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Meta-Analysis

Effect of exercise-based interventions in nonalcoholic fatty liver disease: A systematic review with meta-analysis

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ABSTRACT

Background: The global burden of nonalcoholic fatty liver disease (NAFLD) is rapidly increasing.
Aims: This study aimed to evaluate the effect of exercise on intrahepatic lipid (IHL), serum alanine aminotransferase (ALT), body mass index (BMI), and insulin resistance in NAFLD patients.
Methods: We searched MEDLINE, Embase, Cochrane CENTRAL, KMbase, and the Korean Studies Information Service System through April 2022. The included studies were randomised control trials (RCTs) of exercise, in which IHL was measured using magnetic resonance imaging in adult NAFLD patients.
Results: Eleven RCTs with 577 participants were included in this meta-analysis. Exercise was significantly associated with a reduction in IHL (mean difference (MD), -2.03; 95% CI, -3.26 to -0.79; $P = 0.001$) and a decrease in ALT (MD, -4.17; 95% CI, -6.60 to -1.73; $P = 0.0008$). Regarding the duration of exercise, maintaining exercise for more than 3 months significantly improved IHL (MD, -3.62; 95% CI, -5.76 to -1.48; $P = 0.0009$), while exercise for less than 3 months did not (MD, -1.23; 95% CI, -2.74 to 0.29; $P = 0.11$). BMI and insulin resistance did not improve significantly with exercise.
Conclusions: We found that exercise improved IHL and ALT levels in NAFLD patients. The effect of exercise is particularly increased when one engages in exercises that last longer than 3 months.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide, with a global prevalence of approximately 25% [1]. Due to its rapidly increasing incidence, NAFLD is currently the second most common cause of end-stage liver disease [2] and the incidence of NAFLD-related hepatocellular carcinoma (HCC) has substantially increased [3]. NAFLD is a multisystem disease that is strongly associated with obesity, insulin resistance, and hyperlipidemia caused by metabolic syndrome, leading to substantial liver-related morbidity and mortality. Furthermore, the clinical and economic burden of NAFLD will continue to increase in upcoming decades [4].

A sedentary lifestyle and excessive caloric intake play an important role in the development and progression of NAFLD [5], leading to weight gain and increased insulin resistance and hepatic steatosis. Therefore, changing of sedentary behavior through exercise could be a therapeutic strategy for NAFLD [6]. In addition, given the lack of effective pharmacological therapy for treating NAFLD, lifestyle modifications, including exercise-based intervention, have been advocated as the cornerstone of therapy for patients with NAFLD [7–10]. Current guidelines recommend exercise as part of lifestyle interventions, along with weight loss and a low-calorie diet. However, these guidelines do not explicitly suggest the

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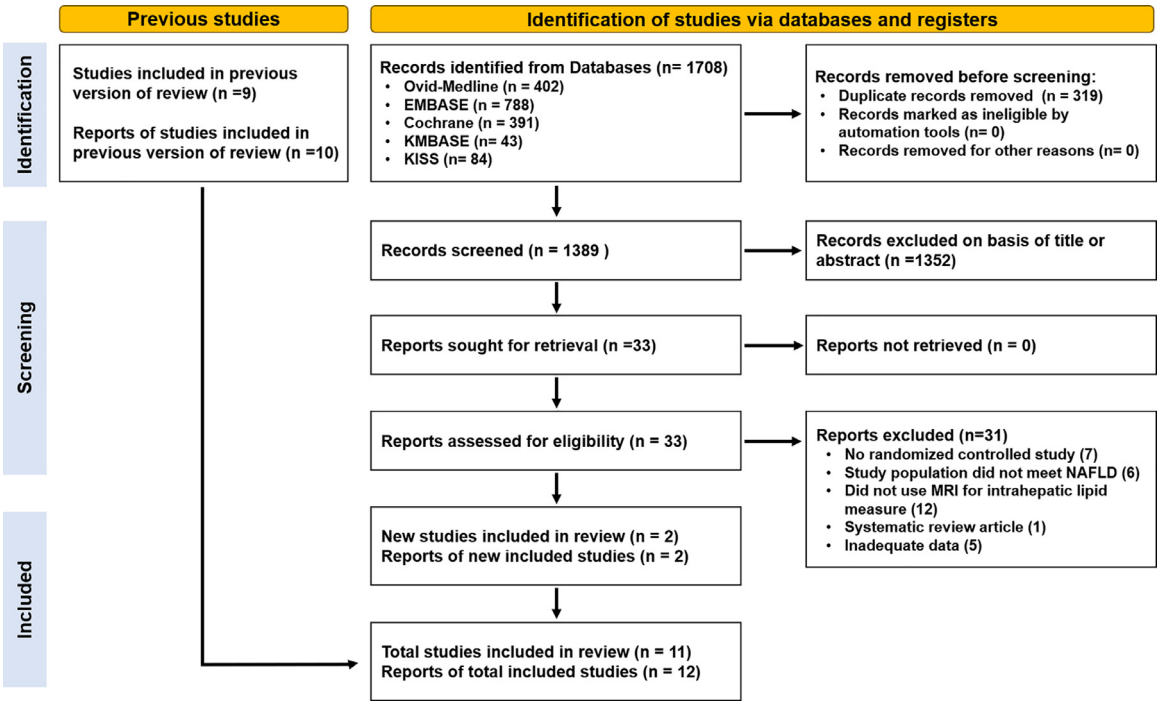

Fig. 1. Flowchart for study selection.

effects of exercise or optimal exercise programs for the improvement of NAFLD. Several meta-analyses have shown that exercise is associated with improved clinical outcomes in NAFLD patients [11–14]. However, there were inconsistencies among these studies in terms of type, frequency, intensity, and duration of optimal exercise, and some studies included participants with comorbid conditions such as type 2 diabetes, obesity, or metabolic syndrome, rather than solely NAFLD patients.

