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Effects of Physical Exercise on Hepatic Biomarkers in Adult Individuals: A Systematic Review and Meta-Analysis

Efectos del ejercicio físico sobre los biomarcadores hepáticos en adultos: revisión sistemática y metanálisis

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Abstract. Objective: This study aimed to analyze the effects of physical exercise on hepatic biomarkers in adult individuals. Methods: We conducted a systematic review and meta-analysis following the PRISMA recommendations and registered in PROSPERO (CRD42022337749). MEDLINE (via PubMed), Scopus, SPORTDiscus, and Web of Science were searched, using the terms of the Medical Subject Headings (MeSH) "exercise", "liver diseases", and "biomarkers". Results: Fourteen studies achieved eligibility with a total of 485 participants. Interventions ranged from 4 to 12 weeks, lasting 24 to 90 minutes per session, with 3 to 5 sessions per week. Interventions with aerobic and resistance exercises, with or without a vibration device and diet implementation, demonstrated a reduction in different hepatic biomarkers, such as aspartate transferase (AST), alanine transferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin (ALB), ferritin (Fe), and indirect bilirubin (Bil). The main results of the meta-analysis showed no significant difference in ALB, GGT, AST, and ALP. However, there was a significant difference in ALT (SMD: – 0.41; 95% CI: – 0.71 to -0.11; p = 0.008; I^2 = 0%). Conclusion: Physical exercise (e.g., resistance training, aerobic training, high-intensity interval training) favored the reduction of AST, ALT, GGT, ALP, ALB, Fe, and Bil. This study pointed out that the regular practice of physical exercise can be an efficient and recommended strategy to minimize the deleterious effects of liver diseases.
Keywords: exercise; liver disease; non-alcoholic fatty liver disease; biomarkers; resistance training; high-intensity interval training.

Resumen. Objetivo: Este estudio tuvo como objetivo analizar los efectos del ejercicio físico sobre biomarcadores hepáticos en individuos adultos. Métodos: Realizamos una revisión sistemática y metanálisis siguiendo las recomendaciones PRISMA y registrados en PROSPERO (CRD42022337749). Se realizaron búsquedas en MEDLINE (a través de PubMed), Scopus, SPORTDiscus y Web of Science, utilizando los términos de Medical Subject Headings (MeSH) "ejercicio", "enfermedades hepáticas" y "biomarcadores". Resultados: Catorce estudios lograron la elegibilidad con un total de 485 participantes. Las intervenciones variaron de cuatro a 12 semanas, con una duración de 24 a 90 minutos por sesión, con tres a cinco sesiones por semana. Las intervenciones con ejercicios aeróbicos y de resistencia, con o sin dispositivo de vibración e implementación de dieta, demostraron una reducción en diferentes biomarcadores hepáticos, como aspartato transferasa (AST), alanina transferasa (ALT), gamma-glutamil transferasa (GGT), fosfatasa alcalina (ALP), albúmina (ALB), ferritina (Fe) y bilirrubina indirecta (Bil). Los principales resultados del metanálisis no mostraron diferencias significativas en ALB, GGT, AST y ALP. Sin embargo, hubo una diferencia significativa en ALT (SMD: – 0,41; IC del 95 %: – 0,71 a -0,11; p = 0,008; I2 = 0 %). Conclusión: El ejercicio físico (por ejemplo, entrenamiento de resistencia, entrenamiento aeróbico, entrenamiento interválico de alta intensidad) favoreció la reducción de AST, ALT, GGT, ALP, ALB, Fe y Bil. Este estudio apuntó que la práctica regular de ejercicio físico puede ser una estrategia eficaz y recomendable para minimizar los efectos deletéreos de las enfermedades hepáticas.
Palabras clave: ejercicio; enfermedad del higado; enfermedad del hígado graso no alcohólico; biomarcadores; entrenamiento de resistencia; entrenamiento por intervalos de alta intensidade.

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Introduction

Liver disease, as an initial condition for chronic non-communicable diseases, is prevalent in obese and non-obese individuals and can lead to premature death. Liver disease is characterized by inflammation, fat accumulation, or structural damage in the liver, and it is prevalent in more than 25% of the world's population. In the period between 1975 and 2016, the global prevalence of obesity has nearly tripled (Simón Mora et al., 2020). In South America, liver diseases affect about 30.45% of people. Visceral fat has been considered a better predictor and associated of insulin resistance and type II diabetes mellitus (T2DM), cardiovascular disease (CVD), and the onset of non-alcoholic fatty liver disease (NAFLD). NAFLD, as a spectrum of liver diseases (including steatosis, fibrosis, and cirrhosis), is associated with fat accumulation in the liver, even in non-obese people (Chalasani et al., 2018; Hernandez-Rodas et al., 2015; Liu et al., 2021; Shi et al., 2020; Simón Mora et al., 2020; Ye et al., 2020; Younossi et al., 2016).

Liver biomarkers represent a less invasive, simple, reproducible, and reliable way to monitor health, as they are important for the diagnosis of liver health, also acting in the prediction of functional changes in the organ and its subsequent response evaluation to the treatment proposed. Among them, we can highlight aspartate transferase (AST), alanine transferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin (ALB), total bilirubin (Bil), indirect Bil and direct Bil (Hernandez-Rodas et al., 2015; Trejo Trejo et al., 2017; Wieckowska et al., 2007).

Lifestyle changes, encompassing diet and regular physical activity will contribute to lowering the risk of health problems in a sedentary lifestyle and increasing the com-

fort of life, these are non-pharmacological therapeutic measures to improve liver health, as they can reduce body weight and improve histopathological characteristics in individuals who have hepatic steatosis (Chalasani et al., 2018; Devi et al., 2023; Kul et al., 2022). In this sense, physical exercise can bring benefits and be an efficient strategy in the prevention and treatment of liver disease. There are recommendations for adopting continuous moderate-intensity training with a minimum of 150 to 300 min or 75 to 150 min of vigorous-intensity exercise per week (Kanaley et al., 2022; Khalafi & Symonds, 2021; Piercy et al., 2018).

