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Nutritional supplementation for nonalcohol-related fatty liver disease: a network meta-analysis (Review)

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[Intervention Review]

Nutritional supplementation for nonalcohol-related fatty liver disease: a network meta-analysis

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ABSTRACT

Background

The prevalence of non-alcohol-related fatty liver disease (NAFLD) varies between 19% and 33% in different populations. NAFLD decreases life expectancy and increases risks of liver cirrhosis, hepatocellular carcinoma, and the requirement for liver transplantation. Uncertainty surrounds relative benefits and harms of various nutritional supplements in NAFLD. Currently no nutritional supplement is recommended for people with NAFLD.

Objectives

• To assess the benefits and harms of different nutritional supplements for treatment of NAFLD through a network meta-analysis
• To generate rankings of different nutritional supplements according to their safety and efficacy

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, the 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) for people with NAFLD, irrespective of 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 performed a network meta-analysis with OpenBUGS using Bayesian methods whenever possible and calculated differences in treatments using hazard ratios (HRs), odds ratios (ORs), and rate ratios with 95% credible intervals (CrIs) based on an available-case analysis, according to National Institute of Health and Care Excellence Decision Support Unit guidance.

Main results

We included in the review a total of 202 randomised clinical trials (14,200 participants). Nineteen trials were at low risk of bias. A total of 32 different interventions were compared in these trials. A total of 115 trials (7732 participants) were included in one or more comparisons. The remaining trials did not report any of the outcomes of interest for this review.

Follow-up ranged from 1 month to 28 months. The follow-up period in trials that reported clinical outcomes was 2 months to 28 months. During this 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.

We did not calculate effect estimates for mortality because of sparse data (zero events for at least one of the groups in the trial). None of the trials reported that they measured overall health-related quality of life using a validated scale. The evidence is very uncertain about effects of interventions on serious adverse events (number of people or number of events).

We are very uncertain about effects on adverse events of most of the supplements that we investigated, as the evidence is of very low certainty. However, people taking PUFA (polyunsaturated fatty acid) may be more likely to experience an adverse event than those not receiving an active intervention (network meta-analysis results: OR 4.44, 95% CrI 2.40 to 8.48; low-certainty evidence; 4 trials, 203 participants; direct evidence: OR 4.43, 95% CrI 2.43 to 8.42). People who take other supplements (a category that includes nutritional supplements other than vitamins, fatty acids, phospholipids, and antioxidants) had higher numbers of adverse events than those not receiving an active intervention (network meta-analysis: rate ratio 1.73, 95% CrI 1.26 to 2.41; 6 trials, 291 participants; direct evidence: rate ratio 1.72, 95% CrI 1.25 to 2.40; low-certainty evidence).

Data were sparse (zero events in all groups in the trial) for liver transplantation, liver decompensation, and hepatocellular carcinoma. So, we did not perform formal analysis for these outcomes. The evidence is very uncertain about effects of other antioxidants (antioxidants other than vitamins) compared to no active intervention on liver cirrhosis (HR 1.68, 95% CrI 0.23 to 15.10; 1 trial, 99 participants; very low-certainty evidence).

The evidence is very uncertain about effects of interventions in any of the remaining comparisons, or data were sparse (with zero events in at least one of the groups), precluding formal calculations of effect estimates.

Data were probably because of the very short follow-up period (2 months to 28 months). It takes follow-up of 8 to 28 years to detect differences in mortality between people with NAFLD and the general population. Therefore, it is unlikely that differences in clinical outcomes are noted in trials providing less than 5 to 10 years of follow-up.

Authors' conclusions

The evidence indicates considerable uncertainty about effects of nutritional supplementation compared to no additional intervention on all clinical outcomes for people with non-alcohol-related fatty liver disease.

Accordingly, high-quality randomised comparative clinical trials with adequate follow-up are needed. We propose registry-based randomised clinical trials or cohort multiple randomised clinical trials (study design in which multiple interventions are trialed within large longitudinal cohorts of patients to gain efficiencies and align trials more closely to standard clinical practice) comparing interventions such as vitamin E, prebiotics/probiotics/synbiotics, PUFAs, and no nutritional supplementation. The reason for the choice of interventions is the impact of these interventions on indirect outcomes, which may translate to clinical benefit. Outcomes in such trials should be mortality, health-related quality of life, decompensated liver cirrhosis, liver transplantation, and resource utilisation measures including costs of intervention and decreased healthcare utilisation after minimum follow-up of 8 years (to find meaningful differences in clinically important outcomes).

PLAIN LANGUAGE SUMMARY

Nutritional supplementation for people with non-alcohol-related fatty liver disease

What is the aim of this Cochrane Review?

To find out if any form of nutritional supplementation decreases effects of non-alcohol-related fatty liver disease on lifespan, health-related quality of life, chronic liver disease, and its complications, and whether nutritional supplementation causes any harm.

Non-alcoholic fatty liver disease (NAFLD) is an accumulation of fat in the liver of people who have no history of significant alcohol consumption, use of medicines, disease 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 (non-alcohol-related steatohepatitis, or NASH) or liver scarring (liver cirrhosis). Various medical treatments have been tried for treatment of NAFLD. However, no current evidence suggests that any of them

work. Nutritional supplementation has the potential to decrease liver damage, but whether this occurs 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. They found 202 randomised clinical trials (studies where participants are randomly assigned to one of two treatment groups). During analysis of data, review authors used standard Cochrane methods, which allow comparison of only two treatments at a time. In addition, review authors used 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.

Key messages
Only 19 trials were at low risk of bias, and because of this, uncertainty about the findings of this review is considerable. Studies that reported clinically important liver damage or its complications studied participants for a period of 2 months to 28 months. During this period, clinically important outcomes related to NAFLD such as death, liver-related complications such as liver cirrhosis (scarring of the liver), liver decompensation (complications caused by scarring of the liver), liver transplantation, hepatocellular carcinoma (liver cancer), and death due to liver disease were rare, even without any treatment. No evidence suggests that any nutritional supplementation decreased these. A possible reason for complications of liver disease being rare in trial participants may be the short follow-up period given in these trials (participants were followed only for a period of 2 months to 28 months). Liver-related complications due to NAFLD develop over 8 to 28 years. Therefore, it is unlikely that differences in clinical outcomes can be noted in trials with less than 5 to 10 years of follow-up.

What was studied in the Review?
This Review looked at people of any sex, age, and ethnic origin, with non-alcohol-related liver disease. Review authors excluded studies of people with previous liver transplantation. The average age of participants, when reported, ranged from 7 to 61 years. Participants were given different treatments including various vitamins and other nutritional supplements. Review authors 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 death due to liver damage ('clinical outcomes').

What were the main results of the Review?
The 202 studies included 14,200 participants. Study data were sparse. In all, 115 studies with 7732 participants provided data for analyses. Follow-up of trial participants ranged from 1 month to 28 months (2 months to 28 months for trials that reported clinical outcomes). The Review shows the following.
- The evidence indicates considerable uncertainty about effects of interventions on all clinical outcomes.
- Well-designed trials that collect data over longer follow-up times are needed in the future to find out the best nutritional supplementation (if any) for people with NAFLD.

Summary of findings 1. Nutritional supplementation for non-alcohol-related fatty liver disease

Patient or population: people with non-alcohol-related fatty liver disease (NAFLD)
Settings: community or primary care
Intervention: various interventions
Comparison: no active intervention
Follow-up period: 2 months to 28 months
Network geometry plots: Figure 1

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Quality of evidence	Comments
		No active intervention	Various interventions	Difference		
Mortality Total studies: 52 Total participants: 3372 **Follow-up period: 2 to 28 months**						
No active intervention	**Reference**					There were no deaths in the reference group
Other supplements (12 trials; 650 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Prebiotics/Probiotics/Synbiotics (15 trials; 763 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
PUFA (9 trials; 750 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Vitamin E (4 trials; 379 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	There was 1 death in the intervention group (1/84; 1.2%) in 1 trial, and there were 2 deaths in the intervention group (2/36; 5.6%) in another trial. Effect estimates could not be calculated because of zero events in the reference group in all trials
Other antioxidants (3 trials; 191 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups

Vitamin D (4 trials; 241 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Amino acids (2 trials; 158 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Vitamin E plus other antioxidants (1 trial; 36 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Other antioxidants plus other supplements (1 trial; 46 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Health-related quality of life						
No trials reported that they measured health-related quality of life						
Serious adverse events (number of people) Total studies: 63 Total participants: 4466 **Follow-up period: 2 to 28 months**						
No active intervention	**Reference**					The weighted median control group proportion shown in this table was derived from studies that were connected to the network. If all trials including those that were excluded because of zero events in both groups were excluded, the weighted median control group proportion was zero We have presented results of trials connected to the network, results of other trials for comparisons included in the network meta-analysis that were excluded because there were zero events in both trials, and results for comparisons that were not included in the network meta-analysis because there were zero events in at least 1 group in the only trials for the comparison
Other supplements (2 RCT; 136 participants)	**OR 2.39** (0.24 to 75.94) **Network estimate**	**53 per 1000**	**119 per 1000** (13 to 811)	**65 more per 1000** (40 fewer to 757 more)	**Very low certainty** [a,c,d]	Other results (20 trials; 1167 participants) were excluded from the network meta-analysis because of zero events in both groups

PUFA (3 RCT; 301 participants)	**OR 1.31** (0.49 to 4.00) **Network estimate**	**53 per 1000**	**69 per 1000** (27 to 184)	**16 more per 1000** (26 fewer to 131 more)	**Very low certainty** a,c,d	Other results (3 trials; 240 participants) were excluded from the network meta-analysis because of zero events in both groups
Vitamin E (2 RCT; 235 participants)	**OR 0.79** (0.35 to 1.77) **Network estimate**	**53 per 1000**	**43 per 1000** (19 to 91)	**11 fewer per 1000** (34 fewer to 37 more)	**Very low certainty** a,c,d	Other results (3 trials; 248 participants) were excluded from the network meta-analysis because of zero events in both groups
Vitamin D (1 RCT; 18 participants)	**OR 1.30** (0.03 to 58.38) **Network estimate**	**53 per 1000**	**68 per 1000** (2 to 767)	**15 more per 1000** (52 fewer to 714 more)	**Very low certainty** a,c,d	Other results (2 trials; 371 participants) were excluded from the network meta-analysis because of zero events in both groups
Other antioxidants (1 RCT; 99 participants)	**OR 1.67** (0.24 to 14.73) **Network estimate**	**53 per 1000**	**86 per 1000** (13 to 454)	**32 more per 1000** (40 fewer to 400 more)	**Very low certainty** a,c,d	Other results (3 trials; 152 participants) were excluded from the network meta-analysis because of zero events in both groups
Prebiotics/Probiotics/Synbiotics (14 trials; 649 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Amino acids (2 trials; 98 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	Only 1 serious adverse event was reported in the amino acid group in 1 trial. Effect estimates could not be calculated as there were zero events in the reference group in both trials
Vitamin E plus other antioxidants (1 trial; 36 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
Other antioxidants plus other supplements (1 trial; 46 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
PUFA plus vitamin E (1 trial; 70 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
Vitamin C plus vitamin E (1 trial; 88 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups

Amino acids plus vitamin C (1 trial; 191 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Oestrogen (1 trial; 78 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Phospholipids plus PUFA plus vitamin E (1 trial; 40 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Phospholipids plus vitamin E plus other antioxidants (1 trial; 138 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Polysaccharides (1 trial; 23 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
PUFA plus other supplements (1 trial; 38 participants)	**Not estimable**	**53 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Serious adverse events (number of events) Total studies: 5 Total participants: 222 **Follow-up period: 3 to 18 months**						
No active intervention	**Reference**					The weighted median control group rate shown in this table was derived from studies that were connected to the network. If all trials including those that were excluded because of zero events in both groups were excluded, the weighted median control group rate was zero We have presented the results of trials connected to the network and the results for comparisons that were not included in the network meta-analysis because there were zero events in at least 1 group in the only trials for the comparison
Vitamin E (1 RCT; 68 participants)	**Rate ratio** 1.46 (0.48 to 4.98)	**156 per 1000**	**229 per 1000** (75 to 778)	**72 more per 1000**	**Very low certainty** [a,c,d]	

