BMJ Open Diabetes Research & Care

Effect of resistance training on HbA1c in adults with type 2 diabetes mellitus and the moderating effect of changes in muscular strength: a systematic review and meta-analysis

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To cite: Jansson AK, Chan LX, Lubans DR, *et al*. Effect of resistance training on HbA1c in adults with type 2 diabetes mellitus and the moderating effect of changes in muscular strength: a systematic review and meta-analysis. *BMJ Open Diab Res Care* 2022;**10**:e002595. doi:10.1136/bmjdrc-2021-002595

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2021-002595).

Received 9 September 2021
Accepted 11 February 2022

Check for updates

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ABSTRACT

Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of diabetes cases globally. Regular physical activity is regarded as one of the key components in T2DM management. Aerobic exercise was traditionally recommended; however, there is a growing body of research examining the independent effect of resistance training (RT) on glycemic control. This systematic review and meta-analysis aimed to conduct an update on the effects of RT on glycosylated hemoglobin (HbA1c) in adults with T2DM and examine the moderating effects of training effect (ie, muscular strength improvements), risk of bias and intervention duration. Peer-reviewed articles published in English were searched across MEDLINE, Embase, CINAHL, Scopus and SPORTDiscus from database inception until January 19, 2021. Each online database was systematically searched for randomized controlled trials reporting on the effects of RT on HbA1c in individuals with T2DM. Twenty studies (n=1172) were included in the meta-analysis. RT significantly reduced HbA1c compared with controls (weighted mean difference=−0.39, 95% CI −0.60 to −0.18, p<0.001, I^2=69.20). Training effect significantly (p<0.05) moderated the results, with larger improvements in muscular strength leading to greater reductions in HbA1c (β=−0.99, CI −1.97 to −0.01). Intervention duration and risk of bias did not significantly moderate the effects. As a secondary analysis, this study found no significant differences in HbA1c when comparing RT and aerobic training (p=0.42). This study demonstrates that RT is an effective strategy to decrease HbA1c in individuals with T2DM. Importantly, RT interventions that had a larger training effect appeared more effective in reducing HbA1c, compared with interventions producing medium and small effects.

PROSPERO registration number CRD42020134046.

INTRODUCTION

The global prevalence of diabetes mellitus for adults aged 20–79 is currently estimated to be 9.3% (463 million) and is projected to increase to 10.9% (700 million) by 2045.[1] The development and urbanization of the global economy have contributed significantly to the rise in diabetes cases; the driving key factors include an overall decrease in physical activity, greater consumption of imbalanced diet and an aging population.[2]

Type 2 diabetes mellitus (T2DM) accounts for the vast majority (85%–90%) of diabetes cases globally.[1] In many cases, T2DM is largely preventable[3] and can often be managed through lifestyle modifications such as physical activity.[4] Traditionally, aerobic exercise was considered the gold standard for the management of T2DM.[5] However, in the past decade, there has been an increase in the number of studies demonstrating the independent benefits of resistance training (RT) in glycemic control.[6–8] While aerobic exercise (alone or in combination with RT) can effectively improve glycemic control, it often requires individuals to perform activities in longer bouts, which can be challenging or even painful for some subpopulations (ie, overweight or obese, knee or hip osteoarthritis).[9–11] The position statement from the American Diabetes Association recommends adults with T2DM should engage in a minimum of 150 min/week of preferably both aerobic exercise and RT and not allow more than 2 days to elapse between exercise sessions.[12]

Glycosylated hemoglobin (HbA1c) is a biomarker that is commonly used to diagnose diabetes mellitus, monitor glycemic control and guide therapy in individuals with T2DM.[13] Recent reviews have highlighted the benefits of RT on HbA1c in individuals with T2DM,[14–17] with meta-analysis effect sizes ranging from −0.34[18] to −0.45.[16] The most recent review and meta-analysis, conducted by Liu and colleagues,[16] investigated the impact of high versus low-to-moderate RT intensity (ie, measured by one repetition maximum) on glycemic control in individuals with T2DM in 20 studies up to September 2018. The results indicated that high-intensity RT (weighted mean difference (WMD)=−0.61) was more effective than low-to-moderate-intensity RT (WMD=−0.23) in reducing HbA1c.[16] However, four studies in Liu and colleagues'[16] review and meta-analysis were not randomized controlled trials (RCTs) (eg, quasi-experimental designs[19–22]) and one study was unclear whether the researchers used an RCT design.[23] In addition, one of their included studies included a dietary component (high protein vs isocaloric diet).[24] Since the publication of this review and meta-analysis, four new RCTs have been published in this field.[25–28] Another review and meta-analysis (n=23 studies; search dates from January 1966 to August 2014) aimed to identify the ideal RT program to improve glycemic control in patients with T2DM and the characteristics of patients that will benefit from RT.[18] The study found larger effect sizes in studies with programs of multiple sets (≥21 vs <21), higher baseline HbA1c (ie, ≥7.5%) and where participants had T2DM for <6 years.[18] A smaller effect size was found in studies where participants had a high mean baseline body mass index (≥32). The study also analyzed several other factors (eg, total sets per week, frequency, intensity, participant age, intervention period), none of which significantly moderated the effect of RT on HbA1c.[18]

