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DIABETIC Medicine

SYSTEMATIC REVIEW OR META-ANALYSIS

Blood glucose response to running or cycling in individuals with type 1 diabetes: A systematic review and meta-analysis

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Abstract

Aims: The aim of this systematic review and meta-analysis was to assess how running and cycling influence the magnitude of blood glucose (BG) excursions in individuals with type 1 diabetes.

Methods: A systematic literature search was conducted in EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and ISI Web of Knowledge for publications from January 1950 until February 2021. Parameters included for analysis were population (adults and adolescents), exercise type, intensity, duration and insulin preparation. The meta-analysis was performed to estimate the pooled mean with a 95% confidence interval (CI) of delta BG levels. In addition, sub-group and meta-regression analyses were performed to assess the influence of these parameters on delta BG.

Results: The database search identified 3192 articles of which 69 articles were included in the meta-analysis. Due to crossover designs within articles, 151 different results were included for analysis. Data from 1901 exercise tests of individuals with type 1 diabetes with a mean age of 29 ± 4 years were included. Overall, exercise tests BG decreased by −3.1 mmol/L [−3.4; −2.8] within a mean duration of 46 ± 21 min. The pooled mean decrease in BG for running was −4.1 mmol/L [−4.7; −2.4], whilst the pooled mean decrease in BG for cycling was −2.7 mmol/L [−3.0; −2.4] ($p < 0.0001$). Overall results can be found in Table S2.

Conclusions: Running led to a larger decrease in BG in comparison to cycling. Active individuals with type 1 diabetes should be aware that current recommendations for glycaemic management need to be more specific to the mode of exercise.

KEYWORDS

blood glucose, carbohydrate metabolism, exercise/physical activity, insulin action, systematic reviews

1 | INTRODUCTION

Regular physical activity is recommended in individuals with type 1 diabetes[1] in order to alleviate cardiovascular risk factors and improve quality of life amongst others. However, the risk of exercise-induced hypoglycaemia (EIH) remains an important limiting factor in these individuals. Everyday fear and challenge of EIH decreases the individuals' efforts to perform the exercise, and prompts them to accept higher glucose values or to consume excessive amounts of carbohydrates around exercise, which subsequently might compromise the aforementioned health benefits of exercise.[2,3]

On the one hand, individual factors such as increased insulin sensitivity, suboptimal glucose control, lack of knowledge about therapy management around exercise or impaired hypoglycaemic awareness are known to represent major contributors to EIH.[2] On the other hand, the type, intensity, duration and frequency of the respective exercise strongly impact the risk EIH.[4,5] The use of modern insulins and advanced diabetes technology systems achieved improvements in the guidance of physically active people with type 1 diabetes. These novel instruments have also contributed to a more careful dedication of the scientific community and meanwhile, several guidelines, supporting the physically active individual with type 1 diabetes have been published.[6–8] Endurance training like running and cycling can be considered one of the most popular types of exercise since these activities can be performed spontaneously and do not require training partners, specific facilities, or environmental conditions. Of great interest for the majority of physically active people with type 1 diabetes is the question of which of these activities corresponds to a greater reduction in blood glucose (BG) presupposing that the individual exhaustion is comparable, and the exercise is metabolically matched. Unexpected rapid changes in BG lead to stress in individuals with type 1 diabetes that deteriorate the actual effect of physical exercise for well-being.[9]

In general, the prolonged, predominantly aerobic exercise by means of cycling or running promotes a decrease in BG in people with type 1 diabetes. This can be mainly explained by (1) the muscle contraction triggering GLUT-4 translocation resulting in increased glucose uptake,[10] (2) increased glucose disposal to cover the energetic muscle demands, (3) an exaggerated muscle blood flow increasing the delivery from glucose to the skeletal muscle inducing a rise in muscle blood flow that increases insulin and glucose delivery from the circulation to the working muscle, and last but not least, (4) an insufficient ability to produce a sufficient level of counterregulatory hormones to maintain glycaemic balance.[6,7,11] Whilst cycling is mainly restricted to the involvement of the lower body musculature, running utilises muscles from the upper body too, raising the assumption that running impacts glucose decrease to a greater extent when compared to cycling.

Evidence supporting this theory is greatly lacking, which can be mainly accused to the circumstance that hardly any studies were conducted on people with type 1 diabetes which compared running versus cycling in a metabolically matched manner. Identifying effective and of utmost importance, safe exercise interventions might improve clinical practice and strengthen confidence in living physically active despite having type 1 diabetes.

To understand which of both types of endurance training types might be more impacting on BG, this systematic review and meta-analysis summarised research studies that investigated people with type 1 diabetes, exercising either cycling on an ergometer or running on a treadmill.

2 | METHODS

This systematic review and meta-analysis were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was registered at the International Prospective Register of Systematic Reviews (Prospero) before the initiation of the literature search (CRD42021239671).

2.1 | Data sources and study selection

The following electronic libraries were searched to identify relevant publications: EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and ISI Web of Knowledge. Studies from the inception of the databases until 15 February 2021, were included in this analysis. The following search items were included: type 1 diabetes mellitus, exercise, cycling, running, cycle ergometer, treadmill, and glucose. Published, randomised, clinical, comparative and observational studies with a minimum number of three participants were included which investigated any aerobic exercise intervention involving either treadmill/running- or cycle ergometer/cycling exercise in individuals with type 1 diabetes. Only published studies were considered. Moreover, no in silico and animal studies were included. Besides that, systematic reviews and meta-analysis were excluded. Also, duplicates of articles were discarded. Study titles and abstracts were reviewed to include relevant studies fulfilling the inclusion criteria. Then, the full text of these studies was digitally saved and read by two independent authors (Sina Böckel and Rebecca T. Zimmer). Another independent author (Max L. Eckstein) has monitored the identified studies and solved potential disagreements. The exact search terminology and strategy of the different databases can be found in the Table S2–S5.

