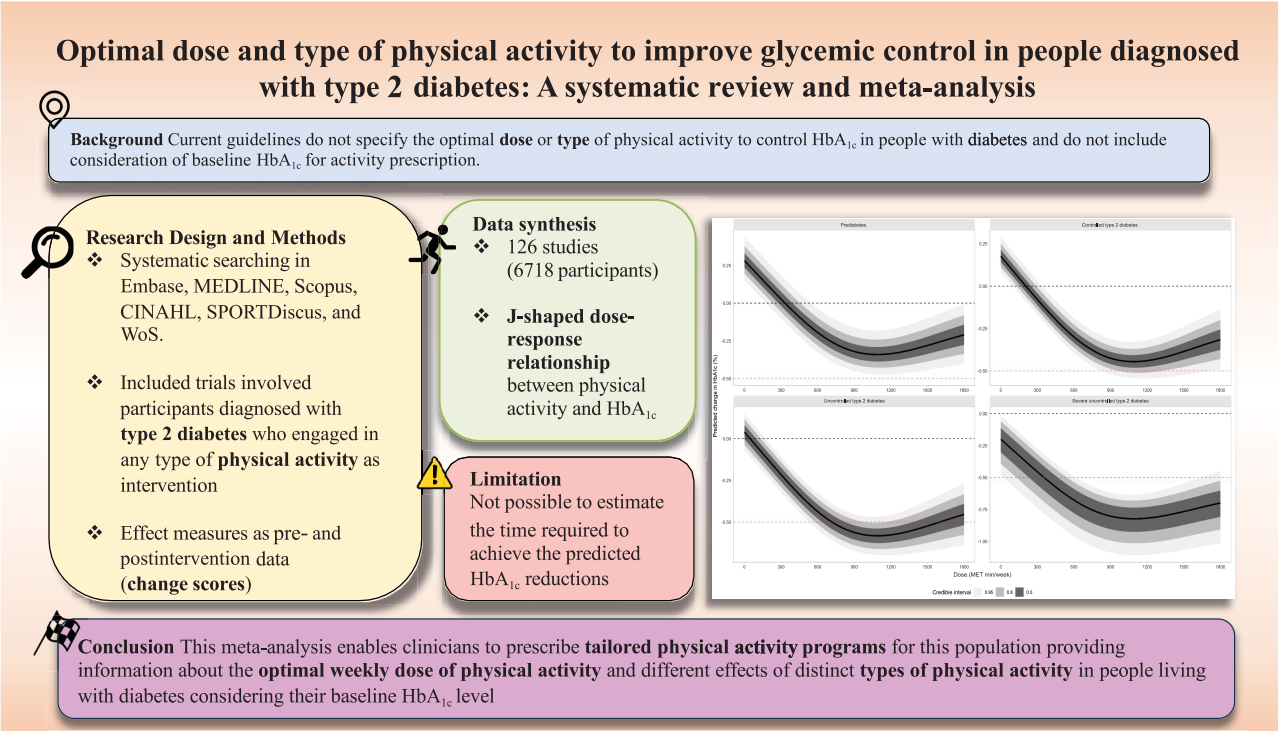
Diabetes Care
American Diabetes Association

Optimal Dose and Type of Physical Activity to Improve Glycemic Control in People Diagnosed With Type 2 Diabetes: A Systematic Review and Meta-analysis

Daniel Gallardo-Gómez, Eduardo Salazar-Martínez, Rosa M. Alfonso-Rosa, Javier Ramos-Munell, Jesús del Pozo-Cruz, Borja del Pozo Cruz, and Francisco Álvarez-Barbosa

Diabetes Care 2024;47(2):295–303 | https://doi.org/10.2337/dc23-0800



ARTICLE HIGHLIGHTS

- The optimal type-dose combination of physical activity to control HbA_{1c} in type 2 diabetes remains unknown.
- We investigated the optimal type-dose combination of physical activity for glucose control in individuals with type 2 diabetes, considering their initial condition.
- For optimization of HbA_{1c} control in this population, people should accumulate 1,100 MET min/week, which corresponds to ~36 minutes/day of brisk walking.
- The results of this meta-analysis provide key information for implementation of effective and tailored physical activity programs according to the patient's necessities and preferences to tackle one of the greatest public health challenges of the 21st century.

Check for updates

Optimal Dose and Type of Physical Activity to Improve Glycemic Control in People Diagnosed With Type 2 Diabetes: A Systematic Review and Meta-analysis

Diabetes Care 2024;47:295–303 | https://doi.org/10.2337/dc23-0800

Daniel Gallardo-Gómez,[1,2]
Eduardo Salazar-Martínez,[2,3]
Rosa M. Alfonso-Rosa,[2,4]
Javier Ramos-Munell,[1,2]
Jesús del Pozo-Cruz,[1,2]
Borja del Pozo Cruz,[2,5,6] and
Francisco Álvarez-Barbosa[1,2]

BACKGROUND

The optimal dose or type of physical activity to control glycosylated hemoglobin (HbA_{1c}) in people with diabetes remains unknown. Current guidelines do not include consideration of baseline HbA_{1c} for activity prescription.

PURPOSE

To examine the dose-response relationship between physical activity and HbA_{1c} (%) in individuals with type 2 diabetes.

DATA SOURCES

A systematic search was performed in Embase, MEDLINE, Scopus, CINAHL, SPORTDiscus, and Web of Science.

STUDY SELECTION

We included trials that involved participants diagnosed with type 2 diabetes that included any type of physical activity as intervention.

DATA EXTRACTION

Pre- and postintervention HbA_{1c} data, population and interventions characteristics, and descriptive statistics were collected to calculate change scores for each study arm.

DATA SYNTHESIS

We used Bayesian random-effects meta-analyses to summarize high-quality evidence from 126 studies (6,718 participants). The optimal physical activity dose was 1,100 MET min/week, resulting in HbA_{1c} reductions, ranging from −1.02% to −0.66% in severe uncontrolled diabetes, from −0.64% to −0.49% in uncontrolled diabetes, from −0.47% to −0.40% in controlled diabetes, and from −0.38% to −0.24% in prediabetes.

LIMITATIONS

The time required to achieve these HbA_{1c} reductions could not be estimated due to the heterogeneity between interventions' duration and protocols and the interpersonal variability of this outcome.

CONCLUSIONS

The result of this meta-analysis provide key information about the optimal weekly dose of physical activity for people with diabetes with consideration of baseline HbA_{1c} level, and the effectiveness of different types of active interventions. These results enable clinicians to prescribe tailored physical activity programs for this population.