It has been well established that RT interventions to date vary in regard to exercise prescriptions (eg, exercise intensity, duration, number of sets, type of exercises);[16 18] however, it remains unclear to what degree of effectiveness an RT program (ie, whether participants improve their muscular strength as a result of the program) has on HbA1c in people with T2DM. To our knowledge, no study to date has measured the overall effect of change in strength of an RT program and if this moderates the effect on HbA1c. In addition, there is large variability between studies examining the effect of RT on HbA1c in terms of intervention duration, ranging from 8 weeks[29 30] to 14 months.[31] Although Ishiguro and colleagues[18] found that intervention period (≥12 weeks vs <12 weeks) did not significantly moderate the effect of RT on HbA1c, their meta-analysis included studies that were not RCT and they did not include a rationale of how they dichotomized the intervention period in their methods. Moreover, no meta-analysis to date has investigated whether the quality of studies (ie, results from risk of bias assessments) moderates the effect of RT on HbA1c.

As such, the objectives of our systematic review and meta-analysis investigating the effect of RT on glycemic control in adults with T2DM were to (1) conduct an update of the RCT literature on the effects of RT on HbA1c; (2) examine the moderating effects of muscular strength improvements (hereafter referred to as training effect), risk of bias and intervention duration; and (3) examine the effect of RT versus aerobic training as a secondary meta-analysis.

METHODS

Protocol and registration

Our systematic review and meta-analysis was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[32] and was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42020134046).

Data sources and searches

We searched the following electronic databases from inception to January 19, 2021 using comprehensive search strings (see online supplemental table S1): MEDLINE, Embase, CINAHL, Scopus and SPORTDiscus. Identified records within each of the databases were downloaded as an Research Information Systems (RIS) file and uploaded to EndNote V.X8. Within EndNote V.X8, uploaded articles were de-duplicated using both automatic and manual processes. Two reviewers (AKJ and LXC) screened the remaining unique articles and identified those that met the eligibility criteria based on title and abstract. Each article was classified into three categories, 'relevant', 'potentially relevant' and 'irrelevant', in EndNote. Full texts were retrieved from the 'relevant' and 'potentially relevant' articles and each was independently assessed against the inclusion criteria by the reviewers (AKJ and LXC). Any disagreements between the two reviewers (AKJ and LXC) were resolved by a third reviewer (RCP). Reference lists from the included articles were searched and forward citation tracking was conducted to identify any articles that may have been missed.

Study selection

Studies were included if they (1) reported on the efficacy or effectiveness of RT on HbA1c in people with T2DM; (2) included at least one intervention group that was prescribed RT only; (3) used an RCT design with any comparator (eg, control, wait-list control, 'sham' or comparison group); (4) included adults aged 18 years and above; and (5) were published in English. Studies were excluded if they (1) did not measure HbA1c as an outcome; (2) used a non-RCT design (eg, quasi-experimental design); and (3) if the intervention group was not RT only (eg, RT was combined and aerobic and/or diet components). Of note, the study had to be clear that it employed an RCT design (eg, either explicitly states it or refers to random allocation or assignment of participants).

Data extraction and quality assessment

Two reviewers (AKJ and LXC) independently extracted the following information from each eligible study: first author, year of publication, study location, sample size, age and sex of participants, control or comparison group, intervention duration, frequency and duration of each exercise session, number of exercises per session, exercise intensity, setting, study retention, study adherence, upper and lower body muscular fitness measure and outcome (within and between group), and HbA1c outcome (within and between group).

