 OPEN

Effect of high-intensity interval training on clinical parameters in patients with metabolic dysfunction–associated steatotic liver disease: a systematic review and meta-analysis of randomized controlled trials

Jie Fu[a,*], Chunlan Liu[a,*], Luping Yang[b,*] Binbin Zhang[c,*], Run Zhou[a,*], Chaohua Deng[d], Huiqin Zhang[d], Jianing Kong[d], Jie Li[e] and Junping Shi[c,f,g]

High-intensity interval training (HIIT) has potential health benefits in the treatment of many chronic diseases. However, the efficacy of HIIT in patients with metabolic dysfunction–associated steatotic liver disease (MASLD) remains unclear. This systematic review and meta-analysis aimed to assess the impact of HIIT on intrahepatic lipids (IHLs) , liver enzymes, and metabolic profiles in individuals with MASLD. All randomized-controlled trials (RCT) that evaluated and compared the effects of HIIT on clinical parameters in patients with MASLD were searched using the PubMed, EMBASE, WOS, and Cochrane databases. Data analysis and integration were performed using RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and Stata version 18 software (StataCorp LLC, College Station, Texas, USA), and outcomes were assessed using the standardized mean difference (SMD). Our results showed that compared with other types of exercise or no exercise, HIIT could reduce the levels of IHL [SMD: −0.56%, 95% confidence interval (CI): −0.99 to −0.13, $P = 0.01$], BMI (SMD: −0.31, 95% CI: −0.62 to −0.01, $P = 0.04$), alanine aminotransferase (ALT) (SMD: −0.61, 95% CI: −0.95 to −0.26, $P = 0.0006$), and aspartate aminotransaminase (AST) (SMD: −0.43, 95% CI: −0.81 to −0.05, $P = 0.03$) in patients with MASLD. In addition, subgroup analyses showed that HIIT had a positive impact on clinical indicators in patients with MASLD with an intervention duration of less than equal to 8 weeks. This study supports the idea that HIIT can significantly reduce IHL, BMI, ALT, and AST levels, and further studies are needed to assess the long-term adherence and treatment effects of HIIT. Eur J Gastroenterol Hepatol 37: 789–798

Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly named as nonalcoholic fatty liver disease (NAFLD), is one of the most common causes of chronic liver disease worldwide [1,2] and is defined as the presence of excess triglyceride (TG) storage in the liver in the presence of at least one cardiometabolic risk factor [3]. In 2023, NAFLD underwent a name change to MASLD [4]. Studies report a 99% overlap between cases of NAFLD and MASLD, and therefore, the term MASLD will be used in the manuscript [5]. MASLD is a global public health concern, it encompasses a spectrum of conditions, ranging from isolated steatosis (characterized by excessive fat in the liver exceeding 5%, verified by liver imaging or biopsy [6]) to metabolic dysfunction–associated steatohepatitis (MASH), which is distinguished by the presence of inflammation, and/or liver fibrosis, and it shows progression to cirrhosis and hepatocellular carcinoma in some cases [7]. It is currently a leading indication for liver transplantation in the USA [8]. The burden of MASLD and its complications is projected to continue to increase in the coming years [9].

On March 2024, the Food and Drug Administration announced the conditional approval of resmetirom for the treatment of MASH. Resmetirom is aimed at patients with stage F2–F3 MASH liver fibrosis [10], whereas the lifestyle interventions are aimed at patients in the early stages of MASLD disease, with differences in the populations of interest. Therefore, lifestyle interventions are still the primary treatment for MASLD [3,11]. Indeed, for patients with MASLD, aerobic exercise training is an established cornerstone of disease management that

European Journal of Gastroenterology & Hepatology 2025, 37:789–798

Keywords: high, intensity interval training, meta, analysis, metabolic dysfunction, associated steatotic liver disease, randomized-controlled trial

[a]College of Nursing, Hangzhou Normal University, [b]Department of Fourth School of Clinical Medicine, Zhejiang Chinese Medical University, [c]Department of Infectious Diseases and Hepatology, The Affiliated Hospital of Hangzhou Normal University, [d]Department of Medical School, Hangzhou Normal University, [e]Department of Infectious Disease, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [f]Zhejiang Key Laboratory of Medical Epigenetics and [g]Institute of Hepatology and Metabolic Diseases, Hangzhou Normal University, Hangzhou, Zhejiang, China

Correspondence to Junping Shi, MD, PhD, Department of Infectious Diseases and Hepatology, The Affiliated Hospital of Hangzhou Normal University, 126 Wenzhou Road, Hangzhou, Zhejiang 310015, China
Tel: +0086 157188358060, e-mail: 20131004@hznu.edu.cn

*Jie Fu, Chunlan Liu, Luping Yang, Binbin Zhang, and Run Zhou contributed equally to the writing of this article.

Received 9 October 2024 **Accepted** 26 January 2025.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.eurojgh.com.

attenuates nutrient overload in the liver by improving substrate metabolism and reducing liver steatosis and serum alanine aminotransferase (ALT) levels [12]. High-intensity interval training (HIIT), which involves short, repeated bouts of high-intensity anaerobic exercise interspersed with low-intensity breaks, can significantly reduce the exercise duration to achieve the same effect as aerobic exercise [13]. This attractive, time-efficient approach is effective in decreasing hepatic steatosis [14,15] and has rapidly emerged as a popular alternative to continuous moderate-intensity exercise [16]. Increasing evidence has suggested that HIIT has numerous potential health benefits. HIIT can rapidly deplete skeletal muscle glycogen and increase the number and activity of mitochondria in the skeletal muscle to meet the energy demands of exercise, thereby promoting health and metabolic function [17]. Poon *et al.* [18] found that high-intensity exercise patterns improved cardiometabolic health in individuals with metabolic syndrome. Petersen *et al.* [19] noted that HIIT efficiently improved insulin sensitivity, VO_2max, and body composition with intact responses in obesity and type 2 diabetes. However, the effectiveness of HIIT in treating MASLD remains unclear [20].

To further investigate the effectiveness of HIIT in improving MASLD, we performed a systematic review and meta-analysis [21] to evaluate its effects on liver steatosis, aminotransferase levels, metabolic parameters, and BMI. This study provides a reference for healthcare providers to make an HIIT exercise prescription.

Methods

Search strategy

Two independent investigators (R.Z. and C.D.) conducted a systematic search of PubMed, Embase, Web of Science, and the Cochrane Library from database inception until March 2024. Relevant studies were identified by combining Medical Subject Headings terms and free text words specific to each database's unique requirements. The following search terms included, but were not limited to: 'non-alcoholic fatty liver disease' OR 'non-alcoholic steatohepatitis' OR 'metabolic-dysfunction-associated steatohepatitis' OR 'metabolic dysfunction-associated steatotic liver disease' AND 'high-intensity interval training' AND 'randomized controlled trial'. The references mentioned in these articles were also obtained. The search strategies applied to all the accessed databases were exhibited in supplementary data, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*.

