The relationship between the level of exercise and hemoglobin A1c in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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Research Article

Keywords: Improvement Heterogeneity, Meta-regression Analysis, Duration of Exercise

Posted Date: April 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-417879/v1>

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Version of Record: A version of this preprint was published at Endocrine on July 23rd, 2021. See the published version at <https://doi.org/10.1007/s12020-021-02817-8>.

Abstract

Background: Several systematic reviews and meta-analyses reported that exercise improved hemoglobin A_{1c} (HbA_{1c}) in patients with type 2 diabetes mellitus, but the improvement reported was heterogeneous. A difference in the level of exercise might be the reason for that heterogeneity.

Objective: The aim of study was to evaluate the relationship between changes in HbA_{1c} and exercise levels when performing various types of exercise.

Methods: The inclusion criteria were randomized controlled trials involving adults with type 2 diabetes mellitus and a mean age of ≥ 18 years, intervention involving exercise alone, the overall duration of intervention ≥ 12 weeks, and reporting HbA_{1c}. The mean difference (defined as difference [intervention group value minus control group value] in change [final value minus baseline value] in the mean value) was calculated. Weighted mean difference (WMD) was defined as the mean difference weighted by the inverse of the squared standard error for each study, and all WMDs were pooled as overall effects. A meta-regression analysis was performed to evaluate the relationship between the exercise level and the WMD in HbA_{1c}. All analyses were performed using restricted maximum likelihood.

Results: Forty-eight studies (2395 subjects) were analyzed. The pooled WMD in HbA_{1c} decreased significantly (-0.5% [95% confidence intervals: -0.6 to -0.4]) but contained significant heterogeneity ($Q=103.8$, $P<0.01$; $I^2=36.6\%$). The pooled WMD in body mass index (BMI) decreased significantly (-0.55 kg/m² [95% confidence intervals: -0.58 to -0.51]) and did not contain heterogeneity ($Q=25.8$, $P=0.99$; $I^2=0.0\%$). A meta-regression analysis showed that the intensity (metabolic equivalents [METs]), time (min/session), or frequency (sessions/week) of exercise was not associated with the HbA_{1c}. However, the overall duration of exercise (weeks) was significantly associated with the WMD in HbA_{1c} (meta-regression coefficient: 0.01 [95% confidence intervals: 0.002 to 0.016]; $R^2=70.0\%$), and that result did not contain significant heterogeneity ($P>0.05$; $I^2=14.7\%$). Even when studies were limited to those involving mean age ≥ 40 years, mean baseline HbA_{1c} $\geq 6.5\%$, mean duration of type 2 diabetes mellitus ≥ 5.0 years, mean baseline BMI ≥ 30 kg/m², calculation of the WMD in BMI, performance of aerobic exercise alone, or no inclusion of a high risk of bias, there was no change in these results.

Conclusions: The exercise intervention decreased HbA_{1c} in type 2 diabetes mellitus patients, but that change likely depended on the overall duration of exercise. HbA_{1c} may increase if exercise is continued, but at least continuing exercise is not necessarily beneficial for type 2 diabetes mellitus patients. This may be the result of intervention in the form of exercise alone.

Key Points

■ The intensity (METs), time (min/session), or frequency (sessions/week) of exercise was not associated with the HbA_{1c} in type 2 diabetes mellitus patients.

■ Since the overall duration of exercise (weeks) was associated with the HbA_{1c}, continuing exercise may not necessarily be beneficial for type 2 diabetes mellitus patients.

1 Introduction

According to the International Diabetes Federation (IDF), an estimated 4.6 hundred million people around the world have diabetes, and approximately 90% of them have type 2 diabetes mellitus (T2DM) [1]. T2DM contributes to cardiovascular disease, cancer, dementia, and worse morbidity and mortality [2–7]. As an example, a meta-analysis of cohort studies

reported that a 1% increase in hemoglobin A_{1c} (HbA_{1c}) in T2DM patients increased the risk of cardiovascular disease by 1.13-fold and stroke by 1.26-fold [7].

The risk of T2DM depends greatly on lifestyle [8], and decreased physical activity is a major factor in the development of T2DM [9]. A meta-analysis of epidemiological studies indicated that a sedentary lifestyle over a prolonged period increased the incidence of T2DM [10]. In order to alleviate T2DM, the American Diabetes Association (ADA) guidelines recommend engaging in exercise at moderate or greater intensity (i.e., ≥ 3.0 metabolic equivalents [METs]; 3.0 METs is equivalent to walking 4.0 km/h on a firm surface [11]) for ≥ 2.5 hours per week [12]. Epidemiological studies reported a relationship between the incidence of cardiovascular disease and the exercise level in T2DM patients [13–18]. For example, a cohort study that followed Japanese T2DM patients for approximately 8 years reported that the risk of stroke decreased if the exercise level per week was ≥ 15.4 METs $\times$ hour [13]. In addition, several systematic reviews and meta-analyses involving randomized controlled trials (RCTs) reported that exercise improved HbA_{1c} in T2DM patients [19–31], although there was heterogeneity in the improvement among the studies [19, 20, 22, 23, 25–27, 29, 30]. One of those meta-analyses reported that decreased HbA_{1c} was associated with high exercise levels [19]; thus, differences in exercise levels might be the reason for the heterogeneity. However, this meta-analysis was limited to RCTs involving only supervised aerobic exercise [19]. Types of exercise have become more varied [11], and systematic reviews and meta-analyses have evaluated the effects of various forms of exercise, including resistance training [22, 23], interval training [24], tai chi [27, 29, 30], yoga [28–30], and aquatic exercise [31], on HbA_{1c} in T2DM patients. No systematic review and meta-analysis have evaluated all types of exercise. We hypothesized that, in line with epidemiological studies [15–18], a meta-analysis of RCTs would indicate that HbA_{1c} improvement depends on the exercise level. In addition, previous systematic reviews [19–31] did not assess quality of individual RCTs or evidence overall and did not adequately discuss a form of exercise to improve HbA_{1c} and evidence for it.

Thus, the aim of the current systematic review and meta-analysis was to evaluate the relationship between changes in HbA_{1c} and the exercise level when performing various types of exercise in T2DM patients and assess quality of individual RCTs and evidence overall.

2 Methods

The current paper reported all 27 items that should be disclosed in a systematic review and meta-analysis as described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [32] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020181566) [33].

