

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

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**Optimal dose and type of physical activity to improve glycemic control in people diagnosed with type 2 diabetes: A systematic review and meta-analysis**

**Background** Current guidelines do not specify the optimal dose or type of physical activity to control HbA<sub>1c</sub> in people with diabetes and do not include consideration of baseline HbA<sub>1c</sub> for activity prescription.

**Research Design and Methods**

- Systematic searching in Embase, MEDLINE, Scopus, CINAHL, SPORTDiscus, and WoS.
- Included trials involved participants diagnosed with **type 2 diabetes** who engaged in any type of **physical activity** as intervention
- Effect measures as pre- and postintervention data (**change scores**)

**Data synthesis**

- 126 studies (6718 participants)
- J-shaped dose-response relationship** between physical activity and HbA<sub>1c</sub>

**Limitation**  
Not possible to estimate the time required to achieve the predicted HbA<sub>1c</sub> reductions

**Conclusion** This meta-analysis enables clinicians to prescribe **tailored physical activity programs** for this population providing information about the **optimal weekly dose of physical activity** and different effects of distinct **types of physical activity** in people living with diabetes considering their baseline HbA<sub>1c</sub> level

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### ARTICLE HIGHLIGHTS

- The optimal type-dose combination of physical activity to control HbA<sub>1c</sub> 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<sub>1c</sub> 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.



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

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## BACKGROUND

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

## PURPOSE

To examine the dose-response relationship between physical activity and  $\text{HbA}_{1\text{c}}$  (%) 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  $\text{HbA}_{1\text{c}}$  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  $\text{HbA}_{1\text{c}}$  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  $\text{HbA}_{1\text{c}}$  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  $\text{HbA}_{1\text{c}}$  level, and the effectiveness of different types of active interventions. These results enable clinicians to prescribe tailored physical activity programs for this population.

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See accompanying article, p. 196.

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<sub>1c</sub>) (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<sub>1c</sub> in people with diabetes, which remains unknown. Additionally, the potential impact of important clinical characteristics such as baseline HbA<sub>1c</sub> 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<sub>1c</sub> (%) responses with adjustment for HbA<sub>1c</sub> 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<sub>1c</sub> (%) 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> (%) for people diagnosed with type 2 diabetes. We modeled HbA<sub>1c</sub> change scores using a normal likelihood with an identity link function, with adjustment for weekly physical activity dosage and baseline HbA<sub>1c</sub> 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 ( $\tau$ ).

Using the model that yielded the best fit, we estimated the physical activity dose at which the predicted maximal significant effect on HbA<sub>1c</sub> (%) 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<sub>1c</sub> (%) 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  $\pm$  SD, since diagnosis was  $7.66 \pm 3.79$  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<sub>1c</sub>

We observed a nonlinear J-shaped dose-response relationship between physical activity dose and HbA<sub>1c</sub> reduction across all ADA categories (Fig. 2). The optimal dose was achieved at 1,100 MET min/week in all categories, resulting in HbA<sub>1c</sub> 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 ( $\tau = 0.23$ ; 95% CrI 0.19–0.28).

Predicted HbA<sub>1c</sub> reductions were plotted with adjustment for baseline HbA<sub>1c</sub>, 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<sub>1c</sub> 8.1% [65 mmol/mol]) to 810 MET min/week (HbA<sub>1c</sub> 8.6% [70 mmol/mol]). Doses needed to move from uncontrolled to controlled diabetes were estimated from 330 MET min/week (HbA<sub>1c</sub> 7.1% [54 mmol/mol]) to 990 MET min/week (HbA<sub>1c</sub> 7.5% [58 mmol/mol]), and doses needed to move from controlled diabetes to prediabetes ranged from 570 MET min/week (HbA<sub>1c</sub> 6.6% [49 mmol/mol]) to 900 MET min/week (HbA<sub>1c</sub> 6.8% [51 mmol/mol]). No maximal tolerated dose was observed. Effect