Risk of bias was assessed using the revised Cochrane risk of bias tool for RCTs.[33] Two reviewers (AKJ and LXC) independently scored each of the eligible studies and any disagreements were resolved by a third reviewer (RCP). For each study, risk of bias was judged based on five domains: (1) arising from the randomization process; (2) due to deviations from the intended interventions (effect of assignment to intervention); (3) due to missing outcome data; (4) in measurement of the outcome; and (5) in selection of the reported results. Each domain was classified as 'low risk', 'some concern' or 'high risk'. For each study, the overall risk of bias was classified as 'low' (ie, if all domains were judged as low risk of bias), 'some concern' (ie, if some concerns regarding risk of bias were identified in one to four domains, but no domains were classified as 'high' risk of bias) or 'high' (ie, if at least one domain was judged as high risk of bias). Inter-rater reliability between the two reviewers was calculated using Cohen's k.

Data synthesis and analysis

All statistical analyses were conducted using the Comprehensive Meta-Analysis software (V.3 for Windows, Biostat, Englewood, New Jersey, USA). Analyses were regarded as statistically significant if $p<0.05$. Meta-analyses were performed to determine the effect of RT versus 'control', and RT versus aerobic training, on HbA1c in individuals with T2DM. For RT versus 'control', the RT intervention was compared with the control group of each study (ie, control, wait-list control or 'sham' exercise (eg, stretching, very light aerobic) group was included). For RT versus aerobic training, the RT intervention was compared with the aerobic training group of each study. Of note, the secondary analysis (RT vs aerobic training) was not included in the PROSPERO registration protocol; however, it was included as a retrospective additional exploratory analysis.

A random effects meta-analysis was conducted using post-test mean and SD for each study. WMD was used to determine the effect of RT on HbA1c when compared with controls or aerobic training. While there are several ways to calculate WMD, according to Chandler and colleagues,[34] using postintervention values will be the same as the differences in mean change scores. This is based on the assumption that mean differences as a result of baseline values address the same intervention effect as analyses based on postintervention values.[34] Heterogeneity was measured using Cochrane's Q statistic and I^2 values, where values <25%, 50% and 75% are indicative of low, moderate and high levels of heterogeneity, respectively.[35] The Rosenthal's classic fail-safe N was used to assess publication bias by providing an estimated number of studies required (with a mean effect of zero) before the overall effect no longer reached statistical significance.[36] The Duval and Tweedie's trim and fill test was used to assess for publication bias.[37]

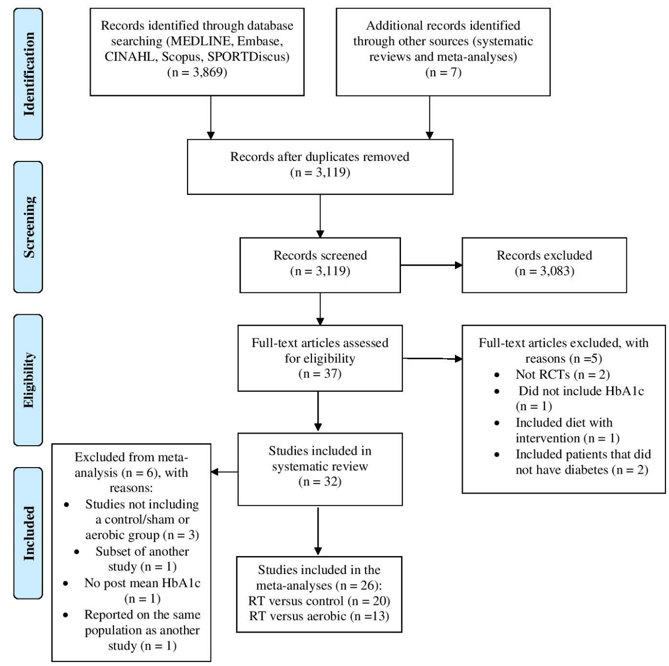

Figure 1 PRISMA diagram for the literature search. From Moher *et al*.[68] HbA1c, glycosylated hemoglobin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; RT, resistance training.

Subgroup moderator analyses were performed if I^2 values demonstrated at least moderate heterogeneity. Mixed model meta-regression analyses investigating the moderating role of (1) risk of bias (categorical), (2) intervention duration (ie, number of weeks) and (3) training effect (ie, changes in muscular fitness) were conducted. Risk of bias was dichotomized as 'high' and 'some concern' (ie, 'low' risk of bias was not included in the analysis as no included studies scored 'low'). To determine training effect, only studies reporting muscular strength as an outcome were included. For each study, all muscular strength data (ie, upper and/or lower body muscular strength outcomes) were converted to standardized mean difference (SMD). In the eight studies that included multiple muscular strength outcomes, the average value of all calculated SMDs was used in the analysis.