Eligibility criteria and quality assessment

Inclusion criteria

Inclusion criteria included (a) original studies that defined clear diagnostic tools or criteria for MASLD; (b) randomized-controlled trials (RCTs); (c) studies that reported one of the following results: intrahepatic lipid (IHL), liver enzymes, including aspartate aminotransferase (AST), ALT; metabolic factors, such as body fat, fat mass, BMI; lipid profiles, including total cholesterol (TC), TGs, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C); homeostatic model assessment of insulin resistance (HOMA-IR); fasting glycemia (FG); hemoglobin A1C (HbA1c) and fasting insulinemia (FINS).

Exclusion criteria

Exclusion criteria included (a) duplicate publications; (b) incomplete or inaccessible data; (c) studies that did not exclude other causes of liver disease, such as drug-induced liver disease, alcoholic fatty liver disease (or excessive alcohol consumption), and viral hepatitis infections; (d) systematic evaluations, review articles, animal experiments, case reports, and guidelines; (e) with dietary interventions.

Data extraction

Two authors (J.F. and L.Y.) independently performed study selection and data extraction. Studies that did not meet the above inclusion criteria were excluded based on the evaluation of abstracts or full-text articles. The following data were extracted from the included studies: name of the first author, publication year, intervention groups, sample size, age, and intervention methods (exercise methods, intensity, and duration). Data were collated and summarized using Microsoft Excel. Any disagreements regarding the inclusion and extraction of basic information and data were resolved through consultation with a third author.

Quality assessment

Two researchers (J.F. and C.L.) independently assessed the quality of the included studies using the Cochrane Collaboration Risk of Bias 2 tool (Cochrane Collaboration, London, UK), which considers factors such as randomization, blinding, allocation concealment, data integrity, selective reporting, and other sources of bias [22]. The overall judgment of the bias was classified as (a) low risk, (b) unclear risk, and (c) high risk.

Statistical analysis

Data analysis and integration were performed using RevMan 5.3 and Stata version 18 software. We inputted the mean and SD data for the change between the start of intervention to end of intervention and performed data synthesis. For all studies, outcomes were assessed using the standardized mean difference (SMD). To assess the heterogeneity among the included studies, the I^2 test and Cochran's test were performed during the systematic review and meta-analysis. The fixed-effects model was used when the heterogeneity was low ($P \geq 0.1$ and $I^2 \leq 50\%$). Alternatively, the random-effects model was utilized when heterogeneity was high ($P < 0.1$ and $I^2 > 50\%$). A sensitivity analysis was conducted to assess the stability of the outcomes by sequentially omitting individual studies. Publication bias was assessed using Begg's test and funnel plots [23].

Results

Database search and article selection

A total of 240 articles were identified through electronic database searches. Of these, 113 were duplicates. After screening the titles and abstracts, 112 articles that did not meet the inclusion criteria were excluded, and 15 articles underwent full-text assessment. A total of 10 articles

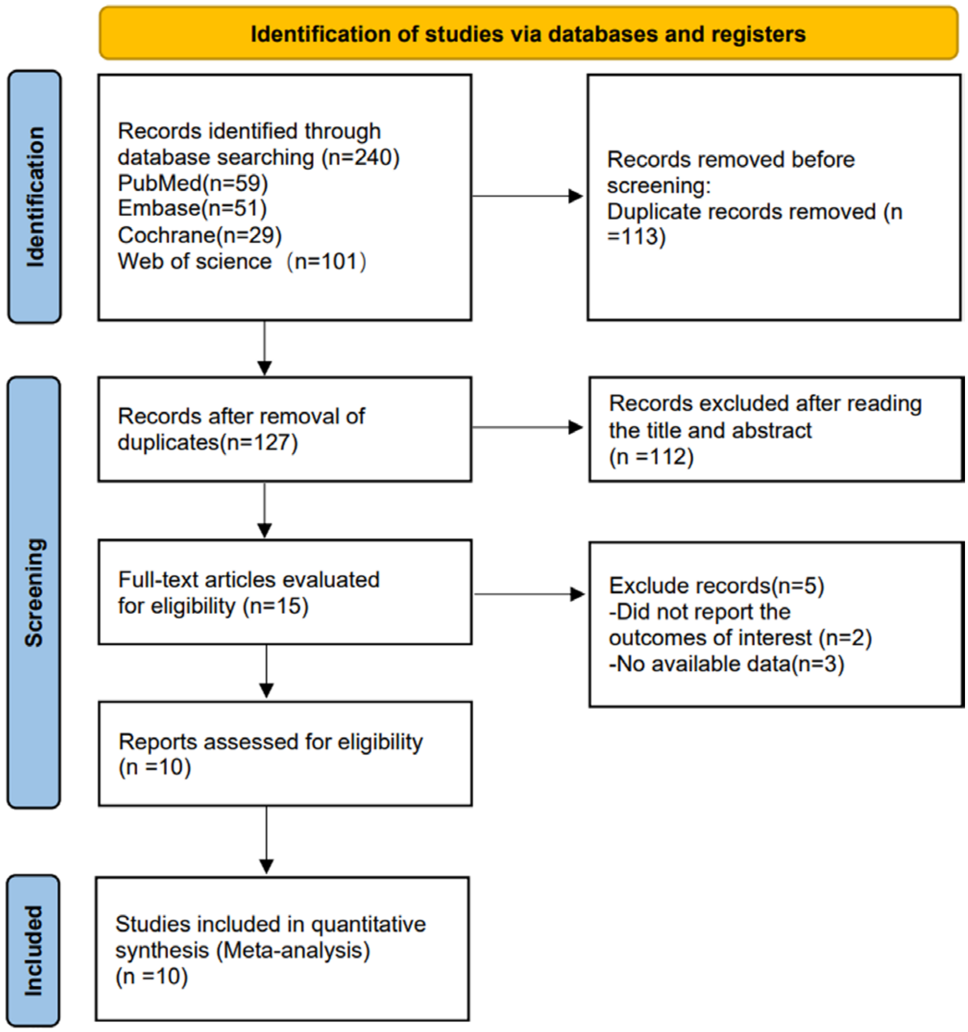

Fig. 1. Flow diagram of the study selection.

[24–33] were included in the final systematic review and meta-analysis. The study identification and selection process are illustrated in Fig. 1.