	Network estimate			(81 fewer to 622 more)		
Vitamin D (1 RCT; 18 participants)	**Rate ratio** 1.23 (0.03 to 42.82) **Network estimate**	**156 per 1000**	**191 per 1000** (5 to 6691)	**35 more per 1000** (151 fewer to 6534 more)	**Very low certainty** a,c,d	
PUFA (2 trials; 58 participants)	**Not estimable**	**156 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	
Amino acids (1 trial; 78 participants)	**Not estimable**	**156 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	
Any adverse events (number of people) Total studies: 51 Total participants: 3285 **Follow-up period: 2 to 28 months**						
No active intervention	**Reference**					We have presented results of trials connected to the network, results of other trials for comparisons included in the network meta-analysis that were excluded because there were zero events in both trials, and results for comparisons that were not included in the network meta-analysis because there were zero events in at least 1 group in the only trials for the comparison
Other supplements (12 trials; 864 participants)	**OR 1.33** (0.78 to 2.26) **Network estimate**	**24 per 1000**	**32 per 1000** (19 to 54)	**8 more per 1000** (5 fewer to 29 more)	**Very low certainty** a,c,d	Another 6 trials (264 participants) were excluded from the network meta-analysis because of zero events in both groups
Prebiotics/Probiotics/Synbiotics (5 trials; 243 participants)	**OR 0.67** (0.30 to 1.46) **Network estimate**	**24 per 1000**	**16 per 1000** (7 to 35)	**8 fewer per 1000** (17 fewer to 11 more)	**Very low certainty** a,c,d	Another 6 trials (278 participants) were excluded from the network meta-analysis because of zero events in both groups
Polyunsaturated fatty acids (5 trials; 252 participants)	**OR 4.44** (2.40 to 8.48) **Network estimate**	**24 per 1000**	**100 per 1000** (56 to 175)	**76 more per 1000** (32 more to 151 more)	**Low certainty** a,c	Another trial (42 participants) was excluded from the network meta-analysis because of zero events in both groups

Vitamin E (1 RCT; 97 participants)	**OR 0.83** (0.36 to 1.91) **Network estimate**	**24 per 1000**	**20 per 1000** (9 to 46)	**4 fewer per 1000** (16 fewer to 21 more)	**Very low certainty** a,c,d	Another 2 trials (151 participants) were excluded from the network meta-analysis because of zero events in both groups
Other antioxidants (1 RCT; 99 participants)	**OR 1.67** (0.64 to 4.50) **Network estimate**	**24 per 1000**	**40 per 1000** (16 to 101)	**16 more per 1000** (9 fewer to 77 more)	**Very low certainty** a,c,d	Another 2 trials (147 participants) were excluded from the network meta-analysis because of zero events in both groups
Amino acids (2 RCT; 152 participants)	**OR 0.61** (0.28 to 1.28) **Network estimate**	**24 per 1000**	**15 per 1000** (7 to 31)	**9 fewer per 1000** (17 fewer to 7 more)	**Very low certainty** a,c,d	
Phospholipids (No direct RCT)	**OR 0.37** (0.04 to 2.01) **Network estimate**	**24 per 1000**	**9 per 1000** (1 to 48)	**15 fewer per 1000** (23 fewer to 24 more)	**Very low certainty** a,c,d	
Amino acids + vitamin C (1 RCT; 191 participants)	**OR 1.76** (0.62 to 5.53) **Network estimate**	**24 per 1000**	**42 per 1000** (15 to 121)	**18 more per 1000** (9 fewer to 97 more)	**Very low certainty** a,c,d	
Oestrogen (1 RCT; 78 participants)	**OR 1.11** (0.03 to 44.88) **Network estimate**	**24 per 1000**	**27 per 1000** (1 to 529)	**3 more per 1000** (24 fewer to 504 more)	**Very low certainty** a,c,d	
Vitamin D (1 trial; 60 participants)	**Not estimable**	**24 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	
Vitamin E plus other antioxidants (1 trial; 36 participants)	**Not estimable**	**24 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	
Other antioxidants plus other supplements (1 trial; 46 participants)	**Not estimable**	**24 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	
PUFA plus vitamin E (1 trial; 70 participants)	**Not estimable**	**24 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	

PUFA plus other supplements (1 trial; 38 participants)	**Not estimable**	**24 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c
Vitamin C plus vitamin E (1 trial; 88 participants)	**Not estimable**	**24 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c
Polysaccharides (1 trial; 23 participants)	**Not estimable**	**24 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c
Any adverse events (number of events) **Total studies: 13** **Total participants: 971** **Follow-up: 2 to 28 months**					
No active intervention	**Reference**				
Other supplements (6 RCTs; 291 participants)	**Rate ratio** 1.72 (1.25 to 2.40) **Direct estimate**	**602 per 1000**	**1036 per 1000** (753 to 1446)	**434 more per 1000** (151 more to 843 more)	**Low certainty** a,c
Polyunsaturated fatty acids (2 RCTs; 252 participants)	**Rate ratio** 0.90 (0.68 to 1.21) **Network estimate**	**602 per 1000**	**544 per 1000** (409 to 728)	**59 fewer per 1000** (193 fewer to 126 more)	**Very low certainty** a,c,d,e
Vitamin E (3 RCTs; 332 participants)	**Rate ratio** 0.91 (0.71 to 1.18) **Network estimate**	**602 per 1000**	**549 per 1000** (425 to 708)	**54 fewer per 1000** (178 fewer to 106 more)	**Very low certainty** a,c,d,e
Vitamin D (1 RCT; 18 participants)	**Rate ratio 1.63** (0.60 to 4.64) **Network estimate**	**602 per 1000**	**981 per 1000** (360 to 2793)	**378 more per 1000** (242 fewer to 2191 more)	**Very low certainty** a,c,d,e
Amino acids (1 RCT; 78 participants)	**Rate ratio 0.81** (0.42 to 1.54) **Network estimate**	**602 per 1000**	**486 per 1000** (252 to 927)	**116 fewer per 1000** (351 fewer to 325 more)	**Very low certainty** a,c,d,e
Liver transplantation Total studies: 20 Total participants: 1204					

Follow-up period: 2 to 12 months						
No active intervention	**Reference**					There were no events in the reference group in any of the trials
Other supplements (7 trials; 396 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Prebiotics/Probiotics/Synbiotics (6 trials; 318 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
PUFA (2 trials; 95 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Vitamin D (1 trial; 60 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
Other antioxidants (3 trials; 191 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Other antioxidants plus other supplements (1 trial; 46 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
Polysaccharides (1 trial; 23 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
Decompensation Total studies: 21 Total participants: 1371 **Follow-up period: 2 to 28 months**						
No active intervention	**Reference**					There were no events in the reference group in any of the trials
Other supplements (7 trials; 396 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Prebiotics/Probiotics/Synbiotics (6 trials; 318 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups

PUFA (2 trials; 95 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Vitamin D (1 trial; 60 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Other antioxidants (3 trials; 191 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Other antioxidants plus other supplements (1 trial; 46 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Polysaccharides (1 trial; 23 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Vitamin E (1 trial; 167 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	1/84 (1.2%) in the vitamin E group and 0/83 (0%) in the no active intervention group developed decompensation. Effect estimates could not be calculated because of zero events in the reference group
Cirrhosis Total studies: 19 Total participants: 1172 **Follow-up period: 2 to 28 months**						
No active intervention	**Reference**					The weighted median control group proportion shown in this table was from the only study in which a formal analysis was performed. If all trials including those that were excluded because of zero events in both groups were excluded, the weighted median control group proportion was zero We have presented results of trials connected to the network, results of other trials for comparisons included in the network meta-analysis that were excluded because there were zero events in both trials, and results for comparisons that were not included in the network meta-analysis because there were zero events in at least 1 group in the only trials for the comparison

Other antioxidants (1 RCT; 99 participants)	**HR 0.25** (0.01 to 2.44) **Network estimate**	**60 per 1000**	**15 per 1000** (0 to 146)	**45 fewer per 1000** (60 fewer to 86 more)	**Very low certainty** a,c,d	Another 2 trials (92 participants) were excluded from the network meta-analysis because of zero events in both groups
Other supplements (7 trials; 396 participants)	**Not estimable**	**60 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Prebiotics/Probiotics/Synbiotics (6 trials; 296 participants)	**Not estimable**	**60 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
PUFA (2 trials; 95 participants)	**Not estimable**	**60 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Vitamin E (1 trial; 167 participants)	**Not estimable**	**60 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	1/84 (1.2%) in the vitamin E group developed cirrhosis and 0/83 (0%) in the no active intervention group developed decompensation. Effect estimates could not be calculated because of zero events in the reference group
Other antioxidants plus other supplements (1 trial; 46 participants)	**Not estimable**	**60 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
Polysaccharides (1 trial; 23 participants)	**Not estimable**	**60 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	The trial had zero events in both groups
Hepatocellular carcinoma Total studies: 18 Total participants: 1058 **Follow-up period: 2 to 12 months**						
No active intervention	**Reference**					There were no events in the reference group in any of the trials
Other supplements (7 trials; 396 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups
Prebiotics/Probiotics/Synbiotics (5 trials; 289 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** a,b,c	All trials had zero events in both groups

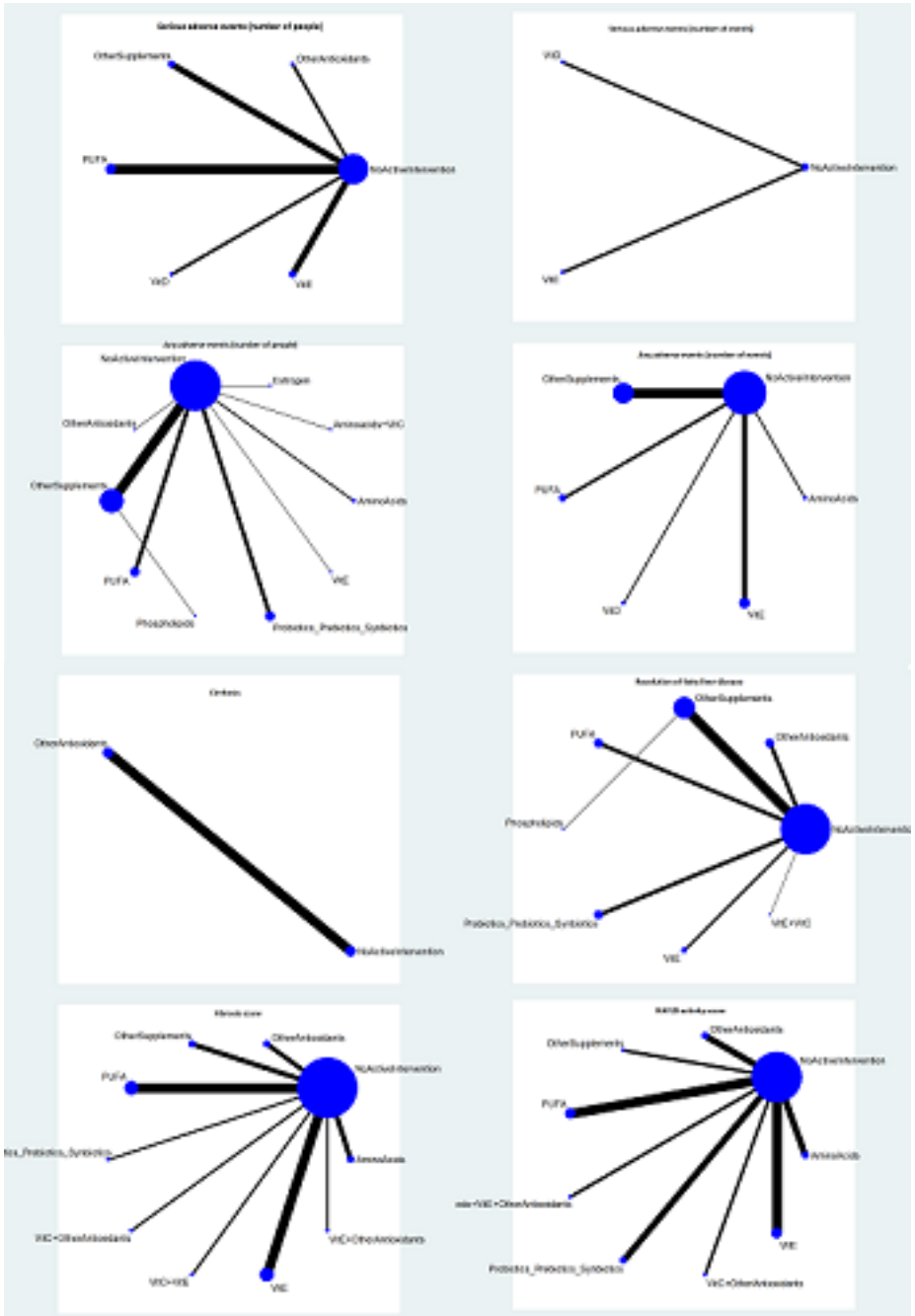
PUFA (2 trials; 95 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Vitamin D (1 trial; 60 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Other antioxidants (3 trials; 191 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	All trials had zero events in both groups
Other antioxidants plus other supplements (1 trial; 46 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Very low certainty** [a,b,c]	The trial had zero events in both groups
Polysaccharides (1 trial; 23 participants)	**Not estimable**	**0 per 1000**	**Not estimable**	**Not estimable**	**Low certainty** [b,c]	The trial had zero events in both groups
Liver-related mortality Total studies: 52 Total participants: 3372 **Follow-up period: 2 to 28 months**						
All 3 deaths mentioned in the mortality section may be related to the liver disease						

*Ranking was not provided because of considerable uncertainty in the ranking.
CrI: credible interval; HR: hazard ratio; OR: odds ratio; PUFA: polyunsaturated fatty acid.

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.

General notes: the overall number of trials included under the outcome may not match the sum of the number of trials included under each comparison. This is because of multi-arm trials and trials not involving 'no active intervention' as the control group.
[a]Downgraded one level for risk of bias because trial(s) included in the analysis was/were at high risk of bias.
[b]Downgraded one level for imprecision because there were no events.
[c]Downgraded one level for imprecision because the sample size was small.
[d]Downgraded one level for imprecision because credible intervals were wide (included clinical benefits and harms).
[e]Downgraded one level for heterogeneity because of significant heterogeneity (when network estimate is indicated, heterogeneity refers to heterogeneity in the network meta-analysis, not in the direct comparison).