Vigorous activity can be combined with high-intensity training, which can be used among sedentary and recreationally active individuals has also been becoming widespread as it provides effective development in an efficient short period of time, in their typologies, suggest improvement in anthropometric variables, body composition, aerobic capacity, abdominal and visceral fat mass, and inflammatory markers, thus reducing cardiometabolic risk. In addition, the implementation of diet and resistance training are also options that collaborate to improve liver health (Kanaley et al., 2022; Khalafi & Symonds, 2021; Kul et al., 2022; Piercy et al., 2018). However, the effects of exercise monitored by liver biomarkers remain controversial.

Exerkines in health have gained scientific protagonism, being substances released in response to acute or chronic exercise, with the potential for the treatment of cardiovascular diseases, type 2 diabetes mellitus, and obesity. Those related to the liver and exercise, hepatokines can improve metabolic diseases such as obesity or type 2 diabetes health (Chow et al., 2022; de Oliveira dos Santos et al., 2021; Severinsen & Pedersen, 2021).

The association of physical exercises and training strategies can promote, when biological individuality is respected, several benefits to the human body, reducing hepatic fat and improving the quality of life (Xiong et al., 2021). In this sense, resistance training, aerobics, or concurrent training, increase the deleterious effects of obesity (Simón Mora et al., 2020).

The increase in information about exercise monitoring through liver biomarkers may influence new approaches that contribute to a better lifestyle, and an improvement in body composition, mainly in the context of reducing visceral fat, improving liver health, and the possibility to add emphasis to a more efficient type of training for these individuals. Thus, the present study aimed to analyse the effects of physical exercise on hepatic biomarkers in adult individuals.

Methods

This study is characterized as a systematic literature review and meta-analysis. The procedures for conducting this research followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Page et al., 2021). The protocol of this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration ID CRD42022337749.

Search strategy

Two independent and experienced researchers conducted an electronic search without language or time filters, in December 2022 in MEDLINE (via PubMed), Scopus, SPORTDiscus, Web of Science, and ScienceDirect databases. Any disagreements between the two investigators were solved through discussion or arbitration by a third investigator. We used the descriptors "exercise", "liver diseases", and "biomarkers", available in the Health Sciences Descriptors (DeCS) and the Medical Subject Headings (MeSH). These words and their synonyms were combined using the Boolean operators OR (between synonyms) and AND (between terms) to form the search phrase (Appendix A).

Eligibility criteria

We included randomized clinical trials (RCTs) and quasi-experimental studies that analyzed the effects of physical exercise on hepatic biomarkers in adult individuals. Articles that did not use physical exercise as the main intervention, studies with children, those that did not inform the results of the interventions, and studies published in conferences, systematic review articles, and meta-analyses were excluded.

Risk of bias assessment

The risk of bias in the quasi-experimental studies was verified using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool, which contains seven elements for classification and is performed in the pre-intervention, intervention, and post-intervention stages. This tool is used in non-randomized studies to evaluate interventions in the health area. Each domain must have the risk of bias classified as "high risk of bias", "severe risk of bias", "critical risk of bias", "moderate risk of bias", or "not informed" (Schünemann et al., 2019; Sterne et al., 2016).

The risk of bias of the RCTs was analyzed using the Cochrane Collaboration tool, available at: <https://training.cochrane.org/handbook/>. The domains that analyze the risk of bias are: 1) random sequence generation; 2) allocation concealment; 3) blinding of evaluators and participants; 4) blinding of outcome evaluators; 5) incomplete results; 6) reports of selective results; 7) report on other sources of bias. Each domain has the risk of bias classified as "high", "uncertain", or "low". The final score is assigned with the highest score among the domains evaluated in each study (Cumpston et al., 2019; Cumpston et al., 2022).

In both instruments, the assessment was performed by two independent researchers, and differences were analyzed by another researcher for consensus.

Data Extraction

Data from the publications included were independently extracted by two investigators, and any discrepancies were solved in a consensus meeting with a third investigator. The variables extracted were authors, year of publication, country, characteristics of the study population (age, sex, and sample size), participant characteristics, intervention data, including general and specific exercises, intervention duration (weeks), volume and training intensity (duration of training session, weekly frequency, and training load), types of exercises, assessment and outcomes related to liver biomarkers.

Meta-Analysis

We used the Review Manager 5.4.1 program, available at http://tech.cochrane.org/revman, accessed on 31 October 2022, to analyze the effects of physical exercise in adults with liver disease and its biomarkers. Meta-analyses were performed when two or more studies could be pooled (DerSimonian & Laird, 1986). As variables were continuous, we used the inverse variance statistical method and the analysis model with the fixed or random effect when appropriate. Most of the data from studies were reported as mean ± standard deviation (SD). Conversely, some data points were reported as median, standard error (SE), or 95% confidence interval (CI) (DerSimonian & Laird, 1986). The effect measure was the difference between the means with a 95% confidence interval from the studies. The meta-analysis and distribution of the studies were analyzed by the weight of each variable in the meta-analysis.

Evidence-Level Assessment

Two independent researchers used the grading of recommendations assessment, development, and evaluation (GRADE) approach to evaluate the evidence level for each investigated outcome. The quality of evidence can be assessed by four classification levels: high, moderate, low, and very low. RCTs start with high-quality evidence, and observational studies begin with low-quality evidence. Five aspects can decrease the quality of the evidence: methodological limitations, inconsistency, indirect evidence, inaccuracy, and publication bias. Contrariwise, three aspects can increase the quality of the evidence: effect size, dose-response gradient, and confounding (Guyatt et al., 2011).

Approach to the Research Question

The decision to carry out a systematic review with meta-analysis on the effect of exercise on liver biomarkers in adults is justified by the understanding of the scientific state of the art as a future contribution factor for the basis for carrying out a new longitudinal experimental study of high-intensity interval training HIIT intensity, in the typology of long HIIT and sprint, where liver alterations will be verified, mainly changes in visceral fat.

Results

In total, 894 studies were identified in the databases (MEDLINE via PubMed = 360; Scopus = 330; SPORTDiscus = 6; Web of Science = 190; ScienceDirect = 8). After using the selection criteria, 14 studies were included in the systematic review (Abdelbasset et al., 2020; Cassidy et al., 2016; Çevik Saldiran et al., 2020; El-Kader et al., 2014; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Moradi et al., 2020; Nayebifar et al., 2020; O'Gorman et al., 2021; Oh et al., 2014; Skrypnik et al., 2016; Winn et al., 2018; Zenith et al., 2014) and seven studies (Abdelbasset et al., 2020; Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021; Zenith et al., 2014) provided data to be included in the meta-analysis (Figure 1).

