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SYSTEMATIC REVIEW

The Effect of Physical Activity Interventions on Glycosylated Haemoglobin (HbA_{1c}) in Non-diabetic Populations: A Systematic Review and Meta-analysis

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Abstract

Background Physical activity is widely perceived to be beneficial for preventing type 2 diabetes mellitus and for controlling glycaemic levels in patients with type 2 diabetes, but evidence supporting a positive effect in the control of glycaemic levels in healthy people is rather weak. The aim of this review was to estimate the effect of physical activity on glycaemic control measured by glycosylated haemoglobin (HbA_{1c}) levels in non-diabetic populations, and to determine which type of physical activity has a greater influence on glycaemic control.

Methods We systematically searched the MEDLINE, EMBASE, Cochrane Library and Web of Science databases, from inception to May 2017, for experimental studies addressing the effect of physical activity on glycaemic control measured by HbA_{1c} levels in non-diabetic populations. The DerSimonian and Laird method was used to compute pooled estimates of effect size (ES) and respective 95% confidence intervals (CIs). The effect of physical activity on HbA_{1c} levels was estimated in two ways: (1) physical activity intervention versus control; and (2) physical activity pre–post intervention. Additionally, subgroup analyses were performed based on age of participants and different aspects of the intervention.

Results Fifteen published studies were included in the meta-analysis. In analyses comparing physical activity intervention and control, we found a decrease of HbA_{1c} levels in favour of the intervention group (ES = 0.32; 95% CI 0.01–0.62) with substantial heterogeneity ($I^2 = 63.2\%$; $p = 0.008$). In the pre–post analysis, there was a decrease in HbA_{1c} levels post physical activity intervention (ES = 0.17; 95% CI 0.01–0.33) with low heterogeneity ($I^2 = 25.8\%$; $p = 0.164$). Additionally, for physical activity intervention versus control, a decrease in HbA_{1c} levels was observed in resistance exercise and in intervention length below 12 weeks. Furthermore, for pre–post effect analyses, a decrease in HbA_{1c} levels was observed in the supervised physical activity programme, other type of exercises, intervention length below 12 weeks and exercise intervention week duration above 150 min subgroups.

Conclusions This systematic review and meta-analysis provides an overview of the evidence supporting physical activity as a suitable intervention for glycaemic control as measured by HbA_{1c} levels in non-diabetic populations.

Trial Registration PROSPERO CRD42016050991.

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Key Points

Resistance exercises [effect size (ES) = 0.32; 95% confidence interval (CI) 0.01–0.62] are the most successful type of physical exercise on glycaemic control in non-diabetic populations.

Supervised physical activity programs (ES = 0.33; 95% CI 0.14–0.52) are more effective for reducing (HbA_{1c}) levels than physical activity counselling (ES = − 0.03; 95% CI − 0.20 to 0.13) in non-diabetic populations.

Physical activity intervention length below 12 weeks (ES = 0.34; 95% CI 0.08–0.60) and above 150 min per week (ES = 0.27; 95% CI 0.05–0.50) are associated with large effects on glycaemic control in non-diabetic populations.

1 Background

Physical inactivity is a major contributor to chronic disease, including ischaemic heart disease, stroke, diabetes mellitus, and breast and colon cancer [1–3]. Global recommendations on physical activity for health [4] underscore the pivotal role that physical activity plays in health promotion and disease prevention. They recommend that individuals should accumulate 150 min of moderate physical activity or 75 min of vigorous physical activity per week. Among US adults, the prevalence of meeting recommendations on physical activity is approximately 51%, whereas only 27% of high school students meet recommendations for younger populations (60 min of daily moderate-to-vigorous activity), and this proportion decreases through adolescence [5].

In the last few years, there has been an increase in the number of authors who have advocated an increase in physical activity promotion health services [6], emphasizing the role of prescription of physical activity as a therapeutic alternative [7]. These recommendations are based on reports of studies that have assessed the cost effectiveness of physical activity prescription, since physical inactivity is estimated to be responsible for 11.1% of aggregate healthcare expenditures [8].

It is widely recognised that increases in physical activity would have important public health benefits; for example, the incidence of diabetes could be reduced by up to 46% by engaging in physical activity programmes [9]. However, few long-term physical activity evaluations have shown improvements in clinical risk indices [4, 10]. Moreover, current evidence has demonstrated that adequate physical activity, considering age, sex, resting and maximum heart rate, and awareness of the body's response to physical activity, improve metabolic risk factors [11].

Diagnosis of diabetes is focused simultaneously on plasma glucose concentrations and its long-term microvascular complications [12]. Glycosylated haemoglobin (HbA_{1c}) has been demonstrated to be an appropriate method for the diagnosis of microvascular complications of diabetes [13]. Currently, much attention has been focused on the role of HbA_{1c} in the identification of dysglycaemia in patients without diabetes [14]. Also, a recent meta-analysis determined the optimal HbA_{1c} range to prevent the risk of all-cause and cardiovascular mortality to be 5.0–6.0% in non-diabetic populations [15]. Since microvascular complications of diabetes are present at early stages of the disease, controlling HbA_{1c} levels should not be restricted to diabetic patients.

Considering the increasing incidence of diabetes in industrialised countries, the promotion of physical activity, as a vital component of diabetes prevention, must be viewed as a high priority [16]. However, as far as we know, no meta-analysis has analysed the effect of physical activity interventions to control HbA_{1c} levels in non-diabetic populations, which seems to be an important public health issue. Similarly, the type of exercise most appropriate for reducing HbA_{1c}, and therefore the risk of diabetes, has also not been reviewed.