RESULTS

Study selection

A PRISMA diagram for the literature search is presented in figure 1. A total of 3868 citations were retrieved from database searches and an additional 7 were identified through forward citation tracking. After title/abstract and full-text screening, a total of 30 independent studies[6–8 25–31 38–59] published between 1998 and 2020 were included in the systematic review. Of these studies, 20 qualified for inclusion in the meta-analysis.

Quality assessment

The risk of bias of the included studies is presented in online supplemental table S2. Based on the risk of bias rating, 16 of 30 (53.3%) studies were regarded as having 'some concern' and 14 of 30 (46.7%) were rated as having a high risk of bias. The inter-rater agreement following independent full-text assessment for all 660 items was considered 'high' (22 questions × 30 studies; k=0.93).[60]

Study characteristics

The characteristics of each study are summarized in online supplemental tables S3 and S4. The 30 included studies were conducted in 19 different countries (Australia, Austria, Brazil, Canada, China, Germany, Greece, India, Italy, Iran, Japan, New Zealand, Norway, Singapore, South Korea, Spain, Sri Lanka, Taiwan and USA). A total of 26 studies with 1489 total participants were included in the meta-analysis. The duration of the interventions ranged from 8 weeks[29 30] to 14 months.[31] Most studies included both male and female participants, except for two studies which included male participants only[39 46] and three studies that only included female participants.[26 59 61] The number of participants in each study ranged from 18[39] to 318.[56] More than half (18 of 30) of the studies included a control group, three used a sham exercise group and nine studies used a comparison group (eg, aerobic, combined aerobic and RT, isometric or home-based RT group). Participant retention was reported in 22 of 30 trials, ranging from 69.2%[48] to 100%.[57 58] Study adherence was reported in 20 of 30 trials; however, it varied in how it was reported (see online supplemental table S3). Of the 30 studies, 7 studies[26 28 43 49 50 55 61] did not include supervision during the intervention from an exercise specialist (eg, exercise instructors or physical trainers). However, not all studies which reported to include supervision specified who carried out the supervision.

RT exercise prescription

The RT exercise prescriptions in each study are summarized in online supplemental table S3 and figure S1. The number of exercises included in each workout ranged from 4[25] to 12.[39] Most studies used weight machines or free weights, with the exception of three studies[28 53 59] which used elastic bands. To determine the intensity of the exercises included in the workouts, 18 studies used 1-repetition maximum and 1 study used 10-repetition maximum. Most studies used a workout frequency of either three,[6 8 26 29 38–54] two to three,[7 30 55 56] or two[27 31 57 58] sessions per week. One study[28] encouraged daily engagement in RT using elastic bands, another study[59] used a frequency of five sessions per week, and one study[25] had their participants work out once per week.

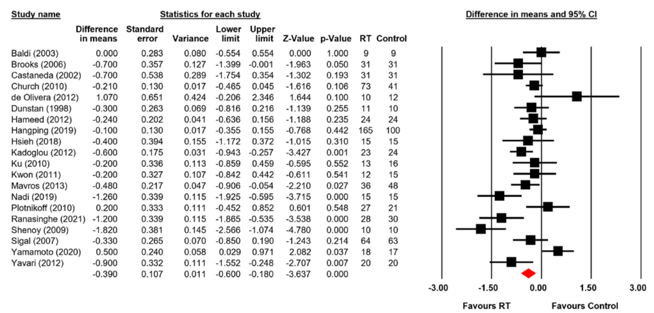

Figure 2 Forest plot of the effect of RT versus control on HbA1c. HbA1c, glycosylated hemoglobin; RT, resistance training.

Meta-analysis

We found a small significant effect of RT on HbA1c relative to control (WMD=−0.390, 95% CI −0.60 to −0.18, I^2=69.20, p<0.001), with moderate-to-high heterogeneity (I^2=69.198). The results of the meta-analysis and the forest plot are outlined in table 1 and figure 2, respectively. Meta-regression analyses using a mixed effects model revealed that training effect had a significant effect on HbA1c, with larger improvements in muscular fitness leading to greater reductions in HbA1c (β=−0.99, CI −1.97 to −0.01, p=0.0470). Study risk of bias (β=0.03, CI −0.41 to 0.48, p=0.878) and duration (β=0.00, CI −0.00 to 0.02, p=0.515) were not significant moderators of effects. The fail-safe N suggests that 177 trials with no effect would be needed before the pooled effect would no longer be statistically significant. Trim and fill analysis suggests that no studies were missing from the right side of the funnel plot (see online supplemental figure S3 and S4). We found no statistically significant effect on HbA1c when comparing RT with aerobic training (p=0.42; see table 1 and online supplemental figure S2).