2.2 | Data extraction and quality assessment

Following information, if available, was recorded on a data extraction sheet for all studies which were screened for eligibility by two independent authors (Max L. Eckstein and Sina Böckel): Authors, year of publication, country of study origin, trial design, sample size, age and sex of participants, method of exercise (treadmill or ergometer), exercise intensity, type of exercise, exercise preparation (e.g. insulin reduction) and exercise duration. Several studies ($N = 54$) reported either interquartile range (IQR), range, confidence interval, or baseline and follow-up standard deviation (SD) values for delta BG. Therefore, the standard deviation for delta BG was computed for these studies using the formula provided in the Data S1 (Table S1). If data were missing, authors were contacted to receive the data. If the main outcome (e.g. BG delta) was not reported, could not be retrieved after contacting the authors, or was computed, the study was excluded. If relevant information with regard to exercise duration, exercise intensity and set-up prior to the start of the exercise was not given, and could not be retrieved, the study was excluded. Studies that included carbohydrate supplementation during the exercise sessions were excluded since their effect on the main outcome (BG delta) would be a confounder of the overall result of the meta-analysis. During the data extraction, we noticed that there are large differences in the style of how the exercise sessions were set up, the types and amount of carbohydrates that were administered prior to exercise and lack of information about the type of insulin, glycaemic control and diabetes duration. These factors may act as confounders in our meta-analysis since a statistical adjustment was not possible due to their versatility.

Studies were independently assessed by two investigators (Sina Böckel and Rebecca T. Zimmer) for methodological quality using the risk of bias assessment tool from the Cochrane Collaboration[12] in its revised version.[13] The following sources of bias were detected: Overall bias, selection of the reported result, the bias of the measurement of the outcome, missing outcome data, deviations from the intended interventions and randomisation process (Figure 1). We did not exclude any studies based on the risk of bias assessment since included trials were judged as low risk of bias regarding the outcome of this systematic review and meta-analysis following the assessment (Figure 1).

2.3 | Data synthesis and analysis

A narrative descriptive analysis was performed to summarise the characteristics of studies such as population, age, type of exercise, duration of exercise and intensity of exercise. Delta BG was defined as BG from the start to the end of the exercise. Exercise types were defined as any type of running exercise which was conducted either on a treadmill or a course. Cycling was defined as any type of cycling exercise on an ergometer. The type of exercise was defined as either continuous exercise or high-intensity-interval exercise (HIIE). The duration of exercise was defined in minutes. The intensity of exercise was defined as low, moderate or vigorous exercise intensity according to the American College of Sports Medicine.[14,15] The SD values were converted to standard error ($SE = SD\sqrt{n}$).[16] If studies included more than one appropriate data set, these data were extracted and analysed separately.

2.4 | Meta-analysis

The meta-analysis was performed using the random effects model and Hedges' g method as a number of studies had small sample sizes. The effect size (delta BG) was summarised and presented as the pooled mean with a corresponding 95% confidence interval (CI). The negative

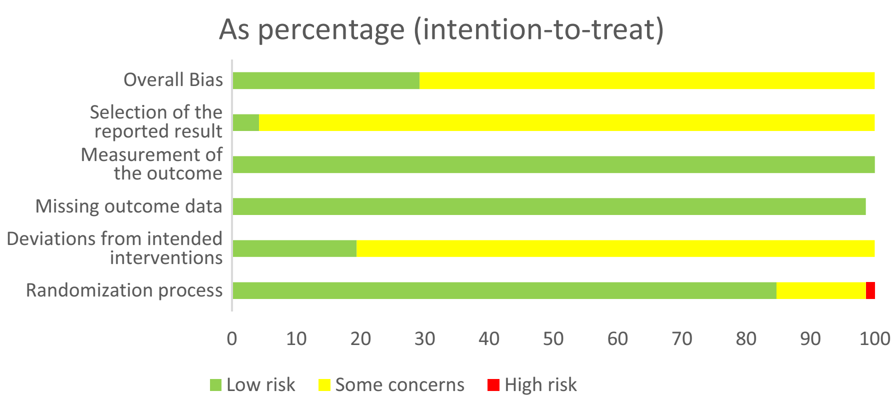

FIGURE 1 Risk of the bias assessment tool. Across trials ($n = 69$). Information is either from trials at low risk of bias (green), trials with some concerns of bias (yellow), or trials at high risk of bias (red).

pooled mean indicated a higher decrease in BG following the exercise. The heterogeneity in the effect size was assessed by estimating I^2 statistics and Cochran's Q test for homogeneity. The difference in effect size with respect to bike versus run studies and other study-level categorical covariates was assessed by performing the sub-group analysis of effect size for each covariate. Group differences in the effect size were assessed via Cochran's Q test for homogeneity. The difference in effect size with respect to study-level continuous covariates was assessed by meta-regression analysis. Furthermore, simple and multiple meta-regression was performed to assess the crude and adjusted association of each study-level covariate with the effect size within the strata of bike and treadmill studies. The results of meta-regression were reported as coefficients with corresponding 95% CI and p-values. Publication bias was assessed in terms of meta-bias using Egger's test and visualised via funnel plot. The results of the meta-analysis are presented in the Data S1.

