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Lifestyle modifications for nonalcohol-related fatty liver disease: a network meta-analysis (Review)

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[Intervention Review]

Lifestyle modifications for nonalcohol-related fatty liver disease: a network meta-analysis

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ABSTRACT

Background

The prevalence of nonalcohol-related fatty liver disease (NAFLD) varies between 19% and 33% in different populations. NAFLD decreases life expectancy and increases the risks of liver cirrhosis, hepatocellular carcinoma, and requirement for liver transplantation. There is uncertainty surrounding the relative benefits and harms of various lifestyle interventions for people with NAFLD.

Objectives

To assess the comparative benefits and harms of different lifestyle interventions in the treatment of NAFLD through a network meta-analysis, and to generate rankings of the different lifestyle interventions according to their safety and efficacy.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, Conference Proceedings Citation Index - Science, World Health Organization International Clinical Trials Registry Platform, and trials registers until February 2021 to identify randomised clinical trials in people with NAFLD.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or status) in people with NAFLD, whatever the method of diagnosis, age, and diabetic status of participants, or presence of non-alcoholic steatohepatitis (NASH). We excluded randomised clinical trials in which participants had previously undergone liver transplantation.

Data collection and analysis

We planned to perform a network meta-analysis with OpenBUGS using Bayesian methods and to calculate the differences in treatments using hazard ratios (HRs), odds ratios (ORs), and rate ratios (RaRs) with 95% credible intervals (CrIs) based on an available-participant

analysis, according to National Institute of Health and Care Excellence Decision Support Unit guidance. However, the data were too sparse for the clinical outcomes. We therefore performed only direct comparisons (head-to-head comparisons) with OpenBUGS using Bayesian methods.

Main results

We included a total of 59 randomised clinical trials (3631 participants) in the review. All but two trials were at high risk of bias. A total of 33 different interventions, ranging from advice to supervised exercise and special diets, or a combination of these and no additional intervention were compared in these trials. The reference treatment was no active intervention. Twenty-eight trials (1942 participants) were included in one or more comparisons. The follow-up ranged from 1 month to 24 months. The remaining trials did not report any of the outcomes of interest for this review.

The follow-up period in the trials that reported clinical outcomes was 2 months to 24 months. During this short follow-up period, clinical events related to NAFLD such as mortality, liver cirrhosis, liver decompensation, liver transplantation, hepatocellular carcinoma, and liver-related mortality were sparse. This is probably because of the very short follow-up periods. It takes a follow-up of 8 years to 28 years to detect differences in mortality between people with NAFLD and the general population. It is therefore unlikely that differences by clinical outcomes will be noted in trials with less than 5 years to 10 years of follow-up.

In one trial, one participant developed an adverse event. There were no adverse events in any of the remaining participants in this trial, or in any of the remaining trials, which seemed to be directly related to the intervention.

Authors' conclusions

The evidence indicates considerable uncertainty about the effects of the lifestyle interventions compared with no additional intervention (to general public health advice) on any of the clinical outcomes after a short follow-up period of 2 months to 24 months in people with nonalcohol-related fatty liver disease.

Accordingly, high-quality randomised clinical trials with adequate follow-up are needed. We propose registry-based randomised clinical trials or cohort multiple randomised clinical trials (a study design in which multiple interventions are trialed within large longitudinal cohorts of participants to gain efficiencies and align trials more closely to standard clinical practice), comparing aerobic exercise and dietary advice versus standard of care (exercise and dietary advice received as part of national health promotion). The reason for the choice of aerobic exercise and dietary advice is the impact of these interventions on indirect outcomes which may translate to clinical benefit. The outcomes in such trials should be mortality, health-related quality of life, decompensated liver cirrhosis, liver transplantation, and resource use measures including costs of intervention and decreased healthcare use after a minimum follow-up of eight years, to find meaningful differences in the clinically important outcomes.

PLAIN LANGUAGE SUMMARY

Lifestyle modifications for people with nonalcohol-related fatty liver disease

What is the aim of this Cochrane Review?
To find out if any lifestyle modifications decrease the effect of nonalcohol-related fatty liver disease on lifespan, health-related quality of life, chronic liver disease and its complications, and whether they cause any harms.

Nonalcoholic fatty liver disease (NAFLD) is an accumulation of fat in the liver in people who have no history of significant alcohol consumption, use of medicines, diseases such as hepatitis C virus infection, or other conditions such as starvation that can damage the liver. Fatty liver can lead to liver damage resulting in inflammation (nonalcohol-related steatohepatitis (NASH)) or liver scarring (liver cirrhosis). Various medical treatments have been tried for the treatment of NAFLD. However, there is currently no evidence that any of them work. Lifestyle modifications have the potential to decrease the liver damage, but whether they achieve this is currently unclear. The authors of this review collected and analysed all relevant randomised clinical trials with the aim of finding out what is the best treatment.

We found 59 randomised clinical trials (studies where participants are randomly assigned to one of two treatment groups). During analysis of data, the review authors used standard Cochrane methods, which allow comparison of only two treatments at a time. We also planned to use advanced techniques that allow comparison of multiple treatments at the same time, usually referred as 'network (or indirect) meta-analysis'.

Date of literature search
February 2021.

What we studied in the review?
This review looked at people of any sex, age (including children), and ethnic origin, with NAFLD. We excluded studies in people who had previously had liver transplantation. The average age of participants, when reported, ranged from 13 years to 65 years. Participants were given different treatments, ranging from advice to supervised exercise and special diets, or a combination of these and no intervention, in addition to the public health advice. We wanted to gather and analyse data on death, quality of life, serious and non-serious adverse events, severe liver damage, complications resulting from severe liver damage, liver cancer, and deaths due to liver damage ('clinical outcomes').

What were the main results of the review?

The 59 studies included a small number of participants (3631 participants). Study data were sparse. Twenty-eight studies with 1942 participants provided data for analyses. The follow-up of the trial participants ranged from 1 month to 24 months. For trials that reported clinical outcomes, follow-up was 2 months to 24 months. Only two small trials did not raise major concerns for bias (deviation from truth because of the way the trials were conducted), and because of this, there is considerable uncertainty about the findings of this review.

The review shows that:

- During a follow-up period of 2 to 24 months, clinically important outcomes related to NAFLD such as deaths were rare and none of the participants developed liver-related complications such as liver cirrhosis (scarring of the liver), liver decompensation (complications because of scarring of the liver), liver transplantation, liver cancer, or deaths due to liver disease. This is probably because the trial participants were followed for too short a time.
- The evidence indicates considerable uncertainty about the effect of the interventions on any of the clinical outcomes.
- Future well-designed randomised clinical trials are needed to find out the best lifestyle modifications for people with NAFLD. Liver-related complications develop over 8 to 28 years. It is therefore unlikely that differences in clinical outcomes will become apparent in trials with less than 5 years to 10 years of follow-up. Sample sizes also need to be much larger.

Summary of findings 1. Lifestyle modifications for nonalcohol-related fatty liver disease

Patient or population: people with nonalcohol-related fatty liver disease (NAFLD)
Settings: community or primary care
Intervention: various interventions
Comparison: no active intervention
Follow-up period: 2 months to 24 months
Network geometry plots: because of the sparse data, there were no connected networks

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Quality of evidence	Comments
		No active intervention	Various interventions	Difference		
Mortality Total studies: 14 Total participants: 1216 **Follow-up period: 2 to 24 months**						
No active intervention	**Reference**					
Aerobic exercise (2 trials; 252 participants)	**Not estimable**	**23 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice (1 trial; 28 participants)	**Not estimable**	**23 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice plus exercise advice (1 trial; 265 participants) (another trial 25 participants had zero events in both groups)	**HR 0.63** (95% CrI 0.07 to 4.06) **Direct estimate**	**23 per 1000**	**14 per 1000** (2 to 92)	**9 fewer per 1000** (21 fewer to 69 more)	**Very low certainty** [a,c,d]	
Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**23 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Aerobic exercise plus calorie-restricted diet (1 trial; 100 participants)	**Not estimable**	**23 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.

Aerobic exercise plus dietary advice (1 trial; 154 participants)	**Not estimable**	**23 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Resistance exercise (1 trial; 45 participants)	**Not estimable**	**23 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Calorie restricted diet (1 trial; 43 participants)	**Not estimable**	**23 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Health-related quality of life						
None of the trials in which no active intervention was the control group reported that they measured health-related quality of life						
Serious adverse events Total studies: 8 Total participants: 448 **Follow-up period: 3 to 6 months**						
No active intervention	**Reference**					
Aerobic exercise (1 trial; 60 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice (1 trial; 28 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice plus exercise advice (1 trial; 22 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Resistance exercise (1 trial; 62 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Any adverse events (number of events) Total studies: 7 Total participants: 426 **Follow-up period: 3 to 6 months**						
No active intervention	**Reference**					

Aerobic exercise (1 trial; 60 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice (1 trial; 28 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Resistance exercise (1 trial; 62 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Liver transplantation Total studies: 7 Total participants: 411 **Follow-up period: 3 to 12 months**						
No active intervention	**Reference**					
Dietary advice (1 trial; 28 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice plus exercise advice (1 trial; 22 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Aerobic exercise plus dietary advice (1 trial; 154 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Decompensation Total studies: 7 Total participants: 411 **Follow-up period: 3 to 12 months**						
No active intervention	**Reference**					
Dietary advice (1 trial; 28 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice plus exercise advice (1 trial; 22 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.

Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Aerobic exercise plus dietary advice (1 trial; 154 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Cirrhosis Total studies: 7 Total participants: 411 **Follow-up period: 3 to 12 months**						
No active intervention	**Reference**					
Dietary advice (1 trial; 28 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice plus exercise advice (1 trial; 22 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Aerobic exercise plus dietary advice (1 trial; 154 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Hepatocellular carcinoma Total studies: 5 Total participants: 229 **Follow-up period: 3 to 6 months**						
No active intervention	**Reference**					
Dietary advice plus exercise advice (1 trial; 22 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Liver-related mortality Total studies: 10 Total participants: 831 **Follow-up period: 3 to 12 months**						

No active intervention	**Reference**					
Aerobic exercise (1 trial; 220 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice (1 trial; 28 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Dietary advice plus exercise advice (2 trials; 287 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Mediterranean diet (1 trial; 98 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	There were no events in either group.
Aerobic exercise plus calorie-restricted diet (1 trial; 100 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.
Aerobic exercise plus dietary advice (1 trial; 154 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There were no events in either group.

*Ranking was not provided because of the considerable uncertainty in the ranking
CrI: Credible interval; **HR:** Hazard ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias.
[b]Downgraded by one level as there were no events in either group.
[c]Downgraded by one level for imprecision because the sample size was small.
[d]Downgraded by one level for imprecision because the credible intervals were wide (included clinical benefit and harms).

BACKGROUND

Description of the condition

Fatty liver disease is steatosis (accumulation of fat, usually triglycerides) in the parenchymal cells of the liver (NCBI 2021). Nonalcohol-related fatty liver disease (also called non-alcoholic fatty liver disease (NAFLD)) is liver steatosis in the absence of significant alcohol consumption, use of medications such as methotrexate, tamoxifen, or steroids; or other disorders that result in fat accumulation, such as hepatitis C virus infection, Wilson's disease, starvation, and lecithin cholesterol acyltransferase (LCAT) deficiency (Angulo 2002; Chalasani 2012). Fatty liver disease includes a spectrum of disorders ranging from simple steatosis or nonalcoholic fatty liver (NAFL) (fat accumulation without evidence of injury to the parenchymal cells of the liver), nonalcoholic steatohepatitis (NASH) (fat accumulation with injury to the liver's parenchymal cells but without cirrhosis), to NASH cirrhosis (advanced liver fibrosis with current or previous NAFL or NASH; (Chalasani 2012; Rinella 2015)). However, it must be noted that the existing non-invasive tests to distinguish NAFLD from alcohol-related liver disease (ALD) are only about 75% to 90% accurate and some people with ALD may be misclassified as NAFLD (Cerovic 2013; Wang 2016a).

The prevalence of NAFLD varies between 19% and 33% in different adult populations, depending upon ethnicity, region of origin (also among people of similar ethnicity), being overweight or obese, and having other disorders such as diabetes mellitus or hypertension (Bedogni 2005; Park 2006; Dassanayake 2009; Koehler 2012; Lazo 2013; Fleischman 2014; Li 2014; Shen 2014; Nishioji 2015). NAFLD can also occur in children and adolescents, although the prevalence of NAFLD in children from general populations is around 8% (lower than in adults), while that in children with obesity is 34% (equivalent to that in adult populations; (Anderson 2015)). The major risk factors associated with increased prevalence of NAFLD are obesity, being male, increasing age, ethnicity (e.g. Mexican-Americans have higher prevalence of fatty liver than other ethnic groups), genetic susceptibility (e.g. genetic variation in patatin-like phospholipase domain containing 3 gene), hypertension, hypercholesterolaemia, diabetes mellitus, lower socioeconomic status, lower-level educational attainment, poor sleep pattern, and lower physical activity (Bedogni 2005; Park 2006; Dassanayake 2009; Sookoian 2011; Koehler 2012; Lazo 2013; Fleischman 2014; Shen 2014; Bernsmeier 2015; Lonardo 2015).

The mean age of people at diagnosis of NAFLD varies between 40 years and 60 years (Bedogni 2005; Dassanayake 2009; Shen 2014). In studies with long-term follow-up, the mean age of people at diagnosis of NAFLD ranged between 45 years and 50 years (Adams 2005; Bedogni 2007; Soderberg 2010; Onnerhag 2014). After a mean follow-up period of 8 to 28 years, the presence of NAFLD increased overall long-term mortality compared to the general population without NAFLD (Adams 2005; Bedogni 2007; Ong 2008; Soderberg 2010; Onnerhag 2014).

People with NAFLD are at risk of dying before reaching the mean life expectancy at birth (Adams 2005; Bedogni 2007; Ong 2008; Soderberg 2010; Onnerhag 2014). It is widely believed that people with simple steatosis rarely progress to advanced liver disease, but people with NASH may develop cirrhosis (Chalasani 2012). It has been reported that in people with NAFLD, liver fibrosis was the only histological feature associated with increased mortality and requirement for liver transplantation (Angulo 2015; Ekstedt 2015). In a study that followed people with simple steatosis and NASH for a mean of 28 years, similar rates of mortality were observed between participants with simple steatosis and those with NASH, but higher mortality rates were observed in people with severe fibrosis, regardless of whether they had bland steatosis (steatosis without inflammation) or NASH (Soderberg 2010). It is noteworthy that NAFLD is associated with metabolic syndrome, that is, the presence of three of the following factors: hypertension, raised triglycerides, lowered high-density lipoprotein cholesterol, raised fasting glucose, and central obesity (Alberti 2009; Ballestri 2016). Increased mortality in people with NAFLD may therefore be related to metabolic syndrome, rather than to NAFLD alone. Furthermore, alcohol-related liver disease (ALD) has a worse prognosis that NAFLD (Dam-Larsen 2005); the difficulty in distinguishing NAFLD from ALD may also contribute to the higher mortality observed in NAFLD.

Nonalcohol-related fatty liver disease is currently one of the most common causes of liver transplantation. Since 2008, NAFLD has been either the second or third most common reason for liver transplantation each year, and the number of people who have undergone liver transplantation for NAFLD has been similar to that of alcohol-related liver disease since 2008 (Cholankeril 2017). The risk of hepatocellular carcinoma (HCC), the most common type of primary liver cancer in adults, is higher in people with NASH cirrhosis compared to people with NAFLD without cirrhosis and the general population: approximately 2% to 13% of people with NASH cirrhosis develop HCC in three to seven years (White 2012). However, HCC can occur in people with NAFLD without them having cirrhosis (Piscaglia 2016).

Fat accumulates within the liver cells when there is an imbalance between the mechanisms that reduce fat in cells (such as oxidation of fatty acids or secretion of lipoproteins) and mechanisms that increase fat in cells, such as increased uptake of fat and increased production of fat. The accumulation of fat leading to NAFLD is believed to be mediated by insulin resistance, because insulin resistance increases the breakdown of peripheral adipose tissue which results in increased influx of free fatty acids (FFAs), promotes the synthesis of new triglycerides within the liver, and decreases the oxidation of FFAs (Abdelmalek 2007; Buzzetti 2016). The accumulation of fat in the liver causes injury due to pro-inflammatory cytokines (Riley 2007). However, the mechanism by which only a proportion of people develop advanced liver fibrosis or primary liver cancer (hepatocellular cancer or hepatocellular carcinoma or HCC) is unclear (Abdelmalek 2007). A 'multiple parallel hits' model, involving nutrition, gut bacteria, and accumulation of fat leading to liver inflammation, has been proposed to explain the development and progression of NAFLD (Tilg 2010; Buzzetti 2016).

Ultrasound is a widely-used method for screening the general population for NAFLD, but it is operator-dependent (Hernaez 2011), and may miss 15 people with fatty liver disease out of every 100 people screened (Hernaez 2011). It may also yield false-positive results in seven out of 100 people without fatty liver disease (Hernaez 2011). While liver biopsy can be considered the definitive investigation to confirm the diagnosis, it is invasive and not suitable for screening the general population.

Description of the intervention

Various interventions have been tried in the treatment of people with NAFLD. This review examines lifestyle modifications such as dietary changes or increased physical activity (Abenavoli 2015; Shojaee-Moradie 2016; Zhang 2016; Houghton 2017) (the focus of the present systematic review), or both. Other interventions not included in this review include nutritional supplementation (probiotics, prebiotics, synbiotics, vitamin supplementation, polyunsaturated fatty acid supplementation; (Nabavi 2014; Sharifi 2014; Li 2015; Nogueira 2016; Mofidi 2017)); pharmacological interventions (Lombardi 2017); and weight reduction surgery (bariatric surgery) in obese people with NAFLD (Adorini 2012; Anstee 2012; Chalasani 2012; Paschos 2012; Abenavoli 2013).

How the intervention might work

Lifestyle modifications, such as dietary changes and increased physical activity, are aimed at decreasing weight and serum lipid profile (Abenavoli 2015; Shojaee-Moradie 2016; Zhang 2016; Houghton 2017). This may lead to resolution or decrease the progression of fatty liver disease (Chalasani 2012). Dietary modifications may also decrease insulin resistance and increase antioxidants, leading to improvement in NAFLD, and improve the vitamins and other micronutrients available naturally from the food (Conlon 2013). Poor sleep pattern is associated with an increased risk of NAFLD due to its correlation with insulin resistance (Bernsmeier 2015). Lifestyle interventions aimed at improving sleep patterns may therefore improve NAFLD by decreasing insulin resistance.

Nutritional supplementation (not included in this review) may work in different ways: vitamin E decreases oxidative damage to liver cells (Chalasani 2012); the effect of vitamin D supplementation may be mediated through its ability to decrease inflammatory markers and lipid peroxidation (Sharifi 2014), that of probiotics may be mediated through its ability to decrease inflammatory markers and alter lipid profile (Al-Muzafar 2017), and that of polyunsaturated fatty acids may be mediated through ability to alter lipid profile (Chalasani 2012). This may lead to resolution or decrease of progression of fatty liver disease. There is currently no effective pharmacological intervention in people with NAFLD or NASH, but there is significant uncertainty about the effect of pharmacological interventions on NAFLD (Lombardi 2017). The reasons for investigating these pharmacological interventions (not included in this review) have been based on their potential to decrease weight, insulin resistance, and/or oxidative damage to liver cells, to alter lipid profile, or their anti-inflammatory and anti-fibrotic properties (Adorini 2012; Anstee 2012; Chalasani 2012; Thoma 2012; Abenavoli 2013). Surgeries resulting in weight loss (not included in this review) may improve fatty liver by reducing weight (Chalasani 2012).

Why it is important to do this review

There is currently no effective pharmacological treatment for NAFLD with or without NASH (Lombardi 2017). Research on treatments to decrease NAFLD and NASH have been identified as top research priorities by patients, carers, and healthcare professionals involved in the treatment of liver diseases in the UK (Gurusamy 2019). Lifestyle modifications have the potential for resolution or to decrease the progression of fatty liver disease. Network meta-analysis enables direct and indirect evidence to be combined, and different interventions to be ranked by different outcomes (Salanti 2011; Salanti 2012). There has been no previous Cochrane Review on this topic. It is therefore important to assess the benefits and harms of lifestyle modifications in the treatment of people with NAFLD. With this systematic review and network meta-analysis, we aim to provide the best level of evidence for the benefits and harms of lifestyle interventions in people with NAFLD. We also present results from direct comparisons whenever possible, as well as performing the network meta-analysis.

OBJECTIVES

To assess the comparative benefits and harms of different lifestyle interventions in the treatment of nonalcohol-related fatty liver disease through a network meta-analysis and to generate rankings of the different lifestyle interventions according to their safety and efficacy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials (including cross-over and cluster-randomised clinical trials, but not quasi-randomised studies) for this network meta-analysis, irrespective of language, publication status, or date of publication. We excluded studies of other designs because of the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our network meta-analysis, but could also be viewed as a strength for assessing rare adverse events. It is well-established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. In the protocol, we stated that we would register and perform a new systematic review and meta-analysis of non-randomised studies for adverse events if there was uncertainty in the balance of benefits and harms of effective treatment(s). We did not register a new systematic review because of the findings of this review, i.e. there is uncertainty about whether any of the interventions improve clinical outcomes.

Types of participants

We include randomised clinical trials with participants who have nonalcohol-related fatty liver disease (NAFLD), irrespective of the method of diagnosis, age or diabetic status of participants, or the presence of non-alcoholic steatohepatitis (NASH). We exclude randomised clinical trials in which participants had previously undergone liver transplantation.

Types of interventions

We include any of the following interventions for comparison with one another, either alone or in combination.

- Supervised physical activity (for example, exercise classes)
- General physical activity advice
- Rationed diet (for example, daily or weekly rations of different foods, calorie-restricted diet)
- Special diets (for example, Mediterranean diet, Atkin's diet, high-fibre diet, or diet with high fruit and vegetable content)
- General dietary advice (for example, information on the fat or carbohydrate content of different foods)

- Lifestyle modifications that promote sleep (for example, nicotine and caffeine restriction)
- No active intervention (including sham or placebo interventions)

We considered no active intervention as the reference group. We considered each of the above subcategories as a 'treatment node'. We considered variations in the subcategories, for example, different frequencies of exercise or dietary advice, as the same treatment node. We treated each different combination of the categories as different treatment nodes. All the above interventions were considered the 'decision set', i.e. all the above interventions were of direct interest.

We included trials in which the above interventions were combined with other interventions aimed at decreasing NAFLD (but considered these as potential effect modifiers), provided that these co-interventions were administered equally in both arms. We included nutritional supplements in the form of tablets, powder, or solution in a different review (Komolafe 2021).

We evaluated the plausibility of the network meta-analysis transitivity assumption by looking at the inclusion and exclusion criteria in the studies. The transitivity assumption means that participants included in the different trials with different treatments (in this case, for NAFLD) can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the interventions (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. The transitivity assumption also means that potential effect modifiers are not systematically different across comparisons. This necessitates that information on potential effect modifiers such as diabetic status and co-interventions (not included in the 'decision set'; those included in the 'decision set' were considered as combination of treatments) are similar across trials of different comparisons. Because of the inclusion criteria, the nature of interventions considered in this review, and lack of systematic methodological differences across treatment interventions, we had no concerns about transitivity assumption for these effect modifiers.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximum follow-up (time to death)
- Health-related quality of life, as defined in the included trials, using a validated scale such as the EQ-5D or 36-Item Short Form Health Survey (SF-36; (EuroQol 2018; RAND 2021)) at maximum follow-up
- Serious adverse events (during or within six months after cessation of intervention). We defined a serious adverse event as any event that would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it (ICH-GCP 1997). However, none of the trial authors defined serious adverse events. We therefore used the list provided by trial authors for serious adverse events (as indicated in the protocol).
  - Proportion of trial participants with one or more serious adverse events
  - Number of serious adverse events per participant

Secondary outcomes

- Any adverse events, during or within six months after cessation of intervention. We defined an adverse event as any untoward medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of intervention, any time after the start of intervention; (ICH-GCP 1997). However, none of the trial authors defined 'adverse event'. We therefore used the list provided by trial authors for adverse events (as indicated in the protocol).
  - Proportion of trial participants with any adverse events
  - Number of any adverse events per participant
- Liver transplantation (time to liver transplantation at maximum follow-up)
- Decompensation (time to decompensation at maximum follow-up)
- Cirrhosis (time to cirrhosis at maximum follow-up)
- Liver-related mortality (time to liver-related death at maximum follow-up)

Exploratory outcomes

- Resolution of fatty liver disease (time to resolution of fatty liver disease at maximum follow-up)
- Fibrosis score at maximum follow-up
- NAFLD activity score (Brunt 2011) at maximum follow-up
- MELD score (Kamath 2001) at maximum follow-up

We had chosen outcomes based on:

- their importance to patients in a survey related to research priorities for people with liver diseases (Gurusamy 2019);
- feedback from the patient and public representative of this project;
- an online survey about the outcomes promoted through the Cochrane Consumer Network;
- the coreNASH project (Clearfield 2021) (which resulted in the addition of liver-related mortality and MELD score).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index - Science (Web of Science) from inception to February 2021 for randomised clinical trials comparing two or more of the above interventions, without applying any language restrictions (Royle 2003). We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN and ClinicalTrials.gov. We also searched the European Medical Agency (EMA) (www.ema.europa.eu/ema/) and USA Food and Drug Administration (FDA) (www.fda.gov) registries for randomised clinical trials. We provided the search strategies along with the date of search in Appendix 1.

Searching other resources

We searched the references of the identified trials to identify additional trials for inclusion. We also contacted the study authors for any other potential studies of which they were aware.

Data collection and analysis

Selection of studies

Two review authors (KG and EB, DR, LB or AL) independently identified trials for inclusion by screening the titles and abstracts of articles identified by the literature search, and sought full-text articles of any references identified by at least one review author for potential inclusion. We selected trials that met the inclusion criteria for this review based on the full-text articles. We listed the references that we excluded and the reasons for their exclusion in the Characteristics of excluded studies table. We also listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We resolved any discrepancies through discussion. We illustrated the study selection process in a PRISMA diagram (see Figure 1).

Data extraction and management

Two review authors (EB, DR, or AL) independently extracted the data below in a prepiloted Microsoft Excel-based data extraction form, after translation of non-English articles. If we found multiple records of the same trial, we collated all the records at the time of data extraction, and obtained the maximum information for the study from the multiple reports.

- Outcome data (for each outcome and for each intervention group whenever applicable):
  - number of participants randomised;
  - number of participants included in the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
  - natural logarithm of hazard ratio and its standard error if this was reported, rather than the number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, diabetic status, method of diagnosis, presence of NASH;
  - details of the intervention and control (including dose, frequency, and duration);
  - length of follow-up;
  - information related to risk of bias assessment (see below).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria.
  - funding and conflicts of interest

We collected data at maximum follow-up but also in the short term (up to three months), and the medium term (from three months to five years) if these were available.

We attempted to contact the trial authors in the case of unclear or missing information. If there was any doubt as to whether trials shared the same participants, completely or partially (by identifying common authors and centres), we planned to contact the trial authors to clarify whether the trial report was duplicated. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risks of bias in included trials (Higgins 2011). Specifically, we assessed sources of bias as defined below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018).

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random-number generation or a random-number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the allocation sequence was described as unknown to the investigators. Hence, the participants' allocations could not have been foreseen in advance of or during enrolment. Allocation was controlled by a central and independent randomisation unit, an onsite locked computer, identical-looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent pharmacist or an independent investigator.
- Unclear risk of bias: it was unclear if the allocation was hidden or if the block size was relatively small and fixed so that intervention allocations may have been foreseen in advance of or during enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or rarely no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of low risk or high risk; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or rarely no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of low risk or high risk; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias in the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: at least one of the outcomes related to the main reason for treatment of people with NAFLD, namely, all-cause mortality or resolution of NAFLD, along with adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If we obtained the trial protocol from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we did not consider those outcomes to be reliable.
- Unclear risk of bias: not all predefined or clinically-relevant and reasonably-expected outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically-relevant and reasonably-expected outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

Other bias

- Low risk of bias: the trial appeared to be free of other components that could put it at risk of bias (e.g. inappropriate control or dose or administration of control, early stopping, baseline differences indicating problems with randomisation, baseline differences in clusters, bias due to loss of clusters, and bias due to individuals being recruited after the randomisation of clusters).
- Uncertain risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. baseline differences, early stopping, entire clusters were lost, individuals in cluster RCTs were recruited after the randomisation of the clusters).

We considered a trial to be at low risk of bias if we assessed the trial to be at low risk of bias across all listed risk of bias domains. Otherwise, we considered the trial to be at high risk of bias. At the outcome level, we classified an outcome to be at low risk of bias if the allocation sequence generation, allocation concealment, blinding of participants, healthcare professionals, and outcome assessors, incomplete outcome data, and selective outcome reporting (at the outcome level) were at low risk of bias for objective and subjective outcomes (Savović 2018).

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we calculated the odds ratio (OR) with a 95% credible interval (CrI) (or Bayesian confidence interval; (Severini 1993)). For continuous variables (e.g. health-related quality of life reported on the same scale), we calculated the mean difference (MD) with a 95% CrI. We planned to use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if included trials used different scales. If we calculated the SMD, we planned to convert it to a common scale, for example, EQ-5D or SF-36 (using the standard deviation of the common scale) for the purpose of interpretation. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we calculated the rate ratio (RaR) with a 95% CrI. This assumes that the events are independent of each other, i.e. if a person has had an event, they are not at an increased risk of further outcomes, which is the assumption in Poisson likelihood. For time-to-event data (e.g. all-cause mortality at maximum follow-up), we calculated hazard ratios (HRs) with 95% CrIs.

Relative ranking

We estimated the ranking probabilities for all interventions of being at each possible rank for each intervention for each outcome when NMA (network meta-analysis) was performed. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with median and CrI for the ranking probabilities for each outcome when NMA was performed (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant undergoing treatment for NAFLD according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

If we identified any cluster-randomised clinical trials, we planned to include them, provided that the effect estimate adjusted for cluster correlation was available or if there was sufficient information available to calculate the design effect (which would allow us to take clustering into account).

Cross-over randomised clinical trials

If we identified any cross-over randomised clinical trials, we planned to include only the outcomes after the period of the first intervention, because the included treatments could have residual effects.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria. The codes that we used for analysis accounted for the correlation between the effect sizes from studies with more than two groups.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992); otherwise, we used the data available to us. When intention-to-treat analysis was not used and the data were not missing at random (for example, treatment was withdrawn due to adverse events or duration of treatment was shortened because of lack of response and such participants were excluded from analysis), this could lead to biased results; we therefore conducted best-worst case scenario analysis (assuming a good outcome in the intervention group and a bad outcome in the control group) and worst-best case scenario analysis (assuming a bad outcome in the intervention group and good outcome in the control group) as sensitivity analyses whenever possible, for binary and time-to-event outcomes where binomial likelihood was used.

For continuous outcomes, we imputed the standard deviation from P values, according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we used the median for meta-analysis when the mean was not available; otherwise, we planned simply to provide a median and interquartile range of the difference in medians. If it was not possible to calculate the standard deviation from the P value or the confidence intervals, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation can decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We also planned to assess the presence of clinical heterogeneity by comparing effect estimates (please see Subgroup analysis and investigation of heterogeneity) in trial reports based on the presence of diabetes and NASH, and based on the co-interventions (for example, both groups received nutritional supplements). Different study designs and risks of bias can contribute to methodological heterogeneity.

We assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, lack of overlap of 95% credible intervals of between-study variance (tau^2) with 0 (after rounding to two decimals), and by calculating the NMA-specific I^2 statistic (Jackson 2014) using Stata/SE 15.1. When possible, we explored substantial clinical, methodological, or statistical heterogeneity and addressed the heterogeneity in subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: presence of diabetes and NASH, and methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we planned to perform a comparison-adjusted funnel plot. However, it is necessary to rank the studies in a meaningful way to interpret it, as asymmetry may be due to small sample sizes in newer studies (comparing newer treatments with older treatments), or higher risk of bias in older studies (Chaimani 2012). As there was no specific change in the risk of bias in the studies, sample size, or the control group used over time (the first trial report for this review was published only in 2008), we judged the reporting bias by the completeness of the search (Chaimani 2012). We also considered lack of reporting of outcomes as a form of reporting bias, by looking at the proportion of trials that reported the outcomes.

Data synthesis

We conducted network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. When two or more interventions were combined, we considered this combination as a separate intervention ('node'). Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We obtained a network plot to ensure that the trials were connected by interventions using Stata/SE 15.1 (Chaimani 2013). We excluded any trials that were not connected to the network from the network meta-analysis, and we reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We modelled the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and the reference group ('basic parameters') using appropriate likelihood functions and links (Lu 2006). We used binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link (a semiparametric model which excludes censored individuals from the denominator of ‘at risk’ individuals at the point when they are censored) for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We used 'no active intervention' as the reference group across the networks, as there is no established 'standard of care' for lifestyle modifications in NAFLD. We performed a fixed-effect model and a random-effects model for the network meta-analysis. We reported both models for comparison with the reference group in a forest plot when the results were different between the models. For each pairwise comparison in a table, we reported the fixed-effect model if the two models reported similar results; otherwise, we reported the more conservative model, i.e. usually the random-effects model.