DISCUSSION

This systematic review and meta-analysis was undertaken to provide an update of the effect of RT on HbA1c in adults with T2DM and investigate the moderating effects of training effect, risk of bias and intervention duration. To our knowledge, this is the first meta-analysis to

Table 1 Meta-analyses of the effect of resistance training on HbA1c

	Effect size and precision					Heterogeneity				
Outcome	Studies	n	Estimate	95% CI	P value	Q value	df (Q)	P value	I^2	Fail-safe N
HbA1c (RT vs CON)	20	1172	−0.390	−0.600 to −0.180	<0.001	61.684	19	<0.001	69.198	177
HbA1c (RT vs AE)	13	640	0.077	−0.110 to 0.264	0.419					

AE, aerobic exercise; CON, control; HbA1c, glycosylated hemoglobin; RT, resistance training.

 BMJ Open Diab Res Care 2022;10:e002595. doi:10.1136/bmjdrc-2021-002595

examine if training effect and risk of bias moderate the effect of RT on HbA1c.

Consistent with previous reviews (eg, refs 16–18 62), our meta-analysis confirmed that RT reduces HbA1c (WMD=−0.39%) in people with T2DM. The effect observed in our review is similar to previous meta-analyses by Ishiguro and colleagues[18] (ie, −0.34%) and Liu and colleagues[16] (ie, −0.45%). The slight differences in values may be due to the inclusion of new studies and the exclusion of seven studies that were included in Liu and colleagues' meta-analysis. The reasons for these studies being excluded from the current study were that four were not RCTs;[19–22] one study was unclear whether they used an RCT design;[23] one paper[57] appeared to report on the same population as another included study[58] (we only included one of the two papers[58]); and one study used a dietary component.[24] In addition, our meta-analysis included seven studies[25–28 41 45 59] not included in Liu and colleagues' study, four of which were published after their publication date.[25–28]

Results of the moderator analyses suggest the more participants improved in their muscular strength outcomes (ie, larger training effect), the greater benefit it yielded on HbA1c. These findings contradict a recent study using an RCT design which investigated whether there is a dose–response relationship between exercise adherence and glycemic control in adults (n=185) with T2DM.[63] The study reported a dosage–response relationship for aerobic and combined aerobic and RT, but not for RT alone.[63] Interestingly, increases in muscular strength have been inversely associated with mortality in several other clinical populations suffering from chronic conditions (ie, cancer, chronic obstructive pulmonary disease, renal disease, and metabolic and vascular diseases).[64] It should also be noted that only 12 studies (60%) included in our meta-analysis included muscular strength as an outcome, and of these 9 were included in the final analysis investigating the moderating effect of training effect. As such, future studies investigating the effect of RT on HbA1c should assess muscular strength and include it as an outcome. While any regular participation in RT may be beneficial, these results suggest that to maximize training benefit on HbA1c, RT programs for this subpopulation should be designed to elicit larger gains in strength. In addition, the inclusion of muscular strength as an outcome will allow future meta-analyses to better establish this finding. Given that most of these studies were supervised, the generalization of results to unsupervised RT programs should be done with caution.

No moderating effect was reported for risk of bias. While half of the studies included in the moderator analysis were scored as 'high risk' and the other half as having 'some concern', no included studies were scored as having 'low risk' of bias. As such, the generalization of results to 'low risk' studies should be done with caution. Future studies should aim for study designs that score 'low' on a risk of bias assessment (eg, include intention-to-treat, concealment, blinding assessors and suitable comparison groups).

