Impact of exercise training on the sarcopenia criteria in non-alcoholic fatty liver disease: a systematic review and meta-analysis

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Abstract

Sarcopenia is a highly prevalent complication of non-alcoholic fatty liver disease (NAFLD). We aimed to conduct a systematic review and meta-analyses to elucidate the exercise training (ET)'s efficacy on NAFLD adult patients' sarcopenia criteria. We identified relevant randomized controlled trials (RCT) in electronic databases PubMed, CINAHL, and Scopus. We selected seven RCT from 66 screened studies. The ET programs included endurance or combined (endurance and resistance) training. No study performed resistance training alone. The physical function improved with endurance or combined training (mean differences [MD] 8.26 mL/Kg*min [95% CI 5.27 to 11.24 mL/Kg*min], $p < 0.0001$); Muscle mass showed no evidence of the beneficial effects of endurance or combined training (MD 1.01 Kg [95% CI -1.78 to 3.80 Kg], $p = 0.48$). None of the selected studies evaluated muscle strength. Endurance and combined training increase physical function criteria but do not improve muscle mass criteria on sarcopenia in NAFLD patients. These results must be interpreted with caution for the small number of patients included in the RCTs analyzed, the different characteristics of the ET carried out, the non-use of resistance training, which prevents assess its effect on sarcopenia despite the evidence that recommends it and does not assessment muscle strength criteria in RCT include. Future research should include muscle strength assessments and resistance training to evaluate the effects in this condition. Exercise training is beneficial for sarcopenia in NAFLD but is necessary more experimental evidence to define the best type of training that positively affects the three criteria of sarcopenia. PROSPERO reference number CRD42020191471.

Key Words: endurance training, resistance training, sarcopenia, non-alcoholic fatty liver disease, skeletal muscle.

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Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease (CLD). It includes a broad spectrum of disorders ranging from accumulating lipids in the liver (steatosis) to the progressive inflammation denoted as non-alcoholic steatohepatitis (NASH) to advanced stages of damage such as fibrosis and cirrhosis.[1,2]

Sarcopenia is one of the most common complications associated with NAFLD, with 30—70% prevalence.[3] According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia diagnosis is based on three criteria: i) low muscle strength (the primary indicator of sarcopenia), ii) small muscle quantity or quality, and iii) low physical performance.[4] Sarcopenia negatively affects NAFLD progression;[5] its severity is more pronounced in the advanced stages of NAFLD, considered an independent predictor of pre- and post-liver transplant complications and mortality.[6,7] Therefore, therapeutic interventions to prevent, revert or improve sarcopenia associated with NAFLD are essential.

Since sarcopenia involves a decline in muscle mass, strength, and physical performance, exercise training

(ET) is a promising tool for treating sarcopenia.[8] Due to low-quality evidence, the results of studies that evaluate the effect of ET on patients with cirrhosis-associated sarcopenia are highly variable and inconclusive.[9] Despite proof that training has a positive impact on liver dysfunction parameters in patients with NAFLD,[10,11] no studies evaluate the effect of training on sarcopenia criteria in NAFLD patients. Besides, to prevent functional decline, it is critical to establish the best exercise type to improve muscle strength, muscle mass, and physical performance in NAFLD patients. Thus, more evidence is required to determine exercise specifications (type, intensity, frequency, supervised vs. domiciliary).[1]

Considering all the antecedents, the effects of ET on sarcopenia criteria associated with NAFLD are not determined. Therefore, our objective was to conduct a systematic review and meta-analyses to elucidate the exercise training's efficacy on strength, muscle mass, and physical performance in adult patients with NAFLD.

Methods

Protocol and Registration

We conducted our systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (See S1). We registered the review protocol in the International Prospective Register of Systematic Reviews (PROSPERO reference number CRD42020191471), available from 3 September 2020.

Search strategy

We performed a systematic search in PubMed, CINAHL, and Scopus from March-May 2020. We included articles published from January 2000–March 2020 containing the critical concepts of sarcopenia, fatty liver disease, exercise, and related words. The essential concepts of the search were different for each database. For example, for PubMed, we used the keywords (‘atrophic muscular disorders’ OR ‘muscle atrophy’ OR ‘muscle degeneration’ OR ‘muscle fiber atrophy’ OR ‘muscle fiber degeneration’ OR ‘muscle wasting’ OR ‘muscular wasting’ OR ‘muscular atrophy’ OR ‘muscular atrophies’ OR ‘muscular degeneration’ OR ‘sarcopenia’) AND (‘non-alcoholic steatosis’ OR ‘non-alcoholic fatty liver disease’ OR ‘fatty liver’ OR ‘hepatic fat’ OR ‘liver fibrosis’ OR ‘liver disease’ OR ‘fatty liver disease’ OR ‘obesity’) AND (‘exercise’ OR ‘physical activity’ OR ‘exercise intervention’ OR ‘training’) (See S2). We filtered the results for clinical randomized controlled trials (RCTs). Then, AG reviewed all titles and abstracts from the articles selected and only downloaded those matching the inclusion criteria.

