Systematic Review and Meta-Analysis of Clinical trials

Exercise as an effective treatment for non-alcoholic fatty liver disease (NAFLD)

Lucia Lopez Clavain

Student number: 2001133

Abstract

Non-alcoholic fatty liver disease (NAFLD) is increasingly emerging as a liver condition globally, approaching approximately 25% of the global population. This systematic review, following PRISMA, aims to assess exercise's impact on ALT levels, with secondary measures like AST, insulin resistance, waist circumference, and BMI. Calculated mean differences with 95% confidence intervals (Cis) determined significance ($P < 0.05$). The outcomes obtained showed that exercise didn't significantly affect ALT or secondary measures. A more thorough search, including additional databases, is crucial for a meta-analysis with a larger sample, providing conclusive results on exercise's efficacy in treating NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is increasingly emerging as a liver condition globally, approaching approximately 25% of the global population. NAFLD and NASH are frequently linked to metabolic conditions such as type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, hyperlipidaemia, metabolic syndrome, and, notably, obesity (Eguchi et al., 2020). NAFLD spans a spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH), characterized by lobular inflammation and ballooning. Fibrosis progression happens across this spectrum, potentially leading to cirrhosis. Importantly, fibrosis tends to progress more rapidly and commonly in NASH compared to simple steatosis (Sarwar et al., 2018).

NAFLD and NASH impose a substantial economic load, mainly attributable to their significant effects on T2DM, obesity, and cirrhosis. In a modeling study conducted in 2016, the annual costs for both incident and prevalent cases of NAFLD were estimated across Germany, United States, Italy, France, and the United Kingdom. The study's findings revealed direct and indirect costs amounting to $103 billion in the U.S. (equivalent to $1613 per patient) and €35 billion in the four European countries (ranging from €354 to €1163 per patient). Notably, advanced fibrosis (F3/4) resulting from NASH accounted for more than half of the overall expenses (Eguchi et al., 2020).

Due to the significant impact of NAFLD/NASH, finding effective treatment is crucial. Lifestyle changes, such as modifying diet, losing weight, and increasing exercise, are the primary approach.

A sedentary lifestyle and excess calories contribute to NAFLD, causing weight gain, insulin resistance, and liver fat build-up. Therefore, exercising and reducing sedentary behaviour can be an effective treatment for NAFLD (Kim. et al., 2019). Numerous meta-analyses and clinical trials indicate that both exercise and diet contribute to enhanced clinical outcomes for NAFLD patients ((Charatcharoenwitthaya et al., 2021), (Keating et al., 2022), (Moradi Kelardeh et al., 2020), (Tutino et al., 2018)). However, in this meta-analysis, my focus is exclusively on exploring the effectiveness of exercise as a treatment for NAFLD. The primary objective is to assess whether exercise positively influences serum ALT levels, with secondary measurements including aspartate aminotransferase (AST), insulin resistance, reductions in waist circumference, and body mass index (BMI).

2. Methods

2.1 Literature search and study characteristics

This systematic review was adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. A detailed literature search was carried out on PubMed, utilizing the following search keywords: "Non-alcoholic Fatty Liver Disease"[Mesh] and ("Exercise"[Mesh] OR "Muscle Stretching Exercises"[Mesh] OR "Circuit-Based Exercise"[Mesh] OR "Cool-Down Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Tolerance"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Post-Exercise Hypotension"[Mesh] OR "Plyometric Exercise"[Mesh] OR "Warm-Up Exercise"[Mesh] OR "Cardiomegaly, Exercise-Induced"[Mesh] OR "Resistance Training"[Mesh]). I adopted a hierarchical method; initially evaluating the papers based on the abstract or title, followed by a review of the full paper (See figure 1). PICOS criteria were used for the inclusion and exclusion of keywords studies.

2.2 Inclusion and exclusion criteria

I reviewed all randomized clinical trials and clinical trials that came up from the search identified from 2018 to 2023 with full-text availability in both English and Spanish. These were trials of physical activity interventions in 18 years old or older NAFLD patients of any nationality or gender. To evaluate the independent effects of exercise, participants were instructed not to modify their dietary intake and physical activity habits (except for supervised exercise) throughout the study.

Exclusion criteria comprised non-randomized controlled trials (non-RCTs), studies in languages other than English and Spanish, those with only abstracts available, studies inaccessible to Abertay, observational studies (such as case control, epidemiologic, or cohort studies) and trials lacking relevant measurements. Additionally, studies involving interventions other than exercise (typically diet), including no non-alcoholic fatty liver disease patients (usually type 2 diabetes and obesity), lacking a pertinent control group, having inadequate or inappropriate data, employing improper statistical analyses, and systematic review articles, were omitted from the analysis (see Figure 1). A study recording form, adapted from the Cochrane collaboration, was utilized to document study characteristics, and reasons for exclusion or inclusion.

2.3 Outcome measure

The focus was on ALT levels as the primary endpoint. Secondary endpoints included AST, body mass index (BMI), waist circumference, and insulin resistance evaluated with the homeostasis model assessment of insulin resistance (HOMA-IR).

