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Weight loss effects of circuit training interventions: A systematic review and meta-analysis

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Summary

This meta-analysis aimed to assess the weight loss effects of circuit training interventions in adults. A computerized search was conducted using the Cochrane Central Register of Controlled Trials, PubMed, and EMBASE online databases. The analysis was restricted to randomized controlled trials that evaluated the effects of circuit training interventions on body weight and body mass index in adults aged 18 years or older. Meta-analyses were conducted using the random-effect model to estimate the weighted mean difference (WMD) with 95% confidence interval (CI). Nine randomized controlled trials (837 participants) were included. Significant intervention effects were identified for body weight (WMD = -3.81 kg, 95% CI -5.60 to -2.02) and body mass index (WMD = -1.77 kg/m^2 , 95% CI -2.49 to -1.04). Subgroup analysis by body mass index status showed that the intervention effect was significant only in participants with obesity or overweight (obesity: WMD = -5.15 kg, 95% CI -8.81 to -1.50 and overweight: WMD = -3.89 kg, 95% CI -7.00 to -0.77, respectively) but not in those with normal weight. Current evidence suggests that circuit training effectively reduces body weight and body mass index in adults with overweight and obesity.

KEYWORDS

circuit training, exercise, weight, obesity

1 | INTRODUCTION

The global prevalence of obesity has considerably increased in recent decades. Globally, in 2016, 13% of adults aged 18 years or older (11% in men; 15% in women) had obesity, and 39% of adults aged 18 years or older (39% in men; 40% in women) were overweight.^{1,2} The main cause of overweight and obesity is the energy imbalance between calorie intake and calorie consumption. Globally, the intake of energy-dense or high-fat foods has increased. Moreover, physical inactivity has increased owing to the increase in sedentary work, changes in the means of transportation, and increased urbanization.²

Cardiovascular diseases, type 2 diabetes, osteoarthritis, and some cancers are strongly associated with elevated body mass index (BMI).^{3,4} Overweight and obesity as well as noncommunicable diseases

associated with them can be largely prevented.^{3,5} The most basic way to manage and prevent overweight and obesity is to choose healthy foods and ensure regular physical activity (PA).^{5,6} Physical inactivity is one of the risk factors for coronary heart disease, type 2 diabetes, and some cancers.⁷ Globally, one-fourth to one-third of adults are physically inactive.^{8,9} Adults with overweight and obesity require moderate-intensity PA for at least 150 minutes per week to maintain and improve health and over 250 minutes per week to lose body weight (BW) significantly.^{10,11} However, a longer exercise time can be a barrier to participation in exercise programs, because a common reason for nonparticipation in PA programs is the lack of time.^{12,13}

In 1953, Morgan and Anderson developed circuit training.¹⁴ The term "circuit" refers to a series of carefully selected exercises arranged in sequence. The program can be conducted with calisthenics, elastic

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resistance, handheld weights, exercise machines, or any combination. During circuit training, each participant performs 8 to 20 repetitions of an exercise at each station in less than a minute, moving from one station to another with little or no break, which results in a short exercise session time. Circuit training can improve muscular strength and cardiorespiratory function.¹⁵⁻¹⁷ The metabolic cost of circuit training is higher than that of general resistance training.¹⁸ In some studies, it is reported that the metabolic cost of circuit training is no different from or even higher than that of a combination of general aerobic and resistance training.^{15,19} Due to the high metabolic cost of circuit training, taking a little less time can achieve the goals required in the guidelines (450-750 MET).¹⁰ In addition, circuit training improves body weight as well as body composition,^{16,20,21} bone metabolism,²² cardiometabolic risk factors,²³⁻²⁵ and motivation to exercise.¹⁷ Therefore, circuit training that can reduce cardiovascular risk as well as BW through short-time exercise is suitable for individuals with overweight and obesity. However, there is no meta-analysis evaluating the effects of circuit training on BW or BMI in adults. We aimed to conduct a systematic review and meta-analysis to evaluate the influence of circuit training on BW or BMI in adults based on a comparison with controls without exercise intervention.