The aims of this systematic review and meta-analysis were to (1) estimate the effect of physical activity on glycaemic control measured by HbA_{1c} levels in non-diabetic populations; and (2) determine which type of physical activity (based on qualitative or quantitative characteristics) has a greater positive influence on glycaemic control.

2 Methods

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17] (Fig. 1), and follows the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* [18]. This systematic review and meta-analysis was registered through PROSPERO (registration number CRD42016050991) and its protocol has been published elsewhere [19].

2.1 Search Strategy

We systematically searched the MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Web of

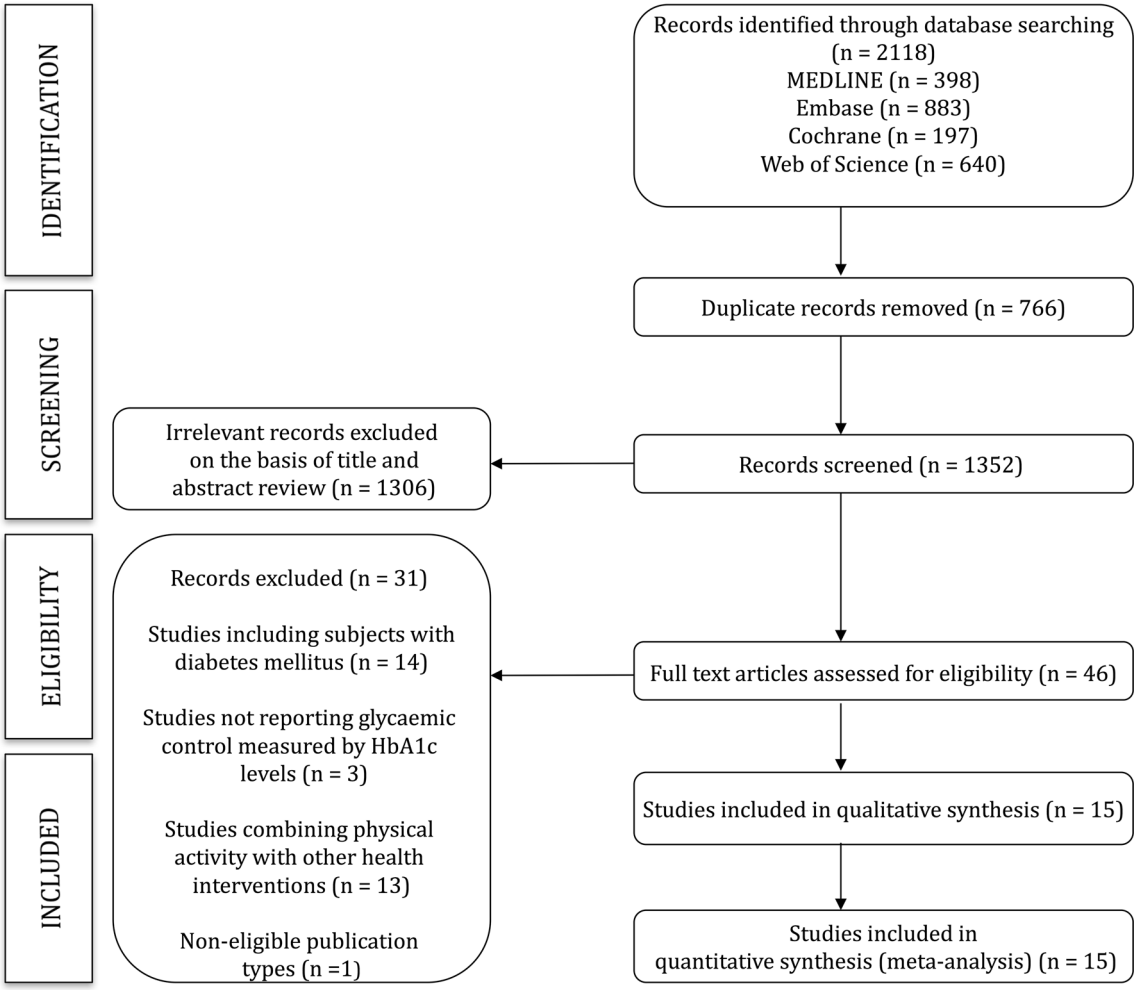

Fig. 1 Literature search Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consort diagram. *HbA_{1c}* glycosylatedhaemoglobin

Science databases from their inception until May 2017. Articles addressing the effect of physical activity on glycaemic control measured by HbA_{1c} levels in non-diabetic populations and based on data from experimental studies were eligible. The search strategy is presented in Electronic Supplementary Material Table S1. The literature search was complemented by reviewing citations of the articles considered eligible for the systematic review.

2.2 Study Selection

The criteria for excluding studies were as follows: (1) reports not written in English, French, Portuguese or Spanish; (2) studies including subjects who had been diagnosed with diabetes; (3) studies not reporting glycaemic control measured by HbA_{1c} levels; (4) studies combining physical activity with other health interventions, such as nutritional interventions; (5) non-eligible publication types, such as review articles, editorials, comments, guidelines or case-reports; (6) studies not providing pre–post intervention HbA_{1c} levels; and (7) duplicate reports of the same study.

When more than one study provided data referring to the same sample, we used the study providing more detailed data with the largest sample size. However, data regarding sample characteristics could also be extracted from multiple reports to obtain the most complete information.