[1]Department of Physical Education and Sport, University of Seville, Seville, Spain
[2]Epidemiology of Physical Activity and Fitness Across the Lifespan (EPAFit) Research Group, University of Seville, Spain
[3]Department of Physical Activity and Sport, Centro de Estudios Universitarios "Cardenal Spínola," University of Seville, Spain
[4]Department of Human Motricity and Sports Performance, University of Seville, Seville, Spain
[5]Department of Clinical Biomechanics and Sports Science, University of Southern Denmark, Odense, Denmark
[6]Biomedical Research and Innovation Institute of Cádiz (INiBICA) Research Unit, University of Cádiz, Spain

Corresponding author: Francisco Álvarez-Barbosa, falvarez5@us.es

Received 3 May 2023 and accepted 19 August 2023

This article contains supplementary material online at https://doi.org/10.2337/figshare.24001908.

This article is featured in a podcast available at diabetesjournals.org/care/pages/diabetes_care_on_air.

See accompanying article, p. 196.

META-ANALYSIS

Type 2 diabetes is one of the world's most common long-term health conditions, affecting 1 in 11 of the adult population, and is responsible for 11% of deaths annually (1,2). Although the trend was estimated to be higher in high-income countries, the relative increase in the prevalence of type 2 diabetes is expected to occur in middle-income countries (2). Consequences and costs remain high (1,3), making type 2 diabetes a major public health concern (4). Thus, with no cure on the near horizon, the American Diabetes Association (ADA) recommends focusing on optimizing healthy lifestyle behaviors, such as physical activity, to improve diabetes care and reduce the risk of associated complications, disability, and all-cause mortality (5).

Physical activity has been shown to be effective in reducing mortality, comorbidities, and clinical parameters such as glycosylated hemoglobin (HbA_{1c}) (6–8). The ADA and other institutions, such as the World Health Organization and the American College of Sports Medicine, recommend, in their physical activity guidelines for people living with diabetes, engaging in at least 150–300 min of moderate-intensity aerobic physical activity per week or 75–150 min of vigorous-intensity aerobic physical activity per week and in muscle-strengthening activities involving major muscle groups two or more times a week (9,10). Investigators in several published meta-analyses have shown the effectiveness of different types of physical activities and exercise modalities (11–14); however, none found the optimal type or dose of physical activity to verify the validity and reliability of these recommendations, and consequently, determine whether the individuals are being sufficiently active.

Bayesian dose-response meta-analysis models have demonstrated efficiency in determining the optimal type and dose of physical activity in specific health outcomes like cognitive function (15). Thus, this evidence synthesis method could shed light on the optimal type-dose combination of physical activity to control HbA_{1c} in people with diabetes, which remains unknown. Additionally, the potential impact of important clinical characteristics such as baseline HbA_{1c} level at which participants enter into a physical activity program has not yet been meta-analyzed. All these factors may hamper the implementation of effective and tailored physical activity protocols. Capitalizing on novel meta-analytic techniques, we aim to inspect the dose-response relationship between physical activity and HbA_{1c} (%) responses with adjustment for HbA_{1c} baseline level of the participants.

METHODS

This preregistered systematic review with meta-analysis (International prospective register of systematic reviews [PROSPERO], no. CRD42022313034) was reported in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (16).

Data Sources and Searches

A systematic search was performed in Embase (Excerpta Medica Database), MEDLINE (with the engine PubMed), Scopus, CINAHL, SPORTDiscus, and Web of Science (WoS). The specific search strategy can be found in PROSPERO and Supplementary Table 1. The reference lists of relevant articles and reviews were also screened for additional studies. Titles/abstract and full text screening were reviewed by two investigators (D.G.-G. and F.A.-B.) independently. In case of discrepancy, a third author resolved the disagreement (E.S.-M.). The last search was performed in September 2022.

Study Selection

We included *1*) randomized controlled trials that *2*) involved participants diagnosed with type 2 diabetes according to ADA criteria and *3*) used any type of physical activity as intervention. Studies had to *4*) include a control group who received usual care or another type of physical activity intervention. Studies also had to *5*) include reporting of HbA_{1c} (%) as a glycemic control outcome. We excluded studies with combination of multiple treatments (e.g., physical activity and dietary changes or supplementation) for which the effects of physical activity could not be isolated. We also excluded studies in which participants also had associated severe conditions (e.g., mental disorders) and those where acute effects of physical activity were reported (i.e., an intervention duration of <4 weeks).

Data Extraction and Quality Assessment

General study information extracted by three reviewers (D.G.-G., E.S.-M., and F.A.-B.) included key characteristics of the included participants (i.e., age, sex, HbA_{1c} baseline level [%]), physical activity parameters (i.e., duration of the intervention, frequency, intensity, and type), control group information, main results of the included studies, and any statistical data that could be used to calculate the change scores for each study arm according to Cochrane methodological guidelines (17). If information was incomplete, we requested that the corresponding author supply information or data for inclusion in the meta-analysis, and when the minimally required data to conduct the dose-response meta-analysis could not be retrieved from the published reports, we contacted the authors and invited them to provide additional data. We contacted nine authors; three supplied the required data, and six did not.

Data Coding and Management

Some data coding definitions should be considered for an understanding of the posterior data synthesis process. First, interventions were coded by attending the protocol detailed in the primary study as two levels of hierarchy: *1*) overall (i.e., physical activity vs. usual care) and *2*) intervention-specific (i.e., different physical activity types vs. usual care) levels. In the second level, we classified the interventions as cycling, high-intensity interval training (HIIT), mind-body, mixed aerobic exercises (i.e., two or more aerobic-based activities were used), multicomponent (i.e., two or more types of activities were used mainly based on the combination of strength and aerobic activities), running, strength, and walking. Second, baseline HbA_{1c} level (%) was modeled as a continuous predictor and then transformed into specific categories according to ADA guidelines (18): $<$6.5% (48 mmol/mol) was categorized as prediabetes, between 6.5% (48 mmol/mol) and 7% (53 mmol/mol) as controlled type 2 diabetes, between 7% (53 mmol/mol) and 8% (64 mmol/mol) as uncontrolled type 2 diabetes mellitus, and $>$8% (64 mmol/mol) as severe uncontrolled type 2 diabetes.

The term "physical activity dose" here refers to the energy expenditure

expressed as MET minutes per week. Following the validated approach of Ainsworth et al. (19), we calculated the different doses associated with each of the included interventions in this meta-analysis (15): *1*) select the activity category that best fit with the specific study protocol, *2*) multiply the associated dose by the duration of one session of the specified intervention, and *3*) multiply this daily dose by the intervention frequency (i.e., sessions per week).

