Effects of lifestyle intervention on adults with metabolic associated fatty liver disease: A systematic review and meta-analysis

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Introduction: This systematic review and meta-analysis evaluates the overall effects of lifestyle interventions upon hepatic fat content and metabolism-related indicators among adults with metabolic associated fatty liver disease.

Methods: It was registered under PROSPERO (CRD42021251527). We searched PubMed, EMBASE, MEDLINE, Cochrane, CINAHL, Scopus, CNKI, Wan-fang, VIP, and CBM from the inception of each database to May 2021 for RCT studies of lifestyle interventions on hepatic fat content and metabolism-related indicators. We used Review Manager 5.3 for meta-analysis and used text and detailed tabular summaries when heterogeneity existed.

Results: Thirty-four RCT studies with 2652 participants were included. All participants were obesity, 8% of whom also had diabetes, and none was lean or normal weight. Through subgroup analysis, we found low carbohydrate diet, aerobic training and resistance training significantly improved the level of HFC, TG, HDL, HbA1c, and HOMA-IR. Moreover, low carbohydrate diet is more effective in improving HFC than low fat diet and resistance training is better than aerobic training in reduction in HFC and TG (SMD, -0.25, 95% CI, -0.45 to -0.06; SMD, 0.24, 95% CI, 0.03 to 0.44, respectively).

Discussion: Overall, this is the first review that systematically synthesizes studies focused on the effects of various lifestyle on adults with MAFLD. The data generated in this systematic review were more applicable to obesity MAFLD rather than lean or normal weight MAFLD.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier (CRD42021251527).

1 Introduction

Metabolic associated fatty liver disease (MAFLD) is a chronic liver disease characterized by the excessive accumulation of fat in liver cells and metabolic dysfunction (1, 2). MAFLD, formerly known as non-alcoholic fatty liver disease (NAFLD), is redefined in the guidelines of the Asia-Pacific Society of Liver Diseases in October 2020. The new definition of MAFLD is based on the presence of fatty liver as indicated by liver biopsy or imaging or blood biomarkers, along with one of three conditions: overweight/ obesity, type 2 diabetes, and metabolic dysfunction. New definition attaches importance to the pathogenesis of MAFLD and makes change to end points of study, which differ from NAFLD that excludes alcohol consumption (3). MAFLD affects approximately one quarter of the global population, which not only causes liver inflammation, fibrosis, and malignant tumors, but also often merges with a variety of metabolic disorders, causing major diseases such as gout, type 2 diabetes, hypertension, and atherosclerosis and posing a major health and economic burden to all societies (1, 4–6). Therefore, an effective approach to address such a serious situation is urgently needed.

The high prevalence of MAFLD is fueled by the rapid rise in unhealthy lifestyle including sedentary behavior and unreasonable dietary structure (7). Currently, lifestyle interventions are the primary recommended therapy for MAFLD, especially in the absence of approved pharmaceutical agents (1, 8). However, lifestyle interventions for MAFLD patients vary widely among studies, which focus on diet and/or exercise, mainly encompassing Mediterranean diet, Dietary Approaches to Stop Hypertension, high-dietary-fiber diet, aerobic exercise, and resistance exercise (9–15). In addition, the effects of lifestyle interventions differ in the available studies. The effects regarding lifestyle interventions on MAFLD are reflected in the hepatic fat content (HFC) and metabolism-related indicators, such as body mass index (BMI), waist circumference (WC), blood pressure (BP), plasma triglycerides (TG), plasma high-density lipoprotein cholesterol (HDL), fasting blood glucose (FBG), HbA1c, homeostasis model assessment of insulin resistance score (HOMA-IR), and plasma high-sensitivity C-reactive protein (CRP) level, yet these indicators are not fully included in the respective studies (10, 12, 16–18).

Although reviews focus on NAFLD(19–23), to date, none have applied systematic approaches to examine the efficacy or effectiveness of various lifestyle interventions on MAFLD after the name changed and the new diagnostic criteria were redefined. Therefore, we conducted a systematic review and meta-analysis to integrate and evaluate the relevant evidence of various lifestyle interventions in adults with MAFLD and to provide reference for clinical care teams.

2 Methods

This study protocol was registered on PROSPERO (CRD42021251527). The study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24).

2.1 Eligibility criteria for this study

2.1.1 Types of participants

NAFLD adults who met the diagnostic criteria of MAFLD and adults diagnosed with MAFLD were included in this review. The diagnostic criteria for MAFLD were based on histological, imaging, or blood biomarker evidence of liver fat accumulation, combined with one of the following three conditions: overweight/obesity, type 2 diabetes, or lean/normal weight but presence of at least two metabolic risk abnormalities (2).

2.1.2 Types of interventions

Interventions included lifestyle interventions, such as diet, physical activity, sleeping, or a combination of two or three. Studies designed to prove the effectiveness of dietary supplements or herbal preparations were excluded.

2.1.3 Types of comparators

Comparators included no intervention, standard/usual care, or other lifestyle interventions.

2.1.4 Types of outcomes

The primary outcomes of interest were changes in HFC assessed by histological, imaging, or blood biomarkers. The secondary outcomes included BMI, WC, BP, plasma TG, plasma HDL, FBG, HbA1c, HOMA-IR, and plasma high-sensitivity CRP level.

2.1.5 Types of study

Only randomized clinical trials were included in this review.

2.2 Search strategy and study selection

Searches were performed in English and Chinese databases, such as PubMed, EMBASE, MEDLINE, Cochrane, CINAHL and Scopus for English literature and CNKI, Wanfang, VIP, and CBM for Chinese literature. The search period was from the inception of each database to May 2021. The Medical Subject Headings and related free words were widely used to capture the literature, including non-alcoholic fatty liver disease, metabolic associated fatty liver disease, lifestyle, diet, exercise, sleep, and all synonyms of these keywords. The detailed search strategy of PubMed is shown in Table 1. Other database search strategies are listed in the Appendix. Articles that satisfied the eligibility criteria and studies published in English or Chinese were included. The screening process included four steps and is shown in Figure 1. First, all titles and abstracts retrieved were downloaded to the Endnote X9 library, and duplicate articles were removed. Second, articles were excluded based on titles and abstracts. Third, the full text of the article was reviewed to determine eligibility based on the inclusion criteria. Finally, the reference lists of the included articles and related reviews were screened for potentially relevant articles. The searching and screening processes were conducted by two independent researchers, and disagreements were resolved by a third researcher.

TABLE 1 Search strategy of PubMed.