Figure 1. Network plots: a high resolution version of this image can be found here. The network plots showing 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 Please see Appendix 2.



BACKGROUND

Description of the condition

Fatty liver disease is steatosis (accumulation of fat, usually triglycerides) in the liver parenchymal cells (NCBI 2018). Non-alcohol-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 such as hepatitis C virus infection, Wilson's disease, starvation, and lecithin cholesterol acyltransferase (LCAT) deficiency resulting in fat accumulation (Angulo 2002; Chalasani 2012). Fatty liver disease includes a spectrum of disorders ranging from simple steatosis or non-alcoholic fatty liver (NAFL) (fat accumulation without evidence of liver parenchymal cell injury), to non-alcoholic steatohepatitis (NASH) (fat accumulation with liver parenchymal injury 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 existing non-invasive tests to distinguish NAFLD from alcohol-related liver disease (ALD) are only about 75% to 90% accurate, and some individuals with ALD may be mis-classified as having NAFLD (Cerovic 2013; Wang 2016).

Prevalence of NAFLD varies between 19% and 33% in different populations, depending upon ethnicity, region of origin (also among people of similar ethnicity), overweight or obesity, and presence of 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). 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 protein coding gene (PNPLA3)), hypertension, hypercholesterolaemia, diabetes mellitus, lower socio-economic level, 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 with NAFLD varies between 40 and 60 years (Bedogni 2005; Dassanayake 2009; Shen 2014). In studies with long-term follow-up, the mean age of people with NAFLD ranged between 45 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 was noted to increase 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). 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 NASH groups, but higher mortality rates were noted in people with severe fibrosis regardless of whether they had bland steatosis or NASH (Soderberg 2010). It is noteworthy that NAFLD is associated with metabolic syndrome (presence of three of the following factors: hypertension, raised triglycerides, lowered high-density lipoprotein cholesterol, raised fasting glucose, central obesity) (Alberti 2009; Ballestri 2016). Therefore increased mortality among people with NAFLD may be related to metabolic syndrome, rather than to NAFLD alone. Furthermore, ALD has a worse prognosis than NAFLD (Dam-Larsen 2005); difficulty involved in distinguishing NAFLD from ALD may also contribute to the higher mortality observed in NAFLD.

Non-alcohol-related fatty liver disease is currently one of the most common reasons for liver transplantation: from 2008, NAFLD was the second or third most common reason for liver transplantation each year; the number of people who underwent liver transplantation was similar to the number with alcohol-related liver disease since 2008 (Cholankeril 2017). Risk of hepatocellular carcinoma (HCC) is increased in people with NASH cirrhosis compared to people with NAFLD without cirrhosis and compared to the general population: approximately 2% to 13% of people with NASH cirrhosis develop HCC in three to seven years (White 2012). However, HCC can also occur in people with NAFLD without cirrhosis (Piscaglia 2016).

Fat accumulates within the liver cells when there is an imbalance between 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 promotes the breakdown of peripheral adipose tissue with resultant increased influx of free fatty acids; promotes synthesis of new triglycerides within the liver; and decreases oxidation of free fatty acids (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 (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 as an explanation for development and progression of NAFLD (Tilg 2010; Buzzetti 2016).

Ultrasound is widely used for screening the general population for NAFLD; however it is operator-dependent, and 15 people with fatty liver disease out of every 100 people screened may be missed (Hernaez 2011). Ultrasound may yield false-positive results in 7 out of 100 people without fatty liver disease (Hernaez 2011). Although liver biopsy can be considered the definitive investigation to confirm the diagnosis, it is invasive and is not suitable for screening the general population.

Description of the intervention

Various interventions have been used in attempts to treat people with NAFLD, including nutritional supplementation (probiotics, prebiotics, synbiotics, vitamin supplementation, polyunsaturated fatty acid supplementation) (Nabavi 2014; Sharifi 2014; Li 2015; Nogueira 2016; Mofidi 2017); lifestyle modifications such as dietary changes and exercise training (not included in this review) (Abenavoli 2015; Shojaee-Moradie 2016; Zhang 2016; Houghton 2017); pharmacological interventions (not included in this review)

(Lombardi 2017); and weight reduction surgery (bariatric surgery) (not included in this review) for obese people with NAFLD (Adorini 2012; Anstee 2012; Chalasani 2012; Paschos 2012; Abenavoli 2013).

How the intervention might work

Nutritional supplementation (the main focus of this review) may work in different ways, for example, 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 the lipid profile (Chalasani 2012). This may lead to resolution or decreased progression of fatty liver disease.

Why it is important to do this review

Research on treatments to decrease NAFLD and NASH has been identified as a top priority by patients, carers, and healthcare professionals involved in the treatment of liver diseases in the UK (Gurusamy 2019). Nutritional supplementation has the potential to result in resolution or decreased progression of fatty liver disease. Network meta-analysis enables direct and indirect evidence to be combined and different interventions to be ranked in terms of different outcomes (Salanti 2011; Salanti 2012). As no previous Cochrane Review has examined this topic, it is important to identify the benefits and harms of nutritional supplementation for treatment of people with NAFLD. With this systematic review and network meta-analysis, we aim to provide the best level of evidence for benefits and harms of nutritional supplementation for people with NAFLD. We have presented results from direct comparisons whenever possible and have performed the network meta-analysis.

OBJECTIVES

- To assess the benefits and harms of different nutritional supplements for treatment of NAFLD through a network meta-analysis
- To generate rankings of different nutritional supplements 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) for this network meta-analysis, irrespective of language, publication status, or date of publication. We excluded studies of other designs (including quasi-randomised trials) because of the risk of bias in such studies. We excluded trials in which participants without NAFLD were included but no separate data were available for those with NAFLD.

Types of participants

We included randomised clinical trials with participants who have non-alcohol-related fatty liver disease (NAFLD), irrespective of 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 or had chronic kidney disease.

Types of interventions

We included any of the following nutritional supplements for comparison with one another, given alone or in combination.

- Vitamin E supplementation.
- Vitamin D supplementation.
- Vitamin C supplementation.
- Multi-vitamin and micronutrient supplementation.
- Other antioxidants including milk thistle.
- Prebiotics/Probiotics/Synbiotics.
- Polyunsaturated fatty acids such as omega-3 fatty acids.
- Phospholipids.
- Amino acids.
- Other nutritional supplements.
- No active intervention (no intervention or placebo).

We updated the list mentioned in the protocol to include any nutritional supplementation used primarily for treatment of NAFLD. We reported findings for all these interventions (including those not mentioned in the protocol) in the Results and Discussion sections of the review.

We considered no active intervention as the reference group. We considered each of the above subcategories as a 'treatment node'. We considered variations in sub-categories, for example, different doses or durations of nutritional supplementation, as the same treatment node. We treated each different combination of categories as a different treatment node. All of the above interventions were considered the 'decision set', that is, all of 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 were considered these as potential effect modifiers), provided these co-interventions were administered equally in both arms. We included in a different review modifications in lifestyle such as dietary modifications that alter nutritional intake (e.g. more fruits and vegetables) (Buzzetti 2021).

We evaluated the plausibility of the network meta-analysis transitivity assumption by looking at inclusion and exclusion criteria in all studies. The transitivity assumption means that participants included in different trials with different treatments (in this case, for NAFLD) can be considered as 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 who 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-intervention status is similar across trials of different comparisons. Because of the inclusion criteria and the nature of interventions considered in this review, we had no obvious concerns about the transitivity assumption with relation to these effect modifiers, although we cannot rule this out completely.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up
- Health-related quality of life, as defined in the included trials, based on a validated scale such as the EuroQoL Group Quality of Life Questionnaire based on 5 dimensions (EQ-5D) or the 36-Item Short Form Health Survey (SF-36) at maximal follow-up (EuroQol 2018; Optum 2018)
- 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 is any important medical event that might jeopardise the person or require intervention for prevention (ICH-GCP 1997). However, none of the trial authors defined serious adverse events. Therefore, we 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 event
  - Number of serious adverse events reported 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 the intervention (any time after commencement of the intervention) (ICH-GCP 1997). However, none of the trial authors defined 'adverse event'. Therefore, we used the list provided by trial authors for adverse events (as indicated in the protocol)
  - Proportion of trial participants with any adverse event
  - Numbers of any adverse events per participant
- Liver transplantation (time to liver transplantation at maximal follow-up)
- Decompensation (time to decompensation at maximal follow-up)
- Cirrhosis (time to cirrhosis at maximal follow-up)
- Liver-related mortality (time to liver-related death at maximal follow-up)

Exploratory outcomes

- Resolution of fatty liver disease (time to resolution of fatty liver disease at maximal follow-up)
- Fibrosis score at maximal follow-up
- NAFLD activity score
- Model for end-stage liver disease (MELD) score

We had chosen outcomes based on:

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

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials, 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. 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 (ictrptest.azurewebsites.net/Default.aspx), which searches various trial registers, including International Standard Randomized Controlled Trial Number (ISRCTN) and ClinicalTrials.gov. We also searched European Medical Agency (EMA) (www.ema.europa.eu/ema/) and US Food and Drug Administration (FDA) (www.fda.gov) registries for randomised clinical trials. We have provided the search strategies along with dates of the search in Appendix 1.

Searching other resources

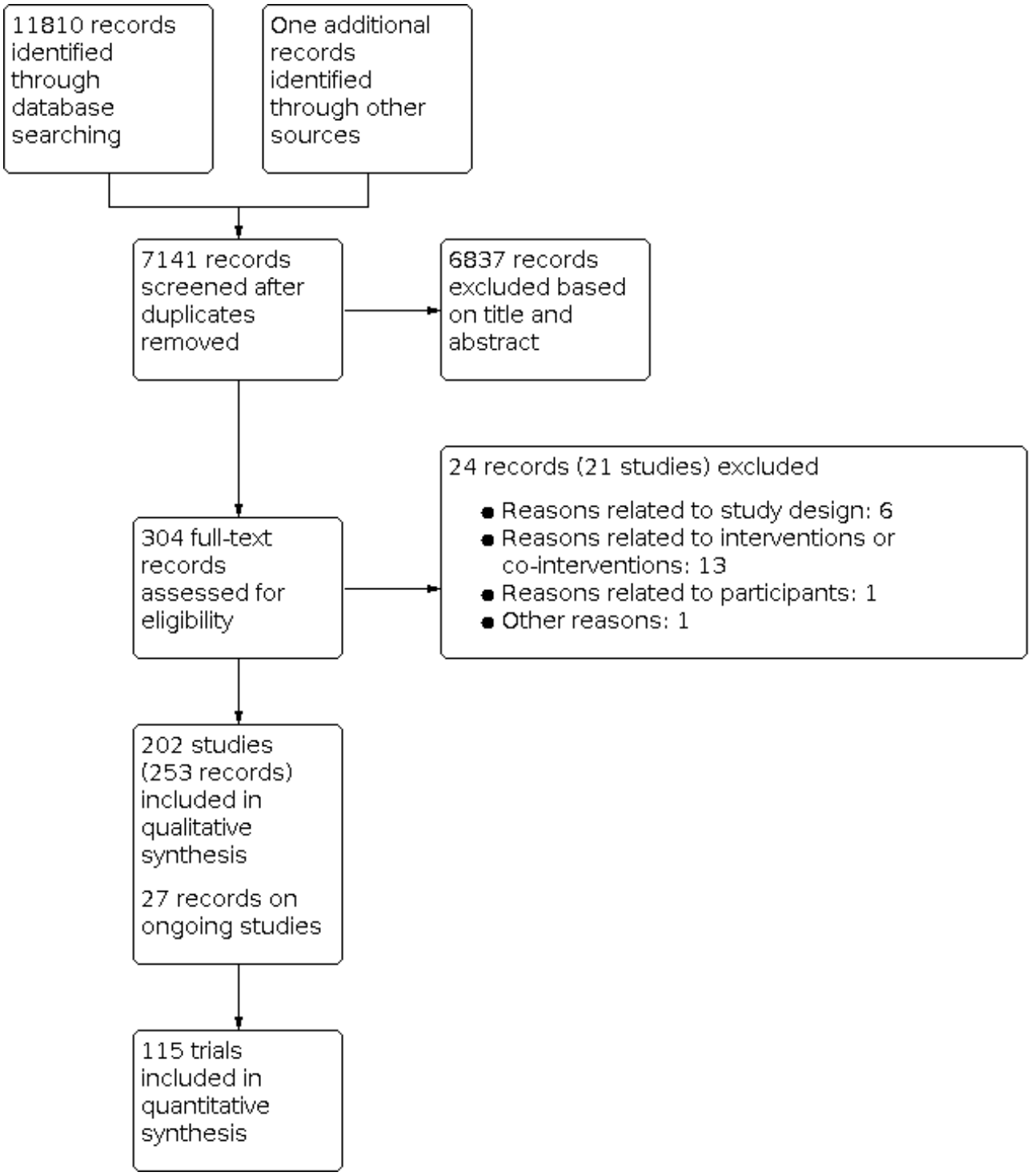
We searched the references of identified trials to gather additional trials for inclusion. We contacted study authors to ask about any other potential studies they were aware of.