Data Synthesis and Analysis

We used Bayesian random-effects dose-response meta-analysis models to investigate the dose-response relationship between physical activity at different levels (i.e., overall and intervention specific) and HbA_{1c} (%) for people diagnosed with type 2 diabetes. We modeled HbA_{1c} change scores using a normal likelihood with an identity link function, with adjustment for weekly physical activity dosage and baseline HbA_{1c} level using linear and nonlinear terms (i.e., natural spline) based on modeling strategies of Harrell (20). Based on model fit parameters (i.e., point estimates and SEs of the expected log pointwise predictive density, the effective number of parameters, and the leave-one-out cross-validation information criterion), the meta-analysis model including physical activity dose and baseline glycemic level modeled with natural splines (4 knots) yielded the best fit. Model assumptions, implementation parameters (i.e., prior knowledge, Markov chain Monte-Carlo iterations, and convergence analysis), and comparisons are detailed in Supplementary Material. Predicted responses are reported as change scores (i.e., mean change from baseline) with 95% credible intervals (CrI) to assess the certainty of our estimates, and the between-study heterogeneity is reported in SD units (τ).

Using the model that yielded the best fit, we estimated the physical activity dose at which the predicted maximal significant effect on HbA_{1c} (%) was achieved (referred to herein as the "optimal dose") for each ADA category (i.e., prediabetes, controlled type 2 diabetes, uncontrolled type 2 diabetes, and severe uncontrolled type 2 diabetes). We also calculated for these diagnosis categories the minimal dose associated with a category shift (e.g., minimal dose required to move from uncontrolled type 2 diabetes diagnosis to controlled type 2 diabetes diagnosis) and the maximal tolerated dose (i.e., the dose from which there were null/worsening effects on our outcome of interest). A clinically relevant HbA_{1c} (%) change was considered when a −0.5% change from baseline was achieved (21).

All analyses were performed in R 4.0.3 (22). We used the brms package (23) (version 2.18.0) to perform Bayesian meta-analysis models, the tidybayes package (24) (version 3.0.2) to integrate Bayesian modeling into tidy data, and the ggplot2 package (25) (version 3.3.6) for data plotting and visualization. The code and data required to reproduce the results presented in this manuscript are available through public repository access (https://github.com/dgalgom/Physical-activity-and-Type-2-Diabetes-).

Risk of Bias, Sensitivity Analysis, and Quality of Evidence

Four reviewers (J.d.P.-C., B.d.P.-C., R.M.A.-R., and J.R.-M.) independently assessed the risk of bias of the included studies according to version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (26). Disagreements were resolved by discussion between the authors. Publication bias was assessed by funnel plot asymmetry visualization.

We conducted a sensitivity analysis excluding from the meta-analyses the studies rated as high-risk bias to determine whether these studies could influence the overall dose-response relationship (i.e., whether the dose-response curve is built on major contributions of high risk-of-bias studies).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to rate the quality of the body of evidence presented in this meta-analysis (27).

RESULTS

The systematic search resulted in identification of 6,346 potential records. After removal of duplicates, 4,633 articles remained for title and abstract review. Authors reviewed the full text of all 484 articles eligible for full text screening. Finally, 126 studies (285 change scores and 6,718 participants) were included in the review and meta-analysis. The full screening and selection process is shown in Fig. 1.

Characteristics of Included Studies

Details about the characteristics of the included studies are presented in Supplementary Table 2. The references of the studies included in this review can be found in Supplementary Material. Median age for the reviewed sample was 58 years old (range 39–73). Mean duration of diabetes, presented as means ± SD, since diagnosis was 7.66 ± 3.79 years. A total of 3,103 (46.19%) participants were male. Median glycemia baseline level was 7.5% (range 5.71% to 11.14% [39–101 mmol/mol). Of all participants, 199 were categorized as having prediabetes (13 arms, 7 studies), 1,253 controlled type 2 diabetes (52 arms, 24 studies), 3,820 uncontrolled type 2 diabetes (152 arms, 68 studies), and 1,446 severe uncontrolled type 2 diabetes (68 arms, 27 arms). Global parameters of the different types of physical activity are shown in Supplementary Table 3.

Dose-Response Relationships Between Physical Activity and HbA_{1c}

We observed a nonlinear J-shaped dose-response relationship between physical activity dose and HbA_{1c} reduction across all ADA categories (Fig. 2). The optimal dose was achieved at 1,100 MET min/week in all categories, resulting in HbA_{1c} change ranging from −1.02% to −0.66% for severe uncontrolled diabetes, from −0.64% to −0.49% for uncontrolled diabetes, from −0.47% to −0.40% for controlled diabetes, and from −0.38% to −0.24% for prediabetes. We found low between-study heterogeneity (τ = 0.23; 95% CrI 0.19–0.28).

Predicted HbA_{1c} reductions were plotted with adjustment for baseline HbA_{1c}, categorized according to ADA guidelines (Supplementary Fig.1). Minimal doses of physical activity needed to move from severe uncontrolled to uncontrolled diabetes ranged from 150 MET min/week (for individuals with HbA_{1c} 8.1% [65 mmol/mol]) to 810 MET min/week (HbA_{1c} 8.6% [70 mmol/mol]). Doses needed to move from uncontrolled to controlled diabetes were estimated from 330 MET min/week (HbA_{1c} 7.1% [54 mmol/mol]) to 990 MET min/week (HbA_{1c} 7.5% [58 mmol/mol]), and doses needed to move from controlled diabetes to prediabetes ranged from 570 MET min/week (HbA_{1c} 6.6% [49 mmol/mol]) to 900 MET min/week (HbA_{1c} 6.8% [51 mmol/mol]). No maximal tolerated dose was observed. Effect