2.4 Data extraction and risk of bias assessment

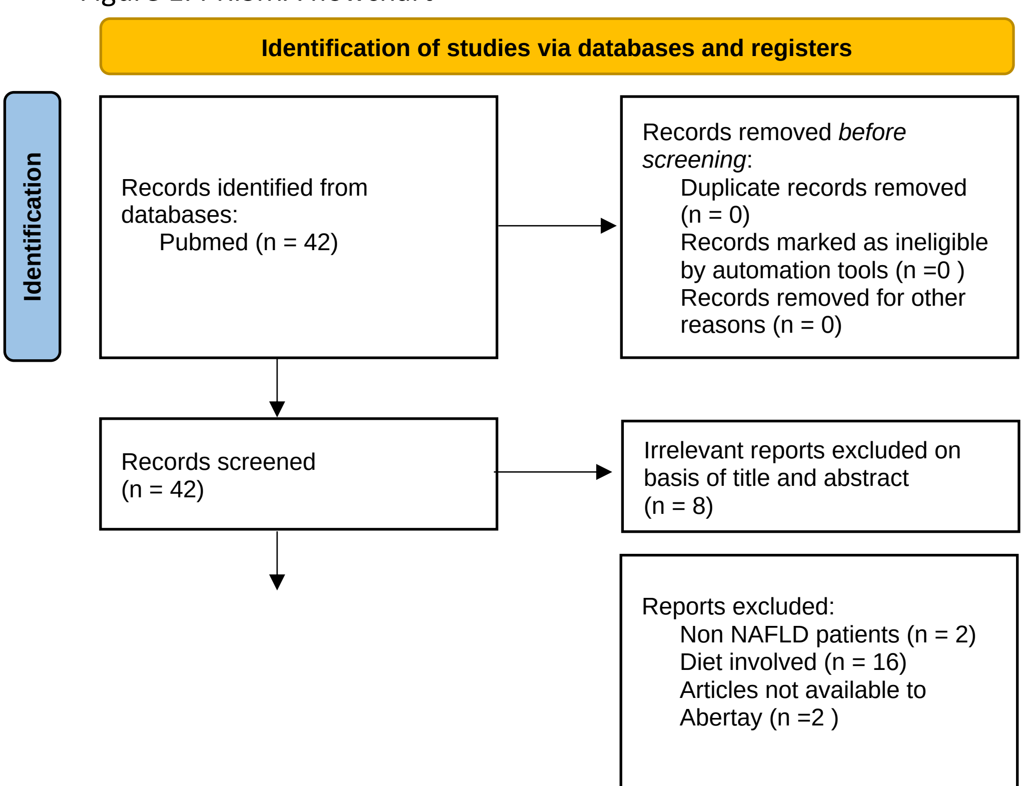
Papers were assessed for bias using PRISMA's methodological threats table (see table 1), examining hypothesis validity (including ambiguous and diffuse statistical hypotheses) and risk factors (such as no pre-treatment assessment, non-randomisation, inadequate sample size, reliance on self-reported data, and no or little acknowledgement of limitations). Participant characteristics, including exercise details (type, duration, intensity, sessions per week, and overall training period), were extracted from each study (see table 2). Excel was used to extract the data.

2.5 Meta-analysis method

Effect size, determined as mean difference (MD) with 95% confidence intervals (CI), determined statistical significance at $P < 0.05$. A p-value greater than 0.05 suggests a tendency not to reject the null hypothesis, indicating results explainable by random variability. The pooled data, represented in forest plots (See figures 2,3,4,5,6), underwent heterogeneity testing with a large Q value and a small p value indicating significant heterogeneity. I^2 values categorized heterogeneity as high (>60%), moderate (30%-60%), or low (<30%) (Thomas & Higgins, 2023). Both random- and fixed-effects models were included, with the random-effects model adopted in cases of high heterogeneity, and otherwise the fixed-effects model was used. Testing was done using Jamovi.