The literature search was independently conducted by two reviewers (ICR and CAB), and disagreements were solved by consensus or involving a third researcher (VMV).

2.3 Data Extraction and Quality Assessment

The following data were extracted from the original reports: (1) year of publication; (2) country; (3) study design; (4) sample characteristics (sample size and age distribution); (5) type of population (non-diabetic,

including information on co-morbidities); (6) methods used in HbA_{1c} assay; (7) HbA_{1c} level before the intervention; and (8) type and characteristics of the physical activity intervention.

The methodological quality of randomised controlled trials (RCTs) was assessed using the Cochrane Collaboration's tool for assessing risk of bias [20]. This tool evaluates the risk of bias according to six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.

The Quality Assessment Tool for Quantitative Studies [21] was used to assess the quality of pre–post studies and non-RCTs. This tool evaluates seven domains: selection bias, study design, confounders, blinding, data collection method, withdrawals and dropouts.

In both quality assessment tools, each domain could be considered as strong, moderate or weak, and studies could be classified as low risk of bias (with no weak ratings), moderate risk of bias (with one weak rating) or high risk of bias (with two or more weak ratings) [22].

Data extraction and quality assessment were independently performed by two reviewers (ICR and CAB), and inconsistencies were solved by consensus or involving a third researcher (VMV). The agreement rate between reviewers was calculated using kappa statistics.

2.4 Statistical Analysis and Data Synthesis

The DerSimonian and Laird method was used to compute a pooled estimate of effect size (ES) and respective 95% confidence intervals (CIs). When studies were RCTs, a standardised mean difference score was calculated for HbA_{1c} levels using Cohen's *d* index as the ES statistic [23], in which positive ES values indicate a decrease in HbA_{1c} level in favour of the intervention versus the control group. In addition, Cohen's *d* index as the ES statistic was used to estimate pre–post physical activity intervention changes in HbA_{1c} levels, with positive ES values indicating decreases in HbA_{1c} level. Cohen's *d* values around 0.2 were considered weak effect, values around 0.5 were considered moderate effect, values around 0.8 were considered strong effect, and values larger than 1.0 were considered very strong effect.

The heterogeneity of results across studies was evaluated using the I^2 statistic. I^2 values are considered as follows: might not be important (0–40%); may represent moderate heterogeneity (30–60%); substantial heterogeneity (50–90%); or considerable heterogeneity (75–100%). The corresponding *p*-values were also taken into account [17].

Additionally, when studies included two intervention groups, their data were analysed as independent samples, and when studies reported two or more follow-up measurements, only the last study was considered.

Sensitivity analyses were conducted to assess the robustness of summary estimates and to detect if any particular study accounted for a large proportion of heterogeneity.

Subgroup analyses were performed based on age of participants (adolescents, adults and elderly) and different aspects of the intervention: (1) type of physical activity intervention (supervised physical activity programme or physical activity counselling); (2) type of exercise [endurance exercise (activities that increase breathing and heart rate for an extended period of time), resistance exercise (activities that require muscles to contract against an external resistance with the expectation of increases in strength, tone and/or mass), combined endurance and resistance exercises, or other type of exercises (such as yoga, Tai Chi, Qigong, Kung Fu)]; (3) intensity of endurance exercise (moderate or moderate/vigorous); (4) intensity of resistance exercise (low or moderate); (5) length of intervention (≤ 12 or > 12 weeks); and (6) minutes per week (< 150 or ≥ 150 min).

Random-effects meta-regression was used to evaluate whether results differed according to the mean age of participants, percentage of males and body mass index (BMI) [24], since this could be considered a source of heterogeneity.

Finally, publication bias was evaluated through visual inspection of funnel plots, as well as using the method proposed by Egger [25]. The trim-and-fill computation was used to assess the effect of publication bias on the interpretation of results [26].

The significance value of the pooled ES was estimated based on the 95% CI. Statistical analyses were performed using STATA® SE software, version 14 (StataCorp, College Station, TX, USA).

3 Results

3.1 Systematic Review

We identified 15 studies (Table 1) [27–41] addressing the effect of physical activity on glycaemic control measured by HbA_{1c} levels in non-diabetic populations, which were conducted in eight countries: two from the Americas (North and South America), two from Asia, three from Europe and one from Oceania. Reports were published between 2000 and 2016, and they included studies using the following experimental designs: eight were RCTs, five were pre–post non-randomised experimental studies and two were controlled pre–post studies.

Table 1 Characteristics of studies included in the systematic review and meta-analysis

