

# Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: A systematic review

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Non-alcoholic fatty liver disease is a serious and growing clinical problem. Despite lifestyle modification, i.e. diet and physical activity, being the recommended therapy, there are currently no systematic evaluations of its efficacy. This review applies a systematic approach to evaluating lifestyle modifications studied to date.

Medline (Pubmed), Scopus, and the Cochrane Controlled Trials Register were searched for studies and study groups assessing the effect of diet, physical activity, and/or exercise modification in adult populations with non-alcoholic fatty liver disease. The outcome markers of interest were indicators of steatosis, histological evidence of inflammation and fibrosis, and glucose control/insulin sensitivity.

We identified 23 studies for inclusion; seven had control groups, but only six were randomised. Eleven groups received diet-only interventions, two exercise-only, and 19 diet and physical activity/exercise. Studies consistently showed reductions in liver fat and/or liver aminotransferase concentration, with the strongest correlation being with weight reduction. Of the 5 studies reporting changes in histopathology, all showed a trend towards reduction in inflammation, in 2 this was statistically significant. Changes in fibrosis were less consistent with only one study showing a significant reduction. The majority of studies also reported improvements in glucose control/insulin sensitivity following intervention. However, study design, definition of disease, assessment methods, and interventions varied considerably across studies.

Lifestyle modifications leading to weight reduction and/or increased physical activity consistently reduced liver fat and improved glucose control/insulin sensitivity. Limited data also

suggest that lifestyle interventions may hold benefits for histopathology.

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses liver conditions ranging from hepatic steatosis through steatohepatitis to cirrhosis [1]. Its prevalence has been estimated at between 20% and 33% of the adult population depending on criteria and country [2]. Prevalence increases with degree of obesity [3] and the condition is very common in those with type 2 diabetes [4,5]. Rising prevalence of obesity and Type 2 diabetes, particularly in younger people, will ensure that NAFLD remains a growing clinical concern for the future [3].

Elevated intrahepatic triacylglycerol concentration (IHTAG) is the first step in the development of steatohepatitis, liver fibrosis, liver cirrhosis, and hepatocellular carcinoma [1]. Excess liver fat is also linked to insulin resistance [6], and is an independent risk factor for Type 2 diabetes [7] and cardiovascular disease [8]. Liver lipid is part of the early adaptive response to stress, and as such, is a biomarker of NEFA flux, oxidative-, ER- and cytokine-mediated stress that result in steatosis and progressive liver damage. Lifestyle modification, encompassing diet, physical activity, and/or exercise related behaviours, is the primary recommended therapy for NAFLD [9], especially in the absence of approved pharmaceutical agents.

Although reviews with NAFLD disease as their focus abound, few have reported using a systematic approach to study selection or reporting, and none, to date, have applied this approach to examining the efficacy or effectiveness of lifestyle management. This systematic approach is necessary to provide clinical care teams with the information to determine whether lifestyle therapy should be used, and if so, what aspects are key to achieving success. Our objective was to perform a systematic assessment of lifestyle interventions in adults with NAFLD to: (i) Define the efficacy of different lifestyle interventions in reducing IHTAG and/or liver aminotransferases; (ii) assess the effect of lifestyle interventions on histological parameters; and (iii) establish the efficacy of different lifestyle interventions on glucose control/insulin sensitivity (Fig. 1).

Keywords: Non-alcoholic fatty liver; Liver fat; Systematic review; Lifestyle modification; Exercise; Physical activity; Diet; Weight reduction.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; IHTAG, intrahepatic triacylglycerol concentration; <sup>1</sup>H-MRS, proton magnetic resonance spectroscopy; CT, computed tomography; ALT, alanine aminotransferase; AST, aspartate aminotransferase.



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## Review

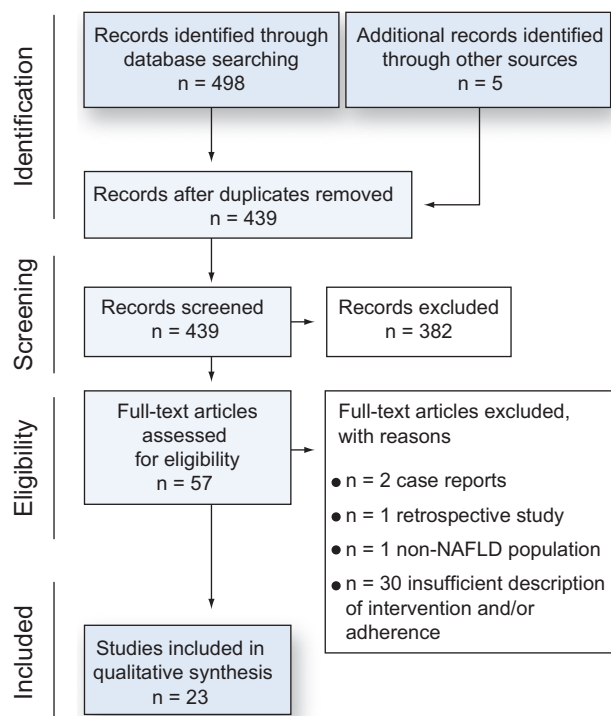


Fig. 1. Flow diagram of study selection.

## Methods

### Eligibility criteria

The review is restricted to published prospective interventions reporting the effects of lifestyle modification on IHTAG, liver enzymes, and/or insulin sensitivity in adults ( $\geq 19$  years) with NAFLD, including non-alcoholic steatohepatitis but not late stage liver diseases i.e. cirrhosis or hepatocellular carcinoma. Eligible publications included: randomised controlled trials or specific arms thereof, and non-randomised interventions. Only full reports were considered to provide sufficient information to allow critical evaluation.

No specific criteria defining NAFLD were set as the methods of diagnosis and cut-offs vary between studies. It was considered sufficient for reports to provide their own diagnostic criteria based on one or more of the following in order of preference: (1) histological examination of biopsies; (2) proton magnetic resonance spectroscopy ( $^1\text{H-MRS}$ ); (3) computed tomography (CT); (4) ultrasound; and/or (5) blood concentrations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST).

Lifestyle modification could include general recommendations or specific diet, physical activity, and/or exercise prescription. Studies or study arms designed to test pharmaceuticals, dietary supplements, or herbal preparations were excluded. Study arms in which pharmaceutical agents were used as part of standard treatment and where participants were receiving these prior to the study, without a reported increase in dose during the study, were eligible for inclusion.

The primary outcomes of interest were changes in IHTAG assessed by liver biopsy,  $^1\text{H-MRS}$ , CT, or ultrasound, and histological indicators of inflammation and fibrosis. Blood ALT and/or AST

concentrations were also considered. The secondary outcome was glucose tolerance and/or insulin sensitivity as assessed directly by insulin clamp techniques or oral glucose tolerance tests, or inferred by validated formulae.