2 | **METHODS**

Our meta-analysis was performed based on Cochrane²⁶ and the Centre for Reviews and Dissemination guidelines²⁷ and was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.²⁸

2.1 Literature search

A systematic search of the effects of circuit training on BW was conducted. Articles published before December 31, 2018 were retrieved using searches of the Cochrane Central Register of Controlled Trials, PubMed, and EMBASE online databases. The search terms used were (circuit*) AND (training OR exercise) AND (obesity OR obese OR weight). The search was limited to randomized controlled trials (RCTs) and English articles, but there were no restrictions on the calendar date. The reference lists of retrieved articles were also reviewed. Information that was unavailable in the selected articles was obtained by contacting the relevant authors.

The two authors (Y-GS and H-MN) independently reviewed the titles and abstracts after removal of duplicates. Discrepancies were resolved either by discussions between the authors or by asking for comments from a third author (SYK). The two authors who reviewed the titles and abstracts then independently analysed the full text of the remaining articles to determine the final inclusion.

2.2 **Eligibility criteria**

We selected the trials to be included in the meta-analysis using the following criteria: (1) The trial was a human RCT written in English,

and the full text was available; (2) participants were aged 18 years or older; (3) the intervention group underwent circuit training intervention alone or along with other lifestyle interventions; (4) the control group did not undergo structured exercise or behavioural modification to increase PA; and the trial included (5) assessment of primary outcomes: BW and BMI and (6) a report of mean values of changes from baseline (or report of postintervention values if not available) with standard deviation (SD) (or data suitable to calculate these parameters: 95% confidence interval [CI] or standard error). RCTs with a comorbidity or covariate unrelated to obesity (eg, cancer, pregnancy, etc) and uncontrolled, cross-sectional, and animal studies were excluded. The selection criteria did not limit the frequency, intensity, volume, and modality of circuit training.

2.3 Risk of bias assessment

We used the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias of the RCTs.²⁶ The sources of bias such as reporting bias (selective reporting), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and selection bias (allocation concealment and random sequence generation) were evaluated. Each domain was assessed in terms of the methodological quality with high or low risk of bias. If data were insufficient to make a reasonable judgment, the domain was described as "unclear risk of bias."

The risk of bias was reported graphically using Review Manager program (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Data extraction 2.4

Data were extracted by the two authors (Y-GS and H-MN) independently in the selected RCTs. From each RCT, the following data were extracted: year of publication, the country where the RCT was performed, name of the first author, participant-related variables (sex, age, BW, and BMI), sample size, study duration, intervention-related variables (type, period, intensity, and frequency), and treatment effects (mean difference and SD of two time point values or mean and SD of postintervention values). Primary outcomes were BW and BMI.

2.5 Data synthesis

The dataset was constructed with the mean differences and SDs between preintervention and postintervention values. When the mean difference and SD were not published, the mean and SD of the postintervention value were used. In one meta-analysis, it is possible to combine both the mean differences and the means of postintervention values, assuming that the relative effects assessed by both the mean differences and the means of postintervention values are the same.²⁶ The final results were calculated and aggregated by one author (Y-GS).

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2.6 | Meta-analysis

For the meta-analysis, we used Stata/MP, version 14.0 (StataCorp, College Station, TX, USA). The weighted mean differences (WMDs) of BW and BMI in the intervention and control groups were calculated. We used Cochran's Q test and l^2 test to test the heterogeneity between study results. For interpretation, I^2 values of 75, 50, and 25 were considered to represent high, moderate, and low heterogeneity, respectively.²⁹ To consider heterogeneity, the DerSimonian and Laird³⁰ random-effect model to estimate WMD with 95% CI was used. The effect size and 95% CI of each study were expressed as forest plots. We checked the symmetry of the funnel plots to evaluate the presence of publication bias. In addition, we used Egger regression tests to evaluate small study effects.³¹ The heterogeneity between studies was analysed using meta-regression. We used covariates that may influence the association between circuit training and BW: BMI status (obesity vs overweight vs normal weight), intervention type (circuit training alone intervention vs circuit training combined with other lifestyle interventions), age (≥50 vs <50 years), intervention period $(\geq 6 \text{ vs } < 6 \text{ months})$, and sex (men vs women vs men and women). The cut-off for age (50 years) was based on age at natural