Moreover, existing meta-analyses included studies that evaluated the amount of intrahepatic lipid (IHL) using inaccurate methods such as serum alanine aminotransferase (ALT) levels or non-quantitative radiologic tests; therefore, their quantitative evaluation was limited and had considerable heterogeneity. It is widely known that magnetic resonance imaging (MRI) is the most accurate method for measuring IHL [15,16]. The advantages of MRI for evaluating IHL are that it can analyze the whole liver and can be used in patients with obesity or ascites. In addition, MRI provides higher performance for the diagnosis of cirrhosis than other methods [17].

Therefore, we conducted a meta-analysis of randomised controlled clinical trials (RCTs) to evaluate the effects of exercise only in patients diagnosed with NAFLD. In addition, this analysis only included studies that quantitatively analysed the amount of IHL using MRI. Our objective was to determine whether exercise improved IHL, serum ALT, aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels, and insulin resistance. Furthermore, the effects of exercise regarding the duration and the type were investigated.

2. Materials and methods

2.1. Literature search and study characteristics

The results of this systematic review are presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [18] which is listed in the Supplementary Table S1. We gathered data from all randomised clinical trials analysing the impact of exercise on markers of IHL and liver enzyme in patients diagnosed with NAFLD. We performed a comprehensive literature search of MEDLINE, Embase, Cochrane CENTRAL, KMbase, and Korean Studies Information Service System through April 2022. In some cases, the reference list of the retrieved articles was used to identify other relevant studies. The search keywords used were: nonalcoholic fatty liver disease, nonalcoholic fatty liver, NAFLD, nonalcoholic steatohepatitis, steatosis, exercise therapy, resistance training, physical fitness, aerobic, endurance, muscle, physical, resistance, weight, training, exercise, lifting, jogging, treadmill, running, and combinations of the above terms. Detailed information regarding the search keywords is provided in Supplementary Table S2. We used a hierarchical approach; screening based on the title or abstract, and then reviewing the full manuscript. (Fig. 1)

2.2. Inclusion and exclusion criteria

Inclusion criteria: RCTs of exercise interventions in adult (aged >18 years) NAFLD patients of any sex or nationality, published in English were included in the analysis. The definition of NAFLD was based on the following criteria: evidence of hepatic steatosis by either radiologic examination or biopsy in the absence of significant alcohol consumption and other competing causes of hepatic steatosis. The exercise was defined as any physical activity performed as a therapeutic intervention regardless of its intensity or duration. To evaluate the independent effects of exercise, studies with the dietary intervention were included only when the same diet was conducted in both the intervention and control groups.

Exclusion criteria: non-human studies, non-RCTs, only abstract available, observational studies (epidemiologic studies or case control studies or cohort studies), studies in which IHL was not measured by MRI, additional intervention other than exercise, studies including non-NAFLD patients (commonly obesity and type 2 diabetes), studies with inadequate data, as well as systematic review articles, were excluded from the analysis. The PICOS criteria for the inclusion and exclusion of studies are shown in Supplementary Table S3.

Table 1
Characteristics of the studies.

Author (year)	Subjects	Intervention	Control	Session duration (min)	Frequency (/week)	Intensity	Duration	Outcome
Abdelbasset (2020)	Obese, T2DM-NAFLD ($n = 47$)	Aerobic exercise ($n = 31$)	Control ($n = 16$)	40–50	3	High: 80–85% $VO_{2\ peak}$ Moderate: 60–70% MHR	8 weeks	IHL, ALT, HOMA-IR, BMI
Babu (2022)	NAFLD ($n = 42$)	Aerobic exercise ($n = 20$)	Control ($n = 22$)	40–50	2	*Vigorous - Aerobic : 85% of maxW4	12 weeks	Intrahepatic fat ALT BMI Weight
Cheng(2017)	NAFLDwith IFG or IGT ($n = 85$)	Aerobic exercise ($n = 22$) Aerobic exercise +diet ($n = 23$)	Control ($n = 18$) Diet ($n = 22$)	30–60	2–3	Moderate to Vigorous: 60–75% $VO_{2\ peak}$	8.6 months	IHL, ALT, Weight
Cuthbertson (2016)	Sedentary NAFLD ($n = 69$)	Aerobic exercise ($n = 38$)	Control ($n = 31$)	30–45	3–5	Moderate: 30–60% MHR	16 weeks	IHL, ALT, BMI, weight
Hallsworth (2011)	Sedentary NAFLD ($n = 19$)	Resistance exercise ($n = 11$)	Control ($n = 8$)	45–60	3	Vigorous: 70% RM	8 weeks	IHL, ALT, HOMA-IR, BMI, weight
Hallsworth (2015)	Sedentary NAFLD ($n = 23$)	Resistance exercise ($n = 11$)	Control ($n = 12$)	30–40	3	Vigorous: 75–80% RM	12 weeks	IHL, ALT, HOMA-IR, BMI, weight
Houghton (2017)	Biopsy proven NASH ($n = 24$)	Aerobic +resistance exercise ($n = 12$)	Control ($n = 12$)	45–60	3	Vigorous -aerobic: 90% MHR -resistance: 60–70% RM	12 weeks	IHL, ALT, HOMA-IR, BMI, Weight
Keating (2017)	Obese NAFLD ($n = 9$)	Resistance exercise ($n = 4$)	Control ($n = 5$)	30–60	3	*Vigorous: 80–85% RM	8 weeks	Intrahepatic fat
Pugh (2014)	NAFLD ($n = 21$)	Aerobic exercise ($n = 13$)	Control ($n = 8$)	30–45	3–5	Moderate: 30–60% MHR	16 weeks	IHL, ALT, HOMA-IR, BMI, Weight
Sullivan (2012)	NAFLD ($n = 18$)	Aerobic exercise ($n = 12$)	Control ($n = 6$)	30–60	5	Moderate: 45–55% $VO_{2\ peak}$	16 weeks	IHL, ALT, BMI
Zhang (2016)	Obese NAFLD ($n = 220$)	Aerobic exercise ($n = 146$)	Control ($n = 74$)	30	5	Vigorous: 8–10METs (65–80% MHR) Moderate: 3–6 METs (45–55% MHR)	12 months	IHL, ALT, Weight