Intervention duration did not emerge as a moderator of effects. We found no significant difference in the effects of RT on HbA1c in studies ranging from 8 to 52 weeks. These results are similar to findings from Ishiguro and colleagues,[18] who also found that intervention duration did not significantly moderate the effect of RT on HbA1c. It should be noted that Ishiguro and colleagues[18] dichotomized the intervention duration (ie, ≥12 weeks vs <12 weeks) as opposed to using meta-regression. It may be that intervention duration is not a determining factor in reducing HbA1c (ie, shorter vs longer programs have similar effects). However, it should be noted that this may not be generalized to other important measures of glycemic control and insulin resistance (eg, fasting blood glucose, plasma insulin, homeostasis model assessment - insulin resistance). In addition, ongoing weekly engagement in physical activity (including RT) is recommended as part of long-term treatment and management of T2DM according to the American Diabetes Association.[12]

In the secondary meta-analysis on RT versus aerobic training, we found no statistically significant difference between the two methods of training on HbA1c (p=0.42). This contradicts two previous meta-analyses which found that aerobic training resulted in a greater effect on HbA1c compared with RT.[14] The most recent meta-analysis by Yang and colleagues[15] included interventions that compared RT versus aerobic training on HbA1c. While the authors found that aerobic training significantly reduced HbA1c compared with RT, they argued that the difference was not clinically meaningful.[15] The contrasting results between Yang and colleagues'[15] review and the current may be due to several factors. One potential factor is the use of post mean and SD in the current review and change scores in their study, and as such some studies were classed differently (ie, favoring RT vs favoring aerobic training). For example, one study was classified as favoring aerobic training in the present review and neutral in Yang and colleagues' study.[48] Future studies should continue to include RT and aerobic training as a comparator.

Only 50% of the included studies in the meta-analysis (ie, RT vs control) reported on study adherence (62.5% of studies in the systematic review). This is concerning given reduced adherence can decrease intervention effectiveness.[65] Therefore, it is recommended that future studies include adequate methods of measuring and reporting intervention adherence. With the exception of one study,[25] all studies met the RT recommendations in terms of frequency per week (ie, minimum twice a week).[12] However, similar to what has been found in previous reviews, there was variability in the RT prescriptions between studies (ie, type of exercises, duration of exercise sessions, exercise intensity and number of sets and repetitions per workout; also see online supplemental figure S1).[16 18] The studies also varied in terms of supervision, with only 25% of studies (5 of 20) in the meta-analysis reporting no supervision. It is highly likely that participants who are supervised are likely to perform better in trials and hence have better glycemic control.[66 67] Therefore, there is a need for more unsupervised RT interventions, particularly for programs that aim to be implemented at scale to reach a larger proportion of the population.

Strengths and limitations

The primary strength of our review was the inclusion of training effect as a moderator for HbA1c as this has not been previously investigated. Further, only studies which clearly used an RCT design were included in this systematic review and meta-analysis. Limitations of this body of literature include the difficulty in generalizing the contribution of the training effect given the relatively small number of studies included in the moderator analysis. In addition, due to the lack of studies reporting on changes in lean tissue, the present study did not include measures of hypertrophy (ie, changes in lean tissue). As such, it is unclear whether the training effect is a function of increased muscle mass. Future studies are recommended to investigate the impact of hypertrophy on HbA1c. It should be noted that while this study investigated the impact of RT on HbA1c only, there are several other important measures of glycemic control and insulin resistance (eg, fasting blood glucose, plasma insulin, homeostasis model assessment - insulin resistance). There is also potential for the results of this study to be affected by multiple biases. For instance, the majority of studies used per-protocol analyses rather than intention-to-treat analyses. In addition, it may be that studies which fail to reach statistical and/or clinical significance may not be published, either due to authors' choice of not attempting to publish or journals not accepting the article for publication. As such, the findings from our meta-analysis should be interpreted with caution.

CONCLUSION

This systematic review and meta-analysis provides further evidence that RT is an effective strategy in reducing HbA1c in adults with T2DM. Importantly, our review found that RT interventions that have a larger effect on muscular strength are more effective in reducing HbA1c than interventions producing a medium or small effect. It is therefore recommended that future studies targeting RT and its effect on HbA1c measure muscular strength as an outcome.

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Contributors RCP, AKJ, LXC and MJD conceptualized the research aims and designed the research protocol. AKJ and LXC contributed to data collection and writing the first draft of the manuscript. DRL performed the meta-analyses and AKJ and DRL contributed to data interpretation. RCP, MJD and DRL contributed to the critical revision of the manuscript. All authors read and approved the final manuscript. RCP is the guarantor of the work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding MJD is supported by a Career Development Fellowship (APP1141606) from the National Health and Medical Research Council. DRL is supported by a Senior Research Fellowship (grant number: APP1154507) from the National Health and Medical Research Council of Australia.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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