3. Results

Figure 1. PRISMA flowchart



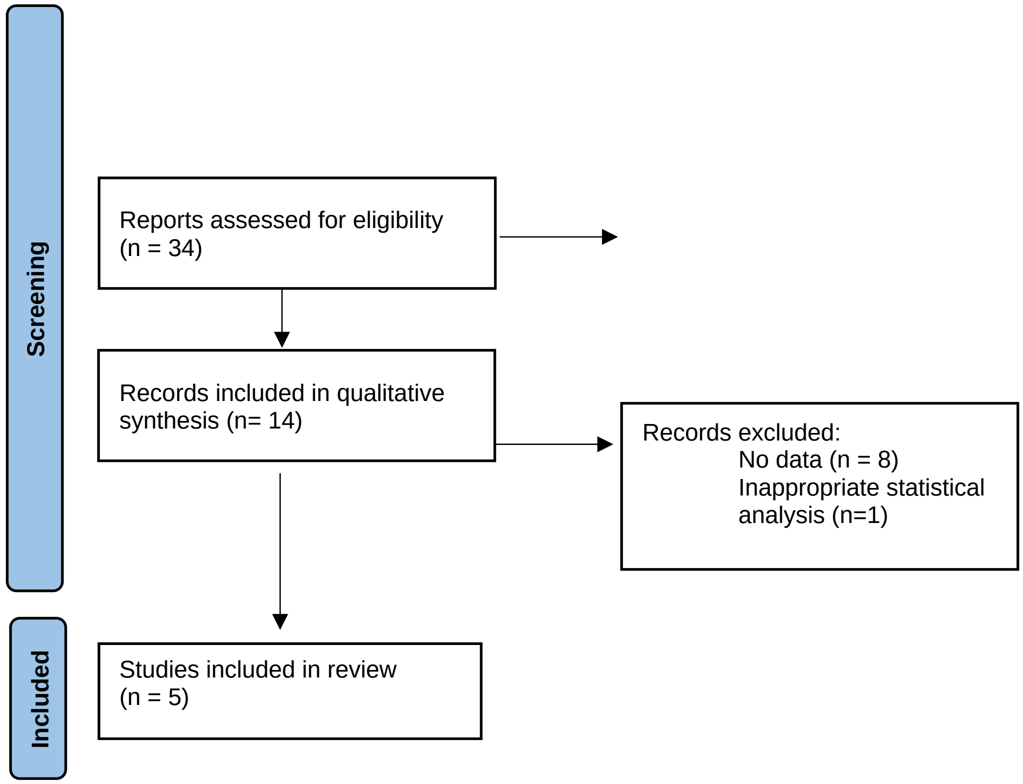


Figure 1: Flowchart illustrating the selection process of studies identified through PubMed (Page et al., 2021). The literature search spanned from 2018 to 2023, incorporating additional search keywords related to exercise and NAFLD. Initially, 42 records were retrieved from the database. Following the removal of duplicates and the exclusion of articles based on title and abstract, 34 studies remained. Among these, two studies involved non-NAFLD patients, 16 involved diet, two articles were inaccessible to Abertay, one was excluded due to inappropriate statistical analysis, and eight were excluded due to inadequate or no data. Ultimately, five studies were included in the final meta-analysis.

Table 1: Risk of bias

STUDY	**Hypothesis Validity**		**Risk of Bias**				
	Ambiguous Hypothesis?	Diffuse statistical Hypothesis and test	No pre-treatment assessment	Non-randomisation	Inadequate sample size	Reliance on Self-reported data	No/Little acknowledgement of limitations
(Winn et al., 2018)	x	x	x	x	v	x	x
(Iwanaga et al., 2020)	x	x	x	x	x	x	x

(Jafarikhah et al., 2023)	x	x	x	x	v	x	v
(Babu et al., 2022)	x	x	x	x	x	v	v
(Curci et al., 2023)	x	x	x	x	x	v	x

Table 1: Assessment of the risk of bias (Page et al., 2021). x denotes no threat; v signifies the presence of a threat. All studies were free from threats related to ambiguous and diffuse statistical hypotheses, lack of pre-treatment assessment, and non-randomization. However, two studies exhibited threats such as inadequate sample size, other two showed reliance on self-reported data, and other two had insufficient acknowledgment of limitations.

Table 2: Study characteristics

Study	Source (author & year)	Sample Size	Intervention	Control (sample size)	Session duration (minutes)	Frequency (/week)	Scheme duration	Intensity	Outcome Measure (significant change)
1	(Curci et al., 2023)	Moderate or severe NAFLD aged 30-60 years old (n=144)	PA1 (Physical activity 1) group: Aerobic (n=18) PA2 (Physical activity 2) group: Aerobic and resistance training (n= 17)	Control (n=17)	50 - 60	3 days	90 days (12,86 weeks)	Moderate: 60%-75% MHR	BMI (kg/m2), Waist circumference (cm), HOMA-IR
2	(Babu et al., 2022)	NAFLD n=46	HIIT (n=20)	Control (n=22)	40-50	2 days	12 weeks	High-intensity interval training: 85% of maxW	ALT(U/L), BMI (kg/m2), WCF, AST(U/L)
3	(IWANAGA et al., 2020)	NAFLD patients (n=32)	Aerobic (n=16)	Control (n=16)	30	3 days	12 weeks	80% electrical stimulation + 30 minutes walking speed of 5.6 km/h	HOMA-IR (mg/dl), AST (IU/L), ALT (IU/L)
4	(Jafarikhah et al., 2023)	NAFLD male 40-55 years	Aerobic (n=8)	Control (n=8)	30	3 days	8 weeks	Increasing level difficulty progressively	BMI (kg/m2), ALT (U/L), AST (U/L)

		old (n=16)							
5	(Winn et al., 2018)	NAFLD individuals (BMI ≥ 30 kg/m2) between 18 and 60 years (n=21)	Group 1: Moderate Intensity continuous training (n=8) . Group 2: HIIT (n=8)	Control (n=5)	50-60	4 days	4.5 wfeeks	MICT: 55% VO2-peak HIIT: 80% VO2peak	BMI (kg/m2), Waist circumference (cm)