Only studies that clearly described or appropriately referenced their intervention, and that provided some direct indicators of protocol adherence, or those conducted under very close supervision, e.g. inpatient protocol delivery, were eligible for inclusion.

### Search strategy and study selection

The following databases were searched: Medline (Pubmed), Scopus, and the Cochrane Controlled Trials Register. The search of Scopus, the most comprehensive of the three databases, was done in duplicate by two authors (CT and MT), whereas the other databases were searched by one author (CT). The last search of all three databases was done on June 26, 2010. However, automatic updates of the Scopus search were reviewed up to October 18, 2010. A medical librarian assisted with the selection of the search strategies.

The selected search terms and related MESH headings were: (NAFLD or "non-alcoholic fatty liver" or "nonalcoholic fatty liver" or "non-alcoholic steatohepatitis" or "nonalcoholic steatohepatitis" or "non-alcoholic steatosis" or "nonalcoholic steatosis" or "non-alcoholic liver steatosis" or "nonalcoholic liver steatosis" or "non-alcoholic hepatic steatosis" or "nonalcoholic hepatic steatosis") AND (lifestyle or exercise or "diet\*" or diet or training or behaviour or behavior or nutrition or sport or "physical activity" or "weight reduction" or "weight loss" or "energy restriction"). These were restricted to title, abstract, and keyword (Scopus only). The database permitting, the following were excluded: reviews; letters; editorials; commentaries; animal studies; and studies in those aged under 19 years. Review of articles was restricted to those published in English.

Titles and abstracts of studies identified were evaluated against eligibility criteria. Studies appearing eligible based on their abstract were read in full. The decision to exclude any of these studies was made by the consensus of two authors (CT & MT).

### Data items

The items of interest from each report included: study type/design; diagnostic criteria for NAFLD; inclusion and exclusion criteria; blinding; similarity of groups at baseline; sex; age; definition of participant adherence; treatment protocol, including professions involved and contact time; reported adherence; criteria for dealing with medication; methods used to assess diet and physical activity; loss to follow-up; intention-to-treat or per-protocol analysis; IHTAG; measures of glucose control; ALT and/or AST concentration.

### Data extraction

Relevant data from included reports were recorded in itemised tables. Results were converted to SI units or otherwise standardised and changes from baseline converted to percentages to facilitate comparison across studies. Where liver fat is given as a percentage, a change from 10% fat to 5% fat is referred to as an *absolute* reduction of 5% (10–5%) and a *relative* reduction of 50%.

Multiple publications from the same study were identified by comparing author names, sample sizes, and intervention protocols. Where papers noted that other reports of the study existed, these were also obtained to allow consistency between different reports to be assessed and/or missing data to be obtained.

#### *Risk of intra- and inter-study reporting and publication bias*

Included studies were compared to their published protocols when available to identify omissions of outcome data. Alternatively, the methods section of each report was compared to the results section to assess reporting bias. The International Clinical Trials Registry, EU Clinical Trial Register, and metaRegister of Controlled Trials were searched using the key words *fatty liver* and *steatohepatitis* to identify trials described as completed. Studies registered prior to 2009 with records not updated in the past 12 months were assumed to be completed. A literature search using the relevant principle investigator was conducted to identify publications resulting from relevant registered trials.

#### *Description and critique of primary outcome indicators*

##### *Liver biopsy*

Histological examination of biopsy samples can assess the presence of necro-inflammation and fibrosis, and can differentiate between macro- and micro-vesicular steatosis; it remains the reference standard for the grading and staging of NAFLD [9]. However, it is subject to sampling error due to histological heterogeneity [10,11], scoring is semi-quantitative limiting its ability to detect modest changes, and scoring systems vary between reports precluding direct comparisons.

##### *Proton magnetic resonance spectroscopy*

<sup>1</sup>H-MRS quantitatively measures IHTAG by differentiating between signals from lipids and water [12]. This technique has superior accuracy and sensitivity to CT and ultrasound [13]. Using <sup>1</sup>H-MRS, IHTAG above 5–5.6% is considered elevated [14,15].

##### *Computed tomography*

CT provides a semi-quantitative method for the evaluation of IHTAG based on the change in image intensity, measured in Hounsfield units, between the liver and either the spleen, which stores no fat, or an external lipid standard [12]. An increase in liver:spleen ratio or liver density is indicative of reduced IHTAG.

##### *Ultrasound*

Ultrasound provides semi-quantitative estimates of hepatic steatosis based on diffuse increases in echogenicity [12]. Reported sensitivity and specificity vary between 60–94% and 66–95%, respectively [12]. A study of inter- and intra-observer variability reported a mean agreement for the presence of steatosis of 72% and 76%, respectively, and intra-observer agreement of severity of 55–68% [16].

##### *Blood biomarkers*

Some studies have based their diagnosis of NAFLD on the liver enzymes ALT and/or AST. However, these are non-specific for steatosis or disease stage. In a cohort of 708 individuals with elevated intrahepatic lipid (>5.6% assessed by <sup>1</sup>H-MRS) it was found that 79% had normal ALT [17]. Further, normal ALT and

AST concentrations have been reported in the presence of histological evidence of steatosis, fibrosis, and cirrhosis [18,19].

##### *Assessment of glucose control*

The euglycemic hyperinsulinaemic clamp is the reference standard for the assessment of insulin sensitivity, with the more commonly performed frequently sampled 2-h oral glucose test showing good correlation with the clamp [20]. Measures of glucose control derived from fasting glucose and insulin ratio, such as the homeostasis model assessment (HOMA) are less sensitive options to assess glucose control [20].

##### *Other sources of bias or confounding*

The following sources of bias are most relevant to this review: inclusion of non-randomised and non-controlled trials; the inability to conceal allocation in lifestyle therapy; methodological heterogeneity for diagnosis; misclassification; and selection bias. Restriction to randomised controlled trials and/or studies using only narrow diagnostic criteria and direct assessment of liver fat would have limited the scope of this review, and thereby its ability to address its aims.

Misclassification of disease is plausible as elevated IHTAG has several potential causes [21], the relative contributions of which are not routinely assessed. A contribution from alcohol is particularly difficult to rule out entirely due to variations in definitions for levels of intake [22], and limitations in existing biomarkers and questionnaires, which often focus on diagnosing dependence rather than accurately quantifying intake [23]. These do not invalidate a link between intervention and outcome, but do increase the chance of attributing the observed change to the wrong factors.