T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; MHR, maximal heart rate; IHL, intrahepatic lipid; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; RM, repetition maximum; NASH, nonalcoholic steatohepatitis; MET, metabolic equivalent of task.

2.3. Data extraction and risk of bias assessment

Data on the participant characteristics were extracted from each study. We extracted data regarding exercise (type of exercise, duration of each session, number of sessions per week, intensity of exercise, and overall study period). Two reviewers independently performed data extraction and risk of bias assessment. If discrepancies occurred, consensus was reached through discussion. The risk of bias of each included study was evaluated using the Cochrane risk-of-bias tools which covered six domains of bias: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias [19].

2.4. Outcome measure

The primary endpoint of interest was IHL content, as assessed using MRI (MRI proton density fat fraction (PDFF) or MR spectroscopy (MRS)). Secondary endpoints were serum ALT, AST, and GGT levels, markers of peripheral insulin resistance, and body mass index (BMI). Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR).

2.5. Statistical analysis

The effect size was calculated as the mean difference (MD) change from baseline along with 95% confidence intervals (CI). Estimates of the effect size measures were weighted by the inverse of their variances. Statistical significance was set at $P < 0.05$. The data for each indicator was pooled and are shown as a forest plot. Heterogeneity was tested using the Cochran's Q test, and inconsistency measured by I^2 (I^2 values >50% were defined as high heterogeneity, between 25% and 50% as moderate heterogeneity, and <25% as low heterogeneity). Both random- and fixed-effects models were considered in all scenarios. The random-effects model was used if high heterogeneity was detected. Else, the fixed-effects model was used. Analyses were conducted using the meta-package of the Review Manager version 5.4 (Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Literature search

We initially performed a literature search on studies published up to November 2020. We identified 967 articles. After removing the duplicates and excluding articles based on eligibility, 9 RCTs were identified for meta-analysis. Details regarding the search

flowchart for the initial meta-analysis are provided in a Supplementary Figure S1.

However, since we conducted the previous meta-analysis, many new studies have been published, raising the need for an update. Accordingly, we extended the literature search period until April 2022 with the additional search keywords related to exercise. The total number of records identified from the database was 1708. After eliminating duplicates and excluding articles based on title and abstract, 33 studies remained. Of the 33 studies, 7 were not randomised controlled studies, 6 were excluded as study participants did not meet the diagnosis of NAFLD, 12 did not use MRI to measure IHL, 1 was a systematic review article, and 5 were excluded due to inadequate data. Eventually, two RCTs were added to the analysis. Combining with previous literature searches, 11 RCTs were finally included in the meta-analysis (Fig. 1).

3.2. Study characteristics

Table 1 shows the characteristics of the included studies with a total of 577 participants (343 in the intervention group and 234 in the control group). In a study by Cheng et al., the effect of combining exercise and diet was compared with the effect of dietary intervention only [20], while in ten other studies, the effect of exercise was compared with that of non-exercise control [21–30]. Our Study included seven aerobic exercise studies [20–23,28–30], three resistance exercise studies [24,25,27], and one combined aerobic and resistance exercise study [26].

The frequency of exercise in the studies with aerobic exercise was as follows: 5 days per week (two studies), 3–5 days per week (two studies), 3 days per week (one study), 2–3 days per week (one study), and 2 days per week (one study). The frequency of exercise was 3 times per week for all studies with resistance exercise alone or in combination with aerobic exercise. Studies were grouped according to the intensity of exercise performed. The intensity of aerobic exercise was determined by the percentage of maximal heart rate (MHR) [31] or peak oxygen consumption ($VO_{2\ peak}$) [32]. The most common exercise intensity in the above studies was 30–60% of MHR or 40–55% of $VO_{2\ peak}$ which is defined as 'moderate intensity'. The intensity of resistance exercise was quantitatively assessed as a percentage of one-repetition maximum (1RM) [33]. All studies with resistance exercise ranged from 70% to 80% of 1RM which is defined as 'vigorous intensity'. The exercise interventions were performed for 8 weeks to 12 months. Five of the eleven studies maintained exercise intervention for more than 3 months [20,23,29,30,34].

The study by Abdelbasset et al., used MRI PDFF to quantify changes in IHL [21], while in ten other studies, MRS was used for the assessments [20,22–30]. Eight studies measured changes in BMI, and five studies used HOMA-IR to assess insulin resistance.