Table 2: Study characteristics. All five studies compared exercise effects to a non-exercise control in patients with NAFLD. My study encompassed two aerobic exercise investigations and one high-intensity interval training (HIIT). Additionally, Curci et al. featured an aerobic group and a second group involved in both aerobic and resistance training, while Winn included groups with moderate intensity and HIIT. The duration of these session ranged between 30 to 60 minutes. Aerobic exercise frequency varied: 4 days/week (1 study), 3 days/week (3 studies), and 2 days/week (1 study). Intensity was based on parameters like maximal heart rate, peak oxygen consumption, maximal power, electrical stimulation, and altered exercise repetition time. Interventions lasted 4.5 weeks to 13 months. Three studies examined alanine aminotransferase (ALT) and aspartate aminotransferase (AST), all studied body mass index (BMI), two analysed Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and three assessed waist circumferences.

3.1 Primary measurement

3.1.1 Effect of physical activity intervention on alanine aminotransferase (ALT)

Author & year

Mean difference (95% confidence interval)

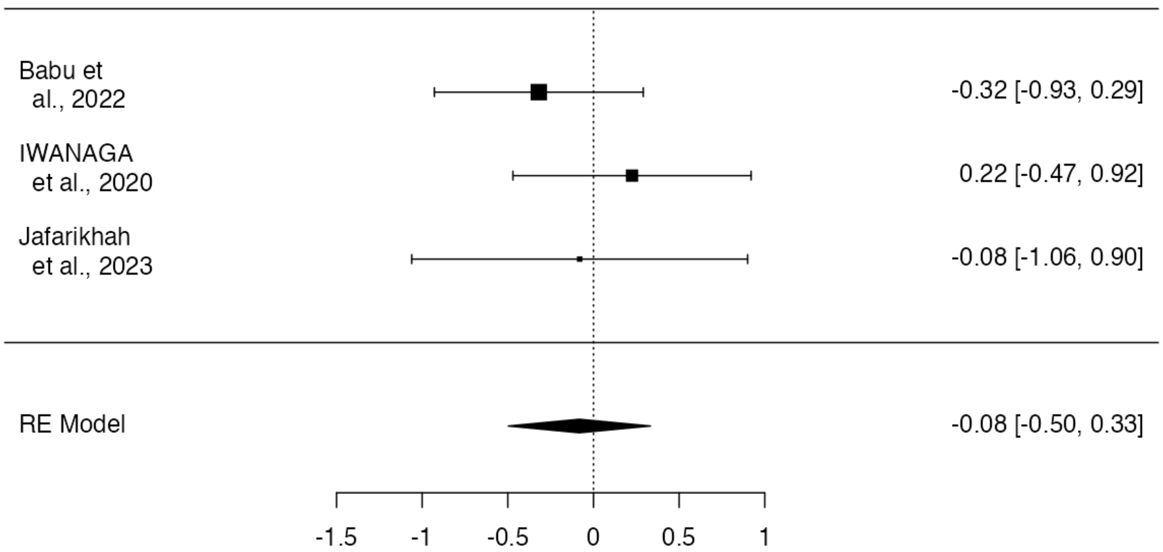


Figure 2: Forest plot showing the three studies supplied sufficient data for the analysis of ALT levels. Each line in the plot depicts study data, with the center point indicating the mean difference. A vertical line represents no effect. The lines extending from each point represent the CI for the effect size estimate. Longer lines indicate wider confidence intervals; if they cross the no-effect line, the effect isn't significant. The diamond at the bottom signifies the overall effect estimate, its width is the confidence interval. Its position left or right of the no-effect line indicates favoring the intervention or control group. The standardized mean differences observed ranged from -0.3191 to 0.2249, with the majority (67%) being negative. The average estimated standardized mean difference using the random-effects model was -0.0824 (95% CI: -0.4975 to 0.3328). Consequently, the average outcome did not show a significant difference from zero (z = -0.3888, p = 0.6974).This means that, on average, the observed effect or result is very close to no effect or no change. According to the Q-test, there was no significant amount of heterogeneity in the true outcomes (Q(2) = 1.3305, p = 0.5141, tau2 = 0.0000, I2 = 0.0000%).

Exercise didn't significantly affect ALT levels (MD, -0.08; 95% CI, −0.50 to 0.33; P = 0.7). The average result wasn't significantly different from zero (z = -0.3888, p = 0.6974), indicating no strong evidence for a distinct effect. Heterogeneity between the groups was not significant (I2 = 0%, P = 0.51).