3 | RESULTS

A total of 69 studies were extracted from 3192 studies that met the objectives. Out of these 69 articles, 20 studies included running whilst 49 studies included cycling. The steps of the article selection process are described as a flow diagram in Figure 2. Studies published between 1983 and 2020 were included summarising data from 613 individuals with a mean age of 29 ± 5 years. Due to the crossover designs of the studies, the results have been split for analysis. Twenty-two studies showed a low risk of bias whilst 47 studies showed some concerns with regards to potential bias.

3.1 | Study type

Thirty-nine randomised controlled trials were included in this systematic review. Out of these, 15 were designed as crossover studies. A total of 11 non-randomised clinical trials were included out of which five were in a crossover design. Furthermore, 12 comparative studies and seven observational studies were included.

3.2 | Participants

The total number of participants in all bicycle studies ranged from 5 to 47. Twenty-four trials included only men (35%), whilst the remaining trials included both women and men. In three studies the gender of the participants was not specified. The age of the participants included ranged from 10 to 65 years. Exercise duration varied from 10 min to 3 hours.

The number of participants in all running studies ranged from 7 to 51 participants. Five trials included only men, whilst the remaining studies included both genders. In one study it was not specified whether the participants were women or men. The age of the included participants ranged from 12 to 56 years. Exercise duration varied from 30 to 180 min (Table 5 and Table 6). The exercise lasted 30 minutes in two studies whilst in all other studies the exercise duration was longer.

Exercise tasks in all included studies were only cycling or running. In order to be able to compare these two activities at the end, their results were evaluated separately below. In total, 49 cycling and 20 treadmill studies were included in the review. For more details on the included studies please see Table 5 and Table 6.

3.3 | Overall results

Overall, blood glucose (BG) decreased by −3.1 mmol/L [−3.4; −2.8] within a mean duration of 46 ± 21 minutes. In the subgroup analysis, overall low-intensity exercise decreased BG by −2.2 mmol/L [−2.9; −1.4], whilst moderate intensity decreased BG by −3.1 mmol/L [−3.3; −2.7] and vigorous intensity by −3.5 mmol/L [−4.1; −2.9] (p = 0.024). The continuous exercise led to a BG decrease of −3.3 mmol/L [−3.7; −3.0] whilst HIIE led to a decrease of −2.2 mmol/L [−2.9; −1.5] (p = 0.004). An exercise duration of <30 minutes led to a BG decrease of −2.1 mmol/L [−2.5; −1.6], an exercise duration of 30–60 minutes led to a BG decrease of −3.5 mmol/L [−3.9; −3.0] and an exercise duration of >60 minutes led to a BG decrease of −3.4 mmol/L [−3.9; −2.8] (p < 0.001). In adolescents, the BG decrease was insignificantly lower with −3.0 mmol/L [−3.9; −2.1] in comparison to adults with −3.1 mmol/L [−3.4; −2.8] (p = 0.805). An insulin reduction led to a BG decrease by −3.9 mmol/L [−4.4; −3.4] whilst no insulin reduction led to a BG decrease of −2.6 mmol/L [−3.0; −2.2] (p < 0.001) (Table 1 and Table 2). The overall results of each study can be reviewed in the Table S1.

3.4 | Running

The mean duration of running was 45 ± 22 minutes. The pooled mean decrease in BG for running was −4.1 mmol/L [−4.7; −3.4]. In running, low-intensity exercise decreased BG by −2.7 mmol/L [−3.3; −2.1], moderate intensity by −3.3 mmol/L [−4.5; −2.1] and vigorous intensity by −4.6 mmol/L [−5.4; −3.7] (p = 0.002). The