## Results

### *General limitations of studies reviewed*

Specific details about individual studies reviewed can be found in Tables 1–4. There was considerable heterogeneity of assessment methods used, diagnostic criteria for NAFLD applied, and the detail with which exclusion criteria were reported. With one exception, studies employing <sup>1</sup>H-MRS either did not report a minimum IHTAG or report including participants <5%. Those employing histological examination of biopsies applied cutoffs, but used different scoring systems. Eligibility based on history of alcohol consumption varied between no alcohol intake and 560 g/week, and assessment methods were seldom cited. Although most studies noted excluding participants with other liver conditions, including potential drug induced steatosis, few provided comprehensive criteria, e.g. of drugs deemed steatogenic, or details of the relevant analytical methods employed. Collectively, these factors suggest considerable heterogeneity in study populations and limit direct inter-study comparisons and extrapolation to patient populations.

Monitoring of adherence to diet or exercise was often limited. No studies reported using objective measures of physical activity such as accelerometers, instead questionnaires were used. Dietary assessment methods were not reported in sufficient detail to assess likely accuracy. The greater the complexity of interventions, the less precisely the actions of participants tended to be described. Interventions involving diet, exercise, and

Table 1. Diet only interventions.

[Ref]	Design	Sample size (M/F)	Clinical Group	Age (yrs)	BMI (kg/m <sup>2</sup> )	Intervention	Duration (wks)	Analysis Type	Outcome Measures and Adherence	Results
[26]	RT	11 (n/r)	NAFLD	45±4	37±1	High CHO: (65% CHO, 20% fat, 15% PRO): 1000 kcal/d below estimated (RMR x 1.3) until 7% BW reduction achieved at wk 6.2 ± 1, then E adjusted to maintain BW until wk 11.	11	PP	IHTAG ('H-MRS), E-HC: HISI, GR <sub>a</sub> , HOMA.  Food provided by metabolic kitchen. Plasma 3-hydroxybutyrate indicated good adherence.	Relative to baseline: <b>High CHO</b> at 48 h (BW -1.6%): IHTAG ↓~10%, HOMA ↓24±6%, HISI ↑~35%, GR <sub>a</sub> ↓~7%, <b>Low CHO</b> at 48 h (BW -2.2%): IHTAG ↓~30%, HOMA ↓40%, HISI ↑~140%, GR <sub>a</sub> ↓23%. IHL, HISI, HOMA, GR <sub>a</sub> were all significantly different between groups. No loss to follow-up.
	RT	11 (n/r)	NAFLD	42±3	36±1	Low CHO: (10% CHO, 75% fat, 15% PRO): 1000 kcal/d below estimated (RMR x 1.3) until 7% BW reduction achieved at wk 5.9 ± 1, then E adjusted to maintain BW until wk 11.	11	PP		<b>High CHO</b> at 11 wk (BW -7.3%): IHTAG ↓~42%, HOMA ↓27.1±5.1%, HISI ↑~28, GR <sub>a</sub> ↓~7%, <b>Low CHO</b> at 11 wk (BW -7.6%): IHTAG ↓~38%, HOMA ↓44%, HISI ↑~115, GR <sub>a</sub> ↓~20%. IMGU was reported for both groups combined: no change after 48 hrs, ↑~30% after 11 weeks. No loss to follow-up.
[32]	Pilot	5 (2/3)	NAFLD	35.6	n/r 102± 12 kg	Ketogenic diet (24 wk): <20 g CHO/d, unlimited meat/fish/poultry, unlimited eggs, 2 cups/d 'salad' vegetables, 133 g cheese, 1 cup/d low-CHO vegetables.	24	PP	Histopathology, ALT, AST Diet records & urinary ketones indicated good compliance in 4 participants. No change in non-compliant participant. Actual intake n/r.	BW ↓14% Adherent (n=4): steatosis, necroinflammation & centrilobular fibrosis ↓1-2 categories (e.g. moderate to mild or none), ALT ↓44%, AST n.s. Non-adherent (n=1): steatosis ↑ from mild to moderate, ALT ↓20%, AST ↓21%.
[30]	UCT	34 (10/24)	NAFLD (~50%)	n/r	31±1	6 wk of 550 kcal/d diet from ready made product (50% CHO, 7% fat, 43% PRO), then 1 wk eucaloric diet before final assessments.	7	n/r	IHTAG ('H-MRS), EGP (euglycaemic clamp with radiolabelled glucose), HbA <sub>1c</sub> .	BW ↓11% IHTAG ↓60%, IS ↑32%, EGP ↓34%, HbA <sub>1c</sub> ↓3.6%.
[28]	UCT	8 (5/3)	Type 2 Diabetes	47±3	30±1	Liquid formula low fat diet (50% CHO, 3% fat, 43% PRO) + 12 g dietary fibre + raw fruit & vegetables to ~ 1200 kcal/d. Diet continued until normoglycaemia, then 4 wk maintenance: 35 kcal/kg/d (60% CHO, 20% fat, 20% PRO).	7-12	PP	IHTAG ('H-MRS), E-HC: HISI, GR <sub>a</sub> , IMGU, MSGP, HOMA. Weekly checkup visits including weigh-ins & provision of food during study.	BW ↓8% IHTAG ↓81±4% (to 2.2±0.8%), GR <sub>a</sub> ↓~18%, IMGU n.s., MSGP ↑221% (to 93±5%).
[33]	UCT	14 (5/9)	Prior to bariatric surgery	24-45	46 (40-57)	CHO restriction to 30 g/d but no other restriction under weekly supervision of a dietician + resources on the CHO content of vegetables & dairy foods.	4	PP	CT: liver:spleen ratio & liver volume; ALT, AST & fasting glucose. Daily food diary indicated: 1520±285 kcal/d (1109-1922 kcal/d) (14% CHO, 56% fat, 29% PRO).	BW ↓3.7%. Liver:spleen ↑16% (p=0.06); liver volume ↓8.2% (223 ml); ALT, AST, & glucose n.s.
[25]	UCT	17 (6/9)		47±3	33±1	All participants prescribed a dietary deficit of 500-1000 kcal/d (55% CHO, 30% fat, 15% PRO) over 6 months, then divided into <b>adherent</b> (weight ↑≥5%).	26	PP	Liver density (CT); ALT, AST, HOMA. Adherent: food dairy reported ↓641 cal/day (47% CHO, 33% fat, 20% PRO)	Change relative to baseline: <b>Adherent</b> BW ↑9.4% Adherent: ALT ↓28%, AST n.s., liver density ↑15%, HOMA ↓42%.
	UCT	14 (7/7)		47±3	35±2	<b>non-adherent</b> (weight ↓<5%)	26	PP	Non-adherent: food dairy reported ↓479 kcal/d (48% CHO, 31% fat, 21% PRO)	<b>Non-adherent:</b> BW ↓1.8% ALT, AST, liver density & HOMA n.s.