3.2 Secondary measurements

3.2.1 Effect of physical activity intervention on aspartate aminotransferase (AST)

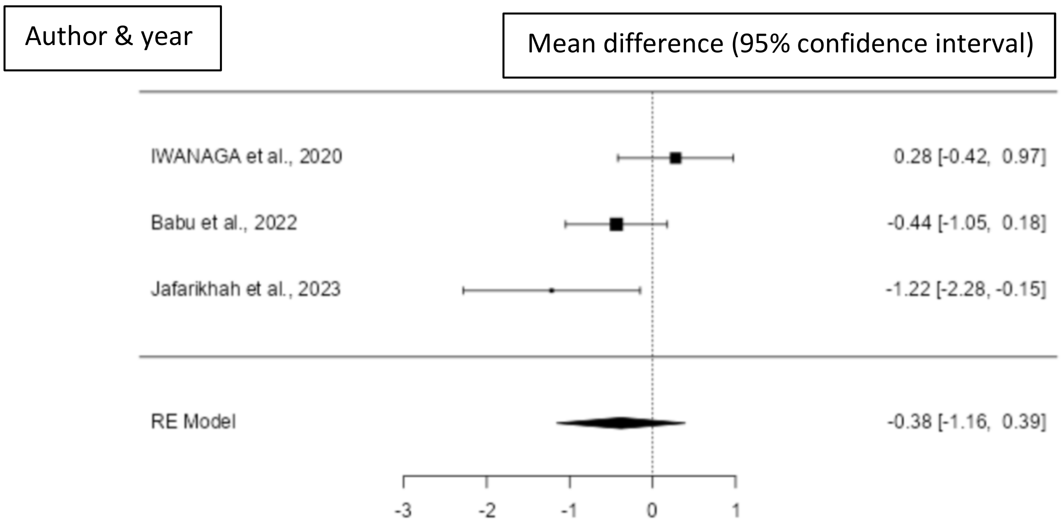


Figure 3: Forest plot showing results from the three trials that were adequate for the analysis of AST levels. In the meta-analysis, a forest plot was utilized to compare the influence of exercise on aspartate aminotransferase serum levels to that of a control group. The observed standardized mean differences ranged from -1.2173 to 0.2775, with the majority of estimates showing a negative trend (67%). Using the random-effects model, the calculated average standardized mean difference was -0.3816 (95% CI: -1.1560 to 0.3929). This means the average result wasn't significantly different from zero (z = -0.9657, p = 0.3342). Although the Q-test for heterogeneity didn't show significance, suggesting similar outcomes, there might still be some diversity in the actual results (Q(2) = 5.6710, p = 0.0587, tau^2 = 0.3093, I^2 = 67.1570%). The 95% prediction interval for the true outcomes ranged from -1.7186 to 0.9555. This implies that, while the average outcome is expected to be negative, in certain studies, the real outcome could actually be positive.

Exercise didn't significantly affect AST levels (MD, -0.38; 95% CI, −1.16 to 0.39; P = 0.33). The average result wasn't significantly different from zero (z = -0.9657, p = 0.3342), indicating no strong evidence for a distinct effect. Heterogeneity between the groups was not significant (I^2 = 67%, P = 0.59).

3.2.2 Effect of physical activity intervention on insulin resistance

Author & year

Mean difference (95% confidence interval)

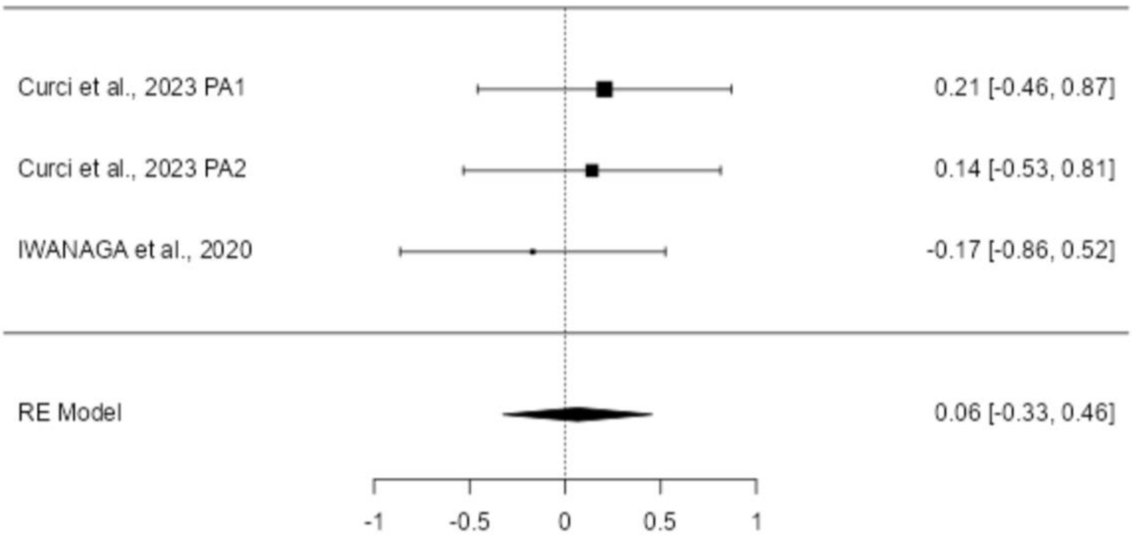


Figure 4: Forest plot showing results from the three trials that were adequate for the analysis of insulin resistance. The standardized mean differences observed varied between -0.3191 and 0.2249, and the majority of estimates indicated a negative trend (67%). Utilizing the random-effects model, the estimated average standardized mean difference was -0.0824 (95% CI: -0.4975 to 0.3328). Consequently, the average outcome did not show a significant deviation from zero (z = -0.3888, p = 0.6974). This means that, on average, the observed effect or result is very close to no effect or no change. As per the Q-test, there was no statistically significant heterogeneity observed in the true outcomes (Q(2) = 1.3305, p = 0.5141, tau^2 = 0.0000, I^2 = 0.0000%).