Inclusion/exclusion criteria

Inclusion and exclusion criteria are listed in Table 1. Two researchers (CH-S and MV-B) independently reviewed the full-text version of the reports. They resolved

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria

- The inclusion criteria are based on the study population, intervention, comparison question (control), and outcomes (**PICO**).[12]
- Investigate adults (18 or older) with liver disease of non-alcoholic origin (expressly, NAFLD or NASH) as confirmed by at least one of these parameters: hepatic biopsy, ultrasonography, computed tomography (CT), nuclear magnetic resonance spectroscopy (MRS), serum bile acids, gamma-glutamyl transpeptidase (GGT), aminotransferases, the ratio of aspartate transaminase (AST)/alanine transaminase (ALT) or bilirubin, alkaline phosphatase, dyslipidemia) (***P**opulation*).[13-17]
- Apply resistance training, endurance training, or both. Combined exercise is defined as interventions that simultaneously used resistance and endurance training (***I**ntervention*).
- Apply exercise alone or in combination with other interventions (educational, nutritional, etc.); must have a control group and a group with exercise only (to determine its independent effect) (***C**ontrol*). Control groups cannot have any intervention that could influence study outcome measures (e.g., nutritional or physical intervention). Moreover, the exercise group participants must perform three or more training sessions per week for at least four weeks to determine the chronic effect of exercise on the variables. Studies must conduct pre- and post-intervention assessments to identify changes in the variables.
- Assay sarcopenia criteria included in the consensus definition of sarcopenia:[1,4] muscle strength, defined as the force generated through muscular contraction against an external load;[18] muscle mass, defined as the part of total body mass composed of skeletal muscle tissue;[19] and physical performance, defined as an objectively measured whole body function related with mobility. [20] Thus, the studies must evaluate sarcopenia criteria, as was described in S3 (***O**utcome*).
- Be a peer-reviewed study
- Be written only in English

Exclusion criteria

- Bibliographic reviews, not controlled or randomized clinical trials, animal models
- The participants had comorbidities: type II diabetes mellitus, viral hepatitis, cardiovascular disease, lung disease, or neurological disease.
- Interventions that would interfer with identifying any exercise-mediated effects.

Table 2. *Included studies—exercise programming details and sarcopenia criteria's assessment*

	n		Endurance training			Resistance Training			Sarcopenia criteria's assessment		
Study	**EX**	**CG**	**Duration**	**Intensity**	**Method**	**Duration**	**Intensity**	**Method**	**PP**	**MM**	**Strength**
Sullivan (2012)[21]	12	6	30-60 min 5x/wk 16 wk	45%-55% $VO_{2\ peak}$	Walking	NA	NA	NA	CPET	DXA	NA
Pugh (2013)[22]	6	5	30-45 min 3-5/wk, 12-16 wk	30%-60% HRR	Gymnasium	NA	NA	NA	CPET	NA	NA
Pugh (2014)[23]	13	8	30-45 min 3-5x/wk 12 wk	30%-60% HHR	Cycle ergometer	NA	NA	NA	CPET	NA	NA
Shojaee-Moradie (2016)[24]	15	12	20-60 min 4-5x/wk 16 wk	40%-60% HRR	Gymnasium and outdoor aerobic activities	20-60 min 4-5x/wk 16 wk	NR	NR	CPET	NA	NA
Hallsworth (2015)[25]	11	12	30–40 min 3x/wk 12wk	RPE 16-17	Cycle ergometer	30–40 min 3x/wk 12wk	Light band resisted	Face-pull, horizontal push, horizontal pull, and 30° push.	CPET	ADP	NA
Houghton (2017)[26]	12	12	45-60 min 3x/wk 12 wk	RPE 16-18	Cycling	45-60 min 3x/wk 12 wk	RPE 14-16	Knee extension, horizontal row, chest press, vertical row	CPET	ADP	NA
Cheng (2017)[27]	29	29	30-60 min 2-3x/wk 6,8-11 months	60%-75% VO_{2max}	Nordic brisk walking	NA	NA	NA	2-Km WT	DXA	NA

discrepancies/disagreements by consensus. When this was not possible, two independent researchers acted as referees (AG and CC-V).

Data extraction

We collected the data from seven final papers (n = 7), which we tabulated and ordered into a Microsoft Excel 2016 database. One researcher extracted the data, and two different researchers reviewed it to ensure data processing accuracy (Table 2). The data included the following parameters: first author's surname; publication year; the number of participants in a group; type, intensity, frequency, and duration of the exercise intervention; sarcopenia criteria assessment methods. When studies presented intention-to-treat (ITT) values, we only extracted ITT data. Data extraction and synthesis for the outcome of interest are shown in the data synthesis section.

TESTEX rating scale application

We assessed study quality using the TESTEX rating scale (Table 3).[28] It includes criteria to evaluate methodological quality as well as ranking the whole article. The scale comprises 12 assessment criteria for a maximum score of 15 points. Higher ratings reflect better study quality and reporting.[28] TESTEX does not yet provide a validated cut-off score,[28] so we categorized the studies depending on the median score.[10,29] We classified studies above the median score as 'high-quality' and those below as 'low-quality'. AG and OA performed TESTEX scoring separately. When different evaluations occurred, they discussed discrepancies until reaching a consensus score.