Study (year)	Country	Study design	Population characteristics				Outcome		Intervention characteristics	
			Age [years (mean ± SD)]	Sample size [*n* (% male)]	BMI (kg/m^2)	Type of population	HbA_{1c} method	Pre-intervention HbA_{1c} levels [% (95% CI)]	Physical activity intervention	Physical activity characteristics
Ando et al. (2009) [27]	Japan	RCT	CG: 56.1 ± 8.7 IG: 55.9 ± 7.8	CG: 27 (33.3) IG: 26 (30.8)	CG: 22.8 CI: 23.9	Non-diabetic population	Ion-exchange HPLC	CG: 5.70 (5.54–5.86) IG: 5.70 (5.58–5.82)	Supervised physical activity programme	IG: moderate-/vigorous-intensity endurance and moderate-intensity resistance exercises 56 weeks 2 days/week 70 min
Fantin et al. (2012) [28]	Italy	Pre–post intervention	IG: 68.2 ± 5.7	IG: 21 (0.0)	IG: 28.6	Non-diabetic population	Ion-exchange HPLC (Bio-Rad Laboratories)	IG: 5.84 (5.68–6.00)	Supervised physical activity programme	IG: moderate-intensity endurance exercise 24 weeks 2 days/week 60 min
Huang et al. (2007) [29]	Japan	Pre–post intervention	IG: 67.5 ± 6.6	IG: 30 (40.0)	IG: 21.8	Non-diabetic population	NR	IG: 4.95 (4.85–5.05)	Supervised physical activity programme	IG: moderate-/vigorous-intensity endurance exercise 24 weeks 5 days/week 30 min
Kallings et al. (2009) [30]	Sweden	RCT	CG: 67.5 ± 0.35 IG: 67.5 ± 0.35	CG: 54 (42.5) IG: 47 (42.5)	CG: 30.4 IG: 29.7	Overweight/obese non-diabetic population	NR	CG: 4.80 (4.78–4.82) IG: 5.00 (4.98–5.02)	Physical activity counselling	IG: moderate-/vigorous-intensity endurance and moderate-intensity resistance exercises 24 weeks 7 days/week 30 min
Lalande et al. (2010) [31]	USA	Non-RCT	CG: 50.0 ± 6.0 IG: 54.0 ± 8.0	CG: 17 (52.9) IG: 29 (48.3)	CG: 28.8 IG: 29.5	Non-diabetic population	NR	CG: 5.50 (5.30–5.70) IG: 5.20 (5.04–5.36)	Physical activity counselling	IG: moderate-/vigorous-intensity endurance exercise 12 weeks 4 days/week 30 min
Liu et al. (2010) [32]	Australia	Pre–post intervention	IG:53.5 ± 6.6	IG: 11 (27.3)	IG: 27.8	Non-diabetic population	Immunoassay (Bayer HealthCare)	IG: 5.59 (5.41–5.77)	Supervised physical activity programme	IG: Tai Chi/Qigong 12 weeks 5 days/week 30 min

Table 1 continued

Study (year)	Country	Study design	Population characteristics				Outcome		Intervention characteristics	
			Age [years (mean ± SD)]	Sample size [*n* (% male)]	BMI (kg/m^2)	Type of population	HbA_{1c} method	Pre-intervention HbA_{1c} levels [% (95% CI)]	Physical activity intervention	Physical activity characteristics
Morey et al. (2012) [33]	USA	RCT	CG: 67.7 ± 6.2 IG: 67.1 ± 6.3	CG: 122 (97.5) IG: 180 (96.1)	CG: 31.0 IG: 31.3	Non-diabetic (prediabetes) population	NR	CG: 5.91 (5.85–5.97) IG: 5.89 (5.83–5.95)	Physical activity counselling	IG: moderate-intensity endurance and moderate-intensity resistance exercises 48 weeks 5 days/week 30 min
Papp et al. (2016) [34]	Sweden	RCT	CG: 27.2 ± 5.5 IG: 26.7 ± 4.9	CG: 23 (13.0) IG: 21 (14.2)	CG: 21.9 IG: 22.2	Non-diabetic population	Ion-exchange HPLC (Bio-Rad Laboratories)	CG: 5.10 (5.00–5.20) IG: 5.10 (5.00-5.20)	Supervised physical activity programme	IG: yoga 6 weeks 1 day/week 60 min
Sixt et al. (2008) [35]	Austria	RCT	CG: 64.0 ± 6.0 IG: 64.0 ± 6.0	CG: 10 (70.0) IG: 13 (77.0)	CG: 31.7 IG: 29.2	Coronary disease non-diabetic (prediabetes) patients	NR	CG: 5.80 (5.43–6.17) IG: 5.60 (5.36–5.84)	Supervised physical activity programme	IG: Moderate-intensity endurance exercise 4 weeks 5 days/week 30 min
Sjöling et al. (2011) [36]	Sweden	Pre–post intervention	IG: 61.6 ± 7.0	IG: 31 (64.0)	IG: 32.0	Hypertensive non-diabetic population	Ion-exchange HPLC (GE Healthcare)	IG: 4.70 (4.48–4.92)	Physical activity counselling	IG: moderate-intensity endurance exercise 60 weeks 1 day/week 60 min
Tsang et al. (2009) [37]	Australia	RCT	IG: 13.1 ± 2.1	IG1: 8 (41.7) IG2: 12 (37.5)	IG1: NR IG2: NR	Overweight/obese non-diabetic population	Ion-exchange HPLC	IG1: 5.43 (4.88–5.98) IG2: 5.41 (5.23–5.59)	Supervised physical activity programme	IG1: Tai Chi 8 weeks 3 days/week 60 min IG2: Kung Fu 8 weeks 3 days/week 60 min
Tibana et al. (2013) [38]	Brazil	Pre–post intervention	IG: 33.9 ± 8.6	IG: 14 (0.0)	IG: 29.6	Overweight/obese non-diabetic population	Immunoassay (Beckman Instruments)	IG: 5.29 (5.04–5.54)	Supervised physical activity programme	IG: Moderate-intensity resistance exercise 8 weeks 3 days/week 50 min