2.1 Data Sources, Study Selection, and Data Extraction

The current systematic review searched six electronic databases (MEDLINE via PubMed, EMBASE, Scopus, SPORTDiscus, CINAHL, and Cochrane library [CENTRAL]) with a combination of search terms related to diabetes mellitus, HbA_{1c}, physical activity, exercise, and sports (Supplementary Material 1). In addition, a search of other sources was conducted by referring to articles cited in the current study and previous systematic reviews that reviewed the effect of exercise in T2DM patients. These searches were performed prior to August 31, 2020.

The inclusion criteria for RCTs were as follows: studies involving subjects with T2DM and a mean age of ≥ 18 years; increased exercise performed by intervention group; no increase in exercise performed by control group; neither group received another intervention (e.g., diet and/or lifestyle change); study reported specifics of exercise (e.g., type, intensity, time [total exercise time per session], frequency [number of exercise sessions per week], and overall duration of intervention); study reported the mean HbA_{1c} and standard deviation (SD) or standard error of mean (SEM) at baseline

and post-intervention for the intervention and control groups; and the overall duration of intervention was ≥ 12 weeks (since HbA_{1c} indicates blood glucose levels over approximately that last 12 weeks [34]). The identified articles were first screened by title and abstract, and the full-text was obtained if the study included subjects with T2DM, intervention involving exercise, and reported HbA_{1c}. The first and second authors determined whether the identified studies should be included in this systematic review. If they disagreed, the third author made the final decision regarding inclusion.

The current study was in accordance with the Cochrane data collection form for intervention review (RCTs only) [35]. The first and second authors independently extracted data (number of subjects, mean age, mean duration of diabetes, mean HbA_{1c}, mean body mass index [BMI], and respective SDs or SEMs for the intervention and control groups) from each study in order to perform the meta-analysis. In addition, the type, intensity, time (min/session), frequency (sessions/week), and overall duration (weeks) of exercise were extracted as specifics of the intervention. METs in each study were estimated as the intensity of exercise. If studies indicated the percentage of maximal oxygen consumption (% O_{2max}), percentage of heart rate reserve (% HRR), percentage of maximal heart rate (% HR_{max}), or Borg rating of perceived exertion (RPE), these values were converted to METs based on the characteristics and modalities of exercise [36]. If studies did not indicate the intensity, METs were estimated based on activity codes and the MET intensities defined by the American College of Sports Medicine (ACSM) [11].

2.2 Risk of Bias

The first and second authors used the version 2 of the Cochrane Collaboration tool to assess the risk of bias in each study [37]. This tool consists of six domains (bias arising from the randomization process generation, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias). Each domain is ranked in one of three categories (low risk, some concerns, or high risk.).

2.3 Data Synthesis

The baseline and form of the exercise (intensity, time, frequency, and overall duration) data were expressed as the mean and SD, weighted by the number of subjects in each study.

The mean difference ([mean value at post-intervention in the exercise group – mean value at baseline in the exercise group] – [mean value at post-intervention in the control group – mean value at baseline in the control group]) was used as the effect size [38] and the mean difference in HbA_{1c} and BMI were calculated for each study. The weighted mean difference (WMD) was defined as the mean difference weighted by the inverse of the squared SEM of differences from baseline to post-intervention for each study; the current study pooled all WMDs as overall effects. The meta-analysis followed a random effects model in accordance with $\gamma = \theta + \varepsilon + \mu$ (Eq. 1), where γ represents the effect size in each study, θ represents the true value, ε represents the sampling error, and μ represents the between-study variance [39]. The pooled WMD was calculated using restricted maximum likelihood (REML) [40]. This approach is a random effects model that takes into account within-study and between-study variances as opposed to the fixed-effect model, which ignores between-study variance and which readily yields positive results. In comparison to the DerSimonian–Laird approach, which is typically used for random effects models, this method avoids underestimation errors [41].

In order to evaluate the relationship between the exercise level and changes in the HbA_{1c} and BMI, we performed a multivariate meta-regression analysis, in which θ was replaced with $\beta_0 x_0 + \beta_1 x_1$ (where β represents the meta-regression coefficient and x represents the explanatory variable) in Eq. 1. Intensity (METs), time (min/session), frequency (sessions/week), and overall duration (weeks) of exercise were selected as x_0 for the analysis. Furthermore, since a previous systematic review and meta-analysis reported that the baseline HbA_{1c} was inversely associated with changes in HbA_{1c} as a result of exercise [25], x_1 was adjusted with the mean baseline HbA_{1c} in the current meta-regression analysis.

The meta-regression equations were calculated, then R^2 (the proportion of between-study variance explained by covariates) was calculated [42].

Sensitivity analyses were used to evaluate the influence of study characteristics and quality, and 7 categories (mean age ≥ 40 years, mean baseline HbA_{1c} $\geq 6.5\%$, mean duration of T2DM ≥ 5.0 years, mean baseline BMI ≥ 30 kg/m², calculation of the WMD in BMI, performance of aerobic exercise alone, and no inclusion of a high risk of bias [37]) were defined. Once studies were limited to those falling into a given category, the pooled WMD in HbA_{1c} was calculated and meta-regression analyses were performed.

The mean difference, pooled WMD, and meta-regression coefficient were expressed with 95% confidence interval (CI). The heterogeneity of the pooled WMD as a result of variations among studies was assessed using Cochran's Q statistic and I^2 statistic. The Q statistic was tested using the chi-squared test. P values of <0.05 were considered to indicate significant heterogeneity. In addition, the degree of heterogeneity was assessed in low ($I^2 < 25\%$), moderate ($I^2: 25-75\%$), and high ($I^2 > 75\%$) risk studies [43].

Publication bias was assessed using funnel plots consisting of the mean difference in the HbA_{1c} or BMI (x-axis) and the inverse of the SEM (y-axis). First, Egger's regression test was performed to evaluate the asymmetry of funnel plots [44], and P values of <0.05 were considered to indicate a significant publication bias. Second, the trim and fill method of Duval and Tweedie was applied to estimate the number of missing studies and coordinates when they were located on a funnel plot [45]. If the results suggested that studies were missing, then the pooled WMDs in HbA_{1c} and BMI were adjusted by the addition of coordinates. The result was expressed as the WMD in light of the effect of these studies and the 95% CI.

The current meta-analyses were performed using the JASP software program (Version 1.3; University of Amsterdam, Netherlands).