menopause^{32,33} and andropause.³⁴ The cut-off for the intervention period (6 months) was based on prior reviews.^{35,36} Statistical significance level was set at 5%. For heterogeneity, the threshold *P* value of .1 estimated by Cochran's *Q* test was considered statistically significant.²⁹

3 | RESULTS

3.1 | Study selection and characteristics

In total, 9 of the initial 264 studies searched in the database were selected according to the inclusion criteria, and they contained sufficient data for meta-analysis (Figure 1). The meta-analysis included 11 datasets (one study had three BMI statuses²¹: obesity, overweight, and normal weight). A total of 425 participants were included in the intervention group (range of the number of participants, 7-256) and 412 (range of the number of participants, 7-250) in the control group. All participants were aged 18 years or older. Of the included studies, three studies evaluated only men,^{23,37,38} four studies evaluated only women,^{20,21,24,39} and the other two studies did not differentiate

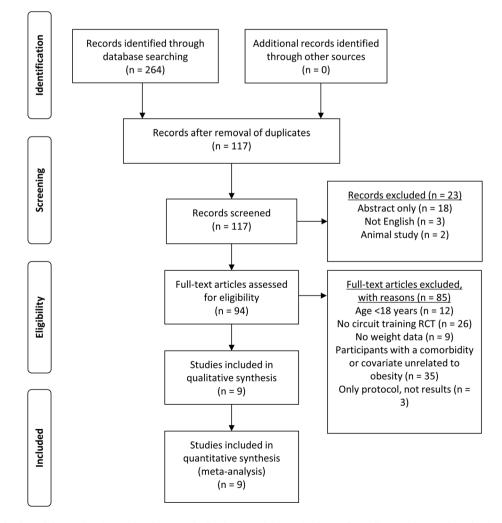


FIGURE 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection. RCT, randomized controlled trial

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between the sex of the participants.^{40,41} Seven out of nine studies had follow-up periods of 12 (44.4%) and 8 weeks (33.3%). Other two studies had follow-up period 40 weeks or more. Circuit training was conducted thrice a week in seven studies (77.8%). In another study, circuit training was conducted twice a week. In the other study, the frequency of circuit training was not reported. According to the studies included in our meta-analysis, it seems to be beneficial for health to perform circuit training twice or thrice a week for at least 8 weeks. The average attendance rate of the participants in the studies was 92.7%. The characteristics of the selected RCTs are summarized in Table 1

3.2 Risk of bias

The blinding of the participants was not possible because of the characteristic of the intervention. Therefore, performance bias was not considered for the risk of bias assessment. There was some risk of bias within individual studies (Figure 2). Only two studies have explicitly described how to generate its randomization sequence. One study did not conceal allocation until after randomization. Only one study described the blinding of outcome assessment. Three studies did not have sufficient data to judge the attrition bias. Five studies did not have sufficient information to judge the study protocol. The risk of bias assessment is reported graphically in Figure S1.

3.3 Synthesis of results

To evaluate the overall intervention effect, we calculated the mean difference in BW for each study. Figure 2 shows the effect size for each study and the overall effect size. The intervention showed a significant effect on BW (WMD = -3.81 kg, 95% CI -5.60 to -2.02). Based on the categorization of intervention type, age and sex appeared to have low or high heterogeneity. For all other categorizations, heterogeneity was low to moderate. We have also calculated the mean difference for BMI to determine the overall intervention effect, and significant intervention effects were identified for BMI $(WMD = -1.77 \text{ kg/m}^2, 95\% \text{ Cl} -2.49 \text{ to} -1.04)$ (Figure S2).