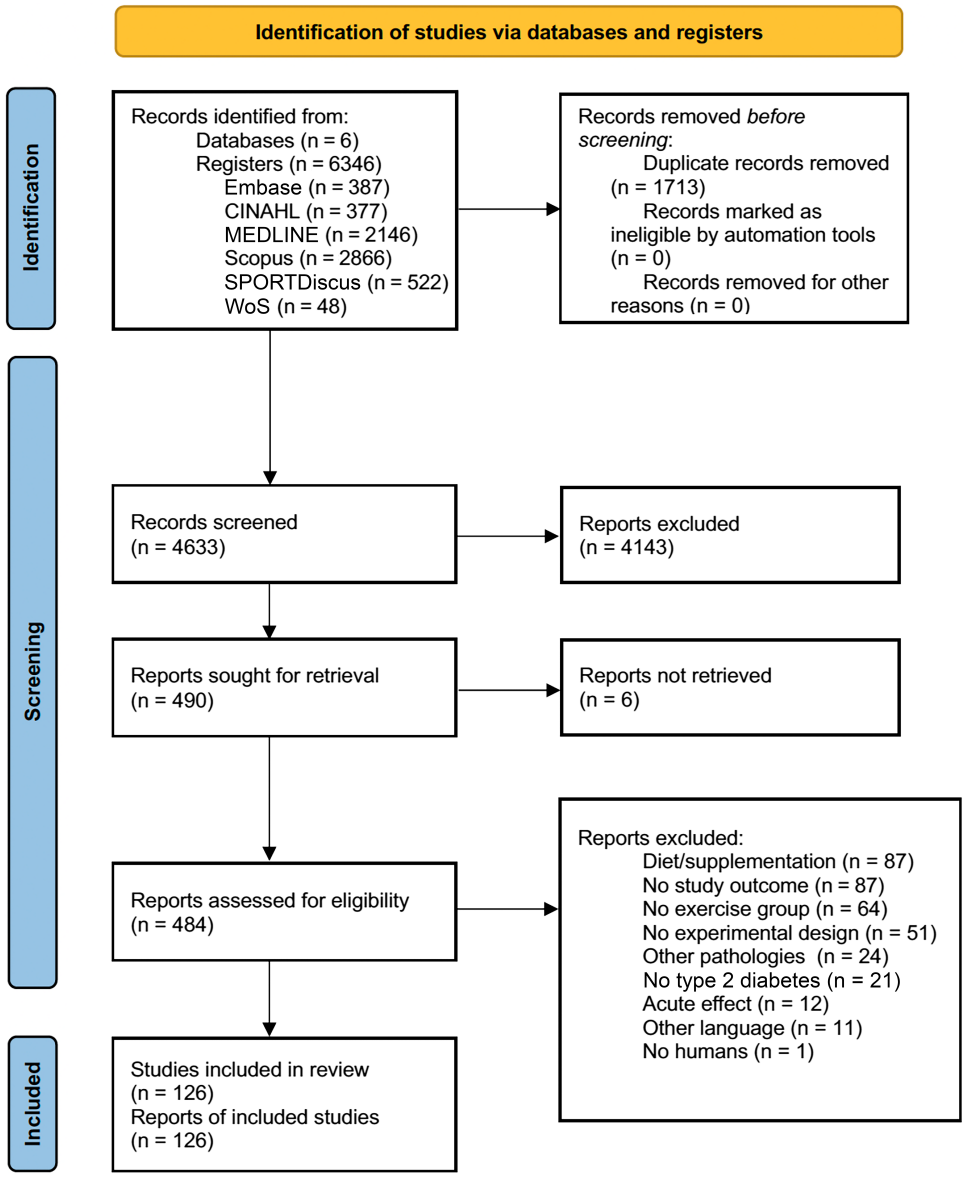


Figure 1—PRISMA flow diagram of study selection.

estimates and associated uncertainty for each 0.1-increase in HbA_{1c} level are shown in Table 1.

At intervention-specific level, the optimal dose for all types of activities was also 1,100 MET min/week (Supplementary Fig. 2). Multicomponent, strength, and walking were ranked as the most effective interventions. When 1,100 MET min/week (i.e., the optimal dose) corresponding to multicomponent interventions were accumulated, clinically important ranges of HbA_{1c} change were achieved for severe uncontrolled (−1.06% to −0.67%) and uncontrolled (−0.65% to −0.50%) diabetes. Statistically significant HbA_{1c} reductions were also observed in controlled diabetes (range −0.48% to −0.37%) and prediabetes (−0.38% to −0.23%). Minimal effective and optimal doses to move across ADA categories for each type of physical activity, their associated responses in HbA_{1c} reduction, and the translation of these doses (i.e., energy expenditure) into moderate- and vigorous-intensity minutes per week are reported in Supplementary Table 4.

Risk of Bias, Sensitivity Analysis, and Quality of Evidence

At overall level, 28 studies were classified to have low risk of bias, 34 studies unclear risk of bias, and 64 studies high risk of bias. Domain-level judgments for studies with an intent-to-treat analysis (*n* = 47) and those with a per-protocol analysis (*n* = 79) are depicted in Fig. 3. The overall-level risk-of-bias analysis for each study is shown in the Supplementary Figs. 3 and 4. The funnel plot did not show a clear pattern of asymmetry, indicating it is unlikely that these are small-studies effects (Supplementary Fig. 5).

A sensitivity analysis that included only studies classified as low risk of bias presented greater effect fluctuations in the physical activity dosage tails (i.e., <600 and >1,400 MET min/week) (Supplementary Table 5). However, the estimated dose-response curves were similar, and thus the optimal dose hardly differed from that of our base-case model (Supplementary Figs. 6 and 7).