3.3. Risk of bias

Assessment of the risk of bias is shown in Fig. 2. Most of studies had a low risk of bias in random sequence generation and four studies that reported information on allocation concealment had a low risk of selection bias. All eleven studies had a high risk of bias in the blinding of participants and personnel. This is because while the researchers can maintain their blinding, study subjects inevitably know which group they belong to due to their exercise state. Eight studies had a low risk of blinding of outcome assessment, and ten studies had a low risk of incomplete outcome data. Nine studies had a low risk of bias in selective reporting.

3.4. Effect of exercise-based interventions on intrahepatic lipid

All eleven studies provided adequate data for the analysis of the effect of exercise on IHL content. The fixed-effects model demonstrated that exercise intervention was associated with a significant reduction in IHL (MD, −2.03; 95% CI, −3.26 to −0.79; $P = 0.001$). The heterogeneity among the studies was insignificant (I^2 =0%, $P = 0.87$). (Fig. 3)

3.5. Effect of duration of exercise on intrahepatic lipid

In the subgroup analysis according to the duration of exercise, the group that continued to exercise for more than 3 months had a significant improvement in IHL compared with the control group (MD, −3.62; 95% CI, −5.76 to −1.48; $P = 0.0009$) (Fig. 4A). The heterogeneity among the studies was insignificant (I^2 =0%, $P = 0.98$). Even in the group that exercised for less than 3 months, the amount of IHL decreased after exercise, but the difference was insignificant compared with that in the control group (MD, −1.23; 95% CI, −2.74 to 0.29; $P = 0.11$) (Fig. 4A). The heterogeneity among the studies was insignificant (I^2 =0%, $P = 0.85$).

3.6. Effect of types of exercise on intrahepatic lipid

In the subgroup analysis regarding exercise type, only aerobic exercise was associated with a significant improvement in IHL, whereas resistance exercise was not. Seven studies that employed aerobic exercise demonstrated significant effectiveness of the intervention (MD, −2.37; 95% CI, −3.93 to −0.81; $P = 0.003$) (Fig. 4B). The heterogeneity among the studies was insignificant (I^2 =0%, $P = 0.60$). In the three studies that employed resistance exercises, resistance exercise was associated with a reduction in IHL, but this was not statistically significant (MD, −1.88; 95% CI, −4.08 to 0.33; $P = 0.09$) (Fig. 4D). The heterogeneity among the studies was insignificant (I^2 =0%, $P = 0.58$).

3.7. Effect of exercise-based interventions on hepatic enzyme

Nine studies provided sufficient data for analysis of ALT levels. The pooled results showed that exercise was significantly associated with a reduction in ALT levels (MD, −4.17; 95% CI, −6.60 to −1.73; $P = 0.0008$) (Fig. 5A). Heterogeneity was not significant for ALT levels (I^2 =0%, $P = 0.78$). Six studies provided sufficient data for analysis of AST levels. The forest plot of meta-analysis of the effect of exercise versus control on AST was as follows. There were no significant effects of exercise on AST (MD, −1.81; 95% CI, −5.11 to 1.48; $P = 0.28$) (Fig. 5B). The heterogeneity among the studies was insignificant (I^2 =0%, $P = 0.50$). Six studies provided sufficient data for analysis of GGT levels. The forest plot of meta-analysis of the effect of exercise versus control on GGT was as follows. There were no significant effects of exercise on GGT (MD, −5.23; 95% CI, −12.61 to 2.15; $P = 0.16$) (Fig. 5C). The heterogeneity among the studies was insignificant (I^2 =14%, $P = 0.33$).

3.8. Effect of exercise-based interventions on insulin resistance

Five studies had sufficient data for inclusion in analysis of HOMA-IR. There were no significant effects of exercise on HOMA-IR (MD, −0.06; 95% CI, −0.46 to −0.34; $P = 0.77$) (Fig. 5D). Heterogeneity between the subgroups for HOMA-IR was moderate (I^2 =27%, $P = 0.24$).

3.9. Effect of exercise-based interventions on BMI

Eight studies that evaluated the effects of exercise on BMI were included in the analysis. There were no significant effects