Table 1 (continued)

[Ref]	Design	Sample size (M/F)	Clinical Group	Age (yrs)	BMI (kg/m <sup>2</sup> )	Intervention	Duration (wks)	Analysis Type	Outcome Measures and Adherence	Results
[27]	RCT	12 (n/r)	9 NASH & 3 NAFLD*	58±3	26±1	<b>Diet:</b> 30 kcal/kg BW/d (20% fat, 1.1–1.2 g PRO/kg BW/d, iron <6 g/kg BW/d).	26	PP	ALT & AST <b>Diet</b> (3-d diet records): At 3 months: 30 kcal/kg BW/d (20% fat, 6.1 g iron/kg BW/d, 1.3 g PRO/kg BW/d), serum ferritin ↓42%. <b>Diet</b> at 6 months: 25 kcal/kg BW/d (20% fat, 5.3 g iron/kg BW/d, 1.2 g PRO/kg BW/d), serum ferritin ↓54%. <b>Control:</b> n/r.	Relative to baseline: <b>Diet</b> at 3 months: BW ↓3.2%, ALT ↓45% & AST ↓34%. <b>Diet</b> at 6 months: BW ↓4.8, ALT ↓60%, AST ↓52%. <b>Control</b> at 6 months: BW (n/r) ALT & AST n.s.
[27]	RCT	6 (n/r)	2 NASH & 4 NAFLD*	58±3	26±1	<b>Control:</b> no intervention.	26	PP	ALT & AST	BW ↓11% Men: ALT ↓21%, AST ↓13% Women: ALT ↑52%, AST ↑32%
[34]	UCT	147 (43/104)	Obese with elevated ALT	44 20–69	38±0	<b>Diet:</b> 800 kcal/d soy-based meal replacement (38% CHO, 17% fat, 45% PRO).	8	PP	ALT & AST	BW ↓4.6% ALT ↓28%, AST ↓48%, HOMA ↓39
[29]	UCT	30 (8/22)	Obese with elevated AST	44±3	37±1	<b>Diet:</b> 1520 kcal/d (52% CHO, 25% fat, 23% PRO).	12	n/r	ALT, AST, HOMA <b>Diet</b> (3-d Diet records): 1509±373 kcal/d (40% CHO, 39% fat, 21% PRO).	BW ↓3.6% ALT ↓52%, AST ↓42%
[31]	UCT	14 (7/7)	NAFLD by US	45±1	28±0	<b>Diet:</b> 25 kcal/kg of ideal BW (1.3 g PRO/kg; 20.8% energy, 0.7 g of fat/kg; 25% E, 3.4 g of CHO/kg; 54.2% E, PUFA:SAFA ratio 1.0–1.5; n-6:n-3 PUFA ratio 3.0–3.5) rich in fish & vegetables & low in meat.	24	PP	ALT & AST <b>Diet</b> (3-d Diet records): 28.6 kcal/kg ideal BW/d (56% CHO, 28% fat, 17% PRO), PUFA:SAFA 0.8:1, n-6:n-3 2.4:1.	BMI ↓3.6% ALT ↓52%, AST ↓42%

Data are mean ± standard errors usually rounded to the nearest full number; changes reported were statistically significant  $p < 0.05$  unless noted otherwise. Sample size reflects those in the final analysis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (kg/m<sup>2</sup>); BW, body weight; d, day(s); CHO, carbohydrate; CT, computed tomography; d, day(s); E, energy; EGP, endogenous glucose production; E-HC, euglycaemic hyperinsulinaemic clamp; GRA, glucose rate of appearance; h, hour(s); HbA1c, glycated haemoglobin; HISI, hepatic insulin sensitivity index; HOMA, homeostasis model assessment; IHTAG, intrahepatic triacylglycerol concentration; IMSGP, insulin-mediated suppression of glucose production; IMGU, insulin-mediated glucose uptake; IS, whole body insulin sensitivity; ITT, intention to treat analysis; LBM, lean body mass; n, sample size of cohort in final statistical analysis; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; n/r, data not reported; n.s., result not statistically significant; PP, per protocol analysis; PRO, protein; PUFA, polyunsaturated fatty acid; RCT, randomised controlled trial; RT, randomised trial with no control; RMR, resting metabolic rate; SAFA, saturated fatty acid; UCT, uncontrolled trial; US, ultrasound; w, week(s).

\* Diagnoses by histopathology at baseline only, no repeat biopsies on completion of the intervention.

## Review

**Table 2. Exercise only interventions.**

[Ref]	Design	Sample Size (M/F)	Clinical Group	Age (yrs)	BMI (kg/m <sup>2</sup> )	Intervention	Duration (weeks)	Analysis Type	Outcome Measures and Adherence	Results
[35]	RCT	12 (n/r)	NAFLD	47±4	31±1	<b>INT:</b> 3 supervised cycle ergometer sessions per wk x 4 wk. Weekly progression of VO <sub>2</sub> peak: 50%, 60%, 70% (wk 3 & 4) for 2-3 bouts of 15 min with 5 min rest between.	4	PP	IHTAG (1H-MRS), ALT, HOMA.  Participants attended all 12 sessions.	IHTAG ↓21% in intervention group (8.55% to 6.79%); no change in ALT. No change in HOMA-IR, fasting glucose, or insulin within or between groups.
[35]	RCT	7 (n/r)	NAFLD	49±2	32±2	<b>CON:</b> 3 home-based whole body stretching sessions/wk.	4			
[36]	UCT	16 (n/r)	Elevated ALT	~37# [35]	23±0	45 min/6 d/wk with 60-70% estimated HR <sub>max</sub> maintained for 20 min/session. Exercise options included walking, jogging, and rhythmic aerobic exercises.	12	PP	ALT & AST.	From baseline: ALT ↓47%, AST ↓48%.

Data are mean ± standard errors; changes were statistically significant  $p < 0.05$  unless noted otherwise.

<sup>1</sup>H-MRS, proton energy magnetic resonance spectroscopy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (kg/m<sup>2</sup>); BW, body weight; d, day(s); HOMA, homeostasis model assessment insulin resistance; IHTAG, intrahepatic triacylglycerol concentration; min, minute; n/r, not reported; n.s., not statistically significant change; PP, per protocol analysis; UCT, uncontrolled trial; VO<sub>2</sub> peak, peak oxygen consumption ml/min/kg; wk, week(s).

\* Age was only reported for the combined study groups – see Table 4 for other study group.

behaviour change methods were reported with a focus on outcomes with limited information on diet and physical activity adherence or how behaviour change methods were applied; thus limiting our ability to provide precise recommendations based on these interventions.

Studies did not report allocation concealment during data analysis except for blinding during the analysis of liver biopsy samples. Some studies doing per protocol analysis did not provide baseline data for the specific group in the final analysis. Most studies did not have a control group; those that did provided this group with some form of limited intervention. IHTAG measured by <sup>1</sup>H-MRS appears stable over a 4-week period, in the absence of any intervention [24]. Therefore, gross overestimation of efficacy is unlikely.