Data synthesis

When at least three included studies reported the same outcome, we pooled data to perform a meta-analysis using Review Manager 5.4 (RevMan 5.4) as per the Cochrane Manual for Systematic Reviews of Interventions.[30] We used a random-effects model for heterogeneity to address study participants' different backgrounds and various exercise interventions (which create differences in training variables such as exercise intensity and duration, session frequency, etc.). Outcome measures also differ among studies depending on the available technology to quantify muscle mass and

***Table 3** Study quality using the TESTEX rating scale.*

Study\Score	1	2	3	4	5	6	7	8	9	10	11	12	TOTAL
2012 Sullivan[21]	1	1	1	1	0	2	0	2	1	0	1	1	11
2013 Pugh[22]	1	0	1	1	0	3	0	2	1	0	1	1	11
2014 Pugh[23]	1	1	1	1	0	1	0	2	1	0	1	1	10
2016 Shojaee-Moradie[24]	1	1	1	1	0	1	0	2	1	0	1	1	10
2015 Hallsworth[25]	1	1	1	1	0	0	0	2	1	0	1	1	9
2017 Hughton[26]	1	1	1	1	0	3	0	2	1	0	1	1	12
2017 Cheng[27]	1	1	1	1	1	2	1	2	1	0	1	1	13
										Median	11		

physical performance. Finally, we expected methodological heterogeneity, as exercise training research uses different designs. We used inverse variance because we analyzed continuous data to compare exercise vs. control or conventional care groups using mean and standard deviations from post-intervention values for each outcome. When other forms of variability measures such as standard error or confidence intervals (CIs) appeared, we calculated the standard deviations using RevMan 5.4.[30] We did not plan to investigate patients' subgroups, as we expected the participants to be homogeneous (see inclusion criteria). However, considering the heterogeneous nature of exercise training protocols, we expected to find different exercise training types classified as either endurance or resistance. In this variety, we planned to perform a subgroup analysis comparing endurance training vs. resistance training, investigate the heterogeneity across subgroup results, and analyze the variability in effect estimates between exercise types using an I^2 statistic. For each outcome analyzed, we present the data as mean differences (MD) with a 95% CI. We used standardized mean differences (SMD) to represent effect sizes and facilitate interpretations,[31] with a value of 0.2 set as small, 0.5 as

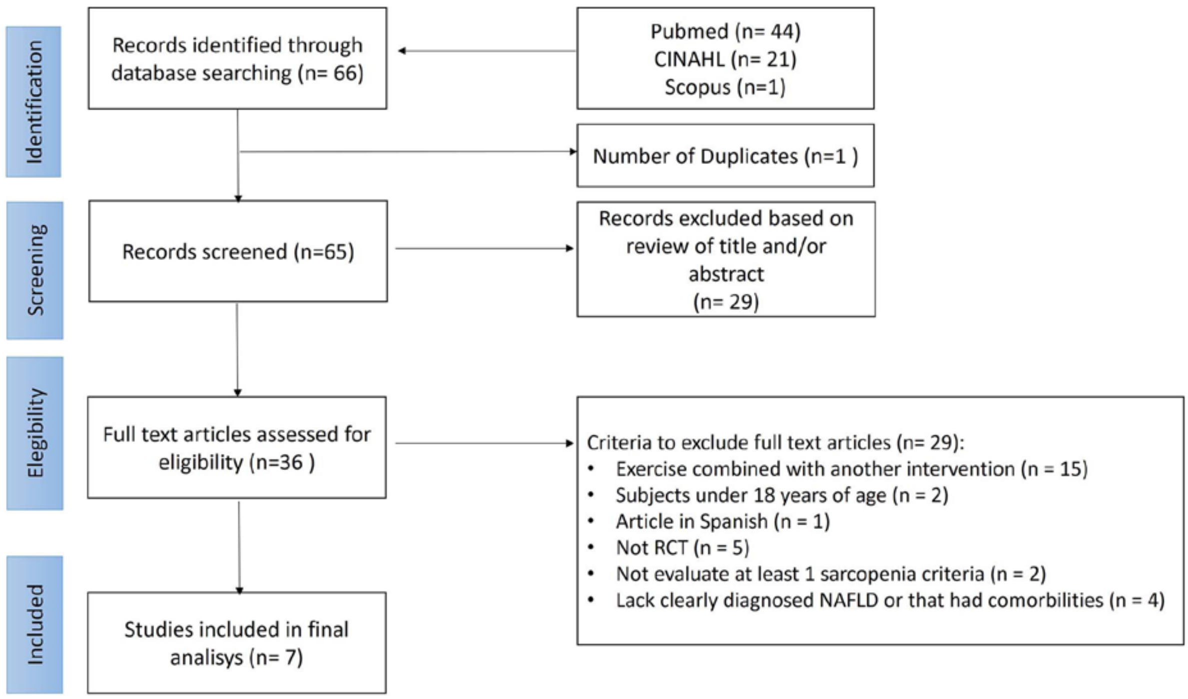

***Fig 1.** Flow chart to the PRISMA statement. Flow chart of search results and study selection according to the PRISMA statement.*