Exercise didn't significantly affect ALT levels (MD, 0.06; 95% CI, −0.33 to 0.46; P = 0.75). The average result wasn't significantly different from zero (z = -0.3888, p = 0.6974), indicating no strong evidence for a distinct effect. Heterogeneity between the groups was not significant (I^2 = 0%, P = 0.51).

3.2.3 Effect of physical activity intervention on body mass index (BMI)

Author & year

Mean difference (95% confidence interval)

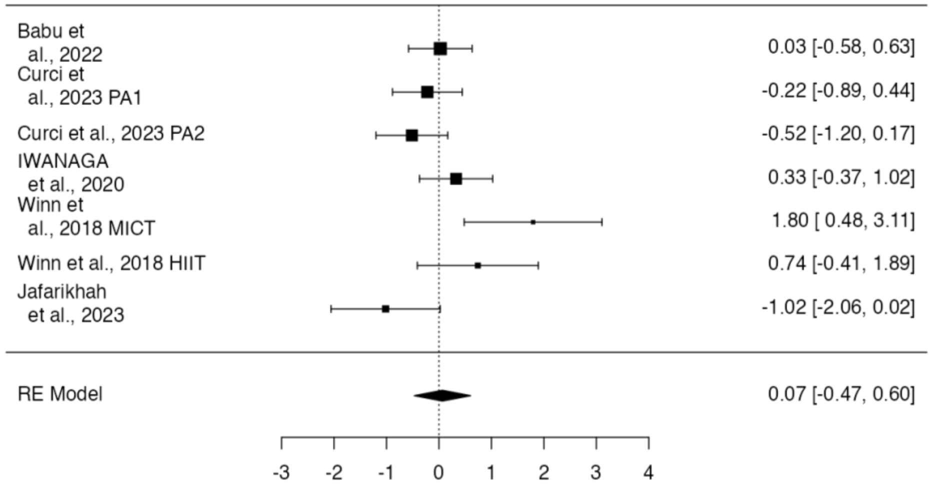


Figure 5: Forest plot showing results from the seven trials that were adequate for the analysis of body mass index. The standardized mean differences observed varied between -1.0170 and 1.7951, with a majority of estimates showing a positive trend (57%). The estimated average standardized mean difference, determined using the random-effects model, was 0.0660 (95% CI: -0.4720 to 0.6041). Therefore, the average outcome did not exhibit a significant deviation from zero (z = 0.2406, p = 0.8099). However, as indicated by the Q-test, the true outcomes seem to display heterogeneity (Q(6) = 15.8786, p = 0.0144, tau^2 = 0.3348, I^2 = 66.8753%).

Exercise didn't significantly affect BMI levels (MD, 0.07; 95% CI, −0.45 to 0.60; P = 0.8). The average result wasn't significantly different from zero (z = 0.2406, p = 0.8099), indicating no strong evidence for a distinct effect. Heterogeneity between the groups was significant (I^2 = 66%, P = 0.01).