We used a hierarchical Bayesian model using three different sets of initial values to start the simulation-based parameter estimation to

assist with the assessment of convergence, using codes provided by NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors) centred at no effect. For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for the between-trial standard deviation parameter and assumed that this variability would be the same across treatment comparisons (Dias 2016). We used a 'burn-in' of 30,000 simulations, checked for convergence (of effect estimates and between-study heterogeneity) visually (i.e. whether the values in different chains mixed very well by visualisation), and ran the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we increased the number of simulations for the 'burn-in' and used the 'thin' and 'over relax' functions to decrease the autocorrelation. If we still did not obtain convergence, we planned to use alternate initial values and priors using methods suggested by Van Valkenhoef 2012. We estimated the probability that each intervention ranked at each of the possible positions based on estimated effect sizes and their corresponding uncertainty using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We assessed inconsistency (statistical evidence of the violation of the transitivity assumption) by fitting both an inconsistency model and a consistency model. We used inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation (Dias 2014). In addition, we used design-by-treatment full interaction model and inconsistency factor (IF) plots to assess inconsistency (Higgins 2012; Chaimani 2013) when applicable. We used Stata/SE 15.1 to create IF plots. In the presence of inconsistency (model fit better with inconsistency models than consistency model, 95% CrI of 'between-design' variance did not overlap 0, and the 95% confidence intervals of inconsistency factor did not overlap 0), we planned to assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the Subgroup analysis and investigation of heterogeneity section or limit the network meta-analysis to a more compatible subset of trials when possible.

Direct comparison

We performed the direct comparisons in the randomised clinical trials using the same codes and the same technical details.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the intervention effect estimates between the following subgroups, and planned to investigate heterogeneity and inconsistency using meta-regression with the help of the codes provided in NICE DSU guidance (Dias 2012a) if we had a sufficient number of trials (when there were at least two trials in at least two of the subgroups). We planned to use the following trial-level markers for subgroup analyses.

- Trials at low risk of bias compared to trials at high risk of bias;
- Participants with NAFLD plus NASH compared to participants with NAFLD without NASH;
- Participants with diabetes mellitus compared to participants without diabetes mellitus;
- Different types of exercises/diets;
- Co-interventions (for example, both groups receive omega-3 fatty acid supplementation);
- Based on the period of follow-up: short-term: up to three months, medium-term: more than three months to five years, and long-term: more than five years;
- Based on the definition used by authors for serious adverse events and any adverse events (ICH-GCP 1997 compared to other definitions).

We planned to calculate a single common interaction term which assumes that each relative treatment effect compared to a common comparator treatment (i.e. 'no active intervention') is impacted in the same way by the covariate in question when applicable (Dias 2012a). If the 95% CrI of the interaction term did not overlap zero, we considered this statistically significant heterogeneity or inconsistency (depending upon the factor being used as the covariate).

Sensitivity analysis

If there were post-randomisation dropouts, we re-analysed the results using the best-worst case scenario and worst-best case scenario as sensitivity analyses whenever possible. We also performed a sensitivity analysis excluding the trials in which mean or standard deviation, or both, were imputed, and we used the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We followed the PRISMA-NMA statement while reporting (Hutton 2015). We presented the effect estimates with 95% CrIs for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We originally planned to present the cumulative probability of the treatment ranks (i.e. the probability that the intervention was within the top two, the probability that the intervention was within the top three, etc.), but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks) in graphs (SUCRA; (Salanti 2011)). We plotted the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms) which are generally considered more informative (Salanti 2011; Dias 2012b), but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the 95% CrI was 0 to 1 for most of the ranks). We uploaded all the raw data and the codes used for analysis in the European Organization for Nuclear Research open source database (Zenodo). You can find this by clicking here.

Recommendations for future research

We provide recommendations for future research in the population, intervention, control, outcomes, time of follow-up, and study design, based on the uncertainties that we identified from the existing research.

Summary of findings and assessment of the certainty of the evidence

We presented summary of findings tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We planned to follow the approach suggested by GRADE Working Group (Brignardello-Petersen 2018; Yepes-Nunez 2019). However, network meta-analysis was not performed for any of the clinical outcomes, primary or secondary. We therefore

rated the certainty of evidence for direct effect estimates using GRADE methodology, which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence, imprecision, and publication bias (Guyatt 2011). For illustration of the absolute measures, we used the weighted median (Edgeworth 1887), control group proportion, or mean. We did not present the summary of findings tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019), as the data on clinical outcomes were sparse (noting there is currently no preferred method of lifestyle intervention recommended).

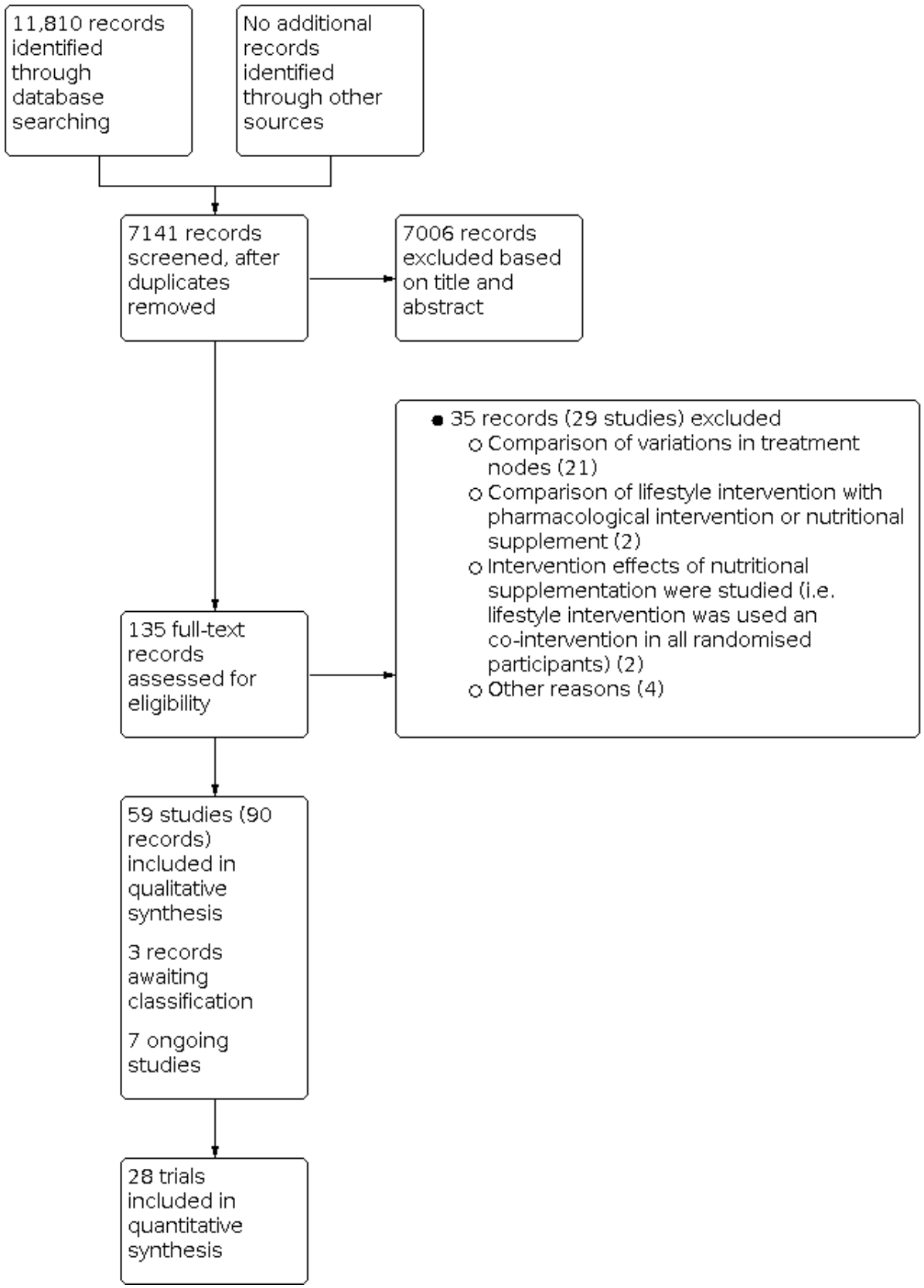
RESULTS

Description of studies

Results of the search

We identified 11,810 references through electronic searches of CENTRAL (Wiley) (n = 2294), MEDLINE Ovid (n = 3654), Embase Ovid (n = 2311), Science Citation Index Expanded and Conference Proceedings Citation Index - Science (n = 2871), ClinicalTrials.gov (n = 393), WHO Trials register (n = 19), FDA (n = 137), and EMA (n = 131). After we removed duplicate references, there were 7141 references. We excluded 7006 clearly irrelevant references through reading titles and abstracts. We retrieved 135 full-text references for further assessment in detail. We excluded 35 references (29 studies) for the reasons stated in the Characteristics of excluded studies. Three references are awaiting classification (Bahrololumi 2014; Jia 2018; Grove 2020) and seven references are ongoing trials (IRCT20100524004010N31; NCT03354247; NCT03518294; NCT04283942; NCT04355910; NCT04369521; NCT04440540). We therefore include a total of 59 trials described in 90 references (Characteristics of included studies). The reference flow is shown in Figure 1. Please note that in the reference flow, we have not included the references for which we sought full text to confirm that the reference was not a RCT and that the trial was not about participants with NAFLD.

Figure 1. Study flow diagram
Date of search: 25 February 2021



Included studies

We include 59 trials (Wang 2008; De Luis 2010; Hallsworth 2011; Rodriguez-Hernandez 2011; De Piano 2012; Sullivan 2012; Al-Jiffri 2013; Bacchi 2013; Eckard 2013; Hickman 2013; Ramon-Krauel 2013; Wong 2013; Kani 2014; Pugh 2014; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Hallsworth 2015; Abd El-Kader 2016; Cuthbertson 2016; Dong 2016; Dynnyk 2016; Kaliora 2016; Ramirez 2016; Rezende 2016; Wang 2016; Zade 2016; Zhang 2016; Arab 2017; Axley 2017; Cheng 2017; Houghton 2017; Misciagna 2017; Monica Dinu 2017; Nikroo 2017; Oh 2017; Roy 2017; Schattenberg 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Nishimori 2018; Properzi 2018; Shidfar 2018; Tutino 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Abdelbasset 2020; Chen 2020; Goss 2020; Moradi 2020; Nourian 2020; Panganiban 2020; Abbate 2021; NCT01327443; NCT02679417; NCT03183193; NCT03461562). A total of 3631 participants were randomised to different interventions in these 59 trials. The number of participants in the trials ranged from 17 to 280. Only a total of 1942 participants from 28 trials were included in one of more outcomes (Wang 2008; Al-Jiffri 2013; Bacchi 2013; Eckard 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Dong 2016; Kaliora 2016; Rezende 2016; Zhang 2016; Axley 2017; Cheng 2017; Houghton 2017; Misciagna 2017; Monica Dinu 2017; Nikroo 2017; Oh 2017; Roy 2017; Schattenberg 2017; Chan 2018; Katsagoni 2018; Properzi 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Moradi 2020; Nourian 2020). There are no cluster-randomised trials or cross-over trials included in this review.

Further summary details of the included trials are available in Table 1. The important characteristics, potential effect modifiers, and follow-up in each trial are reported in Table 2. Overall, there do not seem to be any systematic differences between the comparisons, i.e. there was no immediate overt concern about transitivity assumption.

Excluded studies

The reasons for exclusion of studies are listed in Characteristics of excluded studies. The summary reasons for exclusion of studies are as follows.

- Comparison of variations in the same treatment nodes: St George 2009; Promrat 2010; Arefhosseini 2011; Sun 2012; Aller 2014; Nigam 2014; An 2015; Baldry 2017; Dynnyk 2017; Schweinlin 2018; Rezaei 2019; Austin 2020; Dorosti 2020; Haidari 2020; Nath 2020; Negri 2020; Ristic-Medic 2020; Marin-Alejandre 2021; Simons 2021; NCT04383951; NCT04520724.
- Comparison of lifestyle intervention with pharmacological intervention or nutritional supplement: Dela Cruz 2012; NCT04193982.
- Intervention effects of nutritional supplementation was studied (i.e. lifestyle intervention was used as an co-intervention in all randomised participants): Nobili 2008; Vilar Gomez 2009.
- Other reasons:
  * Type of intervention not relevant to this review: Lim 2020; TCTR20200411004
  * A cross-over trial in which the cross-over was at six weeks of intervention and the outcomes were not reported before the cross-over: this trial was not designed to address the objectives of this review (i.e. benefits and harms of different lifestyle interventions in the treatment of nonalcohol-related fatty liver disease; (Ryan 2013))
  * Included participants with suspected NAFLD rather than those with NAFLD (Whyte 2020).

Risk of bias in included studies

The risk of bias is summarised in Figure 2, Figure 3, Table 3 (domain-level summary) and in Table 4 (study-level summary ordered by comparisons). All the trials but two (Misciagna 2017; Monica Dinu 2017) were at unclear or high risk of bias in at least one of the domains and were considered to be at high risk of bias for individual outcomes and overall.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

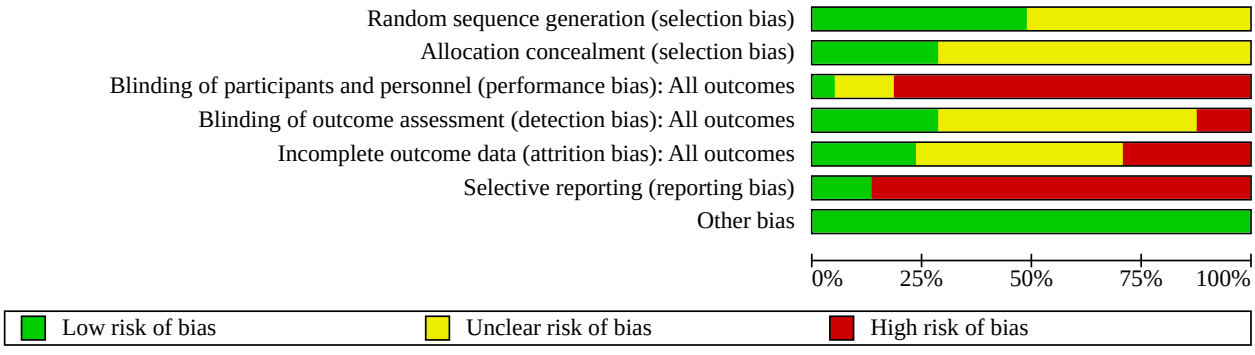


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

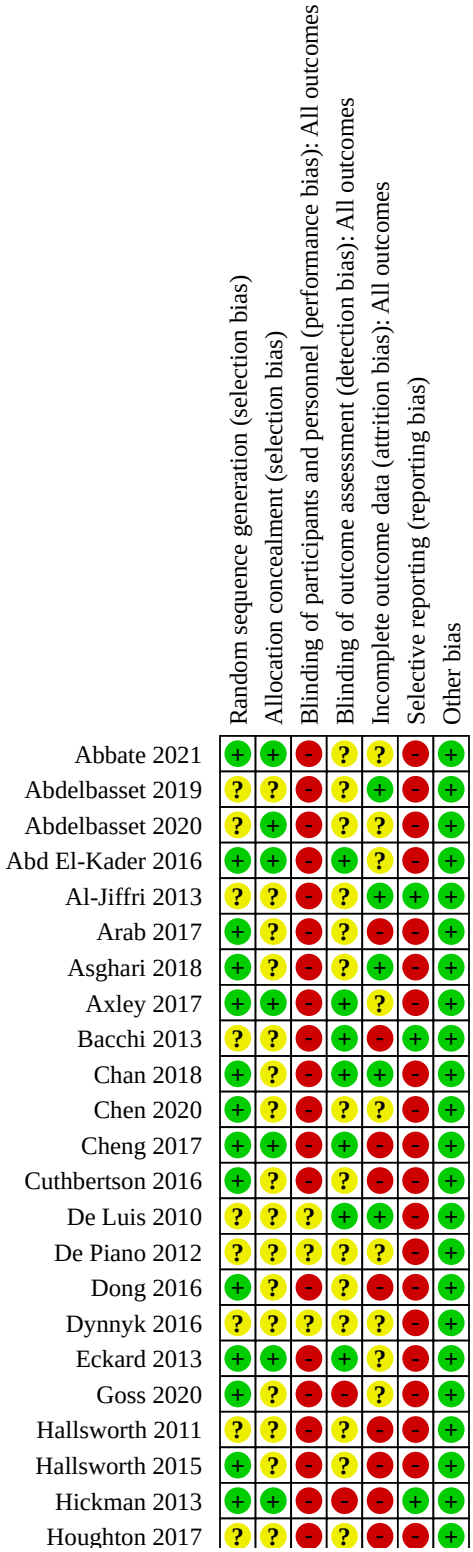
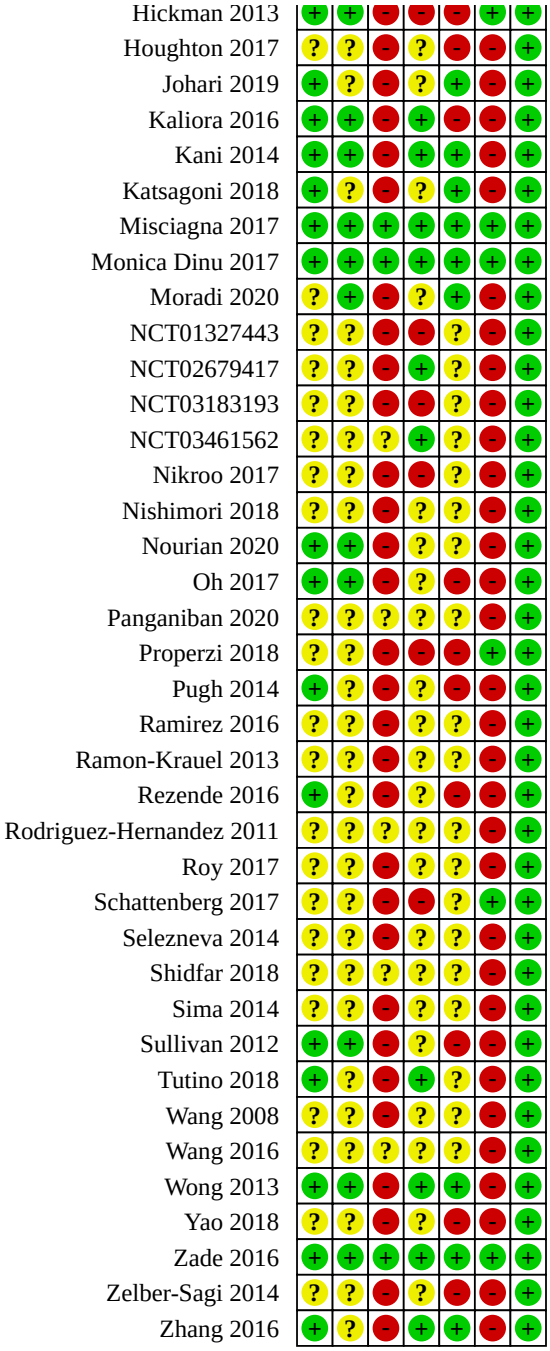


Figure 3. (Continued)



Allocation

Twenty-nine trials were at low risk of selection bias due to lack of random sequence generation; the remaining 30 trials, which did not provide sufficient information, were at unclear risk of sequence generation bias.

Seventeen trials were at low risk of selection bias due to lack of allocation concealment; the remaining 42 trials, which did not provide sufficient information, were at unclear risk of allocation concealment bias.

Blinding

Three trials were at low risk of performance bias as the participants and healthcare providers were blinded; eight trials, which did not provide sufficient information, were at unclear risk of performance bias; the remaining 48 trials were at high risk of performance bias.

Seventeen trials were at low risk of detection bias; 35 trials, which did not provide sufficient information, were at unclear risk of detection bias; the remaining seven trials were at high risk of detection bias.

Incomplete outcome data

Fourteen trials were at low risk of attrition bias as there were no post-randomisation dropouts or an intention-to-treat analysis was used; 28 trials were at unclear risk of incomplete outcome data bias, because it was not clear whether there were post-randomisation dropouts or whether the post-randomisation dropouts were related to the outcomes (if there were post-randomisation dropouts); the remaining 17 trials were at high risk of attrition bias, as the post-randomisation dropouts were probably related to the outcomes.

Selective reporting

Eight trials were at low risk of selective outcome reporting bias, as the important clinical outcomes expected to be reported in such trials were reported; the remaining 51 trials were at high risk of selective outcome reporting bias as a protocol published prior to recruitment was not available and clinically relevant and reasonably expected outcomes were not reported.

Other potential sources of bias

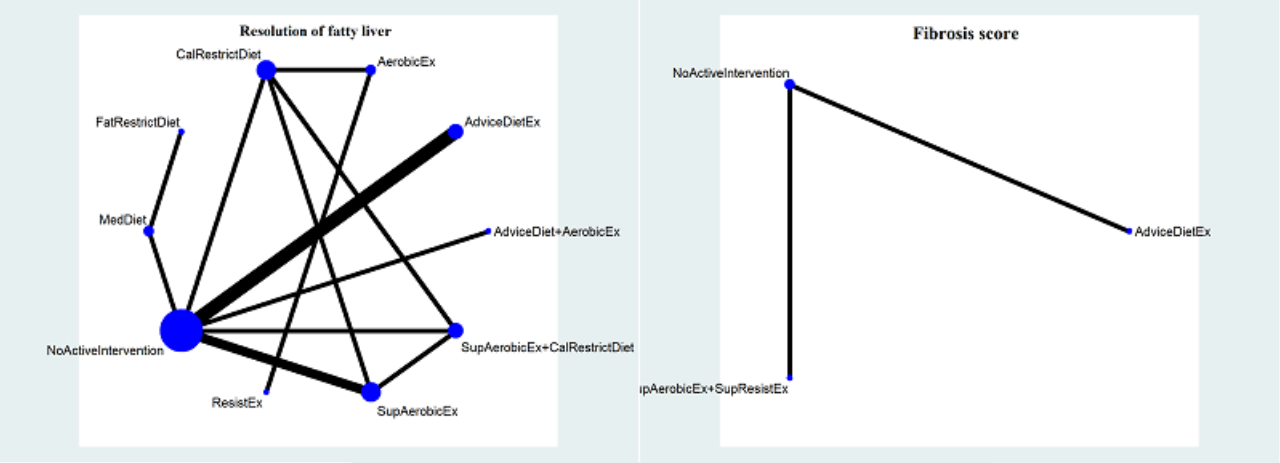
No other potential source of bias was noted in any of the trials.

Effects of interventions

See: **Summary of findings 1** Lifestyle modifications for nonalcohol-related fatty liver disease

The network plots (where relevant) are available in Figure 4. The inconsistency factor plots (where relevant) are available in Figure 5. The model fit when network meta-analysis was performed is available in Table 5. The effect estimates are available when network meta-analysis was performed in Table 6.

Figure 4. Network plots: A high resolution version of this image can be found here. The network plots showing the outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular Intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (Interventions).
Abbreviations AdviceDiet: dietary advice
AdviceDiet+AerobicEx: aerobic exercise plus dietary advice
AdviceDietEx: dietary advice plus exercise advice
AerobicEx: aerobic exercise
CalRestrictDiet: calorie restricted diet
CarbRestrictDiet+AerobicEx: aerobic exercise plus carbohydrate restricted diet
FatRestrictDiet: fat restricted diet
FatRestrictDiet+AerobicEx: aerobic exercise plus fat restricted diet
MedDiet: Mediterranean diet
NoActiveIntervention: no active intervention
ResistEx: resistance exercise
SupAerobicEx: supervised aerobic exercise
SupAerobicEx+CalRestrictDiet: supervised aerobic exercise plus calorie restricted diet
SupAerobicEx+SupResistEx: supervised aerobic exercise plus resistance exercise



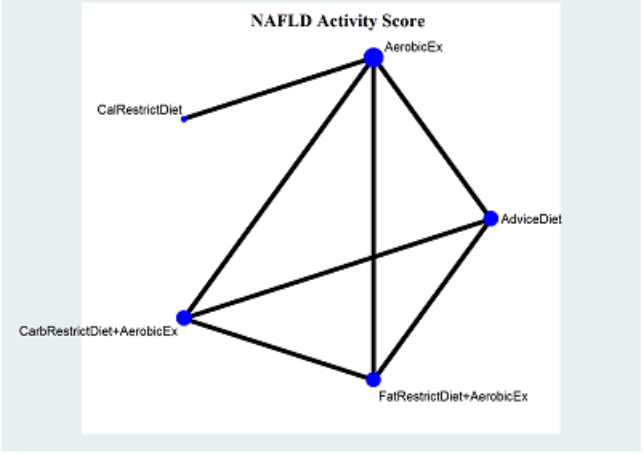
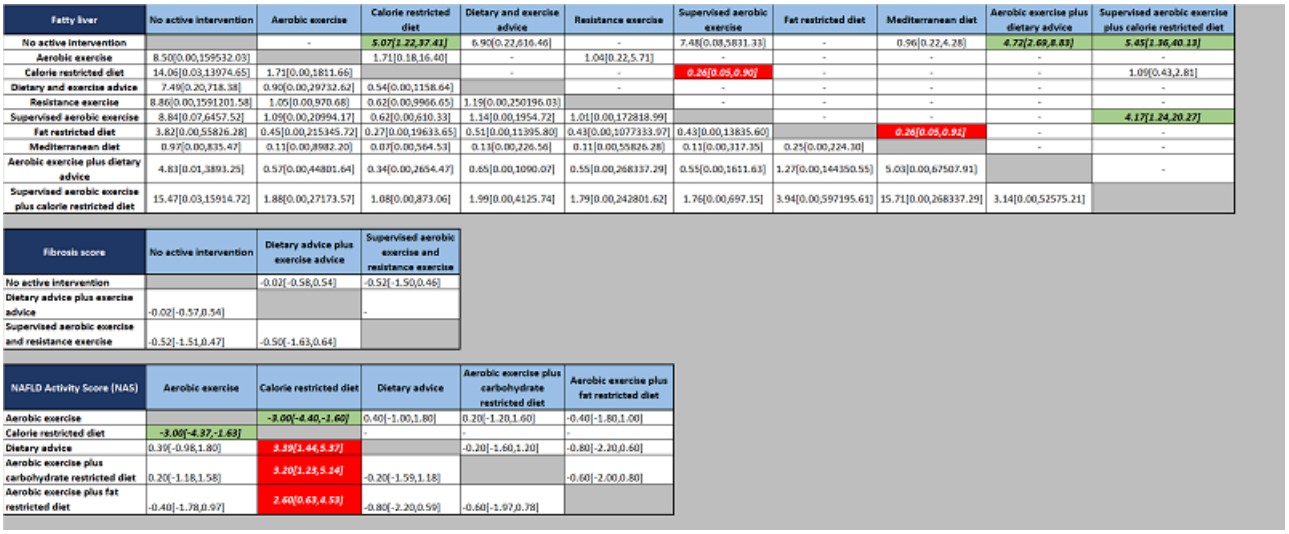


Figure 5. Inconsistency factor plots: The plot shows the inconsistency factors for the only outcome (resolution of fatty liver) where direct and indirect evidence were available for one or more comparisons. Although not attaining formal levels of statistical significance, this may suggest some concern regarding the consistency of the evidence. A higher resolution image of this picture is available here. Abbreviations CalRestrictDiet: calorie restricted diet
NoActiveIntervention: no active intervention
SupAerobicEx: supervised aerobic exercise
SupAerobicEx+CalRestrictDiet: supervised aerobic exercise plus calorie restricted diet

Figure 6. Effect estimates: A picture of Table 6 Effect estimates. Please see Table 6 for further details.



Fatty liver	No active intervention	Aerobic exercise	Calorie restricted diet	Dietary and exercise advice	Resistance exercise	Supervised aerobic exercise	Fat restricted diet	Mediterranean diet	Aerobic exercise plus dietary advice	Supervised aerobic exercise plus calorie restricted diet
No active intervention		-	*5.07[1.22,37.41]*	6.90[0.22,616.46]	-	7.48[0.08,5831.33]	-	0.96[0.22,4.28]	*4.72[2.69,8.83]*	*5.45[1.36,40.13]*
Aerobic exercise	8.50[0.00,159532.03]		1.71[0.18,16.40]	-	1.04[0.22,5.71]	-	-	-	-	-
Calorie restricted diet	14.06[0.03,13974.65]	1.75[0.00,1811.66]		-	-	*0.26[0.05,0.90]*	-	-	-	1.09[0.43,2.81]
Dietary and exercise advice	7.49[0.20,718.38]	0.90[0.00,29732.62]	0.54[0.00,1158.64]		-	-	-	-	-	-
Resistance exercise	8.86[0.00,1591201.58]	1.05[0.00,970.68]	0.62[0.00,9966.65]	1.19[0.00,250196.03]		-	-	-	-	-
Supervised aerobic exercise	8.84[0.07,6457.52]	1.09[0.00,20994.17]	0.62[0.00,610.33]	1.14[0.00,1954.72]	1.01[0.00,172818.99]		-	-	-	*4.17[1.24,20.27]*
Fat restricted diet	3.82[0.00,55826.28]	0.45[0.00,215345.72]	0.27[0.00,19633.65]	0.51[0.00,11395.80]	0.43[0.00,1077333.97]	0.43[0.00,13835.60]		*0.26[0.05,0.91]*	-	-
Mediterranean diet	0.97[0.00,835.47]	0.11[0.00,8982.20]	0.07[0.00,564.53]	0.13[0.00,226.56]	0.11[0.00,55826.28]	0.11[0.00,317.35]	0.25[0.00,224.30]		-	-
Aerobic exercise plus dietary advice	4.83[0.01,3893.25]	0.57[0.00,44801.64]	0.34[0.00,2654.47]	0.65[0.00,1090.07]	0.55[0.00,268337.29]	0.55[0.00,1611.63]	1.27[0.00,144350.55]	5.03[0.00,67507.91]		-
Supervised aerobic exercise plus calorie restricted diet	15.47[0.03,15914.72]	1.88[0.00,27173.57]	1.08[0.00,873.06]	1.99[0.00,4125.74]	1.79[0.00,242801.62]	1.76[0.00,697.15]	3.94[0.00,597195.61]	15.71[0.00,268337.29]	3.14[0.00,52575.21]	

Fibrosis score	No active intervention	Dietary advice plus exercise advice	Supervised aerobic exercise and resistance exercise
No active intervention		-0.02[-0.58,0.54]	-0.52[-1.50,0.46]
Dietary advice plus exercise advice	-0.02[-0.57,0.54]		-
Supervised aerobic exercise and resistance exercise	-0.52[-1.51,0.47]	-0.50[-1.63,0.64]	

NAFLD Activity Score (NAS)	Aerobic exercise	Calorie restricted diet	Dietary advice	Aerobic exercise plus carbohydrate restricted diet	Aerobic exercise plus fat restricted diet
Aerobic exercise		*-3.00[-4.40,-1.60]*	0.40[-1.00,1.80]	0.20[-1.20,1.60]	-0.40[-1.80,1.00]
Calorie restricted diet	*-3.00[-4.37,-1.63]*		-	-	-
Dietary advice	0.39[-0.98,1.80]	*3.39[1.44,5.37]*		-0.20[-1.60,1.20]	-0.80[-2.20,0.60]
Aerobic exercise plus carbohydrate restricted diet	0.20[-1.18,1.58]	*3.20[1.23,5.14]*	-0.20[-1.59,1.18]		-0.60[-2.00,0.80]
Aerobic exercise plus fat restricted diet	-0.40[-1.78,0.97]	*2.60[0.63,4.53]*	-0.80[-2.20,0.59]	-0.60[-1.97,0.78]	

The 95% credible intervals of the probability ranks were wide, and included 0 and 1 in most comparisons for all the outcomes. This was probably because of the sparse data from small trials. We therefore did not present the ranking probabilities (in a table), rankograms, and SUCRA plots, as we considered that presenting this information

would be unhelpful and potentially misleading, and it would ignore the differences in systematic errors in the trials.

The certainty of evidence was moderate, low, or very low for all the comparisons. This was because all the trials included in the comparisons (except for two trials: Misciagna 2017; Monica Dinu 2017) were at unclear or high risk of bias for at least one risk of bias domain at the outcome level (downgraded by one level). For all direct comparisons and network meta-analysis, the number of events were fewer than 300 and we downgraded by one level for imprecision. In comparisons involving clinical outcomes, the credible intervals were wide and overlapped significant clinical effect and no effect: we therefore downgraded by one more level for imprecision. We were unable to check for heterogeneity for any of the clinical outcomes. Overall, the downgrading of evidence resulted in very low certainty of evidence for all comparisons other than the comparisons of Mediterranean diet versus no active intervention (Misciagna 2017) and Khorasan wheat versus organic semi-wholegrain wheat (Monica Dinu 2017), which were low-certainty evidence.

Mortality

Fourteen trials (1216 participants) reported mortality at maximum follow-up of 2 months to 24 months (Al-Jiffri 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Dong 2016; Zhang 2016; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018; Abdelbasset 2019; Johari 2019; Moradi 2020). A total of 12 interventions (aerobic exercise, calorie-restricted diet, dietary advice, dietary and exercise advice, fat-restricted diet, Mediterranean diet, aerobic exercise plus calorie-restricted diet, aerobic exercise plus dietary advice, resistance exercise, Khorasan wheat-based diet, organic semi-wholegrain-based diet, and no active intervention) were compared with each other in these trials. There were no deaths among 951 participants in 13 of the trials (Al-Jiffri 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Zhang 2016; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018; Abdelbasset 2019; Johari 2019; Moradi 2020). The evidence was of very low certainty for the comparisons in 11 trials (813 participants; no events; (Al-Jiffri 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Zhang 2016; Axley 2017; Schattenberg 2017; Properzi 2018; Abdelbasset 2019; Johari 2019; Moradi 2020)) and of low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; Misciagna 2017) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)). In the remaining trial, there were five deaths among 265 participants (1.9%) during a follow-up period of 24 months (Dong 2016). In this trial, which compared dietary advice plus exercise advice versus no active intervention, two died of cardiovascular diseases, two died of cancers, and one died of a car accident (Dong 2016). The type of cancer leading to the death was not reported. Overall, there was no evidence of difference between dietary advice versus no active intervention: hazard ratio (HR) 0.63 (95% CrI 0.07 to 4.06; 1 trial, 265 participants; very low-certainty evidence).

Quality of life

One trial (48 participants) reported quality of life at three months (Properzi 2018). The quality-of-life scale used was the Assessment of Quality Of Life (AQoL-8D) tool. A total of two interventions (Mediterranean diet versus fat-restricted diet) were compared in this trial. Since only one trial reported the outcome, meta-analysis could not be performed.