### Study findings

#### Diet only interventions

We identified 11 eligible study groups including 322 participants (approximately 65% women, 20 controls) prescribing dietary change: six using low-to-moderate fat/moderate-to-high carbohydrate energy restricted diets [25–30], one of which also specifically restricted iron intake [27]; three groups were given low carbohydrate ketogenic diets [26,31,32]; and two high protein diets [30,33]. Two studies employed biopsy [27,31], but only one at follow-up [31], the other used ALT and AST at follow-up [27]; three used <sup>1</sup>H-MRS [26,28,30], two used CT [25,32], three studies relied on ALT and AST [29,33]. Only two studies had a control group [25,27]; in one the control group were those with low adherence to the protocol [25]. Intervention and outcome details are summarised in Table 1.

Interventions lasted 1–6 months and achieved mean body weight reductions of 4–14%. All studies using biopsy or imaging techniques to estimate IHTAG reported reductions. The three studies using <sup>1</sup>H-MRS reported absolute reductions of 4–10%

and relative reductions of 42–81%. The only study to do a post-intervention biopsy (n = 5) reported reduced inflammation and trend towards reduced fibrosis ( $p = 0.07$ ), as well as the reduction in steatosis, following a ketogenic diet and a mean weight reduction of 14% [32]. Five out of seven studies reporting liver enzymes showed reductions and one showed no change. The study that found an increase in ALT and AST, but only in women, suggested this might have been due to the analysis being done before weight had stabilised [33]. Five out of six studies reporting glucose control/insulin sensitivity noted improvements.

#### Exercise only interventions

Two studies published contained exercise only groups [34,35] and are summarised in Table 2. A total of 35 participants (approximately 30% women, 7 controls) were included in the two intervention groups and one control group. The interventions involved moderate intensity aerobic activity. Four weeks of stationary cycling three times per week resulted in a reduction in <sup>1</sup>H-MRS measured IHTAG of 1.8%, relative reduction of 21%, but no statistically significant change in HOMA relative to either baseline or control [34]. Three months of aerobic exercise including brisk walking/jogging or rhythmic aerobic exercise resulted in a 47% and 48% reduction in ALT and AST, respectively [35]. Exercise only intervention groups in both studies maintained their baseline weight suggesting that weight reduction is not a prerequisite for liver fat or biomarker reduction.

#### Exercise combined with diet

Seven studies involving 436 participants (approximately 50% women, 98 controls) employed a selection of behaviour change methods to decrease energy intake and increase physical activity/exercise over 3–12 months [36–42]; these studies provided general physical activity guidelines, but did not prescribe specific exercise protocols. Key study details are summarised in Table 3. The focus was predominantly on body weight reduction and

**Table 3. Interventions combining diet and broad physical activity/exercise advice.**

Study	Design	n (M/F)	Clinical Group	Age (years)	BMI (kg/m <sup>2</sup> )	Intervention	Duration (weeks)	Analysis type	Outcome Measures and Adherence	Results
[37]	RCT	21 (14/7)	NASH	49±2	34±1	<b>LI:</b> weekly sessions for 6 months then biweekly covering: diet (1000-1200 kcal for <91 kg BW & 1200-1500 kcal for >91 kg with 25% E from fat), PA & exercise (progress to 200 min/w mod intensity) & behaviour modification (stimulus control, problem solving & relapse prevention). Goals: 7-10% weight reduction in 6 months then maintenance.	48	n/r	Histopathology (NAS), ALT, AST, HOMA, HbA1c Actual diet & PA achieved was not reported.	<b>LI relative to CON:</b> BW -8.8% NASH score -26%, steatosis -42%; n.s. change in inflammation, ballooning, fibrosis. ALT -39%; n.s. change in AST, HOMA & HbA1c.  <b>LI relative to baseline:</b> NASH score -55%, steatosis score -58%; n.s. change in inflammation, ballooning, fibrosis. ALT -50%; n.s. change in AST, HOMA & HbA1c.
[37]	RCT	10 (8/2)	NASH	48±4	34±2	<b>CON:</b> education session on NASH, healthy eating, PA, & weight management every 12 wk, but without behaviour change skills training.	48	n/r		
[45]	Pilot	16 (8/8)	NASH	50±3	34±1	Weekly (8 wks), biweekly (month 3-6), then monthly visits with dietitian: E restriction n/r (40-45% CHO, 35-40% fat, 15-20% PRO). Weight loss target of 400-800 g/w. Advice to increase PA; frequency & duration n/r.	48	PP	Histopathology (Modified Brunt), ALT, AST, HOMA. E intake ↓195 kcal/d from baseline (food dairy); specific composition n/r. PA ↑ in those with improved NASH Score.	BW ↓3.3% Hepatitis score ↓32% (p=0.06) & ↓47% HOMA p=0.06); steatosis, fibrosis, total NASH score, ALT & AST n.s.
[38]	RCT Subset	46 (n/r)	33% NAFLD	61±1	35±1	<b>LI:</b> Weekly sessions (group to individual ratio 3:1) for 6 months, then 3 sessions/month at 2:1 ratio for 6 months. Portion control & energy intake targets. Meal replacements in first several weeks. Fat intake <30%. Goal to ↓ BW ≥7% & ↑ moderate intensity PA ≥175 min/wk.	48	PP	HTAG (1H-MRS), ALT, AST, HbA1c Actual diet & PA of these subgroups not reported.	<b>LI relative to baseline:</b> BW -8.3% IHTAG -51%, ALT, & AST n.s., HbA1c -8.5%. Changes significantly greater than in CON.
[38]	RCT Subset	50 (n/r)	54% NAFLD	61±1	35±1	<b>CON:</b> standard care + 3 educational group sessions/year.	48	PP		<b>CON:</b> IHTAG ↓23%, ALT & AST n.s., HbA1c n.s.
[42]	UCT	50 (28/2)	NAFLD	47±2	32±1	≤10 sessions with a dietitian to: ↓ E intake, particularly from fat & ↑ fibre intake. Advice to do 3 h/w of moderate aerobic activity.	39	PP	IHTAG (1H-MRS), ALT, AST. VO <sub>2</sub> peak ↑9.4%, 3-day diet records indicated E and SAFA intake decreased, but quantitative data n/r.	BMI ↓3.5% IHTAG ↓35%, ALT ↓18%, AST ↓8.7%, 2 hour glucose ↓11% (75 g OGTT)
[39]	RCT Single-arm	26 (26/0)	Type 2 Diabetes	n/r	32±1	<b>LI:</b> Weekly sessions (group to individual ratio 3:1) for 6 months, then 3 sessions/month at 2:1 ratio for 6 months. Portion control & energy intake targets. Meal replacements in first several weeks. Fat intake <30%. Goal to ↓ BW ≥7% & ↑ moderate intensity PA ≥175 min/wk.	52	PP	Liver:spleen ratio (CT), E-HC.	Men: BW ↓12% Liver: spleen ratio ↑16%, GR <sub>d</sub> ↑56% (E-HC), fasting glucose ↓18%.
[39]	RCT Single-arm	32 (0/32)	Type 2 Diabetes	n/r	35±1	<b>LI:</b> Weekly sessions (group to individual ratio 3:1) for 6 months, then 3 sessions/month at 2:1 ratio for 6 months. Portion control & energy intake targets. Meal replacements in first several weeks. Fat intake <30%. Goal to ↓ BW ≥7% & ↑ moderate intensity PA ≥175 min/wk.	52	PP	Actual diet & PA of these subgroups not reported.	Women: BW ↓8% Liver: spleen ratio ↑14%, GR <sub>d</sub> ↑36% (E-HC), fasting glucose ↓6.4%.