Data collection and analysis

Selection of studies

Two review authors (KG and OK, LB, DR, or AL) independently identified trials for inclusion by screening titles and abstracts of articles identified by the literature search, and sought full-text articles of any records identified by at least one review author for potential inclusion. We selected trials for inclusion based on review of the full-text articles. We listed the records that we excluded and the reasons for their exclusion in the Characteristics of excluded studies table. We listed any ongoing trials identified primarily through the search of the clinical trials registers for further follow-up. We resolved discrepancies through discussion. We illustrated the study selection process in a PRISMA diagram (Figure 2).

Figure 2. Study flow diagram. Date of search: 25 February 2021.



Data extraction and management

Two review authors (KG and OK, LB, DR, or AL) independently extracted the data below onto a pre-piloted Microsoft Excel-based data extraction form (after translation of non-English articles). Non-English articles were translated by performing optical character recognition using OmniPage 18.0 on the electronic version of the article, or on a high-resolution scanned copy of the article when electronic versions were not available, then using Google Translate to translate the words. If we found multiple records of the same trial, we collated all records related to the same study at the time of data extraction and obtained from these reports the following information as related to the study.

- Outcome data (for each outcome and for each intervention group when applicable).
  - Number of participants randomised.
  - Number of participants included for analysis.
  - Number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, numbers of events and mean follow-up period for count outcomes, and numbers of participants with events and mean follow-up period for time-to-event outcomes.
  - Natural logarithm of hazard ratio and its standard error if this was reported rather than numbers of participants with events and 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 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 participants were recruited.
  - Year(s) in which the trial was conducted.
  - Inclusion and exclusion criteria.

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

We attempted to contact 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 trial authors to clarify whether the trial report was duplicated. We resolved differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess risk of bias in included trials (Higgins 2011a). 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 numbers 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 investigators. Hence, 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, or drug bottles or containers prepared by an independent pharmacist or by an independent investigator
- Unclear risk of bias: it is unclear if allocation was hidden or if 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 investigators, who assigned participants

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel ensured, and it is unlikely that blinding could have been broken; or rarely, no blinding or incomplete blinding, but 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 trial did not address this outcome
- High risk of bias: any of the following: no blinding or incomplete blinding and outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that 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 it is unlikely that blinding could have been broken; or rarely, no blinding of outcome assessment, but review authors judged that 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 trial did not address this outcome
- High risk of bias: any of the following: no blinding of outcome assessment and outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that blinding could have been broken and 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: information was insufficient to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results
- High risk of bias: results were likely to be biased due to missing data, for example, missing data were likely to be related to the intervention and outcomes

Selective outcome reporting

- Low risk of bias: the trial reported the following pre-defined 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, 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 had been registered before or at the time 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 pre-defined or clinically relevant and reasonably expected outcomes were reported fully, or it is unclear whether data on these outcomes were recorded
- High risk of bias: one or more pre-defined 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, baseline differences, early stopping)
- 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: other factors in the trial could put it at risk of bias (e.g. baseline differences, early stopping)

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 bias risk 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 allocation sequence generation; allocation concealment; blinding of participants, healthcare professionals, and outcome assessors (at the outcome level); and incomplete outcome data (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 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. fibrosis scores reported on the same scale), we calculated the mean difference (MD) with 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 95% CrI. This assumes that events are independent of each other (i.e. if a person has had an event, he or she is not at increased risk of further outcomes, which is the assumption in Poisson likelihood). For time-to-event data (e.g. all-cause mortality at maximal 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), the rankogram, and the relative ranking table with CrI for 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 cluster-randomised clinical trials, provided that the effect estimate adjusted for cluster correlation was available, or sufficient information was available to calculate the design effect (which would allow us to take clustering into account). We planned to assess additional domains of risk of bias for cluster-randomised trials according to guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Cross-over randomised clinical trials

If we identified any cross-over randomised clinical trials, we planned to include only outcomes after the period of the first intervention because included treatments could have residual effects, provided the period of follow-up before the cross-over was sufficient to address the objectives of this review (Higgins 2011b), noting that the period of follow-up before the cross-over to address the objectives of this review will be around eight years (we are not aware of any cross-over trial with such a long period of follow-up before the cross-over).

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 effect sizes from studies with more than two groups.

Dealing with missing data

We performed an intention-to-treat analysis (including all randomised participants in the analysis according to the group to which they were randomised, regardless of the intervention they received) whenever possible (Newell 1992); otherwise, we used the data available to us. When intention-to-treat analysis was not performed and data were not missing at random (e.g. treatment was withdrawn due to adverse events, duration of treatment was shortened because of lack of response, and such participants were excluded from analysis), this could lead to biased results; therefore, we 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 a good outcome in the control group) as sensitivity analyses, whenever possible (regardless of whether we considered that the data were missing at random or were not missing at random), for binary and time-to-event outcomes when binomial likelihood was used.

For continuous outcomes, we imputed the standard deviation from P values, according to guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 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 to simply provide a median and an interquartile range of the difference in medians. If it was not possible to calculate the standard deviation from the P value or from 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 2011b).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We 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 (e.g. both groups received lifestyle interventions). Different study designs and risk of bias can contribute to methodological heterogeneity.

We assessed statistical heterogeneity by comparing results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, with 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). For direct comparisons, we assessed heterogeneity using Higgins' I^2 (Higgins 2003). When possible, we explored substantial clinical, methodological, or statistical heterogeneity and addressed the heterogeneity in subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption by comparing the distribution of potential effect modifiers (clinical: presence of diabetes and NASH; 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 prepare a comparison-adjusted funnel plot. However, to interpret a comparison-adjusted funnel plot, it is necessary to rank the studies in a meaningful way, 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 risk of bias among studies, in sample size, or in the control group used over time (to put this in perspective, the first trial report for this review was published only in 2000), we judged the reporting bias by completeness of the search (Chaimani 2012). We also considered lack of reporting of outcomes as a form of reporting bias.

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 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 trials were connected by interventions using Stata/SE 15.1 (Chaimani 2013). We excluded from network meta-analysis any trials that were not connected to the network, and we reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of 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 obtained 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 comparison 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 semi-parametric model that 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 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 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 with three different sets of initial values to start the simulation-based parameter estimation to assist with assessment of convergence, employing 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 employing methods suggested by van Valkenhoef 2012. We estimated the probability that each intervention was 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 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 planned to use design-by-treatment full interaction model and inconsistency factor (IF) plots to assess inconsistency when applicable (Higgins 2012; Chaimani 2013). We planned to use 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 95% confidence intervals of inconsistency factor did not overlap 0), we planned to assess whether inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the subgroup analysis and in the investigation of heterogeneity section or by performing limited network meta-analysis of a more compatible subset of trials when possible.

Direct comparison

We performed 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 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 if we included a sufficient number of trials (when there were at least two trials in at least two of the subgroups) for all primary and secondary outcomes (Dias 2012a). We planned to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias compared to trials at high risk of bias.
- Participants with NASH compared to participants with NAFLD but without NASH.
- Participants with diabetes mellitus compared to participants without diabetes mellitus.
- Co-interventions (e.g. both groups receive some pharmacological intervention or lifestyle intervention aimed at decreasing NAFLD).
- Period of follow-up (short term: up to three months; medium term: more than three months to five years; long term: more than five years).
- Definition used by study authors for serious adverse events and any adverse events (ICH-GCP 1997 versus 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 used as covariate).

Sensitivity analysis

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

We considered variations in subcategories, for example, different doses or durations of nutritional supplementation, as the same treatment node. For future updates, if trials are designed to measure clinically meaningful outcomes, we will consider the subnode approach described by del Giovanni et al to assess the impact of considering different doses or durations as the same treatment node (Del Giovane 2013).

Presentation of results

We followed the PRISMA-NMA statement while reporting (Hutton 2015). We presented effect estimates with 95% CrIs for each pairwise comparison calculated from direct comparisons and network meta-analysis. We originally planned to present the cumulative probability of 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 in graphs (SUCRA) 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 ranks) (Salanti 2011). We plotted the probability that each intervention was best, second best, third best, etc., for each of the different outcomes (rankogams), which is 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 raw data and codes used for analysis in the European Organization for Nuclear Research open source database (Zenodo). You can find this information by clicking here.

Recommendations for future research

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

Summary of findings and assessment of the certainty of the evidence

We presented 'Summary of findings' tables for all primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by Yepes-Nunez and colleagues (Yepes-Nunez 2019). First, we calculated direct and indirect effect estimates (when possible) and 95% CrIs using the node-splitting approach (Dias 2010), that is, by calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and by calculating the indirect estimate for each comparison by excluding trials in which there was direct comparison of interventions (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using the GRADE method, which takes into account risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in the GRADE method for inconsistency in network meta-analysis), imprecision, and publication bias (Guyatt 2011). We then presented relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2019). For illustration of absolute measures, we used weighted median control group proportion or mean (Edgeworth 1887). We did not present 'Summary of findings' tables in the second format presenting all outcomes for selected

interventions (Yepes-Nunez 2019), as none of the interventions are routinely used in clinical practice, and there was no clinical benefit in any of the interventions, which would have warranted this approach to help balance benefits and harms of the intervention.

RESULTS

Description of studies

Results of the search

We identified 11,810 references through electronic searches of the Cochrane Central Register of Controlled Trials (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), World Health Organization (WHO) Trials register (n = 19), FDA (n = 137), and EMA (n = 131). We identified one additional reference by handsearching. After duplicate references were removed, there were 7141 references. We excluded 6837 clearly irrelevant records upon reading titles and abstracts. We retrieved a total of 304 full-text records for further detailed assessment. We excluded 24 records (21 studies) for the reasons stated under Characteristics of excluded studies. Twenty-seven records describe ongoing trials. Thus, we included a total of 202 trials described in 253 records (Characteristics of included studies). The reference flow is shown in Figure 2.

Included studies

A total of 202 trials were included (Miglio 2000; Uygun 2000; Harrison 2003; Kugelmas 2003; Deng 2005; Chande 2006; Chou 2006; Dufour 2006; Nobili 2006; Chen 2008; Spadaro 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Gomez 2009; Hashemi 2009; Nelson 2009; Fabbrini 2010; Khoshbaten 2010b; Li 2010; Malaguarnera 2010; Ruan 2010; Sanyal 2010; Aller 2011; Lavine 2011; Tan 2011; Vajro 2011; Basu 2012; Della Corte 2012; Gonciarz 2012; Loguercio 2012; Malaguarnera 2012; Panahi 2012; Basu 2013; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Wong 2013a; Wong 2013b; Aliashrafi 2014; Alisi 2014; Askari 2014; Byrne 2014; Celinski 2014; Chachay 2014; Eslamparast 2014; Farhangi 2014; Foroughi 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Solhi 2014; Somi 2014; Akbarzadeh 2015; Aller 2015; Amiri-Moghadam 2015; Argo 2015; Bae 2015; Bonfrate 2015; Boyraz 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Orr 2015; Pacifico 2015; Qin 2015; Yan 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Boonyagard 2016; Della Corte 2016; Ebrahimi-Mameghani 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Ferolla 2016; Guo 2016; Heeboll 2016; Hong 2016; Li 2016; Nabavi 2016; Naganuma 2016; Nogueira 2016; Panahi 2016; Pezeshki 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Amiri 2017; Ashraf 2017; Behrouz 2017; Chan 2017; Chongsrisawat 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Gavrilescu 2017; Hussain 2017; Jameshorani 2017; Javadi 2017; Jeong 2017; Kobyliak 2017; Manzhalii 2017; Mofidi 2017; Navekar 2017; Palamaru 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Tabatabaee 2017; Wang 2017; Youshari 2017; Zohrer 2017; Ahn 2018; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Bomhof 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Geier 2018; Ghaffari 2018; Hosseini 2018; Javanmardi 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Sayari 2018; Taghvaei 2018; Tobin 2018; Wang 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afsharinasab 2020; Afzali 2020; Babaei 2020; Bahrami 2020; Barbakadze 2020; Boonyagard 2020; Cai 2020; Cerletti 2020; Climax 2020; Dallio 2020; Farzin 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hoseini 2020; Hosseinabadi 2020; Kazemi 2020; Khutsishvili 2020; Kooshki 2020; Mansour 2020; Moradi 2020; Orang 2020; Parsi 2020; Pasdar 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Chiou 2021; Hong 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Poulos 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00816465; NCT00845845; NCT00941642; NCT00977730; NCT01083992; NCT01623024; NCT02690792; NCT04411862). A total of 14,200 participants were randomised to different interventions in these 202 trials. The number of participants in the trials ranged from 8 to 311. Only a total of 7732 participants from 115 trials were included in one of more outcomes. No cluster-randomised trials or cross-over trials are included in this review.

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

Excluded studies

The reasons for exclusion of studies are listed in Characteristics of excluded studies. A summary of reasons for exclusion of studies is provided here.