Main Concept	Search Formula	Results
1. MAFLD	Non-alcoholic Fatty Liver Disease[Mesh] OR Metabolic associated fatty liver disease OR MAFLD OR Metabolic-dysfunction-associated fatty liver disease OR Non alcoholic Fatty Liver Disease OR NAFLD OR Nonalcoholic Fatty Liver Disease OR Fatty Liver, Nonalcoholic OR Fatty Livers, Nonalcoholic OR Liver, Nonalcoholic Fatty OR Livers, Nonalcoholic Fatty OR Nonalcoholic Fatty Liver OR Nonalcoholic Fatty Livers OR Nonalcoholic Steatohepatitis OR Nonalcoholic Steatohepatitides OR Steatohepatitides, Nonalcoholic OR Steatohepatitis, Nonalcoholic	34802
2. Lifestyle	Healthy Lifestyle[Mesh] OR Life Style[Mesh] OR Sedentary Behavior[Mesh] OR Life Styles[Title/Abstract] OR (Lifestyle[Title/Abstract] OR Lifestyles[Title/Abstract] OR Life Style Induced Illness[Title/Abstract] OR Lifestyle Factors[Title/Abstract] OR Factor, Lifestyle[Title/Abstract] OR Lifestyle Factor[Title/Abstract] OR Lifestyle, Healthy[Title/Abstract] OR Lifestyles, Healthy[Title/Abstract] OR Healthy Life Styles[Title/Abstract] OR Healthy Lifestyles[Title/Abstract] OR Healthy Life Style[Title/Abstract] OR Life Style, Healthy[Title/Abstract] OR Life Styles, Healthy[Title/Abstract] OR Behavior, Sedentary[Title/Abstract] OR Sedentary Behaviors[Title/Abstract] OR Sedentary Lifestyle[Title/Abstract] OR Lifestyle, Sedentary[Title/Abstract] OR Physical Inactivity[Title/Abstract] OR Inactivity, Physical[Title/Abstract] OR Lack of Physical Activity[Title/Abstract] OR Sedentary Time[Title/Abstract] OR Sedentary Times[Title/Abstract] OR Time, Sedentary[Title/Abstract] OR Exercise[Mesh] OR Exercises[Title/Abstract] OR Physical Activity[Title/Abstract] OR Activities, Physical[Title/Abstract] OR Activity, Physical[Title/Abstract] OR Physical Activities[Title/Abstract] OR Exercise, Physical[Title/Abstract] OR Exercises, Physical[Title/Abstract] OR Physical Exercise[Title/Abstract] OR Physical Exercises[Title/Abstract] OR Acute Exercise[Title/Abstract] OR Acute Exercises[Title/Abstract] OR Exercise, Acute[Title/Abstract] OR Exercises, Acute[Title/Abstract] OR Exercise, Isometric[Title/Abstract] OR Exercises, Isometric[Title/Abstract] OR Isometric Exercises[Title/Abstract] OR Isometric Exercise[Title/Abstract] OR Exercise, Aerobic[Title/Abstract] OR Aerobic Exercise[Title/Abstract] OR Aerobic Exercises[Title/Abstract] OR Exercises, Aerobic[Title/Abstract] OR Exercise Training[Title/Abstract] OR Exercise Trainings[Title/Abstract] OR Training, Exercise[Title/Abstract] OR Trainings, Exercise[Title/Abstract] OR Diet[Mesh] OR diets[Title/Abstract] OR Sleep[Mesh] OR Sleeping Habits[Title/Abstract] OR Sleep Habits[Title/Abstract] OR Habit, Sleep[Title/Abstract] OR Habits, Sleep[Title/Abstract] OR Sleep Habit[Title/Abstract] OR Sleeping Habit[Title/Abstract] OR (Habit, Sleeping[Title/Abstract] OR (Habits, Sleeping[Title/Abstract]	887252
3. RCT	randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo[Title/Abstract]	888684
#1 AND #2 AND #3		503

2.3 Assessment of methodological quality

The quality of the included articles was assessed by two independent researchers using the Joanna Briggs Institute Critical Appraisal tools for Checklist for RCTs, which contain 13 entries (Figure 2). Each entry was answered with yes, no, or unclear.

2.4 Data extraction

All data were extracted by two independent researchers by using standardized forms, and disagreements were resolved by a third researcher. The standard form included authors and year of publication, country, study design, subject, diagnosis methods, sample size, the intervention of experimental and control groups, duration, outcomes, results, and conclusion. Among the articles included in the systematic review, those studies that provided intervention values of HFC, BMI, WC, BP, TG, HDL, FG, HbA1c, and HOMA-IR were included in the meta-analysis.

2.5 Data synthesis

ReviewManager 5.3 version was used for data consolidation, heterogeneity test, sensitivity analysis, forest map mapping, and subgroup analysis. First, clinical heterogeneity was determined, and if heterogeneity existed, meta-analysis was discarded, and the results were presented in the form of text and detailed tabular summaries. Secondly, statistical heterogeneity could be explored by chi-square test after excluding clinical heterogeneity. The results were presented

as standardized mean difference (SMD) with 95% confidence intervals (CIs), and $P<0.05$ was considered statistically significant. A fixed-effects model was applied when the heterogeneity test indicated no significant difference ($P>0.1$ and $I^2<50\%$); otherwise, a random-effects model was used. Meta-analysis was abandoned, and descriptive methods were used when the source of heterogeneity could not be determined.

3 Results

3.1 Study selection and study characteristics

The PRISMA flow diagram summarized the selection process of the systematic review and meta-analysis (as shown in Figure 1). A total of 8469 studies were identified through search in nine databases. Duplicate references were identified and removed (N=3620). After examining the titles and abstracts, 252 full texts were further screened, and 34 studies met the inclusion criteria and were included in the systematic review and meta-analysis. The reasons for exclusion at this full-text level (N=218) are listed in Figure 1.

The characteristics of the included studies are shown in Table 2. The 34 included studies reported 2929 adults with MAFLD, and 27 of them reported information about participants lost at follow-up; the final total number was 2652. For diagnosis of MAFLD, 93% of them were based on imaging-detected liver fat accumulation combined with obesity; the remaining 7% were biopsy-proven liver fat accumulation combined with obesity. Moreover, all participants were obesity, and 8% of them had a diagnosis of type