2.4 The Certainty of Evidence

The overall evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [46]. The five domains (study limitations [risk of bias], inconsistency, indirectness, impression, and risk of publication bias) were ranked as one of the following: downgraded 2 levels (if very serious), downgraded 1 level (if serious), or not downgraded (if not serious); publication bias was downgraded 2 levels (if very likely), downgraded 1 level (if likely), or not downgraded (if not likely). The body of evidence was assessed as a high level of evidence (if not downgraded in any domain), a moderate level of evidence (if downgraded a total of 1 level), a low level of evidence (if downgraded 1 level in two domains, i.e., downgraded a total of 2 levels), or a very low level of evidence (if the aforementioned criteria were not met).

3 Results

Study Characteristics and Risk of Bias

The literature search yielded 304 studies. These studies involved subjects with T2DM, intervention in the form of exercise, and reported HbA_{1c} data. Among these, 256 studies did not meet the selection criteria and were excluded. Finally, 48 studies were analyzed (Fig. 1) [47–94]. Table 1 shows a general description of the studies. The studies involved 2395 subjects (1514 subjects in exercise groups and 881 subjects in control groups). Table 2 shows baseline and form of exercise data.

Supplementary Material 2 shows the assessed risk of bias. Six studies [49, 54, 63, 74, 79, 86] had a high risk of bias in overall bias.

3.1 Data Synthesis

Fig. 2 shows the baseline results and the forest plot of the mean difference from each study and the pooled WMD in HbA_{1c}. The pooled WMD was significantly decreased but contained significant heterogeneity (moderate risk). The pooled WMD in BMI was calculated and evaluated with 35 studies reporting the mean BMI and its SD or SEM at baseline and post-intervention; the result decreased significantly (-0.55 kg/m^2 ; 95% CI, -0.58 to -0.51) and did not contain heterogeneity ($Q=25.8$, $P=0.99$; $I^2=0.0\%$; low risk). Table 3 shows the results of the sensitivity analyses of HbA_{1c}. When studies were limited to those in a given category, there was a significant decrease in all pooled WMDs in HbA_{1c} and the WMDs contained significant heterogeneity (moderate risk); that is, there was no change in the results.

Tables 4 and 5 show the results of a meta-regression analysis of the relationship between exercise level and WMD in HbA_{1c}; here, the WMD in HbA_{1c} was adjusted by the mean baseline HbA_{1c}. All meta-regression coefficients of the mean baseline HbA_{1c} were <0.00 , and the meta-regression coefficient was significantly associated with the WMD in HbA_{1c}. The intensity of exercise was not significantly associated with the WMD in HbA_{1c}, and that result did not contain significant heterogeneity. The time and frequency of exercise were not significantly associated with the WMD in HbA_{1c}; these results did not contain significant heterogeneity. However, the overall duration of exercise was significantly associated with the WMD in HbA_{1c}, and those results did not contain significant heterogeneity. Sensitivity analyses indicated no change in that relationship in any.

Supplementary Material 3 shows the results of a meta-regression analysis of the relationship between the exercise level and WMD in BMI; here, the WMD in BMI was adjusted by the mean baseline HbA_{1c}. The intensity, time, frequency, and overall duration of exercise were not significantly associated with the WMD in BMI.

Supplementary Material 4 and 5 show funnel plots for publication bias with regard to HbA_{1c} and BMI, respectively. Egger's regression test showed no significant asymmetry in HbA_{1c} and BMI ($P=0.31$ and $P=0.35$, respectively). Duval and Tweedie's trim and fill method suggested that four studies were missing HbA_{1c} data and eight studies were missing BMI data. After adjusting for the effects of these missing studies, the pooled WMD in HbA_{1c} was estimated to be -0.5% (95% CI, -0.6 to -0.4 ; $Q=119.0$, $P<0.05$ for heterogeneity, $I^2=39.5\%$), and the pooled WMD in BMI was estimated to be -0.55 kg/m^2 (95% CI, -0.59 to -0.51 ; $Q=32.7$, $P>0.05$ for heterogeneity, $I^2=0.0\%$).

3.2 The Certainty of Evidence

The study limitations (risk of bias) domain was ranked as serious, but there were no serious concerns in other domains (the inconsistency, indirectness, impression, and publication of bias). Thus, there was a moderate level of evidence for a decrease in HbA_{1c} as a result of exercise.

4 Discussion

This systematic review and meta-analysis were conducted to evaluate the effect of exercise on HbA_{1c} in T2DM patients. The results indicated a decrease in HbA_{1c}; however, the effect contained heterogeneity. In addition, results of meta-regression analyses indicated that changes in HbA_{1c} were associated with the overall duration of exercise (weeks) but not the intensity (METs), time (min/session), or frequency (sessions/week) of exercise.

4.1 Comparison with Other Studies

Several previous meta-analyses reported a decrease in HbA_{1c} as a result of exercise [19–31]. However, the meta-analyses involved aerobic exercise or resistance training alone and the observed effects contained heterogeneity [19, 20, 22, 23, 30],

indicating that the effect on HbA_{1c} differed among RCTs even if those RCTs were limited to studies involving the same type of exercise. The current study assumed that the effect on HbA_{1c} was affected by the exercise level. Results of analyses indicated that the intensity, time, and frequency of exercise were not associated with changes in HbA_{1c}, and those results were similar to the results of an analysis limited to RCTs involving aerobic exercise. Thus, differences due to the type of exercise presumably have no effect on improvement of HbA_{1c}. Notably, a meta-analysis that evaluated the percentage of T2DM patients who dropped out from an exercise intervention reported that a protocol involving vigorous exercise resulted in a higher percentage of drop-outs in comparison to moderate intensity exercise [94]. Given that a difference in intensity of exercise did not affect the improvement in HbA_{1c}, T2DM patients should probably perform exercise at low to moderate intensity. In fact, meta-analyses of studies involving low to moderate intensity exercise, such as walking [20, 30], yoga [30], or tai chi [27], reported that these types of exercise were associated with HbA_{1c} improvement.