Study characteristics

This systematic review and meta-analysis included 10 RCTs involving 224 participants. Published studies ranged from 2013 [29] to 2023 [30]. The mean age of participants ranged from 12.81 ± 1.02 [33] to 61.3 ± 7.1 [28]. Three studies were conducted in Iran [26,31,32], two studies in the UK [27,29], and one each in the USA [33], Japan [28], Finland [30], Australia [25], and Saudi Arabia [24]. Among the 10 RCTs, six studies used no exercise as a control [24,25,27,29–31], while the remaining four studies used school-based exercise (SBE) [26], aerobic interval training (AIT) + resistance training (RT) [32], and moderate-intensity continuous aerobic training (MICT) [28,33] as controls. Three studies assessed exercise intensity in terms of maximal oxygen consumption (VO_2max) [24,28,33], while two studies evaluated it in terms of maximum heart rate (HRmax) [25,32], one study assessed exercise intensity in terms of the maximum aerobic speed associated with VO2peak [26]. The Exercise duration (including rest period) of HIIT protocols is 13–75 min, while that of the control group is 30–75 min. The duration of the intervention ranged from 4 to 12 weeks with the majority of studies having a frequency of three interventions per week. Of the included studies, three studies measured IHL using MRI [24,27,30] and three studies using proton-magnetic resonance spectroscopy [25,29,33], the remaining four studies used ultrasound [26,31,32] for the measurement of IHL and one study used transient elastography [28]. Of the 10 trials included, it was not possible to extract data on blood indicators in two of the trials, so only data on body composition were included [26,28]. Table 1 provides the details of the 10 included articles included in this review.

High-intensity interval training

The mean range of IHL is −5.9 ± 12.39 to −2.3 ± 4.01%, the mean range of ALT is −15 ± 26.28 to 8 ± 18.99 U/L, the mean range of AST is −6.05 ± 4.23 to 3.58 ± 10.27 U/L, the mean range of BMI is −2.2 ± 3.98 to −0.1 ± 0.5 kg/m^2, the mean range of LDL-C is −0.27 ± 0.43 to 0.1 ± 0.19 mmol/L, the mean range of HDL-C is 0 ± 0.18 to 0.08 ± 0.14 mmol/L, the mean range of FG is −0.9 ± 1.59 to 0 ± 0.56 mmol/L, the mean range of FINS is −52.09 ± 32.76 to 8.06 ± 37.68 pmol/L, the mean range of

Table 1. The basic characteristics of studies included in the meta-analysis.

Author (year)	Country	Age (year)		Sample size		Exercise type		Intensity		Duration (min)		Frequency (times/week)	Follow-up time	Assessment of IHL	Outcome indicator
		EG	CG	EG	CG	EG	CG	EG	CG	EG	CG				
Iraji *et al.* (2021)	Iran	12.81 ± 1.02	13.14 ± 1.49	11	12	HIIT	SBE	100–110%/50% MAS	NA	50–60	36–40	3	8 W	US	BMI, BFP
Fakhredin Hoseini *et al.* (2018)	Iran	39.82 ± 5.21	38.69 ± 6.7	17	13	HIIT	No exercise	NA	NA	NA	NA	3	8 W	US	BMI, ALT, AST
Abdelbasset *et al.* (2020)	Saudi Arabia	54.4 ± 5.8	55.2 ± 4.3	16	16	HIIT	No exercise	80–85% VO_2 max	NA	40	NA	3	8 W	MRI	BMI, LDL-C, HDL-C, ALT, FG, HOMA-IR, HbA1c, IHL
Rajabi *et al.* (2021)	Iran	42.09 ± 9.04	44.45 ± 6.47	11	11	HIIT + RT	AIT + RT	85–95% HRmax	70–75% of HRmax	55–75	55–75	3	12 W	US	BMI, FG, FINS, HOMA-IR
Winn (2017)	USA	41 ± 14	51 ± 13	8	5	HIIT	MICT	80% VO_2max	NA	NA	NA	4	4 W	1H-MRS	BMI, BFP, FM, TC, TG, LDL-C, HDL-C, ALT, AST, FG, FINS, HOMA-IR
Hallsworth *et al.* (2015)	UK	54 ± 10	52 ± 12	11	12	HIIT	No exercise	NA	NA	30–40	NA	3	12 W	MRI	BMI, BFP, FM, TC, TG, ALT, AST, FG, FINS, HOMA-IR, HbA1c, IHL
Keating *et al.* (2022)	Australia	53 ± 12	61 ± 5	8	6	HIIT	No exercise	85–95% HRmax	NA	30	30	3	12 W	1H-MRS	BMI, TC, TG, HDL-C, LDL-C, ALT, AST, FG, FINS, IHL
Thoma *et al.* (2013)	UK	52.9 ± 9.6	49.8 ± 10.2	12	8	HIIT	No exercise	NA	NA	NA	NA	3	12 W	1H-MRS	FM, TG, ALT, AST, IHL
Oh (2017)	Japan	48.6 ± 1.8	48.2 ± 2.3	20	13	HIIT	MICT	80–85% VO_2max	60–65% VO_2max	13	40	3	12 W	TE	FM
Csader (2023)	Finland	56.9 ± 12.2	61.3 ± 7.1	7	7	HIIT	No exercise	NA	NA	32–42	NA	3	12 W	MRI	BMI, TC, TG, LDL-C, HDL-C, ALT, AST, HbA1c, IHL, FM, FG, FINS

1H-MRS, proton-magnetic resonance spectroscopic; AIT, aerobic interval training; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BFP, body fat percentage; CG, control group; EG, high-intensity interval training; FG, fasting glycemia; FINS, fasting insulinemia; FM, fat mass; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; HOMA-IR, homeostatic model assessment of insulin resistance; HRmax, maximum heart rate; IHL, intrahepatic lipid; LDL-C, low-density lipoprotein cholesterol; MAS, maximum aerobic speed associated with VO_2peak; MICT, moderate-intensity continuous aerobic training; NA, not available; RT, resistance training; SBE, school-based exercise; TC, total cholesterol; TG, triglyceride; TE, transient elastography; US, ultrasound; VO_2max, maximal oxygen consumption.

TG is −0.5 ± 0.86 to 0.24 ± 0.75 mmol/L, the mean range of TC is −0.7 ± 0.95 to 0.03 ± 1.07 mmol/L, the mean range of body fat is −1.2 ± 6.66 to 0.4 ± 1.6%, the mean range of fat mass is −1.8 ± 7.5 to 0.3 ± 1.7 kg, the mean range of HOMA-IR is −0.91 ± 3.23 to 0.02 ± 0.7, the mean range of HbA1c is −0.4 ± 0.36 to 0.1 ± 2.65%.

Control group

The mean range of IHL is −2.5 ± 8.32 to 0.1 ± 4.17%, the mean range of ALT is −8.71 ± 22.76 to 5 ± 26.62 U/L, the mean range of AST is −3.14 ± 13.66 to 4 ± 11.53 U/L, the mean range of BMI is −0.52 ± 1.94 to 0.5 ± 7.65 kg/m^2, the mean range of LDL-C is −0.27 ± 0.69 to −0.01 ± 0.32 mmol/L, the mean range of HDL-C is −0.1 ± 0.45 to 0.03 ± 0.09 mmol/L, the mean range of FG is −1.17 ± 1.17 to 0.7 ± 1.25 mmol/L, the mean range of FINS is −52.08 ± 61.8 to 12.5 ± 77.54 pmol/L, the mean range of TG is −0.02 ± 0.42 to 0.3 ± 0.79 mmol/L, the mean range of TC is −0.25 ± 0.56 to 0.1 ± 1.08 mmol/L, the mean range of body fat is −0.68 ± 2.03 to 0.3 ± 7.49%, the mean range of fat mass is −1 ± 3.2 to 0.9 ± 6.05 kg, the mean range of HOMA-IR is −3.3 ± 3.9 to 0.18 ± 1.67, the mean range of HbA1c is −0.2 ± 0.55 to 0.1 ± 2.35%.