3.2.4 Effect of physical activity intervention on waist circumference

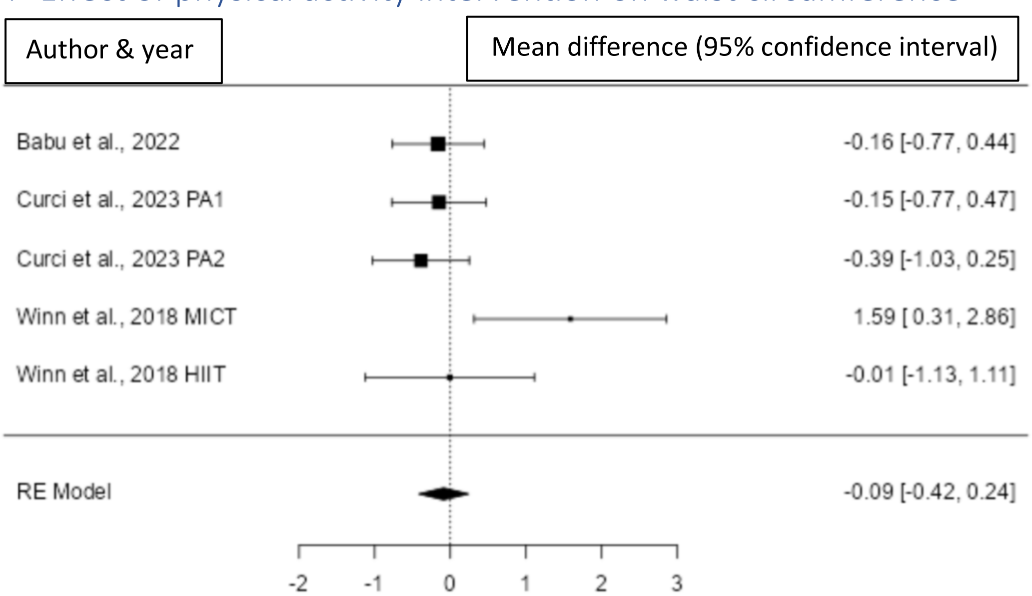


Figure 6: Forest plot showing results from the five groups that were adequate for the analysis of waist circumference. The standardized mean differences observed ranged from -0.3897 to 1.5863, with a majority of estimates leaning towards the negative side (80%). The calculated average standardized mean difference using the random-effects model was -0.0888 (95% CI: -0.4192 to 0.2417). Consequently, the average outcome did not show a significant deviation from zero (z = -0.5264, p = 0.5986). As per the Q-test results, there was no noteworthy heterogeneity detected in the true outcomes (Q(4) = 7.6209, p = 0.1065, tau^2 = 0.0000, I^2 = 0.0002%).

Exercise didn't significantly affect waist circumference measurements between intervention and control group (MD, -0.09; 95% CI, −0.42 to 0.24; P = 0.6). The average result wasn't significantly different from zero (z = -0.3888, p = 0.6974), indicating no strong evidence for a distinct effect. Heterogeneity between the groups was not significant (I^2 = 0%, P = 0.1).

In general, exercise did not have a significant impact on the primary measure ALT or any of the secondary measures. The mean differences were not greater than 0.09. All analysed studies showed notably wide confidence intervals. Achieving more precise results would require a larger population size. Heterogeneity was not significant, except in the case of BMI measurement. The p-value associated with the Q-statistic surpassed the predefined significance level (0.05), demonstrating not enough evidence to reject the null hypothesis of homogeneity. This implies that the statistical test did not detect significant differences among the studies.

4. Discussion

This meta-analysis encompassed five clinical trials, including 163 individuals diagnosed with NAFLD, all of which employed randomized controlled designs. The findings indicate a lack of consistent evidence about the impact of exercise programs on ALT levels across the included studies. In other words, the exercise interventions in the three studies did not demonstrate a statistically significant effect on ALT serum levels in individuals with NAFLD as the primary endpoint. This pattern of non-significant impact was similarly observed in secondary measurements, including BMI, waist circumference, AST, and HOMA-IR. The findings of this study diverge from existing meta-analyses ((Wang et al., 2020), (Orci et al., 2016), (Słomko et al., 2021)).

The study showed low heterogeneity, suggesting observed variability is likely due to chance, even in a homogenous set with small sample sizes. Hence, the study's limitations include a small sample size in clinical trials, a limited number of included studies, and insufficient data and measurements within each study. The limited sample size compromises the metanalysis's power to detect significant differences if they genuinely exist. A larger sample size is crucial for more robust statistical analyses to accurately identify true effects. This limitation is also reflected in the restricted number of studies meeting the inclusion criteria and providing the desired measurements. The study's constrained focus is attributed to the exclusion of dietary interventions and variations in measurement methodologies.

Numerous studies identified in the initial search did not incorporate ALT as part of their measurements. These assessments are integral to the diagnosis and ongoing monitoring of NAFLD. Elevated ALT and AST levels serve as indicators of liver inflammation, functioning as markers for overall liver health. The evaluation of insulin resistance and glucose metabolism is crucial due to the significant connection between metabolic disorders, such as type 2 diabetes, and NAFLD (NICE, 2023). Additionally, anthropometric measurements, such as BMI and waist circumference, represent independent, dose-dependent risk factors for fatty liver. Notably, the reduction of fatty liver should emphasize continuous BMI positive changes (Fan et al., 2018). However, it was surprising that many studies neglected crucial measurements for NAFLD monitoring, such as Fibro Scan, Intrahepatic Triglyceride (IHTG), Intrahepatic Lipid (IHL), or liver ultrasound, opting not to include them in their assessments (Buzzetti et al., 2015).

The baseline data were not considered due to challenges in extracting information from papers with data presented in intricate formats or lacking clarity on the repeated measures experiment nature. Moreover, a limitation was the brief duration of participants' involvement. A study indicated more significant improvements in ALT for participants engaging in exercise for over 3 months, suggesting that longer and more frequent exercise sessions generally result in better improvements (Nam et al., 2023).

4.1 Conclusion

In conclusion, exercise did not demonstrate a statistically significant effect on the ALT serum levels as the primary endpoint, neither on the secondary measurements AST, BMI, waist circumference, and HOMA-IR. A more comprehensive search, incorporating additional databases, is essential to conduct a meta-analysis with an expanded pool of studies and a larger sample size. This approach is crucial for achieving more conclusive results regarding the effectiveness of exercise as a treatment for non-alcoholic fatty liver disease.

