial stiffness or cardiovascular diseases. Thus, synthesizing the  
5 296 evidence in the effectiveness of different types of physical activity on HbA1c levels  
6 297 might provide support for the inclusion of the physical activity in population-based  
7 298 prevention interventions in different population groups (i.e. children, adults, elderly ...).  
8 299 This study would also evidence the weaknesses of the available evidence supporting the  
9 300 relationship between HbA1c levels and glycaemic related disorders, therefore this study  
10 301 could suggest future research areas regarding these issues.

11 302 Potential limitations of this research may be publication bias, information bias, poor  
12 303 statistical analyses, and inadequate reporting of methods and findings of the studies  
13 304 included.<sup>25</sup> However, it is important to summarise the information available on this  
14 305 issue. To overcome these limitations, we will follow the recommendations included in  
15 306 the PRISMA<sup>37</sup> and the Cochrane Collaboration Handbook.<sup>21</sup>

16 307 Numerous meta-analyses synthesizing the effects of physical activity on glycaemic  
17 308 control measured by HbA1c levels in diabetic populations have already been conducted.  
18 309 However, there is no meta-analysis in non-diabetic populations relating physical activity  
19 310 with glycaemic control measured by HbA1c levels, despite the increasing number of  
20 311 intervention studies on this association. Therefore, it seems necessary to conduct a  
21 312 systematic review that may provide a global overview of the current literature and could  
22 313 also improve future research on this topic. This protocol provides a clear and structured  
23 314 procedure for maximising the extraction, and summarising of relevant information on  
24 315 the association of physical activity and HbA1c levels. This study will have important  
25 316 clinical and public health implications, because it could provide support to recommend  
26 317 physical exercise in non-diabetic subjects as this may be useful for preventing type 2  
27 318 diabetes and its complications. According to the findings of this systematic review and  
28 319 meta-analysis, suggestions for future research will be made, and recommendations for  
29 320 evidence-based physical activity interventions for glycaemic control and prevention of  
30 321 diabetes mellitus in healthy subjects will be implemented.

31 322  
32 323 **Authors' contributions:** VMV and ICR designed the study. VMV was the principal  
33 324 investigator and guarantor. ICR and VMV were the main coordinators of the study. BP,  
34 325 CAB and VMV conducted the study. ICR, BP, EA and CAB gave statistical and



1  
2  
3 326 epidemiological support. ICR wrote the article with the support of EA and BP. All  
4 327 authors revised and approved the final version of the manuscript.

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11 330 **Competing interests:** None

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**Table 1.** Search strategy for MEDLINE.

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

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

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

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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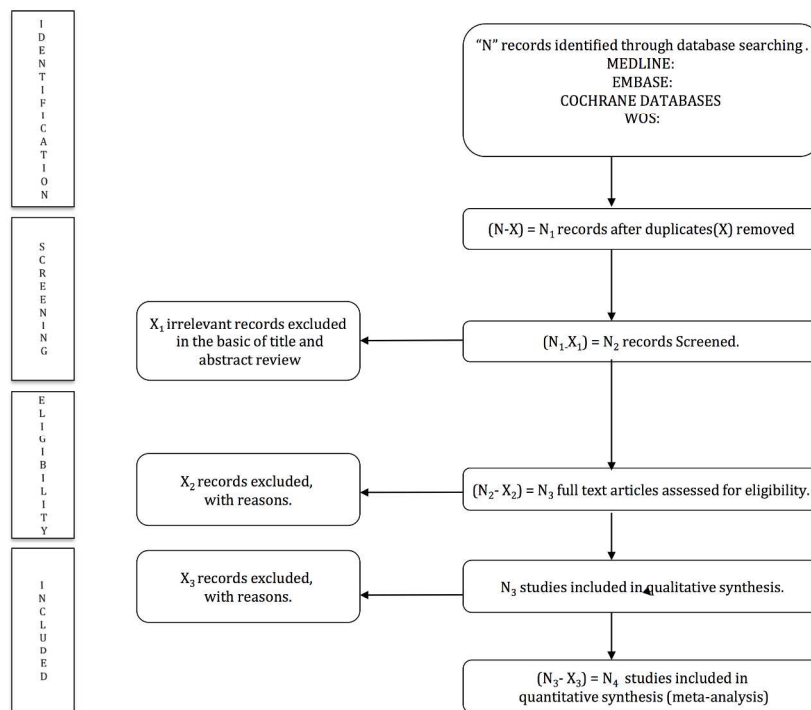


Figure 1. PRISMA flow diagram of identification, screening, eligibility and inclusion of studies.

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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
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

**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 $\tau$ )	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.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

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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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