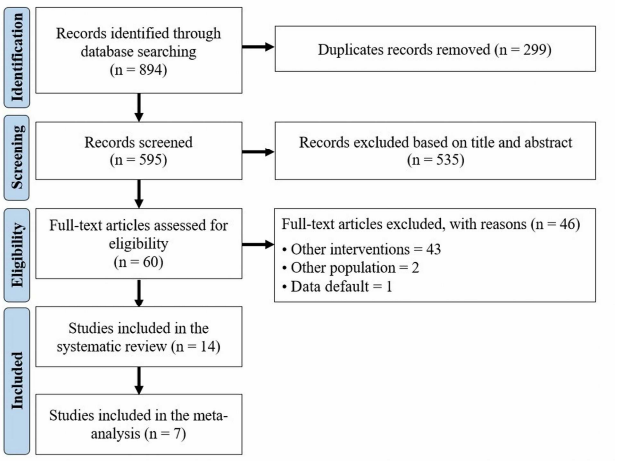

Figure 1. PRISMA flowchart of the study selection.

Table 1 shows the risk of bias for non-randomized studies. It was observed that the study by Oh et al. (2014) presented a severe risk of confounding in the design and monitoring of the intervention. It also obtained a moderate rating for reported data loss. As for the studies by O'Gorman et al. (2021) and Abd El-Kader et al. (2014), the risk of bias was evaluated as low, favorably meeting the criteria listed by the methodological quality tool.

Table 1.
Risk of bias analysis for quasi-experimental studies (ROBINS-I).

Studies	1	2	3	4	5	6	7	Total
O'Gorman et al. (2021)	Low	Low	Low	Low	Low	Low	Low	Low
El-Kader et al. (2014)	Low	Low	Low	Low	Low	Low	Low	Low
Oh et al. (2014)	Severe	Low	Low	Low	Moderate	Low	Low	Serious

1: Bias due to confounding; 2: Bias in the selection of participants in the study; 3: Bias in the classification of interventions; 4: Bias due to deviations from intended interventions; 5: Bias due to missing data; 6: Bias in the measurement of outcomes; 7: Bias in the selection of the reported result.

Table 2 shows the risk of bias assessment of the RCTs. Winn et al. (2018) and Zenith et al. (2014) presented a high risk of bias. Winn et al. (2018) reported non-blinding of researchers and assessments and non-assessment of blood tests in the control group. On the other hand, Zenith et al. (2014) reported not using a blind evaluator for thigh circumference measurements and thigh ultrasonography at the end of the study, which was also classified as having a high risk of bias. Nayebifar et al. (2020), for not presenting clarity in the information regarding the blinding of the results and their evaluators, and Skrypnik et al. (2016) for not clearly describing the randomization process, not presenting clarity in the information regarding the blinding of the results and their evaluators and not presenting clarity in the information in the blinding of the evaluators and the results, obtaining an uncertain overall risk assessment. The other RCTs were evaluated with a low risk of bias. With the classification of low risk of bias, the seven studies (Abdelbasset et al., 2020; Cassidy et al., 2016; Çevik Saldiran et al., 2020; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Moradi et al., 2020) presented a good methodological structure within the evaluation criteria and according to the Cochrane Collaboration tool. Interventions in the included studies presented the description of the warm-up, stretching, intervention-specific exercises, and relaxation phases to improve aerobic capacity, body composition, and biomarkers.

Tables 2.
Risk of bias analysis for randomized studies (Cochrane Collaboration tool)

Studies	1	2	3	4	5	6	7	Total
Abdelbasset et al. (2020)	Low	Low	Low	Low	Low	Low	Low	Low
Moradi et al. (2020)	Low	Low	Low	Low	Low	Low	Low	Low
Nayebifar et al. (2020)	Uncertain	Low	Uncertain	Low	Low	Low	Low	Uncertain
Saldiran et al. (2020)	Low	Low	Low	Low	Low	Low	Low	Low
Winn et al. (2018)	Low	Low	High	Uncertain	High	Low	Low	High
Houghton et al. (2017)	Low	Low	Low	Low	Low	Low	Low	Low
Houghton et al. (2017)	Low	Low	Low	Low	Low	Low	Low	Low
Cassidy et al. (2016)	Low	Low	Low	Low	Low	Low	Low	Low
Skrypnik et al. (2016)	Uncertain	Low	Uncertain	Uncertain	Low	Low	Low	Uncertain
Hallsworth et al. (2015)	Low	Low	Low	Low	Low	Low	Low	Low
Zenith et al. (2014)	Low	Low	Low	High	Low	Low	Low	High

1: Generation of the random sequence; 2: Allocation concealment; 3: Blinding of evaluators and participants; 4: Blinding of outcome evaluators; 5: Incomplete outcomes; 6: Reports of selective outcomes; 7: Report on other sources of bias.

Table 3 shows that the included studies were carried out between 2014 and 2021 in Asia, Europe, and North America. The total sample number was 485 participants. The samples varied between 19 and 72 participants, with balanced participation between sexes, in adults between 20 and 65 years old. NAFLD and obesity were the main topics investigated in the studies filtered in the present review, and there were also participants with liver cirrhosis, T2DM, and hepatitis C.

Tables 3.
Characteristics of the included studies.