FIGURE 1
PRISMA flow diagram.
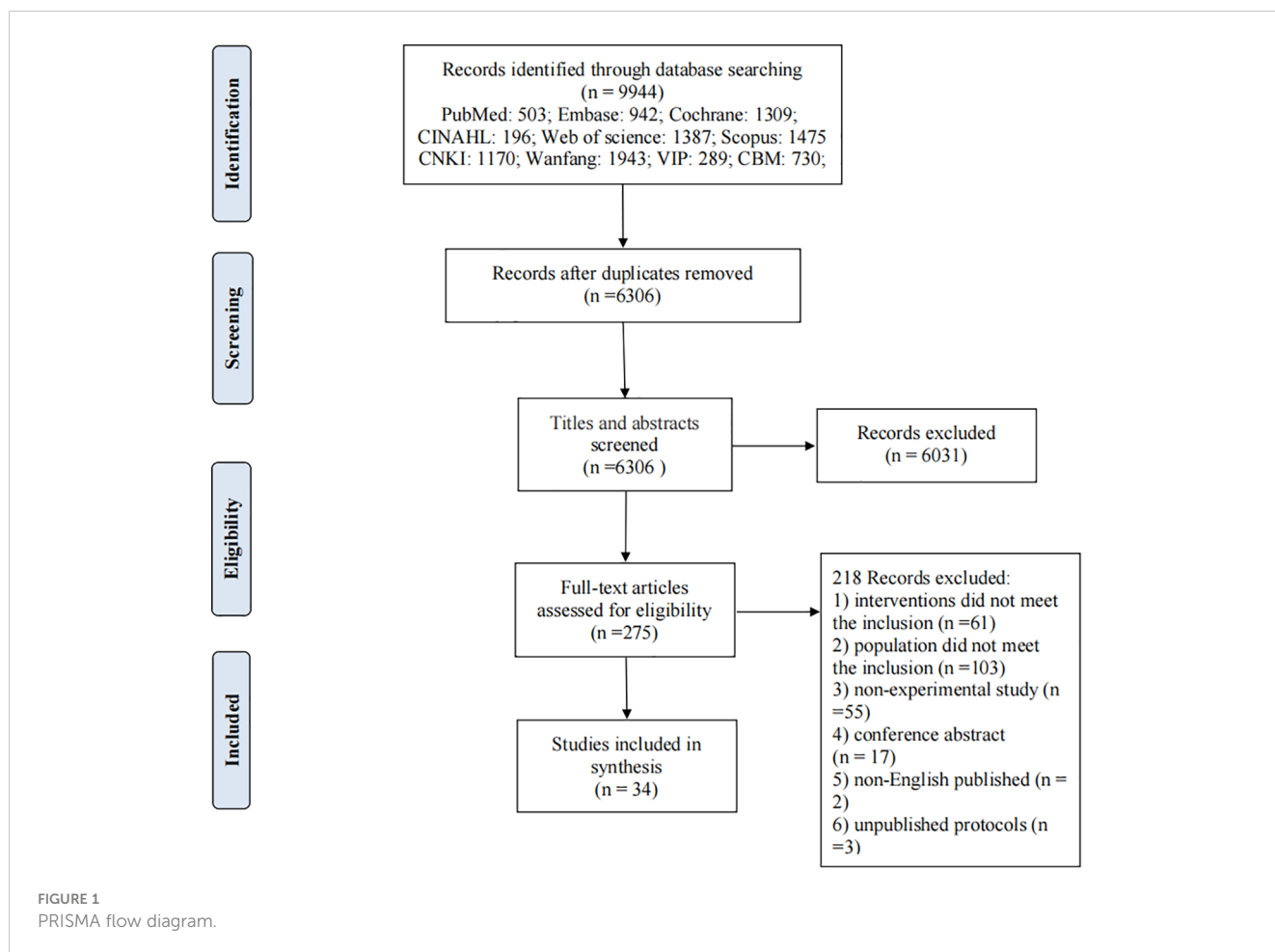
2 diabetes. The sample size of the participants ranged from 18 to 461, and the age of participants ranged from 27 to 68 years. We classified these articles into three categories on the basis of the form of lifestyle interventions: diet interventions, exercise interventions, and diet combined with exercise interventions, which are detailed in Tables 3–5, respectively.

3.2 Methodological quality

The quality assessment details of each study are presented in Figure 2. Twenty studies did not specify whether allocation concealment was performed, which may cause selection bias. Fifteen studies did not perform intention to treat analysis, potentially leading to follow-up bias. Participants, interveners, and outcome assessors were not fully blinded, probably causing performance bias.

3.3 Effects of interventions

3.3.1 Effects of diet interventions

The diet interventions were divided into two categories in this article, as shown in Table 3: 1) the first five studies were reduction in the proportion of carbohydrates, and 2) the last nine studies were

food serving replacement under isocaloric conditions. A meta-analysis of the diet interventions was deemed inappropriate due to the heterogeneity of the diet forms. We found that low carbohydrate diet significantly improved the level of HFC, TG, HDL, HbA1c, and HOMA-IR, but not BMI, BP, FBG, and CRP when compared to low fat diet. In addition, food serving replacement under isocaloric conditions was most significant in improving HOMA-IR in MAFLD, followed by HFC, WC, TG, FBG, BMI, BP, and CRP, but not HDL and HbA1c.

3.3.2 Effects of exercise interventions

The exercise interventions were divided into aerobic training and resistance training, as shown in Table 4. According to the different types of exercise, we will conduct meta-analysis in three subgroups: 1) the effects of aerobic training on MAFLD, 2) the effects of resistance exercise on MAFLD, and 3) the difference between aerobic and resistance exercise, which are shown in Figures 3–5, respectively. Aerobic training was associated with the improvement of the indicator of MAFLD including HFC, BMI, WC, TG, FBG, HbA1c, and HOMA-IR (SMD, -0.25, 95% CI, -0.43 to -0.07; SMD, -0.22, 95% CI, -0.39 to -0.05; SMD, -0.36, 95% CI, -0.55 to -0.17; SMD, -0.46, 95% CI, -0.67 to -0.25; SMD, -0.44, 95% CI, -0.63 to -0.26; SMD, -0.59, 95% CI, -0.95 to -0.23; SMD, -0.44, 95% CI, -0.65 to -0.24, respectively). Resistance training was associated with the improvement of the indicator of MAFLD

Q1. Was true randomization used for assignment of participants to treatment groups?
Q2. Was allocation to treatment groups concealed?
Q3. Were treatment groups similar at the baseline?
Q4. Were participants blinded to treatment assignment?
Q5. Were those delivering treatment blinded to treatment assignment?
Q6. Were outcomes assessors blinded to treatment assignment?
Q7. Were treatment groups treated identically other than the intervention of interest?
Q8. Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed?
Q9. Were participants analyzed in the groups to which they were randomized?
Q10. Were outcomes measured in the same way for treatment groups?
Q11. Were outcomes measured in a reliable way?
Q12. Was appropriate statistical analysis used?
Q13. Was the trial design appropriate, and did any deviations from the standard RCT design (individual randomization, parallel groups) account for the conduct and analysis of the trial?

FIGURE 2
Methodological quality of included studies.

including HFC, BMI, WC, DBP, TG, FBG, and HOMA-IR (SMD, -0.25, 95% CI, -0.45 to -0.06; SMD, -0.25, 95% CI, -0.56 to -0.15; SMD, -0.36, 95% CI, -0.56 to -0.15; SMD, -0.52, 95% CI, -0.73 to -0.32; SMD, -0.58, 95% CI, -0.78 to -0.38; SMD, -0.57, 95% CI, -0.79 to -0.35; SMD, -0.55, 95% CI, -0.77 to -0.33, respectively). Resistance training was better than aerobic training in reduction in HFC and TG (SMD, -0.25, 95% CI, -0.45 to -0.06; SMD, 0.24, 95% CI, 0.03 to 0.44, respectively). Aerobic and resistance training had no effect on HDL and BP.

3.3.3 Effects of diet combined with exercise interventions

A meta-analysis of diet combined with exercise interventions was deemed inappropriate due to the heterogeneity of the intervention forms. As shown in Table 5, diet combined with exercise interventions was most significant in improving HFC, followed by BMI, HOMA-IR, WC, BP, TG, and HDL. However, diet combined with exercise interventions was not significant in improving FBG and HbA1c.

TABLE 2 Characteristics of the included articles.