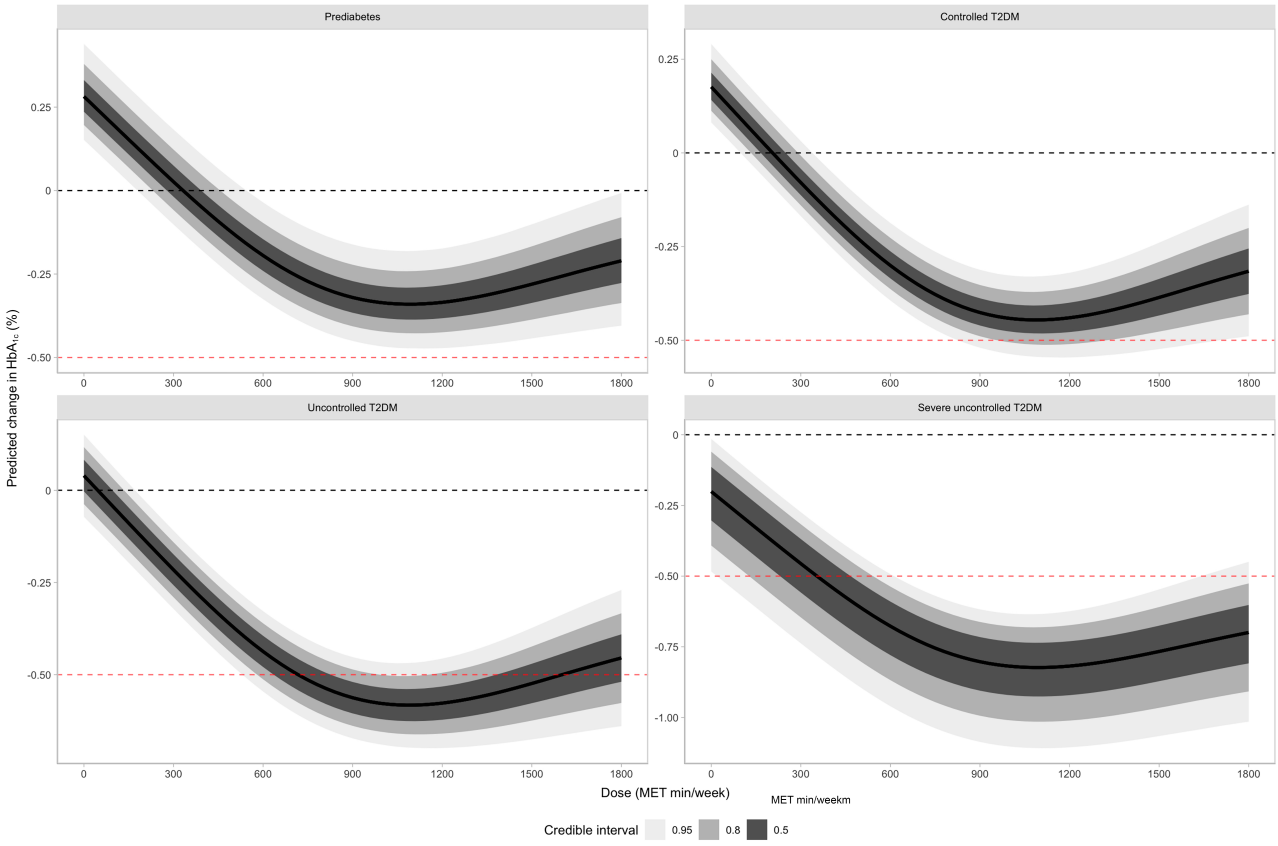


Figure 2—Dose-response relationship between overall physical activity dose and HbA_{1c} reduction across ADA categories. T2DM, type 2 diabetes mellitus.

According to the GRADE approach the certainty of the evidence presented in this meta-analysis is high. The certainty of the evidence was downgraded due to inconsistency between protocol parameters of the interventions. However, the detected dose-response gradient and model adjustment for plausible confounders (i.e., HbA_{1c} baseline level) upgraded the certainty of this body of evidence. Full detailed GRADE analysis can be found in Supplementary Material including tables for indirectness analysis and overall judgements.

DISCUSSION

In this systematic review and meta-analysis we aimed to examine the dose-response relationship between physical activity at different levels (i.e., overall and intervention specific) and glycemic control in people with type 2 diabetes. A nonlinear dose-response relationship between physical activity and HbA_{1c} (%) was observed. The optimal physical activity dose was achieved at 1,100 MET min per week, regardless of HbA_{1c} baseline level. The minimal effective doses to move across ADA categories ranged from 150 MET min/week (in people with HbA_{1c} 8.1% [65 mmol/mol]) to 810 MET min/week (8.6% [70 mmol/mol]) for severe uncontrolled diabetes, from 330 MET min/week (7.1% [54 mmol/mol]) to 990 MET min/week (7.5% [58 mmol/mol]) for uncontrolled diabetes, and from 570 MET min/week (6.6% [49 mmol/mol]) to 900 MET min/week (6.8% [51 mmol/mol]) for controlled diabetes. At the intervention-specific level, different types of physical activities presented clinically meaningful reductions in HbA_{1c}, like multicomponent, strength, or walking interventions. Overall, the results of this meta-analysis provide critical information for implementation of effective and personalized physical activity interventions to control HbA_{1c} levels in people living with diabetes.

Findings in the Context of the Literature

In this dose-response meta-analysis we found important differences between our predicted optimal physical activity dose and the current guidelines' recommendations (5,10). To facilitate clinical interpretation and comparison of our results, we estimated that 1,100 MET min/week (i.e., the optimal dose) is equivalent on average to ∼244 min/week of moderate-intensity aerobic physical activity (ranging from ∼183 to ∼367 min/week, depending on the intensity of the activity, from 3 to 6 MET min), which is above the 80th percentile of the recommended moderate-intensity physical activity per week range for this population. Similarly, 1,100 MET min/week is equivalent on average to ∼157 min/week of vigorous-intensity aerobic physical activity (assuming a vigorous intensity of 7 MET min), which is above the advised full range of minutes per week regarding vigorous-intensity physical activity in these people. In summary, our evidence suggests that people with diabetes may need to be more physically active than recommended to optimize their health outcomes.

Investigators of previous network meta-analyses have concluded that multicomponent activities interventions were more

Table 1—Dose-response relationship between overall physical activity dose and HbA_{1c} reduction across ADA categories. *Statistically significant MCFB % HbA_{1c}. **Clinically and statistically significant MCFB % HbA_{1c}.