There was no evidence of difference in the health-related quality of life between Mediterranean diet versus fat-restricted diet: mean difference (MD) −2.89, 95% CrI −7.25 to 1.41; 1 trial, 48 participants; very low-certainty evidence.

Serious adverse events

Eight trials (448 participants) reported serious adverse events after a follow-up period of three to six months (Al-Jiffri 2013; Hickman 2013; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018; Yao 2018). However, none of the trials clearly reported whether they used the ICH-GCP definition or not. We considered adverse events reported as 'serious' or 'severe' as serious adverse events.

A total of 11 interventions were compared with each other in these trials: aerobic exercise, calorie-restricted diet, dietary advice, dietary exercise plus exercise advice, resistance exercise, fat-restricted diet, Mediterranean diet, aerobic exercise plus calorie-restricted diet, Khorasan wheat-based diet, organic semi-wholegrain-based diet, and no active intervention. None of the 448 participants in these trials developed serious adverse events. The evidence was of very low certainty for the comparisons in six trials (310 participants; no events; (Al-Jiffri 2013; Hickman 2013; Axley 2017; Schattenberg 2017; Properzi 2018; Yao 2018)) and of low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; (Misciagna 2017)) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)).

Any adverse events

Seven trials (426 participants) reported any adverse events after a follow-up period of three to six months (Al-Jiffri 2013; Hickman 2013; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018; Yao 2018). However, none of the trials clearly reported whether or not they used the ICH-GCP definition. We considered events reported as 'adverse events' as any adverse events.

A total of 10 interventions (aerobic exercise, calorie-restricted diet, dietary advice, resistance exercise, fat-restricted diet, Mediterranean diet, aerobic exercise plus calorie-restricted diet, Khorasan wheat-based diet, organic semi-wholegrain-based diet, and no active intervention) were compared with each other in these trials. In six trials, none of the 335 participants developed any adverse events. The evidence was of very low certainty for the comparisons in four trials (288 participants; Al-Jiffri 2013; Hickman 2013; Schattenberg 2017; Properzi 2018) and of low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; (Misciagna 2017)) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)). In the remaining trial, which was three-armed, one of 31 participant (3.2%) who received resistance exercise developed one adverse event (bone fracture by falling down, but not during the exercise sessions; (Yao 2018)). None of the participants in this trial who underwent aerobic exercise (0/29 participants) or no active intervention (0/31) developed any adverse events. The evidence was of very low certainty in the comparisons included in this trial. We did not perform a formal calculation of effect estimates because of the sparse data, i.e. the

only trials for the comparisons included zero events for at least one of the groups.

Liver transplantation

Seven trials (411 participants) reported liver transplantation at maximum follow-up of 3 to 12 months (Hickman 2013; Wong 2013; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018). A total of 10 interventions (aerobic exercise, calorie-restricted diet, dietary advice, dietary exercise plus exercise advice, fat-restricted diet, Mediterranean diet, aerobic exercise plus dietary advice, Khorasan wheat-based diet, organic semi-wholegrain-based diet, and no active intervention) were compared with each other in these trials. None of the participants in these seven trials underwent liver transplantation. The evidence was of very low certainty for the comparisons in five trials (273 participants; no events; (Hickman 2013; Wong 2013; Axley 2017; Schattenberg 2017; Properzi 2018)) and of low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; (Misciagna 2017)) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)).

Decompensation

Seven trials (411 participants) reported liver decompensation after a maximum follow-up of 3 to 12 months (Hickman 2013; Wong 2013; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018). A total of 10 interventions (aerobic exercise, calorie-restricted diet, dietary advice, dietary exercise plus exercise advice, fat-restricted diet, Mediterranean diet, aerobic exercise plus dietary advice, Khorasan wheat-based diet, organic semi-wholegrain-based diet, and no active intervention) were compared with each other in these trials. None of the participants in these seven trials developed liver decompensation. The evidence was of very low certainty for the comparisons in five trials (273 participants; no events; (Hickman 2013; Wong 2013; Axley 2017; Schattenberg 2017; Properzi 2018)) and of low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; (Misciagna 2017)) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)).

Cirrhosis

Seven trials (411 participants) reported liver cirrhosis after a maximum follow-up of 3 to 12 months (Hickman 2013; Wong 2013; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018). A total of 10 interventions (aerobic exercise, calorie-restricted diet, dietary advice, dietary advice plus exercise advice, dietary advice plus aerobic exercise, fat-restricted diet, Mediterranean diet, Khorasan wheat-based diet, organic semi-wholegrain-based diet, and no active intervention) were compared with each other in these trials. In six trials, none of the 390 participants developed liver cirrhosis. The evidence was of very low certainty for the comparisons in four trials (252 participants; no events; Wong 2013; Axley 2017; Schattenberg 2017; Properzi 2018) and low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; (Misciagna 2017)) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)). In one trial, 2 of 13 (15.4%) participants developed cirrhosis in the aerobic-exercise group after a follow-up of six months; none of the eight participants in the calorie-restricted diet group developed cirrhosis in this trial (Hickman 2013). This trial included non-diabetic people with and without NASH, and the evidence was of very low certainty. We did not calculate effect estimates for this trial because of the sparse data, i.e. the only trial for this comparison included zero events for one of the groups (very low-certainty evidence).

Hepatocellular carcinoma

Five trials (229 participants) reported hepatocellular carcinoma after a maximum follow-up of three to six months (Hickman 2013; Axley 2017; Misciagna 2017; Monica Dinu 2017; Properzi 2018). A total of eight interventions (aerobic exercise, calorie-restricted diet, dietary exercise plus exercise advice, fat-restricted diet, Mediterranean diet, Khorasan wheat-based diet, organic semi-wholegrain-based diet, and no active intervention) were compared with each other in these trials. None of the participants in these five trials developed hepatocellular carcinoma. The evidence was of very low certainty for the comparisons in three trials (91 participants; no events; Hickman 2013; Axley 2017; Properzi 2018) and low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; (Misciagna 2017)) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)).

Liver-related mortality

Among the 14 trials which reported mortality, there were deaths in only one trial (Dong 2016) (please see 'Mortality at maximum follow-up'). The reasons for death in this trial were cardiovascular diseases (2), cancers (2), and a car accident (1) (Dong 2016). The type of cancer leading to the death was not reported and our attempts to contact the authors were unsuccessful. It is therefore not clear whether there was liver-related mortality in this trial: the trial could not be included for the analysis of liver-related mortality. In the remaining 13 trials (951 participants), there were no deaths from any cause (including liver-related causes) after a follow-up of 2 to 12 months (Al-Jiffri 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Zhang 2016; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018; Abdelbasset 2019; Johari 2019; Moradi 2020). The evidence was of very low certainty for the comparisons in 11 trials (813 participants; no events; Al-Jiffri 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Zhang 2016; Axley 2017; Schattenberg 2017; Properzi 2018; Abdelbasset 2019; Johari 2019; Moradi 2020) and of low certainty for the Mediterranean diet versus no active intervention trial (98 participants; no events; (Misciagna 2017)) and the Khorasan wheat-based diet versus organic semi-wholegrain-based diet (40 participants; no events; (Monica Dinu 2017)).

Exploratory outcomes

Resolution of fatty liver disease

Thirteen trials (1019 participants) reported resolution of fatty liver disease at maximum follow-up of 1 to 24 months (Wang 2008; Bacchi 2013; Hickman 2013; Wong 2013; Dong 2016; Rezende 2016; Cheng 2017; Misciagna 2017; Monica Dinu 2017; Roy 2017; Chan 2018; Properzi 2018; Nourian 2020). A total of 14 interventions (aerobic exercise, calorie-restricted diet, dietary exercise plus exercise advice, resistance exercise, supervised aerobic exercise, fat-restricted diet, Mediterranean diet, dietary advice, aerobic exercise plus dietary advice, aerobic exercise plus calorie- and fat-restricted diet, supervised aerobic exercise plus calorie-restricted diet, Khorasan wheat-based diet, organic semi-wholegrain wheat-

based diet, and no active intervention) were compared with each other in these trials. The weighted median proportion of participants who developed resolution of fatty liver was 6.8%.

One trial (57 participants) comparing aerobic exercise plus calorie- and fat-restricted diet (38 participants) versus no active intervention (19 participants) was not connected to the network because it had zero events in both arms after a follow-up period of one month (Wang 2008). Another trial (57 participants) comparing resistance exercise (36 participants) versus no active intervention (33 participants) was not connected to the network because it had zero events in one of the arms after a follow-up period of two month (Nourian 2020). We did not calculate the effect estimate for these trials because of their sparse data, i.e. the only trials for these comparisons included zero events in at least one of the groups. One trial (40 participants) was not included in the network meta-analysis because the treatments in this trial (Khorasan wheat diet, organic semi-wholegrain wheat diet) were not connected to the network (Monica Dinu 2017). There was no evidence of differences in resolution of fatty liver disease between the Khorasan wheat diet and organic semi-wholegrain wheat diet groups The remaining 10 trials (853 participants) were included in the network meta-analysis. A total of 10 interventions (aerobic exercise, calorie-restricted diet, dietary exercise plus exercise advice, resistance exercise, supervised aerobic exercise, fat-restricted diet, Mediterranean diet, aerobic exercise plus dietary advice, supervised aerobic exercise plus calorie-restricted diet, and no active intervention) were included in the network.

Direct comparisons

The first intervention had higher resolution of fatty liver disease than the second intervention in the following direct comparisons:

- Aerobic exercise plus dietary advice versus no active intervention: HR 4.72, 95% CrI 2.69 to 8.83; 1 trial, 154 participants;
- Supervised aerobic exercise plus calorie-restricted diet versus no active intervention: HR 5.45, 95% CrI 1.36 to 40.13; 1 trial, 41 participants;
- Supervised aerobic exercise plus calorie-restricted diet versus supervised aerobic exercise: HR 4.17, 95% CrI 1.24 to 20.27; 1 trial, 45 participants.

The first intervention had lower resolution of fatty liver disease than the second intervention in the following direct comparisons:

- Supervised aerobic exercise versus calorie-restricted diet: HR 0.26, 95% CrI 0.05 to 0.90; 1 trial, 44 participants;
- Mediterranean diet versus fat-restricted diet: HR 0.26, 95% CrI 0.05 to 0.91; 1 trial, 48 participants.

There was no evidence of differences between the treatments in the remaining direct comparisons, i.e. the remaining direct comparisons were not statistically significant), as shown in Table 6.

Network meta-analysis

There was no evidence of inconsistency according to model fit and inconsistency factor, but there was evidence of inconsistency based on the between-design variance: the between-design variance was 7.39 (95% CrI 0.04 to 23.89). The between-study variance was 8.90 (95% CrI 0.62 to 23.83). In the network meta-analysis, and there was no evidence of differences in any of the comparisons (Table 6).

Fibrosis score

Six trials (491 participants) reported fibrosis score (Dong 2016; Kaliora 2016; Houghton 2017; Oh 2017; Katsagoni 2018; Properzi 2018). A total of 11 treatments were compared with each other in these trials (aerobic exercise, dietary advice plus exercise advice, dietary advice, resistance exercise, fat restricted diet, Mediterranean diet, raisins plus dietary advice, Mediterranean diet plus dietary advice, Mediterranean diet plus dietary advice plus exercise advice, supervised aerobic exercise plus resistance exercise, and no active intervention). Four trials were not connected to the network because they had treatments unconnected to network (Kaliora 2016; Oh 2017; Katsagoni 2018; Properzi 2018). The network therefore has only two trials and three treatments (dietary advice plus exercise advice, supervised aerobic exercise plus resistance exercise, and no active intervention). There were no triangular or quadrangular loops, so inconsistency was not checked. Only one trial was included in each of the comparisons, so only a fixed-effect model is applicable.

There was no evidence of difference in any of the direct comparisons or the network meta-analysis, i.e. there was no statistically significant difference in any of the comparisons (Table 6).

NAFLD activity score

Two trials (62 participants) reported NAFLD activity score (Eckard 2013; Hickman 2013). A total of five treatments were compared with each other in these two trials (calorie-restricted diet, dietary advice, aerobic exercise plus carbohydrate-restricted diet, aerobic exercise plus fat-restricted diet, and aerobic exercise). Both the trials were connected to the network.

Direct comparisons

Calorie-restricted diet had a lower NAFLD activity score than aerobic exercise: MD −3.00 (95% CrI −4.40 to −1.60); 1 trial, 21 participants.

There was no evidence of differences between the treatments in the remaining direct comparisons, i.e. the remaining direct comparisons were not statistically significant, as shown in Table 6.

Network meta-analysis

The only triangular and quadrangular loops were because of a four-armed trial (Eckard 2013); inconsistency was therefore not checked. Only one trial was included in each of the comparisons, so only a fixed-effect model is applicable.

Calorie-restricted diet had a lower NAFLD activity score than aerobic exercise: MD −3.00 (95% CrI −4.37 to −1.60); direct comparison: MD −3.00 (95% CrI −4.40 to −1.60); 1 trial; 21 participants.

In the network meta-analysis, the first intervention had a higher NAFLD activity score than second intervention in the following comparisons.

- Dietary advice versus aerobic exercise: MD 3.39, 95% CrI 1.44 to 5.37; 1 trial; no direct comparison
- Aerobic exercise plus carbohydrate-restricted diet versus aerobic exercise: MD 3.20, 95% CrI 1.23 to 5.14; no direct comparison

- Aerobic exercise plus fat-restricted diet versus aerobic exercise: MD 2.60, 95% CrI 0.63 to 4.53; no direct comparison

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (Table 6).

MELD score

None of the trials reported that they measured MELD score.

Subgroup analysis

We did not perform any subgroup analysis. This is because of the sparse data (as described above).

Sensitivity analysis

'Best-worst' and 'worst-best' scenario analyses

We performed the 'best-worst' and 'worst-best' scenario analyses for the sensitivity analysis related to missing outcome data for the only outcomes with binomial distribution where formal analyses were performed: mortality and fatty liver resolution.

For mortality, dietary advice had lower mortality than no active intervention when the best-worst scenario analysis was used; dietary advice had higher mortality than no active intervention when the worst-best scenario analysis was used. These results should therefore be interpreted with caution, as the results are susceptible to attrition bias resulting from post-randomisation dropouts.

There were no changes to interpretation of the results for fatty liver resolution based on best-worst or worst-best scenario analyses. The comparisons for fatty liver resolution are therefore robust to post-randomisation dropouts.

Imputation of standard deviation

We did not perform any imputation of standard deviation.

Assessment of reporting biases

We performed a thorough search of the literature, including searches of the trial registers. We therefore identified most of the published or registered studies in the clinical trials register. Since the first publication report of a trial is 2008, we expect that we have identified most registered trials on the topic.

Since there was no meaningful way in which to order these studies, i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time, noting that the first published report for this review was in 2008, we were unable to perform a comparison-adjusted funnel plot. Important clinical outcomes were not reported in many trials, despite the high probability of being recorded.

DISCUSSION

Summary of main results

We performed a systematic review and network meta-analysis of lifestyle modifications for nonalcohol-related fatty liver disease (NAFLD). We included a total of 59 trials (3631 participants) in this review. The trials compared 33 interventions. Twenty-eight trials including 1942 participants were included for one or more comparisons of this review (Wang 2008; Al-Jiffri 2013; Bacchi 2013; Eckard 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Dong 2016; Kaliora 2016; Rezende 2016; Zhang 2016; Axley 2017; Cheng 2017; Houghton 2017; Misciagna 2017; Monica Dinu 2017; Nikroo 2017; Oh 2017; Roy 2017; Schattenberg 2017; Chan 2018; Katsagoni 2018; Properzi 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Moradi 2020; Nourian 2020). The remaining trials did not report any of the outcomes of interest for this review.

The follow-up period in the trials that reported primary or secondary outcomes was 2 months to 24 months. During this follow-up period, clinical events related to NAFLD such as mortality, liver cirrhosis, liver decompensation, and liver transplantation were sparse. This is probably because of the very short follow-up period. It takes a follow-up of 8 to 28 years to detect differences in mortality between people with NAFLD and the general population (Adams 2005; Bedogni 2007; Ong 2008; Soderberg 2010; Onnerhag 2014). It is therefore unlikely that differences in clinical outcomes will be apparent in trials with less than 5 to 10 years of follow-up.

Because these were lifestyle interventions, there is no mandatory requirement to record and report adverse events. In the one trial that reported that a participant developed an adverse event (Yao 2018), the adverse event did not seem to be directly related to the intervention. While there were some differences between the treatments in the surrogate outcomes, the implication of these differences for clinical outcomes are not known. There is therefore considerable uncertainty about whether any of the lifestyle interventions are beneficial in people with NAFLD. We note that there is also considerable uncertainty whether any pharmacological interventions work in NAFLD (Lombardi 2017) and whether any of the nutritional supplements work in NAFLD (Komolafe 2021). However, this does not mean that there is nothing we can do for people with NAFLD: NAFLD decreases life expectancy and increases liver cirrhosis, hepatocellular carcinoma, and requirement for liver transplantation (Adams 2005; Bedogni 2007; Ong 2008; Soderberg 2010; White 2012; Onnerhag 2014; Angulo 2015; Ekstedt 2015; Piscaglia 2016; Cholankeril 2017).

It is unlikely that the ongoing trials will provide an answer as to whether any of the lifestyle interventions improve clinical outcomes in people with NAFLD. As mentioned earlier, it is unlikely that we will be able to detect any differences in important clinical outcomes before 5 to 10 years. It is important that the lifestyle interventions that are proposed are affordable and sustainable over this period of time. In terms of intervention, this systematic review suggests that some surrogate outcomes such as resolution of fatty liver may increase with aerobic exercise combined with general dietary advice or calorie-restricted diet. There is no current evidence that any specific method to improve adherence to lifestyle interventions is effective in people with NAFLD. Neither is there high-quality and strong evidence that any specific method to improve adherence to lifestyle interventions is effective in people with obesity. But potential interventions to improve adherence to lifestyle, include counselling approaches such as motivational interviewing and self-monitoring using digital technologies (Cavero-Redono 2020; Suire 2020) could be investigated as part of a complex factorial trial design. In terms of the outcomes, the major clinical outcomes should include mortality, health-related quality of life, decompensated liver cirrhosis, and liver transplantation.

Sample size estimation for a parallel RCT was made based on two studies of the natural history of NAFLD that followed participants

for a median period of around eight years (Adams 2005; Bedogni 2007). The proportion of participants who died was approximately 6% (Bedogni 2007) and 12.6% (Adams 2005). The hazard ratio for mortality of people with NAFLD versus those without NAFLD was 1.34 (Adams 2005) and 1.47 (Bedogni 2007). It is therefore reasonable to expect a 20% relative reduction in mortality by the intervention, but even this will mean that the mortality in people with NALFD is higher than in those without NAFLD. If we assumed a proportional hazards model with an alpha error of 0.05, power of 0.9, and the mortality of people who received standard care to be 9% at eight years, and we estimated a 20% reduction in mortality by the intervention, with a recruitment period of three years and follow-up period of eight years, we would need 3610 participants in each group prior to loss to follow-up (PS: Power and Sample Size Calculation).

Clearly, such a trial would be expensive to conduct. Some recent and innovative trial designs may allow the conduct of NAFLD trials powered to detect differences in clinically important outcomes rather than relying on unvalidated surrogate outcomes. There are no national registries for NAFLD which can be used for registry-based RCTs. The existing registries for NAFLD, such as European NAFLD, European paediatric NAFLD, and TARGET-NASH study register are observational studies with bio-banking facilities (Barritt 2017; Mann 2018; Hardy 2020). Establishment of a research registry for NAFLD will allow efficient large-scale RCTs (James 2015). In the absence of such registries, another efficient and innovative study design is the cohort multiple RCT (cmRCT; (Relton 2010)), although a staged-informed consent in the design is less contentious in terms of ethical concerns (Young-Afat 2016) than the originally proposed design of cmRCT where some participants do not know of their participation in an RCT (Relton 2010). There are methodological differences such as sample size calculations in such cmRCTs compared to the standard parallel RCT design (Reeves 2018). Furthermore, below a certain proportion of participants allocated to the intervention group consenting to undergo the intervention, the efficiency of cmRCT is lost (Reeves 2018). Because of these methodological challenges, feasibility studies may be necessary to determine the optimal design of a cmRCT. Some innovations such as follow-up based on national electronic health record data (the participants should be consented for linking their details to national electronic health record data at the time of consenting to trial participation) will allow assessment of outcomes such as mortality, liver transplantation, and liver cirrhosis for several decades. However, the use of national electronic health record data brings its own challenges, such as data quality and validation, completeness of data capture, and heterogeneity among systems for international trials (Cowie 2017). Besides, the use of national electronic health record data does not allow the capture of health-related quality of life. Potential solutions include self-reported health-related quality of life and measuring the health-related quality of life in a sample of participants, but there is no current evidence about the validity of these approaches or the inherent biases. Nesting methodological research projects within NAFLD trials can therefore determine the optimal trade-off between the most valid and most efficient study designs in trials involving people with NAFLD.

Overall completeness and applicability of evidence

The trials included only NAFLD people with and without NASH. The results of the review are therefore only applicable to people with NAFLD, with or without NASH, who are able to undergo these interventions. The results are not applicable to people who had previously undergone liver transplantation. Different studies used different methods of diagnosis of NAFLD. Having a consensus on minimum standards for definition of NAFLD in clinical trials can help with the applicability of the evidence from future trials.

It should also be noted that the studies made the diagnosis of NAFLD based on the presence of fatty liver in the absence of excessive alcohol consumption. However, there is ongoing debate about what constitutes excessive alcohol consumption in the context of fatty liver (Eslam 2019). It is therefore possible that the fatty liver may have been caused by alcohol consumption, although such alcohol consumption would be considered non-excessive using the current definition of NAFLD. The findings of the review are applicable to people with NAFLD under the current definitions in 2021. This might change in the future if the nomenclature for fatty liver is changed.

Because of the general belief and health-promotion policies of various governments, it is possible that once people are diagnosed with NAFLD they improve their lifestyle without any additional interventions such as additional dietary advice or intensive exercise regimens. The review therefore addresses only the question of whether interventions work that are aimed at lifestyle modifications in people with NAFLD in addition to public health promotion, rather than whether such lifestyle modifications work in the absence of public health promotion, or whether public health promotions work.

It should be noted that we have covered only lifestyle interventions in this review. Any dietary intervention that resulted in an increase in a potential mediator of change in outcomes, if the potential mediator was isolated and manufactured as a nutritional supplement, this was covered in a nutritional supplementation review (Komolafe 2021). The findings of the review are therefore applicable only to lifestyle interventions and not to nutritional supplementation. However, we did not find any nutritional supplementation that improved clinical outcomes in NAFLD (Komolafe 2021).

The review only provides evidence about what happens within the first two years and does not provide any information on what happens beyond two years.

Quality of the evidence

The overall certainty (quality) of evidence varied between moderate, low, and very low. One of the main reasons for this was the unclear or high risk of bias in all but two trials (Misciagna 2017; Monica Dinu 2017). To provide some information on whether It is possible to perform trials at low risk of bias, we have considered each source of bias. This can give a context for interpretation of the information.

Randomisation can be performed using standard methods, for example, web-based central randomisation; an intention-to-treat analysis can be performed; and a protocol should be published prior to recruitment. However, blinding of healthcare providers and participants may not be possible if advice or exercise interventions are used as one of the interventions. However, it is possible to achieve low risk of performance bias by outlining the protocol clearly for any additional investigations and treatments. Outcome

assessor blinding can be achieved for all comparisons by use of an observer blinded to the groups to assess the outcomes. If that is not possible, using clear highly-reproducible criteria for outcome definitions can decrease detection bias. Even if we exclude lack of blinding while assessing the overall risk of bias, only the same two trials were at low risk of bias (Misciagna 2017; Monica Dinu 2017). Another major reason for the decreased certainty of evidence was imprecision. Clinical events were extremely sparse, resulting in difficulty undertaking a formal analysis, or in the rare instance when calculation of an effect estimate was possible, the credible intervals were extremely wide. The designs of ongoing trials suggest that this imprecision cannot be addressed by these ongoing trials. We used clinical outcomes, meaning that there is no issue of indirectness due to outcomes. There was no suggestion that the potential effect modifiers were systematically different across comparisons, i.e. there was no concern about the transitivity assumption for most outcomes. However, we were unable to perform a formal analysis to assess this because of sparse data. We therefore cannot rule out inconsistency ('incoherence' according to GRADE terminology).

There was no meaningful way to order these studies, i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time, noting that the first trial dates back only to 2008 and there is no evidence that any additional intervention works.

We have completed a thorough search for studies on effectiveness. However, only 15 of 59 (25.4%) trials reported mortality; fewer trials reported other clinical outcomes. These are outcomes which would have been recorded in trials of this nature, but were not reported. Many of them were considered as core outcome measures (Clearfield 2021). We acknowledge that the publication of the core outcome set is very recent, but we expect reporting of the clinical outcomes, even if the primary outcomes of these studies were surrogate outcomes. This may suggest reporting bias for these outcomes.

Potential biases in the review process

We selected a range of databases to search without using any language restrictions, and conducted the network meta-analysis according to NICE DSU guidance. We have also conducted analyses using the fixed-effect model and random-effects models, and assessed and reported inconsistency whenever possible (this was possible only for the exploratory outcomes because of the sparse clinical data). These are the strengths of the review process. We have excluded studies that only compared variations in duration or intensity in the same intervention (treatment node). Hence, this review does not provide information on whether one variation is better than another. The potential effect modifiers in the trials that reported them were broadly similar across comparisons. Concern about the transitivity assumption is therefore low, but cannot be ruled out. However, given the very large uncertainty in the results due to sparse data, this is only of academic interest. We included only randomised clinical trials which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. A significant effort is required to identify non-randomised studies that report on harm, with challenges in assessing their risks of bias. If the ongoing trials result in adequate power to find meaningful differences in mortality and other clinically important outcomes and if the adverse events are collected systematically, a systematic review on adverse events from observational studies may be unnecessary.

Agreements and disagreements with other studies or reviews

This is the first network meta-analysis on the impact of different lifestyle interventions on clinical outcomes in people with NAFLD. We are therefore unable to compare our conclusions with those of other reviews. Our conclusions differ from those of many study authors included in this review, because we relied on clinical outcomes rather than surrogate outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence indicates considerable uncertainty about the effects of the lifestyle interventions compared with no additional intervention to general public health advice on any of the clinical outcomes after a short follow-up period of 2 months to 24 months in people with NAFLD.

Implications for research

Further well-designed randomised clinical trials are necessary. Some aspects of the design of the randomised clinical trials are as follows.

Study design: registry-based randomised clinical trial or cohort multiple randomised clinical trial (cmRCT)

Participants: people with NAFLD

Interventions/control: aerobic exercise and dietary advice versus standard of care (exercise and dietary advice received as part of national health promotion)

Outcomes: *Primary outcome:* mortality. *Secondary outcomes:* health-related quality of life, decompensated liver cirrhosis, liver transplantation, and resource-use measures including costs of intervention, decreased healthcare use. *Minimum length of follow-up:* eight years

Sample size: If we assume a proportional hazards model, alpha error of 0.05, power of 0.9, with mortality of people who received standard care to be 9% at eight years, estimating a 20% reduction in mortality by the intervention, and a recruitment period of three years and follow-up period of eight years, one would need 3610 participants in each group prior to loss to follow-up.

Adjustments to sample size should be made to reflect the loss to follow-up and the proportion of participants who accept the intervention in cmRCT.

Other aspects: trials need to be conducted and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013) and CONSORT statement (Schulz 2010). Methodological research within trials may help with conducting trials in the optimal way.

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The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the 16/114/17 or 14/178/29 Programmes, the NIHR, the NHS, or the Department of Health.

Danish State and The Copenhagen Trial Unit Disclaimer

The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abbate 2021

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 155 Post-randomisation dropouts: 27 (17.4%) Revised sample size: 128 Reasons for post-randomisation dropouts: withdrew consent, lost to follow-up, missing baseline data, complications Average age: 53 years Female: 50 (39.1%) NASH: not stated Diabetes mellitus: 29 (22.7%). Follow-up in months: 6 Years of recruitment: 2018 - 2020

Abbate 2021 *(Continued)*

	Inclusion criteria: aged 40 to 60 years, previous diagnosis of NAFLD by liver ultrasound, body mass index (BMI) between 27 and 40 kg/m^2, and presenting at least 3 of the 5 MetS traits as described in the International Diabetes Federation (IDF) consensus: (1) BMI > 30 kg/m^2 or increased waist circumference: ≥ 94 cm in men and ≥ 80 cm in women; (2) triglycerides (TG) levels ≥ 150 mg/dL (1.7 mmol/L), or specific treatment; (3) reduced high-density lipoprotein cholesterol (HDL-C): < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women, or specific treatment; (4) raised blood pressure (BP): systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension; (5) raised fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L), or previously-diagnosed type 2 diabetes (T2DM) Exclusion criteria: previous cardiovascular disease, liver disease (other than NAFLD), cancer or a history of malignancy in the previous 5 years, haemochromatosis, previous bariatric surgery, non-medicated depression, alcohol and drug abuse, pregnancy, primary endocrinological diseases (other than non-medicated hypothyroidism), concomitant therapy with steroids, or inability to provide informed consent
Interventions	Participants were randomly assigned to 3 groups. Group 1: Mediterranean diet plus supervised aerobic exercise (n = 43) Further details: American Association for the Study of Liver Disease (AASLD) recommendations [1] with energy restriction enough to lose 3% – 5% of body weight to improve steatosis, and 7% – 10% to improve most of the histopathological features of NASH, including fibrosis, following the general guidelines of the U.S. Department of Health and Human Services and U.S. Department of Agriculture (20% – 35% fat, 10% – 35% protein, 45% – 65% carbohydrate) + instructed to accumulate a minimum of 10,000 steps a day (recorded by a personal pedometer) Group 2: Mediterranean diet plus exercise advice (n = 43) Further details: The Mediterranean Diet–high meal frequency (MD-HMF) group, which was instructed to adhere to a Mediterranean Diet based on a distribution of macronutrients of 30% – 35% fat (mainly MUFA and PUFA from extra virgin olive oil, nuts, and omega-3-containing foods), 25% protein (mainly from vegetable sources), and 40% – 45% carbohydrates (50% – 70% of the total carbohydrate intake should be low on glycaemic index and rich in fibre). The total daily caloric intake of this diet was distributed over 7 meals, with the highest calorie meals to be consumed early during the day + instructed to accumulate a minimum of 10,000 steps a day (recorded by a personal pedometer) Group 3: Calorie-restricted diet plus exercise advice (n = 42) Further details: The Mediterranean Diet–physical activity (MD-PA) group, which followed an energy-restricted Mediterranean diet. Meal frequency would be 4 – 5 meals a day including snacks. This group consumed 35% – 40% of total calories from fat (8 – 10% of Saturated Fatty Acids, > 20% of MUFA, > 10% of PUFA and < 300 mg/day of cholesterol), approximately 20% of total calories from proteins and 40 – 45% or more of total calories from carbohydrates (low glycaemic index). Sodium chloride should not exceed 6 g a day (2.4 g of sodium), and dietary fibre should be no less than 30 - 35 g/day + instructed to undergo 35 min interval training session 3 times a week, in the combination of 2 instructor-led on-site training and 1 remote prescribed training session a week for the whole duration of the trial
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "Fundació La Marató TV3 (Spain) project ref. 201630.10. Instituto de Salud Carlos III through the Fondo de Investigación para la Salud (Projects PI14/00636 and PI17/01827, and CIBEROBN CB12/03/30038, and Proyecto Intramural CIBER OBN18PI03), Health Department of the Government of Navarra (61/2015), and Grant of support to research groups no. 35/2011 and 23/2012 (Balearic Islands Government), which are co-funded by the European Regional Development Fund. Other funding received: EU-COST Action CA16112, and IDISBA Grants (FOLIUM, PRIMUS, SYNERGIA, and LIBERI). Catalina M. Mascaró received an FPU PhD Grant from the Spanish Ministry of Education". Trial name/trial registry number: NCT04442620 We tried to contact the authors in March 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out using the MinimPy desktop minimization program".