Study or subgroup	Exercise			Control				Mean Difference	
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Sullivan 2012[21]	24.8	5.2	12	19.9	6.1	6	27.4%	4.90 (-0.80, 10.60)	2012
Pugh 2013[22]	36.5	15.2	6	22.1	4.6	5	5.4%	14.40 (1.59, 27.21)	2013
Pugh 2014[23]	33.4	12.2	13	24.8	11.5	8	8.3%	8.60 (-1.77, 18.97)	2014
Shojaee-Moradie 2016[24]	33	5.8	15	23.8	4.5	12	58.9%	9.20 (5.31, 13.09	2016
Total (95% CI)			**46**			**31**	**100.0%**	**8.25 (5.27, 11.24)**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.45$, df = 3 (P = 0.49); $I^2 = 0\%$									
Test for overall effect: Z = 5.42 (P < 0.000001)									

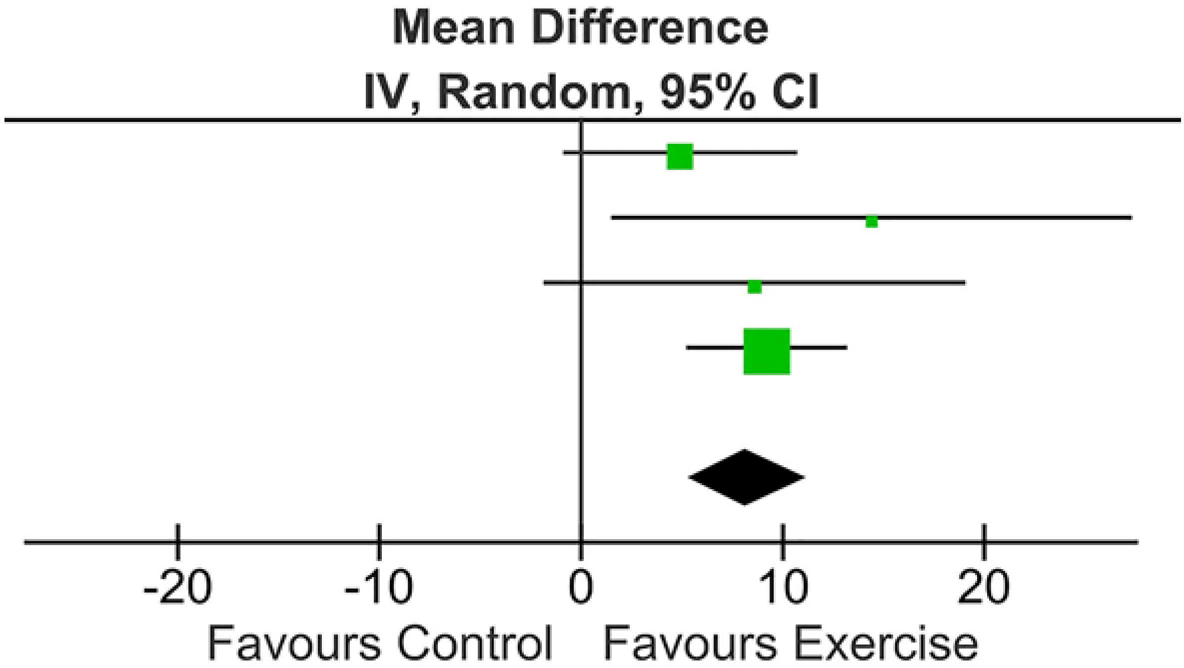

***Fig 2**. Forest Plot for physical performance. A meta-analysis of pooled effect size and confidence intervals (CIs) (95%) of the interventions with exercise versus control group on physical performance evaluated by the cardiopulmonary exercise test (CPET) (mL/Kg * min).*

moderate, and 0.8 or higher as large effect size.[32] Positive values indicated that it was favorable to the exercise intervention and vice versa. Zero value suggested that there was no effect on the analyzed variable.

Heterogeneity

We quantified heterogeneity using the χ^2 test, where a significant *p-value* was indicative of more considerable heterogeneity. We also applied a complementary inconsistency test I^2 and presented this with its corresponding 95% CI to assess the degree of heterogeneity. Higher I^2 values indicated more significant heterogeneity.[33]

Risk of Bias

We assessed all the included RCTs using the Cochrane collaboration risk of bias tool to search for elements that could over- or under-estimate the intervention's effect. We evaluated the following for each study: selection bias (random sequence and generations, allocation concealment), performance bias (blinding of participants and research staff), detection bias (blinding of outcome evaluation), attrition bias (incomplete outcome data), reporting bias (selective reporting), other sources of bias.[30] Two independent reviewers (AG and OA) performed the assessments; they discussed discrepancies until reaching a consensus.