- Reasons related to study design: Chang 2014; Singhal 2015; Semiserin 2016; Abenavoli 2017; Famouri 2017b; NCT04281121.
- Reasons related to interventions or co-interventions: Ersoz 2005; Zhang 2008; Khoshbaten 2010a; Akcam 2011; Dela Cruz 2012; Hajiaghamohammadi 2012; Basu 2014; Han 2014; Chambers 2018; Petyaev 2018; Mahmoudi 2020; Podszun 2020; NCT00820651.
- Reasons related to participants: Saarinen 2011.
- Other reasons: Guo 2014.

Risk of bias in included studies

Risk of bias is summarised in Figure 3, Figure 4, Table 3 (domain-level summary), and Table 4 (study-level summary ordered by comparisons). The risk of bias is presented at trial level, as assessments at outcome level for clinical outcomes were the same.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

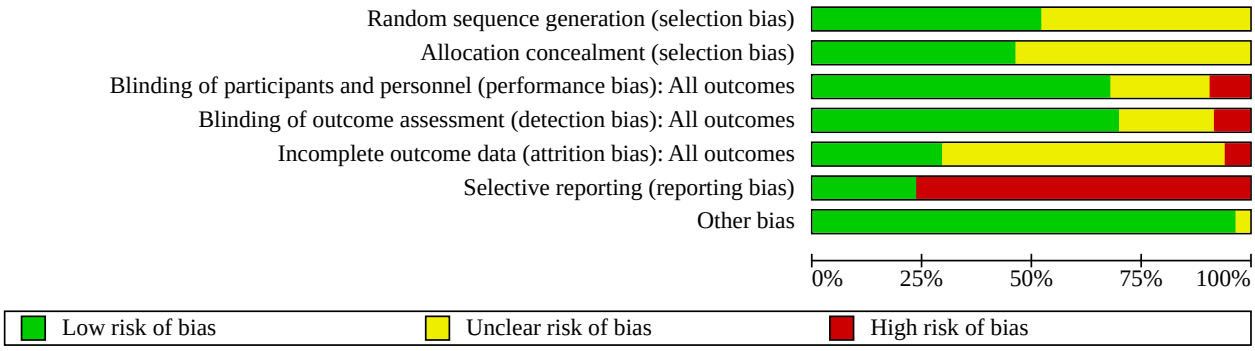


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

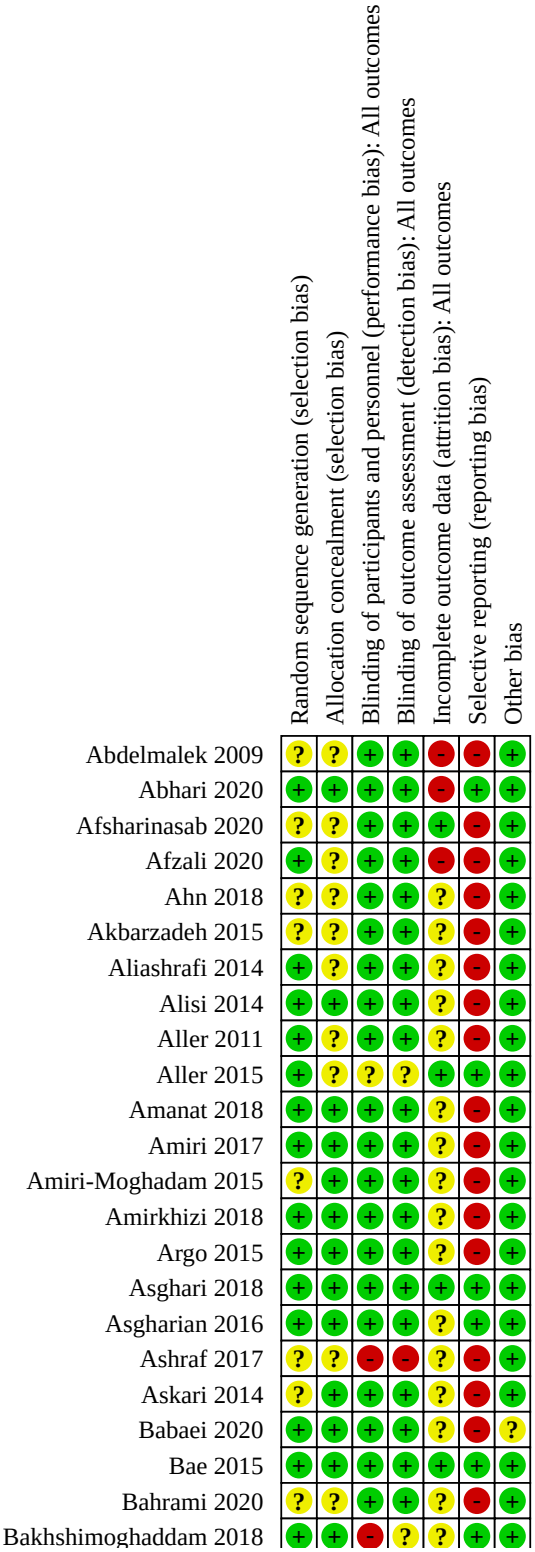


Figure 4. (Continued)

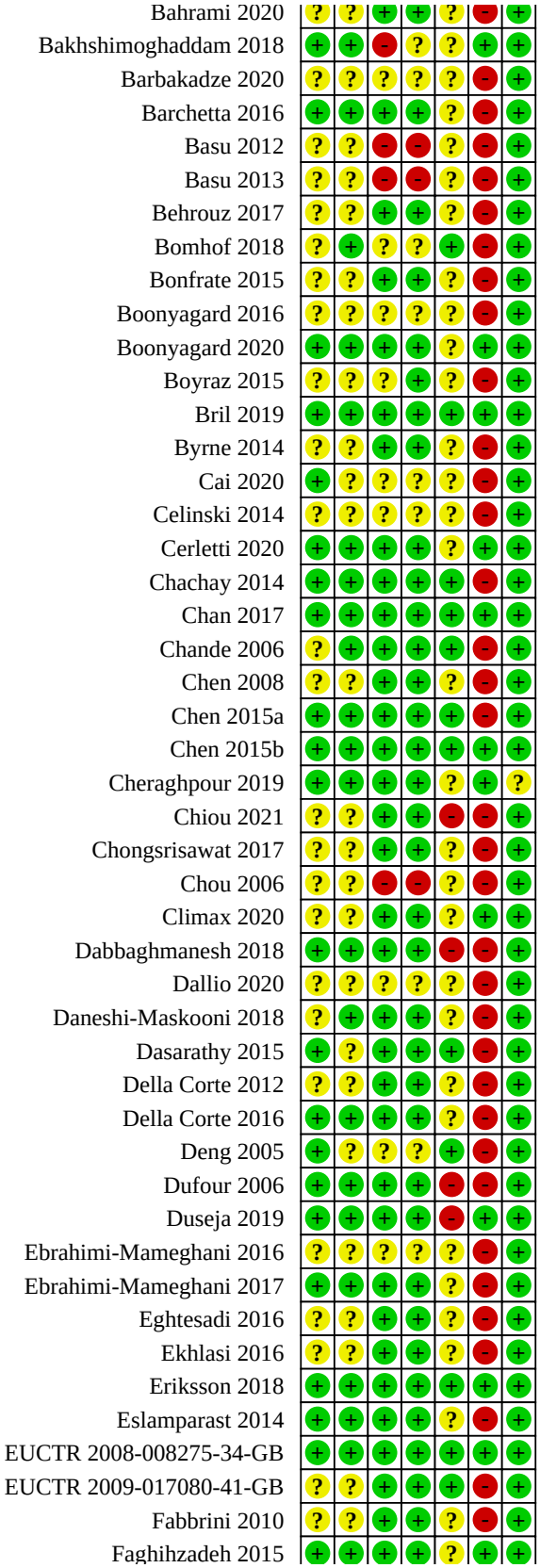


Figure 4. (Continued)

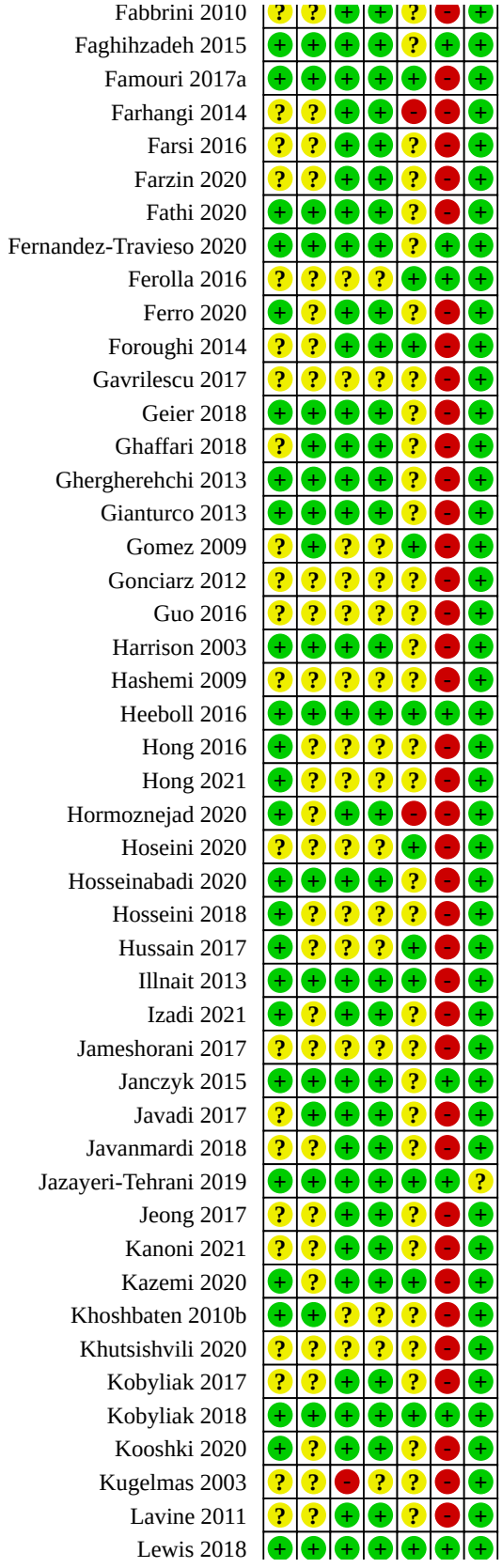


Figure 4. (Continued)

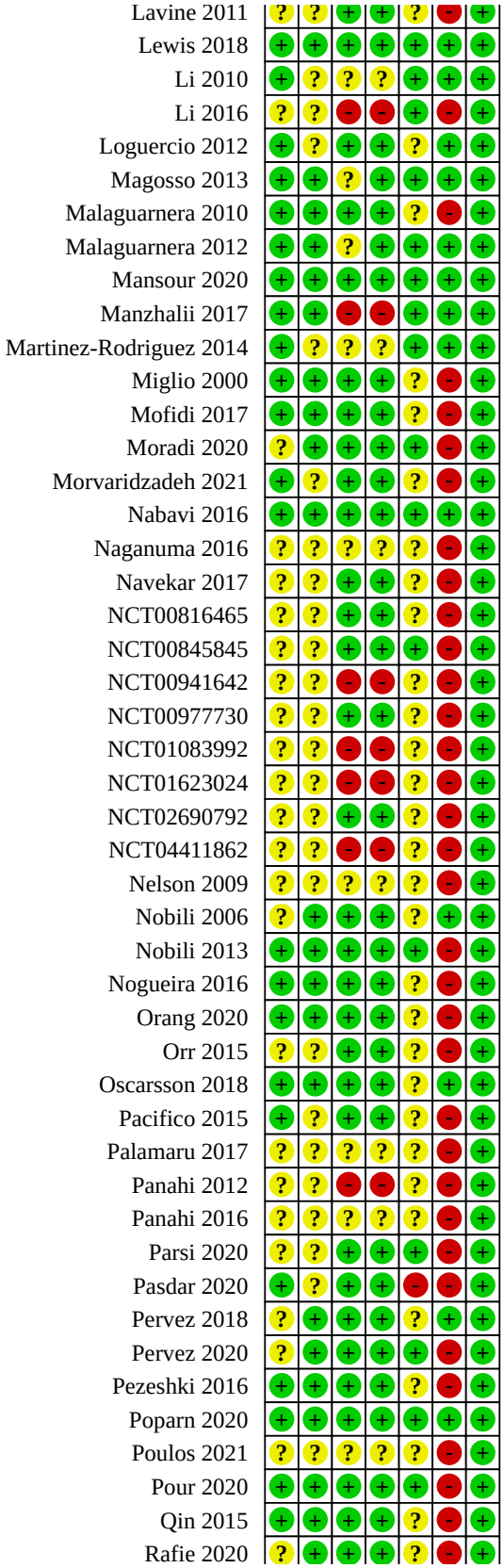
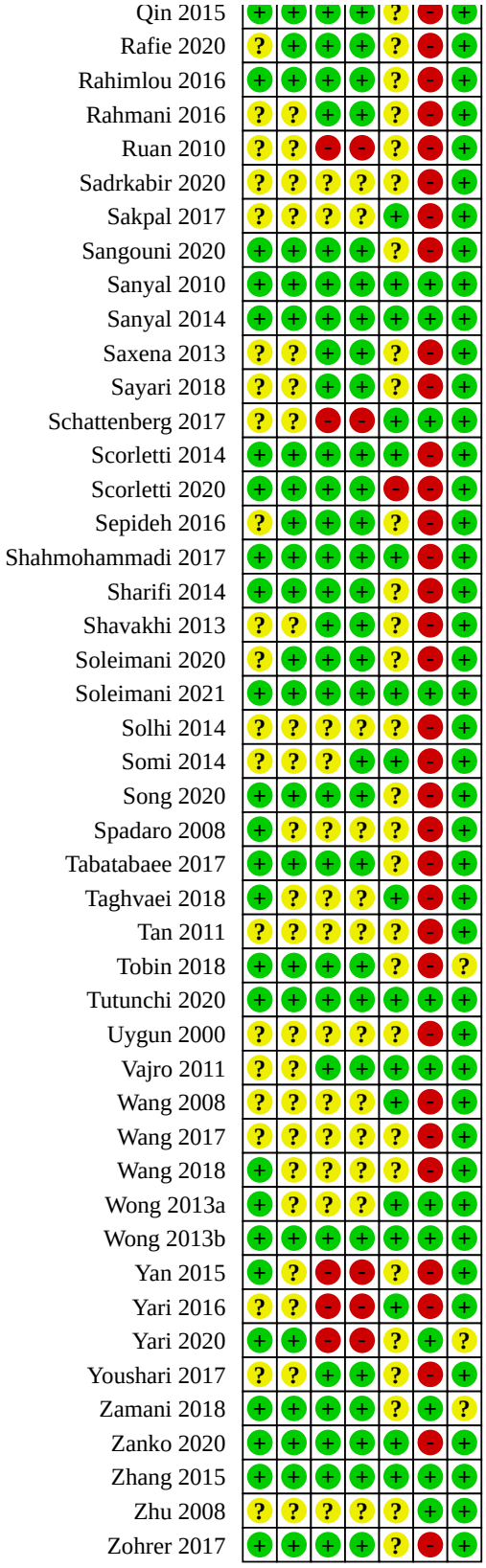