Abbate 2021 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The randomization process was performed by a dedicated person and blinded to all staff and the principal investigator".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: a considerable proportion of participants were excluded from analysis. At least 1 participant was excluded for adverse events, which may be related to the intervention
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and none of the outcomes of interest for this review were reported
Other bias	Low risk	Comment: no other bias noted

Abdelbasset 2019

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Egypt Number randomised: 32 Post-randomisation dropouts: 0 (0%) Revised sample size: 32 Average age: 55 years Female: 13 (40.6%) NASH: not stated Diabetes mellitus: 32 (100%) Inclusion criteria All participants were diagnosed with NAFLD, type 2 diabetes mellitus and class II and III of obesity (BMI ≥ 35kg/m^2)
Interventions	Participants were randomly assigned to 2 groups Group 1: Aerobic exercise (n = 16) Further details: Each participant in this group followed a programme of high-intensity aerobic exercise for 8 weeks, 3 times a week with each exercise session lasting for nearly 40 minutes in the morning. Each participant was instructed to not eat for 2 hours before the exercise session to avoid exercise-induced airway obstruction Group 2: No active intervention (n = 16) Further details: No active intervention
Outcomes	Outcomes reported: mortality Follow-up (months): 1.84
Notes	Source of funding (quote): "The research did not secure any specific grant or source of funding from any specific organization in either the private or public sector" Trial name/trial registry number: not stated We tried to contact the authors in March 2021

Abdelbasset 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was applied using secured envelopes. The examiner arranged the secured envelopes, which contained a piece of colored paper indicating HII group and a piece of uncoloredpaper indicating control group". Comment: further details such as opaqueness of envelope and consecutive numbering were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Abdelbasset 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Saudi Arabia Number randomised: 48 Post-randomisation dropouts: 1 (2.1%) Revised sample size: 47 Reasons for post-randomisation dropouts: lack of adherence to intervention Average age: 55 years Female: 20 (42.6%) NASH: not stated Diabetes mellitus: 47 (100%) Inclusion criteria: Diabetic obese patients with NAFLD, aged 40 to 60 years
Interventions	Participants were randomly assigned to 2 groups Group 1: Aerobic exercise (n = 31) Further details: High-intensity or moderate-intensity aerobic exercise (decided by random allocation); high-intensity group: each participant in this group followed a programme of high-intensity aerobic exercise for 8 weeks, 3 times a week, each exercise session lasting for nearly 40 minutes in the morning. Moderate-intensity group, each participant in the exercise group was recruited to a MIC aerobic exercise programme 3 times weekly for 8 weeks, with a duration of exercise of nearly 40 to 50 minutes Group 2: No active intervention (n = 16)

Abdelbasset 2020 *(Continued)*

Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This publication was supported by the Deanship of Scientific Research at Prince Sattam bin Abdulaziz University" Trial name/trial registry number: NCT03774511 We tried to contact the authors in March 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was carried out before commencing the study program by blinded physiotherapist using secured envelopes, which included a piece of red sheet indicated HII group, a piece of green sheet indicated MIC group, and a piece of white sheet indicated control group"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 1 participant in this small trial was excluded because of lack of compliance. It is not clear whether this leads to biased effect estimates
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and none of the outcomes of interest for this review were reported
Other bias	Low risk	Comment: no other bias noted

Abd El-Kader 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Saudi Arabia Period of recruitment: not stated Number randomised: 100 Post-randomisation dropouts: not stated Revised sample size: 100 Average age (years): 51 Female: 30 (30.0%) NASH: 100 (100.0%) Diabetes mellitus: not stated Inclusion criteria: NASH Exclusion criteria: Smoking, cardiovascular disease, alcohol abuse, hepatic (infectious and viral disease) or renal disease

Abd El-Kader 2016 *(Continued)*

Interventions	Group 1: Aerobic exercise plus calorie-restricted diet (n = 50) Further details: 3 months of 3 x a week sessions, 30 min treadmill (5 min warm-up, 5 min cool down). 1200 low-calorie diet: 15% as protein, 30 to 35% as fat and 50 to 55% as carbohydrate, on average Group 2: No active intervention (n = 50) Further details: control group
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 3
Notes	Source of funding (quote): "funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under grant no.(324/290/1434)" Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were randomly allocated to the experimental group or control group. Each subject was given an envelope containing two cards and was instructed to blindly draw one card on each occasion"
Allocation concealment (selection bias)	Low risk	Quote: "The subjects were randomly allocated to the experimental group or control group. Each subject was given an envelope containing two cards and was instructed to blindly draw one card on each occasion"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This study was single blinded: the person undertaking the assessment and data analysis was unaware of the group of each patient"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Al-Jiffri 2013

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Saudi Arabia Period of recruitment: not stated Number randomised: 100 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 100 Average age (years): not stated

Al-Jiffri 2013 *(Continued)*

	Females: 0 (0.0%) NASH: not stated Diabetes mellitus: 100 (100.0%) Inclusion criteria: NAFLD with T2DM Exclusion criteria: other liver, metabolic or genetic diseases. Smoking, HTN, CV disease, thyroid disease, orthopaedic problems inhibiting treadmill training
Interventions	Group 1: Aerobic exercise plus calorie-restricted diet (n = 50) Further details: 3 months of 3 x a week sessions, 30 min treadmill (5 min warm-up, 5 min cool down). 1200 low-calorie diet: 15% as protein, 30 to 35% as fat and 50 to 55% as carbohydrate, on average Group 2: Calorie-restricted diet (n = 50) Further details: 1200 low-calorie diet: 15% as protein, 30 to 35% as fat and 50 to 55% as carbohydrate, on average
Outcomes	Outcomes reported: mortality at maximum follow-up, serious adverse events (number of people), any adverse events (number of people) Follow-up (months): 3
Notes	Source of funding (quote): "funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under grant no. (49/142/1432)" Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but mortality and adverse events were reported
Other bias	Low risk	Comment: no other bias noted

Arab 2017

Study characteristics

Methods	Randomised clinical trial

Arab 2017 *(Continued)*

Participants	Country: Iran Period of recruitment: not stated Number randomised: 82 Post-randomisation dropouts: 13 (15.9%) Revised sample size: 69 Reasons for post-randomisation dropouts: Did not follow special weight loss plan (3), recurrent lumbar disk (2), unknown reasons (8) Average age (years): 49 Female: 47 (68.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Presence of steatosis and ALT > 31 20 - 50 y/o, BMI ≥ 25, no alcohol Exclusion criteria: missing > 2 out of 8 sessions, weight loss in last 6 months, special dietary/physical activity regimens, menopause or pregnancy before or during intervention, use of medication with known effect on weight, psychosocial disorders, e.g. bulimia, anorexia nervosa, drug use, significant clinical depression, renal or other hepatic disease, malignancy, thyroid disorder and autoimmune disease
Interventions	Group 1: Dietary advice plus exercise advice (n = 41) Further details: 8 sessions of lifestyle modification education based on healthy-eating guidelines during 2 months in which food pyramid, my plate, and each food group in exchange list were expanded and explained for them. Also bad and good choices in each group were explained. Participants were encouraged to consume more fruit and vegetables, low-fat dairy, complex carbohydrates, white meat and fish and avoid the intake of unhealthy fats and refined carbohydrates. Moreover, 1 session was allocated to physical activity and regular 30 – 60 min exercise during at least 5 days of the week was recommended Group 2: No active intervention (n = 41) Further details: control group - treatment as usual
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "No financial support provided" Trial name/trial registry number: IRCT2016071211763N24 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out using computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes

Arab 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Asghari 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 60 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 60 Average age (years): 40 Female: 16 (26.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Aged 20 to 60 years, BMI from 25 to 35 kg/m^2, diagnosis of NAFLD via liver ultrasonography Exclusion criteria: pregnancy; breastfeeding and postmenopausal status; professional athlete status; smoking; consumption of any alcoholic beverages; following a weight-reducing diet within the 3 months before the study; known liver disease (viral, etc.); inherited disorders affecting the liver; history of diagnosed diabetes, thyroid dysfunction and cancer, or cardiovascular, kidney, gastrointestinal, pulmonary, or autoimmune diseases; recent surgery; use of medications such as corticosteroids, hepatotoxic drugs, hormonal drugs (e.g. oral contraceptives and/or oestrogen), antidepressants, psychotropic medications, anticoagulant drugs, or oral antidiabetic and lipid-lowering drugs; and consuming any kind of supplement 3 months prior to the study and/or during the study period
Interventions	Group 1: Calorie-restricted diet (n = 30) Further details: CR diet (received a prescribed low-calorie diet) for 12 weeks. Estimated energy requirements at baseline were individually calculated based on the Harris-Benedict equation with a deficit of 500 to 1000 kcal/d based on body weight, containing 53% carbohydrate, 30% fat, and 17% protein Group 2: No active intervention (n = 30) Further details: No active treatment (received 2 identical-appearing capsules to Resveratrol supplement per day each containing 300 mg starch used as placebo for an intervention excluded from this review) for 12 weeks
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random allocation software was used for generating a random sequence by the study statistician"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available

Asghari 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This study was partially blinded. Patients and researchers were unaware of assignments to resveratrol and placebo groups until the statistical analysis was completed." Comment: although partially blinded for the comparison resveratrol versus placebo (excluded from this review), the participants were probably aware of the interventions included in this review because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "This study was partially blinded. Patients and researchers were unaware of assignments to resveratrol and placebo groups until the statistical analysis was completed" Comment: although partially blinded for the comparison resveratrol versus placebo (excluded from this review), it was not clear whether the outcome assessors were blinded for the comparison of interest for this review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Axley 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 30 Post-randomisation dropouts: 8 (26.7%) Revised sample size: 22 Reasons for post-randomisation dropouts: Missed 6-month visit (8) Average age (years): 53 Female: 19 (86.4%) NASH: not stated Diabetes mellitus: 10 (45.5%) Inclusion criteria: Aged 25 - 75 with NAFLD on US with elevated liver enzymes Exclusion criteria: Other causes of liver disease, alcohol use > 10 g/day. Hx of decompensation, encephalopathy, as cited. Other significant medical/psychiatric or social conditions that would impair participation
Interventions	Group 1: Dietary advice plus exercise advice (n = 8) Further details: 6-month intervention: 3 uni- and bidirectional text messages every week. The messages provided education on different domains including nutrition, exercise and stress management of NAFLD and were sent at 9 am. All participants received standard of care for liver disease with detailed instructions in the clinic on healthy diet and daily exercise for weight loss Group 2: No active intervention (n = 14) Further details: control group - treatment as usual. All participants received standard of care for liver disease with detailed instructions in the clinic on healthy diet and daily exercise for weight loss
Outcomes	Outcomes reported: mortality at maximum follow-up, serious adverse events (number of people), liver transplantation at maximum follow-up, decompensation (number of people), cirrhosis (number of people), hepatocellular carcinoma

Axley 2017 *(Continued)*

	Follow-up (months): 6
Notes	Source of funding (quote): "This study was funded by a faculty development grant from the American College of Gastroenterology. Nina Parikh is affiliated with CareMessage, the text messaging software company that was used in this study." Trial name/trial registry number: NCT03082703 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Quote: "Study coordinator randomizing the patients and physicians evaluating the patients was blinded to the randomization group to which participants were allocated" Comment: although the precise method was not reported, it is clear that the person who randomised the participants was not aware of the next intervention
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Only healthcare professionals were blinded (author replies)" Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Study coordinator randomizing the patients and physicians evaluating the patients was blinded to the randomization group to which participants were allocated"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it was not clear whether these were related to the intervention or outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available, but mortality and adverse events were reported
Other bias	Low risk	Comment: no other bias noted

Bacchi 2013

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: 10 (25.0%) Revised sample size: 30 Reasons for post-randomisation dropouts: Abandoned study (1), lost to follow up - compliance to MRI (6), did not have NAFLD (2), discontinued intervention due to lack of time (1) Average age (years): 56 Female: 9 (30.0%) NASH: not stated Diabetes mellitus: 30 (100.0%)

Bacchi 2013 *(Continued)*

	Inclusion criteria: NAFLD, "Caucasian", aged 40 - 70 y/o, HbA1c 6.5 - 9.0%, BMI 24 - 36. No insulin use Exclusion criteria: advanced diabetic complications, unstable body weight over last 2 months, no other cause of liver disease and < 20 g alcohol/day
Interventions	Group 1: Resistance exercise (n = 17) Further details: 3 times a week for 4 months. Participants performed 9 different exercises involving the major muscle groups on weight machines (chest press, shoulder press, vertical traction, leg press, leg extension, leg curl, abdominal crunch) and free weight (biceps, abdominal). After a learning phase, participants performed 3 series of 10 repetitions at 70% - 80% 1-RM, with 1 minute of recovery between series Group 2: Aerobic exercise (n = 13) Further details: 3 times a week for 4 months. Participants exercised for 60 minutes per session at 60% - 65% of heart rate reserve, as estimated by the Karvonen formula.11 Aerobic activities were performed on treadmill, cycle, or elliptical machines, and participants were free to change the cardiovascular equipment used from 1 session to the next. Heart rate monitors were used to standardise exercise intensity
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up (months): 4
Notes	Source of funding (quote): "Supported in part by grants to Paolo Moghetti from the University ofVerona and from the Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy. The funding sources had no involvement in the design, execution or analysis of the study." Trial name/trial registry number: NCT01182948 - Subproject of RAED2 study We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A single radiologist, who was blinded to participants' clinical details, performed all MRI examinations" Comment: the radiologist who assessed the resolution of fatty liver (the only outcome reported in this trial) was blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Chan 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 52 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 52 Average age (years): 14 Female: 19 (36.5%) NASH: 1 (1.9%) Diabetes mellitus: not stated Inclusion criteria: Post-pubertal Chinese adolescents aged 14 – 18 years with primary obesity with BMI ≥ 95th centile of a local reference and fatty liver. Post-puberty was defined as either breast or genital Tanner stages being stage using a validated self-reported Pubertal Development Scale in Chinese. Exclusion criteria: history of viral hepatitis, alcohol consumption, concurrent participation in another clinical trial, chronic medical illness or being unwilling to attend regular follow-up appointments
Interventions	Group 1: Dietary advice plus exercise advice (n = 26) Further details: weekly patient-centred dietary consultation sessions for 16 weeks. Each participant was given an individualised menu plan. The dietary component and portion sizes of the menu plan were based on the recommendations of the U.S. Department of Health and Human Services and U.S. Department of Agriculture. Participants were encouraged to undergo 30-min aerobic exercise 2 to 3 times a week Group 2: No active intervention (n = 26) Further details: Usual clinical routine paediatric consultations, providing simple diet and exercise and information on medical complications such as NAFLD and metabolic syndrome, were conducted in the Obesity and Lipid Disorder Clinic every 16 weeks during both phase I and II periods. Participants were encouraged to reduce low-glycaemic index carbohydrate and animal fat intake, and to exercise for at least 2 to 3 times a week, 30 mins per session
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up (months): 16
Notes	Source of funding (quote): "The project was funded by a grant from the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (Ref. no: 11122981) and the Direct Grant for Research (Ref. no: 2014.1.065)." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned by computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Measurements were performed by a trained investigator blinded to group allocation of the study subjects"

Chan 2018 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention to treat analysis was performed
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Chen 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Number randomised: 44 Post-randomisation dropouts: not stated Revised sample size: 44 Average age: 38 years Female: 16 (36.4%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Participants having NAFLD and meeting the diagnostic criteria in the Guidelines for Diagnosis and Treatment of Nonalcoholic Fatty Liver Diseases; age 8 – 60 years; and BMI ≥ 25 kg/m^2 Exclusion criteria: Secondary obesity, such as hypothyroid obesity, pituitary obesity, Cushing-syndrome-induced obesity, hypothalamic obesity, and hypogonadal obesity; diseases that require controlled protein intake, such as renal disease; psychiatric disease and malignancy; severe gastrointestinal disease; currently on a weight-loss diet or medical treatment or having undergone surgery in the preceding 3 months; weight fluctuations of more than 5 kg over the preceding 2 months; history of food allergy; in the gestation, preconception, or lactation period; perimenopausal or postmenopausal; and malformations or chronic infectious diseases
Interventions	Participants were randomly assigned to 2 groups Group 1: Carbohydrate-restricted diet plus dietary advice plus exercise advice (n = 22) Further details: The percentage of energy from carbohydrates was 20% – 25%, and food with a low glycaemic index was primarily selected.The main form of education was face-to-face counselling, which was divided into dietary guidance, physical activity guidance, and psychological behavioural counselling Group 2: dietary advice plus exercise advice (n = 22) Further details: The main form of education was face-to-face counselling, which was divided into dietary guidance, physical activity guidance, and psychological behavioural counselling
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This work was supported by the Shanghai Shenkang Hospital Development Center Appropriate Technology Promotion Project: Promotion and Application of Nondrug Treatment Technology for Nonalcoholic Fatty Liver Disease under Grant [number SHDC12012207] and the Shanghai Health and Family Planning Commission Health Industry Clinical Research Project: “Research on the therapeutic effect of weight management based on wearable devices on nonalcoholic fatty liver disease” under Grant [number 201840164]" Trial name/trial registry number: not stated We tried to contact the authors in March 2021

Chen 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random number table"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and none of the outcomes of interest were reported
Other bias	Low risk	Comment: no other bias noted.

Cheng 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 115 Post-randomisation dropouts: 30 (26.1%) Revised sample size: 85 Reasons for post-randomisation dropouts: Family reasons (6), health problems (5), travel (6), lost interest (5), other reason (8) Average age (years): 61 Female: 89 (104.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 50 - 65 y/o with impaired fasting glucose (5.6 - 6.9 mmol/L) or impaired glucose tolerance (7.8 - 11 2 hours after intake of 75 g glucose), NAFLD diagnosed by H-MRS and alcohol < 21 drinks/week in men and < 14 in women, no chronic cardiovascular, musculoskeletal or GI problems and not on extreme diets, last menstruation > 6 months ago but within 10 years Exclusion criteria: BMI > 38, T1DM or T2DM and mental illness
Interventions	Group 1: Calorie-restricted diet (n = 22) Further details: The diet group, after baseline assessments, had a daily lunch plus an individual nutritional consultation programme developed by a clinical nutritionist on the basis of each individual's dietary intakes and body weight. During the intervention, participants were given a daily prepared meal (lunch), which accounted for 30 – 40% of the total daily energy intake. The meal included 37 – 40%

Cheng 2017 *(Continued)*

	carbohydrate with 9 – 13 g as fibre, 35 – 37% fat (SAFA 10%, MUFA 15 – 20%, PUFA 10%) and 25 – 27% protein. To ensure they consumed sufficient amounts of dietary fibre, 5 g of soluble fibre (dietary water-soluble fibre) was also added to the lunch Group 2: Supervised aerobic exercise plus calorie-restricted diet (n = 23) Further details: The Exercise plus Diet (AED) group performed the same exercise programme and followed the same diet as described above for exercise and diet groups Group 3: Supervised aerobic exercise (n = 22) Further details: The exercise (AEx) group, after baseline fitness assessments, participated 2 - 3 times a week in a supervised progressive aerobic exercise training programme (such as Nordic brisk walking plus stretching and other group exercises) which was developed by an exercise researcher. The exercise sessions were performed at the community park areas which were close to the participant's home. The intensity and duration of exercise was increased from 60% to 75% of the maximum oxygen uptake (estimated from fitness test) and from 30 to 60 mins per session Group 4: no active intervention (n = 18) Further details: The no-intervention (NI) group was advised to maintain their current level of physical activity and eating habits during the intervention Additional details: 8 months
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up (months): 8
Notes	Source of funding (quote): "Funding for this study was provided by the China State Sport General Administration (2013B040, 2015B039), the Chinese Nature Science Foundation (NSFC 31571219), and the Shanghai Jiao Tong University Zhiyuan Foundation (CP2014013). Funding to RB was provided by the Sigrid Juselius Foundation, the Instrumentation Research Foundation, the Finnish Medical Foundation, the Paulo Foundation and the Academy of Finland (130557, 270352)." Trial name/trial registry number: ISRCTN 42622771 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer program was used to generate the block randomisation sequence (block size 20) and was controlled by a researcher not involved in the selection of the participants"
Allocation concealment (selection bias)	Low risk	Quote: "A computer program was used to generate the block randomisation sequence (block size 20) and was controlled by a researcher not involved in the selection of the participants"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Although lifestyle interventions cannot be performed in a double-blinded fashion (since study subjects clearly are aware of the type of intervention), investigators were blinded for the tests and analyses during the entire study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Cuthbertson 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: not stated Number randomised: 69 Post-randomisation dropouts: 19 (27.5%) Revised sample size: 50 Reasons for post-randomisation dropouts: Discontinued baseline assessment (4), Discontinued intervention (4), Did not maintain habitual diet (2), declined post-intervention assessments (9) Average age (years): 51 Female: 11 (22.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: NAFLD, sedentary lifestyle (< 2 h/week low-intensity physical activity, no moderate- or high-intensity activity), nonsmokers, alcohol < 14 units (women) and < 21 units/week (men) Exclusion criteria: other causes of liver disease, T2DM, ischaemic heart disease, contraindication to exercise
Interventions	Group 1: Exercise advice (n = 20) Further details: advice about health benefits of exercise Group 2: Aerobic exercise (n = 30) Further details: 3/week 30-min moderate (30% HRR) aerobic exercise, progressing weekly based on HR responses (5/week 45 min at 60% HRR by week 12)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This work was supported by the European Foundation for the Study of Diabetes." Trial name/trial registry number: NCT01834300 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned on a 1:1 basis using a computer-generated sequence"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes

Cuthbertson 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

De Luis 2010

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: not stated Number randomised: 28 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 28 Average age (years): 46 Female: 22 (78.6%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Group I: Obese with BMI ≥ 30 and Group II BMI ≥ 30 and ALT ≥ 43 Exclusion criteria: Alcohol, medications: BP-lowering medications, statins, diabetes, IFG, hepatitis B, C, CMV, EBV, other causes of CLD
Interventions	Group 1: Fat-restricted diet (n = 15) Further details: diet I (low fat, 1500 kcal/day, 53% carbohydrates, 20% proteins, 27% fats) Group 2: Carbohydrate-restricted diet (n = 13) Further details: diet II (low carbohydrate: 1507 kcal/day, 38% carbohydrates, 26% proteins, 36% fats)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "They were blinded to treatment allocation, clinical information and laboratory data" Comment: this refers to assessors of outcomes reported in the trial, none of which were of interest for this review

De Luis 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

De Piano 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: not stated Number randomised: 58 Post-randomisation dropouts: not stated Revised sample size: 58 Average age (years): not stated Female: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Adolescents, postpubertal stage 5, BMI > 95% Exclusion criteria: genetic, metabolic or endocrine disease and previous drug use
Interventions	Group 1: Aerobic exercise plus resistance exercise (n = not stated) Further details: exercise - aerobic plus resistance training (AT plus RT) Group 2: Aerobic exercise (n = not stated) Further details: exercise - aerobic (AT)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "AFIP, FAPESP 2008/53069-0 and 2006/00684-3, FAPESP (CEPID/Sleep #9814303-3 S.T) CNPq, CAPES, CENESP, FADA, and UNIFESP-EPM, supported the CEPE-GEO Interdisciplinary Obesity Intervention Program." Trial name/trial registry number: NCT01358773 We tried to contact the authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available

De Piano 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Dong 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 280 Post-randomisation dropouts: 15 (5.4%) Revised sample size: 265 Reasons for post-randomisation dropouts: Poor compliance (11), declined repeat examinations (4) Average age (years): 57 Female: 0 (0.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: NAFLD, ≥ 45 y/o, men Exclusion criteria: Hx of alcohol > 20 g/day or 140 g/week, viral hepatitis or other causes of CLD, consumption of hypoglycaemic, hypolipidaemic, anti-inflammatory and weight-loss agents, presence of coronary, renal, pulmonary or thyroid diseases, transaminase levels > 2 x the upper limit of normal
Interventions	Group 1: Dietary advice plus exercise advice (n = 132) Further details: All enrolled participants in the test group received lifestyle counselling about their diet and physical activity from 2 professional physicians (1 dietician and 1 exercise physiologist). Doctors conducted a phone visit (the duration of a typical phone visit was approximately 10 minutes) with the participants in the test group every 3 months from July 2012 to July 2014, providing health guidance on diet and exercise Group 2: No active intervention (n = 133) Further details: treatment as usual
Outcomes	Outcomes reported: mortality at maximum follow-up, resolution of fatty liver disease, fibrosis score Follow-up (months): 24
Notes	Source of funding (quote): "This work was supported by a grant from the Science and Technology Commission of Shanghai, China (No: 13DZ2260700), Shanghai New Hundred Talents Program (No: XBR2013091), and Shanghai Key Developing Disciplines Program (No: 2015ZB0501)" Trial name/trial registry number: ChiCTR-IOR-16008949 We tried to contact the authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Dong 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization sequence"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Dynnyk 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Ukraine Period of recruitment: not stated Number randomised: 58 Post-randomisation dropouts: not stated Revised sample size: 58 Average age (years): not stated Female: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: NAFLD and visceral obesity
Interventions	Group 1: Exercise advice (n = not stated) Further details: General recommendations of changing sedentary behaviour by improving physical activity Group 2: Aerobic exercise (n = not stated) Further details: Pedometer with recommendation of walking 10,000 steps a day
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020
Risk of bias	

Dynnyk 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Eckard 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 56 Post-randomisation dropouts: 15 (26.8%) Revised sample size: 41 Reasons for post-randomisation dropouts: deployed overseas (1), lost to follow-up (7), withdrawn (4), moved area (1), lost medical benefits (1), transportation conflict (1) Average age (years): 50 Female: 25 (61.0%) NASH: not stated Diabetes mellitus: 8 (19.5%) Inclusion criteria: 18 - 70 y/o, biopsy confirmed NAFLD including NASH within 6 months prior to enrolment Exclusion criteria: Alcohol > 20 g/day, other causes of CLD < insulin for diabetes, pregnancy
Interventions	Group 1: Fat-restricted diet plus aerobic exercise (n = 12) Further details: low-fat diet (20% fat, 60% carbohydrate, 20% protein) with moderate exercise (LFDE). LFDE and MFDE participants attended a specialised nutrition class conducted by a registered dietitian, developed for this protocol. The class provided a nutrition prescription based on individualised calorie needs and macronutrient distribution (using the MyPyramid food group serving sizes) based on group assignment. Calorie (kcal) needs were calculated using the Mifflin–St Jeor equation using initial, actual body weight, and activity factor of 1.5 (light activity) subtracting 500 kcal/day for weight loss of 1 lb per week. Participants were also instructed on estimating portion sizes using the MyPyramid serving size guidelines, received a set of measuring cups and spoons, and were provided with supplemental refer-

Eckard 2013 *(Continued)*

	ence material on healthy cooking, grocery shopping, and dining out. LFDE and MFDE participants met with 1 of 3 research staff dietitians 3 more times (at 2, 4, and 6 months) for continued guidance on assigned diet Group 2: Carbohydrate-restricted diet plus aerobic exercise (n = 9) Further details: moderate-fat/ low-processed-carbohydrate diet (30% fat, 50% carbohydrate, 20% protein) with moderate exercise (MFDE). LFDE and MFDE participants attended a specialised nutrition class conducted by a registered dietitian, developed for this protocol. The class provided a nutrition prescription based on individualised calorie needs and macronutrient distribution (using the MyPyramid food group serving sizes) based on group assignment. Calorie (kcal) needs were calculated using the Mifflin–St Jeor equation using initial, actual body weight, and activity factor of 1.5 (light activity) subtracting 500 kcal/day for weight loss of 1 lb per week. Participants were also instructed on estimating portion sizes using the MyPyramid serving size guidelines, received a set of measuring cups and spoons, and were provided with supplemental reference material on healthy cooking, grocery shopping, and dining out. LFDE and MFDE participants met with 1 of 3 research staff dietitians 3 more times (at 2, 4, and 6 months) for continued guidance on assigned diet Group 3: Dietary advice (n = 11) Further details: treatment as usual - SC subgroup participants attended 1 healthy-eating class within 2 weeks of enrolment. This class is regularly taught at BAMC for DoD beneficiaries interested in weight loss or general nutrition guidelines Group 4: Aerobic exercise (n = 9) Further details: moderate exercise only. ME participants did not receive any dietary guidance
Outcomes	Outcomes reported: nafld activity score Follow-up (months): 6
Notes	Source of funding (quote): "This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participant randomization occurred by computer-generated random-numbers list"
Allocation concealment (selection bias)	Low risk	Quote: "Participant randomization occurred by computer-generated random-numbers list in blocks of 10 with assignments placed in sealed envelopes, numbered sequentially, and allocated to participants in the order of recruitment by the primary investigator"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a NAS was assigned to each specimen (pre- and post- intervention) by a single hepatopathologist who was blinded to study randomization" Comment: the pathologist who assessed the NAS score (the only outcome reported in this trial) was blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it was not clear whether these were related to the intervention or outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported

Eckard 2013 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Goss 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 32 Post-randomisation dropouts: not stated Revised sample size: 32 Average age: 14 years Female: 16 (50%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: children ages 9 to 17 years, BMI z-score > 85th percentile, diagnosis of NAFLD (ALT > 45 and/or perfusely echogenic liver via ultrasound) and sedentary (< 2 hours/week of intentional exercise, and agreed to maintain their level of activity throughout the study) Exclusion criteria: those with diabetes, unwilling to follow the prescribed diets, recent weight change (± 10 lbs. in previous year), history of eating disorder, digestive diseases, major liver dysfunction, current/recent smoker, current use of oral corticosteroids (> 5 days/month) and using medications for treatment of psychosis or manic-depressive illness
Interventions	Participants were randomly assigned to 2 groups Group 1: Carbohydrate-restricted diet (n = 16) Further details: The CRD diet was designed to minimise intake of refined CHO sources such as added sugars, high glycaemic grains and fructose and provided ≤ 25% energy from CHO, 25% energy from protein and ≥ 50% energy from fat. CHO sources were primarily derived from leafy greens and non-starchy vegetables. Additional CHO sources included in the diet prescription were nuts and nut butters, unsweetened yoghurt and low glycaemic fruits such as apples and berries. Limited amounts of whole grains. Legumes, root vegetables and 'treats' like dark chocolate were permitted. Protein sources included meat, fish, eggs, poultry and whey protein if appropriate. Saturated fat intake was limited to < 10% total energy/day. Other permitted fat sources included olive oil, walnut oil and other sources of poly- and mono-unsaturated fatty acids. A multivitamin was also encouraged to ensure all micronutrient requirements were met. Group 2: fat-restricted diet (n = 16) Further details: The FRD comprised low sugar, high-quality foods with low-energy density, which is the standard of care in the dietary management of children with NAFLD. This diet was based on the USDA MyPlate Daily Food Plan for teenagers with 20% energy from CHO:protein:fat. Participants were asked to avoid consuming foods high in fat such as fried foods, butter, cream cheese and bacon, whereas fruits, vegetables (starchy and non-starchy), whole grains, poultry, lean meats and low-fat dairy products were permitted
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "Research reported in this publication was supported by the Thrasher Research Fund (TRF13337), the National Institute of Diabetes and Digestive and Kidney Diseases (DK079626), the National Center for Advancing Translational Sciences (1TL1TR001418-01), and the National Institute of General Medical Sciences (NIH T32GM008361)" Trial name/trial registry number: NCT02787668 We tried to contact the authors in March 2021

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Goss 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The random allocation sequence was created using a random number generator by PROC PLAN (SAS Version 9.3)".
Allocation concealment (selection bias)	Unclear risk	Quote: "participants were assigned to a diet using a block randomization scheme, and the condition assignments were placed in sealed envelopes that were not opened until a specific participant was assigned". Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because this was a diet intervention study, it was not possible for participants or study personnel to be blinded to group assignment".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Because this was a diet intervention study, it was not possible for participants or study personnel to be blinded to group assignment".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but the publication was after recruitment began. None of the outcomes of interest for this review were reported
Other bias	Low risk	Comment: no other bias noted

Hallsworth 2011

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: not stated Number randomised: 21 Post-randomisation dropouts: 2 (9.5%) Revised sample size: 19 Reasons for post-randomisation dropouts: Change in diabetes medication (1); lost > 5% body weight during 8-week period (1) Average age (years): 56 Female: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Non-advanced NAFLD; sedentary (≤ 60 min vigorous activities per week) Exclusion criteria: Heart or kidney disease; implanted ferrous metal; pre-existing medical conditions preventing participation in the exercise programme; insulin sensitising treatment or dietary change (for people with type 2 diabetes mellitus, diet and metformin were acceptable for inclusion if stable for 6 months); alcohol intake (above 21 units for men or 14 units for women)
Interventions	Group 1: Resistance exercise (n = 11) Further details: Resistance exercise was performed 3 times a week on nonconsecutive days for 8 weeks. The programme consisted of 8 exercises: biceps curl; calf raise; triceps press; chest press; seated hamstrings curl; shoulder press; leg extension and lateral pull down (Precor, Woodinville, USA). Each session lasted between 45 and 60 mins and consisted of a 10-min warm-up at approximately 60% maximum heart rate on a cycle ergometer followed by resistance exercise done as a circuit, ending with a repeat of the warm-up described. The one repetition maximum was measured at baseline and fol-

Hallsworth 2011 *(Continued)*

	lowing the intervention. Initially, participants did 2 circuits using 50% of their 1 repetition maximum, progressing to 3 circuits, using a minimum 70% of their 1 repetition maximum by week 7. Participants were encouraged to increase the resistance used each week when possible. Bi-weekly supervised sessions were used to encourage adherence and progression and to resolve any problems. Heart rate was recorded during each session (Polar RS400; Polar Electro Oy, Kempele, Finland) and was used alongside exercise logs to assess adherence Group 2: No active intervention (n = 8) Further details: treatment as usual
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no Health-F2-2009-241762, for the project FLIP; the Medical Research Council; the UK National Institute for Health Research Biomedical Research Centre on Ageing and Age-Related Diseases and Diabetes UK." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Hallsworth 2015

Study characteristics

Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: not stated Number randomised: 29 Post-randomisation dropouts: 6 (20.7%) Revised sample size: 23

Hallsworth 2015 *(Continued)*

	Reasons for post-randomisation dropouts: Discontinued intervention (2); time commitment (1); prolonged illness (1); non-adherence (1); missing data (1) Average age (years): 53 Female: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Non-advanced NAFLD; sedentary (≤ 60 min vigorous activity per week) Exclusion criteria: Inability to give informed consent; heart or kidney disease; viral hepatitis; uncontrolled thyroid conditions; haemochromatosis; drug-related steatosis; implanted ferrous material; pre-existing medical conditions preventing participation in the exercise programme; medication for T2DM other than metformin; self-reported weekly alcohol intake (above 21 units for men or 14 units for women)
Interventions	Group 1: Aerobic exercise (n = 12) Further details: Participants completed a cycle ergometer-based HIIT protocol 3 times a week on non-consecutive days for 12 weeks. Intensity was based on the 6 – 20 point Borg rating of perceived exertion (RPE). Participants were provided with a portable audio device (iPod shuffle, Apple Inc.) containing pre-recorded and written instructions to guide them through each session. Sessions consisted of a 5-min warm-up progressing from an RPE of 9 – 13 ('very light' to 'somewhat hard') followed by 5 intervals of cycling at an RPE of 16 – 17 ('very hard') interspersed with 3-min recovery periods and followed by a 3-min cool-down after the last interval. Each interval was 2 mins long in the first week with 10 secs added per week, so that intervals were 3 min and 50 secs long by week 12. Sessions therefore lasted 30 – 40 min. Recovery periods included 90 secs of passive recovery, 60 secs of light band resisted upper body exercise and 15 secs each to transition off and on the ergometer. One upper body exercise was performed per recovery period in the following order: face-pull, horizontal push, horizontal pull and 30 ° push. Exercise was performed at commercial fitness facilities, with the first 2 sessions supervised by one of the investigators Group 2: No active intervention (n = 11) Further details: treatment as usual
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "this work was supported by the European Union Seventh Framework Programme [grant number F2-2009-241762]; the Medical Research Council [grant numbers G0700718 (to K.H.) and G1100160 (to K.G.H.)]; the National Institute for Health Research [grant numbers NIHR-SRF-2011-04-017 (to M.I.T.)] and Diabetes, U.K. [grant number 08/0003759 (to C.T.)]. Q.M.A. is the recipient of a Clinical Senior Lectureship Award from the Higher Education Funding Council for England (HEFCE). Q.M.A. and C.P.D. are members of the EPoS (Elucidating Pathways of Steatohepatitis) consortium funded by the Horizon 2020 Framework Programme of the European Union under Grant Agreement 634413." Trial name/trial registry number: ISRCTN78698481 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was undertaken via a random allocation sequence (www.randomization.com)"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: this information was not available