Results

Review studies

We initially identified 66 articles in PubMed, CINAHL, and Scopus. Of these, we excluded one by duplication and 29 after analyzing the title and abstract. Among the remaining 36 articles, we excluded 29 due to the combination of exercise with another intervention (n = 15), participants under 18 years (n = 2), articles written in Spanish (n = 1), reports not RCTs (n = 5), no determination or evaluation of sarcopenia criteria (n = 2), and patients were not diagnosed with NAFLD or had comorbidities (n = 4). S4 contains the excluded studies list with the causes for the exclusion.[34-61] We included seven articles in the final analysis (Figure 1).[21-27]

Description of included studies

A total of 182 participants were included in the analysis. Among them, 98 persons participated in exercise interventions and 84 in control groups (see Table 2). Five studies used a moderate-intensity protocol of endurance training.[21-24,27] Three studies used a combined exercise protocol (endurance and resistance)[24-26,] and no study applied resistance training alone; in all seven studies, the exercise interventions were supervised. All the studies had a control group composed of patients with NAFLD following standard or conventional care, which did not include exercise intervention or any other component that could have influenced interest outcomes.[21-27] Duration of exercise intervention ranged from 12–16 weeks, with training frequency of 2–5 times per week lasting 20–60 min per session. Endurance training intensity varied from 45–75% of oxygen consumption peak (VO_{2peak}), 30–60% of heart rate reserve (HRR), or 16–18/20 (Borg Scale) rating of perceived exertion (RPE). Endurance training varied among cycle ergometer, treadmill, Nordic brisk walking, walking, and self-selected gymnasium exercise routines.

Two articles described high-intensity interval training (HIIT) as a form of endurance training. One of these articles used five intervals of 2 min, adding 10 s to each range per week with 3 min of recovery and an RPE (Borg Scale) intensity of 16–17 (very hard).[25] The other article used cycling intervals with an RPE (Borg scale) intensity of 16–18.[26] In the remaining five studies patients performed continuous training.[21-24,27]

Among the three articles that carried out combined training, one performed a moderate-intensity endurance protocol (40%–60% HRR) combined with resistance training. However, the latter training details were not described. [24] Another study used a combined training protocol by performing endurance interval training in cycling with an intensity based on RPE of 16–18 (very hard) and resistance training with an RPE intensity of 14–16 (hard). The resistance training includes hip and knee extensions, horizontal rows, chest presses, and vertical rows. [26] One article required participants to perform an interval on a cycle ergometer, followed by a light-band-resisted upper body exercise (60 s) in the following order: face-pull, horizontal push, horizontal pull, 30° push. However, it was unclear whether this protocol was a combined workout. [25]

Quality assessment analysis

The TESTEX scale analysis yielded a median score of 11 out of 15 possible points for the studies, [10] with values closer to 15 representing a higher quality than values closer to 1. We evaluated assessment quality by organizing the studies as low-quality if their score was less than the median and high-quality if the score was greater than or equal to the median. [10] Accordingly, six studies were of high quality, and one article was low-quality (Table 3). The main weaknesses TESTEX revealed were the supervision of physical activity in the control groups (0 of 7 articles), intention-to-treat analysis (1 of 7 studies), and blinding of the assessor for at least one key outcome (1 of 7 articles).

Risk of bias assessment

The risk of bias was low in the RCTs included in this systematic review and meta-analyses for every outcome (S5 and S6). However, we had some concerns about their analysis of physical performance regarding blinding the assessors. Only one of the studies performed this key methodological feature, indicating a potential risk of detection bias for articles that used a cardiopulmonary exercise test (CPET) to assess physical performance, as assessors might influence patients' performance in this type of evaluation. The details about the risk of bias assessment can be found in S5 and S6.

Change in muscle strength

The muscle strength criterion for sarcopenia was excluded because none of the selected studies evaluated it.

Change in physical performance

We performed a meta-analysis with the results obtained post-exercise by comparing the control group vs. the exercise group for the physical performance criterion. Data on physical performance were present in four studies, [21-24] which determined the direct maximum oxygen consumption (VO_{2max}) or oxygen consumption peak (VO_{2peak}) based on CPET and expressed in mL/Kg*min. In this regard, we excluded one article because it performed the 2 Km walking test, which does not directly evaluate physical performance.[27] Three studies showed significant increases in VO_{2max} or VO_{2peak}.[22-24] One study showed no change; here, the authors recognized that a type II statistical error could explain the results because of the small number of participants.[21] The pooled analysis of the studies indicated a change in physical performance in favour of exercise (MD 8.26 mL/Kg*min [95% CI 5.27–11.24

Study or subgroup	Exercise			Control				Mean Difference	
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Sullivan 2012[21]	62	12.8	12	65	12	6	5.4%	-3.00 (-15.03, 9.03)	2012
Hallsworth 2015[25]	55.6	11.1	11	58.4	7.3	12	12.9%	-2.80 (-10.55, 4.95)	2015
Houghton 2017[26]	58	10	12	57	7	12	16.3%	1.00 (-5.91, 7.91)	2017
Cheng 2017[27]	42.5	6.6	29	40.4	6.8	29	65.4%	2.10 (-1.35, 5.55)	2017
Total (95% CI)			**64**			**59**	**100.0%**	**1.01 -1.78, 3.80)**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.74$, df = 3 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 0.71 (P = 0.48)