Table 1 continued

Study (year)	Country	Study design	Population characteristics				Outcome		Intervention characteristics	
			Age [years (mean ± SD)]	Sample size [*n* (% male)]	BMI (kg/m^2)	Type of population	HbA_{1c} method	Pre-intervention HbA_{1c} levels [% (95% CI)]	Physical activity intervention	Physical activity characteristics
Tsukui et al. (2000) [39]	Japan	Pre–post intervention	IG:50.0 ± 6.0	IG: 27 (0.0)	IG: 25.2	Overweight/obese non-diabetic population	Ion-exchange HPLC (Kyoto Daiichi Kagaku)	IG: 5.30 (5.10–5.50)	Supervised physical activity programme	IG: moderate-intensity endurance exercise 8 weeks 5 days/week 45 min
Tsuzuku et al. (2007) [40]	Japan	RCT	CG:70.2 ± 3.9 IG: 69.4 ± 2.8	CG: 20 (50.0) IG: 32 (37.5)	CG: 22.7 IG: 22.9	Non-diabetic population	Enzymatic	CG: 5.00 (4.82–5.18) IG: 5.40 (5.16–5.64)	Supervised physical activity programme	IG: low-intensity resistance exercise 12 weeks 3 days/week 60 min
Vizza et al. (2016) [41]	Australia	RCT	CG: 29.0 ± 3.0 IG: 26.7 ± 7.0	CG: 6 (0.0) IG: 7 (0.0)	CG: 33.8 IG: 41.3	Polycystic ovary syndrome non-diabetic patients	NR	CG: 5.10 (4.86–5.34) IG: 5.30 (4.97–5.63)	Supervised physical activity programme	IG: Low-intensity resistance exercise 12 weeks 2 days/week 60 min

BMI body mass index, *CG* control group, *CI* confidence interval, *HbA_{1c}* glycosylated haemoglobin, *HPLC* high-performance liquid chromatography, *IG* intervention group, *NR* not reported, *RCT* randomised controlled trial, *SD* standard deviation

Regarding characteristics of the populations evaluated in the studies, seven studies enrolled subjects with a specific disease status (overweight/obesity, coronary disease, hypertension and polycystic ovary syndrome). Moreover, two studies enrolled pre-diabetic subjects. Included subjects were aged between 13 and 70 years, with sample sizes ranging from 11 to 302 subjects.

Only three studies mentioned the use of certified National Glycohemoglobin Standardization Program methods [42] for the assessment of HbA_{1c} levels. Baseline HbA_{1c} mean levels ranged from 4.70 to 5.91%.

Concerning characteristics of interventions carried out in the studies, 11 were supervised physical activity programmes, whereas four were counselling interventions for increasing physical activity. Regarding supervised physical activity programmes, nine studies were performed indoor (including gym and cycling exercises) and two studies outdoor (including walking and swimming). Furthermore, regarding counselling interventions for increasing physical activity, two studies included physical activity prescriptions by clinicians and another two evaluated instructions by physical activity trainers. Different types of exercises were found among the physical activity interventions, including: endurance, resistance, a mix of both, and other type of exercises (such as yoga, Tai-chi, Qigong, Kung Fu). In addition, when endurance exercise was used, most of the interventions were developed at moderate intensity, and only three studies had a moderate/vigorous intensity. Concerning resistance exercises, all included studies performed calisthenic exercises, most interventions were conducted at moderate intensity, and only two studies were conducted at low intensity. Length of interventions ranged from 6 to 60 weeks, with duration time per session ranging from 60 to 225 min.

3.2 Study Quality

As evaluated by the Cochrane Collaboration's tool for assessing risk of bias [20] for RCTs and the Quality Assessment Tool for Quantitative Studies [21] for pre–post studies and non-RCTs, 26.7% of the studies showed a high risk of bias, 66.7% a moderate risk of bias and 6.6% a low risk of bias. When studies were analysed by individual domains, 100% of the pre–post and non-RCT studies had shortcomings in the blinding domain. On the other hand, 50 and 75% of RCT studies had shortcomings in the performance bias and detection bias domains, respectively, with both domains being related to blinding in the studies (Electronic Supplementary Material Tables S2 and S3).

3.3 Meta-analyses

For the analysis of physical activity intervention versus control, there was a decrease in HbA_{1c} levels in favour of the intervention group (ES = 0.32; 95% CI 0.01–0.62), with substantial heterogeneity ($I^2 = 63.2\%$; $p = 0.009$). Additionally, when ES was estimated considering only the effect in intervention groups, there was a decrease in HbA_{1c} levels after physical activity intervention (ES = 0.17; 95% CI 0.01–0.33), with no important heterogeneity ($I^2 = 25.8\%$; $p = 0.164$) (Fig. 2).

3.4 Sensitivity Analysis

When the impact of individual studies was examined by removing studies from the analysis one at a time, we observed that the pooled ES estimate for physical activity interventions versus control decreased only after removing data from the Kallings et al. [30] study (ES = 0.12, 95% CI − 0.05 to 0.30).

3.5 Subgroup Analyses and Meta-regression

Based on different aspects of the intervention, for physical activity intervention versus control, a decrease in HbA_{1c} levels in favour of the intervention group was observed in low-intensity resistance exercise subgroup (ES = 0.82; 95% CI 0.30–1.33, $I^2 = 62.4\%$) and in intervention length below 12 weeks subgroup (ES = 0.36; 95% CI 0.02–0.71, $I^2 = 18.2\%$).