Quality assessment

Supplemental Figure A, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149* illustrates the bias found in the 10 included studies, with the highest risk observed in the blinding of participants and personnel (performance bias), and outcome assessment (detection bias). The quality was higher because of selection bias, follow-up bias, and reporting bias. The results of the quality assessment showed that four RCTs had low overall bias [24,27,28,32], whereas four articles had high overall bias, mainly focusing on performance bias and detection bias [26,29,31,33]. Funnel plots or Egger's test for publication bias were not used because the number of articles for each outcome indicator was less than 10.

Intrahepatic lipids

The IHL is a measure of the total amount of fat in the liver. Four studies (87 participants) showed low heterogeneity and a borderline reduction in IHL [SMD: −0.56%, 95% confidence interval (CI): −0.99 to −0.13, $I^2 = 0\%$, $P = 0.01$] (Fig. 2) in patients with MASLD following HIIT intervention. Only four studies were included in this outcome measure because IHL data could not be extracted for the remaining six studies. The control groups in all four studies were not exercised; the results can only show that HIIT has a better effect on lowering liver fat than no exercise. Because there were only four studies on this outcome, subgroup analyses were not performed.

Liver transaminases

ALT and AST reflect inflammation and injury of liver cells in patients with MASLD [34]. The effect size was pooled for seven studies (147 participants), which showed a borderline reduction in ALT concentrations (SMD: −0.61, 95%CI: −0.95 to −0.26, $I^2 = 64\%$, $P = 0.0006$) (Supplemental Figure B1, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*) following HIIT intervention in patients with MASLD. The HIIT intervention significantly reduced AST concentrations in six trials (115 participants) (SMD: −0.43; 95% CI: −0.81 to −0.05, $I^2 = 15\%$, $P = 0.03$) (Supplemental Figure B2, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*). We performed subgroup analyses based on intervention time, categorized as less than equal to 8 and greater than 8 weeks (Figs. 3 and 4). The subgroup analysis forest plot indicated that HIIT had comparable effects on ALT and AST levels in patients with MASLD at greater than 8 weeks of intervention, with no statistically significant difference detected. However, positive effects were observed only at less than equal to 8 weeks. Only one study had a control group with MICT, the rest of the studies were no exercise [33]. The forest plot showed high heterogeneity in ALT results, which was reduced after subgroup analysis.

BMI

Data from eight trials examined the impact of HIIT intervention on BMI, resulting in an overall estimate of −0.31 (95% CI: −0.62 to −0.01, $I^2 = 0\%$, $P = 0.04$) (Supplemental Figure B3, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*). The results demonstrated that patients in the HIIT intervention group experienced a significant decrease in BMI compared with those in the control group. In five trials, the control group was no exercise and in the remaining three trials, SBE, MICT, AIT + RT. We similarly performed subgroup analyses, and consistent with the above results, there was a statistical difference at less than equal to 8 weeks of

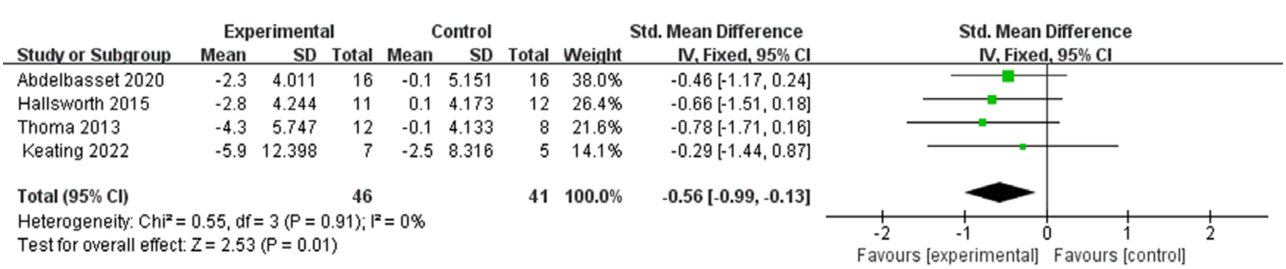

Fig. 2. Results of the effect of high-intensity interval training on intrahepatic lipids (%) levels compared with control. CI, confidence interval; IV, inverse-variance.

intervention (Fig. 5). Of all the trials included six studies measured adiposity, the methods used are electronic scale and air displacement plethysmography [27,29], bioelectrical impedance [30], dual-energy X-ray absorptiometry [28,33], and skinfold caliper [26]. No significant reduction in body fat and fat mass were found (Supplemental Figures B4 and B5, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*). Because few of the included articles assessed skeletal muscle mass, this study did not analyze the effect of HIIT intervention on skeletal muscle mass.

Plasma lipids

The forest plot showed significant decrease in LDL-C with the HIIT intervention (SMD: −0.79, 95% CI: −1.3 to −0.28, I2 = 75%, $P = 0.002$) (Supplemental Figure B9, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*), but no significant differences were found (SMD: 0.27, 95% CI: −0.19 to 0.74, $I^2 = 0\%$, $P = 0.25$) (Supplemental Figure B8, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*) among the four trials reporting on HDL-C concentrations. In only one of the included trials was the MICT control group different from the rest of the no exercise control group [33]. There was no statistical significance found in the studies that looked at TC (SMD: −0.03, 95% CI: −0.52 to 0.46, $I^2 = 0\%$, $P = 0.9$) (Supplemental Figure B7, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*) and TG (SMD: −0.29, 95% CI: −0.73 to 0.14, $I^2 = 0\%$, $P = 0.19$) (Supplemental Figure B6, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*). There were also no significant results for the remaining measures of indicators of glucose metabolism, such as FG, HbA1c, HOMA-IR, and FINS (Supplemental Figures B10–B13, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*).