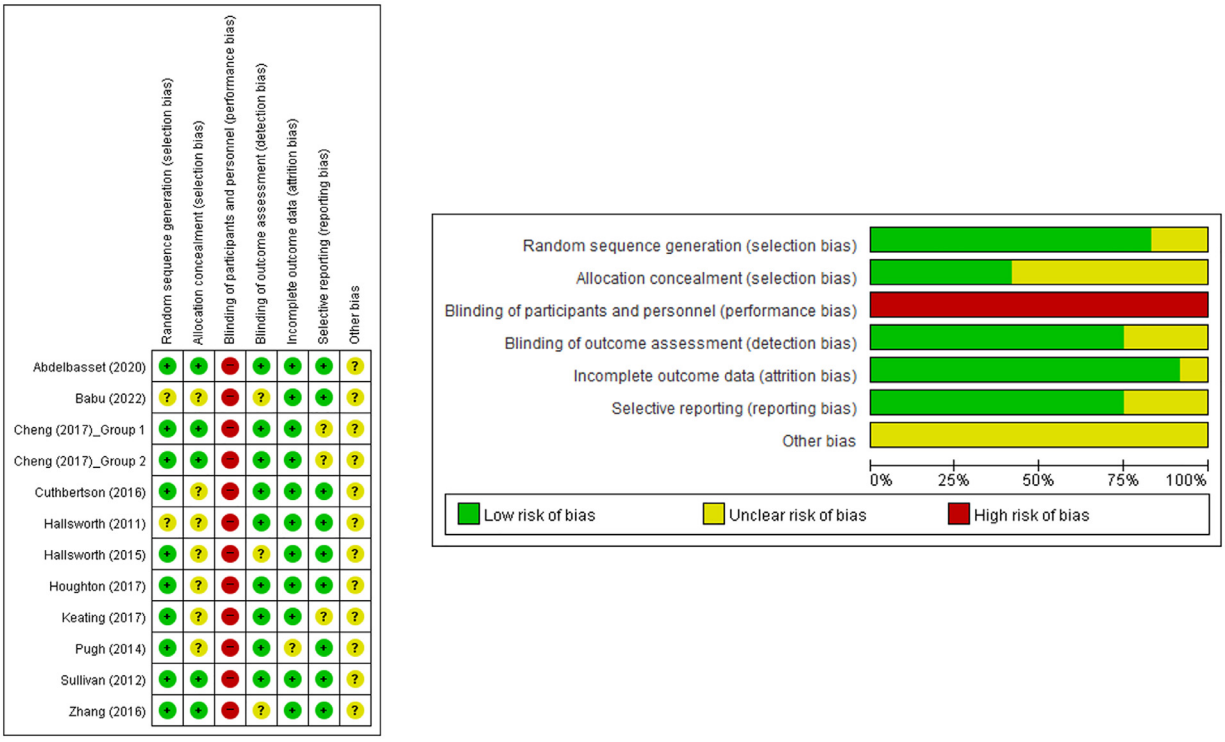

Fig. 2. Risk of bias graphs of the included trials.

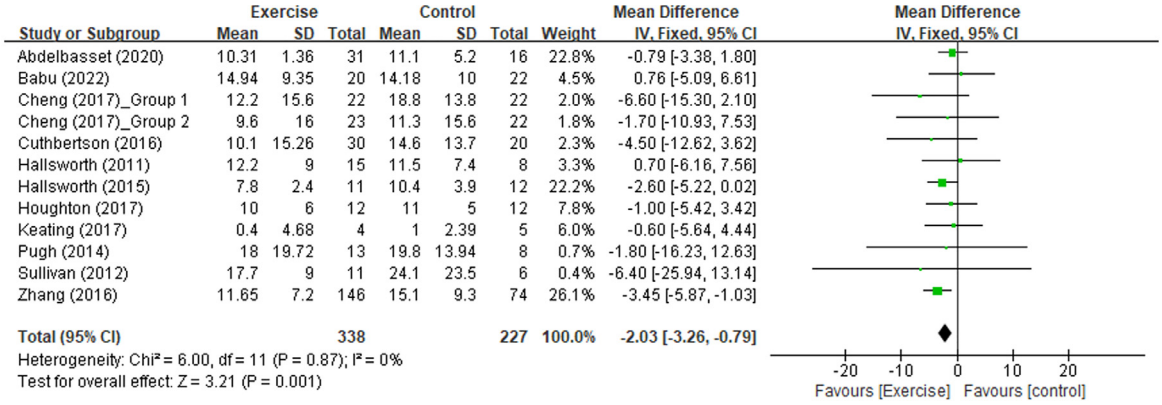

Fig. 3. Forest plot of meta-analysis of the effect of exercise versus control on intrahepatic lipid. Fixed-effects model. Each square represents the effect estimate of an included trial, along with 95% CI. The vertical line depicts the null hypothesis, and the bottom diamond depicts the pooled effect estimate. CI, confidence intervals.

of exercise on BMI (MD, −0.52 kg/m^2; 95% CI, −1.60 to 0.57; $P = 0.35$) (Fig. 5E). Heterogeneity was not significant for BMI (I^2 =0%, $P = 0.89$).

4. Discussion

This analysis combined eleven studies involving a total of 577 patients with NAFLD, all of which had randomised controlled designs. We found clear evidence that exercise significantly reduced IHL and serum ALT levels. Interestingly, we revealed that the improvement in IHL was pronounced in patients who continued exercise for more than 3 months. Aerobic exercise was associated with a significant improvement in IHL. In addition, we did not observe any benefits of exercise on BMI or insulin resistance.

The aforementioned improvements in IHL and serum ALT levels by exercise was in line with existing meta-analyses [11–13,35]. The strength of this study was that only trials that quantitatively measured IHL using MRI were included. Although liver biopsy is considered the gold standard for evaluating the degree of steatosis or fibrosis, it also has the drawback of invasiveness; thus, repeated measurements are limited. MRI is non-invasive and excels in quantifying IHL, making it widely used in most NAFLD clinical trials [15]. In a recent systematic review [36], MRI showed the highest accuracy in the quantitative measurement of hepatic steatosis among the non-invasive methods. Furthermore, reduced hepatic steatosis on MRI was significantly associated with an improvement in the NAFLD activity score and regression of fibrosis.