3.4 | Publication bias

To verify the possible publication bias, we plotted the effect size against the standard error to generate the funnel plot (Figure 3). There was no statistically significant publication bias according to Egger's test (p = .309).

3.5 Meta-regression

The results of the simple meta-regression analysis were not significant for any categorical covariate. A subgroup analysis by BMI status showed that the intervention effect was significant only when the participants' weight was obesity or overweight but not when they were normal weight (obesity: WMD = -5.15 kg, 95% Cl -8.81 to -1.50;

overweight: WMD = -3.89 kg, 95% CI -7.00 to -0.77; and normal weight: WMD = -2.38 kg, 95% CI -7.07 to 2.32, respectively). The intervention effect was statistically significant only in the "circuit training alone" intervention rather than in "circuit training combined with other lifestyle interventions" (WMD = -5.12 kg, 95% CI -7.11 to -3.12; WMD = -2.17 kg, 95% CI -4.82 to 0.47, respectively). Study participants with an average age under 50 years seemed to have a larger effect size than those aged 50 years or more did (WMD = -5.96 kg, 95% CI -9.92 to -2.01; WMD = -3.39 kg, 95% CI -5.36 to -1.43, respectively). Additionally, studies with an intervention period of 6 months or more seemed to have a larger effect size than that of studies with an intervention period of less than 6 months (WMD = -4.27 kg, 95% CI -7.37 to -1.18; WMD = -3.91 kg, 95% CI -6.52 to -1.29, respectively) (Figure S3).

DISCUSSION 4

This study aimed to assess the effects of circuit training on BW and BMI in adults. We found that circuit training is effective in reducing BW (-3.81 kg, 95% CI -5.60 to -2.02) and BMI (-1.77 kg/m², 95% Cl -2.49 to -1.04) in adults and is particularly effective in reducing BW (-4.07 kg, 95% CI -6.04 to -2.09) and BMI (-1.87 kg/m², 95% CI -2.66 to -1.08) in adults with overweight and obesity. A previous meta-analysis demonstrated that 6-month and 1-year aerobic exercise programs are effective in reducing BW (-1.60 kg, 95% CI -1.64 to -1.56 and -1.70 kg, 95% CI -2.29 to -1.11, respectively)⁴² in adults with overweight and obesity. Another network meta-analysis demonstrated that compared with resistance exercise programs, aerobic exercise programs (-1.15 kg, 95% CI 22.23 to 20.07) and combined aerobic and resistance exercise programs are more effective in reducing BW (-2.03 kg, 95% CI 22.94 to 21.12) in adults with overweight and obesity.43 In addition, a recent meta-analysis demonstrated that high-intensity interval training is effective in reducing BW (-1.45 kg, 95% CI -1.85 to -1.05) and BMI (-0.44 kg/m², 95% CI -0.59 to -0.30) in adults with overweight and obesity.⁴⁴ Therefore, although direct comparisons are difficult, at least circuit training affords a weight loss effect similar to those afforded by other types of exercise.

We also found that the degree of weight loss tended to increase with an increase in the average BMI of the participants. In one RCT²¹ included in this meta-analysis, three BMI statuses were analysed, and it was reported that the obese group had significantly higher percentage reductions in BW and BMI than the normal weight and overweight groups. However, information on the percentage reduction according to baseline BMI status was not available from any of the other RCTs included in this meta-analysis. Given the increase in the relative as well as absolute weight loss with an increase in BMI, circuit training is more suitable for individuals with higher BMIs. Therefore, additional RCTs to examine the relative weight loss effect of circuit training are warranted.