For pre–post effect analyses, a decrease in HbA_{1c} levels post physical activity intervention was observed in the supervised physical activity programme subgroup (ES = 0.33; 95% CI 0.14–0.52, $I^2 = 0.0\%$), other type of exercises subgroup (ES = 0.42; 95% CI 0.03–0.84, $I^2 = 0.0\%$), low-intensity resistance subgroup (ES = 0.84; 95% CI 0.38–1.30, $I^2 = 0.0\%$), intervention length below 12 weeks subgroup (ES = 0.34; 95% CI 0.08–0.60, $I^2 = 29.0\%$) and exercise intervention week duration above 150 min subgroup (ES = 0.27; 95% CI 0.05–0.50, $I^2 = 39.7\%$) (Table 2).

The random-effects meta-regression model showed that age, percentage of males and BMI were not related to heterogeneity across studies either for physical activity intervention versus control analysis ($p = 0.665$ for age, $p = 0.752$ for percentage of males and $p = 0.946$ for BMI) or for physical intervention pre–post analysis ($p = 0.489$ for age, $p = 0.195$ for percentage of males and $p = 0.073$ for BMI).

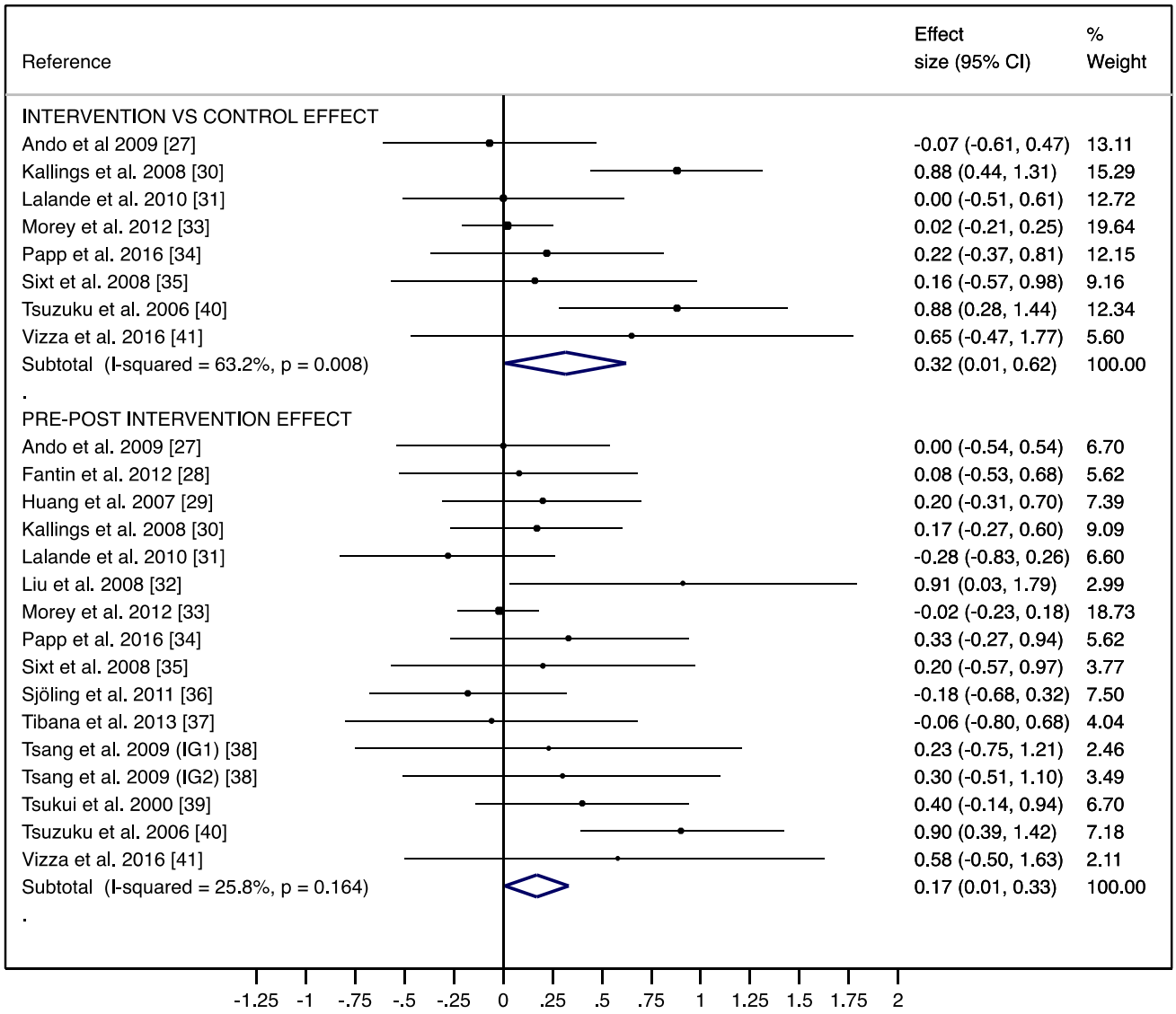

Fig. 2 Forest plots of the effect size for physical activity intervention in non-diabetic populations according to study design. *CI* confidence interval, *IG* intervention group

3.6 Publication Bias

There was no significant publication bias for physical activity intervention versus control analysis, as evidenced by the funnel plot asymmetry and the Egger's test ($p = 0.359$). Conversely, there was evidence of publication bias for pre-post physical intervention effect analysis ($p = 0.092$) (Electronic Supplementary Material Figure S1). Additionally, trim-and-fill computation showed that five studies were needed to remove publication bias for physical intervention effect analysis ($p = 0.762$).