Reference	Clinical group	Country	N	Age	M/F	BMI	Intervention form
(25)	Obesity and biopsy-proven NASH	USA	31/28	35–60	22/9	34(25~40)	Diet combined with exercise
(26)	Obesity and ultrasonography-proven NAFLD	Iran	44	30–49	22/22	28.99 ± 2.72/29.21 ± 2.61	Diet
(9)	Obesity and MRI-proven NAFLD	USA	33/18	44–50	5/13	38.1 ± 4.6	Exercise
(27)	Obesity, DM2, and biopsy-proven steatosis	Saudi Arabia	100	35–55	100/0	32.11 ± 3.54/32.37 ± 3.92	Diet combined with exercise
(28)	Obesity, DM2, and MRI scan-proven NAFLD	Italy	32/31	53–58	22/9	30.5 ± 1.0/28.8 ± 1.1	Exercise
(10)	Obesity and ultrasonography-proven NAFLD	Israel	82/64	36–58	34/30	30.75 ± 4.52/31.3 ± 4.14	Exercise
(29)	Obesity and fibrosis scan-proven NAFLD	UK	29/23	44–64	U	31 ± 4/31 ± 5	Exercise
(30)	Obesity and ultrasonography-proven NAFLD	Egypt	32	33–56	15/17	33.99 ± 2.57/33.13 ± 2.11	Exercise
(16)	Obesity and ultrasonography-proven NAFLD	Greece	55/44	40–61	23/32	29.5 ± 4.3/28.2 ± 3.7	Diet
(11)	Obesity and ultrasonography-proven NAFLD	Iran	60/60	32–53	30/30	28.5 ± 3.2/28.3 ± 3.3	Diet
(12)	Obesity and ultrasonography-proven NAFLD	China	220/211/208	46–62	71/149	27.9 ± 2.7/28.1 ± 3.3/28.0 ± 2.7	Exercise
(31)	Obesity and ultrasonography-proven NAFLD	Saudi Arabia	100	45–57	70/30	32.35 ± 2.54/31.76 ± 2.92	Diet combined with exercise
(32)	Obesity and fibrosis scan-proven NAFLD	Brazil	44/40	48–63	0/40	34.1 ± 4.4/32.0 ± 5.0	Exercise
(33)	Obesity and biopsy-proven NASH	Australia	26/24	42–67	U	33 ± 7/33 ± 5	Exercise
(34)	Obesity and fibrosis scan-proven NAFLD	Japan	61/52	46–53	52/0	27.2 ± 0.9/28.4 ± 0.9/28.8 ± 1.1	Exercise
(13)	Obesity and ultrasonography-proven NAFLD	Greece	63/63	38–60	43/20	30.04/31.67/32.44	Diet combined with exercise
(35)	Obesity and ultrasonography-proven NAFLD	China	474/461	48–62	230/231	75.28 ± 10.18/74.94 ± 10.37/74.69 ± 10.3	Exercise
(14)	Obesity and MRI scan-proven NAFLD	Australia	51/50/50/49/48	38–62	25/26	30.2 ± 5.6/31.5 ± 4.1	Diet
(36)	Obesity and ultrasonography-proven NAFLD	Iran	70/64	36–56	19/45	30.90 ± 3.62/31.36 ± 3.74	Diet
(37)	Obesity and ultrasonography-proven NAFLD	Iran	66/54 (66)	32–60	29/37	30.6 ± 3.6/29.6 ± 3.9	Diet
(38)	Obesity and ultrasonography-proven NAFLD	Iran	66/62	36–56	19/43	30.85 ± 3.53/31.29 ± 3.77	Diet
(39)	Obesity and ultrasonography-proven NAFLD	Iran	60/54	31–49	12/48	32.77 ± 3.63/31.09 ± 3.24	Diet
(40)	Obesity and MRI-proven NASH	Germany	26/22	40–68	13/9	32.2 ± 3.4/32.4 ± 3.7	Diet combined with exercise
(17)	Obesity and ultrasonography-proven NAFLD	China	271/264	27–41	87/184	26.76 ± 1.59/26.12 ± 2.21/26.34 ± 2.73	Diet
(41)	Obesity, DM2, and MRI scan-proven NAFLD	Saudi Arabia	32/32	49–61	19/13	36.3 ± 4.5/35.9 ± 5.3	Exercise
(15)	Obesity and ultrasonography-proven NAFLD	Iran	112/94	34–52	39/55	32.5 ± 4.1/31.8 ± 4.4	Diet
(18)	Obesity, DM2, and MRI scan-proven NAFLD	Saudi Arabia	48/47	46–63	27/20	36.3 ± 4.5/36.7 ± 3.4/35.9 ± 5.3	Exercise
(42)	Obesity and ultrasonography-proven NAFLD	Singapore	108/101 (108)	35–57	68/40	30.1 ± 4.0/30.8 ± 4.8	Diet combined with exercise
(43)	Obesity and fibrosis scan-proven NAFLD	China	158/147	30–55	113/34	27.63 ± 3.46/28.39 ± 2.69/27.11 ± 2.73	Exercise
(44)	Obesity and ultrasonography-proven NAFLD	Turkey	32/31	36–54	12/19	32.74 ± 4.78/33.17 ± 4.91	Exercise

(Continued)

TABLE 2 Continued

Reference	Clinical group	Country	N	Age	M/F	BMI	Intervention form
(45)	Obesity and ultrasonography-proven NAFLD	Serbia	27/24	28–39	U	30.43 ± 1.81/30.17 ± 2.28	Diet
(46)	Obesity and imaging-proven NAFLD	Sweden	74/64	47–67	33/41	32.1 ± 3.8/32.3 ± 2.7/32.9 ± 5.2	Diet
(47)	Obesity and ultrasonography-proven NAFLD	Iran	80/75	33–54	36/39	32.02 ± 4.57/30.06 ± 3.81	Diet
(48)	Obesity and ultrasonography-proven NAFLD	Spain	98/76/72/58	41–60	55/43	33.7 ± 4/33.3 ± 4	Diet

The subjects were included in studies and analysis. M/F, male/female; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; DM2, type-2 diabetes mellitus; MRI, magnetic resonance imaging; CT, computerized tomography; NASH, non-alcoholic steatohepatitis.

4 Discussion

To our knowledge, this is the first systematic review and meta-analysis examining the effects of lifestyle interventions on adults with MAFLD after the name NAFLD changed to MAFLD and the diagnostic criteria redefined. We find that the intervention effects of low carbohydrate diet are significant on MAFLD. After comparing the effects of aerobic exercise and resistance exercise, resistance exercise is more effective than aerobic exercise in improving HFC and TG on MAFLD in our meta-analysis. We also find diet combined with exercise interventions are significant on MAFLD. However, there are insufficient evidence about the effects of lifestyle intervention on lean/normal weight (49)MAFLD and the effects of lifestyle intervention on certain metabolism-related indicators.

We find the intervention effects of low carbohydrate diet are significant on MAFLD. Our results suggest that low carbohydrate diet is more effective in improving HFC than low fat diet in adults with MAFLD. Although meta-analysis was abandoned for the different proportions of carbohydrates, all the five articles showed significant effects. However, the results of a meta-analysis about the effect of low carbohydrate diet on NAFLD showed no significant difference between low carbohydrate diet group and low-fat diet group (50). The possible reason for the discrepancy would be the changed definition and redefined criteria. The inclusion criteria of participants with MAFLD are based on the new diagnostic criteria, which excludes participants with NAFLD unrelated to metabolic dysfunction, therefore, the participants are more homogeneous. A recent randomized controlled trial on Type 2 Diabetes combined

TABLE 3 Diet interventions.