In our meta-analysis, study participants with an average age under 50 years seemed to have a larger effect size than that of participants aged 50 years and older. In addition, studies with an intervention

		Participants' Details					Intervention Details	
Study, Year	Country	Number at Baseline -> Follow-Up	Age Range or Age (Mean ± SD)	BMI Range or BMI (Mean ± SD)	% Males	Sex	Duration; Frequency; Time	Number of Exercises per Circuit; Sets; Reps; Intensity
Kolahdouzi et al. (2018)	Iran	lG 15 -> 13, CG 15 -> 13	20-30 years	Obese; 30.0-40.0 kg/m ²	100%	Male	8 weeks; 3 sessions per week; 15- min warm-up, 8 exercises (35 min), 3-min active rest between each set, 10-min cool-down	8 exercises/circuit; 2 sets (first 4 weeks), 4 sets (second 4 weeks); 8-12 repetitions (first 4 weeks), 6-8 repetitions (second 4 weeks); 65%-75% of 1RM (first 4 weeks), 75%-85% of 1RM (second 4 weeks)
Batrakoulis et al. (2018)	Greece	lG 18 -> 14, CG 22 -> 21	30-45 years; 36.4 ± 4.4 years	Overweight/obese; 25.1-34.9 kg/m ²	%0	Female	40 weeks; 3 sessions per week; 10- min warm-up, 10-12 exercises × 20-40 s, 5-min cool-down	10-12 exercises/circuit; 1 set; as many repetitions as possible at each station; 265% of heart rate reserve
Ghanbari-Niaki et al. (2018)	Iran	lG 12 -> 12, CG 12 -> 12	55.7 ± 4.9 years	27.0 ± 2.7 kg/m ²	%0	Female	8 weeks; 3 sessions per week; 5-min warm-up, 12 exercises × 30 s, 3- min active rest between each set	12 exercises/circuit; 2 sets; as many repetitions as possible at each station; 55% of 1RM
Ibrahim et al. (2018)	Malaysia	lG 12 -> 12, CG 12 -> 10	19-26 years	21.1 ± 2.7 kg/m²	100%	Male	12 weeks; 3 sessions per week; 10 exercises, work to rest ratio of 1:2, 5-min rest between circuits	10 exercises/circuit; weeks 1-8: 2 sets, weeks 9-12: 3 sets; progressively increase 1-2.5 kg after 5 weeks
Franklin et al. (2015)	USA	IG 10 -> 10, CG 10 -> 8	18-40 years	Obese; 30.0-40.0 kg/m ²	%0	Female	8 weeks; 2 sessions per week; 5-min warm-up, 8-10 exercises, 30-s rest period between exercises, 1- min rest period between circuits, 5-min cool-down	8-10 exercises/circuit; 2-3 sets; 8- 10 repetitions; 80%-90% of 10RM
Bocalini et al. (2012)	Brazil	Appropriate weight (IG 20 -> 18, CG 9 -> 9); overweight (IG 14 -> 14, CG 10 -> 10); obese (IG 16 -> 9, CG 9 -> 9)	>60 years	Normal weight; 18.5- 24.9 kg/m ² , overweight; 25.0- 29.9 kg/m ² , obesity; >30.0 kg/m ²	%0	Female	12 weeks; 3 sessions per week; 5- min warm-up, 50-min exercise, 40-s rest between sets	12 exercises/circuit; 70% of work × (MHR - baseline heart rate) + baseline heart rate
Camargo et al. (2008)	Brazil	IG 7 -> 7, CG 7 -> 7	IG 29 ± 3 years, CG 30 ± 4 years	IG 27.3 ± 2 kg/m ² , CG 28.8 ± 2 kg/m ²	100%	Male	12 weeks; 3 sessions per week; 5- min warm-up	3 sets; 15 repetitions; 60% of MHR
Eriksson et al. (2006)	Sweden	IG 75 -> 60, CG 76 -> 63	18-65 years	Normal weight, overweight, obesity	43.0%	Male/ female	12 weeks; 3 sessions per week; 10- min warm-up, 40-60-min exercise, 10-min cool-down	12 exercises/circuit; 2 sets; 10-15 repetitions; 60%-80% of MHR
Lindstrom et al. (2003)	Finland	IG 265 -> 256, CG 257 - > 250	40-64 years	Overweight; >25 kg/m ²	33.0%	Male/ female	NR	moderate intensity
	-							-