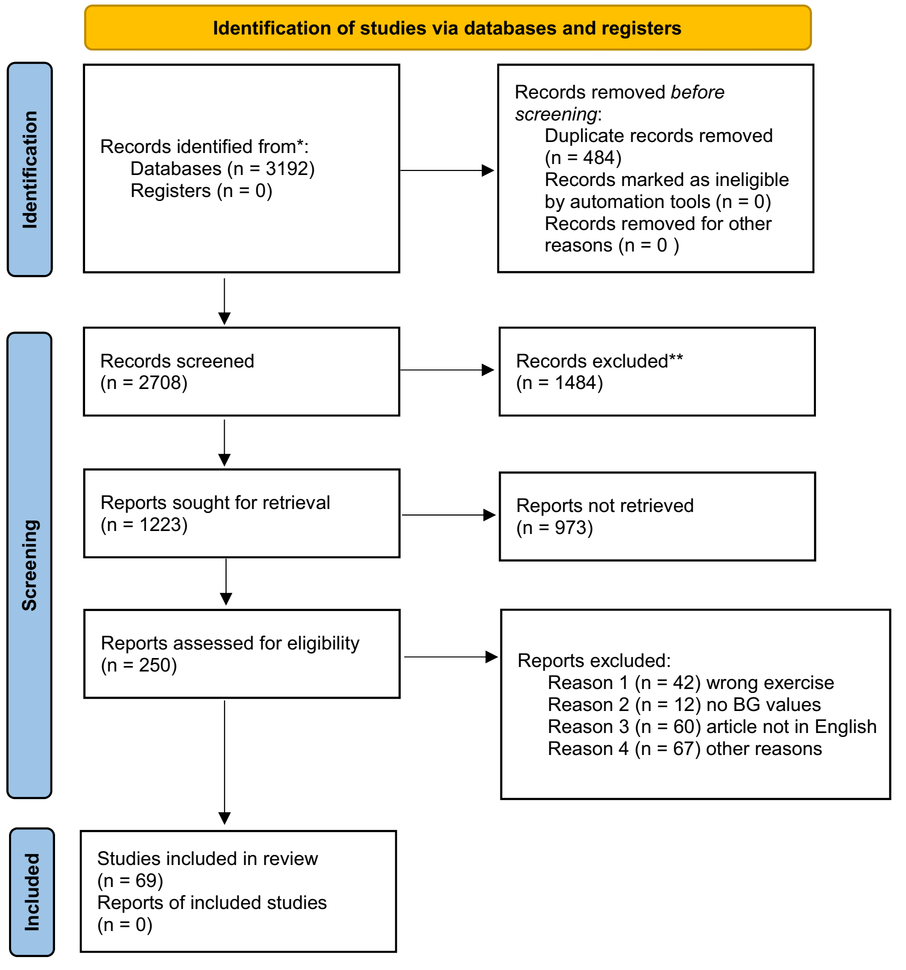

FIGURE 2 Prisma flow diagram (accessed on 11th of April 2022).[17] *MedLine/PubMed, Web of Science, Embase, Cochrane (Central). **Type 2 diabetes, no glucose measurement, no physical exercise, animal study, the wrong type of physical exercise, education program.

continuous exercise led to a BG decrease of −4.4 mmol/L [−5.0; −3.8] whilst HIIE led to a decrease of −1.1 mmol/L [−1.9; −4.3] ($p < 0.001$). An exercise duration of <30 minutes led to a BG decrease in −1.7 mmol/L [−2.4; −0.9], an exercise duration of 30–60 minutes led to a BG decrease in −4.5 mmol/L [−5.2; −3.8] and an exercise duration of >60 min led to a BG decrease in −3.5 mmol/L [−4.8; −2.2] ($p < 0.001$). In adolescents, the BG during running decreased by −4.1 mmol/L [−4.5; −3.7] whilst in adults, the BG decreased by −4.1 mmol/L [−4.7; −3.4] ($p = 0.896$). An insulin reduction prior to running led to a BG decrease in −4.7 mmol/L [−5.5; −3.9] whilst no insulin reduction led to a BG decrease in −2.6 mmol/L [−3.3; −1.9] ($p < 0.001$) (Table 3).

3.5 | Cycling

The mean duration in cycling was 46 ± 21 minutes. The pooled mean decrease in BG for cycling was −2.7 mmol/L [−3.0; −2.4]. In cycling, low-intensity exercise led to a BG decrease of −1.9 mmol/L[−2.9; −0.8], whilst moderate-intensity exercise led to a BG decrease of −3.1 mmol/L [−3.5; −2.7] and vigorous intensity exercise led to a BG decrease of −2.3 mmol/L [−2.9; −1.6] ($p = 0.021$). Continuous exercise led to a BG decrease of −2.8 mmol/L [−3.2; −2.5] whilst HIIE led to a decrease of -2.4 mmol/L [−3.1; −1.6] ($p = 0.300$). An exercise duration of <30 minutes led to a BG decrease of −2.1 mmol/L [−2.6; −1.6], a duration of 30–60 minutes led to a decrease of −2.7 mmol/L [−3.3; −2.2] and duration of >60 minutes led to a decrease of −3.3 mmol/L [−3.9; −2.7] ($p = 0.010$). In adolescents, the BG during cycling decreased by −2.9 mmol/L [−3.8; −1.9], whilst in adults BG decreased by −2.7 mmol/L [−3.0; −2.3] ($p = 0.709$). An insulin reduction prior to cycling led to a BG decrease of −3.0 mmol/L [−3.4; −2.7] whilst no insulin reduction led to a decrease of −2.6 mmol/L [−3.0; −2.2] ($p = 0.090$) (Table 4).

Even though women and men were included in most of the studies included in this systematic review and meta-analysis, a subgroup analysis was not possible, as gender-specific effect size was not estimated in the studies. Unfortunately, no study showed differentiated results of BG decrease following either cycling or running between men and women, hence an analysis was not possible within this results section.

TABLE 1 Summary of subgroup-analysis of BG decrease following running or cycling

Covariates	Running BG (mmol/L) Pooled mean [95% CI]	p-Value	Cycling BG (mmol/L) Pooled mean [95% CI]	p-Value
Year of publication				
<2000	−6.7 [−6.1; −1.8]	0.440	−2.5 [−3.1; −1.8]	0.316
2000–2009	−3.7 [−4.7; −2.7]		−3.1 [−3.8; −2.9]	
≥2010	−4.1 [−4.9; −3.4]		−2.6 [−3.0; −2.2]	
Age group				
Adolescents	−4.1 [−4.5; −3.7]	0.896	−2.9 [−3.8; −1.9]	0.709
Adults	−4.1 [−4.7; −3.4]		−2.7 [−3.0; −2.3]	
Exercise intensity				
Low intensity	−2.7 [−3.3; −2.0]	0.002	−1.9 [−2.9; −0.8]	0.021
Moderate intensity	−3.8 [−4.5; −2.1]		−3.1 [−3.5; −2.7]	
Vigorous intensity	−4.6 [−5.4; −3.7]		−2.3 [−2.9; −1.6]	
Exercise type				
Continuous exercise	−4.4 [−5.0; −3.8]	<0.001	−2.8 [−3.2; −2.5]	0.300
HIIE	−1.1 [−1.9; −0.4]		−2.4 [−3.1; −1.6]	
Exercise duration				
<30 minutes	−1.7 [−2.4; −0.9]	<0.001	−2.1 [−2.6; −1.6]	0.010
30–60 minutes	−4.5 [−5.2; −3.8]		−2.7 [−3.3; −2.2]	
>60 minutes	−3.5 [−4.8; −2.2]		−3.3 [−3.9; −2.7]	
Insulin reduction				
Insulin reduction	−4.7 [−5.5; −3.9]	<0.001	−3.1 [−3.4; −2.7]	0.090
No insulin reduction	−2.6 [−3.3; −1.9]		−2.6 [−3.0; −2.2]	

Note: *p*-Value is estimated for Cochran's *Q* test.