Since the current study indicated that changes in HbA_{1c} were associated with the overall duration of exercise and that heterogeneity in the changes improved, the overall duration of exercise may depend on changes in HbA_{1c} and it may be a cause of that heterogeneity. However, these findings indicate that HbA_{1c} increases rather than decrease as a result of continuing exercise. Therefore, exercise may not necessarily be beneficial for patients with T2DM. One reason for this is that all of the RCTs analyzed in this meta-analysis involved an exercise intervention alone (without diet, medication, or lifestyle modifications). Although in the minority, a previous meta-analysis reported that HbA_{1c} decreased as a result of a combination of diet and exercise recommendations but was not by the recommendation of exercise alone [26]. Thus, HbA_{1c} may not necessarily tend to decrease in T2DM patients, if they perform exercise alone for a long duration. A recent meta-analysis on nutrition reported that HbA_{1c} and BMI improved in the short term following intervention in the form of a low-carbohydrate diet alone; however, these effects were not sustained over the long term [96]. Thus, previous studies and the current study only indicated the effect of intervention in the form of nutrition or exercise alone, instead of evaluating the effects of multiple interventions. A meta-analysis of RCTs involving subjects without T2DM reported that exercise and diet significantly decreased the incidence of T2DM while exercise alone or diet alone did not [97]. Thus, intervention combining exercise and diet may be essential to alleviate T2DM. A recent meta-analysis of cohort studies found that the combination of exercise and diet should be emphasized for T2DM patients [18]. RCTs and/or meta-analyses of multiple interventions should be conducted in the future.

4.2 Mechanisms

The mechanisms responsible for the alleviation of T2DM by exercise have been attributed to several physiological processes [98]. Several epidemiological studies reported that BMI was associated with insulin resistance [99, 100]; the current study indicated that BMI was significantly decreased as a result of exercise but that the effect did not contain significant heterogeneity; changes in BMI were not significantly associated with the exercise level. Thus, a decrease in HbA_{1c} may differ from changes in BMI. In addition, adipocytokines dramatically affect the action of insulin. A previous meta-analysis of RCTs involving T2DM patients examined the effects of exercise on adipocytokines; the results indicated improvements in leptin and interleukin-6 but no change in adiponectin [101]. Interleukin-6 is considered to a factor associated with enhanced insulin secretion [102]; thus improvement in interleukin-6 as a result of exercise may cause a decrease in HbA_{1c}. However, few studies have evaluated adipocytokines [56, 57, 59, 60, 84], a fact that became apparent from the RCTs analyzed in the current study. Furthermore, the mechanisms underlying the lack of decrease in HbA_{1c} after continued exercise, a finding from the current study, are unclear. Although a stand-alone finding, a systematic review suggested that continued exercise inhibited the gastrointestinal function and depressed the immune system in healthy individuals [103]. Excessive exercise may have some effect on the immune system and/or glucose metabolism. The underlying mechanisms should be investigated in the future.

4.3 Strengths and Limitations

One strength of the current meta-analysis is that it attempted to account for the effects of confounding factors in order to indicate the relationship between the exercise level and HbA_{1c}. Subject characteristics (age, state of blood glucose levels at baseline, duration of T2DM, and overweight) and the form of exercise (aerobic exercise alone) were considered in sensitivity analyses, and the results did not change even when analyses were limited to certain RCTs. Furthermore, the change in HbA_{1c} was adjusted based on the mean baseline level in the current meta-regression analyses; thus, the influence of the aforementioned factors was presumably minimized. In addition, previous studies [19–31] did not assess the quality of each RCT using the version 2 of the risk of bias tool [37] and/or evidence overall using the GRADE approach [46], so evidence of the effects of exercise on HbA_{1c} in T2DM patients may have been insufficient. The use of these assessments in the current study is presumably another one of its strengths. Nevertheless, approximately 10% of the RCTs analyzed in the current study included a high risk of bias and in particular had issues in terms of the random allocation process and/or missing outcome data, so this study had limitations. The influence of this bias contributed to a moderate level of evidence overall according to the GRADE approach. When studies were limited to those not including a high risk of bias in sensitivity analyses, heterogeneity did not change as a result of exercise. However, these issues with the intervention need to be considered and addressed in the future.

Another limitation of this study is that findings did not provide sufficient evidence of the effect of exercise over a prolonged period. All RCTs analyzed in this systematic review and meta-analysis involved an intervention for ≤ 1 year; thus, a systematic review and meta-analysis of RCTs involving an exercise intervention for ≥ 1 year should be conducted.

5 Conclusions

In conclusion, the current results indicated that HbA_{1c} decreased as result of intervention of exercise in T2DM patients; however, the changes in HbA_{1c} were associated with the overall duration of exercise. Therefore, continuing exercise may not necessarily be beneficial for patients with T2DM. This may be the result of intervention in the form of exercise alone.

Declarations

Acknowledgment

The authors wish to sincerely thank the staff of Osaka City University Media Center Library Service for collecting the articles used in this analysis and to thank the staff of Tooin University of Yokohama Library, National Museum of Ethnology, and National Institute of Public Health for facilitating a search of the literature in electronic databases.

Data Availability Statement

All data are available in submitted manuscript or as electronic supplementary material.

Funding

No sources of funding were used to assist in the preparation of this article.

Conflict of interest

Conflict of interest Yutaka Igarashi, Nobuhiko Akazawa, and Seiji Maeda have no conflicts of interest relevant to the content of this article.

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Tables

Table 1 Characteristics of the studies

Subjects						Intervention of exercise		
Study name (year; country)	n	Female, %	Mean age, years (SD)	T2DM duration, years (SD)	MED, %	Description [type, intensity, time, and frequency]	Estimated intensity of exercise, METs	Overall duration, weeks
Ronnemaa et al. [47] (1986; Finland)	25	20.0	52.5 (NR)	7.1 (NR)	92.0	Walking, jogging or skiing, 70% O_{2max} , 45 min/session, and 5-7 sessions/week	7.0	17
Verity et al. [48] (1989; United States)	10	100	59.2 (7.9)	NR	0.0	Walking, 65-80% HRR, 60-90 min/week, and 3 sessions/week	7.6	17
Raz et al. [49] (1994; Israel)	38	63.2	56.6 (7.1)	NR	100	Ergometry bicycle, treadmill, and rowing machine, 65% O_{2max} , 45 min/session, and 3 sessions/week	5.7	12
Tessier et al. [50] (2000; Canada)	39	41.0	69.4 (7.0)	6.5 (5.8)	74.4	Aerobic training: walking, 35-79% HR_{max} , 20 min/session; aerobic/resistance training: major muscle group, 20 repetitions/set, 2 sets, 20 min/session, and 3 sessions/week	5.5	16
Tsujiuchi et al. [51] (2002; Japan)	26	NR	62.9 (7.3)	NR	NR	Qi-gong relaxation exercise, and 120 min/week	3.0	17
Cuff et al. [52] (2003a; Canada)	15	100	62.3 (6.7)	4.0 (3.1)	73.3	Aerobic training: treadmills, stationary bicycles, recumbent steppers, elliptical trainers, and rowing machines), 60-75% HRR; resistance training: five exercises (leg press, leg curl, hip extension, chest press, and latissimus pull down), 12 repetitions/set, 2 set; total 75 min/session, and 3 sessions/ week	5.3	16
Cuff et al. [52]	14	100	59.6 (7.0)	3.7 (2.6)	71.4	Aerobic training (treadmills,	7.0	16