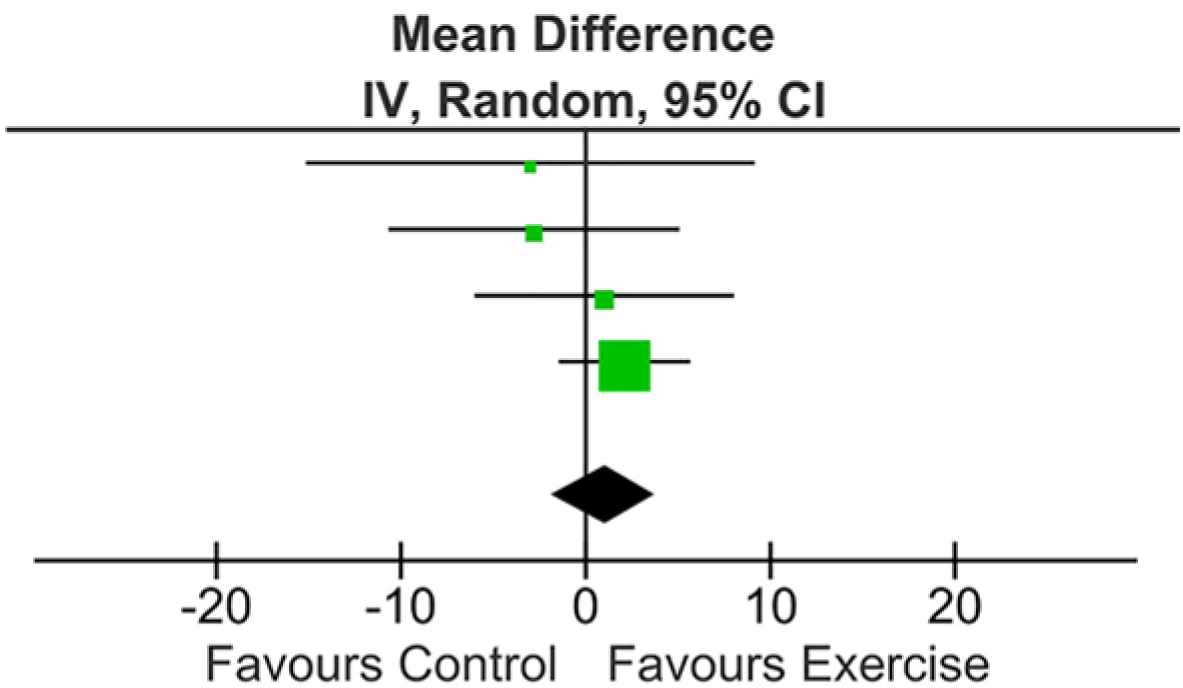

Fig 3. *Forest Plot for Lean body mass. A meta-analysis of pooled effect size (ES) and confidence intervals (CIs) (95%) of the intervention with exercise versus control group on lean mass evaluated by dual-energy X-ray absorptiometry (DXA) and air displacement plethysmograph (Kg).*

mL/Kg*min], p < 0.0001, Figure 2) and a large effect size (SMD 1.10 [0.60–1.60], p < 0.0001, $I^2 = 0\%$). Studies that analysed physical performance had low heterogeneity (Chi^2 2.43, p = 0.49; I^2 0%; $Tau^2 = 0.00$).

Change in muscle mass

Four studies determined muscle mass as lean body mass (LBM).[21,25-27] They evaluated LBM by different methods, including dual-energy X-ray absorptiometry (DXA) and air displacement plethysmography. Despite this, we could compare the values they reported because they expressed the results in kilograms (Kg). None of these studies reported changes in LBM. The studies that we used to analyse this outcome had low heterogeneity (Chi^2 1.74, p = 0.63; I^2 0%; $Tau^2 = 0.00$); our meta-analysis found no evidence of a difference in the effect between exercise and control groups (MD 1.01 Kg [95% CI -1.78 to 3.80 Kg], p = 0.48, Figure 3). There was a small effect size (SMD 0.09 [-0.27 to 0.44], p = 0.64, $I^2 = 0\%$).

Discussion

Following our results, we established the effect of exercise training, specifically endurance training and combined training in two of the three criteria for sarcopenia in NAFLD patients. According to our results, endurance and combined training positively impact physical performance and no impact on the LBM of NAFLD patients. It was impossible to determine the effect of exercise on NAFLD patients' muscle strength because no study determined it.

Effect of exercise on muscle strength

Some antecedents show the relationship between NAFLD status and muscle strength. [62] A recent study suggests that a higher hepatic steatosis index (HIS), a clinical feature of NAFLD patients, is associated with lower muscle strength in both sexes. [62] This antecedent suggests the relevance of muscle strength on NAFLD. Therefore, it is crucial to establish and analyze the influence of factors that could improve muscle strength in patients with NAFLD. There is consistent evidence that resistance training increases muscle strength. [63-65] Despite clear antecedents that link increased muscle strength with resistance exercise, none of the RCTs included here featured resistance training as a sole intervention. Three studies used a combined exercise protocol (endurance and resistance). [24-26] Despite the combined training, we expected them to evaluate physical qualities such as aerobic capacity and muscular strength; however, all the articles only assessed aerobic capacity. None of them evaluated muscle strength.