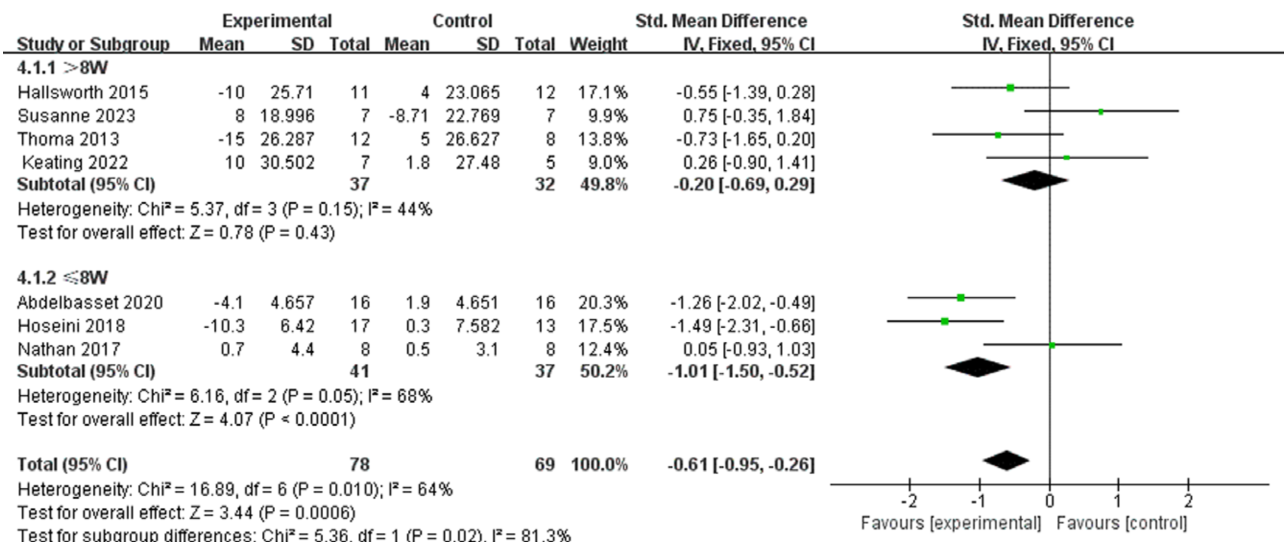

Fig. 3. Results of subgroup analysis on alanine aminotransferase levels. CI, confidence interval; IV, inverse-variance.

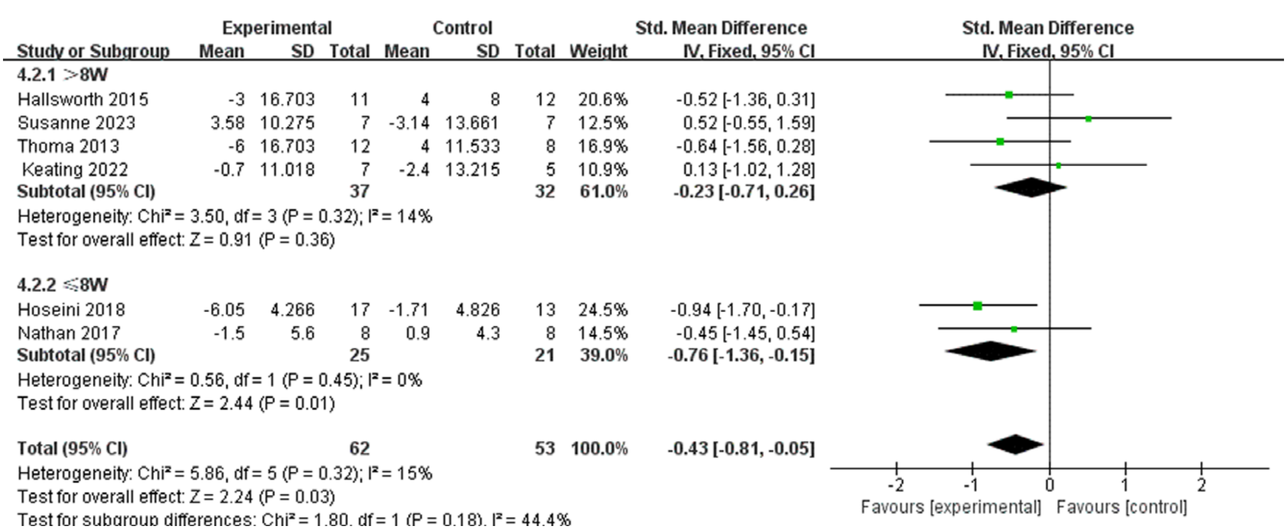

Fig. 4. Results of subgroup analysis on aspartate aminotransferase levels. CI, confidence interval; IV, inverse-variance.

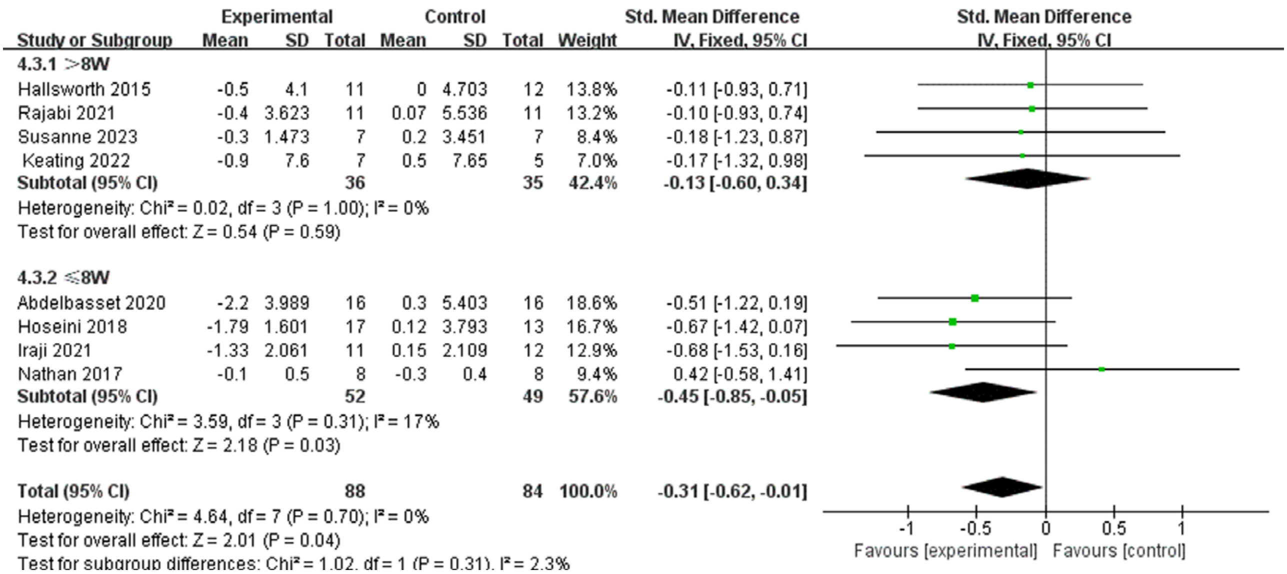

Fig. 5. Results of subgroup analysis on BMI. CI, confidence interval; IV, inverse-variance.