Reference	Interventions	Interveners	Control	Duration	Outcomes	Measurer	Results
(26)	Low carbohydrate diet: carbohydrate:fat:protein: 40:40:20 500 kcal less than energy requirement	Dietitians	Low fat diets: carbohydrate:fat:protein: 55:25:20 500 kcal less than energy requirement	6 weeks	HFC, BMI, TG, HDL	Same trained assessor	TG decreased 18.09% in low carbohydrate diet. HFC and BMI decreased in both groups. Low carbohydrate diet. is better than low fat diet in improving HFC
(14)	Low carbohydrate diet: carbohydrate:fat:protein:40:40:20	Dietitians	Low-fat diets: carbohydrate:fat:protein: 50:30:20	12 weeks	HFC, BMI, WC, SBP, DBP, TG, HDL, FBG, HbA1c, HOMA-IR	Unmentioned	TG and HbA1c decreased in low carbohydrate diet. HFC decreased in both groups. Low carbohydrate diet. is better than low fat diet in improving HFC
(45)	Low carbohydrate diet: carbohydrate:fat:protein: 50:30+:15, 600–800 kcal less than energy requirement	Nutritionists	Low-fat diets: carbohydrate:fat:protein: 60:25:15 600–800 kcal less than energy requirement	3 months	HFC, BMI, WC, TG, HDL, FBG, HOMA-IR, CRP	Unmentioned	HFC and TG decreased in low carbohydrate diet. HDL increased in low carbohydrate diet. WC, FBG, and HOMA-IR decreased in both groups.

(Continued)

TABLE 3 Continued

Reference	Interventions	Interveners	Control	Duration	Outcomes	Measurer	Results
(46)	Low carbohydrate diet: carbohydrate:fat:protein: 5–10:50–80:10–40	Dietitians	Low-fat diets: carbohydrate: fat:protein: 45–60:20:10–20	12 weeks	HFC, BMI, SBP, DBP, TG, HDL, HbA1c, HOMA-IR	Unmentioned	HFC decreased 7.2% in LCHF diet. HFC decreased 6.1% in 5:2 diet.
(48)	Low carbohydrate diet: carbohydrate:fat:protein: 40–45:30–35:25, 7 meals/day, 30% less than energy requirement	Unmentioned	Low-fat diets: carbohydrate: fat:protein: 55:30:15, 3–5 meals/day, 30% less than energy requirement	24 months	HFC, BMI, WC, SBP, DBP, TG, HDL, HbA1c, HOMA-IR	Unmentioned	HFC, WC, and HOMA-IR decreased in FLiO group.
(16)	Currant replacing snacks of similar caloric content and dietary counseling	Dietitians	Dietary counseling	24 weeks	HFC, BMI, WC, SBP, DBP, TG, HDL, HbA1c	Unmentioned	WC and FBG reduced in the currant arm. HFC, BMI, HbA1c, and CRP reduced in both arms.
(11)	Rich in fruits, vegetables, whole grains, and low-fat dairy products and low in saturated fats, cholesterol, refined grains, and sweets 350–700 kcal less than energy requirement	Dietitians	Usual diets 350–700 kcal less than energy requirement	8 weeks	HFC, BMI, WC, TG, HDL, FBG, HOMA-IR, CRP	Same trained examiner	BMI, WC, HOMA-IR, TG, and CRP decreased in DASH diet.
(37)	Olive oil 20 g per day 500 kcal less than energy requirement	Dietitians	Sunflower oil 20 g per day 500 kcal less than energy requirement	12 weeks	HFC, BMI, WC, SBP, DBP, TG, HDL, FBG, HOMA-IR	Unmentioned	HFC and TG reduced in olive group. WC, SBP, and DBP reduced in both groups.
(36)	Soy milk instead of 1 serving of grains and fats 500 kcal less than energy requirement	Unmentioned	Usual diets 500 kcal less than energy requirement	8 weeks	HFC, BMI, WC, TG, HDL, CRP	Unmentioned	CRP decreased in soy milk group.
(38)	Soy milk instead of 1 serving of grains and fats 500 kcal less than energy requirement	Unmentioned	Usual diets 500 kcal less than energy requirement	8 weeks	SBP, DBP, FBG, HOMA-IR	Unmentioned	DBP and HOMA-IR reduced in soy milk group.
(39)	Purslane seeds 10 g/day before breakfast and dinner 500 kcal less than energy requirement	Unmentioned	Usual diets 500 kcal less than energy requirement	8 weeks	SBP, DBP, TG, HDL, FBG, HOMA-IR	Unmentioned	FBG and HOMA-IR reduced in purslane seed group
(15)	At least half of cereal servings from whole-grain foods each day	Dietitians	Usual cereals	12 weeks	HFC, SBP, DBP, TG, HDL, FBG, HOMA-IR	Same trained assessor	HFC, SBP, and DBP decreased in whole-grain foods
(17)	A fast day with 25% of energy requirement and a feed day with ad libitum food An 8-h window for food intake and a 16-h window of fasting	Unmentioned	Control: 80% of energy requirement	12 weeks	HFC, BMI, WC, TG, HDL, FBG	Unmentioned	BMI and TG decreased in both ADF and TRF groups.
(47)	Protein restraining in meat products, 500 kcal less than energy requirement	Unmentioned	Protein freely 500 kcal less than energy requirement	3 months	HFC, BMI, WC, SBP, DBP, TG, HDL, FBG, HOMA-IR	Same trained assessor	HFC, BMI, WC, SBP, TG, FBG, and HOMA-IR decreased in LOV-D.

HFC, hepatic fat content; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL, high density lipoprotein; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HOMA-IR, homoeostasis model of assessment-estimated insulin resistance; CRP, high-sensitivity C-reactive protein.

TABLE 4 Exercise interventions.

Reference	Types	Intervention			Control		Duration	Outcome	Result
		Types	Intensity	Supervision	Types	Intensity			
(9)	Aerobic training	Aerobic training: 30–60 min×5 times/week	45%–55% of VO2 peak	Under supervision: 1 time/week	Daily activities	Unmentioned	16 weeks	HFC, BMI, TG, HDL	HFC decreased in aerobic training group.
(28)	Both	Aerobic training: 60 min×3 times/week	45%–55% of VO2 peak	Under supervision All	Resistance training: 10repetitions×3×3times/week	70%–80% 1RM	4 months	HFC, BMI, TG, HDL, HbA1c	HFC and HbA1c decreased in both groups.
(10)	Resistance training	Resistance training: 8–12 repetitions×3×3 times/week	Unmentioned	Under supervision ≥2 times	Daily activities	Unmentioned	3 months	HFC, BMI, WC, BP, TG, HDL, FBG, HbA1c	HFC, BMI, and WC decreased in resistance training group.
(29)	Aerobic training	Aerobic training: 30–40min×3 times/week	Unmentioned	Under supervision first 2 sessions	Daily activities	Unmentioned	12 weeks	HFC, BMI, TG, FBG, HbA1c, HOMA-IR	HFC and BMI decreased in HIIT group.
(30)	Both	Resistance exercise: 10 repetitions×2–3×3 times/week	70%–80% 1RM, RPE: 13–14	Under supervision Closely	Aerobic training: 20–30 min×3times/week	75% of max HR	12 weeks	HFC, BMI, WC, TG, HDL	HFC and WC decreased in resistance training group.
(12)	Aerobic training	Aerobic training I: Moderate 6month; 30 min×5 times/week and vigorous 6months 30 min×5times/week×6months	60%–80% of max HR for vigorous exercise; 45%–55% of max HR for moderate exercise	Under supervision 1 time/week	Daily activities	Unmentioned	12 months	HFC, BMI, WC, BP, TG, HDL	WC and SBP reduced in aerobic training I group. HFC reduced in both aerobic training groups.
		Aerobic training II: 30min×5times/week×12months	45%–55% of max HR						
(32)	Aerobic training	Aerobic training: 30–50 min×2times/week	10% below RCP	Under supervision	Daily activities	Unmentioned	24 weeks	HFC, BMI, WC, TG, HDL,HbA1c, HOMA-IR	WC decreased and HDL increased in aerobic group.
(34)	Both	Aerobic trainingI: 3min×3vigorous +2 min×2 rests)×3 times/week	80%–85% of VO2 peak	Unmentioned	Resistance training: 3times/week	1RM	12 weeks	HFC, TG, HOMA-IR	HFC reduced in both aerobic groups.
		Aerobic training II: 40min×3times/week	60%–65% of VO2 peak						
(33)	Both	Aerobic training and/or Resistance training:45–60 min×3 times/week	Aerobic training: RPE: 16–18; Resistance training: RPE: 14–16	Under supervision	Daily activities	Unmentioned	12 weeks	HFC, TG, HbA1c, HOMA-IR, CRP	HFC and TG reduced in interventions group.