5. References

Babu, A.F. *et al.* (2022) ‘Effects of exercise on NAFLD using non-targeted metabolomics in adipose tissue, plasma, urine, and stool’, *Scientific Reports*, 12(1). doi:10.1038/s41598-022-10481-9.

Charatcharoenwitthaya, P. *et al.* (2021) ‘Moderate-intensity aerobic vs resistance exercise and dietary modification in patients with nonalcoholic fatty liver disease: A randomized clinical trial’, *Clinical and Translational Gastroenterology*, 12(3). doi:10.14309/ctg.0000000000000316.

CKS is only available in the UK (2023) *NICE*. Available at: https://cks.nice.org.uk/topics/non-alcoholic-fatty-liver-disease-nafld/management/management/ (Accessed: 04 December 2023).

Curci, R. *et al.* (2023) 'Lifestyle modification: Evaluation of the effects of physical activity and low-glycemic-index Mediterranean diet on fibrosis score', *Nutrients*, 15(16), p. 3520. doi:10.3390/nu15163520.

Eguchi, Y. *et al.* (2020) 'Epidemiology of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in Japan: A focused literature review', *JGH Open*, 4(5), pp. 808–817. doi:10.1002/jgh3.12349.

Fan, R., Wang, J. and Du, J. (2018) 'Association between body mass index and Fatty Liver Risk: A dose-response analysis', *Scientific Reports*, 8(1). doi:10.1038/s41598-018-33419-6.

IWANAGA, S. *et al.* (2020) 'The effect of walking combined with neuromuscular electrical stimulation on liver stiffness and insulin resistance in patients with non-alcoholic fatty liver disease: An exploratory randomized controlled trial', *The Kurume Medical Journal*, 67(4), pp. 137–146. doi:10.2739/kurumemedj.ms674001.

Jafarikhah, R. *et al.* (2023) 'Effect of functional resistance training on the structure and function of the heart and liver in patients with non-alcoholic fatty liver', *Scientific Reports*, 13(1). doi:10.1038/s41598-023-42687-w.

Keating, S.E. *et al.* (2022) 'High-intensity interval training is safe, feasible and efficacious in nonalcoholic steatohepatitis: A randomized controlled trial', *Digestive Diseases and Sciences*, 68(5), pp. 2123–2139. doi:10.1007/s10620-022-07779-z.

Kim, Y. *et al.* (2019) 'Obesity and weight gain are associated with progression of fibrosis in patients with nonalcoholic fatty liver disease', *Clinical Gastroenterology and Hepatology*, 17(3). doi:10.1016/j.cgh.2018.07.006.

Moradi Kelardeh, B. *et al.* (2020) 'Effects of non-linear resistance training and curcumin supplementation on the liver biochemical markers levels and structure in older women with non-alcoholic fatty liver disease', *Journal of Bodywork and Movement Therapies*, 24(3), pp. 154–160. doi:10.1016/j.jbmt.2020.02.021.

Nam, H. *et al.* (2023) 'Effect of exercise-based interventions in nonalcoholic fatty liver disease: A systematic review with meta-analysis', *Digestive and Liver Disease*, 55(9), pp. 1178–1186. doi:10.1016/j.dld.2022.12.013.

Orci, L.A. *et al.* (2016) 'Exercise-based interventions for nonalcoholic fatty liver disease: A meta-analysis and meta-regression', *Clinical Gastroenterology and Hepatology*, 14(10), pp. 1398–1411. doi:10.1016/j.cgh.2016.04.036.

Sarwar, R., Pierce, N. and Koppe, S. (2018) 'Obesity and nonalcoholic fatty liver disease: Current perspectives', *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, Volume 11, pp. 533–542. doi:10.2147/dmso.s146339.

Słomko, J. *et al.* (2021) ‘Evidence-based aerobic exercise training in metabolic-associated fatty liver disease: Systematic review with meta-analysis’, *Journal of Clinical Medicine*, 10(8), p. 1659. doi:10.3390/jcm10081659.

Thomas, J. and Higgins, J. (2023) *Cochrane Handbook for Systematic Reviews of interventions*, *Cochrane Training*. Available at: https://training.cochrane.org/handbook/current (Accessed: 01 December 2023).

Tutino, V. *et al.* (2018) ‘Aerobic physical activity and a low glycemic diet reduce the AA/EPA ratio in red blood cell membranes of patients with NAFLD’, *Nutrients*, 10(9), p. 1299. doi:10.3390/nu10091299.

Wang, S. *et al.* (2020) ‘Physical activity intervention for non-diabetic patients with non-alcoholic fatty liver disease: A meta-analysis of randomized controlled trials’, *BMC Gastroenterology*, 20(1). doi:10.1186/s12876-020-01204-3.

Winn, N.C. *et al.* (2018) ‘Energy-matched moderate and high intensity exercise training improves nonalcoholic fatty liver disease risk independent of changes in body mass or abdominal adiposity — a randomized trial’, *Metabolism*, 78, pp. 128–140. doi:10.1016/j.metabol.2017.08.012.