(2003b; Canada)						stationary bicycles, recumbent steppers, elliptical trainers, and rowing machines), 60-75% HRR, 75 min/session, and 3 sessions/week		
Loimaala et al. [53] (2003; Finland)	49	0.0	53.8 (6.3)	NR	73.5	Aerobic training: jogging or walking, 65-75% O_{2max} , 30 min/session; resistance training: eight exercises for large muscle groups from the trunk and upper and lower extremities, 70-80% maximum voluntary contraction, 10-12 repetitions/set, 3 sets, and 2 sessions/week	5.1	52
Dela et al. [54] (2004a; Denmark)	8	NR	50.1 (4.3)	4.4 (2.7)	NR	Ergometer cycle, 40-75% O_{2max} , 30-40 min/session, and 5 sessions/week or more	6.9	12
Dela et al. [54] (2004b; Denmark)	16	NR	53.6 (8.5)	6.0 (3.9)	NR	Ergometer cycle, 40-75% O_{2max} , 30-40 min/session, and 5 sessions/week or more	6.9	12
Bjørgaas et al. [55] (2005; Norway)	23	0.0	57.4 (7.5)	2.0 (NR)	91.3	Light jogging, co-ordination exercises, knee bends and stretching, 50-85% HR_{max} , 45 min/session; resistance exercise: 15 min/session, and 2 sessions/week	5.6	12
Brooks et al. [56] (2006; United States)	62	35.5	66.0 (7.0)	9.5 (5.6)	93.5	Five exercises using pneumatic machines (upper back, chest press, leg press, knee extension, and flexion), 60-80% 1RM, 8 repetitions/set, 3 sets, 35 min/session, and 3 sessions/week	4.4	16

Gordon et al. [57] (2006; United States)	30	50.0	67.0 (8.0)	10.5 (9.9)	93.3	Five exercises (knee extension, chest press, leg curl, upper back, and leg press), 60-80% of 1 RM, 8 repetitions/set, 3 sets, 45-60 min/session, and 3 sessions/week	5.0	16
Middlebrooke et al. [58] (2006; United Kingdom)	55	53.8	63.4 (8.0)	4.4 (4.3)	55.8	Aerobic exercise, 80% HR _{max} , 30 min/session, and 3 sessions/week	5.5	26
Kadoglou et al. [59] (2007; Greece)	56	58.9	61.5 (7.4)	6.8 (4.1)	90.0	Walking or running on the treadmill, cycling and calisthenics involving the upper and lower limbs, 50-75% O _{2peak} , 30-40 min/session, and 4 sessions/week	6.2	26
Lam et al. [60] (2008; Australia)	44	54.5	62.1 (9.8)	NR	NR	Tai chi (yang and sun style 20-form), 60 min/session, and 1-2 sessions/week	3.0	26
Lambers et al. [61] (2008a; Belgium)	23	54.3	56.2 (5.9)	NR	97.7	Circuit training (walking or jogging, elbow flexion and extension, cycling, knee flexion and extension, and stepping), 60-85% HRR and 60-85% 1RM, 50 min/session, and 3 sessions/week	5.6	13
Lambers et al. [61] (2008b; Belgium)	24	18.8	53.5 (5.8)	NR	97.6	Walking (or jogging), cycling, stepping, 60-85% HRR, 50 min/session, and 3 sessions/week	8.0	13
Ribeiro et al. [62] (2008; Brazil)	21	66.7	55.2 (8.5)	8.6 (8.0)	85.7	Cycle-ergometer, AT level and respiratory compensation point, 40 min/session, and 3 sessions/week	7.0	17
Murrock et al. [63] (2009; United States)	38	100	62.6 (7.8)	10.3 (NR)	78.9	Dance, own pace, 45 min/session, and 2 sessions/week	4.0	12
Shenoy et al. [64]	14	57.1	52.7 (4.7)	5.3 (2.1)	92.9	Seven exercises (biceps curls,	4.7	16

(2009a; India)							triceps curls, front lateral pull down, back lateral pull down, knee extension exercises, hamstring curls, and abdominal curls), 60-100% 1RM, 10 repetitions/set, 3 sets, and 2 sessions/week		
Shenoy et al. [64] (2009b; India)	15	40.0	54.3 (4.5)	4.9 (2.2)	73.3		Walking, 70% HR _{max} , 30 min/session, and 3 sessions/week	6.0	16
Church et al. [65] (2010a; United States)	87	60.1	57.2 (4.5)	7.2 (5.5)	100		Nine exercises (bench press, seated row, shoulder press, pull down, leg press, extension, flexion, abdominal crunches, and back extensions), 10-12 repetitions/set, 2-3 sets, and 2 sessions/week (141 min/week)	3.5	39
Church et al. [65] (2010b; United States)	86	63.1	54.5 (4.5)	7.4 (5.9)	93.5		Aerobic exercise, 12 kcal/kg/week, and 150 min/week	6.4	39
Church et al. [65] (2010c; United States)	90	64.8	55.9 (4.4)	6.8 (5.4)	97.8		Aerobic training: aerobic exercise, 10 kcal/kg/week, 150 min/week; resistance training: 9 exercises (bench press, seated row, shoulder press, pull down, leg press, extension, flexion, abdominal crunches, and back extensions), 10-12 repetitions/set, 2-3 sets, and 2 sessions/week	6.0	39
Hosaka et al. [66] (2010; Japan)	24	58.3	59.0 (8.4)	NR	NR		Mechanical horseback riding apparatus, 30 min/session, and 7 session/week	4.0	13
Plotnikoff et al. [67] (2010; Canada)	48	66.7	54.6 (9.3)	NR	NR		Total of 8 exercise, 4 of core exercises (squats, seated row, chest press, shoulder	5.0	16