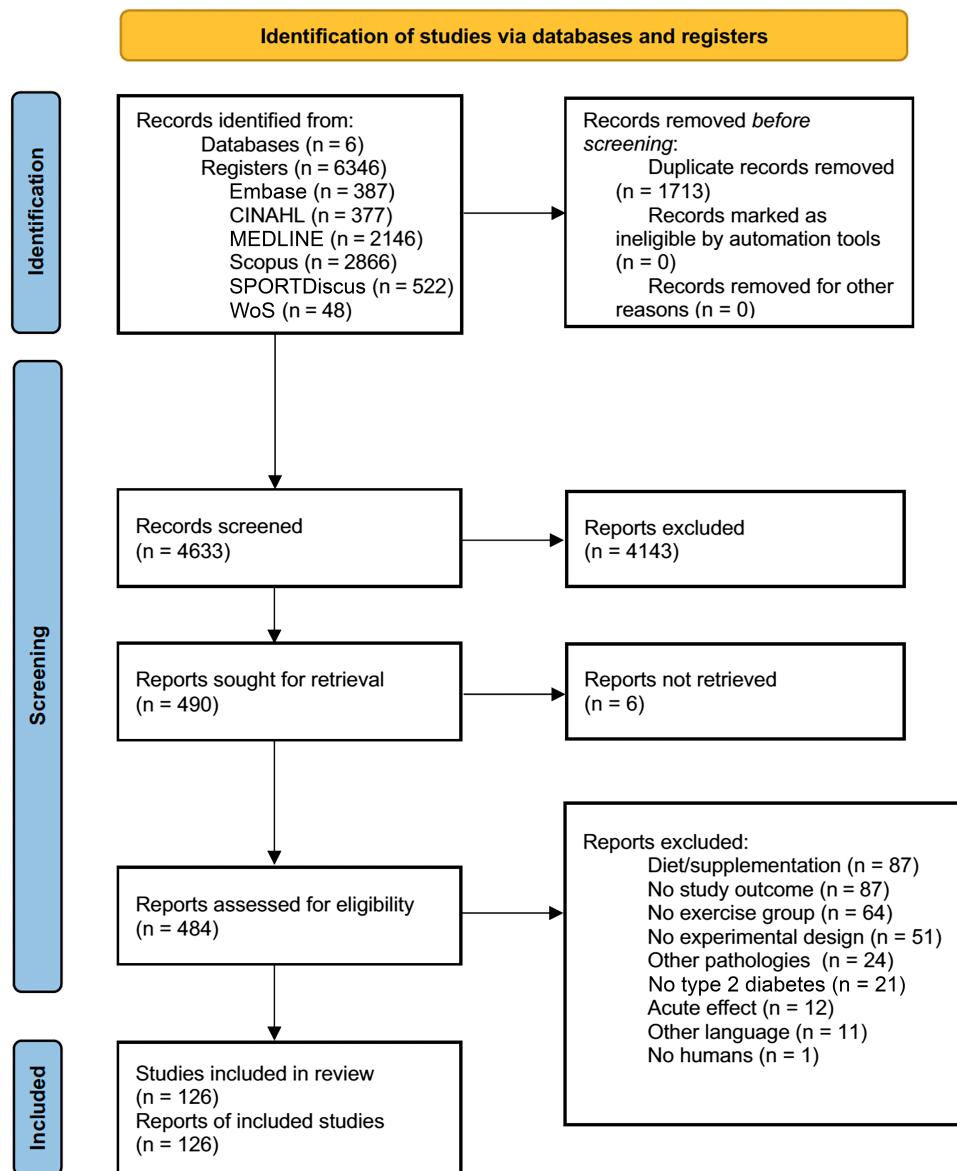


Figure 1—PRISMA flow diagram of study selection.