For this reason, we could not analyze muscle strength as a criterion of sarcopenia. Besides the conceptual importance of measuring muscle strength in studies that include resistance training, there are also methodological reasons. In general, muscle strength assessments are more straightforward and require less equipment than direct VO_{2max} or VO_{2peak} determination. Concerning the methodology to measure muscle strength, the handgrip strength (HGS) test is one of the most used evidence-based methods for evaluating muscle strength.[1] HGS is a better predictor of adverse clinical outcomes than muscle mass.[66] If HGS cannot be used, several alternative methodologies are available: knee flexion/extension, dynamometer, one maximum repetition (1RM), ten maximum repetitions (10RM), Isokinetic evaluation, and peak expiratory flow (specific to respiration).[1] One recent study evaluated the relationship between NAFLD status and HGS using a cohort declared representative of the general Korean population.[62] The results indicate that a higher HIS is associated with lower HGS in both sexes.[62] Therefore, HGS, an assessment of overall strength in sarcopenia and NAFLD, is quick and easy to perform and should be used as a base procedure for evaluating muscle strength in patients with liver pathologies.[1,62] Future research should include muscle strength assessments to investigate the effects of exercise, especially resistance training, in NAFLD patients' sarcopenia.

Effect of exercise on physical performance

Physical performance, one of the criteria for a sarcopenia diagnosis, is widely evaluated using the CPET, which provides a global assessment of integrative physiological responses.[67,68] Our study's meta-analysis indicates that most of the articles showed increased physical performance after the endurance and combined training protocol. Only one study found no changes in VO_{2peak} after exercise training, which may be explained by the small sample size.[21] The overall analysis revealed low heterogeneity and improved physical performance under exercise regardless of its features (type, intensity, duration). Three studies performed endurance training without another intervention,[21-23] while one article performed combined resistance and endurance training.[24] The endurance training parameters applied in these studies were consistent with the clinical practice guidelines for managing NAFLD from European associations to study the liver, diabetes, and obesity (EASL, EASD, EASO); they describe a comprehensive lifestyle approach for treating these patients.[69] All the studies performed CPET and reported the VO_{2max} or VO_{2peak} as maximal aerobic capacity indicators, reflecting the respiratory and circulatory systems' ability to supply oxygen to skeletal muscles during exercise.[70] They predicted an increase in oxygen consumption after endurance training, which induces adaptations in the cardiovascular system and increases mitochondrial biogenesis and capillary density in the skeletal muscles, improving the transport and oxygen use to generate energy.[63,71] Zenith et al. in 2014 observed increases in VO_{2peak} in cirrhotic patients after eight weeks of endurance training.[60] This antecedent is consistent because the primary adaptation to endurance training is cardiorespiratory fitness improvement.[72] Therefore, our meta-analysis showed that planned and supervised endurance and combined training improved physical performance in patients with sarcopenia associated with NAFLD. It is essential to mention that these patients should perform regular exercise to preserve its beneficial effects. This recommendation is based on the substantial benefits exercise training has on hepatic metabolism and the fat loss induced by endurance training.[73-75] Thus, training is a therapeutic strategy for improving cardiorespiratory fitness in fatty liver disease.[76] Furthermore, before liver transplantation, regular physical activity is essential to combatting patients' immediate stress post-transplant; it is also a critical determinant in long-term health after hepatic transplant.[77] CPET is the gold standard for assessing cardiorespiratory fitness and functional capacity. Unlike tests that estimate oxygen consumption, CPET measures respiratory, cardiovascular, and neuromuscular system function.[67,68] We excluded one study incorporated in our meta-analysis (in the muscle mass outcome) from the physical performance results, as oxygen consumption was determined from a 2 Km walking test.[27] In addition to the CPET assessment, the studies on patients with sarcopenia associated with NAFLD could include other validated muscle function tests for primary sarcopenia. For example, the short physical performance battery test (SPPB) evaluates gait, strength, and balance through a performance scoring system – it is an easy and quick test to implement.[1,78] SPPB can assess sarcopenia's severity and predict mortality on the liver transplant waitlist. [79,80] Future studies should use the SPPB to gain additional information on muscle function in NAFLD patients, as the European Association for the Study of the Liver (EASL) suggests.[81]

Effect of exercise on muscle mass

As shown in Figure 3, our results showed that endurance and combined training does not affect NAFLD patients' LBM – a conclusion based on our analysis of four studies.[21,25-27] These studies determined LBM using plethysmography and DXA. Both methods are widely used to assess body composition in research. The studies showed considerable variability, but the variability across the studies was very consistent. The lack of significance in the overall effect may be because DXA determinations have low reproducibility, dependent upon the equipment used. The gold standard methods for measuring body composition, especially for muscular mass, are CT and magnetic resonance imaging (MRI).[4]
Considering that all the studies in the meta-analysis mainly comprised endurance training protocols as the central exercise intervention, it is possible that endurance training does not affect NAFLD patients' LBM. Our results are consistent with a systematic review of cirrhotic patients trained with endurance protocols, which reported no LBM changes.[9,82] Contrary to these results, a study in cirrhotic patients featuring resistance training showed an increased muscle size.[83] This observation suggests that the type of exercise training determines the effects on muscle mass and that resistance training could positively impact muscle mass in NAFLD patients.

Exercise conditions to regulate sarcopenia

Therapies to revert muscular mass loss in NAFLD patients include pharmacological and nutritional approaches. However, exercise-based treatments should not be excluded because they can improve the patients' generalized physical condition and life quality.[8] It is widely established that resistance training is the most promising method to increase muscle strength and mass as well as balance;[84] further, it can induce muscular hypertrophy, translating to increased muscle mass.[84] Based on these antecedents, resistance training should be indicated as a therapy, alone or in combination, for sarcopenia in NAFLD patients. It is necessary to consider the conditions of resistance training to use in NAFLD patients. The standard conditions suggest that a high load induces a higher hypertrophic response in skeletal muscle;[85] however, loads below 30% of 1RM seem sufficient to trigger a hypertrophic response. The current recommendation for hypertrophic training is an intensity of 40–80% of the individual 1RM, with loads >60% to increase maximal force and muscular mass.[86] Thus, the best conditions for resistance training in NAFLD patients require further study.