ADA category	Baseline HbA_{1c}	Dose		MCFB % HbA_{1c} (95% CrI)
		Optimal or minimal	MET min/week	
Severe uncontrolled diabetes	10.0% (86 mmol/mol)	Optimal**	1,100	−1.02 (−1.23 to −0.822)
	9.9% (85 mmol/mol)	Optimal**	1,100	−1.00 (−1.19 to −0.811)
	9.8% (84 mmol/mol)	Optimal**	1,100	−0.981 (−1.16 to −0.800)
	9.7% (83 mmol/mol)	Optimal**	1,100	−0.959 (−1.13 to −0.788)
	9.6% (81 mmol/mol)	Optimal**	1,100	−0.939 (−1.10 to −0.775)
	9.5% (80 mmol/mol)	Optimal**	1,100	−0.918 (−1.07 to −0.762)
	9.4% (79 mmol/mol)	Optimal**	1,100	−0.898 (−1.05 to −0.749)
	9.3% (78 mmol/mol)	Optimal**	1,100	−0.878 (−1.02 to −0.736)
	9.2% (77 mmol/mol)	Optimal**	1,100	−0.859 (−0.996 to −0.722)
	9.1% (76 mmol/mol)	Optimal**	1,100	−0.840 (−0.97 to −0.709)
	9.0% (75 mmol/mol)	Optimal**	1,100	−0.821 (−0.947 to −0.696)
	8.9% (74 mmol/mol)	Optimal**	1,100	−0.803 (−0.924 to −0.683)
	8.8% (73 mmol/mol)	Optimal**	1,100	−0.786 (−0.901 to −0.67)
	8.7% (72 mmol/mol)	Optimal**	1,100	−0.768 (−0.878 to −0.658)
	8.6% (70 mmol/mol)	Minimal**	810	−0.706 (−0.806 to −0.606)
		Optimal**	1,100	−0.751 (−0.856 to −0.646)
	8.5% (69 mmol/mol)	Minimal**	630	−0.607 (−0.701 to −0.513)
		Optimal**	1,100	−0.735 (−0.834 to −0.635)
	8.4% (68 mmol/mol)	Minimal*	480	−0.492 (−0.579 to −0.405)
		Optimal**	1,100	−0.718 (−0.813 to −0.624)
	8.3% (67 mmol/mol)	Minimal*	360	−0.384 (−0.464 to −0.304)
		Optimal**	1,100	−0.702 (−0.792 to −0.612)
	8.2% (66 mmol/mol)	Minimal*	270	−0.294 (−0.369 to −0.219)
		Optimal**	1,100	−0.686 (−0.772 to −0.601)
	8.1% (65 mmol/mol)	Minimal*	150	−0.177 (−0.249 to −0.105)
		Optimal**	1,100	−0.670 (−0.752 to −0.589)
	8.0% (64 mmol/mol)	Optimal**	1,100	−0.655 (−0.733 to −0.576)
Uncontrolled diabetes	7.9% (63 mmol/mol)	Optimal**	1,100	−0.639 (−0.715 to −0.563)
	7.8 (62 mmol/mol)	Optimal**	1,100	−0.623 (−0.697 to −0.549)
	7.7% (61 mmol/mol)	Optimal**	1,100	−0.608 (−0.680 to −0.535)
	7.6% (60 mmol/mol)	Optimal**	1,100	−0.592 (−0.664 to −0.519)
	7.5% (58 mmol/mol)	Minimal**	990	−0.570 (−0.638 to −0.502)
		Optimal**	1,100	−0.575 (−0.647 to −0.503)
	7.4% (57 mmol/mol)	Minimal*	720	−0.477 (−0.543 to −0.412)
		Optimal*	1,100	−0.559 (−0.631 to −0.487)
	7.3% (56 mmol/mol)	Minimal*	570	−0.378 (−0.442 to −0.313)
		Optimal*	1,100	−0.542 (−0.614 to −0.470)
	7.2% (55 mmol/mol)	Minimal*	450	−0.277 (−0.341 to −0.213)
		Optimal*	1,100	−0.525 (−0.598 to −0.452)
	7.1% (54 mmol/mol)	Minimal*	330	−0.165 (−0.229 to −0.101)
		Optimal*	1,100	−0.507 (−0.582 to −0.433)
	7.0% (53 mmol/mol)	Optimal*	1,100	−0.490 (−0.566 to −0.414)
Controlled diabetes	6.9% (52 mmol/mol)	Optimal*	1,100	−0.471 (−0.550 to −0.393)
	6.8% (51 mmol/mol)	Minimal*	900	−0.433 (−0.511 to −0.354)
		Optimal*	1,100	−0.453 (−0.535 to −0.371)
	6.7% (50 mmol/mol)	Minimal*	690	−0.338 (−0.422 to −0.254)
		Optimal*	1,100	−0.434 (−0.521 to −0.347)
	6.6% (49 mmol/mol)	Minimal*	570	−0.251 (−0.341 to −0.160)
		Optimal*	1,100	−0.415 (−0.509 to −0.322)
	6.5% (48 mmol/mol)	Optimal*	1,100	−0.396 (−0.497 to −0.295)
Prediabetes	6.4% (46 mmol/mol)	Optimal*	1,100	−0.377 (−0.486 to −0.268)
	6.3% (45 mmol/mol)	Optimal*	1,100	−0.357 (−0.476 to −0.238)
	6.2% (44 mmol/mol)	Optimal*	1,100	−0.338 (−0.468 to −0.207)
	6.1% (43 mmol/mol)	Optimal*	1,100	−0.318 (−0.460 to −0.176)
	6.0% (42 mmol/mol)	Optimal*	1,100	−0.298 (−0.453 to −0.143)
	5.9% (41 mmol/mol)	Optimal*	1,100	−0.278 (−0.446 to −0.110)
	5.8% (40 mmol/mol)	Optimal*	1,100	−0.258 (−0.440 to −0.0771)
	5.7% (39 mmol/mol)	Optimal*	1,100	−0.239 (−0.434 to −0.0435)

MCFB % HbA_{1c}. Mean Change from Baseline % HbA_{1c}. *Indicates that MCFB is statistically significant but is not considered clinically meaningful because the 95% Cr include values greater than –0.50%. **Indicates that MCFB % HbA_{1c} (95% CrI) is clinically and statistically significant.

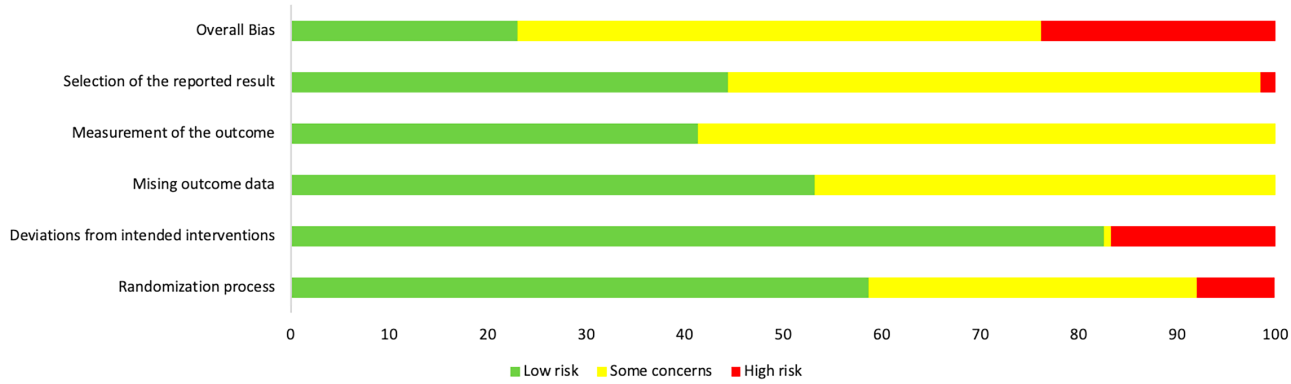


Figure 3—RoB 2.

effective in glycemic control than isolated aerobic or resistance activities (13,14). Our results are in line with this evidence, as we ranked multicomponent, strength, and walking as the most effective interventions, respectively. However, in observing the effectiveness of different physical activity types, there was not a great between-intervention variation when the estimated optimal dose was applied, which leads us to consider that the dose of physical activity may be potentially more relevant for glycemic control than the activity type performed (28).