estimates and associated uncertainty for each 0.1-increase in HbA<sub>1c</sub> 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<sub>1c</sub> change were achieved for severe uncontrolled ( $-1.06\%$  to  $-0.67\%$ ) and uncontrolled ( $-0.65\%$  to  $-0.50\%$ ) diabetes. Statistically significant HbA<sub>1c</sub> reductions were also observed in controlled diabetes (range  $-0.48\%$  to  $-0.37\%$ ) and

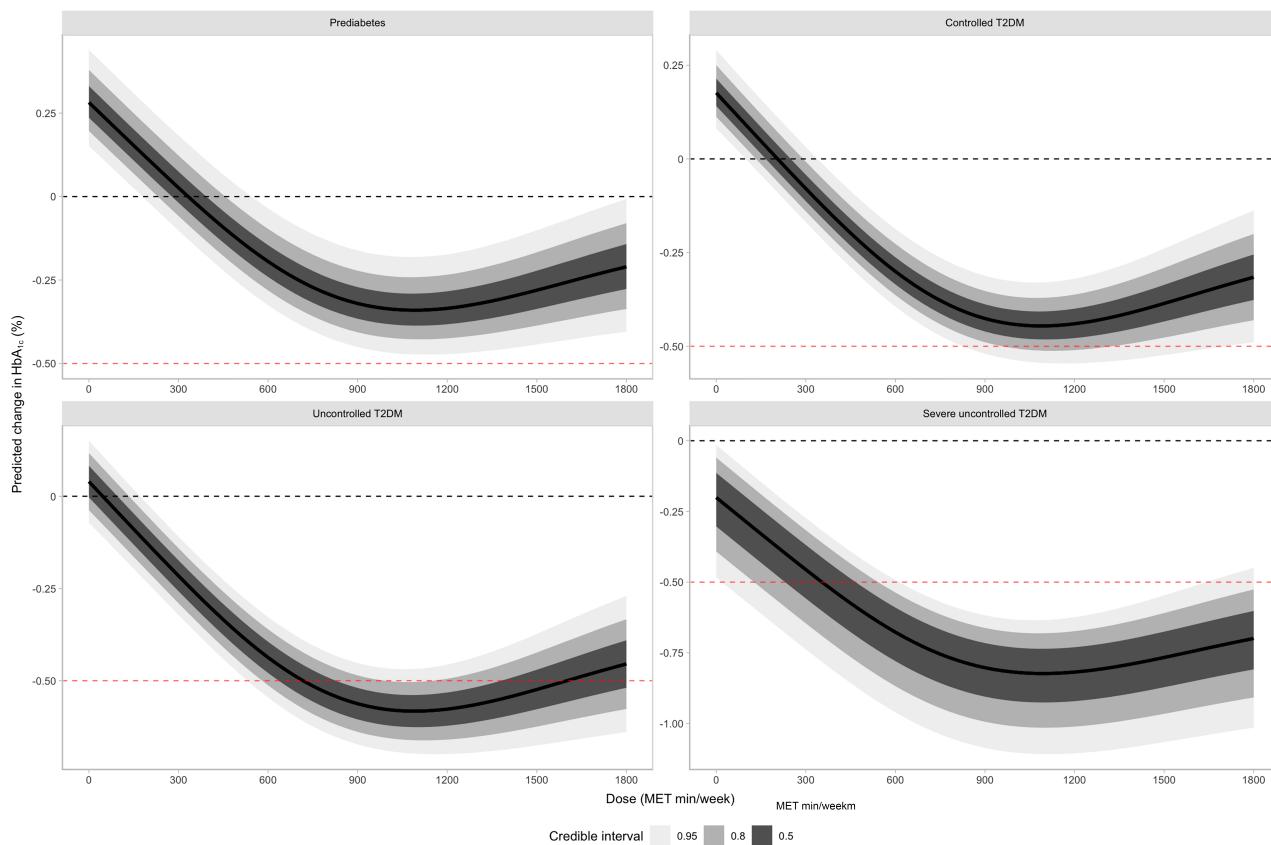
prediabetes ( $-0.38\%$  to  $-0.23\%$ ). Minimal effective and optimal doses to move across ADA categories for each type of physical activity, their associated responses in HbA<sub>1c</sub> reduction, and the translation of these doses (i.e., energy expenditure) into moderate- and vigorous-intensity 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> (%) was observed. The optimal physical activity dose was achieved at 1,100 MET min per week, regardless of HbA<sub>1c</sub> baseline level. The minimal effective doses

to move across ADA categories ranged from 150 MET min/week (in people with HbA<sub>1c</sub> 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<sub>1c</sub>, 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<sub>1c</sub> 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