Author	Year	Country	EG (n)	CG (n)	Total (n)	Sex	Age (mean ± SD, in years)	Participants characteristics
O'Gorman et al. (2021)	2021	Ireland	13	18	31	18 ♂ 13 ♀	40 ± 8	Hepatic C
Abdelbasset et al. (2020)	2020	Saudi Arabia	EG1: 16 EG2: 15	16	47	27 ♂ 20 ♀	40 – 60	Obese with NAFLD and T2DM
Moradi et al. (2020)	2020	Iran	EG1: 12 EG2: 11 EG3: 11	11	45	♀	65.27 ± 3.16	Older obese women with NAFLD
Nayebifar et al. (2020)	2020	Iran	EG1: 8 EG2: 8 EG3: 8	8	32	♂	20 – 30	Sedentary people
Saldiran et al. (2020)	2020	Turkey	EG1: 15 EG2: 16	–	31	12 ♂ 19 ♀	45.07 ± 9.11	NAFLD
Winn et al. (2018)	2018	USA	EG1: 9 EG2: 9	5	23	NR	46 ± 18	Obese
Houghton et al. (2017)	2017	UK	14	13	27	♀ ♂	54 ± 11	Overweight or obese alcohol drinkers
Houghton et al. (2017)	2016	UK	12	12	24	NR	59 ± 12	NASH
Cassidy et al. (2016)	2015	UK	11	12	23	18 ♂ 5 ♀	60 ± 9	T2DM
Skrypnik et al. (2016)	2016	Poland	EG1: 21 EG2: 17	–	38	♀	49.8 ± 9.8	Obese
Hallsworth et al. (2015)	2015	UK	11	12	23	NR	54 ± 10	NAFLD
El-Kader et al. (2014)	2014	Saudi Arabia	EG1: 25 EG2: 25	–	50	♂ ♀	51 ± 6	NAFLD
Oh et al. (2014)	2014	Japan	52	20	72	♂	51.2 ± 1.7	NAFLD
Zenith et al. (2014)	2014	Canada	9	10	19	♂ ♀	57.6 ± 6.7	Cirrhotic

USA: United States of America; UK: United Kingdom; SD: standard deviation; EG: exercise group; CG: control group; NAFLD: non-alcoholic fatty liver disease; T2DM: type 2 diabetes mellitus; NASH: nonalcoholic steatohepatitis; ♂: man; ♀: woman; NR: not reported.

Table 4 shows that the same study may have used multiple types of interventions. It is observed that the exercise on the stationary bike was used in eight studies (Çevik Saldiran et al., 2020; Houghton, Hallsworth, et al., 2017; O'Gorman et al., 2021; Skrypnik et al., 2016; Zenith et al., 2014). Four studies (El-Kader et al., 2014; Houghton, Hallsworth, et al., 2017; Moradi et al., 2020; Skrypnik et al., 2016) used resistance training with free weights or machines and five studies (El-Kader et al., 2014; Nayebifar et al., 2020; O'Gorman et al., 2021; Oh et al., 2014; Winn et al., 2018) used running, walking, or treadmill. It was observed as an aspect common to all studies, the choice of the frequency of three times a week in their intervention protocols and the variation of its duration between 24 and 90 minutes per training session. The total longitudinal period of the interventions ranged from 4 to 12 weeks of intervention, being prevalent in nine studies (Cassidy et al., 2016; El-Kader et al., 2014; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Moradi et al., 2020; O'Gorman et al., 2021; Oh et al., 2014; Skrypnik et al., 2016) the choice for 12 weeks of training. It was also observed that seven studies (Çevik Saldiran et al., 2020; El-Kader et al., 2014; O'Gorman et al., 2021; Oh et al., 2014; Skrypnik et al., 2016; Winn et al., 2018; Zenith et al., 2014) opted for aerobic exercises, four studies used resistance training (El-Kader et al., 2014; Houghton, Hallsworth, et al., 2017; Moradi et al., 2020; Skrypnik et al., 2016) and seven studies (Abdelbasset et al., 2020; Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Nayebifar et al., 2020; Winn et al., 2018) opted for high-intensity interval training (HIIT). The biochemical indicator ALT was found in all studies. Following the prevalence of choices of biochemical variables, nine analyses (Çevik Saldiran et al., 2020; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Moradi et al., 2020; Nayebifar et al., 2020; O'Gorman et al., 2021; Oh et al., 2014; Skrypnik et al., 2016) included the GGT and/or the ALP. Four analyses (Çevik Saldiran et al., 2020; Moradi et al., 2020; Skrypnik et al., 2016; Zenith et al., 2014) included bilirubin. Five studies (Çevik Saldiran et al., 2020; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Oh et al., 2014; Zenith et al., 2014) chose albumin and/or ferritin and only three studies (Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Winn et al., 2018) used the analysis of hepatic triglyceride content (HTGC).

Tables 4.
Intervention data and outcomes from included studies.

Study	Intervention	Training volume	Results
O'Gorman et al. (2021)	EG: Moderate-to-vigorous intensity aerobic exercise using treadmills, ASEC, and elliptical exercises training intensity of exercise HR reserve 40–75 % increasing in progress alongside the aerobic duration (21–42'). CG: No exercise.	3 ×/wk 12 wks 28–47'	EG: ↔ ALT, p = 0.384 ↔ AST, p = 0.586 ↔ ALP, p = 0.179 ↔ GGT, p = 0.948
Abdelbasset et al. (2020)	EG1 (ASEC HIIT training): 5′ warm-up + 3 sets of 4′ bouts (80–85%) HR_{max} 2′rest at 50% of the VO_{2max} between sets + 5′ cool-down EG2: 5′ warm-up + MIC 40–50′ (60–70%) HR_{max} + 5′ cool-down. CG: No exercise.	3 ×/wk 8 wks 40'	EG1: ↓ ALT, p = 0.01 EG2: ↓ ALT, p = 0.04
Moradi et al. (2020)	EG1 (RT in the gym) and EG3 (RT in the gym + Curcumin supplement group): 5-8' warm-up + 5' stretching + RT (nonlinear RT program) gym exercises: knee extension, bench press, incline bench press, seated row, deadlift, pully crunches, lat pull-downs, calf raise, hamstring curl, press behind neck, upright row, and arm curl) + 20' cool-down. Rest period: very light: 1'; light and moderate: 1–2'; heavy: 3–4'; very heavy: 5–7' + 1 set 20 reps 40% of 1 repetition maximum. EG2: Curcumin supplement. CG: No exercise and placebo.	3 ×/wk 12 wks 60–70'	EG1: ↓ ALT, p < 0.05 ↓ AST, p < 0.05 ↔ Total Bil, p > 0.05 ↔ ALP, p > 0.05 EG2: ↔ ALT, p > 0.05 ↔ AST, p > 0.05 ↔ Total Bil, p > 0.05 ↔ ALP, p > 0.05 EG3: ↓ ALT, p < 0.05 ↓ AST, p < 0.05 ↔ Total Bil, p > 0.05 ↔ ALP, p > 0.05
Nayebifar et al. (2020)	EG1 (omega 3 supplement + 40-mSRT HIIT) and EG3 (40-mSRT HIIT): 4–8 bouts of 30" (85–95%) HR_{max} with 30" rest + 20' warm-up. 1–4-week bouts increasing 1 bout each week. 5th and 6th remain 8 bouts. EG2: Omega 3 supplements only. CG: No exercise and placebo.	3 ×/wk 6 wks 24–28'	EG1: ↓ ALT, p < 0.05 ↓ AST, p < 0.05 ↓ ALP, p < 0.05 EG3: ↓ ALT, p < 0.05 ↓ AST, p < 0.05 ↓ ALP, p < 0.05
Saldiran et al.	EG1: ASEC training, 5' warm-up, 30' ASEC 60-80% HR, and 5' cool-down + 15' in	3 ×/wk	EG1:

(2020)	vertical-sinusoidal vibration platform whole-body vibration. Amplitude intensity of 2–4 mm and frequency of 30 Hz. Rest for 60" between exercises. EG2: ASEC training and exercises with whole-body vibration (load increased 5% a week), 5' warm-up, 30' ASEC 60-80% HR, and 5' cool-down + 15' not whole-body vibration. CG: No exercise.	8 wks 40'	↓ ALT, $p < 0.05$ ↓ AST, $p < 0.05$ ↔ ALP, $p > 0.05$ ↔ GGT, $p > 0.05$ ↑ Total Bil, $p < 0.05$ ↑ Direct Bil, $p < 0.05$ ↔ Fer, $p > 0.05$ ↔ ALB, $p > 0.05$ EG2: ↓ ALT, $p < 0.05$ ↔ AST, $p > 0.05$ ↔ ALP, $p > 0.05$ ↔ GGT, $p > 0.05$ ↔ Total Bil, $p < 0.05$ ↔ Direct Bil, $p > 0.05$ ↔ Fer, $p > 0.05$ ↔ ALB, $p > 0.05$
Winn et al. (2018)	EG1 (treadmill running training moderate-intensity continuous training): 10' of stretching + 5' warm-up + 30' treadmill moderate-intensity continuous training (55% VO_2 peak) + 5' cool-down. EG2 (treadmill running training HIIT): 10' of stretching + 5' warm-up + treadmill HIIT (4' 80% VO_2peak / 3' active recovery, 50% VO_2 peak) + 5' cool-down. CG: No exercise.	3 ×/wk 4 wks 50'	EG1: ↔ ALT, $p > 0.05$ ↔ AST, $p > 0.05$ ↔ HTGC, $p > 0.05$ EG2: ↔ ALT, $p > 0.05$ ↔ AST, $p > 0.05$ ↔ HTGC, $p > 0.05$
Houghton et al. (2017)	EG (HIIT ASEC training and circuit of RT using free weights and machines): 45–60`ASEC with 5' warm-up and 3' intervals on a stationary bike for 2' with 1' rest in between. Ergometer cycling HIIT exercise corresponding to a Borg rating of perceived exertion of 16–18 ('very hard'), and free weights and machines, hip and knee extension, horizontal row, chest press, vertical row, and knee extension weight for each RT using Borg rating of 14-16 ('hard'). CG: No exercise and alcohol consumption (144–336 g/wk for men and 88–224 g/wk for women).	3 ×/wk 12 wks 45–60'	EG: ↔ ALT, $p = 0.47$ ↔ AST, $p = 0.27$ ↔ GGT, $p = 0.33$ ↓ Fer, $p = 0.049$ ↔ ALB, $p = 0.31$ ↔ HTGC, $p = 0.34$ ↔ AST/ALT, $p = 0.20$ ↔ FIB-4 score, $p = 0.15$
Houghton et al. (2017)	EG (ASEC HIIT training): 5′warm-up + 3 sets for 2′ with 1′ rest. Exercise intensity 6–20 points Borg RPE with bike intervals corresponding to an RPE of 16–18 ('very hard') + RT 5 exercises: hip and knee extension, horizontal row, chest press, vertical row, and knee extension. CG: No exercise.	3 ×/wk 12 wks 60'	EG: ↔ ALT, $p = 0.31$ ↔ AST, $p = 0.17$ ↓ GGT, $p = 0.04$ ↔ ALB, $p = 0.31$
Cassidy et al. (2016)	EG (ASEC HIIT training): 5′warm-up with RPE of 9–13 ('very light' to 'somewhat hard') + 5 sets for 2′ with 90" of passive recovery, and 4 light band exercises: face-pull, horizontal push, horizontal pull, and 30° push + 5' cool-down. CG: No exercise.	3 ×/wk 12 wks 30' – 40'	EG: ↔ ALT, $p = 0.14$ ↔ AST, $p = 0.25$ ↓ ALP, $p = 0.03$
Skrypnik et al. (2016)	EG1 (ASEC training): 5' warm-up (50–60% HR_{max}) + 45' (50–80% HR_{max}), 5' without load + 5' cool-down. EG2 (RT and ASEC training): 5' warm-up 50–60% HR_{max} + 20' strength (neck barbell and gymnastic ball) + 25' endurance on ASEC (50 and 80% HR_{max}) + 5' cycling without load + 5' cool-down.	3 ×/wk 12 wks 60'	EG1: ↔ ALT, $p > 0.05$ ↔ AST, $p > 0.05$ ↓ GGT, $p < 0.05$ ↔ Total Bil, $p > 0.05$ ↔ Direct Bil, $p > 0.05$ ↔ Indirect Bil, $p > 0.05$ ↔ ALP, $p > 0.05$ EG2: ↔ ALT, $p > 0.05$ ↔ AST, $p > 0.05$ ↓ GGT, $p < 0.05$ ↔ Total Bil, $p > 0.05$ ↔ Direct Bil, $p > 0.05$ ↓ Indirect Bil, $p < 0.05$ ↔ ALP, $p > 0.05$
Hallsworth et al. (2015)	EG (ASEC HIIT training): 5′warm-up with RPE of 9–13 ('very light' to 'somewhat hard') + 5 sets for 2′ with 90" passive recovery, and 4 light band exercises: face-pull, horizontal push, horizontal pull, and 30º push + 5' cool-down. CG: No exercise.	3 ×/wk 12 wks 30' – 40'	EG: ↓ ALT, $p = 0.03$ ↓ AST, $p = 0.04$ ↔ GGT, $p = 0.55$ ↓ HTGC, $p = 0.03$
El-Kader et al. (2014)	EG1 (aerobic training walking or running): 10' of stretching + 5' warm-up + 30' walking or running, and + 5' cool-down 1st to 2nd weeks: 60–70% of HR_{max}, 3rd to 12th weeks (70–80% HR_{max}) walking or running. EG2 (RT machines): 10' of stretching + 40' RT exercises (3 sets of 8–12 reps, 60" rest between each set). Resistance 5 pounds plus/3 sets of 8 reps on 3rd days 60–80% of 1 repetition maximum. RT exercises chest press, bicep curl, triceps extension, lower back, abdominals, leg press, leg curl, and leg extension.	3 ×/wk 12 wks 50'	EG1: ↓ ALT, $p < 0.05$ ↓ AST, $p < 0.05$ EG2: ↓ ALT, $p < 0.05$ ↓ AST, $p < 0.05$
Oh et al. (2014)	EG1 (walking or running): 15–20' warm-up + 40–60' walking or running $HR_{max} > 40\%$ + 15–20' cool-down, and Diet.	3 ×/wk 12 wks	EG1: ↓ ALT, $p < 0.05$