TABLE 2 Unadjusted and adjusted meta-regression of BG decrease following both running or cycling

Covariates	Unadjusted meta-regression Coefficient [95% CI]	p-Value	Adjusted meta-regression Coefficient [95% CI]	p-Value
Type of exercise				
Cycling	Reference		Reference	
Running	−1.3 [−2.0; −0.7]	<0.001	−0.9 [−1.7; −0.1]	0.022
Year of publication				
<2000	Reference		Reference	
2000–2009	0.8 [−1.6; 0.1]	0.096	−0.6 [−1.5; 0.2]	0.157
≥2010	0.7 [−1.5; 0.0]	0.064	−0.2 [−1.0; 0.7]	0.688
Age group				
Adolescents	Reference		Reference	
Adults	−0.1 [−1; 0.8]	0.787	0.6 [−0.4; 1.6]	0.220
Exercise intensity				
Low intensity	Reference		Reference	
Moderate intensity	−0.9 [−1.8; 0.0]	0.043	−1.1 [−2.0; −0.1]	0.026
Vigorous intensity	−1.3 [−2.2; −0.4]	0.006	−1.0 [−1.9; −0.60]	0.040
Exercise type				
HIIE	Reference		Reference	
Continuous exercise	−1.1 [−1.8; −0.4]	0.003	−0.8 [−1.7; 0.1]	0.068
Exercise duration				
<30 minutes	Reference		Reference	
30–60 minutes	−1.4 [−2.1; −0.7]	<0.001	−0.8 [−1.6; −0.1]	0.034
>60 minutes	−1.3 [−2.1; −0.46]	0.002	−1.1 [−1.9; −0.2]	0.012
Insulin reduction				
Insulin reduction	Reference		Reference	
No insulin reduction	1.3 [0.7; 31.9]	<0.001	0.8 [0.1; 1.5]	0.024

TABLE 3 Unadjusted and adjusted meta-regression of BG decrease following running or cycling

Covariates	Unadjusted meta-regression Coefficient [95% CI]	*p*-Value	Adjusted meta-regression Coefficient [95% CI]	*p*-Value
Running				
Year of publication				
<2000	Reference		Reference	
2000–2009	3.0 [−3.5; 9.5]	0.363	5.3 [−0.7; 11.4]	0.084
≥2010	2.6 [−3.8; 8.9]	0.432	4.4 [−1.6; 10.4]	0.152
Age group				
Adolescents	Reference		Reference	
Adults	0.1 [−2.9; 3.0]	0.973	1.6 [−1.3; 4.4]	0.277
Exercise intenity				
Low intensity	Reference		Reference	
Moderate intensity	−0.7 [−2.9; 1.6]	0.554	1.2 [−1.0; 3.4]	0.275
Vigorous intensity	−1.9[−3.4; −0.4]	0.016	- 0.1[−2.1; 1.9]	0.916
Exercise type				
HIIE	Reference		Reference	
Continuous exercise	−3.3 [−5.1; −1.4]	0.001	−4.8[−6.6; −3.1]	<0.001
Exercise duration				
<30 minutes	Reference		Reference	
30–60 minutes	−2.7 [−4.4; −1.0]	0.002	0.7 [−1.0; 2.4]	0.429
>60 minutes	−1.8 [−4.2; 0.6]	0.142	−0.6 [−2.9; 1.8]	0.640
Insulin reduction				
Insulin reduction	Reference		Reference	
No insulin reduction	2.0 [0.8; 3.3]	0.001	3.2 [1.4; 5]	<0.001
Cycling				
Year of publication				
<2000	Reference		Reference	
2000–2009	−0.7 [−1.5; 0.2]	0.126	−0.9[−1.8; 0.0]	0.055
≥2010	−0.2 [−0.9; 0.6]	0.682	−0.3 [−1.2; 0.6]	0.512
Age group				
Adolescents	Reference		Reference	
Adults	0.2 [−0.7; 1.0]	0.703	0.1 [−1.0; 1.1]	0.854
Exercise intensity				
Low intensity	Reference		Reference	
Moderate intensity	−1.2 [−2.2−0.3]	0.012	−1.1 [−2.2; −0.1]	0.031
Vigorous intensity	−0.4 [−1.5; 0.7]	0.443	−0.5 [−1.6; 0.7]	0.395
Exercise type				
HIIE	Reference		Reference	
Continuous exercise	−0.4 [−1.2; 0.3]	0.234	−0.0 [−1.0; 0.9]	0.923
Exercise duration				
<30 minutes	Reference		Reference	
30–60 minutes	−0.6 [−1.4; 0.1]	0.111	−0.7 [−1.5; 0.1]	0.088
>60 minutes	−1.2 [−2.0; −0.40]	0.004	−1.0[−1.9; −0.1]	0.030
Insulin reduction				
Insulin reduction	Reference		Reference	
No insulin reduction	0.5 [−0.3; 1.2]	0.214	0.4 [−0.4; 1.2]	0.347

TABLE 4 Summary of subgroup-analysis of BG decrease following both running and cycling