Hallsworth 2015 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Hickman 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Australia Period of recruitment: not stated Number randomised: 21 Post-randomisation dropouts: 5 (23.8%) Revised sample size: 16 Reasons for post-randomisation dropouts: Group 1: 2 excluded from analysis because discontinued treatment; Group 2: 2 excluded because discontinued treatment, 1 excluded because of weight loss; no loss to follow-up Average age (years): 48 Female: 8 (50.0%) NASH: 11 (68.8%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: NAFLD (diagnosed by liver biopsy). Exclusion criteria: Type 2 diabetes, cirrhosis, decompensated liver disease, presence of other causes of liver disease, and daily ethanol consumption > 20 g in women or > 40 g in men
Interventions	Group 1: Calorie-restricted diet (n = 8) Further details: dietary-induced weight-loss intervention was individually tailored to induce an energy restriction calculated (based on Harris-Benedict predicted energy requirements and sedentary activity factors) for 5 to 10% body weight loss over a 16-week intensive phase whereby participants were reviewed weekly by a dietician. This was followed by an 8-week weight-maintenance phase involving dietetic review every 2 weeks. Participants were instructed not to change their usual physical activity habits. The intervention was supported by an educational manual, which included information about energy content of food portions, macro- and micronutrient content of individual foods and combination dishes, food-label reading, shopping, cooking and eating-out guidelines, motivational tools and goal-setting skills and activities. A dietary composition of 40% carbohydrate, 40% fat and 20% protein sources of energy was encouraged, with specific advice on reduced saturated fat, lowering sugar (including reduced sugary drinks), avoiding micronutrient poor/energy dense food options and aiming for regular meal patterns. Weekly weight and waist measures and 24-hour diet recall interviewing assisted compliance and encouraged ongoing self-monitoring. Motivational interviewing and behavioural management techniques were used throughout the programme Group 2: Aerobic exercise (n = 13) Further details: The exercise programme involved 3 sessions a week of circuit exercise training for 6 months, without dietary changes, with the aim to improve physical fitness and muscle strength without significant body weight loss. Exercise was conducted using pneumatic resistance training equipment (AbHurOy, Kokkola, Finalnd). Each circuit consisted of 15 moderate-intensity resistance exercises covering the main muscular groups. Some machines were bi-functional, allowing participants to exercise 2 different muscular groups, usually antagonistic. On the bi-functional machines, participants exercised alternately the agonist or the antagonist muscle. The training programme consisted of 30-second exercise intervals and 30-second rest periods, during which participants moved to the next sta-

Hickman 2013 *(Continued)*

	tion and prepared themselves for the following exercise period. A digital timed audio signal was used to indicate the start and the end of the 30 seconds exercise or rest period. Training intensity over the whole duration of the training programme was fixed at 50% of 1 repetition maximum (1- RM). Number of circuits, and consequently session duration, was progressively increased from 1 circuit (12 mins) in week 1 to 5 circuits in week 12 (60 mins) and was kept constant from week 16 to the end of the training programme (week 24). A 1-RM was completed on each of the 15 exercises the week prior to the beginning of the programme, and was then reassessed every 4 weeks to account for any strength adaptations over the course of the training period
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximum follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma, nafld activity score Follow-up (months): 6
Notes	Source of funding (quote): "The study was funded by the National Health and Medical Research Council of Australia and the Lions Medical Research Foundation." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised by the study co-ordinator, using random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "Random allocation to groups was concealed in an envelope by an independent research assistant who was not involved in recruitment (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The assessors for primary outcome histology and body composition were all blinded to group allocation for the duration of the study (author replies)" Comment: the assessors of the clinical outcomes were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the study authors reported mortality, adverse events, and resolution of fatty liver
Other bias	Low risk	Comment: no other bias noted

Houghton 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: UK

Houghton 2017 *(Continued)*

	Period of recruitment: not stated Number randomised: 26 Post-randomisation dropouts: 2 (7.7%) Revised sample size: 24 Reasons for post-randomisation dropouts: Pre-existing knee problem (1); pre-existing back problem (1) Average age (years): 52 Female: not stated NASH: 24 (100.0%) Diabetes mellitus: not stated Inclusion criteria: Biopsy-proven NASH; sedentary (≤ 60 min of moderate-vigorous activity per week) Exclusion criteria: Heart or kidney disease; implanted ferrous metal; pre-existing medical conditions preventing participation in the exercise programme; insulin-sensitising treatment; dietary change over the preceding 6 months; evidence of other liver disease; history of excessive alcohol consumption (alcohol intake > 20g/day for women and > 30g/day for men)
Interventions	Group 1: Supervised aerobic exercise plus SupResistance exercise (n = 12) Further details: Exercise was supervised and performed 3 times a week on nonconsecutive days for 12 weeks. The exercise programme consisted of aerobic (cycling) and resistance training and is detailed in the Supplementary Clinical Trial Study Pro- tocol. The cycling included a 5-minute warm-up and 3 intervals on a fixed bike for 2 minutes with a 1-minute rest in between. Exercise intensity was based on the Borg (6 – 20 points) rating of perceived exertion with bike intervals corresponding to a rating of perceived exertion of 16 to 18 (very hard). This was followed by a resistance exercise circuit that comprised 5 exercises: hip and knee extension, horizontal row, chest press, vertical row, and knee extension (Precor, Woodinville, WA). Participants were provided with a suitable weight for each resistance exercise based on a rating of perceived exertion of 14 to 16 (hard). The rating of perceived exertion was used to guide intensity for safety, time effectiveness, its translational use in clinical practice, and its effectiveness at determining 1 repetition maximum. Each session lasted between 45 and 60 minutes. All sessions were conducted at an accredited sports centre and supervised by a certified exercise specialist, who recorded progress to ensure adherence and encouraged exercise progression through adding resistance on the bike and increasing the weights lifted as able. This also helped to improve safety, adherence, and the opportunity to resolve any problems Group 2: No active intervention (n = 12) Further details: Standard care consisted of volunteers continuing any prescription medication and going for regular monitoring of their condition(s) with their normal general practitioner or consultant(s), or both
Outcomes	Outcomes reported: fibrosis score Follow-up (months): 3
Notes	Source of funding (quote): "This research has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement Health-F22009-241762 for the Fatty Liver Inhibition of Progression project, The Medical Research Council, Diabetes UK, The Newcastle Centre for Ageing and Vitality, The UK National Institute for Health Research Biomedical Research Centre on Ageing and Age-Related Diseases, and was supported by a Senior Fellowship from the National Institute for Health Research (M.I.T.)." Trial name/trial registry number: ISRCTN16070927 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available

Houghton 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Johari 2019

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Malaysia Number randomised: 43 Post-randomisation dropouts: 0 (0%) Revised sample size: 43 Average age: 47 years Female: 10 (23.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: NAFLD patients who attended the Gastroenterology Clinic. To be eligible, participants of either sex were required to have elevated alanine transferase (ALT) and or aspartate transferase (AST) level (ALT > 41 and or AST > 34 IU/L), age that ranged from 18 to 70 years old, BMI between 17.5 and 40 Kg/m^2 and no evidence of other forms of liver diseases. For those with diabetes mellitus and dyslipidaemia, they must be on a stable therapy for at least 6 months prior to study enrolment Exclusion criteria: significant alcohol consumption (> 1 standard drink per day), pregnancy, and involvement in an active weight loss programme or taking weight-loss medications, substance abuse and significant psychiatric problems. Withdrawn participants were those unable to tolerate the fasting intervention during the trial and those who dropped out by their own choice
Interventions	Participants were randomly assigned to 2 groups Group 1: Calorie-restricted diet (n = 33) Further details: On fasting day, all participants were instructed to restrict 70% of their calorie requirement per day and on non-fasting day, they ate ad libitum. They were told to eat on the non-fasting day what they normally ate and to the point of satisfaction but not to intentionally overeat. The calorie-restriction and feeding days began at 9 am each day, but on fasting day, calorie-deficient meals were only consumed between 2 pm and 8 pm. Diet plans were not provided to participants but were self-selected using detailed individualised food portion lists, meal plans, and recipes. To ensure maximum adherence to dietary plan, participants received intermittent phone calls from the investigator and 2-weekly appointments (total 4 appointments) with a dietitian. Total duration: 8 weeks. Group 2: No active intervention (n = 10)
Outcomes	Outcomes reported: mortality Follow-up (months): 1.84

Johari 2019 *(Continued)*

Notes	Source of funding (quote): "We thanked the following grants for funding the current study including USM short term grant (reference no: 304/PPSP/61313173) and Research University Individual (RUI) grant (reference no: 1001/PPSP/812151)" Trial name/trial registry number: not stated We tried to contact the authors in March 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random number was generated using the Microsoft Office Excel"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Kaliora 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: not stated Number randomised: 55 Post-randomisation dropouts: 11 (20.0%) Revised sample size: 44 Reasons for post-randomisation dropouts: Personal reasons (5); modified lipid lowering treatment (5); started antimetabolite treatment (1) Average age (years): 51 Female: 32 (72.7%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Age 18 - 65; BMI > 25; Adherence to 'western diet' (Mediterranean diet. Score values < 35) Exclusion criteria: Chronic viral hepatitis; congenital or acquired liver disease; prior exposure to hepatotoxic drugs; liver cirrhosis; bariatric surgery; daily consumption of alcohol more than 20 g for women and more than 30 g for men (for over 6 months during the last 5 years); medications which could impact

Kaliora 2016 *(Continued)*

	on fatty liver disease; psychiatric disorders impairing the patient's ability to provide written informed consent; pregnant or lactating women; supplementation with n-3 fatty acids; probiotics/synbiotics, antioxidants, vitamins and/ or phytochemicals
Interventions	Group 1: Raisins plus dietary advice (n = 23) Further details: The aim of nutritional counselling was a weight loss of approximately 5% of the initial BW within 6 months. Participants attended appointments with experienced dietitians to receive guidance on calorie restriction. Nutritional counselling was centred on the distribution of nutrients for the total caloric value as follows: 30% of the total energy as fat (< 10% as SFAs, ~ 10% as MUFAs, and ~ 10% as PUFAs), 20% as protein, 50% as carbohydrate, 300 mg d−1 as dietary cholesterol, and 20 – 30 g fibre per day. Participants in the Control arm received the above dietary counselling. Participants in the Currant arm received dietary counselling and incorporated in their daily diet the consumption of 36 g of Corinthian currants equal to 2 fruit servings replacing snacks of similar nutritional value (low-fat yogurt, mini-crackers, or bread with low-fat cheese) Group 2: Dietary advice (n = 21) Further details: The aim of nutritional counselling was a weight loss of approximately 5% of the initial BW within 6 months. Participants attended appointments with experienced dietitians to receive guidance on calorie restriction. Nutritional counselling was centred on the distribution of nutrients in relation to the total caloric value as follows: 30% of the total energy as fat (< 10% as SFAs, ~ 10% as MUFAs, and ~ 10% as PUFAs), 20% as protein, 50% as carbohydrate, 300 mg d−1 as dietary cholesterol, and 20 – 30 g fibre per day. Participants in the Control arm received the above dietary counselling. Participants in the Currant arm received dietary counselling and incorporated in their daily diet the consumption of 36 g of Corinthian currants equal to 2 fruit servings replacing snacks of similar nutritional value (low-fat yogurt, mini-crackers, or bread with low-fat cheese).
Outcomes	Outcomes reported: fibrosis score Follow-up (months): 6
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomisation sequence was computer generated"
Allocation concealment (selection bias)	Low risk	Quote: "After randomisation, the statistician sent the randomisation list to the trial principal investigator who completed a participant form for each subject, including the treatment and the patient trial number and put it in a sealed envelope. Blinding of the allocated treatment was maintained to data analysts and was exposed only after the assessment of outcomes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinding of the allocated treatment was maintained to data analysts and was exposed only after the assessment of outcomes"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes

Kaliora 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Kani 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2012 Number randomised: 45 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 45 Average age (years): 48 Female: 21 (46.7%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: diagnosis of NAFLD
Interventions	Group 1: Carbohydrate-restricted and calorie-restricted diet (n = 30) Further details: In addition to focusing on a low-calorie diet, group 2 also received a low-carbohydrate diet. In group 3, the composition of the macronutrients was similar to the group 2 diet except in this diet 30 g of soy nut was incorporated instead of 30 g of red meat Group 2: Calorie-restricted diet (n = 15) Further details: The low-calorie diet (group 1) was 200 to 500 calories lower than the required calories for each participant. Calorie restriction was considered according to participant's BMI category. A 200-calorie reduction was considered for overweight individuals and up to a 500-calorie reduction for obese participants
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This study was supported by Food Security Research Center and School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran" Trial name/trial registry number: NCT01419912; IRCT201105282839 N2 We tried to contact the authors in December 2020.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned to one of three groups in which sequentially numbered containers were used as a mechanism to implement the random allocation sequence"
Allocation concealment (selection bias)	Low risk	Quote: "Participants were randomly assigned to one of three groups in which sequentially numbered containers were used as a mechanism to implement the random allocation sequence"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "As this study was a dietary intervention, it was not blinded for the patients or the dietitian"

Kani 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "However, laboratory staff and individuals who analyzed the data were blinded to the groups of interventions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Katsagoni 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: not stated Number randomised: 63 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 63 Average age (years): 46 Female: 20 (31.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Age 18 - 65; BMI 25 - 40; diagnosis of NAFLD Exclusion criteria: Hepatitis B/C or HIV; alcohol consumption (> 140 g/week for women or > 210 g/week for men); hepatotoxic or steatogenic agents (e.g. amiodarone, tamoxifen, methotrexate); metabolic or autoimmune liver disease; diabetes; known systemic disease with potential live involvement
Interventions	Group 1: Mediterranean diet plus dietary advice plus exercise advice (n = 21) Further details: all 3 groups were given an indicative energy restriction regimen with similar percentage of macronutrients, namely 45% carbohydrates, 20% protein and 35% lipids, which provided 6276 kJ (1500 kcal) for women and 7531 kJ (1800 kcal) for men. Participants in MDG and MLG followed a more intensive counselling programme, consisting of 7 x 60-min small-group sessions (3 - 5 people), held every 2 weeks for the first 2 months and every month for the next 4 months, co-ordinated by a research dietitian (C. N. K.). Nutritional counselling was based on the goal-setting theory aiming at improving diet quality and promoting energy restriction by enhancing adherence to the Mediterranean food pattern, as described in the MD pyramid and the Dietary Guidelines for Greeks. In the MDG, no further instructions were given for other lifestyle parameters. In the MLG, goals were also set for enhancing activity through a moderate–vigorous intensity physical activity programme of at least 30 min/d (fast or very fast walking, slow or fast running, dancing, tennis and so on), as well as for optimal sleep duration (i.e. ≥ 7 and ≤ 9 h/d) and mid-day rest (e.g. naps, siesta) Group 2: Mediterranean diet plus dietary advice (n = 21) Further details: all 3 groups were given an indicative energy restriction regimen with similar percentage of macronutrients, namely 45% carbohydrates, 20% protein and 35% lipids, which provided 6276 kJ (1500 kcal) for women and 7531 kJ (1800 kcal) for men. Participants in MDG and MLG followed a more intensive counselling programme, consisting of 7 x 60-min small-group sessions (3 - 5 people), held every 2 weeks for the first 2 months and every month for the next 4 months, co-ordinated by a research dietitian (C. N. K.). Nutritional counselling was based on the goal-setting theory aiming at improving diet quality and promoting energy restriction by enhancing adherence to the Mediterranean food pattern, as described in the MD pyramid and the Dietary Guidelines for Greeks. In the MDG, no further instructions were given for other lifestyle parameters. In the MLG, goals were also set for enhancing activ-

Katsagoni 2018 *(Continued)*

	ity through a moderate–vigorous intensity physical activity programme of at least 30 min/d (fast or very fast walking, slow or fast running, dancing, tennis and so on), as well as for optimal sleep duration (i.e. ≥ 7 and ≤ 9 h/d) and mid-day rest (e.g. naps, siesta) Group 3: Dietary advice (n = 21) Further details: all 3 groups were given an indicative energy restriction regimen with similar percentage of macronutrients, namely 45% carbohydrates, 20% protein and 35% lipids, which provided 6276 kJ (1500 kcal) for women and 7531 kJ (1800 kcal) for men. The CG received also general written dietary guidelines for a healthy lifestyle at baseline, without any other intervention until the end of the 6-month period
Outcomes	Outcomes reported: fibrosis score Follow-up (months): 6
Notes	Source of funding (quote): "This research received no specific grant from any funding agency, commercial or not-for-profit sectors." Trial name/trial registry number: NCT01894438 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was made using a random numbers system"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention-to-treat analysis was performed
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Misciagna 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 98 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 98

Misciagna 2017 *(Continued)*

	Average age (years): not stated Female: 26 (26.5%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Moderate to severe NAFLD Exclusion criteria: Overt cardiovascular disease and revascularisation procedures; stroke; peripheral artery disease; type 2 diabetes mellitus; alcohol intake (> 20 g daily); severe medical condition that may impair the person's ability to participate in a nutritional intervention study; following a special diet or involved in a programme for weight loss or recent weight loss; inability to follow a modified diet for religious or other reasons
Interventions	Group 1: Mediterranean diet (n = 50) Further details: Foods in LGIMD all have all a low glycaemic Index (GI) and no more than 10% of total daily calories coming from saturated fats. The LGIMD was high in MUFAs from olive oil and contained also ω3PUFAs, from both plant and marine sources Group 2: No active intervention (n = 48) Further details: No active intervention
Outcomes	Outcomes reported: mortality at maximum follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximum follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma, liver-related mortality Follow-up (months): 6
Notes	Source of funding (quote): "this study was funded by a research grant from the Italian Ministry of Health." Trial name/trial registry number: NCTO1798719 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerized random numbers sequence"
Allocation concealment (selection bias)	Low risk	Quote: "Before the recruitment by an operator who followed the allocation list. Obviously the operator was not the physician or the dietitian who recruited that day (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind...Blinding and equipoise were strictly maintained by emphasizing to the intervention staff and participants that each diet adhered to healthy principles..With the exception of the dietitians, investigators and staff were unaware of the subjects' diet assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Staff members who obtained outcome measurements were not informed about diet assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the study authors reported mortality, adverse events, and resolution of fatty liver
Other bias	Low risk	Comment: no other bias noted

Monica Dinu 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age (years): 55 Female: 28 (70.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: presence of bright liver echotexture based on ultrasonography; at least 18 years of age. Exclusion criteria: wheat allergies including celiac disease and gluten intolerance; excessive alcohol consumption (> 30 g daily), T2DM, viral hepatitis, NASH, and other chronic liver diseases (including autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hereditary haemochromatosis, Wilson's disease, and alpha- 1 antitrypsin deficiency)
Interventions	Group 1: Organic semi-wholegrain wheat diet (n = 20) Further details: organic semi-whole-grain wheat Group 2: Khorasan wheat diet (n = 20) Further details: Khorasan wheat (n = 20) or control (n = 20) products in the place of habitually-consumed bakery products
Outcomes	Outcomes reported: mortality at maximum follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximum follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma, liver-related mortality Follow-up (months): 3
Notes	Source of funding (quote): "The study was sponsored in part by a grant from the Kamut Enterprise of Europe (KEE), Oudenaarde, Belgium" Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomized with a 1:1 randomization to study arms by a statistician, using a web-based online randomization procedure (author replies)" Comment: this information was not available
Allocation concealment (selection bias)	Low risk	Quote: "The allocation concealment was ensured using a centralized service, and was not be possible for the investigators to know the allocation sequence in advance (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind parallel trial" Comment: the bakery products were produced with a different form of wheat; so blinding could be achieved
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind parallel trial"

Monica Dinu 2017 *(Continued)*

All outcomes		Comment: the bakery products were produced with a different form of wheat; so blinding could be achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the study authors reported mortality, adverse events, and resolution of fatty liver
Other bias	Low risk	Comment: no other bias noted

Moradi 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Number randomised: 45 Post-randomisation dropouts: 0 (0%) Revised sample size: 45 Average age: 65 years Female: 45 (100%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: being obese, elderly and female in addition to having fatty liver disease, which was confirmed by ultrasonography Exclusion criteria: addiction to smoking, alcohol abuse, doing regular physical exercises in the last 6 months, having lung disease, kidney disease, cardiovascular disease, liver transplantation, oestrogen intake, high blood pressure, chronic disorders, taking special medications such as statins, additive effects on insulin sensitivity, hepatotoxic medications intake, having a special dietary programme
Interventions	Participants were randomly assigned to 2 groups Group 1: Resistance exercise (n = 23) Further details: Each session took about 60 - 70 mins for main training (plus about 20 mins for warm-up and cool-down), 3 days a week (nonconsecutive) which lasted 12 weeks Group 2: No active intervention (n = 22) Both groups took curcumin or placebo supplementation which was decided at random
Outcomes	Outcomes reported: mortality Follow-up (months): 2.76
Notes	Source of funding (quote): "Funding: none" Trial name/trial registry number: IRCT20190103042219N1 We tried to contact the authors in March 2021

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A third party was asked to classify the participants randomly, using the (labelled) codes. Study groups had codes instead of names. The laboratory was uninformed from name of groups and only used the codes. Groups codes were used for statistical analysis" Comment: further details of random sequence generation were not available

Moradi 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "A third party was asked to classify the participants randomly, using the (labelled) codes. Study groups had codes instead of names. The laboratory was uninformed from name of groups and only used the codes. Groups codes were used for statistical analysis"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The laboratory was uninformed from name of groups and only used the codes". Comment: it was not clear whether the outcomes assessors of clinical outcomes were blinded to the groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

NCT01327443

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 17 Post-randomisation dropouts: not stated Revised sample size: 17 Average age (years): not stated Female: not stated NASH: 17 (100.0%) Diabetes mellitus: not stated Inclusion criteria: sedentary, adults 18 - 60, elevated Liver Function Tests with fatty liver on ultrasound and biopsy-proven NASH Exclusion criteria: significant history of alcohol consumption > 20 gm/day (> 2 drinks / day), evidence of other causes of hepatitis including positive screening B & C, autoimmune hepatitis, haemochromatosis, coeliac disease, Wilson's disease, alpha 1 antitrypsin deficiency or medication-induced hepatitis, Patients with planned exercise > 30 - 60 minutes a week, BMI < 25 or > 44 kg/m^2, clinical or biochemical evidence of decompensated liver disease, advanced cardiac or renal disease, changes in last 3 months to the dose of oral hypoglycaemic medication and statin, positive stress test, pregnant women, demented individuals who cannot give consent
Interventions	Group 1: Supervised aerobic exercise (n = not stated) Further details: 24 weeks of directly supervised aerobic exercise Group 2: Dietary advice (n = not stated) Further details: 10% weight loss in 24 weeks time period through nutritional counselling Group 3: no active intervention (n = not stated) Further details: No change in usual exercise or food intake

NCT01327443 *(Continued)*

Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: NCT01327443 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open label"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

NCT02679417

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: not stated Post-randomisation drop-outs: not stated Revised sample size: 0 Average age (years): not stated Female: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: moderate or severe NAFLD enrolled in nutriep trial (list of patients from primary care in southern Italy)
Interventions	Group 1: Aerobic exercise plus resistance exercise (n = not stated) Further details: Participants have followed a programme combining endurance activity (EA) and resistance training (RT) consisting in a 60-minute work session, 3 times/week consisting of: walk (30 minutes): exercise intensity started from the 60% of the maximum heart rate and raised up to the 75%.

NCT02679417 *(Continued)*

	Musculation (30 minutes): training of the bigger muscle groups (chest, shoulders, arms, abdomen, back, glutei and legs). Exercise intensity started from 65% of the maximum rated load and raised up to 75% Group 2: Aerobic exercise (n = not stated) Further details: Participants have followed a programme of endurance activity consisting of a 30-minute walk, 5 times/week. Exercise intensity started from 60% of the maximum heart rate and raised up to 75%
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: NCT02367742 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single blinded (outcome assessors)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Single blinded (outcome assessors)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

NCT03183193

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: not stated Number randomised: not stated Post-randomisation dropouts: not stated Revised sample size: 0 Average age (years): not stated Female: not stated NASH: not stated Diabetes mellitus: not stated

NCT03183193 *(Continued)*

	Inclusion criteria: Overweight or obese, diagnosis of NAFLD; age: 30 - 80 years Exclusion criteria: Known liver disease (other than NAFLD); abuse of alcohol (> 21 and > 14 units of alcohol a week for men and women, respectively, e.g. 1 unit = 125 mL of wine); drug treatments: immunosuppressants, cytotoxic agents, systemic corticosteroids, agents potentially causing fatty liver disease or abnormal liver tests or weight modifiers, Active cancer or a history of malignancy in the last 5 years, Problems of massive oedemas; obesity known endocrine origin (except treated hypothyroidism); surgical procedure for weight loss, ≥ 3 kg weight loss in the last 3 months; severe psychiatric disorders; lack of autonomy or inability to follow the diet (including food allergies or intolerances) or/and lifestyle recommendations as well as to follow scheduled visits; consumption of any type of food supplements (antioxidants, prebiotics, probiotics, etc.)
Interventions	Group 1: Mediterranean diet (n = not stated) Further details: The participants follow a strategy based on a distribution of macronutrients 30 - 35% lipid (extra virgin olive oil and fatty acids Ω3 in detriment of saturated, trans and cholesterol)/ protein 25% (vegetable against animal)/carbohydrates 40 - 45% (low glycaemic index, fibre 30 - 35 g/day); high adherence to the Mediterranean diet and natural antioxidants; meal frequency of 7 meals/day; size/composition of the ration suitable for each moment; including traditional foods with no additional economic cost that will allow diet adherence without abandonment; avoid inappropriate mealtimes and the eating manners as the eating rate. The participants are instructed to follow this strategy within a personalised energy-restricted diet (- 30%) and under healthy lifestyle advice to achieve AASLD objectives Group 2: No active intervention (n = not stated) Further details: The participants follow a conventional and balanced distribution of macronutrients (30% fat, 15% protein, 55% carbohydrates), adequate fibre (25 - 30 g/day) and dietary cholesterol (< 250 mg/day) intake according to AHA guidelines. This strategy was included within a personalised energy-restricted diet (- 30% individual needs) under healthy lifestyle advice in order to achieve the objectives of AASLD (loss of at least 3 - 5% of the initial body weight and up to 10% needed to improve necroinflammation)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "Clinica Universidad de Navarra, Universidad de Navarra Complejo Hospitalario de Navarra" Trial name/trial registry number: NCT03183193 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single (participant)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Single (participant)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available

NCT03183193 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

NCT03461562

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Turkey Period of recruitment: not stated Number randomised: 31 Post-randomisation dropouts: not stated Revised sample size: 31 Average age (years): not stated Female: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Clinical diagnosis of NAFLD, Age 8 - 65 years, not in an active exercise programme, not on an active diet programme Exclusion criteria: Pregnancy; chronic inflammatory process; rheumatic disease; cognitive disorders; obstacles to achieve physical performance tests; presence of other conditions that may cause liver steatosis; Inability to do WBVT or aerobic exercises
Interventions	Group 1: Aerobic exercise (n = not stated) Further details: Aerobic exercise will be held for 40 minutes. Dynamic exercises will be accompanied by physiotherapist on the vibration platform for 15 minutes Group 2: No active intervention (n = not stated) Further details: Same exercises will be held on a stable platform (with the devices turned off) by control group for 15 minutes
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: NCT03461562 We tried to contact the authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Masking: Double (Participant, Outcomes Assessor)" Comment: not clear how it is possible to blind the participants to the exercise they performed
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Masking: Double (Participant, Outcomes Assessor)"

NCT03461562 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Nikroo 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2010 - 2011 Number randomised: 25 Post-randomisation dropouts: 2 (8.0%) Revised sample size: 23 Reasons for post-randomisation dropouts: Not stated Average age (years): 37 Female: 0 (0.0%) NASH: 23 (100.0%) Diabetes mellitus: not stated Inclusion criteria: age 18 - 55. ALT > 1.5 times upper limit of normal, for a minimum period of 3 months, and evidence of fatty liver on liver ultrasonography Exclusion criteria: history of significant alcohol consumption (> 20 gr/day for women, > 30 gr/day for men), and other liver diseases (viral hepatitis B and C, autoimmune hepatitis, coeliac disease, Wilson's Disease, α1-antitrypsin deficiency and haemochromatosis); medical problems such as hypothyroidism, ischaemic heart disease, renal failure and use of hepatotoxic drugs
Interventions	Group 1: Supervised aerobic exercise (n = 12) Further details: The aerobic training programme designed according to guideline of American College of Sports Medicine (ACSM) and performed by professionally-qualified instructors. Exercises programmes were individualised, under the supervision of experienced exercise physiologists, which allowed participants to achieve their target heart rate reserve (HRR). It consisted of walking, jogging or running, for a period of 8 weeks/ 3 days a week. The time of exercises were 35 to 50 minutes (15 minutes of warm-up, 10 to 25 minutes of aerobic exercise and 10 minutes of cool-down), with 55% - 60% of HRR during each training session. The first session of aerobic exercise lasted for 10 minutes and the next sessions, 1 minute added to every aerobic exercise, so by the end of sixth, seventh and eighth weeks duration of aerobic exercises was maintained in 25 minutes Group 2: Dietary advice (n = 11) Further details: diet was individualised after the measurement of body composition and calculation of daily energy requirements of participants. The participants were controlled and managed by a nutritionist. Calorie-restricted diet in both groups included 500 kilocalories (kcal) of energy less than the estimated daily energy requirement. The percentage distribution of macronutrients consisted of 60% carbohydrate, 25% fat and 15% protein with emphasis on selecting a variety of all food groups and reducing saturated fat intake and simple sugar consumption
Outcomes	Outcomes reported: quality of life (maximum follow-up) Follow-up (months): 1.84
Notes	Source of funding (quote): "This study was funded by the research ethics committee of Mashhad University that project code number was 89878."