Based on the results of a meta-analysis [37], the pooled prevalence of NAFLD was 55.5% (95% CI, 47.3 to 63.7) among patients with type 2 diabetes and 46.0% (95% CI, 36.3 to 56.1) in obese patients. Nearly half of the patients with diabetes or obesity do not have NAFLD. Existing meta-analyses have included studies not only

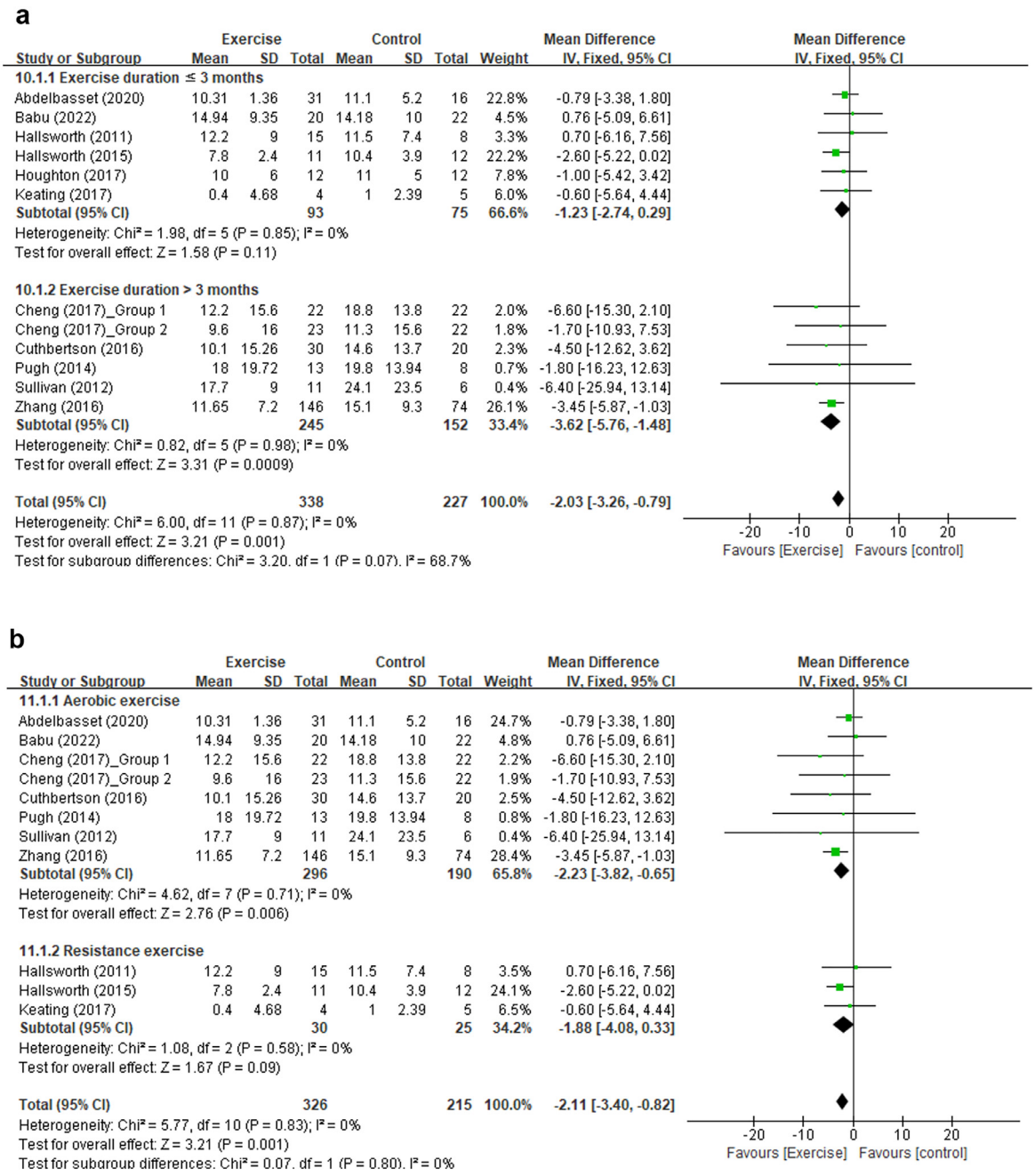

Fig. 4. Forest plot of meta-analysis of the effect of exercise versus control on intrahepatic lipid with subgroup analysis of exercise duration and type. Fixed-effects model. Each square represents the effect estimate of an included trial, along with 95% CI. The vertical line depicts the null hypothesis, and the bottom diamond depicts the pooled effect estimate. (a) Duration of exercise (b) Type of exercise CI, confidence intervals.

on NAFLD patients, but also on patients with pre-existing medical conditions. The present study analysed trials that included only patients diagnosed with NAFLD based on liver biopsy or standard guidelines. Since this meta-analysis was performed on a homogeneous sample that is less likely to include non-NAFLD patients, we believe that all the aforementioned outcomes are strongly reliable.

Performing exercise for more frequently over a longer duration is generally thought to provide better improvement; however, there is no established standard exercise program for NAFLD patients. Since the current NAFLD guidelines do not provide an optimal exercise program for improvement, we conducted analyses to provide evidence regarding the frequency and duration of exercise. The aforementioned results on the effect of exercise on the reduction of IHL were derived from studies in which exercise was performed at least 3 times per week, except for two studies. Moreover, studies that continued exercise for more than 3 months demonstrated a significant reduction in IHL, whereas exercise of less than 3 months did not. Based on the current findings, exercising at least three times a week for more than 3 months is strongly recommended for NAFLD management.