(continued on next page)

Table 3 (continued)

Study	Design	n (M/F)	Clinical Group	Age (years)	BMI (kg/m <sup>2</sup> )	Intervention	Duration (weeks)	Analysis type	Outcome Measures and Adherence	Results
[40]	RCT	38 (20/18)	Elevated AST	49±2	32±1	Personalised exercise & diet advice: PA - 150 or 200 min/wk of mod intensity exercise for health or weight reduction, respectively: diet - reduced E by 406-574 kcal/day, low in SAFA, high in n-3 fats & fibre. Using: Social Cognitive Theory, Transtheoretical Model, Theory of Self-Determination, and Motivational Interviewing. <b>MI:</b> 6 fortnightly sessions. <b>LI:</b> 3 counselling sessions in first month. <b>CON:</b> 1 baseline session.	12	n/r	ALT, AST, HOMA.  <b>MI:</b> PA ↑124 min/wk, BMI ↓3.2%, E intake ↓266±31 kcal/day. <b>LI:</b> PA ↑115 min/wk, BMI ↓2.2%, E intake n.s. <b>CON:</b> PA, & E intake n.s.	<b>Relative to CON:</b> MI: ALT ↓28%, AST & HOMA n.s. LI: ALT ↓22%, AST & HOMA n.s.
		76 (50/26)		48±2	32±1					
		38 (25/13)		47±2	32±1					
[41]	RCT	Same group as [39] divided as described in next column. Baseline data for the post hoc groups were not reported. N = These analyses do not include the participants with hepatitis C.				Reanalysis of data set from [39] on the basis of changes in physical activity relative to controls rather than group allocation: <b>Increased</b> - increased PA by ≥60 min/week; <b>Maintained</b> - maintained baseline PA of >150 min/wk; <b>Low</b> - maintained or ↓ PA from baseline at 60-150 min/wk; <b>Sedentary</b> - maintained or ↓ PA <60 min/wk.	12	N/A	ALT, AST, HOMA.  As per Intervention column.	Results relative to sedentary group: <b>Increased</b> (n=85): ALT ↓15 U/L, AST ↓7.6 U/L, 2 h glucose n.s. & HOMA ↓1. <b>Maintained</b> (n=29): ALT ↓20 U/L, AST n.s., 2 h glucose n.s., HOMA ↓0.3. <b>Low</b> (n=19): ALT ↓15 U/L, AST ↓10 U/L, 2 h glucose & HOMA n.s.
[43]	UCT	31 (15/16)	Pilot	55±2	27±1	Home-based lifestyle modification targeting 5% BW reduction: daily weighing, monthly 30 min visit for lifestyle advice, additional nutrition counselling every 3 months, target 25-30 kcal/kg BW/d, 23 MET/wk of PA + 4 MET/wk exercise.	12	PP	Liver: spleen ratio (CT), ALT, AST, HOMA.  Diet records were collected but findings n/r; PA n/r.	<b>Post 3 months:</b> BW ↓8.5% ALT ↓21%, AST ↓7%, liver spleen ratio ↑13%, HOMA ↓48%.
[43]	UCT	31 (15/16)	Pilot	55±2	27±1		24	PP		<b>Post 6 months</b> (from baseline n=22): BW ↓7.6% ALT ↓41%, AST ↓23%, liver spleen ratio ↑11%, HOMA ↓33%.

Data are mean ± standard errors usually rounded to the nearest full number; changes reported were statistically significant  $p < 0.05$  unless noted otherwise. Sample size based reflects those in the final analysis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (kg/m<sup>2</sup>); BW, body weight; d, day(s); CHO, carbohydrate; CT, computed tomography; d, day(s); E, energy; E-HC, euglycaemic-hyperinsulinaemic clamp; GRA, glucose rate of appearance; GRD, glucose rate of disappearance; h, hour(s); HbA1c, glycated haemoglobin; HOMA, homeostasis model assessment; IHTAG, intrahepatic triacylglycerol concentration; IS, whole body insulin sensitivity; IIT, intention to treat analysis; MET, metabolic equivalent of task; n, sample size of cohort in final statistical analysis; NAFLD, non-alcoholic fatty liver disease; NASH, non-