Nikroo 2017 *(Continued)*

Trial name/trial registry number: IRCT201104286319N1
We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open label"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but clear whether these were related to the intervention or outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Nishimori 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Japan Period of recruitment: not stated Number randomised: 28 Post-randomisation dropouts: not stated Revised sample size: 28 Average age (years): 50 Female: not stated NASH: not stated Diabetes mellitus: 28 (100.0%) Inclusion criteria: NAFLD; type 2 diabetes mellitus
Interventions	Group 1: Carbohydrate-restricted diet (n = 14) Further details: LCD (70 - 130 g/day of carbohydrate) Group 2: Calorie-restricted diet (n = 14) Further details: CRD (calories of 25 kcal/kg of ideal body weight per day)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated

Nishimori 2018 *(Continued)*

	Trial name/trial registry number: not stated We tried to contact the authors in December 2020.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Nourian 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Number randomised: 82 Post-randomisation dropouts: 13 (15.9%) Revised sample size: 69 Reasons for post-randomisation dropouts: lost to follow-up Average age: 49 years Female: 47 (68.1%) NASH: not stated Diabetes mellitus: 4 (5.8%) Inclusion criteria: diagnosis of NAFLD by an expert physician (NAFLD was confirmed by sonography, and was associated with higher levels of both ALT and AST more than 31 in men and women), aged 20 - 50 years old; being overweight or obese (BMI ≥ 25); absence of drinking alcohol; and willingness to participate in the study Exclusion criteria: missing more than 2 education sessions; weight loss during last 6 months; menopause, pregnancy or breastfeeding; any medical condition such as renal disorders, malignancies, thyroid disorders, psychosis and autoimmune diseases and consumption of some medications such as anti-oxidant or weight loss supplements
Interventions	Participants were randomly assigned to 2 groups Group 1: Dietary advice (n = 36)

Nourian 2020 *(Continued)*

	Further details: Participants were encouraged to increase their intake of fruits, vegetables, complex carbohydrate, low dairy fat, healthy fat, white meat and fish and also avoid the intake of unhealthy fats and refined carbohydrate Group 2: No active intervention (n = 33)
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up (months): 2
Notes	Source of funding (quote): "This study was supported by the Isfahan University of Medical Sciences, Isfahan, Iran" Trial name/trial registry number: IRCT2014101811763N17 We tried to contact the authors in March 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done using computer-generated random numbers and by a trained personnel who was blinded to participant's characteristics"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done using computer-generated random numbers and by a trained personnel who was blinded to participant's characteristics"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: many participants were excluded, with the reason for exclusion loss to follow-up. It is not clear whether this may be related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Oh 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Japan Period of recruitment: not stated Number randomised: 61 Post-randomisation dropouts: 9 (14.8%) Revised sample size: 52 Reasons for post-randomisation dropouts: Group 1: 1 lost to follow-up; Group 2: 5 lost to follow-up; 1 abandoned the study, 2 discontinued intervention Average age (years): 49

Oh 2017 *(Continued)*

	Female: 0 (0.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: NAFLD; sedentary (≤ 1 exercise session per week and ≤ 30 minutes per session); obese Exclusion criteria: Adverse medical problems; declined to participate
Interventions	Group 1: Resistance exercise (n = 19) Further details: The RT program referred to the ACSM 2009 position paper on "Progression Models in Resistance Training for Healthy Adults". The programme consisted of 1) sit-ups, 2) leg presses, 3) leg extensions, 4) leg curls, 5) chest presses, 6) seated rows, and 7) pull-downs (Selection MED, Technogym, Cesena, Italy). The amount of load lifted was updated according to the results of the monthly direct 1-RM strength test. The total energy expenditure for the RT programme was estimated to be about 180 kcal in our preliminary experiment. These values are similar to HIAT Group 2: Aerobic exercise (n = 33) Further details: the HIAT consisted of 3 sets of 3-min cycling sessions at 80 ~ 85% VO2Max with a 2-min active rest at 50% VO2Max between sets (13 mins, 180 kcal), the MICT consisted of 40 mins of cycling at 60 ~ 65% VO2Max (40 min, 360 kcal)
Outcomes	Outcomes reported: fibrosis score Follow-up (months): 3
Notes	Source of funding (quote): "This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 2604307, No. 15K15037, No. 14F04009, and No. 16H03255)." Trial name/trial registry number: UMIN000022901 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjects were assigned in a 1:1:1 ratio to one of the three intervention groups by a computerized method (EXCEL 2010; Microsoft Corp, Redmond, USA)"
Allocation concealment (selection bias)	Low risk	Quote: "A research assistant who had no interaction with the subjects generated the random allocation sequence and enrolled the subjects"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Panganiban 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 42 Post-randomisation dropouts: 3 (7.1%) Revised sample size: 39 Reasons for post-randomisation dropouts: lack of adherence, MRI bore size was exceeded Average age: not stated Female: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Obese children and adolescents with biopsy-proven NAFLD and metabolic syndrome
Interventions	Participants were randomly assigned to 2 groups Group 1: Carbohydrate-restricted diet (n = 19) Further details: 20% CHO: 35% protein: 45% fat for 6 months Group 2: Calorie-restricted diet (n = 20) Further details: 50% CHO: 20% protein: 30% fat for 6 months Both groups received dietary and behavioural advice
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in March 2021

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: some participants were excluded for lack of adherence- these may be related to the intervention and the outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and none of the outcomes of interest for this review were reported
Other bias	Low risk	Comment: no other bias noted.ere

Properzi 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Australia Period of recruitment: not stated Number randomised: 51 Post-randomisation dropouts: 3 (5.9%) Revised sample size: 48 Reasons for post-randomisation dropouts: Group 1: 1 withdrawn for personal reason, Group 2: 1 dropout for non-compliance with diet; 1 excluded due to excess alcohol Average age (years): 52 Female: 25 (52.1%) NASH: not stated Diabetes mellitus: 15 (31.3%) Inclusion criteria: diagnosis of NAFLD, with HS > 5.5% as determined by MRS; average alcohol consumption of < 20 g/day or 140 g/week for women or < 30 g/day or 210 g/week for men Exclusion criteria: secondary causes of NAFLD (e.g. medication-induced); unstable body weight (variation > 5% within the preceding 3 months); current use of weight-loss medications (e.g. Orlistat); current use of pioglitazone; other liver disease (viral hepatitis, autoimmune or cholestatic liver disease, Wilson's disease, haemochromatosis, or alpha-1 anti-trypsin deficiency); unstable diabetes (HbA1c >8.5%); decompensated cirrhosis (international normalised ratio > 1.3, platelets < 100 × 109/mm, bilirubin > 20 mmol/L, albumin < 35 g/L, ascites, or hepatic encephalopathy); renal failure; malignancy (aside from skin cancer); inability to provide informed consent; claustrophobia preventing MRS examination; current smoking; atrial fibrillation preventing SphygmoCor assessment; and pregnancy or lactation
Interventions	Group 1: Mediterranean diet (n = 24) Further details: The MD was based on analysis of actual foods consumed in traditional Cretan diets (18) with alterations to allow for standardisation of protein intake with the LF diet. Target macronutrient energy contributions were 40% from carbohydrate; 35 - 40% from fat (with < 10% of energy as saturated fat); 20% of energy as protein Group 2: Fat restricted diet (n = 24) Further details: The LF diet was based on National Health and Medical Research Council and American Heart Association Dietary recommendations. Target macronutrient energy contributions for the LF diet were 50% from carbohydrate; 30% from fat (with < 10% of energy as saturated fat); 20% from protein. Additional details: 12 weeks
Outcomes	Outcomes reported: mortality at maximum follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximum follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma, quality of life (maximum follow-up), fibrosis score Follow-up (months): 3
Notes	Source of funding (quote): "Catherine Properzi received an Australian Government Research Training Program Scholarship. Cobram Estate Olive Oil donated a portion of the olive oil supplied on the Mediterranean intervention." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomized in a 1:1 fashion using randomly selected envelope-concealed allocations in blocks of four, which were prepared prior to trial commencement." Comment: further information was not available

Properzi 2018 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomized in a 1:1 fashion using randomly selected envelope-concealed allocations in blocks of four, which were prepared prior to trial commencement." Comment: further information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and principal investigators were blinded (author replies)" Comment: the healthcare professionals were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "assessor of the primary outcome was blinded (author replies)" Comment: the assessors of the clinical outcomes were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the study authors reported mortality, adverse events, and resolution of fatty liver
Other bias	Low risk	Comment: no other bias noted

Pugh 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: not stated Number randomised: 31 Post-randomisation dropouts: 10 (32.3%) Revised sample size: 21 Reasons for post-randomisation dropouts: discontinued baseline assessment (4), discontinued intervention (1), did not maintain habitual diet (2), declined post-intervention assessments (3) Average age (years): 48 Female: 12 (57.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Obese (waist circumference > 94 cm for men, > 80 cm for women) and sedentary (< 2 hours low-intensity physical activity/week, with none performing any structured or vigorous physical activity) "Caucasian", no history of excessive alcohol intake (average weekly consumption < 21 units for men, < 14 units for women). No participant had a history of type 2 diabetes mellitus or ischaemic heart disease, nor any contraindications to exercise. Only nonsmokers were recruited. Premenopausal women (n = 4) were tested during the early follicular phase of the menstrual cycle (days 1 – 7 of the menstrual cycle, immediately following the onset of menstruation)
Interventions	Group 1: Supervised aerobic exercise (n = 13) Further details: Following a familiarisation session, participants attended the university gymnasium on a weekly basis and were provided with full supervision and guidance from a trained exercise physiologist. Exercise training comprised a combination of treadmill and cycle ergometer-based exercise which progressively increased in both intensity and duration throughout the course of the intervention. Based on individual basal fitness level, participants began the intervention with 30 mins moderate-intensity aerobic exercise 3 times/wk at 30% of HRR for the initial 4 wks. Intensity increased to 45% HRR for the following 4 wks, until week 8, where HRR remained at 45%, but the duration of each session in-

Pugh 2014 *(Continued)*

	creased to 45 mins. From week 12, participants were exercising 5 times/wk for 45 mins at 60% of their individual HRR. There were no dietary modifications throughout the course of the exercise intervention, confirmed by the use of a standard food diary. 3-day food diaries were collected immediately prior to and following the exercise intervention and subsequently analysed for macronutrient intake (total energy, carbohydrate, fat, protein, and sugars) Group 2: Dietary advice plus exercise advice (n = 8) Further details: Conventional care consisted of lifestyle advice provided at clinical consultation. Participants were simply advised by their hepatologist or specialist nurse to modify their lifestyle by healthy eating and increasing their physical activity. There was no supervision or guidance beyond the initial advice
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: "We thank the European Foundation for the Study of Diabetes (EFSD) for funding this study [09/H1008/1]." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned via a single-blinded computer-generated sequence"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Ramirez 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 19 Post-randomisation dropouts: not stated Revised sample size: 19

Ramirez 2016 *(Continued)*

	Average age (years): not stated Female: 5 (26.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Age 11 - 17 years; metabolic syndrome; biopsy-proven NAFLD
Interventions	Group 1: Carbohydrate-restricted diet (n = not stated) Further details: carbohydrate–restricted diet (20% carbohydrates, 35% protein and 45% fat) Group 2: Calorie-restricted diet (n = not stated) Further details: calorie-restricted diet (50% carbohydrate, 15 - 20% protein and 30 - 35% fat)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Ramon-Krauel 2013

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 17 Post-randomisation dropouts: 1 (5.9%) Revised sample size: 16

Ramon-Krauel 2013 *(Continued)*

	Reasons for post-randomisation dropouts: Difficulty attending study visits (1) Average age (years): 13 Female: 3 (18.8%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Age 8 - 17 years; elevated ALT; obesity defined as a BMI ≥ 95th percentile for age and sex; ability to tolerate MRI; willingness to attend study sessions; ≥ 9% liver fat as measured by MRS Exclusion criteria: Any major systemic disease (including diabetes); other hepatic disease (including viral or autoimmune hepatitis; Wilson's disease, a-1-antitrypsin deficiency); any alcohol consumption; medication or vitamin supplements that could affect liver fat or body weight; weight > 300 pounds; weight change > 10% of total body weight within the last 6 months; pregnancy
Interventions	Group 1: Low glycaemic-index diet (n = 7) Further details: The diets were prescribed ad libitum, and the participants were educated to eat to satiety and snack when hungry. Both groups had a targeted proportion of energy from protein of 20 – 25%. The low-GL prescription emphasised the selection of carbohydrate-containing foods with a low to moderate glycaemic load (nonstarchy vegetables, fruits, legumes, and dairy). The targeted proportion of energy from carbohydrate and fat were 40% and 35 – 40%, respectively Group 2: Fat-restricted diet (n = 9) Further details: The diets were prescribed ad libitum, and the participants were educated to eat to satiety and snack when hungry. Both groups had a targeted proportion of energy from protein of 20 – 25%. The low-fat diet was based on 2003 American Diabetes Association and 2002 American Gastroenterological Association recommendations to limit total fat to < 30% of total calories and saturated fat to < 10%. We aimed for 55 – 60% of energy from carbohydrates and 20% from fat with < 10% from saturated fat
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This study was supported by grants from the Allen Foundation, the New Balance Foundation, and the National Institute of Diabetes and Digestive and Kidney Diseases (K24DK082730 and T32DK07699). Additional support was provided from the National Center for Research Resources (UL1 RR025758) to the Harvard Catalyst Clinical and Translational Science Center at Harvard University." Trial name/trial registry number: NCT00480922 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it was not clear whether these were related to the intervention or outcomes

Ramon-Krauel 2013 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Rezende 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: not stated Number randomised: 44 Post-randomisation dropouts: 4 (9.1%) Revised sample size: 40 Reasons for post-randomisation dropouts: Non-adherence to exercise programme (2); non-adherence to protocol (1); insertion of intra-gastric balloon (1) Average age (years): 55 Female: 40 (100.0%) NASH: not stated Diabetes mellitus: 31 (77.5%) Inclusion criteria: Postmenopausal women; non-smoker; biopsy-proven NAFLD Exclusion criteria: Hormone therapy; alcohol abuse (ethanol consumption > 20 g/d); HIV, hepatitis B or C; any other chronic liver diseases; any physical or cardiovascular limitation that could preclude the participant from undergoing physical testing or exercise training; significant changes in dietary habits and/or having begun a physical activity programme in the past 3 months; non-adherence to the study protocol
Interventions	Group 1: Supervised aerobic exercise (n = 19) Further details: 24 weeks of a supervised exercise training programme, performed twice a week. Training sessions were composed of a 5-minute warm-up followed by 30 to 50 minutes of treadmill aerobic exercise and 5 minutes of cooling down. Exercise sessions lasted 30 to 50 minutes, with increases in exercise duration every 8 weeks. The intensity was increased from VAT up to 10% below RCP Group 2: No active intervention (n = 21) Further details: control group
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up (months): 6
Notes	Source of funding (quote): "Funding/support: National Council of Technological and Scientific Development (CNPQ). We thank the Alves de Queiroz Family Fund for Research and CNPq for financial support." Trial name/trial registry number: NCT02427087 We tried to contact the authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The random sequence generator was obtained by www.random.org"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available

Rezende 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Rodriguez-Hernandez 2011

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Mexico Period of recruitment: not stated Number randomised: 59 Post-randomisation dropouts: 5 (8.5%) Revised sample size: 54 Reasons for post-randomisation drop-outs: Lost to follow-up Average age (years): 46 Female: 54 (100.0%) NASH: not stated Diabetes mellitus: 8 (14.8%) Inclusion criteria: obese women, aged 20 to 65 years, healthy, non-pregnant, diagnosis of NAFLD, similar social and economic background Exclusion criteria: Previous diagnosis of hepatic disease, serum creatinine level > 1.5 mg/dL, severe life-limiting medical illness, pregnancy, active participation in other dietary programme, use of weight-loss drugs, or alcohol consumption > 30 g per day
Interventions	Group 1: Fat-restricted diet (n = 26) Further details: LFD was based on 21% of daily energy intake from fat, < 10% saturated fat, 25% protein, and 54% carbohydrate Group 2: Carbohydrate-restricted diet (n = 28) Further details: the LCD was based on the following percentage of total energy intake per nutrient: 27% protein, 28% fat and 45% carbohydrate
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This work was partially supported by Fundación IMSS, A.C." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Rodriguez-Hernandez 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it was not clear whether these were related to the intervention or outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Roy 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: not stated Period of recruitment: not stated Number randomised: 60 Post-randomisation dropouts: not stated Revised sample size: 60 Average age (years): not stated Female: not stated NASH: not stated Diabetes mellitus: 60 (100.0%) Inclusion criteria: Outpatient type 2 diabetics with NAFLD
Interventions	Group 1: Dietary advice plus exercise advice (n = 30) Further details: Lifestyle modification counselling plus standard care Group 2: No active intervention (n = 30) Further details: Standard care
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up (months): 4
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020
Risk of bias	

Roy 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Schattenberg 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: not stated Number randomised: 29 Post-randomisation drop-outs: 1 (3.4%) Revised sample size: 28 Reasons for post-randomisation drop-outs: not stated Average age (years): 45 Female: 7 (25.0%) NASH: 28 (100.0%) Diabetes mellitus: not stated Inclusion criteria: Histologically-confirmed NASH or a combination of M30 levels above 200 U/l and hepatic steatosis on ultrasound; age 18 - 75
Interventions	Group 1: Dietary advice (n = 15) Further details: LcS plus N (Lactobacillus casei Shirota plus dietary counselling): dietary counselling aiming at a reduction of fructose consumption by 50% compared to screening, 6.5 x 109 counts of lactobacillus casei Shirota plus 2.1 g soluble fibre twice daily Group 2: No active intervention (n = 13) Further details: Lactobacillus alone
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximum follow-up, decompensation (number of people), cirrhosis (number of people) Follow-up (months): 3

Schattenberg 2017 *(Continued)*

Notes	Source of funding (quote): "This study was partly funded by H2020 under grant no. 634413 for the EPoS projects and by Yakult Europe." Trial name/trial registry number: NCT02366052, NUCES NASH We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Blinded lab analysis (author replies)" Comment: the assessors of the clinical outcomes were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but unclear whether these were related to the intervention or outcomes
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but mortality and adverse events were reported
Other bias	Low risk	Comment: no other bias noted

Selezneva 2014

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Russia Period of recruitment: not stated Number randomised: 174 Post-randomisation dropouts: not stated Revised sample size: 174 Average age (years): not stated Female: 86 (49.4%) NASH: 174 (100.0%) Diabetes mellitus: not stated Inclusion criteria: NASH patients
Interventions	Group 1: Isocalorie diet (n = 116) Further details: for ICD the caloric consumption was established according to the recommended daily values for proteins, fat and carbohydrates for ideal BMI for every participant Group 2: Calorie-restricted diet (n = 58) Further details: Caloric restriction was achieved by decreasing consumption of carbohydrates and fat in LCD

Selezneva 2014 *(Continued)*

Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and none of the outcomes of interest for this review were reported
Other bias	Low risk	Comment: no other bias noted

Shidfar 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Number randomised: 50 Post-randomisation dropouts: 7 (14%) Revised sample size: 43 Reasons for post-randomisation dropouts: not stated Average age: 46 years Female: 17 (39.5%) NASH: not stated Diabetes mellitus: 0 (0%) Inclusion criteria: increase of the AST and ALT enzymes, the elimination of all other causes for the increase in the liver enzymes (other liver diseases), age of 20 – 65 years, BMI of 25 – 40 kg/m^2 Exclusion criteria: no use of hepatotoxic medicines, no history of ≥ 30 gr/d alcohol consumption, no cardiovascular disease, no diabetes, no pregnancy or breastfeeding, no smoking, no consumption of mineral and multivitamins supplements, no consumption of olive products, and lipid-lowering medicines in the last 3 months

Shidfar 2018 *(Continued)*

Interventions	Participants were randomly assigned to 2 groups Group 1: Mono-unsaturated fatty acid plus calorie-restricted diet (n = 21) Further details: hypocaloric diet enriched with olive oil (20% of total energy intake) for 12 weeks Group 2: Calorie-restricted diet (n = 22) Further details: hypocaloric diet with normal fat for 12 weeks
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: "This paper was supported by the Khoramshahr Oil Company. The authors would like to thank Javad Salimi, head of the oil factory of Ganjeh, Roudbar, and Aboozar Falahzadeh, head of the oil factory laboratory" Trial name/trial registry number: IRCT201111022709N20 We tried to contact the authors in March 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "None of the participants know about the other group and alternative treatment". Comment: information about blinding of healthcare professionals was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 7 participants excluded from analysis: the reasons for exclusion were not provided.
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and none of the outcomes of interest for this review were reported
Other bias	Low risk	Comment: no other bias noted

Sima 2014

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 25 Post-randomisation dropouts: not stated Revised sample size: 25 Average age (years): not stated Female: not stated NASH: 25 (100.0%)

Sima 2014 *(Continued)*

	Diabetes mellitus: not stated Inclusion criteria: NASH; age 18 - 55 years
Interventions	Group 1: Calorie-restricted diet plus aerobic exercise (n = 12) Further details: Calorie-restricted diet plus aerobic exercise:CR-diet included 500 kcal of energy less than the estimated daily energy requirement and aerobic exercise consisted of 35 to 50 minutes walking, jogging and running, for a period of 8 weeks, 3 days a week with 55 - 60% of the HRR Group 2: Calorie-restricted diet (n = 13) Further details: Calorie-restricted diet: CR-diet included 500 kcal of energy less than the estimated daily energy requirement
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Sullivan 2012

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 33 Post-randomisation dropouts: 15 (45.5%) Revised sample size: 18

Sullivan 2012 *(Continued)*

	Reasons for post-randomisation dropouts: Dropped out during baseline testing (4); self-withdrew (5); hospitalisation or work-related injury (4); did not follow study protocol (2) Average age (years): 48 Female: 13 (72.2%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Obesity; NAFLD; sedentary (< 1 hour of self-reported exercise per week) Exclusion criteria: Chronic liver disease other than NAFLD; Michigan Alcohol Screening Test score > 4; diabetes; plasma triglyceride concentration > 400 mg/dL
Interventions	Group 1: Aerobic exercise (n = 12) Further details: Participants in the exercise group were instructed to exercise for 30 - 60 mins, 5 times a week at 45% - 55% of their V̇O2 peak (i.e. brisk walk). Participants initiated their exercise programme by walking on a treadmill for 15 - 30 minutes at a heart rate equivalent to 45 - 55% of their pretraining V̇O2 peak, and progressively increased the duration of exercise during the initial 4 weeks until 30 - 60 mins of moderate intensity exercise 5 times a week was achieved. Participants exercised under direct supervision once a week in our exercise facility; the remaining sessions were completed at home. Compliance with home exercises was assessed by recording heart rate (Polar Electro heart rate monitor, Kempele, Finland) during all exercise sessions. Participants were required to complete 16 weeks of exercise training; those who completed < 3 exercise sessions in any week were required to extend their training period by an additional week Group 2: No active intervention (n = 6) Further details: Participants in the control group were instructed to continue their current activities of daily living; they were contacted once a week to review compliance with the study protocol and reported to the research centre once a month to obtain accurate body weight measurements
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This research was supported by National Institutes of Health grants UL1 RR24992 KL2 RR024994 (Washington University Clinical and Translational Science Award), DK052574 (Digestive Disease Research Core Center), DK56341 (Nutrition Obesity Research Center), DK78738, DK37948, and HD57796." Trial name/trial registry number: NCT00771108 We tried to contact the authors in December 2020.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization scheme"
Allocation concealment (selection bias)	Low risk	Quote: "randomized into the control or the exercise group by an independent statistician who did not participate in subject enrolment "
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes

Sullivan 2012 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Tutino 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 83 Post-randomisation dropouts: 21 (25.3%) Revised sample size: 62 Reasons for post-randomisation dropouts: not stated Average age (years): 51 Female: 34 (54.8%) NASH: not stated Diabetes mellitus: 5 (8.1%) Inclusion criteria: Age 30 - 60; BMI > 25; moderate to severe NAFLD Exclusion criteria: Stroke; peripheral arterial disease; cardiovascular disease or revascularisation procedures; treatment with insulin or oral hypoglycaemic drugs; fasting glucose > 126 mg/dL; alcohol intake > 20g daily; severe medical condition that may impair participation in a nutritional intervention study; special diets or involved in a weight-loss programme; recent weight loss, and those who cannot follow a diet for religious or other reasons
Interventions	Group 1: Aerobic exercise plus resistance exercise (n = 29) Further details: Physical activity interventions included 2 different types of exercise programmes: PA1 based on the aerobic activity programme and PA2 based on the combination of aerobic activity and resistance training Group 2: Mediterranean diet (n = 18) Further details: Low-glycaemic index Mediterranean diet (LGIMD) based on consumption of bread and pasta derived from real wholemeal flour (not reconstituted), vegetables and seasonal fruit, legumes, nuts, oily fish and white meats in moderate amounts, low-fat cheese and eggs weekly, and extra virgin olive oil Group 3: no active intervention (n = 15) Further details: Control Diet (CD) based on CREA-AN guidelines
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This work was supported by RC 2012-2014, Linea 4, C. 32 (D.D.G. n. 110/2014) and “PO Puglia FESR 2007-2013, Asse I, Linea 1.2, Accordo di Programma Quadro in materia di Ricerca Scientifica, intervento “Reti di Laboratori Pubblici di Ricerca”, progetto L.A.I.F.F.—RETE DI LABORATORI PER L’INNOVAZIONE NEL CAMPO DEGLI ALIMENTI FUNZIONALI (codice n. 47)" Trial name/trial registry number: CT02347696 We tried to contact the authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computerized random numbers sequence"

Tutino 2018 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Interviewers and staff members who obtained outcome measurements, were not informed about diet or physical activity programs assigned"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it was not clear whether these were related to the intervention or outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Wang 2008

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 57 Post-randomisation dropouts: not stated Revised sample size: 57 Average age (years): 14 Female: 24 (42.1%) NASH: 57 (100.0%) Diabetes mellitus: not stated Inclusion criteria: Age 10 - 17 years; obesity Exclusion criteria: History of alcohol intake; positive markers for other liver diseases (e.g. hepatitis)
Interventions	Group 1: Aerobic exercise plus FatRestrict Calorie-restricted diet (n = 19) Further details: They took part in the summer camp without their parents. The Nuote Nutrient Center which was in charge of the camp, consisted of nutrient experts, physical experts and paediatricians. Physical exercises, including swimming, playing basketball and table tennis, were taken freely for 3 hours of aerobic exercise each day. The diet management followed the principle of low-calorie (high in carbohydrate (50%) and low in fat (10%)) with the aim of a reduction in daily intake by 250 kcal. A total daily calorie intake was controlled from 1300 kcal to 1600 kcal based on the individual's age. 2 eggs and a bowl of soy milk were supplied at breakfast. Pork, egg, fish, shrimp, fresh vegetable, rice and corn were served at lunch and dinner. No beverage but mineral water was provided. They were requested to get up at 6:30 am and take aerobic physical exercise in the morning and afternoon. In the evening they did their homework and watched TV for an hour, then went to sleep at 21:00 pm. The summer camp lasted 1 month Group 2: No active intervention (n = 38) Further details: control group
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up (months): 1

Wang 2008 *(Continued)*

Notes	Source of funding (quote): "Supported by Science and Technology Department of Zhejiang Province of China, No. 2005C24001, No. 2004C30064" Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Wang 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2014 - 2015 Number randomised: 120 Post-randomisation dropouts: not stated Revised sample size: 120 Average age (years): 37 Female: 50 (41.7%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: diagnosis of NAFLD
Interventions	Group 1: Aerobic exercise plus calorie-restricted diet (n = 80) Further details: Exercise outdoors at a speed of 4 km/h. The total daily caloric intake of all participants was reduced by 2092 kJ compared with the initial (500 kcal) Group 2: Calorie-restricted diet (n = 40) Further details: no further details

Wang 2016 *(Continued)*

Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Wong 2013

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Hong Kong Period of recruitment: not stated Number randomised: 154 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 154 Average age (years): 51 Female: 82 (53.2%) NASH: not stated Diabetes mellitus: 12 (7.8%) Inclusion criteria: Age 18 - 70 years; fatty liver on H-MRS plus ALT above 30 in men and 19 in women Exclusion criteria: Hepatitis B/C; alcohol consumption above 20 g per day in men and 10 g per day in women; liver decompensation; terminal illness and cancer (including hepatocellular carcinoma)
Interventions	Group 1: Dietary advice plus aerobic exercise (n = 77) Further details: The participants attended dietary consultation sessions weekly in the first 4 months, and monthly in the following 8 months. Each participant was given an individualised menu plan. The

Wong 2013 *(Continued)*

	dietary component and portion sizes of the menu plan were based on the recommendations of the American Dietetic Association. A varied balanced diet with an emphasis on fruit and vegetables, and moderate-carbohydrate, low-fat, low-glycaemic index and low calorific products in appropriate portions was encouraged. The diet resulted in a relative increase in energy consumption from proteins, which also promoted satiety. moderate-intensity aerobic exercise for 30 mins, 3 to 5 days a week Group 2: No active intervention (n = 77) Further details: control: participants were encouraged to reduce carbohydrate and fat intake, and to exercise for at least 3 times a week, 30 mins per session
Outcomes	Outcomes reported: mortality at maximum follow-up, liver transplantation at maximum follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease Follow-up (months): 12
Notes	Source of funding (quote): "This study was supported in part by the Nutritional Research Foundation of the United Kingdom, the direct grant of the Chinese University of Hong Kong (ref 2011.1.025) and a grant from the Research Grants Council of the Hong Kong SAR (Project No. SEG CUHK_02)." Trial name/trial registry number: NCT00868933 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated list of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Treatment assignments were concealed in consecutively-numbered sealed envelopes, which were opened sequentially upon patient enrolment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinicians and radiographers who analyzed 1H-MRS results were blinded to the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Yao 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 103 Post-randomisation dropouts: 12 (11.7%)

Yao 2018 *(Continued)*

	Revised sample size: 91 Reasons for post-randomisation dropouts: Group 1: 4 dropped out (2 did not have enough time to participate, 2 refused to answer the phone); 1 lack of compliance; Group 2: 1 lived far away (and dropped out), 1 had fracture from wrestling; 1 lack of compliance; group 3: 1 withdrew, 3 lost to follow-up Average age (years): 58 Female: 55 (60.4%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: consistent with 2010 edition of guidelines for the diagnosis and treatment of NAFLD; grade 5 muscle strength; without regular exercise; aged between 18 and 75 years; conscious and able to communicate Exclusion criteria: a variety of acute and chronic infections, cancer, and other immune diseases; serious acute and chronic diseases, such as acute cerebral infarction, lumbar disc herniation; proliferative retinopathy; pregnant or lactating women; long-term drinking history defined as a long history of alcohol consumption for more than 5 years, which was equivalent to male alcohol > 140 g/weeks, female > 70 g/weeks; had no history of viral and autoimmune hepatitis, and drug-induced liver diseases
Interventions	Group 1: Resistance exercise (n = 31) Further details: Resistance training consists of 3 phases: warm-up (5 mins joint movement), training (50 mins), and relaxing (5 mins). Participants performed the training from 3 series of 8 repetitions at intensity of 30% - 40% of 1 repetition maximum (1RM) for 40 mins per day in the early stage of the exercise (within 2 weeks), gradually moving to 3 series of 10 repetitions at intensity of 60% - 70% 1RM for 60 mins per day, with 1 minute of recovery between series. The exercise was performed 3 times per week on non-consecutive days for 22 weeks. The load gradually increased depending on the individual ability of the participant and with consultation of professional personnel. Participants were considered to have finished the study if they attended 66 times or more in 22 weeks. All participants came to centres, and carried out the exercise under the guidance of professional personnel Group 2: Aerobic exercise (n = 29) Further details: aerobic exercise consisted of 3 phases: warming-up (5 mins), training (50 mins) and relaxing (5 mins). Aerobic exercise progressed from 40 mins per day at 45% - 55% maximum heart rate intensity in the initial stage of training (within 2 weeks), and gradually increased to 60 mins per day at 60% - 70% maximum heart rate intensity. Exercise was performed 3 times per week on non-consecutive days for 22 weeks. Participants who attended 66 times or more in 22 weeks were considered to have finished the study Group 3: no active intervention (n = 31) Further details: Control group
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people) Follow-up (months): 5.5
Notes	Source of funding (quote): "Funded by National Natural Scientific Foundation of China (81370923) and State Administration of Traditional Chinese Medicine (JDZX2015132)." Trial name/trial registry number: not stated We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly divided into three groups including aerobic, resistance and control group by sealed envelopes" Comment: further details were not available

Yao 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Zade 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 60 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 60 Average age (years): 41 Female: 30 (50.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: Age 25 - 75; ultrasound-diagnosed NAFLD Exclusion criteria: Alcohol consumption; pregnancy and lactation; hereditary haemochromatosis; jejunoileal bypass surgery or gastroplasty; hepatotoxic drugs (e.g.calcium channel blockers); hypothyroidism; Cushing's syndrome; renal failure; kidney stones
Interventions	Group 1: FatRestrict Calorie-restricted diet (n = 30) Further details: a DASH eating plan that consisted of 52 – 55% carbohydrates, 16 – 18% proteins and 30% total fats. The DASH diet was rich in fruits, vegetables, whole grains, and low-fat dairy products and low in saturated fats, cholesterol, refined grains, and sweets. Suggested sodium in the DASH diet was < 2400 mg/day. both diets were designed to be calorie-restricted Group 2: Calorie-restricted diet (n = 30) Further details: The control diet was also designed to contain 52 – 55% carbohydrates, 16 – 18% protein and 30% total fats. Both diets were designed to be calorie-restricted
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This study was founded by a grant from the Vicechancellor for Research, KUMS, and Iran." Trial name/trial registry number: IRCT201311215623N14 We tried to contact the authors in December 2020
Risk of bias	

Zade 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment was performed using computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization and allocation were done by a trained nutritionist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomization and allocation were done by a trained nutritionist and were concealed from the researcher and patients until the main analyses were completed"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization and allocation were done by a trained nutritionist and were concealed from the researcher and patients until the main analyses were completed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Zelber-Sagi 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Israel Period of recruitment: not stated Number randomised: 82 Post-randomisation dropouts: 18 (22.0%) Revised sample size: 64 Reasons for post-randomisation dropouts: Lost to follow up (6); withdrew from study (4); > 3 kg weight change (5); adverse events: knee pain (1), shoulder pain (1), back pain (1); Average age (years): 46 Female: 30 (46.9%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Age 20 - 65 years; ultrasound-proven fatty liver Exclusion criteria: Known secondary liver disease (including hepatitis B/C); excessive alcohol consumption (defined as ≥ 30 g/day in men or ≥ 20 g/day in women); medication that may elevate ALT or lead to hepatic steatosis; diabetes; major chronic diseases (e.g. renal, cardiovascular, lung); uncontrolled hypertension; inflammatory bowel disease; active cancer; autoimmune disorders; orthopaedic contraindications for resistance training; patients regularly performing resistance training
Interventions	Group 1: Resistance exercise (n = 33) Further details: The RT programme was according to the ACSM 2009 position paper on “Progression Models in Resistance Training for Healthy Adults”. Exercises included: leg press, leg extension, leg curl, seated chest press, seated rowing, latissimus pull down, biceps curl and shoulder press with 8 - 12 repetitions, 3 sets for each exercise with 1 - 2 mins rest between sets, for a total duration of about 40 mins Group 2: Aerobic exercise (n = 31)

Zelber-Sagi 2014 *(Continued)*

	Further details: 8 stretching exercises for the major muscle/tendon groups using the static stretching technique. The participants performed 4 repetitions of these static stretches each lasting 20 secs. Each session was performed on 3 non-consecutive days a week
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: NCT01264198 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed envelopes randomization stratified by gender" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it is not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation drop-outs; some were related to the intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and neither mortality nor resolution of fatty liver was reported
Other bias	Low risk	Comment: no other bias noted

Zhang 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 220 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 220 Average age (years): 54 Female: 149 (67.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: Age 40 - 65 years; central obesity (waist circumference ≥ 90 cm in men and ≥ 85 cm in women); NAFLD