	EG2: Diet caloric intake of 1680 kcal per day and no exercise.	90'	↓ AST, p < 0.05 ↓ GGT, p < 0.05 EG2: ↓ ALT, p < 0.05 ↓ AST, p < 0.05 ↓ GGT, p < 0.05
Zenith et al. (2014)	EG (ASEC endurance training): At 60–80% peak VO_2, 5' warm-up of low-level cycling + 30'cycling (increasing 150'' per session each week until study completion) + 5' cool-down. CG: No exercise.	3 ×/wk 8 wks 40–55'	EG: ↔ ALT, p = 0.83 ↔ AST EG1, p = 0.35 ↔ Bil, p = 0.54 ↔ ALB, p = 0.59

EG: exercise group; CG: control group; HR: heart rate; RT: resistance training; VO_{2max}: maximum oxygen volume; ASEC: aerobic static ergometer cycling; RPE: rating of perceived exertion; 40-mSRT: 40 meters shuttle run test; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HTGC: hepatic triglyceride content; ALB: albumin; Fer: ferritin; Bil: bilirubin; MIC: moderate-intensity continuous exercise; ×/wk: times per week; wks: weeks; ': minutes; '': seconds; reps: repetitions; mm: millimeters; ↔: no change; ↓: decreased; ↑: increased.

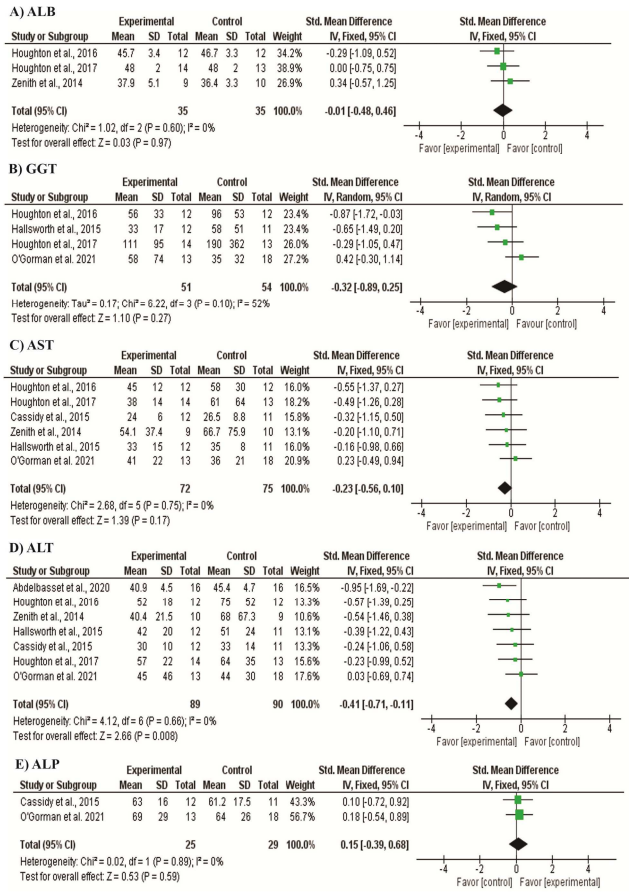

Figure 2. Forest Plot ALB, GGT, AST, ALT, and ALP.

Figure 2 shows the results of the meta-analyses of the ALB (Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Zenith et al., 2014), GGT (Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021), AST (Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021; Zenith et al., 2014), ALT (Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021), AST (Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021; Zenith et al., 2014), and ALP (Cassidy et al., 2016; O'Gorman et al., 2021). The effect size was calculated by the standardized mean difference (SMD) with a confidence interval (CI) of 95%. When calculating the effect size, the negative sign means greater effects on the EG compared to the CG. In the forest plot, lines on the left side of the graph denote participants who received HIIT and presented significant positive changes compared to control participants. The average effect size of all RCTs is represented by the diamond and should be interpreted equally. About ALB biomarker there was no significant difference (95% CI: – 0.48 to 0.46) with inconsistency I^2 = 0% and *p*-value = 0.97. For the GGT biomarker there was no significant difference (95% CI: – 0.89 to 0.25) with inconsistency I^2 = 52% and *p*-value = 0.27. For AST there was no significant difference (95% CI: – 0.56 to 0.10) with inconsistency I^2 = 0% and *p*-value = 0.17. For the meta-analyses of studies that used ALP for biomarkers assessment. There was no significant difference in ALP (95% CI: – 0.39 to 0.68) with inconsistency I^2 = 0% and *p*-value = 0.59. For the meta-analyses of studies that used ALT for biomarkers assessment there was a significant difference in ALT (95% CI: – 0.71 to –0.11) with inconsistency I^2 = 0% and *p*-value = 0.008.

Table 5 shows the level of evidence of the included studies (Abdelbasset et al., 2020; Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021; Zenith et al., 2014), which was considered high, according to the GRADE tool. This means that there is high confidence in the estimated effect.