**Table 4. Interventions combining diet and specific physical activity/exercise advice.**

Study	Design	n (M/F)	Clinical Group	Age (years)	BMI (kg/m <sup>2</sup> )	Intervention	Duration (weeks)	Analysis type	Outcome Measures and Adherence	Results
47	RCT single arm	30 (16/14)	NASH	49±2	32±2	<b>Diet:</b> 500 kcal/d reduction (64% CHO, 22% fat, 14% PRO). <b>Physical Activity:</b> walking or jogging 40 min ≥5 d/wk.	26	ITT	Histopathology (NAS), ALT, AST, HOMA Daily E deficit of 370 kcal, macronutrient composition as prescribed (recall method n/r), PA related adherence was a score (questionnaire).	BW ↓10.6% NAS ↓51%, steatosis ↓40%, ballooning ↓58%, necroinflammation ↓65%, fibrosis ↓55%. ALT ↓41%, AST ↓48%, HOMA ↓35%.
48	NRCT	15 (8/7)	NAFLD	39±3.5	31±1	<b>LI:</b> 25 kcal/kg ideal BW/day (height (cm)-100x0.9) (50% CHO, 30% fat, 20% PRO) + exercise: 3000 steps/d increased by 500 every 3 days until 10,000, then jogging for 20 min 2/d.	12	ITT	Histopathology ALT, AST, fasting glucose.	<b>Relative to baseline:</b> BMI ↓9.7%. Steatosis ↓43%; n.s. change in portal or lobular infiltration, or fibrosis. ALT ↓67%, AST ↓59%, fasting glucose ↓14%.
		10 (5/5)	NAFLD	54±3	31±1	<b>CON</b> (not randomised - inability to undertake inpatient protocol): no intervention.	12		<b>LI</b> were inpatients for 4 wks then food provided.	N.s. changes in outcome measures. BMI ↑3.4%.
46	RCT single arm	22 (8/14)	Type 2 Diabetes	52±2	36±1	2002 American Diabetes Association position stand diet. Weekly dietitian visits. Fat ≤30% of E & negative E balance of ~500 kcal/d. Advice to increase moderate activity by 40-60 min/d.	26	PP	CT liver to spleen ratio. Glucose clamp & indirect calorimetry: GR <sub>d</sub> , EGP. HbA1c Diet (24 hr recall): -568 kcal/d, no change in macronutrients from baseline. No physical activity: n/r.	BW ↓9.8% Liver:spleen ratio ↑24%, GR <sub>d</sub> ↑35%, EGP ↓47%, HbA1c ↓12%.
36	UCT	28 (n/r)	Elevated ALT	~37 (n/r)	29±1	Diet of 25 kcal/kg ideal BW ((height in cm - 100) x 0.9)) NCEP step 1 (60% CHO, 20% fat, 20% PRO & 200 mg cholesterol). PA: 45 min 6 d/wk at 60-70% estimated HRmax.	12	PP	ALT, & AST Some sessions supervised. Only results for those completing ≥4 sessions/week included. Diet: n/r.	BMI ↓9.7% ALT ↓35%, AST ↓38%.
43	RCT	64 (31/33)	Type 2 Diabetes	56±1	32±0.5	American Diabetes Association: 23 kcal/kg/d (50-55% mixed GI CHO, 30% fat, 15-20% PRO). PA: 30 min aerobic activity ≥3 d/wk.	52	PP	ALT Diet (FFQ): 2089 kcal (46% CHO, 37% fat, 19% PRO) & energy ↓39% vs. baseline (1348 kCal). PA: n/r	BW n/r ALT ↓22%.
43	RCT	73 (40/33)	Type 2 Diabetes	57±1	31±0.5	Low GI Diet: 23 kcal/kg/d (50-55% low GI CHO, 30% fat, 15-20% PRO). PA: 30 min aerobic activity ≥3 d/wk.	52	PP	ALT Diet (FFQ): 1987 kCal (45%CHO, 36% fat, 20% PRO) ↓37% vs. baseline (1189 kCal). PA: n/r.	BW n/r ALT ↓18%.
43	RCT	64 (32/32)	Type 2 Diabetes	55±1	31±0.5	Modified Mediterranean Diet: 23 kcal/kg/d (35% low GI CHO, 45% high MUFA fat, 20% PRO). PA: 30 min aerobic activity ≥3 d/wk	52	PP	ALT Diet (FFQ): 2226 kCal (42% CHO, 41% fat, 19% PRO) & energy ↓37% vs. baseline (1189 kCal). PA: n/r.	BW n/r ALT ↓40%.

Data are mean ± standard errors usually rounded to the nearest whole number. Changes reported as percentages where possible. Changes reported were statistically significant  $p < 0.05$  unless noted otherwise. 2 h Glucose, blood glucose concentration at 2 h post-oral glucose tolerance challenge; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (kg/m<sup>2</sup>); BW, body weight; d, day(s); CHO, carbohydrate; CT, computed tomography; d, day; E, energy; EGP, endogenous glucose production; E-HC, euglycaemic-hyperinsulinaemic clamp; FFQ, food frequency questionnaire; GI, glycaemic index; GR<sub>a</sub>, glucose rate of appearance; GR<sub>d</sub>, glucose rate of disappearance; HbA1c, hepatic insulin sensitivity index; HOMA, homeostasis model assessment; IHTAG, intrahepatic triacylglycerol concentration; ITT, intention to treat analysis; MET, metabolically equivalent tasks; min, minute; mod, moderate; MUFA, monounsaturated fatty acid; NAFLD, non-alcoholic fatty liver disease; n/r, data not reported; n.s., no statistically significant change; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; LBM, lean body mass; NRCT, non-randomised control group; OGTT, oral glucose tolerance test; PA, physical activity; PP, per protocol; PRO, protein; wk, week.

## Review

maintenance with mean reductions of 2.2–8.8%. Only two studies reported an objective measure of physical activity adherence, specifically changes in cardiorespiratory fitness [39–41]. One reported energy intake [39], another specifically stated target energy intakes were achieved but did not report any details [41], and one reported energy intake reductions but not macronutrient composition. Six of seven reported reductions in IHTAG and/or circulating liver enzyme in the intervention groups, with absolute mean reductions in IHTAG, measured by <sup>1</sup>H-MRS, of 2–4.6% [37,41]. Relative mean reductions assessed by biopsy [36], CT [38,42], or <sup>1</sup>H-MRS were 13–51%. Six out of the seven studies reported improvements in glucose control/insulin sensitivity [37,38,40–42].

Promrat *et al.* assessed histopathology, reported significant ( $p \leq 0.05$ ) reductions in overall NAFLD histological activity score (NAS) and steatosis, but reductions in parenchymal inflammation and ballooning injury were not significant, and there was no mean change in fibrosis in the intervention relative to the control group or baseline [37]. Huang *et al.* also assessed histopathology, but reported only significant reductions in hepatitis score ( $p = 0.06$ ) [45]; this study is discussed further below.

Five studies involving 306 participants (approximately 50% women, 10 controls) prescribed specific diets and aerobic exercise programs for 3–6 months [35,43–46]. Key study details are summarised in Table 4. The focus was predominantly on body weight reduction and maintenance with mean reductions of 4.2–10.6%. All studies reported reductions in direct measures of liver fat and/or liver enzymes; none used <sup>1</sup>H-MRS. Two studies reported histological endpoints [45,46]. Villar-Gomez *et al.* had the single largest cohort of biopsy assessed participants of the studies reviewed ( $n = 30$ ) and reported significant ( $p < 0.5$ ) reductions in inflammation, ballooning injury, and fibrosis, relative to baseline, following a six month intervention with a mean 10.6% weight reduction [47]. Ueno *et al.* reported significant reductions in steatosis, but reductions in other parameters were not statistically significant [48]. Relative mean reductions in IHTAG based on biopsy scores were 40–43% [45,46]. The four studies reporting glucose control/insulin sensitivity showed improvements [44–46].