Figure 4. (Continued)



A total of 19 trials were at low risk of bias (Sanyal 2010; Wong 2013b; Sanyal 2014; Bae 2015; Chen 2015b; Zhang 2015; Heeboll 2016; Nabavi 2016; Chan 2017; Asghari 2018; Eriksson 2018; Kobyliak 2018; Lewis 2018; Bril 2019; Mansour 2020; Poparn 2020; Tutunchi 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). The remaining 182 trials were at unclear or high risk of bias in at least one domain and were considered to be at high risk of bias overall.

Allocation

A total of 106 trials were at low risk of selection bias due to lack of random sequence generation; the remaining 96 trials, which did not provide sufficient information, were at unclear risk of selection bias due to lack of random sequence generation.

In all, 94 trials were at low risk of selection bias due to lack of allocation concealment; the remaining 108 trials, which did not provide sufficient information, were at unclear risk of selection bias due to lack of allocation concealment.

Blinding

A total of 138 trials were at low risk of performance bias, as participants and healthcare providers were blinded; 46 trials, which did not provide sufficient information, were at unclear risk of performance bias; the remaining 18 trials were at high risk of performance bias, as it is clear that either participants or healthcare providers, or both, were not blinded.

In all, 142 trials were at low risk of detection bias; 44 trials, which did not provide sufficient information, were at unclear risk of detection bias; the remaining 16 trials were at high risk of detection bias, as it is clear that outcome assessors were not blinded.

Incomplete outcome data

A total of 60 trials were at low risk of attrition bias, as there were no post-randomisation dropouts, or an intention-to-treat analysis was used; 129 trials were at unclear risk of attrition bias because it is not clear whether there were post-randomisation dropouts, or whether post-randomisation dropouts were related to outcomes (if there were post-randomisation dropouts); the remaining 13 trials were at high risk of attrition bias, as post-randomisation dropouts were probably related to the intervention and to outcomes.

Selective reporting

In all, 48 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 154 trials were at high risk of selective outcome reporting bias as outcomes were changed from the protocol published prior to recruitment without sufficient justification, or trials did not report reasonably expected clinical outcomes if no protocol was published prior to recruitment.

Other potential sources of bias

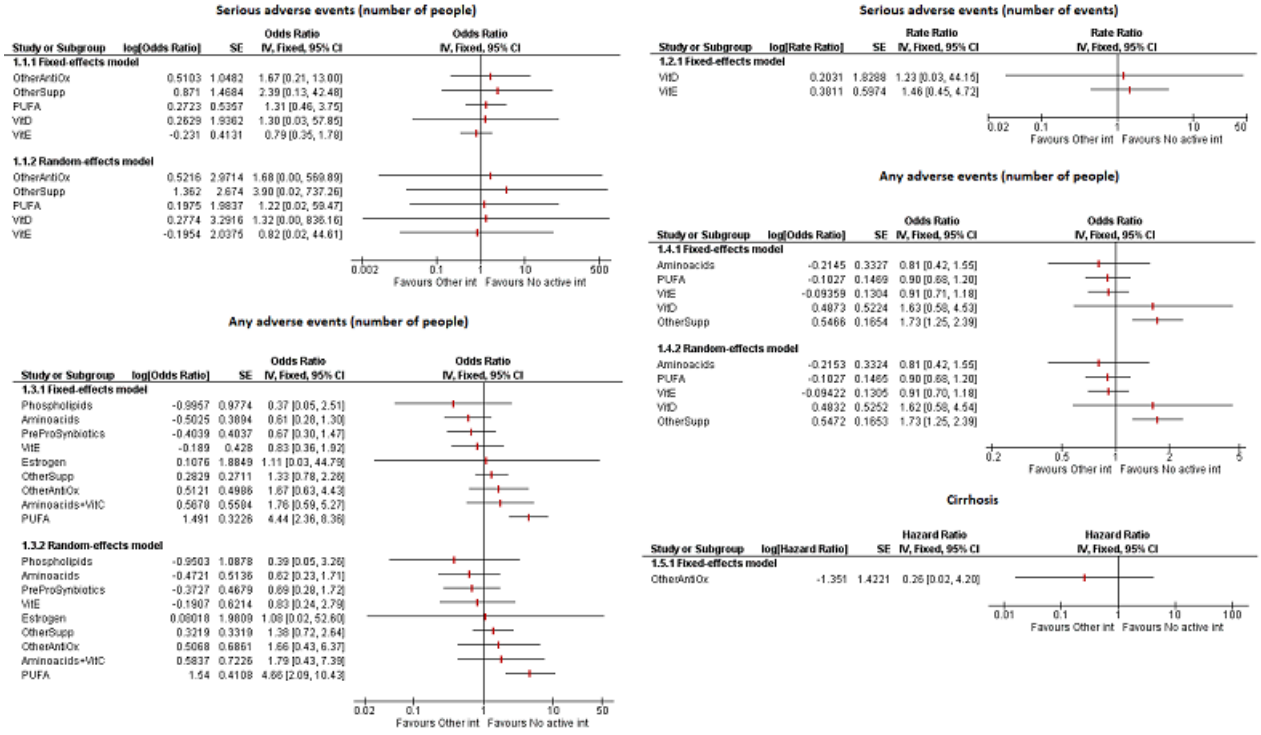
A total of 196 trials were at low risk of other bias; the remaining 6 trials were at unclear risk of other bias because there were baseline differences in important prognostic factors.

Effects of interventions

See: **Summary of findings 1** Nutritional supplementation for non-alcohol-related fatty liver disease

The network plots (when relevant) are available in Figure 1. The forest plots (when relevant) are available in Figure 5. The model fit when network meta-analysis was performed is available in Table 5. The effect estimates when network meta-analysis was performed are available in Table 6.

Figure 5. Forest plots showing the network estimates for outcomes for which a formal analysis was performed. The more conservative random-effects model was used when there were differences between fixed-effect and random-effects models. A higher resolution image of this picture is available here. Abbreviations Please see Appendix 2.



The 95% credible intervals (CrIs) of probability ranks were wide and included 0 and 1 in most comparisons for all outcomes. This was probably because of the sparse data derived from small trials. Therefore, we did not present the ranking probabilities (in a table), in rankograms, and in 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 low or very low for all clinical outcomes because all trials included in the comparisons were at unclear or high risk of bias for at least one risk of bias domain at the outcome level (downgraded one level). For all direct comparisons and for network meta-analysis involving clinical outcomes, events were fewer than 300, and we downgraded one level for imprecision. In comparisons involving clinical outcomes, the credible intervals were wide and overlapped significant clinical effect and no effect; therefore, we downgraded one more level for imprecision for comparisons with wide confidence intervals. For outcomes for which we were able to assess heterogeneity, there was evidence of heterogeneity for any adverse events (number of events); therefore, we downgraded one more level for heterogeneity for this outcome. Overall, downgrading of evidence resulted in very low certainty of evidence for all comparisons of clinical outcomes.

Mortality

A total of 52 trials (3372 participants) reported mortality at maximal follow-up of 2 to 28 months (Wang 2008; Gomez 2009; Sanyal 2010; Vajro 2011; Malaguarnera 2012; Illnait 2013; Magosso 2013; Nobili 2013; Shavakhi 2013; Wong 2013a; Chachay 2014; Foroughi 2014; Sanyal 2014; Scorletti 2014; Somi 2014; Aller 2015; Bae 2015; Chen 2015a; Dasarathy 2015; Zhang 2015; Ferolla 2016; Heeboll 2016; Li 2016; Nabavi 2016; Yari 2016; Chan 2017; Famouri 2017a; Hussain 2017; Manzhalii 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Bakhshimoghaddam 2018; Eriksson 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Taghvaei 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Scorletti 2020; Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). These trials compared a total of 13 treatments (amino acids, other antioxidants, other antioxidants plus other supplements, other supplements, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, vitamin C plus other antioxidants, vitamin D, vitamin E, vitamin E plus other antioxidants, vitamin E plus other antioxidants plus other supplements, no active intervention).

None of the 3137 participants in 50 trials died during follow-up ranging from 2 to 24 months (Wang 2008; Gomez 2009; Vajro 2011; Malaguarnera 2012; Illnait 2013; Magosso 2013; Nobili 2013; Shavakhi 2013; Wong 2013a; Chachay 2014; Foroughi 2014; Sanyal 2014; Scorletti 2014; Somi 2014; Aller 2015; Bae 2015; Chen 2015a; Dasarathy 2015; Zhang 2015; Ferolla 2016; Heeboll 2016; Li 2016; Nabavi 2016; Yari 2016; Chan 2017; Famouri 2017a; Hussain 2017; Manzhalii 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Bakhshimoghaddam 2018; Eriksson 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Taghvaei 2018; Zamani 2018; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Scorletti 2020; Yari 2020; Soleimani 2021; EUCTR

2008-008275-34-GB). In the remaining 2 trials that compared vitamin E with no active intervention, 2 of 36 (5.6%) in Bril 2019 and 1 of 84 (1.2%) in Sanyal 2010 in the intervention groups died, while none of the participants receiving no active intervention (0/32; 0% in Bril 2019; 0/83 participants; 0% in Sanyal 2010) died. Reasons for death were sepsis in a participant who had fibrosis in Sanyal 2010, and ischaemic and haemorrhagic stroke in two participants who had NASH in Bril 2019.

Because all trials had zero events in at least one of the intervention groups, we did not calculate effect estimates using formal statistical methods.

Quality of life (maximal follow-up)

None of the trials reported that they measured overall health-related quality of life using a validated scale. However, some trials measured and reported specific components of health-related quality of life (Chande 2006; Sanyal 2010; Lavine 2011).