Covariates	Pooled mean [95% CI]	*p*-Value
Overall	−3.1 [−4.3; −2.8]	–
Type of exercise		
Running	−4.1 [−4.7; −3.4]	<0.001
Cycling	−2.7 [−3.0; 2.4]	
Year of publication		
<2000	−2.5 [−3.2; −1.8]	0.163
2000–2009	−3.3 [−3.81; −2.7]	
≥2010	−3.3 [−3.7; −2.8]	
Age group		
Adolescents	−3.0 [−3.9; −2.1]	0.805
Adults	−3.1 [−3.4; −2.8]	
Exercise intensity		
Low intensity	−2.2 [−2.9; −1.4]	0.024
Moderate intensity	−3.1 [−3.5; −2.7]	
Vigorous intensity	−3.5 [−4.1; −2.9]	
Exercise type		
Continuous exercise	−3.3 [−3.7; −3.0]	0.004
HIIE	−2.2 [−2.9; −1.5]	
Exercise duration		
<30 minutes	−2.1 [−2.5; −1.6]	<0.001
30–60 minutes	−3.5[−4.0; −3.0]	
>60 minutes	−3.4 [−3.9; −2.8]	
Insulin reduction		
Insulin reduction	−3.9 [−4.4; −3.4]	<0.001
No insulin reduction	−2.6 [−3.0; −2.2]	

3.6 | Meta-regression

In running studies, vigorous-intensity exercise resulted in −1.9 mmol/L [−3.4; −0.4] reduction in BG compared to low-intensity exercise in unadjusted meta-regression; however, this difference became insignificant in the adjusted analysis. Continuous exercise achieved more reduction in BG compared to HIIE in both unadjusted (−3.3 mmol/L [−5.1; −1.4]) and adjusted (−4.8 mmol/L [−6.6; −3.1]) analysis. A longer duration of exercise was associated with more reduction in BG in the unadjusted analysis; however, it did not retain significance in the adjusted analysis. No insulin reduction was significantly associated with a 2.0 mmol/L [0.8; 3.3] lower reduction in BG compared to insulin reduction in unadjusted regression and 3.2 mmol/L [1.4; 5.0] lower reduction in the adjusted analysis. In cycling studies, higher intensity and duration of exercise were significantly associated with a higher reduction in BG in both unadjusted and adjusted meta-regression analyses. Please see more details in Tables 2 and 3.

3.7 | Year of publication

The decrease in glucose was not significantly different with respect to the year of publication in both cycling and running studies.

3.8 | Heterogeneity

Egger's test for the bike resulted in $p = 0.022$ and for the treadmill $p = 0.65$. Funnel Plots are shown in Figure S1.

4 | DISCUSSION

Our meta-analysis indicated that, overall, running leads to a more pronounced decrease in BG in comparison to cycling in individuals with Type 1 diabetes. Our hypothesis that the whole-body movement running, in comparison to cycling, utilises more energy in form of glucose from the blood stream is therefore confirmed.

However, further subgroup analyses have shown that different exercise intensities and exercise duration lead to similar changes in BG decrements in both, running and cycling.

This meta-analysis also revealed findings which may appear unexpected at first since insulin reductions led to larger BG decrements in running and cycling. Insulin reductions prior to exercise lead to higher BG levels that allow a higher BG decrement in comparison to no insulin reduction and hence smaller decrements in BG [87]. The increased starting BG may therefore protect from EIH and, once insulin was reduced prior to exercise may also lead to a lower risk of post-EIH[26,88,89]. Consumed meals and targeted carbohydrate consumption prior-to exercise to avoid EIH may have a severe impact on our study result. Pre-exercise carb-loading leads to an increased BG level prior to the start of exercise and may even though described elsewhere[87] lead to a lower reduction in BG throughout the exercise session. In addition, several studies conducted within this field aim to investigate how EIH can be avoided, from this aspect studies applying different carbohydrate supplementation protocols had to be excluded due to the potential bias[88]. A differentiated analysis was not possible to be conducted due to the versatility of time of meal consumption until the start of exercise as well as the amount of carbohydrates and type of carbohydrates supplemented during the exercise sessions. Nevertheless, we believe that the

TABLE 5 Baseline characteristics of running studies

Article	Year	Study design	*n* Men	*n* Women	Age (years)	Exercise	Duration	Exercise type	Exercise intensity
Reddy R[18]	2019	Crossover Randomised Controlled Trial	4	6	Adults	running	45 min	continuous	moderate
Yardley JE[19]	2013	Crossover Clinical Trial	10	2	Adults	running	45 min	continuous	moderate
Tagougui S[20]	2020	Crossover Randomised Controlled Trial	20	10	Adults	running	60 min	continuous	moderate
Zaharieva DP[21]	2015	Crossover Clinical Trial	5	8	Adults	running	45 min	continuous	moderate/ vigorous
Charlton J[22]	2015	Comparative Study	5	4	Adults	running	40 min	continuous	vigorous
West DJ[23]	2010	Randomised Controlled Trial	6	1	Adults	running	45 min	continuous	vigorous
Campbell MD[24]	2013	Crossover Randomised Controlled Trial	11	0	Adults	running	45 min	continuous	vigorous
Campbell MD[25]	2014	Crossover Randomised Controlled Trial	8	0	Adults	running	45 min	continuous	vigorous
Campbell MD[26]	2015	Randomised Controlled Trial	10	0	Adults	running	45 min	continuous	vigorous
West DJ[27]	2011	Randomised Controlled Trial	6	1	Adults	running	45 min	continuous	vigorous
Campbell MD[28]	2014	Randomised Controlled Trial	10	0	Adults	running	45 min	continuous	vigorous
West DJ[29]	2011	Randomised Controlled Trial	7	1	Adults	running	45 min	continuous	vigorous
Bracken RM[30]	2012	Comparative Study	2	5	Adults	running	38 min	HIIE	vigorous
Gray BJ[31]	2016	Randomised Controlled Trial	2	5	Adults	running	36 min	HIIE	vigorous
Campbell MD[32]	2015	Clinical Trial	7	2	Adults	running	45 min	continuous	vigorous
Van Bon AC[33]	2012	Clinical Trial	8	2	Adults	running	30 min	continuous	moderate
van Loon BJ[34]	1992	Comparative Study	7	0	Adults	running	180 min	continuous	moderate
Jacobs PG[35]	2016	Crossover Randomised Controlled Trial	21	Adults	running	45 min	continuous	low	
Mauras N[36]	2010	Crossover Randomised Controlled Trial	5	5	Adolescents	running	60 min	continuous	low
Arutchelvam V[37]	2009	Crossover Randomised Controlled Trial	34	17	Adults	running	30 min	continuous	low