According to a recent meta-analysis by Stomko et al., [35] aerobic exercise significantly improved intrahepatic triglyceride lev-

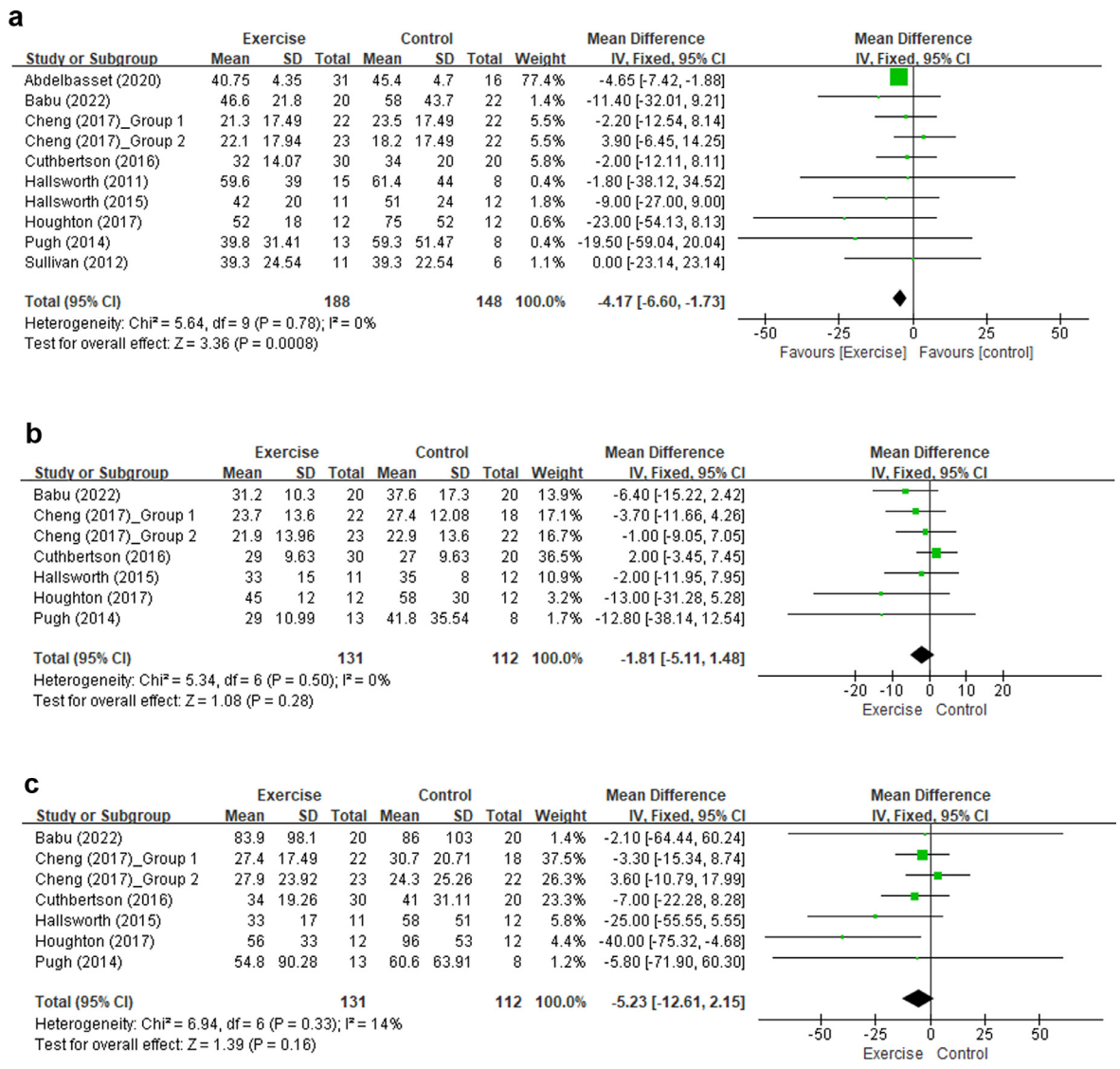

Fig. 5. Forest plot of meta-analysis of the effect of exercise versus control. Fixed-effects model. Each square represents the effect estimate of an included trial, along with 95% CI. The vertical line depicts the null hypothesis, and the bottom diamond depicts the pooled effect estimate. (a) Serum ALT levels (b) serum AST levels (c) serum GGT levels (d) HOMA-IR (e) BMI CI, confidence intervals; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index.

els in patients with NAFLD. In studies involving obese adolescents [38,39], aerobic exercise, but not resistance exercise, was effective in reducing IHL. In this meta-analysis, aerobic exercise was significantly associated with a reduction of IHL, whereas resistance exercise was not. Nevertheless, careful interpretation was necessary because only three studies that evaluated the effect of resistance exercise were included in this analysis, and all of them were performed with less than 3 months of exercise. However, some studies have shown that both aerobic and resistance exercises have similar IHL reduction effects [40,41]. In particular, resistance exercise can reduce IHL with only low energy consumption [42], therefore, it has the advantage of being applicable to patients with cardiopulmonary dysfunction. This meta-analysis could not include enough studies because of the lack of sufficient studies evaluating the effectiveness of resistance exercise with MRI. Therefore, further studies on the effect of longer-duration resistance exercise using MRI are needed.

Obesity and insulin resistance are known to play crucial roles in the development and progression of NAFLD [43]. However, our analysis did not demonstrate a significant improvement in BMI or insulin resistance after exercise, which is consistent with previous meta-analyses [11–13]. Due to the complexity of the pathophysiology of NAFLD, the effects of exercise on BMI or insulin resistance are unclear. Exercise can reduces intrahepatic fat independent of weight loss. [24,44,45], and insulin resistance has been demonstrated to be influenced by a variety of factors, including gut microbiota and food intake [46]. However, as in the previous interpretation of the results regarding the type of exercise, the aforementioned results should consider the duration of exercise. In this analysis, most of studies evaluating the effect of exercise on insulin resistance were performed for a short period of less than 3 months. Therefore, a follow-up study involving a longer period of exercise is necessary to accurately evaluate the effects of exercise on insulin resistance.