 TABLE 1
 Characteristics of studies included in the meta-analysis

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Abbreviations: SD, standard deviation; BMI, body mass index; IG, intervention group; CG, control group; RM, repetition maximum; MHR, maximum heart rate; NR, not reported.

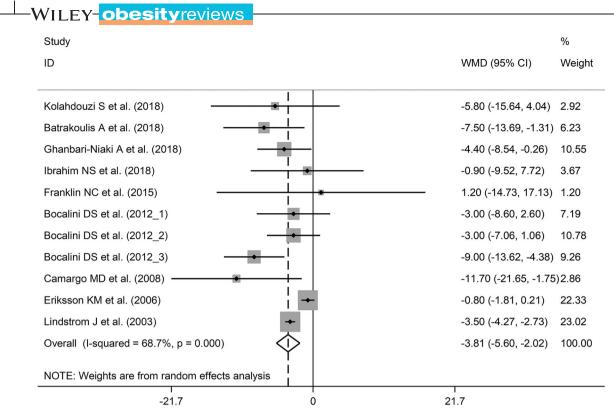


FIGURE 2 Forest plot for changes in body weight. Meta-analysis of the effect of circuit training on body weight (kg). The mean difference for each study reporting changes in body weight is depicted along with the 95% confidence interval (Cl). The random-effect model was used to estimate the weighted mean differences (WMDs) with 95% Cls. Negative values favour circuit training because the circuit training group experienced more weight reduction than the control group did. WMD, weighted mean difference

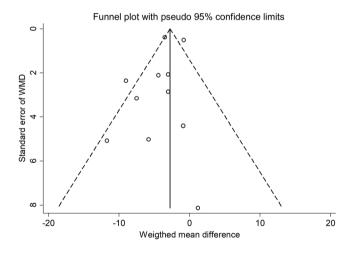


FIGURE 3 Funnel plot for changes in body weight. The funnel plots of standard error of weighted mean difference (WMD) against WMD for body weight to assess for publication bias. WMD, weighted mean difference

period of 6 months or more seemed to have a larger effect size than studies with an intervention period of less than 6 months. A recent meta-analysis of high-intensity interval training showed that younger individuals lost more BW than older individuals. In addition, an even further reduction in BW was observed with an increase in the number of sessions of high-intensity interval training.⁴⁴ However, another meta-analysis of general aerobic and resistance training showed that the inclusion of individuals aged 50 years and older had a slightly more

significant effect than the inclusion of individuals aged under 50 years.⁴³ In our meta-analysis of circuit training and high-intensity interval training, a greater effect was observed on the BW of relatively younger individuals, whereas in the meta-analysis of general aerobic and resistance training, older individuals lost more BW. The metabolic cost or intensity of circuit training is higher than that of general resistance training¹⁸ and is no different from or even higher than the cost or intensity of a combination of general aerobic and resistance training.^{15,19} Therefore, relatively high-intensity circuit training can be a more appropriate exercise for younger individuals.

The intervention effect was statistically significant only in "circuit training alone" intervention rather than in "circuit training combined with other lifestyle interventions." Among the RCTs included in our meta-analysis, two RCTs^{40,41} included other lifestyle intervention methods. One study⁴⁰ reported that circuit training combined with other lifestyle interventions could have a beneficial effect on several cardiometabolic risk factors. However, there was no significant effect on weight loss. According to the protocol, exercise intensity and time were increased over time. The attendance rate of this study was 80%, which is also lower than the average attendance rate of the RCTs included in our meta-analysis. Therefore, it is considered that the intensity of the intervention is high when other lifestyle interventions are considered together. The other study,⁴¹ which reported percentage weight change, was successful in achieving 5% or greater weight change in the intervention group. However, there was no detailed description of exercise intervention protocols. Therefore, additional

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RCTs to examine the weight loss effect of circuit training combined with other lifestyle interventions are warranted.