4 Discussion

This systematic review and meta-analysis provides an overview of the evidence supporting that physical activity is a suitable intervention in non-diabetic populations for glycaemic control as measured by HbA_{1c} levels. Our data show that physical activity interventions result in a significant decrease in HbA_{1c} levels. Furthermore, this meta-analysis supports the hypothesis that resistance is the most effective type of physical exercise for achieving glycaemic control in non-diabetic populations.

As in many other diseases, the prevention of diabetes and cardiovascular disease is the keystone for improving efficiency in the health systems of industrialised countries [43]. Prevention should be directed at avoiding the

Table 2 Subgroup analyses based on study intervention characteristics

Subgroup analyses	Physical activity intervention vs. control				Physical activity pre–post intervention			
	Number of studies	Effect size (95% CI)	I^2	*p*-value	Number of studies	Effect size (95% CI)	I^2	*p*-value
Age								
Adolescents (12–20 years)	0				2	0.27 (− 0.35, 0.89)	0.0	0.914
Adults (20–60 years)	4	0.09 (− 0.22, 0.40)	0.0	0.663	7	0.19 (− 0.09, 0.46)	21.3	0.267
Elderly (≥ 60 years)	4	0.48 (− 0.06, 1.01)	81.7	0.001	7	0.17 (− 0.08, 0.41)	50.5	0.060
Type of intervention								
Supervised physical activity programme	5	0.33 (− 0.04, 0.70)	32.5	0.205	12	*0.33 (0.14, 0.52)*	0.0	0.511
Physical activity counselling	3	0.30 (− 0.28, 0.88)	83.5	0.002	4	− 0.03 (− 0.20, 0.13)	0.0	0.578
Type of physical activity								
Endurance/resistance combined exercises	3	0.27 (− 0.29, 0.84)	84.2	0.002	3	0.01 (− 0.16, 0.19)	0.0	0.740
Endurance exercise	2	0.06 (− 0.43, 0.55)	0.0	0.760	6	0.05 (− 0.17, 0.28)	0.0	0.503
Resistance exercise	2	*0.82 (0.30, 1.33)*	62.4	0.009	3	0.50 (− 0.13, 1.13)	54.1	0.113
Other type of exercise	1	0.22 (− 0.37, 0.81)	–	–	4	*0.42 (0.03, 0.81)*	0.0	0.681
Intensity of endurance exercise								
Moderate/vigorous intensity	3	0.29 (− 0.36, 0.94)	78.3	0.010	5	0.05 (− 0.18, 0.28)	36.2	0.195
Moderate intensity	2	0.03 (− 0.19, 0.25)	0.0	0.749	4	0.02 (− 0.16, 0.19)	0.0	0.835
Intensity of resistance exercise								
Moderate intensity	0				1	− 0.06 (− 0.80, 0.68)		
Low intensity	2	*0.82 (0.30, 1.33)*	62.4	0.009	2	*0.84 (0.38, 1.30)*	0.0	0.596
Intervention length								
≤ 2 weeks	5	*0.36 (0.02, 0.71)*	18.2	0.299	10	*0.34 (0.08, 0.60)*	29.0	0.178
> 12 weeks	3	0.27 (− 0.29, 0.84)	84.2	0.002	6	0.02 (− 0.14, 0.17)	0.0	0.883
Minutes per week								
< 150 min	4	0.09 (− 0.23, 0.23)	0.0	0.667	6	0.00 (− 0.24, 0.24)	0.0	0.581
≥ 150 min	4	0.48 (− 0.06, 1.02)	81.4	0.001	10	*0.27 (0.05, 0.50)*	39.7	0.093

Italicised values indicate $p < 0.05$

CI confidence interval

appearance of risk factors, which is known as primary prevention [44]. There is consistent evidence supporting physical activity, nutrition and treatment with antidiabetic drugs as the most effective interventions for the prevention of diabetes and its complications [45]. Thus, a principal public health objective is to increase the proportion of the population that is physically active and following a proper diet, which can prevent obesity, hyperglycaemia, hypertension or hypercholesterolaemia.

In diabetic populations, evidence supports that, although both aerobic and resistance training have some beneficial effect on glycaemic control, programmes that combine aerobic and resistance training are the most effective in improving HbA_{1c} levels [46]. Our data support that physical activity also has a positive effect on the control of

glycaemic levels in healthy people (or people with conditions other than diabetes). This finding could have relevance because it consolidates evidence supporting exercise as a powerful strategy for preventing type 2 diabetes, particularly in industrialised countries, which are suffering an epidemic of sedentariness.

There is an extensive body of literature supporting the benefits of exercise training on cardiometabolic risk, and particularly on type 2 diabetes [47–50]. The main mechanisms behind this beneficial effect, in short, are that exercise increases insulin sensitivity in the trained muscle, and muscle work induces glucose uptake in the muscle [51]. Exercise training enlarges muscle capillary network and blood flow, which increases skeletal muscle glucose transporter protein 4 (GLUT4) expression, promotes glucose synthesis, and reduces release of and increases the clearance of free fatty acids [52]. With fewer blood glucose molecules available, binding of glucose to the haemoglobin heteroprotein decreases, resulting in lower HbA_{1c}.

Overall, characteristics of the intervention associated with a larger effect were the following: (1) supervised physical activity programmes; (2) resistance exercises; (2) intervention length below 12 weeks; and (4) intervention duration above 150 min per week.

Physical activity interventions that involve a health professional giving written advice to patients to increase their physical activity have obtained variable success [53]. On the other hand, supervised physical activity programme interventions are widely known to improve physical activity levels, quality of life and/or cardiometabolic parameters [54]. Our findings show that supervised physical activity programmes were more effective for reducing HbA_{1c} levels than physical activity counselling, which is consistent with prior findings [55].