Additional *post-hoc* analyses to identify key determinants of liver fat reduction were done in three studies [36,40,41]. The percentage change in body weight was positively correlated with reductions in liver enzymes ( $r = 0.5$ ), reductions in hepatic steatosis ( $r = 0.6$ ), and overall NASH disease activity ( $r = 0.5$ ) [36]. Cardiorespiratory fitness at baseline was found to be a better predictor of change in liver fat than baseline IHTAG, visceral, or total adipose tissue mass following a combined diet and physical activity intervention [41]. Improvements in overall NASH Score, steatosis, inflammation, ballooning injury, and fibrosis were significantly ( $p < 0.05$ ) greater in those achieving weight reductions  $\geq 7\%$  of baseline body weight compared to those with smaller reductions [37]. When dividing their group ( $n = 15$ ) into responders and non-responders based on total NASH Score, Huang *et al.* reported statistically significantly greater weight reduction ( $-6.6$  vs.  $+1.8$  kg) and questionnaire reported physical activity among responders compared with non-responders [45]. Further, increased duration and frequency of physical activity was associated with increasing reductions in liver enzymes [40]. A similar relationship was observed between changes in cardiorespiratory fitness and liver enzymes, but only when results were compared relative to baseline rather than controls [40].

### Publication and study selection bias

A search of clinical trial registers indicated three potentially relevant studies that may have been completed but unpublished – based on the records of recruitment status not being recently updated. All other studies either did not fit our criteria or had been published and considered for inclusion. As only two studies considered for inclusion were registered, this information provides little indication of the degree of publication bias.

Only the Look AHEAD study had a separately published protocol, but this was not specific to the two sub-studies included herein [38,39]. A comparison of expected outcome measures in the method section of reviewed papers and those reported in the results showed good agreement. As above, markers of adherence were consistently less well reported.

### Discussion

The studies reviewed demonstrate that a range of lifestyle modifications are effective in reducing IHTAG and circulating liver enzymes, and improving measures of glucose control and/or insulin sensitivity in patients with NAFLD. Energy restriction, with and without increased physical activity, and weight reduction were the most frequently employed methods to reduce IHTAG. Weight reductions of 4–14% resulted in statistically significant relative reductions in IHTAG of 35–81%. The magnitude of change strongly correlated to degree of weight reduction [36]. There is also limited evidence that physical activity/exercise can lead to modest reductions in IHTAG without weight change.

Low (800–1800 kCal/day) and very low-calorie diets (<800 kCal/day), and/or carbohydrate restriction (20–50 g/d) resulted in the most rapid reductions in body weight and IHTAG. The combination of caloric and carbohydrate restriction resulted in a  $\sim 30\%$  reduction in IHTAG and equally substantial improvements in glucose control and insulin sensitivity within 48 h; a time when weight reduction can only be small and largely accounted for by glycogen depletion and water loss [26]. The pool of studies in patients with NAFLD is small and long-term follow-up is absent. However, a meta-analysis of randomised controlled trials, not specifically in NAFLD patients, reported comparable long-term (1–5 years) 5–6% body weight reduction from low and very-low calorie diets [47]. Nonetheless, such diets do not constitute long-term lifestyle modification as their use is necessarily time limited and may require medical supervision [49]. Use of such diets in routine clinical care remains to be tested.

The best dietary solution for weight maintenance in patients with NAFLD remains unclear. Several of the studies reviewed did not report either actual nutrient intake or physical activity and many used indirect or low accuracy methods to assess IHTAG. Study design and limited reporting of participant adherence preclude firm conclusions being made on differential effects of diet and physical activity. Increased cardiorespiratory fitness was positively related to reductions in IHTAG [25] and liver enzymes [38].

Two reviewed studies reported a reduction in liver enzymes following aerobic exercise without dietary intervention or weight reduction [34,35], but only one study assessed IHTAG directly [34]. It showed a modest 1.8% absolute reduction in IHTAG after four weeks, but no change in HOMA assessed insulin sensitivity. This lack of change may be attributable to the insensitivity of the

HOMA technique or short study duration. In other conditions with metabolic dysregulation such as type 2 diabetes, physical activity and exercise have been shown to improve glucose control in [48], and adiposity, in particular visceral adiposity [49]. In light of the close relationship between IHTAG, glucose control, and adiposity it is likely that exercise improves liver lipid through a combination of lipid redistribution and changes in insulin sensitivity.

Overall, the studies on lifestyle intervention in patients in NAFLD have several limitations; most notably considerable heterogeneity in the populations studied, and limited detail on adherence to specific aspects of the interventions. We therefore make the following recommendations for reporting:

- Transparent and comprehensive descriptions of diagnostic markers of NAFLD including inclusion and exclusion criteria;
- thorough assessment of potential contributors to NAFLD, such as nutrient excess or deficiency where these are likely to be influenced by the intervention; *and*
- publication of supplementary material describing complex lifestyle interventions.

#### Selection of methods

- Quantitative assessments of hepatic steatosis;
- quantitative assessment of NASH activity via biopsy or closely correlated activity scores such as the NAS Activity Score;
- objective physical activity monitoring methods;
- validated dietary assessment methods;
- comprehensive exclusion of specific causes of steatosis, e.g. nutrient excess or deficiency; *and*
- validated methods to assess alcohol consumption.

For future research:

- Definition of the dose response relationship for physical activity/exercise intervention and IHTAG reduction;
- the effect of dietary macronutrient composition on IHTAG, especially carbohydrate restriction and higher protein intakes;
- a graduated progression from Phase II to Phase III trials; *and*
- a focus on how both diet and physical activity/exercise can be used to produce sustained benefit in NAFLD.

#### Conclusions

This systematic review of studies done to date provides consistent evidence that lifestyle interventions designed to reduce energy intake and/or increase physical activity reduce IHTAG and improve insulin sensitivity in patients with NAFLD. A more limited data set indicates a trend for reductions in necroinflammation. The effect on fibrosis is least consistent across studies. Degree of weight reduction is positively correlated with these improvements. However, increased physical activity and/or cardiorespiratory fitness, as well as macronutrient composition, may also act independently to prevent or reverse disease progression. Studies published to date do not allow clear differentiation of the effects of physical activity relative to diet or the importance of diet composition. This is partly due to the paucity of studies, par-

ticularly ones reporting histopathology, but also to study design limitations, minimal reporting of specific aspects of intervention adherence, and the use of variable diagnostic criteria.

Given the clinical impact of NAFLD and the lack of therapies for its management, developing effective, reproducible lifestyle interventions is crucial. Future studies should employ accurate methods to establish the most effective means of producing a sustained reduction in liver fat, necroinflammation, and, if possible, fibrosis, and report their interventions, including objective indicators of adherence, in sufficient detail to be readily translatable to clinical practice.

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#### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

#### Key Points

- Lifestyle interventions producing weight loss significantly improve liver lipid.
- The magnitude of body weight change was reflected in liver fat.
- Exercise only interventions produce a modest but significant effect upon liver lipid, without weight loss.
- Limited data suggest that lifestyle interventions may assist histopathology.
- Improvements in describing the interventions are needed to assist translating these studies into clinical care.
- Studies assessing whether lifestyle interventions target the progression of liver disease should be the focus of future research.

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