Zhang 2016 *(Continued)*

	Exclusion criteria: Acute or chronic viral hepatitis; drug-induced liver diseases, or autoimmune hepatitis; diabetes; uncontrolled hypertension; chronic kidney disease; hyperthyroidism; myocardial infarction within 6 months, or heart failure (NYHA class III or IV); participating in weight loss programmes; medical condition-limiting exercise capability; alcohol excess, consuming more than a mean of 140 g of ethanol (10 alcoholic drinks) per week in men and 70 g of ethanol (5 drinks) in women, during the past 6 months
Interventions	Group 1: Aerobic exercise (n = 146) Further details: vigorous-moderate exercise group were instructed to participate in a 6-month vigorous exercise programme followed by a 6-month moderate exercise programme. Vigorous exercise was jogging on treadmill for 30 mins, 5 sessions a week. Moderate exercise was brisk walking, 120 steps/minute, 30 min/session, 5 sessions a week. or moderate exercise programme were instructed to participate in a 12-month moderate exercise programme. Moderate exercise was brisk walking, 120 steps/minute, 30 min/session, 5 sessions a week Group 2: No active intervention (n = 74) Further details: control group
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 12
Notes	Source of funding (quote): "This study was supported by grant 3502Z20100001 from the First Affiliated Hospital of Xiamen University and Xiamen Systems Biology Research Program for Metabolic Disease." Trial name/trial registry number: NCT01418027 We tried to contact the authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization schedules were generated using SAS PROC PLAN in SAS statistical software (SAS Institute Inc) and concealed until an eligible participant was ready for enrolment"
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization schedules were generated using SAS PROC PLAN in SAS statistical software (SAS Institute Inc) and concealed until an eligible participant was ready for enrolment" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: because of the nature of the intervention, it was not possible to blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "study staff who collected data on study outcomes were unaware of study group assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: a pre-published protocol was not available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CLD: chronic liver disease; CMV: cytomegalovirus; CVD: cardiovascular disease: EBV: Epstein-Barr virus; GI: gastrointestinal; HRR: heart rate ratio; HTN: hypertension; H-MRS (or 1H-MRS or

MRS): magnetic resonance spectroscopy; IFG: impaired fasting glycaemia; MUFA: mono-unsaturated fatty acid: NASH: nonalcoholic steatohepatitis; PUFA: poly-unsaturated fatty acid; RCP: respiratory compensation point; T1DM, T2DM: type 1, type 2 diabetes mellitus; US: ultrasound; VAT: ventilatory anaerobic threshold; y/o: years old

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aller 2014	Comparison of variations in low-calorie diets
An 2015	Comparison of variations in dietary advice
Arefhosseini 2011	Comparison of variations in low-calorie diets
Austin 2020	Comparison of variations in lifestyle advice
Baldry 2017	Comparison of variations in low-calorie diets
Dela Cruz 2012	Comparison of lifestyle intervention with pharmacological intervention or nutritional supplement
Dorosti 2020	Comparison of variations in dietary advice
Dynnyk 2017	Comparison of variations in dietary advice
Haidari 2020	Comparison of variations in low-calorie diets
Lim 2020	Intervention not related to this review
Marin-Alejandre 2021	Comparison of variations in low-calorie diets
Nath 2020	Comparison of variations in aerobic exercise
NCT04193982	Comparison of lifestyle intervention with nutritional and pharmacological intervention
NCT04383951	Comparison of variations in dietary advice
NCT04520724	Comparison of variations in low-calorie diets
Negri 2020	Comparison of variations in low-calorie diets
Nigam 2014	All groups contained a mixture of PUFA and MUFA. The proportion of PUFA and MUFA differed between the groups (i.e. comparison of variations in intervention)
Nobili 2008	Intervention effects of nutritional supplementation were studied
Promrat 2010	Comparison of variations in dietary advice plus exercise advice
Rezaei 2019	All groups contained a mixture of PUFA and MUFA. The proportion of PUFA and MUFA differed between the groups (i.e. comparison of variations in intervention)
Ristic-Medic 2020	Comparison of variations in low-calorie diets
Ryan 2013	In this cross-over trial, the cross-over was at 6 weeks of intervention and the outcomes were not reported before the cross-over; this study is therefore not designed to address the objectives of this review and does not provide information to meet the objectives of this review
Schweinlin 2018	Comparison of variations in high-protein, low-carbohydrate diet

Study	Reason for exclusion
Simons 2021	Comparison of variations in low-carbohydrate diet
St George 2009	Comparison of variations in exercise advice
Sun 2012	Comparison of variations in dietary advice
TCTR20200411004	Intervention not related to this review
Vilar Gomez 2009	Intervention effects of nutritional supplementation was studied (i.e. not an intervention of interest for this review)
Whyte 2020	Included participants with suspected NAFLD rather than those diagnosed with NAFLD

Characteristics of studies awaiting classification *[ordered by study ID]*

Bahrololumi 2014

Methods	Randomised clinical trial
Participants	People with fatty liver
Interventions	Olive oil versus other oil
Outcomes	None of the outcomes of interest were reported in the abstract
Notes	Awaiting full text to confirm the composition of 'other oil' was different from that of olive oil (i.e. whether these were simply variations of lifestyle modification) and whether any outcomes of interest are reported in this trial

Grove 2020

Methods	Randomised clinical trial
Participants	People with fatty liver
Interventions	Dietary intervention versus not clear
Outcomes	None of the outcomes of interest were reported in the abstract
Notes	Awaiting full publication to confirm what the control group was and whether the trial will be eligible for the review

Jia 2018

Methods	Possible randomised clinical trial
Participants	People with fatty liver

Jia 2018 *(Continued)*

Interventions	Aerobic exercise plus dietary advice versus resistance exercise plus dietary advice versus dietary advice alone
Outcomes	None of the outcomes of interest were reported in the abstract
Notes	Awaiting full text to confirm whether this is a randomised clinical trial and whether any outcomes of interest are reported in this trial

Characteristics of ongoing studies *[ordered by study ID]*

IRCT20100524004010N31

Study name	IRCT20100524004010N31
Methods	Randomised clinical trial
Participants	People with NASH
Interventions	Hypocaloric diet (2 versions) versus no active intervention
Outcomes	None of the outcomes of interest for this review will be measured in this trial
Starting date	2020
Contact information	Azita Hekmatdoost (hekmat@sina.tums.ac.ir)
Notes	

NCT03354247

Study name	NCT03354247
Methods	Randomised clinical trial
Participants	People with fatty liver
Interventions	Mediterranean diet plus dietary advice plus exercise advice versus dietary advice plus exercise advice
Outcomes	The only outcome of interest for this review in this trial is resolution of fatty liver
Starting date	2017
Contact information	Piero Portincasa (NCT03354247, piero.portincasa@uniba.it)
Notes	

NCT03518294

Study name	NCT03354247

NCT03518294 *(Continued)*

Methods	Randomised clinical trial
Participants	People with non-alcoholic steatohepatitis (NASH)
Interventions	Supervised aerobic exercise versus no active intervention
Outcomes	The only outcomes of interest for this review in this trial are health-related quality of life and fibrosis
Starting date	2018
Contact information	Gloriany Rivas (NCT03518294, grivas@pennstatehealth.psu.edu)
Notes	

NCT04283942

Study name	NCT04283942
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Hypocaloric diet versus no active intervention
Outcomes	None of the outcomes of interest for this review will be assessed in this trial
Starting date	2020
Contact information	Hua Bian (NCT04283942, bianhuaer@126.com)
Notes	

NCT04355910

Study name	NCT04283942
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Hypocaloric diet versus no active intervention
Outcomes	None of the outcomes of interest for this review will be assessed in this trial
Starting date	2020
Contact information	Peiwen Zhang (NCT04355910, 313743920@qq.com)
Notes	

NCT04369521	
Study name	NCT04440540
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Calorie restricted diet plus dietary advice plus exercise advice versus dietary advice plus exercise advice
Outcomes	Liver fibrosis
Starting date	2020
Contact information	Azita Hekmatdoost (NCT04369521,a_hekmat2000@yahoo.com)
Notes	

NCT04440540	
Study name	NCT04440540
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Dietary advice versus no active intervention
Outcomes	None of the outcomes of interest for this review will be assessed in this trial
Starting date	2020
Contact information	Winnie CW Chu (NCT04440540, winniechu@cuhk.edu.hk)
Notes	

ADDITIONAL TABLES

Table 1. Summary of characteristics of included studies

Variables	Summary
Participant characteristics	The mean or median age in the trials ranged from 13 to 65 years in the trials that reported this information (Wang 2008; De Luis 2010; Hallsworth 2011; Rodriguez-Hernandez 2011; Sullivan 2012; Bacchi 2013; Eckard 2013; Hickman 2013; Ramon-Krauel 2013; Wong 2013; Kani 2014; Pugh 2014; Zelber-Sagi 2014; Hallsworth 2015; Abd El-Kader 2016; Cuthbertson 2016; Dong 2016; Kaliora 2016; Rezende 2016; Wang 2016; Zade 2016; Zhang 2016; Arab 2017; Axley 2017; Cheng 2017; Houghton 2017; Monica Dinu 2017; Nikroo 2017; Oh 2017; Schattenberg 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Nishimori 2018; Properzi 2018; Shidfar 2018; Tutino 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Abdelbasset 2020; Chen 2020; Goss 2020; Moradi 2020; Nourian 2020; Abbate 2021). Four trials included male participants only (Al-Jiffri 2013; Dong 2016; Nikroo 2017; Oh 2017).

Table 1. Summary of characteristics of included studies *(Continued)*

	Four trials included female participants only (Rodriguez-Hernandez 2011; Rezende 2016; Cheng 2017; Moradi 2020). In the remaining trials that reported the number of female participants, the proportion ranged from 18.8% to 86.4% (Wang 2008; De Luis 2010; Sullivan 2012; Bacchi 2013; Eckard 2013; Hickman 2013; Ramon-Krauel 2013; Wong 2013; Kani 2014; Pugh 2014; Selezneva 2014; Zelber-Sagi 2014; Abd El-Kader 2016; Cuthbertson 2016; Kaliora 2016; Ramirez 2016; Wang 2016; Zade 2016; Zhang 2016; Arab 2017; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Properzi 2018; Shidfar 2018; Tutino 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Abdelbasset 2020; Chen 2020; Goss 2020; Nourian 2020; Abbate 2021). Ten trials reported the proportion of participants who had NASH: eight trials included only participants with NASH (Wang 2008; Selezneva 2014; Sima 2014; Abd El-Kader 2016; Houghton 2017; Nikroo 2017; Schattenberg 2017; NCT01327443); in the remaining two trials, the proportion of participants who had NASH were 1.9% (Chan 2018) and 68.8% (Hickman 2013). Twenty-eight trials reported the proportion of participants who had diabetes mellitus: in 13 trials, none of the participants had diabetes mellitus (De Luis 2010; Sullivan 2012; Hickman 2013; Ramon-Krauel 2013; Zelber-Sagi 2014; Cuthbertson 2016; Dong 2016; Zhang 2016; Cheng 2017; Misciagna 2017; Asghari 2018; Katsagoni 2018; Shidfar 2018); in six trials, all the participants had diabetes mellitus (Al-Jiffri 2013; Bacchi 2013; Roy 2017; Nishimori 2018; Abdelbasset 2019; Abdelbasset 2020); in the remaining nine trials, the proportion of participants who had diabetes mellitus ranged from 5.8% to 77.5% (Rodriguez-Hernandez 2011; Eckard 2013; Wong 2013; Rezende 2016; Axley 2017; Properzi 2018; Tutino 2018; Nourian 2020; Abbate 2021). The diagnosis of NAFLD was made using biopsy (seven trials: Al-Jiffri 2013; Eckard 2013; Hickman 2013; Rezende 2016; Houghton 2017; Panganiban 2020; NCT01327443); ultrasound (10 trials: Zelber-Sagi 2014; Abd El-Kader 2016; Kaliora 2016; Misciagna 2017; Monica Dinu 2017; Nikroo 2017; Asghari 2018; Shidfar 2018; Abbate 2021; Moradi 2020); ultrasound and transaminases (10 trials: Wang 2008; Kani 2014; Dong 2016; Zade 2016; Arab 2017; Axley 2017; Oh 2017; Katsagoni 2018; Goss 2020; Nourian 2020); ultrasound and M30 (biomarker of liver damage) or biopsy (one trial: Schattenberg 2017); BMI and transaminases (one trial: De Luis 2010); magnetic resonance spectroscopy (seven trials: Sullivan 2012; Wong 2013; Cuthbertson 2016; Zhang 2016; Cheng 2017; Chan 2018; Properzi 2018); magnetic resonance spectroscopy and transaminases (one trial: Ramon-Krauel 2013); transaminases (two trials: Pugh 2014; Johari 2019); CT scan (one trial: Nishimori 2018); and clinical diagnosis (one trial: NCT03461562). The method of diagnosis of NAFLD was not stated in 18 trials (Hallsworth 2011; Rodriguez-Hernandez 2011; De Piano 2012; Bacchi 2013; Selezneva 2014; Sima 2014; Hallsworth 2015; Dynnyk 2016; Ramirez 2016; Wang 2016; Roy 2017; Tutino 2018; Yao 2018; Abdelbasset 2019; Abdelbasset 2020; Chen 2020; NCT02679417; NCT03183193).
Interventions compared	The interventions compared in these 59 trials included: dietary advice, exercise advice, dietary advice plus exercise advice, aerobic exercise, resistance exercise, aerobic exercise plus resistance exercise, supervised aerobic exercise, supervised aerobic exercise plus resistance exercise, calorie-restricted diet, carbohydrate-restricted diet, fat-restricted diet, Mediterranean diet, fat- and calorie-restricted diet, carbohydrate- and calorie-restricted diet, isocaloric diet, low glycaemic index diet, Khorasan wheat diet, organic semi-wholegrain wheat diet, aerobic exercise plus dietary advice, aerobic exercise plus calorie-restricted diet, raisins plus dietary advice, Mediterranean diet plus dietary advice, Mediterranean diet plus dietary advice plus exercise advice, aerobic exercise plus carbohydrate-restricted diet, aerobic exercise plus fat-restricted diet, aerobic exercise plus calorie- and fat-restricted diet, supervised aerobic exercise plus calorie-restricted diet, mono-unsaturated fatty acid plus calorie-restricted diet, Mediterranean diet plus exercise advice, Mediterranean diet plus supervised aerobic exercise, carbohydrate-restricted diet plus dietary advice plus exercise advice, calorie-restricted diet plus exercise advice, and no active intervention.
Trials reporting outcomes	28 trials reported one or more outcomes for this review (Wang 2008; Al-Jiffri 2013; Bacchi 2013; Eckard 2013; Hickman 2013; Wong 2013; Abd El-Kader 2016; Dong 2016; Kaliora 2016; Rezende 2016; Zhang 2016; Axley 2017; Cheng 2017; Houghton 2017; Misciagna 2017; Monica Dinu 2017; Nikroo 2017; Oh 2017; Roy 2017; Schattenberg 2017; Chan 2018; Katsagoni 2018; Properzi 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Moradi 2020; Nourian 2020).
Follow-up	The follow-up period in the trials ranged from 1 to 24 months in the trials that reported this information.

Table 1. Summary of characteristics of included studies *(Continued)*

	In 28 trials, the follow-up was up to 3 months (Wang 2008; Hallsworth 2011; Kani 2014; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Hallsworth 2015; Abd El-Kader 2016; Cuthbertson 2016; Dynnyk 2016; Zade 2016; Arab 2017; Houghton 2017; Monica Dinu 2017; Nikroo 2017; Oh 2017; Schattenberg 2017; Nishimori 2018; Properzi 2018; Shidfar 2018; Tutino 2018; Abdelbasset 2019; Johari 2019; Abdelbasset 2020; Chen 2020; Goss 2020; Moradi 2020; Nourian 2020); In 25 trials, the follow-up was between 3 months and 24 months (De Luis 2010; Rodriguez-Hernandez 2011; De Piano 2012; Sullivan 2012; Al-Jiffri 2013; Eckard 2013; Hickman 2013; Ramon-Krauel 2013; Wong 2013; Pugh 2014; Dong 2016; Kaliora 2016; Ramirez 2016; Rezende 2016; Wang 2016; Zhang 2016; Cheng 2017; Misciagna 2017; Roy 2017; Asghari 2018; Katsagoni 2018; Yao 2018; Panganiban 2020; Abbate 2021; NCT01327443); In the remaining six trials, the follow-up period was not reported (Bacchi 2013; Axley 2017; Chan 2018; NCT02679417; NCT03183193; NCT03461562).
Funding	The source of funding for four trials was industrial organisations who would benefit from the results of the study (Axley 2017; Schattenberg 2017; Properzi 2018; Shidfar 2018); 39 trials were funded by neutral organisations who have no vested interests in the results of the study (Wang 2008; Hallsworth 2011; De Piano 2012; Sullivan 2012; Al-Jiffri 2013; Bacchi 2013; Eckard 2013; Hickman 2013; Ramon-Krauel 2013; Wong 2013; Kani 2014; Pugh 2014; Hallsworth 2015; Abd El-Kader 2016; Cuthbertson 2016; Dong 2016; Rezende 2016; Zade 2016; Zhang 2016; Arab 2017; Cheng 2017; Houghton 2017; Misciagna 2017; Monica Dinu 2017; Nikroo 2017; Oh 2017; Chan 2018; Katsagoni 2018; Tutino 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Abbate 2021; Chen 2020; Goss 2020; Abdelbasset 2020; Nourian 2020; Moradi 2020; NCT03183193); The source of funding for the remaining 16 trials was unclear (De Luis 2010; Rodriguez-Hernandez 2011; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Dynnyk 2016; Kaliora 2016; Ramirez 2016; Wang 2016; Roy 2017; Asghari 2018; Nishimori 2018; Panganiban 2020; NCT01327443; NCT02679417; NCT03461562).

Table 2. Characteristics of included studies (ordered by comparisons)

Study name	Intervention 1 (number of participants) versus intervention 2 (number of participants)	NASH only	Diabetes mellitus	Period of recruitment	Diagnosis of fatty liver	Follow-up in months	Overall risk of bias
Abdelbasset 2019	Aerobic exercise (n = 16) versus no active intervention (n=16)	Not stated	All participants had diabetes mellitus	2017	Not stated	1.84	High
Abdelbasset 2020	Aerobic exercise (n = 31) versus no active intervention (n = 16)	Not stated	All participants had diabetes mellitus	Not stated	Not stated	1.84	High
Hallsworth 2015	Aerobic exercise (n = 12) versus no active intervention (n = 11)	Not stated	Not stated	Not stated	Not stated	3	High
NCT03461562	Aerobic exercise (n = not stated) versus no active intervention (n = not stated)	Not stated	Not stated	Not stated	Clinical diagnosis	Not stated	High
Sullivan 2012	Aerobic exercise (n = 12) versus no active intervention (n = 6)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	4	High
Yao 2018	Aerobic exercise (n = 29) versus no active intervention (n = 31)	Not stated	Not stated	Not stated	Not stated	5.5	High
Zhang 2016	Aerobic exercise (n = 146) versus no active intervention (n = 74)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	12	High
Asghari 2018	Calorie restricted diet (n = 30) versus no active intervention (n = 30)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	3	High
Cheng 2017	Calorie restricted diet (n = 22) versus no active intervention (n = 18)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	8	High
Johari 2019	Calorie restricted diet (n = 33) versus no active intervention (n = 10)	Not stated	Participants with and without diabetes mellitus	2015 - 2016	Transaminases	1.84	High

Table 2. Characteristics of included studies (ordered by comparisons) *(Continued)*

NCT01327443	Dietary advice (n = not stated) versus no active intervention (n = not stated)	All participants had NASH	Not stated	Not stated	Biopsy	6	High
Nourian 2020	Dietary advice (n = 36) versus no active intervention (n = 33)	Not stated	Participants with and without diabetes mellitus	2017 - 2018	Ultrasound and transaminases	2	High
Schattenberg 2017	Dietary advice (n = 15) versus no active intervention (n = 13)	All participants had NASH	Not stated	Not stated	Ultrasound and increased M30 (biomarker of severe liver disease)	3	High
Cheng 2017	Supervised aerobic exercise (n = 22) versus no active intervention (n = 18)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	8	High
NCT01327443	Supervised aerobic exercise (n = not stated) versus no active intervention (n = not stated)	All participants had NASH	Not stated	Not stated	Biopsy	6	High
Rezende 2016	Supervised aerobic exercise (n = 19) versus no active intervention (n = 21)	Not stated	Participants with and without diabetes mellitus	Not stated	Biopsy	6	High
Arab 2017	Dietary advice plus exercise advice (n = 41) versus no active intervention (n = 41)	Not stated	Not stated	Not stated	Ultrasound and transaminases	2	High
Axley 2017	Dietary advice plus exercise advice (n = 8) versus no active intervention (n = 14)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Ultrasound and transaminases	6	High
Chan 2018	Dietary advice plus exercise advice (n = 26) versus no active intervention (n = 26)	Participants with and without NASH	Not stated	Not stated	Magnetic resonance spectroscopy	16	High
Dong 2016	Dietary advice plus exercise advice (n = 132) versus no active intervention (n = 133)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound and transaminases	24	High

Table 2. Characteristics of included studies (ordered by comparisons) *(Continued)*

Roy 2017	Dietary advice plus exercise advice (n = 30) versus no active intervention (n = 30)	Not stated	All participants had diabetes mellitus	Not stated	Not stated	4	High
Hallsworth 2011	Resistance exercise (n = 11) versus no active intervention (n = 8)	Not stated	Not stated	Not stated	Not stated	2	High
Moradi 2020	Resistance exercise (n = 23) versus no active intervention (n = 22)	Not stated	Not stated	Not stated	Ultrasound	2.76	High
Yao 2018	Resistance exercise (n = 31) versus no active intervention (n = 31)	Not stated	Not stated	Not stated	Not stated	5.5	High
Misciagna 2017	Mediterranean diet (n = 50) versus no active intervention (n = 48)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	6	Low
NCT03183193	Mediterranean diet (n = not stated) versus no active intervention (n = not stated)	Not stated	Not stated	Not stated	Not stated	not stated	High
Tutino 2018	Mediterranean diet (n = 18) versus no active intervention (n = 15)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	1.5	High
Tutino 2018	Aerobic exercise plus resistance exercise (n = 29) versus no active intervention (n = 15)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	1.5	High
Abd El-Kader 2016	Aerobic exercise plus calorie restricted diet (n = 50) versus no active intervention (n = 50)	All participants had NASH	Not stated	Not stated	Ultrasound	3	High
Cheng 2017	Supervised aerobic exercise plus calorie restricted diet (n = 23) versus no active intervention (n = 18)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	8	High
Wong 2013	Aerobic exercise plus dietary advice (n = 77) versus no active intervention (n = 77)	Not stated	Participants with and without diabetes mellitus	Not stated	Magnetic resonance spectroscopy	12	High
Houghton 2017	Supervised aerobic exercise plus resistance exercise (n = 12) versus no active intervention (n = 12)	All participants had NASH	Not stated	Not stated	Biopsy	3	High

Table 2. Characteristics of included studies (ordered by comparisons) *(Continued)*

Wang 2008	Aerobic exercise plus calorie and fat restricted diet (n = 19) versus no active intervention (n = 38)	All participants had NASH	Not stated	Not stated	Ultrasound plus ALT>= 1.5 times normal	1	High
Hickman 2013	Calorie restricted diet (n = 8) versus aerobic exercise (n = 13)	Participants with and without NASH	No participants had diabetes mellitus	Not stated	Biopsy	6	High
Eckard 2013	Dietary advice (n = 11) versus aerobic exercise (n = 9)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Biopsy	6	High
Bacchi 2013	Resistance exercise (n = 17) versus aerobic exercise (n = 13)	Participants with and without NASH	All participants had diabetes mellitus	Not stated	Unclear	4	High
Oh 2017	Resistance exercise (n = 19) versus aerobic exercise (n = 33)	Not stated	Not stated	Not stated	Ultrasound and transaminases	3	High
Yao 2018	Resistance exercise (n = 31) versus aerobic exercise (n = 29)	Not stated	Not stated	Not stated	Not stated	5.5	High
Zelber-Sagi 2014	Resistance exercise (n = 33) versus aerobic exercise (n = 31)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	3	High
De Piano 2012	Aerobic exercise plus resistance exercise (n = not stated) versus aerobic exercise (n = not stated)	Not stated	Not stated	Not stated	Not stated	12	High
NCT02679417	Aerobic exercise plus resistance exercise (n = not stated) versus aerobic exercise (n = not stated)	Not stated	Not stated	Not stated	Not stated	not stated	High
Eckard 2013	Aerobic exercise plus carbohydrate restricted diet (n = 9) versus aerobic exercise (n = 9)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Biopsy	6	High
Eckard 2013	Aerobic exercise plus fat restricted diet (n = 12) versus aerobic exercise (n = 9)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Biopsy	6	High

Table 2. Characteristics of included studies (ordered by comparisons) *(Continued)*

Cuthbertson 2016	Exercise advice (n = 20) versus aerobic exercise (n = 30)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	4	High
Dynnyk 2016	Exercise advice (n = not stated) versus aerobic exercise (n = not stated)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	2.76	High
Cheng 2017	Supervised aerobic exercise (n = 22) versus calorie restricted diet (n = 22)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	8	High
Nishimori 2018	Carbohydrate restricted diet (n = 14) versus calorie restricted diet (n = 14)	Not stated	All participants had diabetes mellitus	Not stated	CT scan	3	High
Panganiban 2020	Carbohydrate restricted diet (n = 19) versus calorie restricted diet (n = 20)	Not stated	Not stated	Not stated	Biopsy	6	High
Ramirez 2016	Carbohydrate restricted diet (n = not stated) versus calorie restricted diet (n = not stated)	Not stated	Not stated	Not stated	Not stated	6	High
Al-Jiffri 2013	Aerobic exercise plus calorie restricted diet (n = 50) versus calorie restricted diet (n = 50)	Participants with and without NASH	All participants had diabetes mellitus	Not stated	Biopsy	3	High
Sima 2014	Aerobic exercise plus calorie restricted diet (n = 12) versus calorie restricted diet (n = 13)	All participants had NASH	Not stated	Not stated	Not stated	3	High
Wang 2016	Aerobic exercise plus calorie restricted diet (n = 80) versus calorie restricted diet (n = 40)	Not stated	Not stated	2014-2015	Not stated	5.54	High
Cheng 2017	Supervised aerobic exercise plus calorie restricted diet (n = 23) versus calorie restricted diet (n = 22)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	8	High
Kani 2014	Carbohydrate and calorie restricted diet (n = 12) versus calorie restricted diet (n = 13)	Not stated	Not stated	Not stated	Not stated	1.84	High
Selezneva 2014	Isocalorie diet (n = 116) versus calorie restricted diet (n = 58)	All participants had NASH	Not stated	Not stated	Not stated	1	High

Table 2. Characteristics of included studies (ordered by comparisons) *(Continued)*

Shidfar 2018	Mono unsaturated fatty acid plus calorie restricted diet (n = 21) versus calorie restricted diet (n = 22)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2.76	High
Zade 2016	Fat and calorie restricted diet (n = 30) versus calorie restricted diet (n = 30)	Not stated	Not stated	Not stated	Ultrasound and increased levels of serum ALT	2	High
NCT01327443	Supervised aerobic exercise (n = not stated) versus dietary advice (n = not stated)	All participants had NASH	Not stated	Not stated	Biopsy	6	High
Nikroo 2017	Supervised aerobic exercise (n = 12) versus dietary advice (n = 11)	All participants had NASH	Not stated	2010-2011	Ultrasound	1.84	High
Eckard 2013	Aerobic exercise plus carbohydrate restricted diet (n = 9) versus dietary advice (n = 11)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Biopsy	6	High
Eckard 2013	Aerobic exercise plus fat restricted diet (n = 12) versus dietary advice (n = 11)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Biopsy	6	High
Katsagoni 2018	Mediterranean diet plus dietary advice (n = 21) versus dietary advice (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound plus raised ALT or biopsy	6	High
Katsagoni 2018	Mediterranean diet plus dietary advice plus exercise advice (n = 21) versus dietary advice (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound plus raised ALT or biopsy	6	High
Kaliora 2016	Raisins plus dietary advice (n = 23) versus dietary advice (n = 21)	Not stated	Not stated	Not stated	Ultrasound	6	High
Cheng 2017	Supervised aerobic exercise plus calorie restricted diet (n = 23) versus supervised aerobic exercise (n = 22)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy	8	High
Pugh 2014	Supervised aerobic exercise (n = 13) versus dietary advice plus exercise advice (n = 8)	Not stated	Not stated	Not stated	Raised transaminases	3.68	High

Table 2. Characteristics of included studies (ordered by comparisons) *(Continued)*

Chen 2020	Carbohydrate restricted diet plus dietary advice plus exercise advice (n = 22) versus dietary advice plus exercise advice (n = 22)	Not stated	Not stated	2015 - 2017	Not stated	2	High
De Luis 2010	Fat restricted diet (n = 15) versus carbohydrate restricted diet (n = 13)	Not stated	No participants had diabetes mellitus	Not stated	BMI>=30 and ALT >=43 UI/L	3	High
Rodriguez-Hernandez 2011	Fat restricted diet (n = 26) versus carbohydrate restricted diet (n = 28)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	6	High
Goss 2020	Carbohydrate restricted diet (n = 16) versus fat restricted diet (n = 16)	Not stated	Not stated	2016 - 2017	Ultrasound and transaminases	1.84	High
Properzi 2018	Mediterranean diet (n = 24) versus fat restricted diet (n = 24)	Participants with and without NASH	Not stated	Not stated	Magnetic resonance spectroscopy	3	High
Ramon-Krauel 2013	Low glycaemic index diet (n = 7) versus fat restricted diet (n = 9)	Not stated	No participants had diabetes mellitus	Not stated	Magnetic resonance spectroscopy plus raised ALT	6	High
Tutino 2018	Aerobic exercise plus resistance exercise (n = 29) versus Mediterranean diet (n = 18)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	1.5	High
Eckard 2013	Aerobic exercise plus fat restricted diet (n = 12) versus aerobic exercise plus carbohydrate restricted diet (n = 9)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Biopsy	6	High
Abbate 2021	Mediterranean diet plus exercise advice (n = 43) versus calorie restricted diet plus exercise advice (n = 42)	Not stated	Participants with and without diabetes mellitus	2018-2020	Ultrasound	6	High
Abbate 2021	Mediterranean diet plus supervised aerobic exercise (n = 43) versus calorie restricted diet plus exercise advice (n = 42)	Not stated	Participants with and without diabetes mellitus	2018 - 2020	Ultrasound	6	High

Table 2. Characteristics of included studies (ordered by comparisons) *(Continued)*

Abbate 2021	Mediterranean diet plus supervised aerobic exercise (n = 43) versus Mediterranean diet plus exercise advice (n = 43)	Not stated	Participants with and without diabetes mellitus	2018-2020	Ultrasound	6	High
Katsagoni 2018	Mediterranean diet plus dietary advice plus exercise advice (n = 21) versus Mediterranean diet plus dietary advice (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound plus raised ALT or biopsy	6	High
Monica Dinu 2017	Organic semi-wholegrain wheat diet (n = 20) versus Khorasan wheat diet (n = 20)	Not stated	Not stated	Not stated	Ultrasound	3	Low

Table 3. Summary of risk of bias

Domain	Classification
Allocation (selection bias)	29 trials were at low risk of selection bias due to lack of random sequence generation (Sullivan 2012; Eckard 2013; Hickman 2013; Wong 2013; Kani 2014; Pugh 2014; Hallsworth 2015; Abd El-Kader 2016; Cuthbertson 2016; Dong 2016; Kaliora 2016; Rezende 2016; Zade 2016; Zhang 2016; Arab 2017; Axley 2017; Cheng 2017; Misciagna 2017; Monica Dinu 2017; Oh 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Tutino 2018; Johari 2019; Chen 2020; Goss 2020; Nourian 2020; Abbate 2021); the remaining 30 trials, which did not provide sufficient information, were at unclear risk of sequence generation bias (Wang 2008; De Luis 2010; Hallsworth 2011; Rodriguez-Hernandez 2011; De Piano 2012; Al-Jiffri 2013; Bacchi 2013; Ramon-Krauel 2013; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Dynnyk 2016; Wang 2016; Ramirez 2016; Houghton 2017; Nikroo 2017; Roy 2017; Schattenberg 2017; Nishimori 2018; Properzi 2018; Shidfar 2018; Yao 2018; Abdelbasset 2019; Abdelbasset 2020; Moradi 2020; Panganiban 2020; NCT01327443; NCT02679417; NCT03183193; NCT03461562). Seventeen trials were at low risk of selection bias due to lack of allocation concealment (Sullivan 2012; Eckard 2013; Hickman 2013; Wong 2013; Kani 2014; Abd El-Kader 2016; Kaliora 2016; Zade 2016; Axley 2017; Cheng 2017; Misciagna 2017; Monica Dinu 2017; Oh 2017; Abdelbasset 2020; Moradi 2020; Nourian 2020; Abbate 2021); the remaining 42 trials, which did not provide sufficient information, were at unclear risk of allocation concealment bias (Wang 2008; De Luis 2010; Hallsworth 2011; Rodriguez-Hernandez 2011; De Piano 2012; Al-Jiffri 2013; Bacchi 2013; Ramon-Krauel 2013; Pugh 2014; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Hallsworth 2015; Cuthbertson 2016; Dong 2016; Dynnyk 2016; Ramirez 2016; Rezende 2016; Wang 2016; Zhang 2016; Arab 2017; Houghton 2017; Nikroo 2017; Roy 2017; Schattenberg 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Nishimori 2018; Properzi 2018; Shidfar 2018; Tutino 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Chen 2020; Goss 2020; Panganiban 2020; NCT01327443; NCT02679417; NCT03183193; NCT03461562).
Blinding (performance bias and detection bias)	Three trials were at low risk of performance bias as the participants and healthcare providers were blinded (Zade 2016; Misciagna 2017; Monica Dinu 2017); eight trials, which did not provide sufficient information, were at unclear risk of performance bias (De Luis 2010; Rodriguez-Hernandez 2011; De Piano 2012; Dynnyk 2016; Wang 2016; Shidfar 2018; Panganiban 2020; NCT03461562); the remaining 48 trials were at high risk of performance bias (Wang 2008; Hallsworth 2011; Sullivan 2012; Al-Jiffri 2013; Bacchi 2013; Eckard 2013; Hickman 2013; Ramon-Krauel 2013; Wong 2013; Kani 2014; Pugh 2014; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Hallsworth 2015; Abd El-Kader 2016; Cuthbertson 2016; Dong 2016; Kaliora 2016; Ramirez 2016; Rezende 2016; Zhang 2016; Arab 2017; Axley 2017; Cheng 2017; Houghton 2017; Nikroo 2017; Oh 2017; Roy 2017; Schattenberg 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Nishimori 2018; Properzi 2018; Tutino 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Abdelbasset 2020; Chen 2020; Goss 2020; Moradi 2020; Nourian 2020; Abbate 2021; NCT01327443; NCT02679417; NCT03183193). Seventeen trials were at low risk of detection bias (De Luis 2010; Bacchi 2013; Eckard 2013; Wong 2013; Kani 2014; Abd El-Kader 2016; Kaliora 2016; Zade 2016; Zhang 2016; Axley 2017; Cheng 2017; Misciagna 2017; Monica Dinu 2017; Chan 2018; Tutino 2018; NCT02679417; NCT03461562); 35 trials, which did not provide sufficient information, were at unclear risk of detection bias (Wang 2008; Hallsworth 2011; Rodriguez-Hernandez 2011; De Piano 2012; Sullivan 2012; Al-Jiffri 2013; Ramon-Krauel 2013; Pugh 2014; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Hallsworth 2015; Cuthbertson 2016; Dong 2016; Dynnyk 2016; Ramirez 2016; Rezende 2016; Wang 2016; Arab 2017; Houghton 2017; Oh 2017; Roy 2017; Asghari 2018; Katsagoni 2018; Nishimori 2018; Shidfar 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Abdelbasset 2020; Chen 2020; Moradi 2020; Nourian 2020; Panganiban 2020; Abbate 2021); the remaining seven trials were at high risk of detection bias (Hickman 2013; Nikroo 2017; Schattenberg 2017; Properzi 2018; Goss 2020; NCT01327443; NCT03183193).
Incomplete outcome data (attrition bias)	Fourteen trials were at low risk of attrition bias as there were no post-randomisation dropouts or an intention-to-treat analysis was used (De Luis 2010; Al-Jiffri 2013; Wong 2013; Kani 2014; Zade 2016; Zhang 2016; Misciagna 2017; Monica Dinu 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Abdelbasset 2019; Johari 2019; Moradi 2020); 28 trials were at unclear risk of incomplete outcome data bias (Wang 2008; Rodriguez-Hernandez 2011; De Piano 2012; Eckard 2013; Ramon-Krauel 2013; Selezneva 2014; Sima 2014; Abd El-Kad-

Table 3. Summary of risk of bias *(Continued)*

	er 2016; Dynnyk 2016; Ramirez 2016; Wang 2016; Axley 2017; Nikroo 2017; Roy 2017; Schattenberg 2017; Nishimori 2018; Tutino 2018; Shidfar 2018; Abdelbasset 2020; Chen 2020; Goss 2020; Nourian 2020; Panganiban 2020; Abbate 2021; NCT01327443; NCT02679417; NCT03183193; NCT03461562), because it was not clear whether there were post-randomisation dropouts or whether the post-randomisation dropouts were related to the outcomes (if there were post-randomisation dropouts); the remaining 17 trials were at high risk of attrition bias (Hallsworth 2011; Sullivan 2012; Bacchi 2013; Hickman 2013; Pugh 2014; Zelber-Sagi 2014; Hallsworth 2015; Cuthbertson 2016; Dong 2016; Kaliora 2016; Rezende 2016; Arab 2017; Cheng 2017; Houghton 2017; Oh 2017; Properzi 2018; Yao 2018), as the post-randomisation dropouts were probably related to the outcomes.
Selective reporting (reporting bias)	Eight trials were at low risk of selective outcome reporting bias (Al-Jiffri 2013; Hickman 2013; Abd El-Kader 2016; Axley 2017; Misciagna 2017; Monica Dinu 2017; Schattenberg 2017; Properzi 2018), as the important clinical outcomes expected to be reported in such trials were reported; the remaining 51 trials were at high risk of selective outcome reporting bias (Wang 2008; De Luis 2010; Hallsworth 2011; Rodriguez-Hernandez 2011; De Piano 2012; Sullivan 2012; Bacchi 2013; Eckard 2013; Ramon-Krauel 2013; Wong 2013; Kani 2014; Pugh 2014; Selezneva 2014; Sima 2014; Zelber-Sagi 2014; Hallsworth 2015; Cuthbertson 2016; Dong 2016; Dynnyk 2016; Kaliora 2016; Ramirez 2016; Rezende 2016; Zade 2016; Zhang 2016; Wang 2016; Arab 2017; Cheng 2017; Houghton 2017; Nikroo 2017; Oh 2017; Roy 2017; Asghari 2018; Chan 2018; Katsagoni 2018; Nishimori 2018; Shidfar 2018; Tutino 2018; Yao 2018; Abdelbasset 2019; Johari 2019; Abdelbasset 2020; Chen 2020; Goss 2020; Moradi 2020; Nourian 2020; Panganiban 2020; Abbate 2021; NCT01327443; NCT02679417; NCT03183193; NCT03461562), as a protocol published prior to recruitment was not available and clinically relevant and reasonably expected outcomes were not reported.
Other potential sources of bias	No other potential source of bias was noted in any of the trials.