						press) and 4 of 9 assistance exercise (lunges, lateral pull-down, standing triceps extension, standing pulley abdominal twists, biceps curl, triceps press, reverse rhomboid flies, lateral pulley deltoid raise, or pulley abdominal curls), 50-85% 1RM, 8-12 repetitions/set, 2-3 sets, and 3 sessions/week		
Reid et al. [68] (2010a; Canada)	74	34.2	53.7 (4.9)	5.2 (4.7)	NR	Aerobic training: treadmills and/or bicycle ergometers, 60-75% HR _{max} , 45 min; resistance training: 8 exercises on weight machines each session, 8 RM, 8 repetitions, 2-3 sets, and 3 sessions/week	5.1	26
Reid et al. [68] (2010b; Canada)	68	35.1	54.8 (4.8)	5.9 (4.7)	NR	Eight exercises on weight machines each session, 8 RM, 8 repetitions, 2-3 sets, and 3 sessions/week	3.5	26
Reid et al. [68] (2010c; Canada)	75	35.7	54.2 (5.1)	5.1 (3.8)	NR	Treadmills and/or bicycle ergometers, 60-75% HR _{max} , 45 min, and 3 sessions/week	6.6	26
Sun et al. [69] (2010a; United States)	16	NR	56.3 (8.1)	NR	100	Qigong, 30-60 min/session, and 3 sessions/week	3.0	12
Sun et al. [69] (2010b; United States)	16	NR	56.3 (8.1)	NR	100	Progressive resistance training, 30-60 min/session, and 3 sessions/week	3.5	12
Yavari et al. [70] (2010; Iran)	60	53.3	49.8 (6.7)	4.5 (2.5)	100	Aerobic training (treadmill, bicycle, elliptical, ergometers), 50-75% HR _{max} , 50-60 min/session, and 3 sessions/week	5.2	16
Belli et al. [71]	19	100	54.7	4.1 (3.2)	78.9	Walking, VT	7.5	12

(2011; Brazil)			(7.4)			intensity, 20-60 min/session, and 3 sessions/week		
Kurban et al. [72] (2011; Turkey)	60	51.7	53.7 (7.0)	6.4 (4.9)	100	Walking, moderate-intensity, 50 min/session, and 3 sessions/week	4.0	13
Kwon et al. [73] (2011a; Republic of Korea)	21	100	56.8 (5.9)	6.0 (6.0)	100	Brisk walking using an accelerometer, moderate intensity (3.6-6.0 METs), 60 min/session, and 5 sessions/week	3.1	12
Kwon et al. [73] (2011b; Republic of Korea)	20	100	57.3 (6.0)	4.7 (3.6)	100	Ten exercises using bands (bicep curls, tricep extensions, upright rows, shoulder chest press, seated rows, trunk side bends, leg press, hip flexions, leg flexions, and leg extensions), 1.2-3.2 kg of resistance, 3 sets, 40 min/session, and 3 sessions/week	4.8	12
de Oliveira et al. [74] (2012a; Brazil)	15	58.0	52.4 (6.3)	5.4 (4.0)	100	Cycle-ergometer, LT intensity, 20-50 min/session, and 3 sessions/week	6.7	12
de Oliveira et al. [74] (2012b; Brazil)	14	62.1	53.9 (6.5)	7.0 (3.8)	100	Circuit of 7 exercises (leg press, bench press, lat pull down, seated rowing, shoulder press, abdominal curls, and knees curls), 50% 1RM or 8-12 RM, 15 repetitions/set, 1-4 sets, and 3 sessions/week	4.9	12
de Oliveira et al. [74] (2012c; Brazil)	14	62.1	56.6 (6.5)	6.7 (4.6)	100	Aerobic training: cycle-ergometer, LT intensity, 10-25 min/session; resistance training: circuit of 7 exercises (leg press, bench press, lat pull down, seated rowing, shoulder press, abdominal curls, and knees curls), 50% 1RM	4.0	12

						or 8-12 RM, 15 repetitions/set, 1-4 sets; half the volume of aerobic and resistance training, and 3 sessions/week		
Nuttamonwarakul et al. [75] (2012; Thailand)	40	60.0	NR	NR	NR	Aquatic exercise, 70% HR _{max} , 30 min/session, and 3 sessions/week	4.5	12
Swift et al. [76] (2012a; United States)	62	62.4	56.3 (5.1)	7.5 (5.7)	94.7	Aerobic exercise, 50-80% O _{2max} , and 122 min/week (average)	8.0	39
Swift et al. [76] (2012b; United States)	70	58.1	58.7 (4.8)	7.6 (5.6)	99.6	Nine exercises (bench press, seated row, shoulder press, pull down, leg press, extension, flexion, abdominal crunches, and back extensions), 2-3 sets, 10-12 repetitions, and 3 sessions/week	3.5	39
Swift et al. [76] (2012c; United States)	71	63.0	57.0 (4.7)	6.8 (5.5)	98.2	Aerobic training: aerobic exercise, 50-80% O _{2max} ; resistance training: 9 exercises (bench press, seated row, shoulder press, pull down, leg press, extension, flexion, abdominal crunches, and back extensions), 10-12 repetitions/set, 2-3 sets and 106 min/week (average)	5.8	39
Tan et al. [77] (2012; China)	25	64.0	65.5 (6.7)	16.2 (6.9)	100	Aerobic training: walking/running, 55-70% HR _{max} , 30 min; resistance training: 5 leg exercise (knee flexion, knee extension, hip abduction, hip adduction, and standing calf raise), 50-70% 1RM, 10-12 repetitions/set, 2 set, 10 min, and 3 sessions/week	4.8	26

Fritz et al. [78] (2013; Sweden)	47	34.0	61.2 (7.2)	5.1 (3.7)	64.0	Nordic walking, a pace with slight shortness of breath and perspiration, and 3.9 hours/week	3.5	17
Karstoft et al. [79] (2013a; Denmark)	16	34.4	59.9 (5.7)	5.8 (5.0)	59.4	Continuous-walking, 55% of the peak energy-expenditure, 60 min/session, and 5 sessions/week	5.5	17
Karstoft et al. [79] (2013b; Denmark)	16	40.6	57.4 (5.7)	3.8 (3.0)	59.4	Interval-walking, consisting of 3min fast walking and 3min slow walking above or below the targeted of 70% of the peak energy-expenditure, 60 min/session, and 5 sessions/week	5.5	17
Sparks et al. [80] (2013a; Netherlands)	15	58.0	55.5 (5.0)	6.6 (6.0)	NR	Aerobic exercise, 50-80% O_{2peak} , and 150 min/week	8.0	39
Sparks et al. [80] (2013b; Netherlands)	21	55.7	55.4 (5.0)	8.8 (6.4)	NR	Nine exercises (bench press, seated row, shoulder press, lat pull down, leg press, leg extension, leg flexion, abdominal crunches, and back extensions), 10-12 repetitions/set, 2-3 sets, 45-50 min/session, and 3 sessions/week	3.5	39
Sparks et al. [80] (2013c; Netherlands)	15	58.0	60.5 (4.2)	6.1 (4.0)	NR	Aerobic training: aerobic exercise, 50-80% O_{2peak} , and 125 min/week; resistance training: 9 exercises (bench press, seated row, shoulder press, lat pull down, leg press, leg extension, leg flexion, abdominal crunches, and back extensions), 10-12 repetitions/set, 1 sets, 45-50 min/session and 2 sessions/week	7.8	39