Tables 5.
Level of evidence (GRADE).

Certainty Assessment							No. of Participants		Effect		Certainty	Importance
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	EG	CG	Relative (95% CI)	Absolute (95% CI)		
Biomarkers (analyzed with ALB)												
3	RCTs	not serious	not serious	not serious	not serious	none	35	35	—	mean 0.16 highest (−0.47 lower to 0.79 higher)	⊕⊕⊕⊕ HIGH	Important
Biomarkers (analyzed with AST)												
6	RCTs	not serious	not serious	not serious	not serious	none	72	75	—	mean −0.09 highest (−0.57 lower to 0.38 higher)	⊕⊕⊕⊕ HIGH	Important
Biomarkers (analyzed with GGT)												
4	RCTs	not serious	not serious	not serious	not serious	none	51	54	—	mean –0.14 highest (−0.42 lower to 0.69 higher)	⊕⊕⊕⊕ HIGH	Important
Biomarkers (analyzed with ALT)												
7	RCTs	not serious	not serious	not serious	not serious	none	89	90	—	mean -0.41 highest (−0.71 lower to −0.11 higher)	⊕⊕⊕⊕ HIGH	Important
Biomarkers (analyzed with ALP)												
2	RCTs	not serious	not serious	not serious	not serious	none	25	29		mean -0.15 highest (−0.39 lower to 0.68 higher)	⊕⊕⊕⊕ HIGH	Important

RCTs: randomized controlled trials; EG: experimental group; CG: control group; CI: confidence interval; ALB: albumin; AST: aspartate transferase; GGT: gamma-glutamyl transferase; ALT: alanine transferase; ALP: alkaline phosphatase; ⊕⊕⊕⊕: represents high confidence in the estimated effect.

Discussion

This systematic review and meta-analysis focused on analyzing the effects of physical exercise on hepatic biomarkers in adult individuals. The analysis of the 14 included studies showed that the practice of physical exercise, for at least 4 to 12 weeks, lasting 24 to 90 minutes per training, with 3 to 5 sessions per week, can be positive in improving liver health and reducing its biomarkers in exercise program participants (Abdelbasset et al., 2020; Cassidy et al., 2016; Çevik Saldiran et al., 2020; El-Kader et al., 2014; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Moradi et al., 2020; Nayebifar et al., 2020; O'Gorman et al., 2021; Oh et al., 2014; Skrypnik et al., 2016; Winn et al., 2018; Zenith et al., 2014).

Notably, most of the studies selected in the present review about the liver disease had patients with NAFLD as a sample, with different typologies and intervention strategies, whose samples varied in relation to age and sex. The studies involved aerobic exercise and body vibration apparatus (Çevik Saldiran et al., 2020), resistance training and turmeric diet (Moradi et al., 2020), aerobic training with caloric control (Oh et al., 2014), and aerobic and resistance training (El-Kader et al., 2014). This points to specific knowledge for patients with NAFLD, corroborating with data on worldwide prevalence (Barros et al., 2021; Li et al., 2019; Ye et al., 2020; Younossi et al., 2016).

Seven studies (Abdelbasset et al., 2020; Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; Nayebifar et al., 2020; Winn et al., 2018) involved HIIT. Nayebifar et al. (2020), after 6 weeks of exercise found reductions ($p<0.05$) in ALT, AST, triglyceride marker, and improvements ($p>0.05$) in body composition, VO_2 peak capacity, and insulin resistance. Houghton et al. (2017) partially corroborated these results, also presenting favorable results ($p<0.05$) for body composition. In contrast, Winn et al. (2018) showed favorable results ($p<0.05$) only for intrahepatic fat content. Thompson (2019) corroborates that HIIT training remains a strong worldwide trend for users who practice physical activity.

Nayebifar et al. (2020) presented a reduction in ALT e AST levels ($p<0.05$) with an intervention with HIIT, lasting 6 weeks and a short HIIT of 30/30 sec, with a difference in the percentage of intensity applied of 85–95% HRmax. The protocol used by Winn et al. (2018) was a long HIIT, lasting 4 weeks using 4 min 80% VO2peak/3 min active recovery at 50% VO2peak that showed no differences in biomarkers, aerobic capacity, and body composition, but showed reduction in biomarkers results ($p<0.05$) only in intrahepatic fat content (Andreato, 2020; Buchheit & Laursen, 2013a, 2013b; Hallsworth et al., 2015a; Khalafi & Symonds, 2020; Madueno et al., 2019; Perrier-Melo et al., 2021; Reljic et al., 2019; 2019; Słomko et al., 2021; Viana et al., 2019; Xiong et al., 2021). In the same direction, some studies (Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Thoma, et al., 2017) found a reduction in different biomarkers (GGT, ALT, AST, and ALP) with

the use of long HIIT, lasting 12 weeks and training intensity controlled by rating of perceived exertion (RPE) (hard to very hard), alternating with passive and active recovery (light intensity resistance training).

The studies analyzed in the present systematic review used different interventions. Eight studies used a cycle ergometer (Abdelbasset et al., 2020; Cassidy et al., 2016; Çevik Saldiran et al., 2020; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021; Skrypnik et al., 2016; Zenith et al., 2014), and four studies adopted running, walking, or treadmill (El-Kader et al., 2014; Nayebifar et al., 2020; Oh et al., 2014; Winn et al., 2018), which indicates good options for interventions with individuals with NAFLD. Aerobic exercises are identified as movement activities that are beneficial to health and have an impact on longevity for their practitioners. There was no specific report of an intervention study conducted outdoors or on an athletics track, which is a gap in scientific knowledge to be investigated in future studies (Celis-Morales et al., 2017; Dinu et al., 2019; Lee et al., 2017; Nordengen et al., 2019a, 2019b).

Alcohol abuse is one of the causes of liver cirrhosis. Houghton et al. (2017) involved overweight and obese patients who consumed alcohol and performed HIIT on a cycle ergometer. The authors found no changes in liver biomarkers of inflammatory signaling in patients who consumed more than 20g/day of alcohol, although Niemelä (2016) presented that ethanol-sensitive biomarkers respond to the state of oxidative stress and their levels are modulated by lifestyle factors, including weight gain, exercise, or coffee consumption dependent on age and gender. These results indicate that alcohol consumption may decrease the benefits of exercise for liver health (Aamann et al., 2018; Kruger et al., 2018; Sirisunhirun et al., 2022).