(Continued)

TABLE 4 Continued

Reference	Types	Intervention			Control		Duration	Outcome	Result
		Types	Intensity	Supervision	Types	Intensity			
(35)	Both	Aerobic training: 45 min×5 times/week,	50%–70% of max HR	Unmentioned	Daily activities	Unmentioned	6 months	HFC, BMI, WC, BP, TG,HLD,FBG, HOMA-IR	HFC, WC, DBP, TG, FBG, and HOMA-IR reduced in both interventions groups.
		Resistance training:: 10–15 repetitions×3×3/week	Unmentioned						
(41)	Aerobic training	Aerobic training: 4 min×3vigorous+2 min ×2 rests)×3/week	80%–85% of VO2 peak	Unmentioned	Daily activities	Unmentioned	8 weeks	HFC, BMI, TG, FBG, HbA1c, HOMA-IR	HFC, FBG, and HbA1c decreased in the aerobic group.
(44)	Resistance training:	Resistance training:: 40 min×4 times/week	60%–80% of max HR	Under supervision	Usual activities	Unmentioned	8 weeks	HFC, TG, HDL, FBG, HbA1c, HOMA-IR	HOMA-IR decreased in resistance training group.
(43)	Aerobic training	Aerobic training 30–60 min×5 times/week	60%–80% of max HR	Under supervision 1 time/week	Daily activities	Unmentioned	3 months	HFC, BMI, WC, BP, TG, FBG	HFC, WC, and TG reduced in aerobic training group.
(18)	Both	Aerobic training I:(4 min×3 vigorous+2 min×2rests)×3times/week	80%–85% of VO2 peak	Under supervision	Daily activities	Unmentioned	8 weeks	HFC, BMI, TG, HDL, HbA1c, HOMA-IR	HFC reduced in both intervention groups.
		Aerobic training II:(4 min×3 ME at +2 min×2rests)×3 times/week	60%–70% of max HR						

HFC, hepatic fat content; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL, high-density lipoprotein; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HOMA-IR, homoeostasis model of assessment-estimated insulin resistance; CRP, high-sensitivity C-reactive protein; RPE, rating of perceived exertion; CWT, circuit weight training; HR, heart rate; RCP, respiratory compensation point.

TABLE 5 Diet combined with exercise interventions.

Reference	Intervention	Control	Duration	Outcome Measures	Result
(25)	Diet: 1000–1500 kcal/day, 25% from fat Exercise: 10,000 steps/day, 200 min/week	Usual lifestyle	48 weeks	HFC, BMI, WC, TG, HDL, HbA1c, HOMA-IR	HFC reduced in intervention group.
(27)	Diet: 1200 kcal/day, Carbohydrate:fat:protein: 55:30–35:15 Exercise: 40 min×36 times, 65%–75% of maximum HR	No intervention	3 months	BMI, HOMA-IR	BMI and HOMA-IR reduced in intervention group.
(31)	Diet: 1200 kcal/day, carbohydrate:fat:protein: 55:30–35:15 Exercise: 40 min×3 times/week, 65%–75% of maximum HR	No intervention	3 months	BMI, TG, HDL, HOMA-IR	BMI, TG, and HOMA-IR reduced in intervention group. HDL increased in intervention group.
(13)	Diet: 1500 kcal/day for women, 1800 kcal/day for men, carbohydrate:fat:protein: 45:35:20, Exercise: 30min/day, optimal sleep Diet: 1500 kcal/day for women, 1800 kcal/day for men, carbohydrate:fat:protein: 45:35:20	Usual lifestyle	6 months	HFC, BMI, TG, HDL, FBG, HOMA-IR	HFC decreased in both intervention groups.
(40)	Diet: first 6 weeks: 2 daily meals replace soy–yogurt–honey Following 18 weeks, 1 daily meal replace soy–yogurt–honey	Usual lifestyle	24 weeks	HFC, BMI, WC, HG, HDL, FBG, HbA1c	HFC reduced in intervention group.
(42)	Individualized caloric goal 10,000 steps/day	Usual lifestyle	6 months	BMI, WC, SBP, DBP	WC, SBP, and DBP reduced in intervention group.

HFC, hepatic fat content; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL, high-density lipoprotein; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HOMA-IR, homoeostasis model of assessment-estimated insulin resistance.

with NAFLD showed that low carbohydrate diet had greater clinically meaningful improvements in glycemic control and weight compared with low fat diet, which is in line with our results. The participants in this RCT meet the diagnostic criteria for MAFLD (49). However, the participants in this RCT are part of the MAFLD, which are not representative of the MAFLD as a whole. Furthermore, the RCT also showed the changes were not sustained 3 months after intervention. The Mechanisms maybe that carbohydrate, the main raw material for liver's fat synthesis, reduced in diets would inhibit the fat accumulation in hepatocytes, while initiating lipolysis to reduce HFC (51). In a word, it deserves our attention that the results are different after MAFLD redefinition and more researches about comparing low carbohydrate diet with low fat diet are needed.

Our meta-analysis compares the intervention effects of aerobic and resistance training in adults with MAFLD. We find that resistance exercise is more effective than aerobic exercise in improving HFC and TG. This result is supported by a previous meta-analysis (52). Their results showed that resistance exercise leads to more effective outcomes in improving the metabolic syndrome and cardiovascular risk parameters compared to aerobic exercise. Resistance exercise was the most significant effective training method in ameliorating body fat while aerobic exercise was best in improving BMI significantly. The possible reason is that resistance exercise increases muscular strength, endurance, and muscle mass. Muscle mass engaged during exercise stimulates more IL-6 release that has a direct impact on glucose and lipid metabolism (53).

However, a recent RCT showed that aerobic training and resistance training with dietary modification are equally effective for reducing HFC and improving underlying insulin resistance among patients with NAFLD (54). The possible reason for the discrepancy would be the different interventions. Hence, future research should distinguish aerobic and resistance exercise and focus on the advantages of resistance exercise in improving HFC and TG.

We also find diet combined with exercise interventions are significant on MAFLD. This finding is consistent with a published systematic review, which shows that a range of lifestyle interventions significantly improve NAFLD (19). Meanwhile, this finding is similar to two other systematic reviews in children with NAFLD, which reports that lifestyle interventions significantly improve NAFLD (22, 23). The results are also in line with a recent RCT study, which shows lifestyle intervention with diet and regular exercise improved functional fitness in middle-aged patients with NAFLD and Metabolic Syndrome (55). However, none studies have compared the differences of diet, exercise and diet combined exercise interventions on MAFLD. Hence, further research should consider diet combined exercise interventions, and comparing their effects from diet only or exercise only intervention on MAFLD.