Sensitivity analysis

As minimal heterogeneity was observed in the results of IHL, AST, BMI, across HIIT intervention studies, we performed sensitivity analyses using a fixed-effects model. The results showed that none of the individual studies had a significant impact on the robustness of the pooled results (Supplementary Figures C1–C3, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*). Because significant heterogeneity was observed in the ALT and LDL-C results across the studies, we conducted a sensitivity analysis using the random-effects model, which indicated that none of the individual studies had a notable effect on the overall robustness of the pooled results (Supplementary Figures C4 and C5, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B149*).

Discussion

In this systematic review and meta-analysis, we systematically reviewed all available RCTs assessing the efficacy of HIIT for patients with MASLD, totally 10 RCTs with aggregate data on 224 individuals. Our findings showed that patients with MASLD who underwent HIIT intervention had lower degrees of IHL, ALT concentrations, AST concentrations, BMI, and LDL-C, compared to those without HIIT intervention. However, HIIT intervention did not affect body fat, fat mass, FINS, HOMA-IR, FG, HbA1c, TC, TG, or HDL-C in patients with MASLD.

In clinical practice, exercise is commonly used to guide patients with MASLD, obesity, and type 2 diabetes mellitus. Regular exercise training results in a significant decrease in hepatic fat content by reducing lipogenesis and increasing fatty acid oxidation in skeletal muscle [35]. HIIT is a type of combined aerobic training (AT) and anaerobic training that saves exercise time by alternating short bursts of high-intensity anaerobic exercise with low-intensity recovery exercise. However, the intensity increases. HIIT protocols often feature low volume (i.e. <15 min of high-intensity exercise per session) and require less time compared with more traditional forms of aerobic exercise training such as MICT, making them potentially more time-efficient for some individuals to incorporate into their daily routines [18]. Our study suggests that HIIT may ameliorate MASLD by reducing IHL and liver transaminases. This is clinically important because IHL plays an important pathogenic role in metabolic diseases [36,37]. In a study of 23 patients with type 2 diabetes, 12 weeks of HIIT resulted in a significant reduction in liver fat [38]. The mechanisms underlying the improvement of hepatic steatosis by HIIT remain to be elucidated. However, it has been suggested that HIIT considerably enhances the levels of muscle mitochondrial beta-hydroxy acyl-CoA dehydrogenase, which may increase fat loss [39]. A meta-analysis revealed that HIIT could result in significant improvements in liver fat in overweight and obese adults with metabolic disorders despite no weight loss [40]. Keating *et al*. reported a significant reduction in liver fat after exercise therapy, despite minimal or no weight loss [25]. Although the mechanism through which HIIT reduces liver fat independent of weight loss is unknown, reduced liver fat may reflect metabolic adaptions and improved hepatic lipid oxidation, decreased circulating free fatty acids, and increased free fatty acid uptake by the skeletal muscle [40]. Our results are mostly consistent with these findings: HIIT is an effective training method for decreasing liver fat content.

We found that HIIT could reduce BMI, but subgroup analyses showed that less than equal to 8 weeks of intervention was statistically significant, whereas up to 12 weeks of intervention did not demonstrate a difference between the experimental and control groups. This may be related to changes in body fat and skeletal muscle. While BMI only reflects weight gain and loss, it is the distribution of body fat and skeletal muscle that patients with fatty liver disease need to be more concerned about. A study showed that 12 weeks of HIIT significantly increased the muscle strength [41]. The accuracy of the results is likely to be reduced by the small number of articles evaluating fat mass and body fat in the studies we included. Therefore, other factors such as waist circumference and body composition should also be considered as BMI alone does not provide a complete picture of health. In addition, different tools for measuring adiposity can lead to differences in results.

We found that HIIT is effective in reducing the serum levels of liver enzymes, specifically ALT and AST, which is consistent with previous findings that exercise helps reduce transaminase levels by increasing metabolic rate, reducing liver lipids, and activating liver autophagy [42]. Liver enzymes are important indicators for diagnosing MASH and liver fibrosis, which are key indicators of MASLD progression and prognosis [43]. Because of the high heterogeneity in ALT outcomes, we performed subgroup analyses and found that studies with an intervention duration of 12 weeks did not show significant ALT improvements compared with controls. This was the same for AST. We reviewed the original literature and found that studies with 12 weeks of intervention did not show significant improvement in liver enzymes [25,30,44], which may be a result of exercise stress [30]. Some studies have shown that this may be related to skeletal muscle damage caused by strenuous exercise, which leads to an increased release of transaminases [45]. Keating *et al*. [25] included people with biopsy-confirmed MASH, and liver enzyme levels did not change after 12 weeks of exercise therapy, demonstrating that exercise therapy alone does not significantly improve hepatic histological inflammatory injury and fibrosis in patients with metabolism-related fatty liver disease, which is in agreement with the reviews of Houghton *et al*. [46]. Liver enzyme levels were within the normal range at baseline in many reports, which may be another reason why the changes in liver enzyme levels before and after the intervention were not significant [33,44]. The lack of a significant pooled effect on ALT and AST levels at 12 weeks in the present analysis does not negate the use of exercise per se, given the multiplicity of exercise benefits.

Dyslipidemia is an important complication of MASLD and changes in liver lipid and lipoprotein metabolism are important factors that increase the risk of cardiovascular disease in patients with MASLD [47]. However, in our study, we found that HIIT only reduced LDL-C, no statistical significance was found for TG, TC, and HDL-C levels. Our results broadly agree with a meta-analysis [48]. Of the six experiments that reported lipid results, the majority were of middle and older age, and it has been shown that age can play a role in the relationship between exercise and dyslipidemia [49]. As individuals age, their lipid and lipoprotein levels tend to increase, and the response to exercise may be less pronounced [50]. Our study found that HIIT intervention did not lead to significant changes in FINS, HOMA-IR, FG, and HbA1c in patients with MASLD, we are of the view that HIIT has a potential effect on central insulin sensitivity considering the decrease in liver fat content. We did not conduct subgroup analyses for this subset of indicators because only a few studies were included.

Although HIIT has potential benefits, its therapeutic effect on MASLD remains controversial. A newly published systematic review and network meta-analysis showed that AT and RT are the best exercise methods to improve patients with MASLD compared with HIIT [51]. This may be related to the exercise cycle; most of the studies included in this network meta-analysis were 12 weeks or longer, and one study found that MIIT induced fewer immune system perturbations and less muscle pain and was perceived as more tolerable than HIIT sessions in adults with obesity [52]. Our research also showed that HIIT was effective in reducing BMI and liver enzyme levels at less than equal to 8 weeks of intervention but did not significantly improve at more than 8 weeks of prolonged intervention. Although there is much evidence to explain this phenomenon, adherence may also play an important role. Santos *et al*. indicated that the average adherence rates to unsupervised real-world HIIT interventions were moderate [53]. The participants' compliance with the exercise plans may vary, and some may not strictly adhere to the study requirements. This could lead to actual exercise intensity and frequency that differ from the study's design, influencing the results; only a few studies performed supervised exercise sessions [25–27,30,44], which may have affected the effectiveness of the exercise intervention. It would be interesting for future syntheses to compare compliance and adherence rates to different HIIT exercise protocols to determine whether optimal protocols that elicit the highest completion rates exist. With the growing body of evidence on the clinical efficacy of HIIT for the treatment of MASLD, external regulators of behavior, including supervision and social support, are critical enablers for sustaining exercise routines in MASLD [54]. Future research could explore HIIT interventions through concurrent mHealth, eHealth, and activity tracker interventions; the implementation of behavior change techniques; and/or the development of unsupervised interventions based on theoretical frameworks.