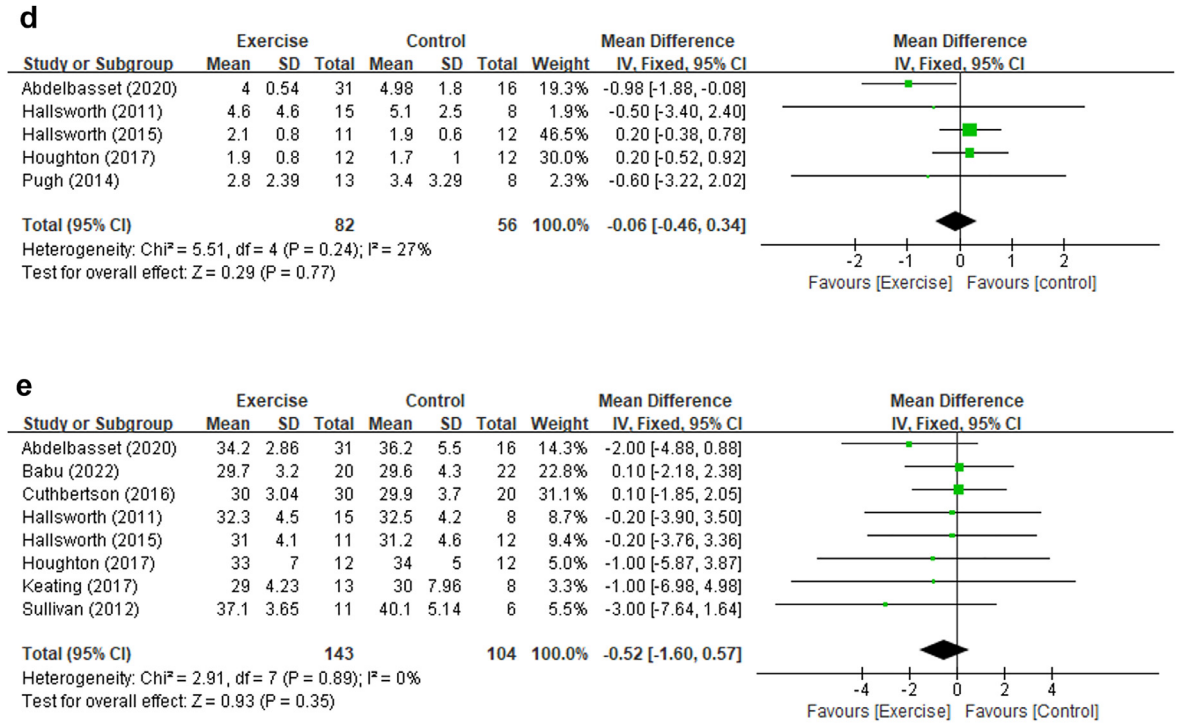

Fig. 5. Continued

The current study had several limitations. First, this meta-analysis could not investigate histological improvement due to a lack of information, especially on inflammation. However, MRI is known to be the most accurate non-invasive tool for assessing hepatic steatosis. Although histological improvement was not determined in this study, it was possible to quantitatively evaluate IHL using MRI. Second, insufficient included studies (or insufficient data for relevant subgroups) are limited to performing meta-analyses on specific subgroups. Out of the 11 included studies, 3 studies were conducted with resistance exercise and only 1 study conducted with combined exercise (aerobic + resistance). In addition, subgroup analysis considering sex or metabolic conditions (obesity or type 2 diabetes) was not available because detailed outcomes by those subgroups were not reported in the included studies. Third, the results of our study on AST and GGT levels, insulin resistance, and BMI were limited by lack of available data. Fourth, all studies included in this analysis had a high risk of bias in the blinding of participants and personnel. This is because perfect blinding is impossible due to the nature of the exercise intervention. However, since only RCT was included in this analysis and the objective assessment was performed by MRI, it is thought that the effect of bias could be minimized. Fifth, we used the 3 months as the cut-off for evaluating effective exercise duration; however, the rationale for this duration is insufficient. Since the evidence for effective exercise duration has not yet been established, we applied an arbitrary cut-off of 3 months according to the characteristics of the included studies. We hope that subsequent studies will establish clear evidence for the appropriate exercise duration. Last, we could not perform a detailed analysis of patients with comorbidities such as diabetes, obesity, or metabolic syndrome

5. Conclusion

The current meta-analysis provides clear evidence that exercise effectively reduces IHL and serum transaminase levels in patients with NAFLD. To improve NAFLD, regular exercising at least 3 times per week for more than 3 months is strongly recommended. Further studies are required to evaluate the long-term effects of exercise.

Data availability statement

The data sources and search strategies of this systematic review and meta-analysis are shown in Supplementary Table S2. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

None declared.

Authorship statement

Guarantor of article: Do Seon Song and Miyoung Choi.

Author contributions

JY, DSS, MC designed the research study. DSS, MC collected and analysed the data. HN, DSS, MC performed research and draft the manuscript. YC, SHK, SBA, HWL, DWJ contributed to the design of the study and critical review of the manuscript. ALL authors approved the final version of the article, including the authorship list.

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None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.12.013.

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