In relation to the type of activity, it should be appreciated that low-intensity exercises are associated with lower glucose consumption, which means that changes in blood sugar levels will take place more slowly [56]. The results of this meta-analysis show that low-intensity resistance exercises and other types of exercise (whose intensity tends to be low) are effective in controlling HbA_{1c} levels. These types of exercise may modulate autonomic function and beneficially alter markers of sympathetic and parasympathetic activity [57]. Through practicing low-intensity exercises, the effect of stress could be reduced, leading to a positive impact on neuroendocrine status, metabolic and cardio-vagal function, and related inflammatory responses [58]. Additionally, low-intensity exercises for more than 150 min per week were more effective (ES = 0.69; 95% CI 0.33–1.05) than those for less than 150 min per week. If HbA_{1c} is a marker of blood glycaemia in the last 3 months, it seems logical to suggest that low-intensity exercises over longer periods of time are more closely associated with changes in HbA_{1c} in non-diabetic individuals.

Endurance or combined endurance/resistance exercises are more common and usually practiced by the general population [59, 60], and previous studies have concluded that these types of exercises are effective in reducing HbA_{1c} in diabetic patients [49, 50]. Our results have, however, elucidated that endurance exercises were not effective for reducing HbA_{1c} levels in non-diabetic populations. This could be due to endurance exercise-induced changes in energy balance which may stimulate compensatory adjustments that alter daily food intake [61], even though the target population of these interventions are healthy subjects who have no dietary prescriptions.

In addition, a previous study suggested that changes in HbA_{1c} levels would require between 8 and 12 weeks before reaching a plateau [62]. Our results reinforce these findings, showing that physical activity interventions of ≤ 12 weeks duration were more effective in reducing HbA_{1c} among non-diabetics. This may be due to the peak effect of physical activity on HbA_{1c} being evident at 12 weeks given that HbA_{1c} is a biomarker that quantifies the 12-week average plasma glucose concentration. Furthermore, our results did not show that interventions of >12 weeks duration had the opposite effect and therefore the practice of physical activity over this length should be considered, although compensatory food intake changes or reductions in non-exercise activity thermogenesis might mitigate some of the long-term intervention benefits [63, 64]. Finally, our data support global recommendations on physical activity for health [4], detecting beneficial effects with physical activity of more than 150 min per week.

The importance of control groups to isolate the impact of the independent variable on the dependent variable has been defined. In addition, using a control group eliminates a variety of threats to internal and external validity [65]. Without evidence from a control group, it is not possible to correct a single study estimate for the influence of extraneous factors, which may have magnified or diminished its influence [66]. Our pooled estimates including studies comparing physical activity interventions versus control groups showed a greater effect on HbA_{1c} decrease than those that included only pre–post physical intervention effects.

Some limitations of this review that could compromise our results should be stated. First, data extraction were non-blinded, which is a potential source of bias. Second, the studies were of medium quality overall. Third, programmes were heterogeneous regarding type, length and intensity of physical exercise. This variability in the characteristics of the physical activity intervention makes the size of some groups very small for subgroups analysis. Fourth, none of

the studies assessed the daily physical activity performed by subjects outside of the programmes (either by recall or accelerometer); thus, the effect of intervention on non-exercise physical activity could not be controlled for by meta-regression analyses. Fifth, only three studies mentioned the use of certified National Glycohemoglobin Standardization Program methods. Sixth, small sample size undermines the reliability of some studies included in this meta-analysis [67]. Seventh, there was evidence for significant publication bias in Egger's test for physical intervention effect analysis, and results from studies that are not published could have modified the results of our meta-analysis; thus, the effect of publication bias on the interpretation of results was assessed using the trim-and-fill computation methods. Finally, most of studies were not designed for observed effects on glycaemic control and HbA_{1c} levels were not the main outcome variable.

5 Conclusions

Our meta-analysis allows us to conclude that physical activity interventions are effective for reducing HbA_{1c} levels in non-diabetic populations. Also, it provides clinical evidence that physical activity could reduce HbA_{1c} levels by between 0.01 and 0.22% depending on the characteristics of physical activity interventions. Thus, our review has important clinical and public health implications because it provides support for recommending physical exercise in non-diabetic subjects as a population strategy for preventing type 2 diabetes and its complications. Moreover, in light of the findings of this review, and considering that HbA_{1c} is a glycaemic marker that has been consistently associated with cardiovascular disease and mortality, the clinical guidelines for preventing diabetes and cardiovascular disease should include support for low-intensity resistance exercise, with a weekly duration of more than 150 min, as an effective strategy to reduce cardiometabolic risk.

Author Contributions VM-V and IC-R designed the review and meta-analysis. VM-V was the principal investigator and guarantor. IC-R and VM-V were the main coordinators of the review. BP, CA-B and VM-V conducted the review. MG-M, EGA and CA-B gave statistical and epidemiological support. IC-R wrote the article with the support of CA-B, EGA and BP. All authors revised and approved the final version of the manuscript.

Compliance with Ethical Standards

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Conflict of interest Ivan Cavero-Redondo, Barbara Peleteiro, Celia Alvarez-Bueno, Enrique Garcia Artero, Miriam Garrido-Miguel and Vicente Martinez-Vizcaino declare that they have no conflicts of interest relevant to the content of this review.

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