TABLE 6 Baseline characteristics of cycling studies

Article	Year	Study design	*n* Men	*n* Women	Age (years)	Exercise	Duration	Exercise type	Exercise intensity
Simonson DC[38]	1984	Randomised Controlled Trial	6	1	Adults	cycling	40 min	continuous	low
Bussau VA[39]	2006	Randomised Controlled Trial	7	0	Adults	cycling	20 min	continuous/HIIE	low
Guelfi[40]	2005	Randomised Controlled Trial	4	3	Adults	cycling	30 min	continuous/HIIE	low
Dubé MC[41]	2005	Randomised Controlled Trial	6	3	Adults	cycling	60 min	continuous	moderate
Dubé MC[42]	2013	Randomised Controlled Trial	5	6	Adults	cycling	60 min	continuous/HIIE	moderate
Trovati M[43]	1988	Randomised Controlled Trial	6	0	Adults	cycling	45 min	continuous	moderate
Biankin SA[44]	2003	Comparative Study	A: 6; B: 3	A: 7; B: 4	Adults	cycling	45 min	continuous	moderate
Dubé MC[45]	2012	Randomised Controlled Trial	7	3	Adolescents	cycling	60 min	continuous	moderate
Dubé MC[46]	2006	Comparative Study	6	3	Adults	cycling	60 min	continuous	moderate
Trovati M[47]	1992	Observational Study	6	0	Adults	cycling	45 min	continuous	moderate
Abraham MB[48]	2017	Randomised Controlled Trial	4	4	Adolescents	cycling	30 min	HIIE	moderate
Giani E[49]	2018	Clinical Trial	9	8	Adolescents	cycling	45 min	HIIE	vigorous
Mcniven Temple MY[50]	1995	Comparative Study	9	0	Adolescents	cycling	85 min	HIIE	moderate
Laaksonen DE[51]	1996	Observational Study	9	0	Adults	cycling	40 min	continuous	moderate
Ramires PR[52]	1993	Comparative Study	15	0	Adults	cycling	66 min	continuous	moderate
Moser O[53]	2019	Crossover Randomised Controlled Trial	6	4	Adults	cycling	55 min	continuous	vigorous
Moser O[54]	2019	Crossover Randomised Controlled Trial	5	4	Adults	cycling	55 min	continuous	vigorous
Larose S[55]	2019	Randomised Controlled Trial	22	Adults	cycling	45 min	continuous	moderate	
Roy-Fleming A[56]	2019	Randomised Controlled Trial	11	11	Adults	cycling	45 min	continuous	moderate
Admon G[57]	2005	Crossover Randomised Controlled Trial	4	6	Adolescents	cycling	40–45 min	continuous	moderate
McCarthy O[58]	2020	Crossover Clinical Trial	11	2	Adults	cycling	45 min	continuous	moderate
Riddell MC[59]	2000	Clinical Trial	8	0	Adolescents	cycling	60 min	HIIE	moderate
Ramires PR[60]	1997	Randomised Controlled Trial	21	Adults	cycling	74 min	continuous	moderate	
Soo K[61]	1996	Comparative Study	8	1	Adults	cycling	45 min	continuous	moderate
Rudberg S[62]	1993	Crossover Clinical Trial	4	10	Adults	cycling	30 min	continuous	moderate
Mauvais-Jarvis F[63]	2003	Randomised Controlled Trial	12	Adults	cycling	60 min	continuous	vigorous	
Rosa JS[64]	2010	Observational Study	22	25	Adolescents	cycling	30 min	HIIE	vigorous

TABLE 6 (Continued)

Article	Year	Study design	n Men	n Women	Age (years)	Exercise	Duration	Exercise type	Exercise intensity
Jayawardene DC[65]	2017	Crossover Randomised Controlled Trial	3	9	Adults	cycling	45 min	continuous/HIIE	low
Scott SN[66]	2019	Crossover Randomised Controlled Trial	6	8	Adults	cycling	35 min	continuous/HIIE	vigorous
Lee AS[67]	2020	Crossover Randomised Controlled Trial	3	9	Adults	cycling	38 min	continuous/HIIE	low/vigorous
Adolfsson P[68]	2012	Comparative Study	6	6	Adolescents	cycling	60 min	continuous/HIIE	low/vigorous
Rabasa-Lhoret R[69]	2001	Crossover Clinical Trial	8	0	Adults	cycling	30/60 min	continuous	low/moderate/ vigorous
Dovc K[70]	2017	Crossover Randomised Controlled Trial	11	9	Adolescents	cycling	40 min	HIIE	vigorous
Rönnemaa T[71]	1991	Randomised Controlled Trial	8	0	Adults	cycling	45 min	continuous	moderate
Carter MR[72]	2014	Comparative Study	5	3	Adults	cycling	90 min	continuous	moderate
McGinn R[73]	2015	Observational Study	5	3	Adults	cycling	90 min	continuous	vigorous
Radermecker RP[74]	2013	Observational Study	5	5	Adults	cycling	30 min	continuous	vigorous
Żebrowska A[75]	2018	Comparative Study	7	7	Adults	cycling	40 min	continuous/HIIE	moderate/vigorous
Gooch BR[76]	1983	Comparative Study	5	0	Adults	cycling	60 min	continuous	moderate
Koivisto VA[77]	1983	Comparative Study	11	0	Adults	cycling	40 min	continuous	moderate
van Bon AC[78]	2011	Observational Study	8	3	Adults	cycling	30 min	continuous	vigorous
Frid A[79]	1990	Comparative Study	5	5	Adults	cycling	40 min	continuous	vigorous
Koivisto VA[80]	1993	Observational study	9	0	Adults	cycling	180 min	continuous	moderate
Hoogenberg K[81]	1992	Comparative Study	15	11	Adults	cycling	20 min	continuous	moderate
Hübinger A[82]	1985	Clinical Trial	4	5	Adults	cycling	30 min	continuous	moderate
Coiro V[83]	1990	Randomised Controlled Trial	29	0	Adults	cycling	30 min	continuous	low
Kosinski C[84]	2020	Crossover Randomised Controlled Trial	14	0	Adults	cycling	60 min	continuous	moderate
Iscoe KE[85]	2011	Randomised Controlled Trial	5	6	Adults	cycling	45 min	continuous/HIIE	moderate/vigorous
Moser O[86]	2015	Clinical Trial	7	0	Adults	cycling	30 min	continuous/HIIE	moderate