Youngwanichsetha et al. [81] (2013; Thailand)	64	100	35.6 (5.3)	2.6 (1.2)	0.0	Tai chi qigong exercise, 50 min/session, and 3 sessions/week	3.0	12
Mitranun et al. [82] (2014a; Thailand)	22	63.6	61.4 (7.3)	20.9 (1.7)	100	Continuous aerobic training, 50-65% O_{2peak} , 30 min/session, and 3 sessions/week	5.1	12
Mitranun et al. [82] (2014b; Thailand)	22	63.6	61.1 (7.3)	20.3 (1.7)	100	Interval aerobic training, 50-85% O_{2peak} , 30 min/session, and 3 session/week	5.5	12
Yan et al. [83] (2014; United States)	41	0.0	53.5 (5.9)	NR	90.2	No reported type of exercise, 50-75% O_{2peak} , 45 min/session, and 3-5 sessions/week	5.7	12
Dede et al. [84] (2015; Turkey)	60	51.7	54.0 (7.9)	6.4 (4.9)	100	Aerobic exercise on a treadmill, 60-75% HR_{max} , 45 min/session, and 3 sessions/week	6.5	12
Lee et al. [85] (2015; Taiwan)	80	51.3	56.1 (8.5)	7.4 (5.7)	NR	Brisk walking, jogging or riding an exercise bike, 60-80% HR_{max} , 30 min/session, and 5 sessions/week	5.8	12
Park et al. [86] (2015; Republic of Korea)	37	54.1	70.7 (5.4)	NR	97.3	Circuit training: strengthening exercise, 6 exercises (leg extension, leg curl, seated rowing, seated chest press, abdominal crunch, and lower back extension), 65-75% 1RM, 10-12 repetitions/set, 1-3 sets; aerobic exercise, stationary bicycle and cross-walker, 9-14 RPE, 3-5 min/set, 1-3 sets, 40 min/session, and 3 sessions/week	4.0	12
Xiao et al. [87] (2015; China)	32	NR	65.5 (NR)	NR	NR	Tai chi ball, 60-120 min/session, and 3 sessions/week	3.0	13
Cassidy et al. [88] (2016; United Kingdom)	23	21.7	60.0 (8.2)	4.5 (2.6)	100	High intensity intermittent training: cycle ergometry, RPE 9-	4.8	12

						17, 4-5 min/set, 5 set; resistance training: 4 exercises using bands (face pull, horizontal push, horizontal pull, and 30° push), 1 min/set, 4 set, and 3 sessions/week		
Keshavarz et al. [89] (2016; Iran)	20	100	49.4 (6.2)	7.6 (4.3)	100	Rhythmic movements, 60% HR _{max} , 20-45 min/session, and 3 session/week	3.8	12
Tomas-Carus et al. [90] (2016; Portugal)	30	43.3	59.4 (6.3)	10.4 (7.0)	NR	Aerobic exercise: 60-65% HR _{max} , 25 min/session; resistance exercise: lower and upper limbs (using subject's own weight as resistance, light weight loads, or soft rubber bands), 15 min/session, and 3 sessions/week	4.0	12
Annibalini et al. [91] (2017; Italy)	16	0.0	58.5 (7.3)	9.0 (6.3)	100	Aerobic training: walking, 40-65% HRR, 60 min/session; resistance training: 4 exercises (horizontal leg press, lat pull-down, lat machine, and chest press), 40-60% 1RM, 12-20 repetitions/set, 2-4 sets, and 2-3 sessions/week	5.7	16
Botton et al. [92] (2018; Brazil)	26	42.3	69.6 (7.7)	11.0 (7.7)	100	Functional exercises (squat and steps up and down), additional load or step if <6 on OMNI scale, 10-15 repetitions/set, 2-3 sets; traditional exercises: 9 exercises (leg press, leg extension, leg curl, hip abduction, inclined bench press, low row, biceps curl, triceps, and crunch), 12-15 RM, 10-12	3.0	12

						repetitions/set, 2-3 sets, and 3 sessions/week		
Hsieh et al. [93] (2018; Taiwan)	30	63.3	71.2 (6.8)	12.5 (7.3)	NR	Eight exercises (chest press, shoulder press, biceps curl, hip abduction, standing hip flexion, leg press, standing calf raise, and abdominal crunch), 40-75% 1RM (or Borg scale 12-16), 8-12 repetitions/set, 3 sets, and 3 sessions/week	8.0	12
Stubbs et al. [94] (2019a; United States)	15	6.7	61.7 (5.4)	11.4 (6.7)	100	Treadmill walking, 71-90% O_{2peak} , 30-45 min/session, and 3 sessions/week	6.8	12
Stubbs et al. [94] (2019b; United States)	15	0.0	63.3 (5.4)	10.8 (8.1)	100	Leg extensions, 10 repetitions/set, 3-6 sets, and 3 sessions/week	2.8	12
Stubbs et al. [94] (2019c; United States)	15	6.7	62.5 (5.4)	9.9 (7.9)	100	Aerobic training: treadmill walking, 71-90% O_{2peak} , 30-45 min/session; resistance training: leg extensions, 10 repetitions/set, 3-6 sets, and 3 sessions/week	6.4	12

AT, anaerobic threshold; HR_{max} , maximum heart rate; HRR, heart rate reserve; LT, lactate threshold; MED, subjects taking medication; n, number of subjects; NR, not reported; RM, repetition maximum; T2DM, type 2 diabetes mellitus; O_{2max} , maximal oxygen uptake; VT, ventilation threshold