Limitations

As mentioned, the RCTs' main limitations included here were difficulty in blinding participants, therapists, and assessors and participants' non-adherence to the assigned intervention regimes. Blinding participants and researchers are a significant challenge in exercise RCTs, as lifestyle interventions require patients and therapists to be fully aware of the type of intervention to be delivered. Nonetheless, reducing the risk of bias is crucial to blind the outcome assessors, which must be clearly stated in the RCT report. As for non-adherence, researchers should include an intention to treat analyses in a pre-specified fashion, considering that attrition is a common feature in exercise RCTs. Another limitation was the lack of supervision for not performing the physical activity in the control group. This monitoring is essential to ensuring a low level of physical activity that does not influence the results. If this variable is not controlled, then the sedentary controls could belong to a group that performs an unsupervised and undeclared exercise. These limitations should be considered in future RCTs. In our meta-analysis, the RCTs have a minimal sample size, making it necessary to interpret the results with very caution. In future RCTs, it would be essential to increase the sample size. The exercise training programs were significantly different among the studies regarding exercise intensity, total duration, session frequency, and modality (endurance or combined training). Among these, training modalities had special consideration since resistance training is one of the most potent interventions for increasing muscle size and quality in healthy and ill subjects. [87] This issue is caused by increased synthesis of myofibrillar and mitochondrial proteins in untrained individuals and increased strength, muscle mass, and effort tolerance.[63-65,72,88] Nevertheless, none of the studies used resistance training to treat NAFLD patients. Therefore, we strongly recommend including resistance training as the main component of exercise protocols in future research on sarcopenia in NAFLD patients. This high variability in physical training characteristics forces us to interpret the results of this research with caution.
The lack of categorization of NAFLD severity in the RCT participants is another limitation of the studies. This categorization is fundamental to determine if the effect of exercise training on sarcopenia depends on the stage of the disease. Future RCTs should include this classification when planning and executing exercise protocols. Finally, this research limitation is the low amount of RCTs found for the meta-analysis, which hinders this analysis's conclusions.

Conclusions

Exercise training is a beneficial strategy to treat sarcopenia in NAFLD patients. Endurance and combined training increase physical function criteria but do not improve muscle mass criteria on sarcopenia in NAFLD patients. Nevertheless, these results might have been influenced by several independent factors, which were raised after analyzing the data for this review. Among these factors are the small number of patients included in the analyzed RCTs, the heterogeneity of the ET used in every study, the non-use of resistance training as part of the intervention, which is known to prevent sarcopenia and, the absence of muscle strength assessments in the RCTs included.

Therefore, we recommend that future research should consider resistance training and muscle strength evaluations to estimate its effects in this condition. The exercise training is beneficial for sarcopenia in NAFLD, but it is necessary more evidence to determine the best type of training that positively affects all the sarcopenia components.

List of acronyms

ADP - Air-displacement plethysmography
AST - aspartate transaminase
ALT - alanine transaminase
CG – control group
CINAHL - Cumulative Index of Nursing and Allied Health Literature
CIs - confidence intervals
CLD - chronic liver disease
CPET - cardiopulmonary exercise test
CT - computed tomography
DXA - dual-energy X-ray absorptiometry
ET- exercise training
EWGSOP - European Working Group on Sarcopenia in Older People
EX – exercise group
GGT - gamma-glutamyl transpeptidase
HGS - handgrip strength
HIIT - high-intensity interval training
HRR - heart rate reserve
ITT - intention-to-treat
LBM - lean body mass
MD - mean differences
MM – muscle mass
MRS - nuclear magnetic resonance spectroscopy
NA - not applicable
NAFLD - Non-alcoholic fatty liver disease
NASH - non-alcoholic steatohepatitis
NR - not reported
PICO - population, intervention, comparison question (control), and outcomes
PP - Physical performance
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO - Prospective Register of Systematic Reviews
PubMed – Public MEDLINE
RCTs - randomized controlled trials
RPE - rating of perceived exertion
SMD - standardized mean differences
TESTEX - Tool for the assEssment of Study qualiTy and reporting in EXercise
VO_{2max} - maximum oxygen consumption
VO_{2peak} - oxygen consumption peak
1RM - one maximum repetition
10RM - ten maximum repetitions
2-Km WT - 2 km walking test
x/wk - times per week
wk - week

Authors contributions

AG, CC-V, FS, and OA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; OA contributed to the study design, statistical analysis, and interpretation of the results, and CH-S, FS, and M.V-B contributed to the study design and writing of the manuscript.
All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the work's integrity as a whole, and have given their approval for this version to be published.

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Conflict of Interest

The author declares no competing interests.

Ethical Publication Statement

I confirm that I have read the Journal's position on ethical publication issues and affirms that this report is consistent with those guidelines.

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