recommendations made in the position statement are valid. The numerous uncontrollable factors in our systematic review and meta-analysis may play a role in biasing the interactions shown in our results.

In general, physical exercise in individuals with type 1 diabetes demands preparation that may include pre-exercise carbohydrate consumption, insulin adaptions and a plan about the type, duration and intensity of the exercise session. Regarding this set-up, the type of exercise has a major impact that is contrary to what is proclaimed in numerous position statements around physical exercise[8,90]. Running involves a higher amount of musculature and hence a higher glucose uptake via GLUT-4 translocation induces a higher decrement in BG which is reflected by our overall finding. When comparing exercise intensities of low, moderate and vigorous nature, between both types of exercise, the results confirmed the overall findings towards a higher decrement in BG during running. From this aspect it is important to note for individuals with type 1 diabetes that not all types of endurance exercise are the same and their BG levels may respond differently hence the risks of EIH may increase.

An interesting finding from our systematic review and meta-analysis is that publication year had no effect on our outcome. Insulin kinetics have substantially improved within the last decades and newer basal insulin generations have proven to be associated with a reduced risk of hypoglycaemia[91]. Nevertheless, to the best of our knowledge, no scientific evidence is available investigating older generation insulins (e.g. NPH-insulin) compared to modern basal insulins (e.g. insulin degludec U100, insulin glargine U300) during physical activity[92]. However, we anticipate that the non-inferiority in glucose decline according to the year of study publication as seen in our study is diminished by the fact that people in exercise studies are closely monitored regarding their glucose and analyses were mostly not objecting hypoglycaemia as an outcome Furthermore, most of the studies did not define the specific insulins used and sub-analysis in this context remain technically impossible.

This systematic review and meta-analysis highlight the urgent need for comparative studies with metabolic matching. Even though our review was conducted comprehensively, several aspects arose during the search and analytical process, that future studies should consider. This concerns the exact monitoring of pre-exercise carbohydrate consumption and insulin management and additionally the post-exercise glucose management since with our data we can solely discuss the BG levels during physical activity.

Our systematic review and meta-analysis are not without limitations. In addition, the calculation of how the preliminary cardio-pulmonary exercise was conducted and the exercise intensity prescribed afterwards for the initial exercise session may be a potential source of bias. Several studies prescribed exercise intensity according to the percentage of the heart rate which is not suitable for individuals with type 1 diabetes and should be reconsidered in future studies[93,94]. Ventilatory or metabolic thresholds would be the correct choice since those offer more precise options to prescribe exercise adequately[93,95]. A further limitation in the interpretation of the results is the complexity of preparation prior to physical exercise since pre-exercise meals and different types of bolus−/basal insulins, pump systems and variably utilised protocols and individual investigator decisions could have led to an increased bias. We were unable to statistically adjust for these variables due to the diverse study protocols and lack of data that was presented in published studies.

Future studies should focus on standardised protocols that demand expertise from exercise scientists and health care professionals so that individuals with type 1 diabetes receive the best advice prior to physical exercise.

5 | CONCLUSION

Running leads to a larger decrease in BG in comparison to cycling in individuals with type 1 diabetes. When preparing for exercise, regularly physically active individuals with type 1 diabetes must be aware of what type of endurance exercise, intensity and duration will be conducted to avoid EIH and to safely conduct the physical exercise. Recommendations around physical exercise should be given according to the amount of musculature used during endurance exercise and not just by its type.

AUTHORS CONTRIBUTION

Conceptualisation: Max L. Eckstein, data curation: Max L. Eckstein and Maximilian P. Erlmann, formal analysis: Faisal Aziz, methodology: Max L. Eckstein, Maximilian P. Erlmann, Felix Aberer, Sina Böckel, Rebecca T. Zimmer, Harald Sourij and Othmar Moser, supervision: Othmar Moser, validation: Max L. Eckstein, Maximilian P. Erlmann and Faisal Aziz, writing—original draft: Max L. Eckstein, writing—review and editing: Max L. Eckstein, Felix Aberer, Sina Böckel, Rebecca T. Zimmer, Maximilian P. Erlmann, Harald Sourij and Othmar Moser.

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CONFLICT OF INTEREST

The authors have no relevant competing interests pertinent to the topic to disclose.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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