Clinical Implications

We adjusted the effect estimates considering HbA_{1c} baseline level, which is a key point to consider for physical activity program implementation in this population. The optimal dose of physical activity (1,100 MET min/week) achieved a clinically significant decrease for participants with HbA_{1c} baseline level $\geq$7.5% (59 mmol/mol) and a statistically significant HbA_{1c} reduction for those with lower baseline levels. Current guidelines on glycemic management in diabetes indicate the need for physical activity; however, only duration is indicated based on the intensity of physical activity (5,9,29). The optimal physical activity dose here represents a more objective approach, use of which can achieve a decrease of up to >1% for patients with severe uncontrolled diabetes, attenuating the risk of microvascular complications, macrovascular complications, and diabetes all-cause mortality (30).

A "healthy" HbA_{1c} threshold of <7% (53 mmol/mol) has been established in type 2 diabetes indicating controlled blood glucose (30). HbA_{1c} levels below this threshold could reduce risk of ischemic stroke, coronary heart disease, and cardiovascular disease (30) for patients with diabetes, metabolic disease, neuropathy, nephropathy, and peripheral vascular disease (31). These guidelines state that individuals with type 2 diabetes who have cognitive impairment or functional dependence should aim to achieve a goal of <8% (64 mmol/mol) to be considered to have controlled blood glucose (32). Similarly, in prescribing physical activity, there may be complications to reach the reported optimal physical activity dose (33). Therefore, here we offer a minimum dose of physical activity and different types of physical activity to individualize the glycemic goal, promoting changes in type 2 diabetes category classification that reflect important physiological improvement. These minimum effective doses of physical activity predicted in this meta-analysis have been evidenced to impact our outcome of interest (HbA_{1c}), but the transference to other health outcomes in this population has not been contrasted.

The effects of physical activity on HbA_{1c} could be explained by several physiological mechanisms like increased skeletal muscle glucose uptake (34), lower cytokine production and improved adipocyte function (35), reduced autonomic tone (36), greater endothelial (37) and cardiac function (38), and higher arterial stiffness (39). However, there is high interindividual variability in the response of blood glucose to physical activity (40). Excessive physical activity has also been associated with mitochondrial impairment and impaired glucose tolerance (41), which may play a role in determining the relationship between physical activity and HbA_{1c} change.

In addition, we provide information about the most effective dose of different types of physical activity types for controlling glycemia across a range of HbA_{1c} levels. This information allows us to translate a specific physical activity dose (MET minutes per week) into minutes per week of any categorized activity in the Compendium of Physical Activities (19). However, the magnitude of these effects could differ between types of interventions (8,14,42), despite them presenting "statistically" or "clinically" meaningful effects. It enables the individualization of glycemic goals, taking into consideration the patient needs and preferences, potentially improving the adherence to the physical activity program (43).

Strengths and Limitations

There are several key strengths to our study. First, this meta-analysis comprised a large sample size of people with type 2 diabetes, providing adequate statistical power for the study aims. Second, we pooled data from different trials using cutting-edge evidence synthesis methods (i.e., Bayesian-based dose-response meta-analysis models), which allowed us to precisely predict the dose-response relationship between physical activity and glycemic control. This novel method allowed us to determine the optimal and minimal effective doses of physical activity for a wide range of HbA_{1c} values (i.e., 6% to 10% [42–86 mmol/mol]) that people with diabetes should accumulate to impact their glycemic control. This plays a role in

the implementation of physical activity programs in this population. Third, we used a physical activity dose calculation process that allows the reproducibility of the conducted analyses, making possible the comparison of future research results with those presented in this meta-analysis. Lastly, this body of evidence included several types of physical activity, allowing participants to select the one that best matched with their preferences and/or requirements. This study also has limitations. First, the certainty of the evidence may decrease due to the heterogeneity presented between trials' protocols, some of which were poorly reported regarding physical activity type (i.e., detailed program with specific activities) and parameters (e.g., intensity, duration, frequency . . .). However, it is important to highlight the detected dose-response gradient and the potential confounding adjustment, which upgraded this evidence. Second, several studies were assessed to have high risk of bias according to RoB 2, most due to the per-protocol analysis performed, resulting in many being of some concern regarding risk of bias. Third, the diabetes categorization derived by the authors was based on the mean/median data provided for each of the studies due to the lack of participant-level data. However, large variations in baseline HbA_{1c} levels were taken into account in the risk-of-bias analysis. Fourth, the available number of data points >1,100 MET min/week (i.e., optimal dose) was scarce, which means that the effects from this dose point were extrapolated with use of modeling techniques, with no clear evidence to contrast these predicted effects of very high physical activity doses. Finally, due to the interpersonal variability and physiological mechanisms by which blood glucose decreases, it was not possible to establish how long it would take to achieve the predicted HbA_{1c} changes (Supplementary Fig. 8).

In this systematic review and meta-analysis we have identified a new nonlinear dose-response relationship between physical activity and glucose control in people with type 2 diabetes. The optimal physical activity dose to achieve the greatest reductions in HbA_{1c} regardless of baseline HbA_{1c} level was 1,100 MET min/week. This dose of physical activity can be translated into minutes per week of some of the different types of interventions included in this review: ~314 min/week moderate-intensity or ~138 min/week vigorous-intensity multicomponent activities, ~314 min/week moderate-intensity or ~183 min/week vigorous-intensity strength activities, or ~256 min/week moderate-paced or ~157 min/week brisk walking. Also, minimal effective doses that could trigger an ADA category diagnosis change are provided. Ultimately, the evidence presented in this meta-analysis is informative with regard to key physical activity parameters needed to implement effective and tailored physical activity programs according to the patient's necessities and preferences to tackle one of the greatest public health challenges of the 21st century (44).

Acknowledgments. The authors thank the authors of the original studies for providing the data that was requested.

Funding. D.G.-G. is supported by a predoctoral teaching and research fellowship via I+D+i Research Program of the University of Seville (PIF20/VI-PPITUS). J.d.P.-C. is supported by the government of Andalusia Research, Development, and Innovation Program (PAIDI) (P20_1181). J.R.-M. is supported by a predoctoral teaching and research fellowship from the Spanish government (FPU20/0067). B.d.P.C. is supported by the government of Andalusia Research Talent Recruitment Program (EMERGIA 2020/00158).