Our results remind evidence about lean/normal weight MAFLD is insufficient. According to the new diagnostic criteria of MAFLD, MAFLD could be divided into three subgroups, including overweight/obesity, type 2 diabetes and lean/normal weight. We
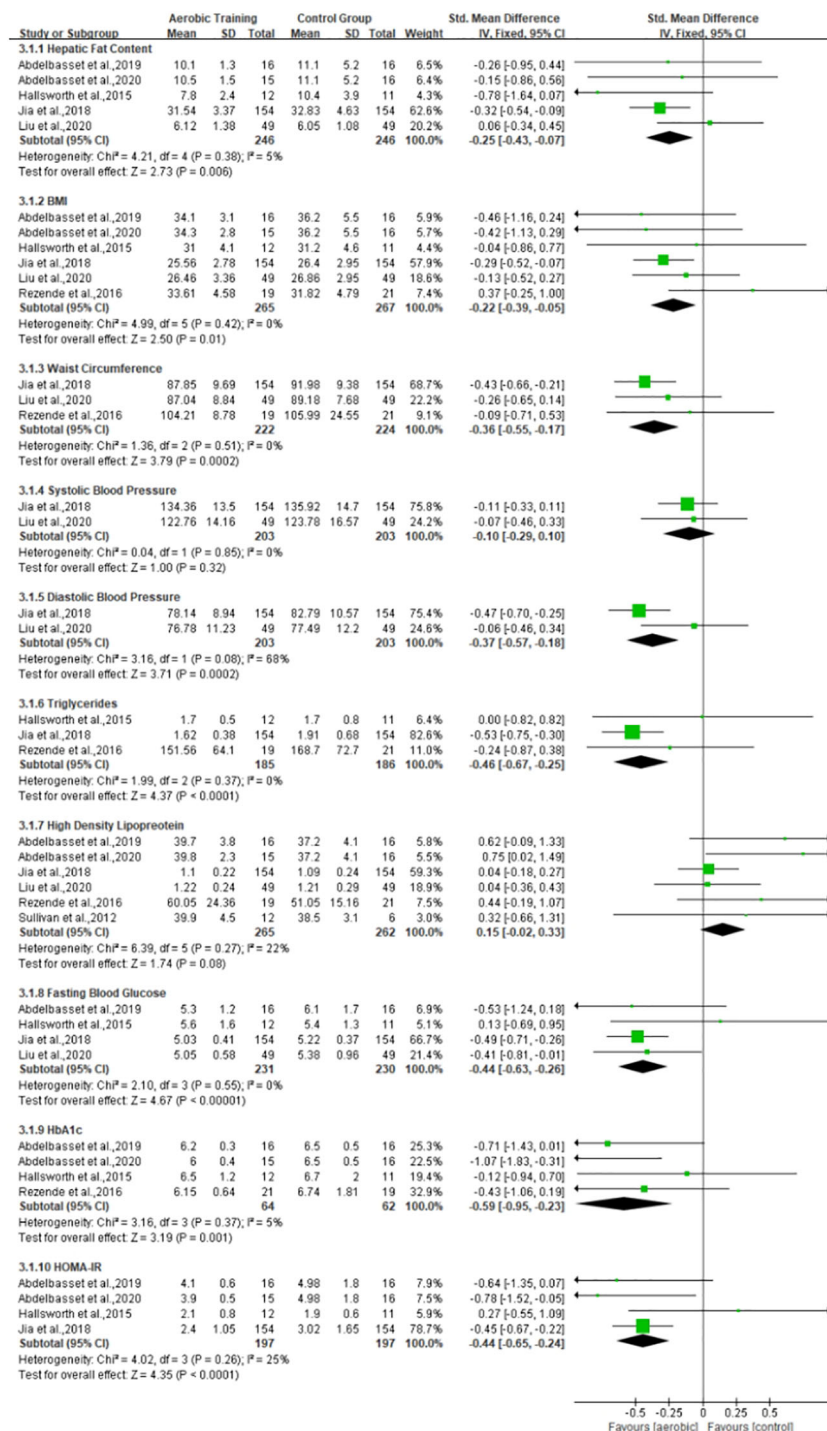
FIGURE 3
Effect of aerobic training *vs.* control group on MAFLD.

find that all the participants included in this article are obesity, 8% of them have diabetes together, but none is lean or normal weight, which makes the results more applicable to obesity MAFLD rather than lean or normal weight MAFLD. A retrospective cohort study shows improvement in histological liver steatosis on liver biopsy in non-obese patients with NAFLD treated with diet combined with exercise after a mean of 10 weeks (56). A Japanese meta-analysis showed lean NAFLD individuals makeup 20% of the NAFLD population, were older, and had higher mortality (57). A recent meta-analysis also found that a higher mortality in patients with lean NAFLD than those with non-lean NAFLD (58). The results remind that further research about the risk factors and effective
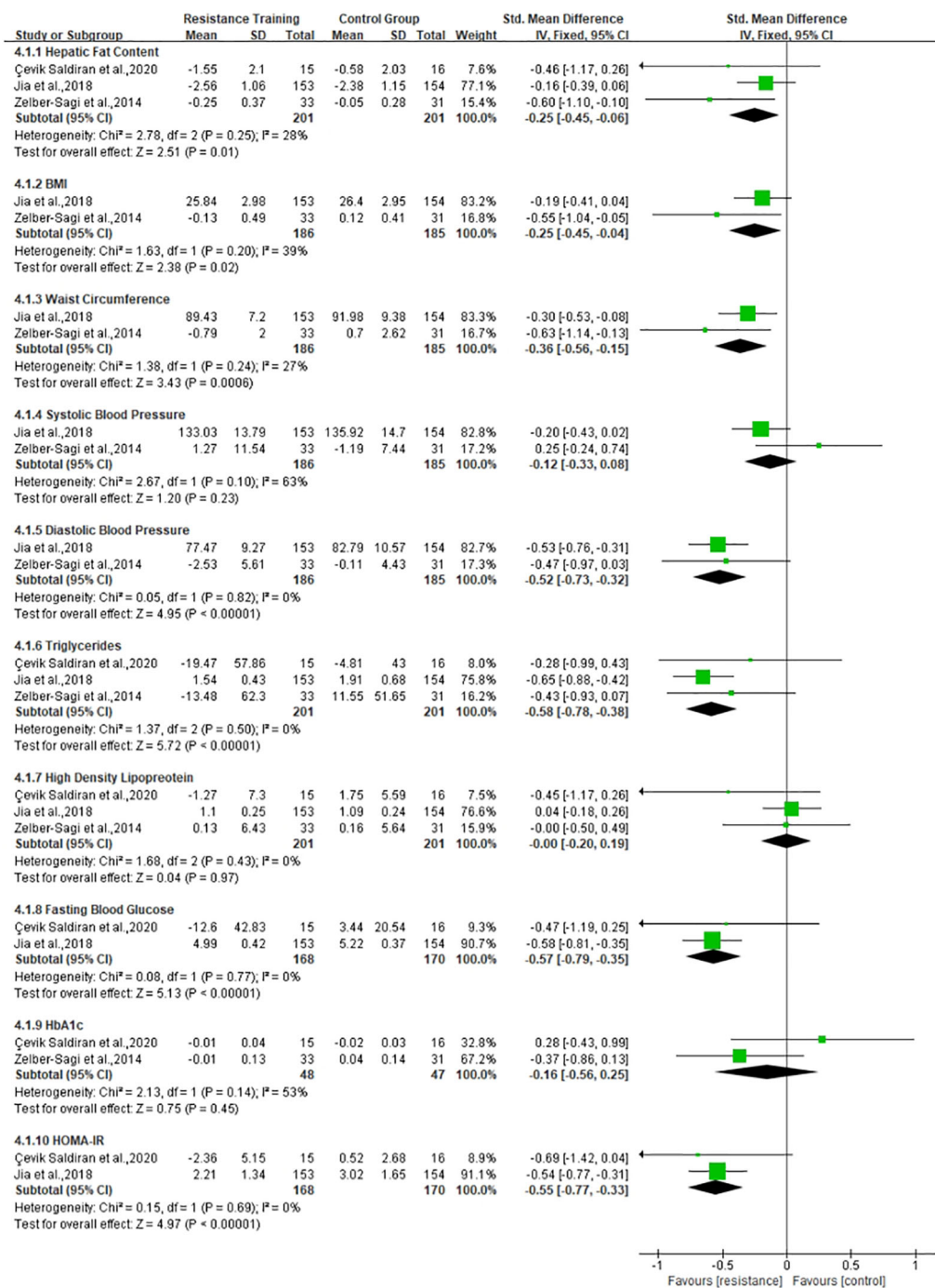
FIGURE 4
Effect of resistance training *vs.* control group on MAFLD.