Table 2 Baseline and form of exercise data

Characteristic	
Female [n (%)]	1192 (52.4)
Age, years [mean (SD)]	55.2 (6.4)
BMI, kg/m ² [mean (SD)]	31.4 (5.0)
Duration of T2DM, years [mean (SD)]	7.2 (5.1)
Subjects with medication, % [mean (SD)]	88.1 (21.9)
Intensity of exercise, METs [mean (SD)]	5.1 (1.4)
Time of exercise, min/session [mean (SD)]	54 (17)
Frequency of exercise, sessions/week [mean (SD)]	3.2 (0.9)
Overall duration of exercise, weeks [mean (SD)]	21.5 (11.3)

BMI, body mass index; METs, metabolic equivalents; n, number of subjects; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Table 3 Results of sensitivity analyses of study on HbA_{1c}

Category	N (n)	Baseline (SD)	Pooled WMD (95% CI)	Q	I ² (%)
Mean age ≥40 years	47 (2331)	7.6 (1.3)	-0.5 (-0.6 to -0.4)	103.1 [‡]	37.0
Mean baseline HbA _{1c} ≥6.5%	47 (2370)	7.6 (1.3)	-0.5 (-0.6 to -0.4)	103.7 [‡]	37.4
Mean duration of T2DM ≥5.0 years	28 (1598)	7.5 (1.1)	-0.5 (-0.6 to -0.4)	73.2 [‡]	42.0
Mean baseline BMI ≥30 kg/m ²	29 (1701)	7.6 (1.2)	-0.4 (-0.5 to -0.3)	73.8 [‡]	39.9
Calculation of the WMD in BMI	35 (1730)	7.6 (1.3)	-0.4 (-0.5 to -0.3)	79.7 [‡]	38.3
Aerobic exercise alone	28 (1046)	7.7 (1.4)	-0.5 (-0.7 to -0.3)	45.7 [‡]	39.6
Did not include a high risk of bias	42 (2183)	7.5 (1.2)	-0.5 (-0.6 to -0.4)	98.6 [‡]	42.3

CI, confidence interval; HbA_{1c}, hemoglobin A1c; N, number of trials; n, number of subjects; SD, standard deviation; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference. [‡]Significant heterogeneity (P<0.05).

Table 4 The relationship between the WMD in HbA_{1c} and the intensity or time of exercise according to a meta-regression analysis and sensitivity analysis

Category	Intensity of exercise (METs)				Time of exercise (min/session)			
	MRC (95% CI)	R ² , %	Q	I ² , %	MRC (95% CI)	R ² , %	Q	I ² , %
Trials not limited	0.01 (-0.05 to 0.07)	41.5	81.7	24.4	0.01 (-0.34 to 0.36)	47.2	71.7	21.4
Mean age ≥40 years	0.01 (-0.06 to 0.07)	42.6	81.5	25.0	0.01 (-0.34 to 0.36)	44.4	71.6	22.2
Mean baseline HbA _{1c} ≥6.5%	0.01 (-0.05 to 0.07)	47.3	79.6	23.5	0.02 (-0.33 to 0.36)	50.9	69.9	20.5
Mean duration of T2DM ≥5.0 years	0.02 (-0.05 to 0.10)	30.2	56.9 [‡]	32.6	-0.22 (-0.76 to 0.33)	34.0	48.5 [‡]	29.1
Mean baseline BMI ≥30 kg/m ²	-0.02 (-0.09 to 0.05)	54.0	51.6	22.4	0.13 (-0.27 to 0.54)	54.0	46.1	21.0
Calculation of the WMD in BMI	0.02 (-0.05 to 0.08)	42.9	58.9	25.5	0.08 (-0.34 to 0.49)	44.9	51.9	22.6
Aerobic exercise alone	0.08 (-0.01 to 0.17)	62.9	30.7	18.3	-0.06 (-0.67 to 0.54)	33.9	32.9	26.5
Did not include a high risk of bias	0.01 (-0.05 to 0.08)	42.6	77.3 [‡]	29.0	0.00 (-0.36 to 0.36)	44.3	67.3	26.3

BMI, body mass index; CI, confidence interval; HbA_{1c}, hemoglobin A1c; METs, metabolic equivalents; MRC, meta-regression coefficient; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference. [‡]Significant heterogeneity (P<0.05).

Table 5 The relationship between the WMD in HbA_{1c} and the frequency or overall duration of exercise according to a meta-regression analysis and sensitivity analysis

Category	Frequency of exercise (sessions/week)				Overall duration of exercise (weeks)			
	MRC (95% CI)	R ² , %	Q	I ² , %	MRC (95% CI)	R ² , %	Q	I ² , %
Trials not limited	-0.04 (-0.16 to 0.08)	54.7	70.7	18.7	0.01 (0.002 to 0.016)	70.0	72.3	14.7
Mean age ≥40 years	-0.04 (-0.16 to 0.08)	53.7	70.5	19.5	0.01 (0.002 to 0.016)	68.5	72.3	15.4
Mean baseline HbA _{1c} ≥6.5%	-0.05 (-0.17 to 0.07)	60.0	68.6	17.5	0.01 (0.002 to 0.017)	74.5	69.8	13.1
Mean duration of T2DM ≥5.0 years	0.03 (-0.15 to 0.20)	32.1	49.8 [‡]	29.0	0.01 (0.002 to 0.018)	67.9	48.1	18.5
Mean baseline BMI ≥30 kg/m ²	-0.21 (-0.46 to 0.04)	62.0	51.3	17.4	0.01 (0.003 to 0.018)	72.0	47.2	17.0
Calculation of the WMD in BMI	-0.12 (-0.29 to 0.05)	63.3	48.7	16.3	0.01 (0.002 to 0.017)	69.4	51.4	15.2
Aerobic exercise alone	0.28 (-0.15 to 0.20)	35.5	33.0	26.6	0.01 (0.003 to 0.024)	99.9	27.3	0.0
Did not include a high risk of bias	-0.03 (-0.17 to 0.11)	50.8	66.7	24.0	0.01 (0.002 to 0.017)	70.5	67.2	17.0

BMI, body mass index; CI, confidence interval; HbA_{1c}, hemoglobin A1c; MRC, meta-regression coefficient; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference. [‡]Significant heterogeneity (P<0.05).

Figures

Figure 1

PRISMA flow diagram regarding article selection for meta-analysis. HbA_{1c}, hemoglobin A1c; RCT, randomized controlled trial; SD, standard deviation; SEM, standard error of mean.

Figure 2

Baseline mean HbA1c and forest plot for the WMD in the HbA1c. Each study is presented by black squares (WMD) and width (95% CI). The pooled WMD is represented by black rhombuses and widths (95% CI). HbA1c, hemoglobin A1c; WMD, weighted mean difference.

Supplementary Files

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