Our study has some limitations. Our findings should be interpreted with caution because of the low overall quality of the included studies, and there may be subjective subject or researcher influences on research outcomes. Furthermore, the number of RCTs included in the analysis of the effect of HIIT in MASLD was limited, which resulted in our inability to assess publication bias, and the absence of additional outcome metrics may have affected the accuracy of the results. We also did not conduct subgroup analyses based on other conditions, such as the frequency of interventions and mode of intervention in the control group, because of insufficient and missing data.

Conclusions

Our study suggests that HIIT could potentially improve liver steatosis and liver enzyme levels in patients with MASLD. These results provide evidence that HIIT is a promising and time-efficient approach for MASLD treatment. However, it is important to note that monitoring and management of MASLD should still receive significant attention. Treatment of MASLD is a long-term process, and additional high-quality multicenter studies are necessary to extend follow-up to observe the long-term effects of HIIT on patients with MASLD.

Acknowledgements

This research was supported by the Zhejiang Provincial Natural Science Foundation of China under Grant No. LQ23H270016, National Natural Science Funds of China

No. 82204827 and Noncommunicable Chronic Diseases-National Science and Technology Major Project No. 2023ZD0508704.

All authors contributed substantially to the work presented in this article and have reviewed and consented to the final version of the manuscript.

J.F., C.L., L.Y., and B.Z. were involved in the study concept and design and drafting of the manuscript. C.D. and R.Z. performed data retrieval. J.F. and L.Y. acquired the data. J.F., H.Z., and J.K. performed analysis and interpretation of data. J.S. and J.L. were involved in study supervision.

Conflicts of interest

There are no conflicts of interest.

References

1 Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, *et al*. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology (Baltimore, Md)* 2019; 69:2672–2682.

2 Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, *et al*. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2019; 4:389–398.

3 European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024; 81:492–542.

4 Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, *et al*; NAFLD Nomenclature Consensus Group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 2023; 79:1542–1556.

5 Mondal T, Smith CI, Loffredo CA, Quartey R, Moses G, Howell CD, *et al*. Transcriptomics of MASLD pathobiology in African American patients in the Washington DC area. *Int J Mol Sci* 2023; 24:16654.

6 Guo X, Yin X, Liu Z, Wang J. Non-alcoholic fatty liver disease (NAFLD) pathogenesis and natural products for prevention and treatment. *Int J Mol Sci* 2022; 23:15489.

7 Chan W-K, Chuah K-H, Rajaram RB, Lim L-L, Ratnasingam J, Vethakkan SR. Metabolic dysfunction-associated steatotic liver disease (MASLD): a state-of-the-art review. *J Obes Metab Syndr* 2023; 32:197–213.

8 Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; 148:547–555.

9 Estes C, Chan HLY, Chien RN, Chuang W-L, Fung J, Goh GB-B, *et al*. Modelling NAFLD disease burden in four Asian regions 2019-2030. *Aliment Pharmacol Ther* 2020; 51:801–811.

10 Noureddin M, Charlton MR, Harrison SA, Bansal MB, Alkhouri N, Loomba R, *et al*. Expert panel recommendations: practical clinical applications for initiating and monitoring resmetirom in patients with MASH/NASH and moderate to noncirrhotic advanced fibrosis. *Clin Gastroenterol Hepatol* 2024; 22:2367–2377.

11 Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, *et al*. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology (Baltimore, Md)* 2023; 77:1797–1835.

12 Younossi ZM, Zelber-Sagi S, Henry L, Gerber LH. Lifestyle interventions in nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol* 2023; 20:708–722.

13 García-Hermoso A, Cerrillo-Urbina AJ, Herrera-Valenzuela T, Cristi-Montero C, Saavedra JM, Martínez-Vizcaíno V. Is high-intensity interval training more effective on improving cardiometabolic risk and aerobic capacity than other forms of exercise in overweight and obese youth? A meta-analysis. *Obes Rev* 2016; 17:531–540.

14 Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; 57:157–166.

15 Xiong Y, Peng Q, Cao C, Xu Z, Zhang B. Effect of different exercise methods on non-alcoholic fatty liver disease: a meta-analysis and meta-regression. *Int J Environ Res Public Health* 2021; 18:3242.

16 Gibala MJ, Little JP, Macdonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol* 2012; 590:1077–1084.

17 Ruegsegger GN, Pataky MW, Simha S, Robinson MM, Klaus KA, Nair KS. High-intensity aerobic, but not resistance or combined, exercise training improves both cardiometabolic health and skeletal muscle mitochondrial dynamics. *J Appl Physiol (1985)* 2023; 135:763–774.

18 Poon ET, Wongpipit W, Li HY, Wong SH, Siu PM, Kong AP, Johnson NA. High-intensity interval training for cardiometabolic health in adults with metabolic syndrome: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* 2024; 58:1267–1284.

19 Petersen MH, de Almeida ME, Wentorf EK, Jensen K, Ørtenblad N, Højlund K. High-intensity interval training combining rowing and cycling efficiently improves insulin sensitivity, body composition and VO_2max in men with obesity and type 2 diabetes. *Front Endocrinol (Lausanne)* 2022; 13:1032235.

20 Zhou BJ, Huang G, Wang W, Zhu LH, Deng YX, He YY, Ma F-H. Intervention effects of four exercise modalities on nonalcoholic fatty liver disease: a systematic review and Bayesian network meta-analysis. *Eur Rev Med Pharmacol Sci* 2021; 25:7687–7697.

21 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*; PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4:1.

22 Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019; 10:ED000142.

23 Jun-xia Z. Study on Stata software in investigating publication bias in meta-analysis. *Mod Prevent Med* 2008; 35:2819–2822.

24 Abdelbasset WK, Tantawy SA, Kamel DM, Alqahtani BA, Elnegamy TE, Soliman GS, Ibrahim AA. Effects of high-intensity interval and moderate-intensity continuous aerobic exercise on diabetic obese patients with nonalcoholic fatty liver disease: a comparative randomized controlled trial. *Medicine (Baltim)* 2020; 99:e19471.

25 Keating SE, Croci I, Wallen MP, Cox ER, Thuzar M, Pham U, *et al*. High-intensity interval training is safe, feasible and efficacious in nonalcoholic steatohepatitis: a randomized controlled trial. *Dig Dis Sci* 2023; 68:2123–2139.