The funders had no role in considering the study design or in the collection, analysis, or interpretation of data, writing of the report, or decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. D.G.-G., J.d.P.-C., B.d.P.C., and F.A.-B. conceptualized the study. D.G.G., E.S.M., and F.A.B. extracted data from studies. J.d.P.-C., B.d.P.C., J.R.-M., and R.M.A.-R. assessed and rated the studies according to RoB 2 and rated the quality of this body of evidence using the GRADE system. D.G.-G. conducted the formal statistical analyses. D.G.-G., B.d.P.C., and F.A.-B. drafted the manuscript. All authors revised the manuscript and provided critical input. All authors approved the final version of the manuscript.

References

1. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88–98
2. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119
3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–928
4. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. J Epidemiol Glob Health 2020;10:107–111
5. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 5. Facilitating positive health behaviors and well-being to improve health outcomes: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1):S68–S96
6. Hemmingsen B, Gimenez-Perez G, Mauricio D, Roqué I Figuls M, Metzendorf MI, Richter B. Diet, physical activity or both for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus. Cochrane Database Syst Rev 2017;12:CD003054
7. Chang CH, Kuo CP, Huang CN, Hwang SL, Liao WC, Lee MC. Habitual physical activity and diabetes control in young and older adults with type II diabetes: a longitudinal correlational study. Int J Environ Res Public Health 2021;18:1330
8. Hou L, Wang Q, Pan B, et al. Exercise modalities for type 2 diabetes: a systematic review and network meta-analysis of randomized trials. Diabetes Metab Res Rev 2023;39:e3591
9. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. Lippincott Williams & Wilkins, 2013, p. 456
10. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451–1462
11. Liu Y, Ye W, Chen Q, Zhang Y, Kuo CH, Korivi M. Resistance exercise intensity is correlated with attenuation of HbA1c and insulin in patients with type 2 diabetes: a systematic review and meta-Analysis. Int J Environ Res Public Health 2019;16:140
12. Grace A, Chan E, Giallauria F, Graham PL, Smart NA. Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol 2017;16:37
13. Mannucci E, Bonifazi A, Monami M. Comparison between different types of exercise training in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2021;31:1985–1992
14. Pan B, Ge L, Xun YQ, et al. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Int J Behav Nutr Phys Act 2018;15:72
15. Gallardo-Gómez D, Del Pozo-Cruz J, Noetel M, Álvarez-Barbosa F, Alfonso-Rosa RM, Del Pozo Cruz B. Optimal dose and type of exercise to improve cognitive function in older adults: a systematic review and bayesian model-based network meta-analysis of RCTs. Ageing Res Rev 2022;76:101591
16. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol 2021;134:103–112
17. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons, 2019, p. 728

18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. In Clinical Practice Recommendations. Diabetes Care 2014; 37(Suppl. 1):S81–S90
19. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575–1581
20. Harrell FE. *Regression Modeling Strategies With Applications to Linear Models, Logistic Regression, and Survival Analysis.* New York, NY, Springer, 2001. Accessed 29 March 2023. Available from https://link.springer.com/book/10.1007/978-1-4757-3462-1
21. Ang SH, Thevarajah M, Alias Y, Khor SM. Current aspects in hemoglobin A1c detection: a review. Clin Chim Acta 2015;439:202–211
22. R Core Team. *R: A Language and Environment for Statistical Computing.* Vienna, Austria, R Foundation for Statistical Computing, 2022
23. Bürkner P-C. Advanced bayesian multilevel modeling with the R package brms. 15 October 2017 [preprint]. arXiv:1705.11123
24. Kay M. *tidybayes: tidy data and geoms for Bayesian models. R package version 3.0.0.* Vienna, Austria, R Foundation for Statistical Computing, 2021
25. Wickham H. ggplot2. Wiley Interdiscip Rev Comput Stat 2011;3:180–185
26. Higgins JPT, Altman DG, Gøtzsche PC, et al.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928
27. Kavanagh BP. The GRADE system for rating clinical guidelines. PLoS Med 2009;6:e1000094
28. Yang Z, Scott CA, Mao C, Tang J, Farmer AJ. Resistance exercise versus aerobic exercise for type 2 diabetes: a systematic review and meta-analysis. Sports Med 2014;44:487–499
29. Edelman SV. *Diagnosis and Management of Type 2 Diabetes.* 7th ed. Professional Communications, 2008
30. Chen YY, Lin YJ, Chong E, et al. The impact of diabetes mellitus and corresponding HbA1c levels on the future risks of cardiovascular disease and mortality: a representative cohort study in Taiwan. PLoS One 2015;10:e0123116
31. Boye KS, Thieu VT, Lage MJ, Miller H, Paczkowski R. The association between sustained HbA1c control and long-term complications among individuals with type 2 diabetes: a retrospective study. Adv Ther 2022;39:2208–2221
32. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 13. Older adults: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1):S216–S229
33. Del Pozo-Cruz J, Alvarez-Barbosa F, Gallardo-Gomez D, Del Pozo Cruz B. Optimal number of steps per day to prevent all-cause mortality in people with prediabetes and diabetes. Diabetes Care 2022;45:2156–2158
34. Holloszy JO. Exercise-induced increase in muscle insulin sensitivity. J Appl Physiol (1985) 2005;99:338–343
35. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis 2010;20:608–617
36. Jin L, Min G, Wei C, Min H, Jie Z. Exercise training on chronotropic response and exercise capacity in patients with type 2 diabetes mellitus. Exp Ther Med 2017;13:899–904
37. Qiu S, Cai X, Yin H, et al. Exercise training and endothelial function in patients with type 2 diabetes: a meta-analysis. Cardiovasc Diabetol 2018;17:64
38. Anand V, Garg S, Garg J, Bano S, Pritzker M. Impact of exercise training on cardiac function among patients with type 2 diabetes: a systematic review and meta-analysis. J Cardiopulm Rehabil Prev 2018;38:358–365
39. Magalhães JP, Melo X, Correia IR, et al. Effects of combined training with different intensities on vascular health in patients with type 2 diabetes: a 1-year randomized controlled trial. Cardiovasc Diabetol 2019;18:34
40. Solomon TPJ. Sources of inter-individual variability in the therapeutic response of blood glucose control to exercise in type 2 diabetes: going beyond exercise dose. Front Physiol 2018;9:896
41. Flockhart M, Nilsson LC, Tais S, Ekblom B, Apró W, Larsen FJ. Excessive exercise training causes mitochondrial functional impairment and decreases glucose tolerance in healthy volunteers. Cell Metab 2021;33:957–970.e6
42. Zhu X, Zhao L, Chen J, et al. The effect of physical activity on glycemic variability in patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne) 2021;12:767152
43. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 6. Glycemic targets: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1):S97–S110
44. McKinlay J, Marceau L. US public health and the 21st century: diabetes mellitus. Lancet 2000; 356:757–761