In our meta-analysis, the weight loss effect of circuit training was statistically significant only in women. Recent studies found that cardiometabolic demand was significantly higher among women compared with men during high-intensity circuit training⁴⁵ or highintensity interval training.⁴⁶ Gender differences in response to exercise are likely to be due to differences in muscle mass and muscle function.⁴⁷ However, the number of studies and participants involving only men in our meta-analysis could have affected the outcome. Therefore, additional RCTs for men to examine the weight loss effect of circuit training are warranted.

Circuit training has the following advantages: It improves body weight as well as body composition,^{16,20,21} bone metabolism,²² cardiometabolic risk factors,²³⁻²⁵ and physical fitness.¹⁵⁻¹⁷ Some studies have reported that the metabolic cost of circuit training is no different from or even higher than that of a combination of general aerobic and resistance training.^{15,19} Among the RCTs included in our metaanalysis. four RCTs^{20,24,38,40} reported changes in maximal oxygen uptake (VO_{2max}). We have calculated the mean difference for VO_{2max} to determine the overall intervention effect, and significant intervention effects were identified for VO_{2max} (WMD = 4.44 mL/kg/min, 95% CI 1.48 to 7.40) (Figure S4). In addition to many of the above advantages, the circuit training consists of short rest periods and short exercise times, which enhances motivation to exercise more effectively than moderate aerobic exercise.¹⁷ In the same context, the average attendance rate of the participants in the included studies exceeded 90%, and therefore, it is considered that circuit training could be recommended to adults with overweight and obesity, taking into account individual preferences and circumstances.

4.1 | Strength

Our meta-analysis has the following strengths. First, to our knowledge, this is the first meta-analysis to evaluate the weight loss effects of circuit training intervention in adults. Second, we examined the differences in weight loss effects among subgroups according to BMI status, age, sex, and the type and duration of intervention. We found that circuit training alone is effective for weight loss in adults with overweight and obesity who continue to exercise for more than 6 months.

4.2 | Limitation

Our meta-analysis has some limitations. First, the heterogeneity between the included RCTs was moderate. The RCTs included in our meta-analysis were heterogeneous in the country where the RCT was performed, and sex, age, and intervention-related variables (type, period, intensity, and frequency). However, the heterogeneity in the obesity subgroup was low, and most circuit training interventions consisted of short rest periods, short exercise times, and exercises with more than moderate intensity; hence, there was no difference in the basic framework. Second, some of the included studies had small sample size because of the characteristics of exercise intervention. However, at least there was no small study effect. Third, the effects on only BW and BMI were evaluated, and those on body composition or cardiovascular risk could not be examined. Therefore, additional RCTs to evaluate the effect of circuit training on cardiovascular risk should be conducted, and a meta-analysis should be conducted through these RCTs. Fourth, the relative reduction compared with the baseline BW or BMI could not be analysed. Among the RCTs included in our meta-analysis, nine studies reported total weight change, while only one study⁴¹ reported percentage weight change. This RCT, which reported percentage weight change, was successful in achieving 5% or greater weight change in the intervention group. A 5% weight loss of initial BW is considered a benchmark for clinically meaningful weight loss.48,49 Therefore, additional RCTs to examine the relative weight loss effect of circuit training are also warranted. Finally, the methodological quality of the included RCTs is largely unclear.

5 | CONCLUSIONS

Current evidence suggests that circuit training effectively reduces BW and BMI in adults with overweight and obesity.

CONFLICT OF INTEREST

No conflict of interest was declared.

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SUPPORTING INFORMATION

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

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