Serious adverse events

Serious adverse events (number of people)

A total of 63 trials (4466 participants) reported serious adverse events (number of people) (Miglio 2000; Chande 2006; Chou 2006; Nobili 2006; Zhu 2008; Li 2010; Sanyal 2010; Lavine 2011; Vajro 2011; Loguercio 2012; Magosso 2013; Saxena 2013; Wong 2013a; Wong 2013b; Martinez-Rodriguez 2014; Sanyal 2014; Aller 2015; Bae 2015; Chen 2015b; Faghihzadeh 2015; Janczyk 2015; Qin 2015; Yan 2015; Zhang 2015; Ferolla 2016; Guo 2016; Nabavi 2016; Naganuma 2016; Rahimlou 2016; Sepideh 2016; Chan 2017; Manzhalii 2017; Mofidi 2017; Schattenberg 2017; Zohrer 2017; Amanat 2018; Asghari 2018; Bakhshimoghaddam 2018; Geier 2018; Kobyliak 2018; Lewis 2018; Pervez 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Pour 2020; Sangouni 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Izadi 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00845845). These trials compared a total of 19 treatments (amino acids, amino acids plus vitamin C, oestrogen, other antioxidants, other antioxidants plus other supplements, other supplements, phospholipids, phospholipids plus PUFA plus vitamin E, phospholipids plus vitamin E plus other antioxidants, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, PUFA plus other supplements, PUFA plus vitamin E, vitamin D, vitamin E, vitamin E plus other antioxidants, vitamin E plus vitamin C, no active intervention). A total of 53 trials (3599 participants) were not connected to the network because they had zero events in both arms (Miglio 2000; Chande 2006; Chou 2006; Nobili 2006; Zhu 2008; Li 2010; Lavine 2011; Vajro 2011; Loguercio 2012; Magosso 2013; Saxena 2013; Wong 2013a; Martinez-Rodriguez 2014; Aller 2015; Chen 2015b; Faghihzadeh 2015; Janczyk 2015; Qin 2015; Yan 2015; Zhang 2015; Ferolla 2016; Guo 2016; Nabavi 2016; Naganuma 2016; Rahimlou 2016; Sepideh 2016; Manzhalii 2017; Mofidi 2017; Schattenberg 2017; Zohrer 2017; Amanat 2018; Asghari 2018; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Pervez 2018; Zamani 2018; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Sangouni 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Izadi 2021; Soleimani 2021; EUCTR 2009-017080-41-GB); one trial was not connected to the network because it was the only trial for the comparison and had zero events in one arm (Bae 2015). We did not calculate effect estimates for these trials using formal statistical methods because of sparse data. In the remaining 9 trials, six treatments (PUFA, vitamin E, vitamin D, other supplements, other antioxidants, no active intervention) were compared and could be included in the network meta-analysis. The weighted median of the proportion of people who developed serious adverse events in the no intervention group in trials included in the analysis was 5.3% (this was 0% across all trials including those with zero events).

Direct comparisons

There was no evidence of differences between first and second interventions in any of the comparisons (very low-certainty evidence) (Table 6).

Network meta-analysis

The fixed-effect model was used because it had similar fit and provided equivalent results as the random-effects model. Between-study variance was 3.27 (95% CrI 0.01 to 22.97).

There were no closed loops in the network; therefore inconsistency was not checked. There was no evidence of differences between first and second interventions in any of the comparisons (very low-certainty evidence) (Table 6).

Serious adverse events (number of events)

Five trials (222 participants) reported serious adverse events (number of events) (Bae 2015; Geier 2018; Bril 2019; EUCTR 2008-008275-34-GB; NCT00845845). A total of five treatments (PUFA, vitamin E, vitamin D, amino acids, no active intervention) were compared in these trials. Three trials were not connected to the network because they were the only trials for the comparison and had zero events in one arm (Bae 2015; EUCTR 2008-008275-34-GB; NCT00845845). We did not calculate effect estimates for these trials using formal statistical methods because of sparse data. In the remaining 2 trials, three treatments (vitamin E, vitamin D, no active intervention) were compared and could be included in the network meta-analysis. The weighted median of the number of serious adverse events in the no intervention group in trials included in the analysis was 15.6 per 100 participants (this was 0 per 100 participants across all trials including those with zero events).

Direct comparisons

There was no evidence of differences between first and second interventions in any of the comparisons (very low-certainty evidence) (Table 6).

Network meta-analysis

The fixed-effect model was used because there was only one trial for each comparison. There was no evidence of differences between first and second interventions in any of the comparisons (very low-certainty evidence) (Table 6).

Any adverse events

Any adverse events (number of people)

A total of 51 trials (3285 participants) reported any adverse events (number of people) (Miglio 2000; Nobili 2006; EUCTR 2008-008275-34-GB 2008; EUCTR 2009-017080-41-GB; NCT00845845; Khoshbaten 2010b; Li 2010; Malaguarnera 2010; Lavine 2011; Vajro 2011; Malaguarnera 2012; Magosso 2013; Saxena 2013; Wong 2013a; Wong 2013b; Martinez-Rodriguez 2014; Aller

2015; Bae 2015; Janczyk 2015; Qin 2015; Guo 2016; Heeboll 2016; Nabavi 2016; Chan 2017; Jeong 2017; Manzhalii 2017; Schattenberg 2017; Amanat 2018; Asghari 2018; Daneshi-Maskooni 2018; Eriksson 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Zamani 2018; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Boonyagard 2020; Cerletti 2020; Fernandez-Travieso 2020; Mansour 2020; Poparn 2020; Pour 2020; Rafie 2020; Soleimani 2020; Song 2020; Yari 2020; Kanoni 2021). These trials compared a total of 18 treatments (amino acids, amino acids plus vitamin C, oestrogen, other antioxidants, other antioxidants plus other supplements, other supplements, phospholipids, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, PUFA plus other supplements, PUFA plus vitamin E, vitamin C, vitamin D, vitamin E, vitamin E plus other antioxidants, vitamin E plus vitamin C, no active intervention). In all, 22 trials were not connected to the network because they had zero events in both arms (Nobili 2006; Khoshbaten 2010b; Vajro 2011; Magosso 2013; Saxena 2013; Aller 2015; Qin 2015; Nabavi 2016; Manzhalii 2017; Schattenberg 2017; Asghari 2018; Lewis 2018; Pervez 2018; Cheraghpour 2019; Abhari 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Rafie 2020; Song 2020; Yari 2020; Kanoni 2021). We did not calculate effect estimates for these trials using formal statistical methods because of sparse data. In the remaining 29 trials (2064 participants), 10 interventions (other supplements, prebiotics/probiotics/synbiotics, PUFA, vitamin E, other antioxidants, amino acids, phospholipids, amino acids plus vitamin C, oestrogen, no active intervention) were compared and could be included in the network meta-analysis. The weighted median of the proportion of people who developed any adverse events in the no intervention group was 2.4%.

Direct comparisons

PUFA had higher adverse events (number of people) than no active intervention (odds ratio (OR) 4.43; 95% CrI 2.43 to 8.42; low-certainty evidence; 5 trials, 252 participants). There was no evidence of differences between first and second interventions in any of the remaining comparisons (very low-certainty evidence) (Table 6).

Network meta-analysis

The fixed-effect model was used because it had similar fit and provided equivalent results as the random-effects model. Between-study variance was 0.09 (95% CrI 0.00 to 1.04).

There were no closed loops in the network; therefore inconsistency was not checked.

The first intervention had higher numbers of adverse events (number of people) than the second intervention in the following comparisons (Table 6).

- PUFA versus no active intervention: OR 4.44, 95% CrI 2.40 to 8.48; low-certainty evidence; 4 trials, 203 participants; direct evidence: OR 4.43, 95% CrI 2.43 to 8.42).
- PUFA versus other supplements: OR 3.35, 95% CrI 1.48 to 7.71; low-certainty evidence; no direct evidence.
- PUFA versus prebiotics/probiotics/synbiotics: OR 6.68, 95% CrI 2.46 to 18.67; low-certainty evidence; no direct evidence.

The first intervention had lower numbers of adverse events (number of people) than the second intervention in the following comparisons.

- Amino acids versus PUFA: OR 0.14, 95% CrI 0.05 to 0.36; low-certainty evidence; no direct evidence.
- Phospholipids versus PUFA: OR 0.08, 95% CrI 0.01 to 0.51; low-certainty evidence; no direct evidence.

There was no evidence of differences between first and second interventions in any of the remaining comparisons (very low-certainty evidence) (Table 6).

Any adverse events (number of events)

Thirteen trials (971 participants) reported any adverse events (number of events) (Chande 2006; EUCTR 2009-017080-41-GB 2009; NCT00845845 2009; Sanyal 2010; Lavine 2011; Sanyal 2014; Yan 2015; Bae 2015; Heeboll 2016; Jeong 2017; Geier 2018; Bril 2019; Soleimani 2020a). These trials compared a total of six treatments (amino acids, other supplements, PUFA, vitamin D, vitamin E, no active intervention). All trials were connected to the network. The weighted median of the proportion of people who developed serious adverse events in the no intervention group was 60.2 events per 100 participants.

Direct comparisons

The number of adverse events was higher with other supplements than with no active intervention: rate ratio 1.72, 95% CrI 1.25 to 2.40; 6 trials, 291 participants; low-certainty evidence.

There was no evidence of differences between first and second interventions in any of the remaining comparisons (very low-certainty evidence) (Table 6).

Network meta-analysis

The fixed-effect model was used because it had similar fit and provided equivalent results as the random-effects model. Between-study variance was 6.35 (95% CrI 0.02 to 23.79).

The number of adverse events was higher with other supplements than with no active intervention: rate ratio 1.73, 95% CrI 1.26 to 2.41; 6 trials, 291 participants; direct evidence: rate ratio 1.72, 95% CrI 1.25 to 2.40; low-certainty evidence.

The first intervention had fewer adverse events (number of people) than the second intervention in the following comparisons.

- PUFA versus other supplements: rate ratio 0.52, 95% CrI 0.34 to 0.80; no direct evidence; low-certainty evidence.
- Vitamin E versus other supplements: rate ratio 0.53, 95% CrI 0.35 to 0.79; no direct evidence; low-certainty evidence.
- Amino acids versus other supplements: rate ratio 0.47, 95% CrI 0.22 to 0.96; no direct evidence; low-certainty evidence.

There was no evidence of differences between first and second interventions in any of the remaining comparisons (very low-certainty evidence) (Table 6).

Liver transplantation

A total of 20 trials (1204 participants) reported liver transplantation at maximal follow-up of 2 to 12 months (Zhang 2015; Heeboll 2016; Chan 2017; Schattenberg 2017; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Zamani 2018; Cheraghpour 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Scorletti 2020;

Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). These trials compared a total of 10 treatments (other antioxidants, other antioxidants plus other supplements, other supplements, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, vitamin D, vitamin E plus other antioxidants, vitamin E plus other antioxidants plus other supplements, no active intervention). None of the 1204 participants in these 20 trials underwent liver transplantation during the follow-up period. We did not calculate effect estimates using formal statistical methods for this outcome because of sparse data.

Decompensation

A total of 21 trials (1371 participants) reported liver decompensation at maximal follow-up of 2 to 28 months (Sanyal 2010; Zhang 2015; Heeboll 2016; Chan 2017; Schattenberg 2017; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Zamani 2018; Cheraghpour 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Scorletti 2020; Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). These trials compared a total of 11 treatments (other antioxidants, other antioxidants plus other supplements, other supplements, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, vitamin D, vitamin E, vitamin E plus other antioxidants, vitamin E plus other antioxidants plus other supplements, no active intervention). None of the 1204 participants in 20 trials developed any decompensation events during the follow-up period (Zhang 2015; Heeboll 2016; Chan 2017; Schattenberg 2017; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Zamani 2018; Cheraghpour 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Scorletti 2020; Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). In one trial (167 participants), one participant in the vitamin E group (1/84; 1.2%) and no participants in the no active intervention group (0/83; 0%) developed decompensation (Sanyal 2010). We did not calculate effect estimates using formal statistical methods for this outcome because of sparse data.

Cirrhosis

A total of 19 trials (1172 participants) reported liver cirrhosis at maximal follow-up of 2 to 28 months (Sanyal 2010; Zhang 2015; Heeboll 2016; Chan 2017; Schattenberg 2017; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Zamani 2018; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Mansour 2020; Scorletti 2020; Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). These trials compared a total of eight treatments (other antioxidants, other antioxidants plus other supplements, other supplements, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, vitamin E, no active intervention). None of 906 participants in 17 trials developed cirrhosis (Zhang 2015; Heeboll 2016; Schattenberg 2017; Zamani 2018; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Mansour 2020; Scorletti 2020; Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). In one trial, 1 of 83 participants in the vitamin E group (1/83; 1.2%) and none of 84 participants in the no active intervention group (0/84; 0%) developed cirrhosis (Sanyal 2010). We did not calculate effect estimates using formal statistical methods for these 18 trials because of sparse data. In the remaining trial (99 participants), there was no evidence of differences in proportions of participants who developed liver cirrhosis between other antioxidants versus no active intervention (hazard ratio (HR) 1.68, 95% CrI 0.23 to 15.10; very low-certainty evidence) (Chan 2017).

Hepatocellular carcinoma

A total of 18 trials (1058 participants) reported hepatocellular carcinoma at maximum follow-up of 2 to 12 months (Zhang 2015; Heeboll 2016; Chan 2017; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Zamani 2018; Cheraghpour 2019; Jazayeri-Tehrani 2019; Abhari 2020; Boonyagard 2020; Mansour 2020; Poparn 2020; Scorletti 2020; Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB). These trials compared a total of eight treatments (other antioxidants, other antioxidants plus other supplements, other supplements, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, vitamin D, no active intervention). None of 1058 participants in these 18 trials developed hepatocellular carcinoma during the follow-up period. We did not calculate effect estimates using formal statistical methods for this outcome because of sparse data.

Liver-related mortality

Of the 52 trials that reported mortality, deaths were reported in only two trials (please see above). The reasons for death were sepsis in a participant who had fibrosis in Sanyal 2010, and ischaemic and haemorrhagic stroke in two participants who had NASH in Bril 2019. All these deaths may be related to liver disease. Because these trials had zero events in the no intervention group (please see mortality; we did not calculate effect estimates using formal statistical methods).