26 Iraji H, Minasian V, Kelishadi R. Changes in liver enzymes and metabolic profile in adolescents with fatty liver following exercise interventions. *Pediatr Gastroenterol Hepatol Nutr* 2021; 24:54–64.

27 Hallsworth K, Thoma C, Hollingsworth KG, Cassidy S, Anstee QM, Day CP, Trenell MI. Modified high-intensity interval training reduces liver fat and improves cardiac function in non-alcoholic fatty liver disease: a randomized controlled trial. *Clin Sci (Lond)* 2015; 129:1097–1105.

28 Oh S, So R, Shida T, Matsuo T, Kim B, Akiyama K, *et al*. High-intensity aerobic exercise improves both hepatic fat content and stiffness in sedentary obese men with nonalcoholic fatty liver disease. *Sci Rep* 2017; 7:43029.

29 Thoma C, Hallsworth K, Hollingsworth K, Anstee Q, Taylor R, Day C, Trenell M. 1369 High-intensity intermittent exercise therapy reduces liver fat and improves body composition in adults with non-alcoholic fatty liver disease. *J Hepatol* 2013; 58:S550–S551.

30 Csader S, Ismaiah MJ, Kuningas T, Heinäniemi M, Suhonen J, Männistö V, *et al*. Twelve weeks of high-intensity interval training alters adipose tissue gene expression but not oxylipin levels in people with non-alcoholic fatty liver disease. *Int J Mol Sci* 2023; 24:8509.

31 Fakhredin Hoseini S, Rahmati M, Gollop ND, Mirnasuri R. The effects of high intensity interval training on the levels of liver enzymes associated with non-alcoholic fatty liver and selected anthropometric indices in obese men. *Sci Sports* 2019; 34:59–60.

32 Rajabi S, Askari R, Haghighi AH, Razavianzadeh N. The effects of two different intensities of combined training on C1q/TNF-related protein 3 (CTRP3) and insulin resistance in women with non-alcoholic fatty liver disease. *Hepatitis Monthly* 2021; 21:e108106.

33 Winn NC, Liu Y, Rector RS, Parks EJ, Ibdah JA, Kanaley JA. 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* 2018; 78:128–140.

34 Liu W-X, Liu L. Predictive value of serum alanine aminotransferase for fatty liver associated with metabolic dysfunction. *World J Hepatol* 2024; 16:990–994.
35 Heinle JW, DiJoseph K, Sabag A, Oh S, Kimball SR, Keating S, Stine JG. Exercise is medicine for nonalcoholic fatty liver disease: exploration of putative mechanisms. *Nutrients* 2023; 15:2452.
36 Björntorp P. Metabolic implications of body fat distribution. *Diabetes Care* 1991; 14:1132–1143.
37 Taylor R. Type 2 diabetes: etiology and reversibility. *Diabetes Care* 2013; 36:1047–1055.
38 Cassidy S, Thoma C, Hallsworth K, Parikh J, Hollingsworth KG, Taylor R, *et al*. High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia* 2016; 59:56–66.
39 Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, *et al*. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001; 120:1183–1192.
40 Khalafi M, Symonds ME. The impact of high intensity interval training on liver fat content in overweight or obese adults: a meta-analysis. *Physiol Behav* 2021; 236:113416.
41 Caparrós-Manosalva C, Garrido-Muñoz N, Alvear-Constanzo B, Sanzana-Laurié S, Artigas-Arias M, Alegría-Molina A, *et al*. Effects of high-intensity interval training on lean mass, strength, and power of the lower limbs in healthy old and young people. *Front Physiol* 2023; 14:1223069.
42 Guo D, Sun J, Feng S. Comparative analysis of the effects of high-intensity interval training and traditional aerobic training on improving physical fitness and biochemical indicators in patients with non-alcoholic fatty liver disease. *J Sports Med Phys Fitness* 2024; 65:132–139.
43 Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan W-K, *et al*. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol* 2020; 5:362–373.
44 de Lira CT, Dos Santos MA, Gomes PP, Fidelix YL, Dos Santos AC, Tenório TR, *et al*. Aerobic training performed at ventilatory threshold improves liver enzymes and lipid profile related to non-alcoholic fatty liver disease in adolescents with obesity. *Nutr Health* 2017; 23:281–288.
45 Pettersson J, Hindorf U, Persson P, Bengtsson T, Malmqvist U, Werkström V, Ekelund M. Muscular exercise can cause highly pathological liver function tests in healthy men. *Br J Clin Pharmacol* 2008; 65:253–259.
46 Houghton D, Thoma C, Hallsworth K, Cassidy S, Hardy T, Burt AD, *et al*. Exercise reduces liver lipids and visceral adiposity in patients with nonalcoholic steatohepatitis in a randomized controlled trial. *Clin Gastroenterol Hepatol* 2017; 15:96–102.e3.
47 Golabi P, Fukui N, Paik J, Sayiner M, Mishra A, Younossi ZM. Mortality risk detected by atherosclerotic cardiovascular disease score in patients with nonalcoholic fatty liver disease. *Hepatol Commun* 2019; 3:1050–1060.
48 Su L, Fu J, Sun S, Zhao G, Cheng W, Dou C, Quan MH. Effects of HIIT and MICT on cardiovascular risk factors in adults with overweight and/or obesity: a meta-analysis. *PLoS One* 2019; 14:e0210644.
49 Mosteoru S, Gaiţă L, Gaiţă D. Sport as medicine for dyslipidemia (and other risk factors). *Curr Atheroscler Rep* 2023; 25:613–617.
50 Pataky MW, Young WF, Nair KS. Hormonal and metabolic changes of aging and the influence of lifestyle modifications. *Mayo Clin Proc* 2021; 96:788–814.
51 Xue Y, Peng Y, Zhang L, Ba Y, Jin G, Liu G. Effect of different exercise modalities on nonalcoholic fatty liver disease: a systematic review and network meta-analysis. *Sci Rep* 2024; 14:6212.
52 Maaloul R, Ben Dhia I, Marzougui H, Turki M, Kacem FH, Makhlouf R, *et al*. Is moderate-intensity interval training more tolerable than high-intensity interval training in adults with obesity? *Biol Sport* 2023; 40:1159–1167.
53 Santos A, Braaten K, MacPherson M, Vasconcellos D, Vis-Dunbar M, Lonsdale C, *et al*. Rates of compliance and adherence to high-intensity interval training: a systematic review and meta-analyses. *Int J Behav Nutr Phys Act* 2023; 20:134.
54 Keating SE, Croci I, Wallen MP, Cox ER, Coombes JS, Burton NW, *et al*. High-intensity interval training for the management of nonalcoholic steatohepatitis: participant experiences and perspectives. *J Clin Transl Hepatol* 2023; 11:1050–1060.