Table 4. Risk of bias (ordered by comparison)

Study name	Intervention 1 (number of participants) versus intervention 2 (number of participants)	Sequence generation	Allocation concealment	Blinding of participants and health-care providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Other bias	Overall risk of bias
Abdelbasset 2019	Aerobic exercise (n = 16) versus no active intervention (n = 16)	Unclear	Unclear	High	Unclear	Low	High	Low	High
Abdelbasset 2020	Aerobic exercise (n = 31) versus no active intervention (n = 16)	Unclear	Low	High	Unclear	Unclear	High	Low	High
Hallsworth 2015	Aerobic exercise (n = 12) versus no active intervention (n = 11)	Low	Unclear	High	Unclear	High	High	Low	High
NCT03461562	Aerobic exercise (n = not stated) versus no active intervention (n = not stated)	Unclear	Unclear	Unclear	Low	Unclear	High	Low	High
Sullivan 2012	Aerobic exercise (n = 12) versus no active intervention (n = 6)	Low	Low	High	Unclear	High	High	Low	High
Yao 2018	Aerobic exercise (n = 29) versus no active intervention (n = 31)	Unclear	Unclear	High	Unclear	High	High	Low	High
Zhang 2016	Aerobic exercise (n = 146) versus no active intervention (n = 74)	Low	Unclear	High	Low	Low	High	Low	High
Asghari 2018	Calorie restricted diet (n = 30) versus no active intervention (n = 30)	Low	Unclear	High	Unclear	Low	High	Low	High
Cheng 2017	Calorie restricted diet (n = 22) versus no active intervention (n = 18)	Low	Low	High	Low	High	High	Low	High
Johari 2019	Calorie restricted diet (n = 33) versus no active intervention (n = 10)	Low	Unclear	High	Unclear	Low	High	Low	High
NCT01327443	Dietary advice (n = not stated) versus no active intervention (n = not stated)	Unclear	Unclear	High	High	Unclear	High	Low	High
Nourian 2020	Dietary advice (n = 36) versus no active intervention (n = 33)	Low	Low	High	Unclear	Unclear	High	Low	High

Table 4. Risk of bias (ordered by comparison) *(Continued)*

Schatten-berg 2017	Dietary advice (n = 15) versus no active intervention (n = 13)	Unclear	Unclear	High	High	Unclear	Low	Low	High
Cheng 2017	Supervised aerobic exercise (n = 22) versus no active intervention (n = 18)	Low	Low	High	Low	High	High	Low	High
NCT01327443	Supervised aerobic exercise (n = not stated) versus no active intervention (n = not stated)	Unclear	Unclear	High	High	Unclear	High	Low	High
Rezende 2016	Supervised aerobic exercise (n = 19) versus no active intervention (n = 21)	Low	Unclear	High	Unclear	High	High	Low	High
Arab 2017	Dietary advice plus exercise advice (n = 41) versus no active intervention (n = 41)	Low	Unclear	High	Unclear	High	High	Low	High
Axley 2017	Dietary advice plus exercise advice (n = 8) versus no active intervention (n = 14)	Low	Low	High	Low	Unclear	Low	Low	High
Chan 2018	Dietary advice plus exercise advice (n = 26) versus no active intervention (n = 26)	Low	Unclear	High	Low	Low	High	Low	High
Dong 2016	Dietary advice plus exercise advice (n = 132) versus no active intervention (n = 133)	Low	Unclear	High	Unclear	High	High	Low	High
Roy 2017	Dietary advice plus exercise advice (n = 30) versus no active intervention (n = 30)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Hallsworth 2011	Resistance exercise (n = 11) versus no active intervention (n = 8)	Unclear	Unclear	High	Unclear	High	High	Low	High
Moradi 2020	Resistance exercise (n = 23) versus no active intervention (n = 22)	Unclear	Low	High	Unclear	Low	High	Low	High
Yao 2018	Resistance exercise (n = 31) versus no active intervention (n = 31)	Unclear	Unclear	High	Unclear	High	High	Low	High
Misciagna 2017	Mediterranean diet (n = 50) versus no active intervention (n = 48)	Low	Low	Low	Low	Low	Low	Low	Low
NCT03183193	Mediterranean diet (n = not stated) versus no active intervention (n = not stated)	Unclear	Unclear	High	High	Unclear	High	Low	High

Table 4. Risk of bias (ordered by comparison) *(Continued)*

Tutino 2018	Mediterranean diet (n = 18) versus no active intervention (n = 15)	Low	Unclear	High	Low	Unclear	High	Low	High
Tutino 2018	aerobic exercise plus resistance exercise (n = 29) versus no active intervention (n = 15)	Low	Unclear	High	Low	Unclear	High	Low	High
Abd El-Kader 2016	Aerobic exercise plus calorie restricted diet (n = 50) versus no active intervention (n = 50)	Low	Low	High	Low	Unclear	Low	Low	High
Cheng 2017	Supervised aerobic exercise plus calorie restricted diet (n = 23) versus no active intervention (n = 18)	Low	Low	High	Low	High	High	Low	High
Wong 2013	Aerobic exercise plus dietary advice (n = 77) versus no active intervention (n = 77)	Low	Low	High	Low	Low	High	Low	High
Houghton 2017	Supervised aerobic exercise plus resistance exercise (n = 12) versus no active intervention (n = 12)	Unclear	Unclear	High	Unclear	High	High	Low	High
Wang 2008	Aerobic exercise plus calorie and fat restricted diet (n = 19) versus no active intervention (n = 38)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Hickman 2013	Calorie restricted diet (n = 8) versus aerobic exercise (n = 13)	Low	Low	High	High	High	Low	Low	High
Eckard 2013	Dietary advice (n = 11) versus aerobic exercise (n = 9)	Low	Low	High	Unclear	Unclear	High	Low	High
Bacchi 2013	Resistance exercise (n = 17) versus aerobic exercise (n = 13)	Unclear	Unclear	High	Low	High	High	Low	High
Oh 2017	Resistance exercise (n = 19) versus aerobic exercise (n = 33)	Low	Low	High	Unclear	High	High	Low	High
Yao 2018	Resistance exercise (n = 31) versus aerobic exercise (n = 29)	Unclear	Unclear	High	Unclear	High	High	Low	High
Zelber-Sagi 2014	Resistance exercise (n = 33) versus aerobic exercise (n = 31)	Unclear	Unclear	High	Unclear	High	High	Low	High

Table 4. Risk of bias (ordered by comparison) *(Continued)*

De Piano 2012	aerobic exercise plus resistance exercise (n = not stated) versus aerobic exercise (n = not stated)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
NCT02679417	aerobic exercise plus resistance exercise (n = not stated) versus aerobic exercise (n = not stated)	Unclear	Unclear	High	Low	Unclear	High	Low	High
Eckard 2013	Aerobic exercise plus carbohydrate restricted diet (n = 9) versus aerobic exercise (n = 9)	Low	Low	High	Unclear	Unclear	High	Low	High
Eckard 2013	Aerobic exercise plus fat restricted diet (n = 12) versus aerobic exercise (n = 9)	Low	Low	High	Unclear	Unclear	High	Low	High
Cuthbertson 2016	Exercise advice (n = 20) versus aerobic exercise (n = 30)	Low	Unclear	High	Unclear	High	High	Low	High
Dynnyk 2016	Exercise advice (n = not stated) versus aerobic exercise (n = not stated)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Cheng 2017	Supervised aerobic exercise (n = 22) versus calorie restricted diet (n = 22)	Low	Low	High	Low	High	High	Low	High
Nishimori 2018	Carbohydrate restricted diet (n = 14) versus calorie restricted diet (n = 14)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Panganiban 2020	Carbohydrate restricted diet (n = 19) versus calorie restricted diet (n = 20)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Ramirez 2016	Carbohydrate restricted diet (n = not stated) versus calorie restricted diet (n = not stated)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Al-Jiffri 2013	Aerobic exercise plus calorie restricted diet (n = 50) versus calorie restricted diet (n = 50)	Unclear	Unclear	High	Unclear	Low	High	Low	High
Sima 2014	Aerobic exercise plus calorie restricted diet (n = 12) versus calorie restricted diet (n = 13)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Wang 2016	Aerobic exercise plus calorie restricted diet (n = 80) versus calorie restricted diet (n = 40)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High

Table 4. Risk of bias (ordered by comparison) *(Continued)*

Cheng 2017	Supervised aerobic exercise plus calorie restricted diet (n = 23) versus calorie restricted diet (n = 22)	Low	Low	High	Low	High	High	Low	High
Kani 2014	Carbohydrate and calorie restricted diet (n = 12) versus calorie restricted diet (n = 13)	Low	Low	High	Low	Low	High	Low	High
Selezneva 2014	isocaloric diet (n = 116) versus calorie restricted diet (n = 58)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Shidfar 2018	Mono unsaturated fatty acid plus calorie restricted diet (n = 21) versus calorie restricted diet (n = 22)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Zade 2016	Fat and calorie restricted diet (n = 30) versus calorie restricted diet (n = 30)	Low	Low	Low	Low	Low	High	Low	High
NCT01327443	Supervised aerobic exercise (n = not stated) versus dietary advice (n = not stated)	Unclear	Unclear	High	High	Unclear	High	Low	High
Nikroo 2017	Supervised aerobic exercise (n = 12) versus dietary advice (n = 11)	Unclear	Unclear	High	High	Unclear	High	Low	High
Eckard 2013	Aerobic exercise plus carbohydrate restricted diet (n = 9) versus dietary advice (n = 11)	Low	Low	High	Unclear	Unclear	High	Low	High
Eckard 2013	Aerobic exercise plus fat restricted diet (n = 12) versus dietary advice (n = 11)	Low	Low	High	Unclear	Unclear	High	Low	High
Katsagoni 2018	Mediterranean diet plus dietary advice (n = 21) versus dietary advice (n = 21)	Low	Unclear	High	Unclear	Low	High	Low	High
Katsagoni 2018	Mediterranean diet plus dietary advice plus exercise advice (n = 21) versus dietary advice (n = 21)	Low	Unclear	High	Unclear	Low	High	Low	High
Kaliora 2016	Raisins plus dietary advice (n = 23) versus dietary advice (n = 21)	Low	Low	High	Low	High	High	Low	High
Cheng 2017	Supervised aerobic exercise plus calorie restricted diet (n = 23) versus supervised aerobic exercise (n = 22)	Low	Low	High	Low	High	High	Low	High

Table 4. Risk of bias (ordered by comparison) *(Continued)*

Pugh 2014	Supervised aerobic exercise (n = 13) versus dietary advice plus exercise advice (n = 8)	Low	Unclear	High	Unclear	High	High	Low	High
Chen 2020	Carbohydrate restricted diet plus dietary advice plus exercise advice (n = 22) versus dietary advice plus exercise advice (n = 22)	Low	Unclear	High	Unclear	Unclear	High	Low	High
De Luis 2010	Fat restricted diet (n = 15) versus carbohydrate restricted diet (n = 13)	Unclear	Unclear	Unclear	Low	Low	High	Low	High
Rodriguez-Hernandez 2011	Fat restricted diet (n = 26) versus carbohydrate restricted diet (n = 28)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Goss 2020	Carbohydrate restricted diet (n = 16) versus fat restricted diet (n = 16)	Low	Unclear	High	High	Unclear	High	Low	High
Properzi 2018	Mediterranean diet (n = 24) versus fat restricted diet (n = 24)	Unclear	Unclear	High	High	High	Low	Low	High
Ramon-Krauel 2013	Low glycaemic index diet (n = 7) versus fat restricted diet (n = 9)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Tutino 2018	aerobic exercise plus resistance exercise (n = 29) versus Mediterranean diet (n = 18)	Low	Unclear	High	Low	Unclear	High	Low	High
Eckard 2013	Aerobic exercise plus fat restricted diet (n = 12) versus aerobic exercise plus carbohydrate restricted diet (n = 9)	Low	Low	High	Unclear	Unclear	High	Low	High
Abbate 2021	Mediterranean diet plus exercise advice (n = 43) versus calorie restricted diet plus exercise advice (n = 42)	Low	Low	High	Unclear	Unclear	High	Low	High
Abbate 2021	Mediterranean diet plus supervised aerobic exercise (n = 43) versus calorie restricted diet plus exercise advice (n = 42)	Low	Low	High	Unclear	Unclear	High	Low	High
Abbate 2021	Mediterranean diet plus supervised aerobic exercise (n = 43) versus Mediterranean diet plus exercise advice (n = 43)	Low	Low	High	Unclear	Unclear	High	Low	High

Table 4. Risk of bias (ordered by comparison) *(Continued)*

Katsagoni 2018	Mediterranean diet plus dietary advice plus exercise advice (n = 21) versus Mediterranean diet plus dietary advice (n = 21)	Low	Unclear	High	Unclear	Low	High	Low	High
Monica Dinu 2017	Organic semi-wholegrain wheat diet (n = 20) versus khorasan wheat diet (n = 20)	Low	Low	Low	Low	Low	Low	Low	Low

Table 5. Fit statistics for fixed-effect, random-effects, and inconsistency model

Fatty Liver	Fixed-effect model	Random-effects model	Inconsistency model
Dbar	103.4	90.03	90.15
DIC	122	110.6	110.8
pD	18.6	20.56	20.63
Fibrosis Score	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	0.6826	-	-
DIC	4.692	-	-
pD	4.009	-	-
NAFLD Activity Score	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	8.662	-	-
DIC	14.61	-	-
pD	5.952	-	-

Dbar: posterior mean of deviance; DIC: deviance information criteria; pD: effective number of parameters or leverage.
Empty cells for random-effects model indicate that the presence of only a single trial for all comparisons of any two interventions; empty cells for inconsistency model indicates absence of direct and indirect effect estimates for all comparisons of any two interventions for the outcome.

Table 6. Effect estimates

This table is too wide to be displayed in RevMan. A picture of this table can be found in Figure 6. The full table can be found here.

The table provides the effect estimates of each pairwise comparison for the different outcomes (hazard ratio and its 95% credible interval (CrI) for resolution of fatty liver and mean difference and its CrI for fibrosis score and nonalcohol-related fatty liver disease (NAFLD) activity score. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the effect estimate that is obtained directly. For example, if you wanted to know the effect of supervised aerobic exercise versus calorie-restricted diet, the network meta-analysis estimates are available in cell D7, which corresponds to the supervised aerobic exercise in row 7 and calorie-restricted diet in column D.
For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. For example, if you wanted to know the effect of supervised aerobic exercise versus calorie-restricted diet, the direct comparison estimates are available in cell G4, which corresponds to the supervised aerobic exercise in column G and calorie-restricted diet in row 4.
If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number (i.e. 1/number for hazard ratio and change signs for mean differences) to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.
Statistically significant results are shown in italics. Green colour indicates that intervention A is better than B and red colour indicates that intervention A is worse than B.
The results of resolution of fatty liver have extremely wide credible intervals. This was because of sparse data with heterogeneity.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2021, Issue 2	#1 MeSH descriptor: [Fatty Liver] explode all trees #2 (liver and (fatty or steatosis or steatoses)) #3 NAFLD #4 #1 or #2 or #3 #5 (((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacteria) #6 MeSH descriptor: [Dietary Supplements] explode all trees #7 (vitamin* or micronutrient* or (trace near/1 (element* or mineral*)) or antioxidant*) #8 MeSH descriptor: [Vitamins] explode all trees #9 MeSH descriptor: [Micronutrients] explode all trees #10 MeSH descriptor: [Antioxidants] explode all trees #11 (((unsaturated or polyunsaturated) and (fatty near/1 acid*)) or PUFA or (linoleic near/1 acid*) or (docosahexaenoic near/1 acid*) or (eicosapentaenoic near/1 acid)) #12 MeSH descriptor: [Fatty Acids, Unsaturated] explode all trees #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 #14 MeSH descriptor: [Exercise] this term only #15 MeSH descriptor: [Exercise Therapy] this term only #16 MeSH descriptor: [Physical Exertion] this term only #17 MeSH descriptor: [Motor Activity] this term only #18 MeSH descriptor: [Sports] this term only #19 (sport*) #20 MeSH descriptor: [Physical Education and Training] explode all trees #21 (physical near/3 (activit* or education* or exertion* or training)) #22 (exercise*) #23 MeSH descriptor: [Diet Therapy] explode all trees #24 ((diet or dieting) near/5 (health* or weight*)) #25 (calorie near/3 (control or reduc* or restriction)) #26 "food choice*" #27 ("fat camp*" or "weight loss camp*") #28 "nutrition education" #29 MeSH descriptor: [Nutrition Therapy] this term only #30 MeSH descriptor: [Behavior Therapy] this term only #31 MeSH descriptor: [Cognitive Therapy] this term only #32 MeSH descriptor: [Psychotherapy] this term only #33 (behavio?r* near/3 (therap* or technique* or modif* or intervention*)) #34 (cognit* near/3 (therap* or technique* or modif* or intervention*)) #35 CBT #36 (psychotherap* or psycho-therap*) #37 (psycho-social or psychosocial) #38 MeSH descriptor: [Health Promotion] explode all trees #39 MeSH descriptor: [Health Education] this term only #40 (health* near/3 (promot* or educat* or lifestyle)) #41 MeSH descriptor: [Life Style] this term only #42 (lifestyle* or life-style*) #43 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 #44 #13 or #43 #45 #4 and #44

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MEDLINE Ovid	January 1947 to February 2021	1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized.ab. 4. placebo.ab. 5. drug therapy.fs. 6. randomly.ab. 7. trial.ab. 8. groups.ab. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp animals/ not humans.sh. 11. 9 not 10 12. exp Fatty Liver/ 13. (liver and (fatty or steatosis or steatoses)).ti,ab. 14. NAFLD.ti,ab. 15. 12 or 13 or 14 16. (((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacteria).ti,ab. 17. exp Dietary Supplements/ 18. (vitamin* or micronutrient* or (trace adj1 (element* or mineral*)) or antioxidant*).ti,ab. 19. exp Vitamins/ or exp MICRONUTRIENTS/ or exp ANTIOXIDANTS/ 20. (((unsaturated or polyunsaturated) and (fatty adj1 acid*)) or PUFA or (linoleic adj1 acid*) or (docosahexaenoic adj1 acid*) or (eicosapentaenoic adj1 acid)).ti,ab. 21. exp Fatty Acids, Unsaturated/ 22. 16 or 17 or 18 or 19 or 20 or 21 23. Exercise/ or Exercise Therapy/ or Physical Exertion/ or Motor Activity/ or Sports/ 24. sport*.tw. 25. exp "Physical Education and Training"/ 26. (physical adj3 (activit* or education* or exertion* or training)).tw. 27. exercise*.tw. 28. exp diet therapy/ 29. ((diet or dieting) adj5 (health* or weight*)).tw. 30. (calorie adj3 (control or reduc* or restriction)).tw. 31. food choice*.tw. 32. (fat camp* or weight loss camp*).tw. 33. nutrition education.tw. 34. Nutrition Therapy/ or behavior therapy/ or Cognitive Therapy/ or psychotherapy/ 35. (behavio?r* adj3 (therap* or technique* or modif* or intervention*)).tw. 36. (cognit* adj3 (therap* or technique* or modif* or intervention*)).tw. 37. CBT.tw. 38. (psychotherap* or psycho-therap*).tw. 39. (psycho-social or psychosocial).tw. 40. exp Health Promotion/ or Health Education/ 41. (health* adj3 (promot* or educat* or lifestyle)).tw. 42. lifestyle/ 43. (lifestyle* or life-style*).tw. 44. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 45. 22 or 44 46. 11 and 15 and 45
Embase Ovid	January 1974 to February 2021	1. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 2. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af.

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		3. 1 or 2 4. exp fatty liver/ 5. (liver and (fatty or steatosis or steatoses)).ti,ab. 6. NAFLD.ti,ab. 7. 4 or 5 or 6 8. (((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacteria).ti,ab. 9. exp dietary supplement/ or probiotic agent/ or prebiotic agent/ or synbiotic agent/ 10. (vitamin* or micronutrient* or (trace adj1 (element* or mineral*)) or antioxidant*).ti,ab. 11. exp vitamin/ or exp trace element/ or exp antioxidant/ 12. (((unsaturated or polyunsaturated) and (fatty adj1 acid*)) or PUFA or (linoleic adj1 acid*) or (docosahexaenoic adj1 acid*) or (eicosapentaenoic adj1 acid)).ti,ab. 13. exp polyunsaturated fatty acid/ 14. 8 or 9 or 10 or 11 or 12 or 13 15. exercise/ or kinesiotherapy/ or motor activity/ or sport/ 16. sport*.tw. 17. (physical adj3 (activit* or education* or exertion* or training)).tw. 18. exercise*.tw. 19. exp diet therapy/ 20. ((diet or dieting) adj5 (health* or weight*)).tw. 21. (calorie adj3 (control or reduc* or restriction)).tw. 22. food choice*.tw. 23. (fat camp* or weight loss camp*).tw. 24. nutrition education.tw. 25. behavior therapy/ or Cognitive Therapy/ or psychotherapy/ 26. (behavio?r* adj3 (therap* or technique* or modif* or intervention*)).tw. 27. (cognit* adj3 (therap* or technique* or modif* or intervention*)).tw. 28. CBT.tw. 29. (psychotherap* or psycho-therap*).tw. 30. (psycho-social or psychosocial).tw. 31. exp Health Promotion/ or Health Education/ 32. (health* adj3 (promot* or educat* or lifestyle)).tw. 33. lifestyle/ or lifestyle modification/ 34. (lifestyle* or life-style*).tw. 35. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 36. 14 or 35 37. 3 and 7 and 36
Science Citation Index Expanded (Web of Science)	January 1945 to February 2021	#1 TS = ((liver and (fatty or steatosis or steatoses)) or NAFLD) #2 TS=(((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacterial or vitamin* or micronutrient* or (trace near1 (element* or mineral*)) or ((unsaturated or polyunsaturated) and (fatty near1 acid*)) or antioxidant* or PUFA or (linoleic near1 acid*) or (docosahexaenoic near1 acid*) or (eicosapentaenoic near1 acid)) #3 TS=(sport* or (physical near/3 (activit* or education* or exertion* or training)) or exercise* or ((diet or dieting) near/5 (health* or weight*)) or (calorie near/3 (control or reduc* or restriction)) or "food choice*" or "fat camp*" or "weight loss camp*" or "nutrition education" or (behavio?r* near/3 (therap* or technique* or modif* or intervention*)) or (cognit* near/3 (therap* or technique* or modif* or intervention*)) or CBT or psychotherap* or psycho-therap* or psycho-social or psychosocial or (health* near/3 (promot* or educat* or lifestyle)) or lifestyle* or life-style* or (alcohol* near/2 (drink* or intoxicat* or

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		use* or abus* or misus* or risk* or consum* or withdraw* or detox* or treat* or therap* or excess* or reduc* or cessation or intervention*))) #4 #3 OR #2 #5 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #6 #5 AND #4 AND #1
Conference Proceedings Citation Index-Science (Web of Science)	January 1990 to February 2021	#1 TS = ((liver and (fatty or steatosis or steatoses)) or NAFLD) #2 TS=(((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacterial or vitamin* or micronutrient* or (trace near1 (element* or mineral*)) or ((unsaturated or polyunsaturated) and (fatty near1 acid*)) or antioxidant* or PUFA or (linoleic near1 acid*) or (docosahexaenoic near1 acid*) or (eicosapentaenoic near1 acid)) #3 TS=(sport* or (physical near/3 (activit* or education* or exertion* or training)) or exercise* or ((diet or dieting) near/5 (health* or weight*)) or (calorie near/3 (control or reduc* or restriction)) or "food choice*" or "fat camp*" or "weight loss camp*" or "nutrition education" or (behavio?r* near/3 (therap* or technique* or modif* or intervention*)) or (cognit* near/3 (therap* or technique* or modif* or intervention*)) or CBT or psychotherap* or psycho-therap* or psycho-social or psychosocial or (health* near/3 (promot* or educat* or lifestyle)) or lifestyle* or life-style* or (alcohol* near/2 (drink* or intoxicat* or use* or abus* or misus* or risk* or consum* or withdraw* or detox* or treat* or therap* or excess* or reduc* or cessation or intervention*))) #4 #3 OR #2 #5 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #6 #5 AND #4 AND #1
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	25 February 2021	"fatty liver" and Study design: "Randomised: yes" (after importing the references into Excel file)
ClinicalTrials.gov	25 February 2021	Fatty Liver, Nonalcoholic | Phase 2, 3, 4
European Medical Agency (www.ema.europa.eu/ema/)	25 February 2021	"Fatty liver"
US Food and Drug Administration (www.fda.gov)	25 February 2021	"Fatty liver"

Footnote: These are common search strategies that were used for this review and nutritional supplementation review (Komolafe 2021).

Appendix 2. Data

This table is too wide to be displayed in RevMan. This table can be found here.

Appendix 3. Abbreviations

AdviceDiet: dietary advice

AdviceDiet+AerobicEx: aerobic exercise plus dietary advice

AdviceDiet+Raisins: raisins plus dietary advice

AdviceDietEx: dietary advice plus exercise advice

AdviceEx: exercise advice

AerobicEx: aerobic exercise

AerobicEx+CalRestrictDiet: aerobic exercise plus calorie restricted diet

AerobicEx+FatRestrictCalRestrictDiet: aerobic exercise plus calorie and fat restricted diet

AerobicEx+ResistEx: aerobic exercise plus resistance exercise

CalRestrictDiet: calorie restricted diet

CalRestrictDiet+AerobicEx: aerobic exercise plus calorie restricted diet

CarbRestrictCalRestrictDiet: carbohydrate and calorie restricted diet

CarbRestrictDiet: carbohydrate restricted diet

CarbRestrictDiet+AerobicEx: aerobic exercise plus carbohydrate restricted diet

FatRestrictCalRestrictDiet: fat and calorie restricted diet

FatRestrictDiet: fat restricted diet

FatRestrictDiet+AerobicEx: aerobic exercise plus fat restricted diet

FattyLiver: fatty liver

FibrosisScore: fibrosis score

IsoCalorieDiet: isocalorie diet

KhorasanWheatDiet: Khorasan wheat diet

LowGIDiet: low glycaemic index diet

MedDiet: Mediterranean diet

MedDiet+AdviceDiet: Mediterranean diet plus dietary advice

MedDiet+AdviceDietEx: Mediterranean diet plus dietary advice plus exercise advice

NAFLDActivity: NAFLD activity score (NAS)

NoActiveIntervention: no active intervention

ResistEx: resistance exercise

Semi-OrganicWheatDiet: organic semi-wholegrain wheat diet

SupAerobicEx: supervised aerobic exercise

SupAerobicEx+CalRestrictDiet: supervised aerobic exercise plus calorie restricted diet

SupAerobicEx+SupResistEx: supervised aerobic exercise plus resistance exercise

HISTORY

Protocol first published: Issue 10, 2018

CONTRIBUTIONS OF AUTHORS

Protocol

Conceiving the protocol: KG
Designing the protocol: KG
Co-ordinating the protocol: KG
Designing search strategies: KG
Writing the protocol: KG
Providing general advice on the protocol: ET, AM
Securing funding for the protocol: KG
All authors approved of the current protocol version

Performing previous work that was the foundation of the current study: not applicable

Review

Co-ordinating the review: KG
Study selection: KG, EB
Data extraction: KG, EB, AL, DR, TC, AY, LB, DF
Writing the review: KG
Providing advice on the review: SF, AJS, NC, AM, KW, EJM, CP, BRD, ET
Securing funding for the review: KG
All authors approved the current review version for publication.

DECLARATIONS OF INTEREST

None known for any of the authors

SOURCES OF SUPPORT

Internal sources

- University College London, UK

  Writing equipment, software, etc

External sources

- National Institute for Health Research, UK

  Payment for writing reviews, writing equipment, software

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We have added information about treatment nodes and the decision set in the Types of interventions section.
- We removed the sentence "We excluded such quasi-randomised studies" from the two risk of bias domains on randomisation sequence and concealment. Instead, we made it clear at the beginning of 'Study design' section that we will exclude quasi-randomised studies.
- We have added liver-related mortality and MELD score based on the coreNASH project (Clearfield 2021). This was a planned modification mentioned in the protocol.
- We have removed the sentence "In general, we will classify the risk of bias as low if the method used for allocation concealment suggested that it was extremely likely that the sequence was generated randomly (for example, use of interactive voice response system)". We have also removed: 'For profit bias'. These changes were made following the current guidance for risk of bias classification of CHB Group.
- We did not perform Trial Sequential Analysis (TSA) because of the current Cochrane guidance not to use the sequential methods to draw main conclusions (Cochrane Scientific Committee 2018).
- We used the latest guidance from the GRADE Working group (Brignardello-Petersen 2018; Yepes-Nunez 2019) rather than the previous guidance (Puhan 2014) for presenting the summary of findings table.
- We used 30,000 iterations (instead of 10,000 iterations) as a minimum for burn-in of the simulation sampler used to estimate quantities in the statistical models to ensure convergence of the simulation sampler.
- We did not present some information such as ranking probability tables, rankograms, and surface area under the curve (SUCRA) plots because of concern about the misinterpretation of the results. We have highlighted this clearly within the text of the review, along with the reasons for not presenting them.

NOTES

The Methods section of this review is based on a standard Cochrane Hepato-Biliary Group template incorporating advice by the Complex Reviews Support Unit for a network meta-analysis protocol (Best 2018).