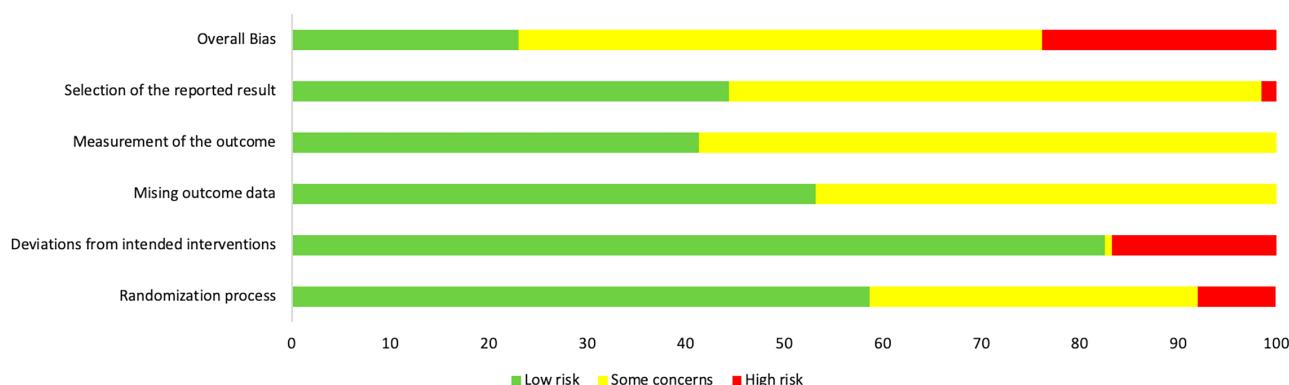
the current guidelines' recommendations (5,10). To facilitate clinical interpretation and comparison of our results, we estimated that 1,100 MET min/week (i.e., the optimal dose) is equivalent on average to ~244 min/week of moderate-intensity aerobic physical activity (ranging from ~183 to ~367 min/week, 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<sub>1c</sub> reduction across ADA categories.**\*Statistically significant MCFB % HbA<sub>1c</sub>. \*\*Clinically and statistically significant MCFB % HbA<sub>1c</sub>.

ADA category	Baseline HbA <sub>1c</sub>	Dose		
		Optimal or minimal	MET min/week	MCFB % HbA <sub>1c</sub> (95% CrI)
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)
Uncontrolled diabetes	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)
		Optimal*	1,100	-0.490 (-0.566 to -0.414)
	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)
Controlled diabetes	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)
Prediabetes	7.0% (53 mmol/mol)	Optimal*	1,100	-0.490 (-0.566 to -0.414)
	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)

MCFB % HbA<sub>1c</sub>. Mean Change from Baseline % HbA<sub>1c</sub>. \*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<sub>1c</sub> (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<sub>1c</sub> 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<sub>1c</sub> baseline level  $\geq 7.5\%$  (59 mmol/mol) and a statistically significant HbA<sub>1c</sub> 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<sub>1c</sub> threshold of  $<7\%$  (53 mmol/mol) has been established in

type 2 diabetes indicating controlled blood glucose (30). HbA<sub>1c</sub> 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<sub>1c</sub>), but the transference to other health outcomes in this population has not been contrasted.

The effects of physical activity on HbA<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> changes (Supplementary Fig. 8).

In this systematic review and meta-analysis we have identified a new non-linear 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<sub>1c</sub> regardless of baseline HbA<sub>1c</sub> 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).

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