interventions of lean NAFLD is warranted. Hence, we suggest that future research should focus not only on obesity MAFLD, but also on lean or normal weight MAFLD.

Our results also remind evidence about certain metabolism-related indicators is needed. NAFLD focus on glutathione aminotransferase, aspartate aminotransferase and fatty fibrosis, while MAFLD focus on HFC and metabolism-related indicators.

The outcomes of interest in our study include HFC, WC, BP, TG, HDL, FBG, HbA1c, HOMA-IR, and CRP. However, not all metabolism-related indicators were analyzed in each included study, especially CRP. We could not analysis the effects of lifestyle interventions on CRP in MAFLD according to available data. These suggest that certain metabolism-related indicators deserve attention in future research.
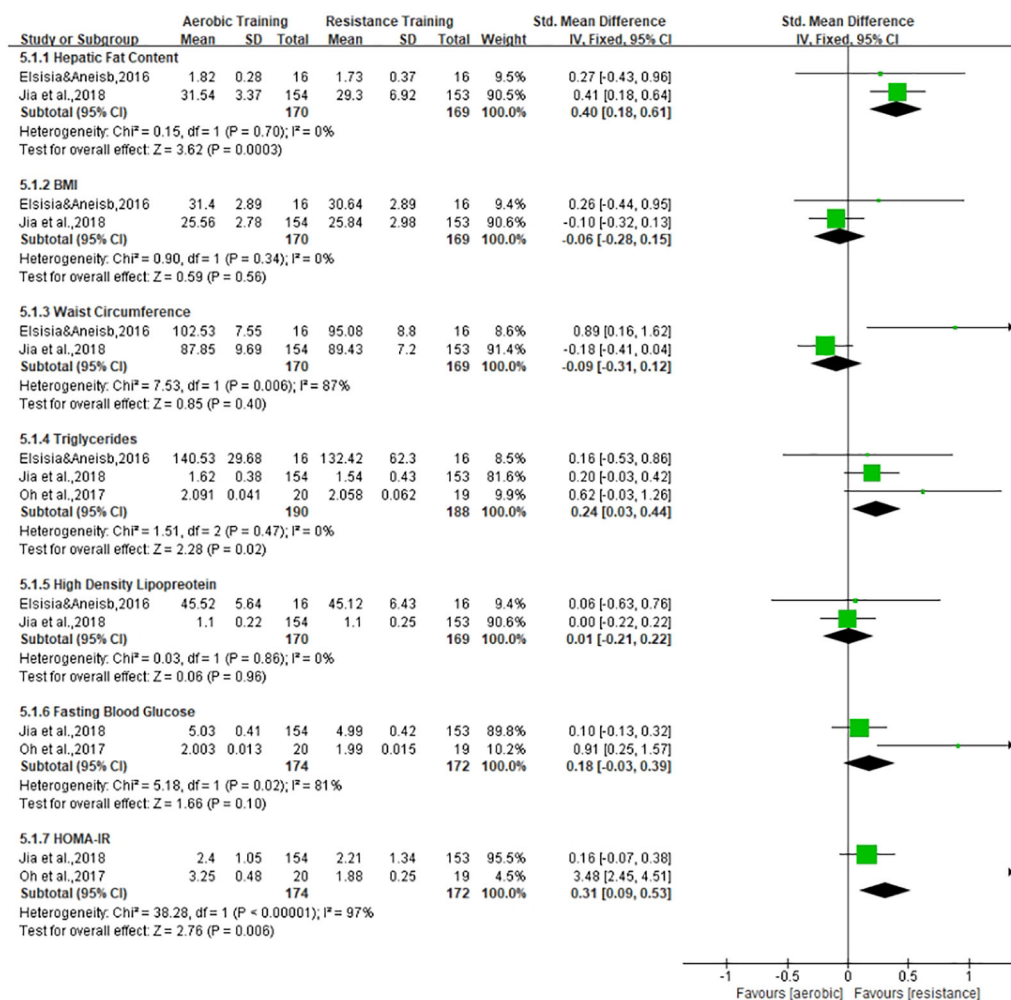
FIGURE 5
Effect of aerobic training *vs*. resistance training on MAFLD.

4.1 Limitations

This review has several limitations. First, there is moderate heterogeneity among the analyzed studies, in part due to the differences in inclusion criteria and type and duration of lifestyle interventions. Second, not all interesting end points are reported in the included studies. For example, CRP is not reported in a majority of included studies, and the effect of lifestyle on CRP could not be evaluated. Third, selection bias, performance bias, and follow-up bias in some of the analyses could be another limitation. Therefore, the results should be taken with caution, and more studies on the effect of lifestyle interventions are required to reinforce the recommendations of lifestyle in the treatment and prevention of MAFLD.

4.2 Implications for practice

The recommendations for future research are provided as follows. First, the MAFLD subjects can be divided into overweight/obesity, type 2 diabetes, or lean/normal weight, and subjects with lean/normal weight MAFLD should be focused more because they are more likely to be overlooked and there is insufficient evidence from existing studies. Second, lifestyle interventions should include both diet and exercise and respect for preferences of MAFLD; for example, resistance training may be more feasible than aerobic training for MAFLD patients who are less fit or unable to tolerate aerobic training. Lastly, future studies should focus more on all metabolism-related indicators, especially CRP.

5 Conclusion

This systematic review and meta-analysis examine the effects of lifestyle interventions on adults MAFLD for the first time after the name changed. Low carbohydrate diet is more effective in improving HFC than low fat diet in adults with MAFLD. Resistance exercise is more effective than aerobic exercise in improving HFC and TG in adults MAFLD. Diet combined with exercise interventions are significant on MAFLD. However, our results more applicable to obesity MAFLD rather than lean or normal weight MAFLD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1081096/full#supplementary-material

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