Zenith et al. (2014) analyzed cirrhotic patients and indicated a marked improvement ($p<0.05$) in VO_2 peak with the use of beta-blockers that did not seem to affect this primary outcome, with an improvement in body composition. The study by Kruger et al. (2018) corroborates these findings, albeit with less quantitative results ($p>0.05$). On the other hand, Sirisunhirun et al. (2022) and Aamann et al. (2018) found no positive changes in aerobic capacity in cirrhotic patients.

Resistance training was used in 4 studies selected in this review (El-Kader et al., 2014; Houghton, Hallsworth, et al., 2017; Moradi et al., 2020; Skrypnik et al., 2016). Except for Houghton et al. (2017), the other studies observed that resistance training modified liver function promoting a decrease in ferritin levels. The meta-analysis by Xiong et al. (2021) partially corroborates this review, as it identifies that for resistance training only the decrease ($p<0.05$) in the biomarker AST seems to improve liver health (El-Kader et al., 2014; Khalafi & Symonds, 2021; Xiong et al., 2021).

Two studies of the present systematic review and metanalysis investigated physical exercise and supplementation with curcumin and omega-3 (Moradi et al., 2020; Nayebifar et al., 2020). Due to the aim of our study, we only extracted information from the exercise groups (without supplementation) and control groups. Moradi et al. (2020) used turmeric supplementation, Nayebifar et al. (2020) used the consumption of omega-3, and Oh et al. (2014) applied a calorie-restricted diet. Moradi et al. (2020) found positive results ($p<0.05$) in the exercise and turmeric supplementation groups regarding the biomarkers AST and ALT ($p<0.05$). Nayebifar et al. (2020) also found a reduction ($p<0.05$) in ALT and AST biomarkers with training in conjunction with omega-3 supplementation. Oh et al. (2014) did not found improvement in liver biochemical markers and it was methodologically evaluated with a severe risk of bias. In this sense, Yabe et al. (2021) presented that low-quality in diet and physical inactivity are risk factors for NAFLD. In contrast, for Baker et al. (2021), the use of diet is not an essential factor for effectiveness in improving liver health, but the control of the lipid profile and the measurement of liver biomarkers are shown to be positive in the mapping, monitoring, and evaluation of the treatment of metabolic syndrome and liver disease (Ye et al., 2020).

The meta-analysis of the RCTs (Abdelbasset et al., 2020; Cassidy et al., 2016; Hallsworth et al., 2015b; Houghton, Hallsworth, et al., 2017; Houghton, Thoma, et al., 2017; O'Gorman et al., 2021; Zenith et al., 2014) (Figures 2) showed the results of the hepatic biomarkers ALB, GGT, AST, ALP, and ALT. The reduction in these hepatic biomarkers after the intervention period can be explained by the physiological adaptations that can occur as a consequence of physical exercise practice (Celis-Morales et al., 2017; Viana et al., 2019).

This systematic review highlights a better understanding between the biochemical markers of liver health and the effects of physical exercise. ALT was evaluated in all included studies. On the other hand, the present systematic review has some limitations. A limitation to be highlighted was the presence of different intervention methods in the analysis of the effects of exercise on liver biomarkers, which difficult a better comparison between training methods. Due to the limited number of quality studies, the results must be taken cautiously, especially for the metanalysis. Experimental studies are expected to investigate the metabolic dysfunction of NAFLD. Interventions are expected to be concerned with the equalization of volume/intensity by arbitrary units or by the caloric expenditure spent, thus conveying more qualitative isonomy in the comparison of their results (Andreato, 2020; Khalafi & Symonds, 2021).

Conclusion

The analysis of the included studies revealed that physical exercise with resistance training, aerobic training, and HIIT interventions favored the reduction of biochemical markers (AST, ALT, GGT, ferritin, indirect bilirubin, and ALP). The meta-analysis showed a reduction in ALT in

exercise groups. Moreover, new proposals for scientific experiments involving physical training with an outcome for liver health need to be conducted. Our study points out that those interventions can be proposed to improve the health of individuals with liver disease associated or not with comorbidities. In this way, the present study is limited by the fact of not being able to point out the best training strategy, but the regular practice of physical exercise, associated with new methods and new training trends, can be an efficient and recommended intervention strategy to minimize the deleterious effects of NAFLD and provide a better perception of human health and well-being.

It is recommended that future experimental studies investigate the effect of high-intensity exercise on liver health, with equalization of training variables (volume, duration, interval, and intensity) in obese and non-obese participants.

Authorship

Conceptualization, L.L.d.S. and R.G.d.S.V.; methodology, L.L.d.S., J.B.P.d.C., and D.G.L.; writing—original draft preparation, L.L.d.S., J.B.P.d.C., D.G.L., A.O.B.d.S., L.d.S.C., C.J.B.-P., and R.G.d.S.V.; writing—review and editing, L.L.d.S., J.B.P.d.C., D.G.L., C.J.B.-P., A.O.B.d.S., and R.G.d.S.V.; supervision, J.B.P.d.C., C.J.B.-P., and R.G.d.S.V. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Protocol

This systematic review follows the PRISMA recommendations and is registered in PROSPERO (CRD42022337749).

Appendix A:

Database	Search phrase
MEDLINE (PubMed)	("exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields] OR "exercising"[All Fields]) AND ("liver diseases"[MeSH Terms] OR ("liver"[All Fields] AND "diseases"[All Fields]) OR "liver diseases"[All Fields] OR ("liver"[All Fields] AND "disease"[All Fields]) OR "liver disease"[All Fields]) AND ("biomarker s"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields])
Scopus	(TITLE-ABS-KEY (exercise) AND TITLE-ABS-KEY (liver AND disease) AND TITLE-ABS-KEY (biomarkers))
SPORTDiscus	exercise AND liver disease AND biomarkers
Web of Science	((ALL=(exercise)) AND ALL=(liver disease)) AND ALL=(biomarkers)
ScienceDirect	(exercise) AND ("liver disease") AND (biomarkers)

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