Exploratory outcomes

Resolution of fatty liver disease

A total of 45 trials (2913 participants) reported resolution of fatty liver disease at maximal follow-up of 2 to 28 months (Nobili 2006; Spadaro 2008; Zhu 2008; Li 2010; Ruan 2010; Sanyal 2010; Loguercio 2012; Illnait 2013; Magosso 2013; Nobili 2013; Shavakhi 2013; Wong 2013b; Martinez-Rodriguez 2014; Sharifi 2014; Somi 2014; Chen 2015b; Faghihzadeh 2015; Janczyk 2015; Asgharian 2016; Farsi 2016; Heeboll 2016; Rahmani 2016; Chan 2017; Famouri 2017a; Navekar 2017; Asghari 2018; Bakhshimoghaddam 2018; Kobyliak 2018; Lewis 2018; Pervez 2018; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Bahrami 2020; Boonyagard 2020; Fathi 2020; Fernandez-Travieso 2020; Hormoznejad 2020; Hosseinabadi 2020; Mansour 2020; Pervez 2020; Tutunchi 2020; Yari 2020; EUCTR 2008-008275-34-GB). These trials compared a total of 13 treatments (amino acids, other antioxidants, other antioxidants plus other supplements, other supplements, phospholipids, phospholipids plus vitamin E plus other antioxidants, polysaccharides, prebiotics/probiotics/synbiotics, PUFA, vitamin D, vitamin E, vitamin E plus vitamin C, no active intervention). None of the 646 participants in 12 trials developed resolution of fatty liver disease (Loguercio 2012; Sharifi 2014; Heeboll 2016; Navekar 2017; Asghari 2018; Lewis 2018; Pervez 2018; Duseja 2019; Abhari 2020; Boonyagard 2020; Mansour 2020; Yari 2020). One trial (80 participants) was not connected to the network because this was the only trial for the comparison and it included zero participants in one arms (Somi 2014). In this trial, 9 of 40 (22.5%) participants in the amino acids group and 0 of 40 (0%) participants developed fatty liver resolution. We did not calculate effect estimates using formal statistical methods for

these trials because of sparse data. The remaining 32 trials (2187 participants) were connected to the network (Nobili 2006; Spadaro 2008; Zhu 2008; Li 2010; Ruan 2010; Sanyal 2010; Illnait 2013; Nobili 2013; Magosso 2013; Shavakhi 2013; Wong 2013b; Martinez-Rodriguez 2014; Chen 2015b; Faghihzadeh 2015; Janczyk 2015; Asgharian 2016; Farsi 2016; Rahmani 2016; Chan 2017; Famouri 2017a; Bakhshimoghaddam 2018; Kobyliak 2018; Cheraghpour 2019; Jazayeri-Tehrani 2019; Bahrami 2020; Fathi 2020; Fernandez-Travieso 2020; Hormoznejad 2020; Hosseinabadi 2020; Pervez 2020; Tutunchi 2020; EUCTR 2008-008275-34-GB).

Direct comparisons

In the following comparisons, the first intervention had higher resolution of fatty liver than the second intervention.

- Other supplements versus no active intervention: HR 3.00, 95% CrI 2.12 to 4.74; 12 trials, 715 participants.
- Prebiotics/Probiotics/Synbiotics versus no active intervention: HR 4.50, 95% CrI 2.76 to 7.70; 5 trials, 319 participants.

There was no evidence of differences between first and second interventions in any of the remaining comparisons (very low-certainty evidence) (Table 6).

Network meta-analysis

The random-effects model was used because we could not obtain convergence for the fixed-effect model despite various measures. Between-study variance was 0.06 (95% CrI 0.00 to 0.56).

There were no closed loops in the network; therefore inconsistency was not checked.

In the following comparisons, the first intervention had higher resolution of fatty liver than the second intervention.

- Other supplements versus no active intervention: HR 3.03, 95% CrI 2.02 to 4.74; 12 trials, 715 participants; direct evidence: 3.00, 95% CrI 2.12 to 4.74.
- Prebiotics/Probiotics/Synbiotics versus no active intervention: HR 4.64, 95% CrI 2.58 to 9.09; 5 trials, 319 participants; direct evidence: 4.50, 95% CrI 2.76 to 7.70.
- PUFA versus no active intervention: HR 3.31, 95% CrI 1.67 to 7.58; 5 trials, 343 participants; direct evidence: 4.78, 95% CrI 0.99 to 123.72.
- Vitamin E versus no active intervention: HR 2.15, 95% CrI 1.15 to 4.39; 3 trials, 325 participants; direct evidence: 0.55, 95% CrI 0.08 to 1.51.
- Other antioxidants versus no active intervention: HR 3.43, 95% CrI 1.37 to 9.63; 5 trials, 309 participants; direct evidence: 3.19, 95% CrI 0.44 to 15.50.

There was no evidence of differences between first and second interventions in any of the remaining comparisons (Table 6).

Fibrosis score

A total of 18 trials (1429 participants) reported fibrosis score (Harrison 2003; Dufour 2006; Abdelmalek 2009; Gomez 2009; Sanyal 2010; Malaguarnera 2010; Lavine 2011; Malaguarnera 2012; Wong 2013a; Gianturco 2013; Sanyal 2014; Zhang 2015; Dasarathy 2015; Aller 2015; Li 2016; Nogueira 2016; Chan 2017; Bril 2019). These trials compared a total of 10 treatments (prebiotics/probiotics/synbiotics, PUFA, vitamin E, amino acids, vitamin E plus other antioxidants, vitamin C plus other antioxidants, vitamin C plus vitamin E, other supplements, other antioxidants, no active intervention). All trials were connected to the network.

Direct comparisons

There was no evidence of differences between first and second interventions in any of the direct comparisons (Table 6).

Network meta-analysis

The random-effects model was used because it was conservative, although it had similar fit as the fixed-effect model. Between-study variance was 0.04 (95% CrI 0.00 to 0.25).

There were no closed loops in the network; therefore inconsistency was not checked.

There was no evidence of differences between first and second interventions in any of the comparisons in the network meta-analysis (Table 6).

NAFLD activity score

A total of 15 trials (1279 participants) reported NAFLD activity score (Dufour 2006; Abdelmalek 2009; Gomez 2009; Malaguarnera 2010; Sanyal 2010; Lavine 2011; Loguercio 2012; Malaguarnera 2012; Gianturco 2013; Wong 2013b; Sanyal 2014; Dasarathy 2015; Nogueira 2016; Chan 2017; Bomhof 2018). These trials compared a total of nine treatments (prebiotics/probiotics/synbiotics, PUFA, vitamin E, amino acids, vitamin C plus other antioxidants, phospholipids plus vitamin E plus other antioxidants, other supplements, other antioxidants, no active intervention). All trials were connected to the network.

Direct comparisons

Vitamin C plus other antioxidants had lower NAFLD activity scores than no active intervention: mean difference (MD) -1.66, 95% CrI -1.94 to -1.38; 1 trial, 60 participants.

There was no evidence of differences between first and second interventions in any of the direct comparisons (Table 6).

Network meta-analysis

The random-effects model was used because it was conservative, although it had similar fit as the fixed-effect model. Between-study variance was 0.31 (95% CrI 0.00 to 2.35).

There were no closed loops in the network; therefore inconsistency was not checked.

In the following comparisons, the first intervention had lower NALFD scores than the second intervention.

- Vitamin E versus no active intervention: MD -1.28, 95% CrI -2.36 to -0.24; 3 trials, 270 participants; direct evidence: -1.28, 95% CrI -3.14 to 0.50.
- Vitamin C plus other antioxidants versus no active intervention: -1.66, 95% CrI -3.18 to -0.14; 1 trial, 60 participants; direct evidence: -1.66, 95% CrI -1.94 to -1.38.
- Vitamin E versus PUFA: -1.68, 95% CrI -3.13 to -0.24; no direct evidence.

- Vitamin C plus other antioxidants versus PUFA: -2.06, 95% CrI -3.85 to -0.22; no direct evidence.

There was no evidence of differences between first and second interventions in any of 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 because of the sparse data (as described above). However, we acknowledge the heterogeneity in trials in terms of how NAFLD was diagnosed, age groups included in the trials, and interventions and co-interventions that trial participants received.

Sensitivity analysis

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

We performed 'best-worst' and 'worst-best' scenario analyses for the sensitivity analysis related to missing outcome data. There were changes to interpretation of results for any adverse events (number of people) and for fatty liver resolution (Table 7). The 'main analysis' refers to results without any imputation of data.

Results for these outcomes should be interpreted with caution, as they are susceptible to attrition bias resulting from post-randomisation dropouts. There were no changes to interpretation of results for the remaining analyses or outcomes. These outcomes and comparisons are therefore robust to post-randomisation dropouts.

Imputation of standard deviation

Fibrosis score

Exclusion of two trials in which mean or standard deviation or both were imputed did not alter the results (Dufour 2006; Chan 2017).

NAFLD activity score

Exclusion of three trials in which mean or standard deviation or both were imputed resulted in changes in the results (Dufour 2006; Chan 2017; Bomhof 2018). There was no evidence of differences between first and second interventions in any of the comparisons in the network meta-analysis.

Assessment of reporting biases

There was no meaningful way in which to rank these studies (i.e. there was no specific change in risk of bias in studies, in sample size, or in the control group used over time, noting that first published report for this review was in 2000 and the second trial report was in 2006); therefore we were unable to perform the comparison-adjusted funnel plot. Important clinical outcomes were not reported in many trials despite high probability of being recorded. We performed a thorough search of literature including search of trial registers. Therefore, we identified most published studies and studies registered in the clinical trials register. All but one trial were published after 2006; therefore we expect that most registered trials on the topic have been identified.

DISCUSSION

Summary of main results

We performed a systematic review and network meta-analysis of lifestyle modifications for non-alcohol related fatty liver disease. We included in this review a total of 202 trials (14,200 participants). These trials compared a total of 32 interventions. A total of 115 trials including 7732 participants were included for one or more comparisons in this review (Miglio 2000; Harrison 2003; Chande 2006; Chou 2006; Dufour 2006; Nobili 2006; Spadaro 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Gomez 2009; Khoshbaten 2010b; Li 2010; Malaguarnera 2010; Ruan 2010; Sanyal 2010; Lavine 2011; Vajro 2011; Loguercio 2012; Malaguarnera 2012; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Wong 2013a; Wong 2013b; Chachay 2014; Eslamparast 2014; Foroughi 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Somi 2014; Aller 2015; Bae 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Qin 2015; Yan 2015; Zhang 2015; Asgharian 2016; Farsi 2016; Ferolla 2016; Guo 2016; Heeboll 2016; Li 2016; Nabavi 2016; Naganuma 2016; Nogueira 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Chan 2017; Famouri 2017a; Hussain 2017; Jeong 2017; Manzhalii 2017; Mofidi 2017; Navekar 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Zohrer 2017; Amanat 2018; Asghari 2018; Bakhshimoghaddam 2018; Bomhof 2018; Daneshi-Maskooni 2018; Eriksson 2018; Geier 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Taghvaei 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Bahrami 2020; Boonyagard 2020; Cerletti 2020; Climax 2020; Fathi 2020; Fernandez-Travieso 2020; Hormoznejad 2020; Hosseinabadi 2020; Mansour 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Izadi 2021; Kanoni 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00845845). The remaining trials did not report any outcomes of interest for this review.

The follow-up period in trials that reported primary or secondary outcomes was 2 months to 28 months. During this follow-up period, clinical events related to non-alcohol-related fatty liver disease (NAFLD) such as mortality, liver cirrhosis, liver decompensation, and liver transplantation were sparse, probably because of the very short follow-up period (2 months to 28 months). It takes 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). Therefore, it is unlikely that differences in clinical outcomes are noted in trials with less than 5 to 10 years of follow-up.

There was no evidence of increased serious adverse events with nutritional supplements at prescribed doses. There were some differences in any adverse events in some comparisons, but the impact of these adverse events on patients is not clear in the absence of health-related quality of life information. Although there were some differences between treatments in surrogate outcomes, the implication of these differences for clinical outcomes is not known. Therefore, there appears to be considerable uncertainty about whether any of the nutritional supplements are beneficial for people with NAFLD. We note that there is also considerable uncertainty about whether any pharmacological interventions work in NAFLD (Lombardi 2017), or whether any

lifestyle interventions work in NAFLD (Buzzetti 2021). However, this does not mean there is nothing we can do and we should ignore 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; Cholankeril 2017; Piscaglia 2016).

It is unlikely that ongoing trials will provide an answer to whether any nutritional supplements improve clinical outcomes in people with NAFLD. As mentioned earlier, it is unlikely that it is possible to note any differences in important clinical outcomes before 5 to 10 years. It is important that any nutritional supplements 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 and NAFLD activity score may improve with prebiotics/probiotics/synbiotics, PUFA, and vitamin E. For this review, we did not explore the optimum dose and duration; additional research may be required to identify the optimum dose and duration of these interventions. In terms of outcomes, major clinical outcomes should include mortality, health-related quality of life, decompensated liver cirrhosis, and liver transplantation.

Sample size estimation for a parallel randomised controlled trial (RCT) was made on the basis of two studies of natural history of NAFLD that followed participants for a median period of around 8 years (Adams 2005; Bedogni 2007). The proportion of participants who died was approximately 6% in Bedogni 2007 and 12.6% in Adams 2005. The hazard ratio for mortality of people with NAFLD versus those without NAFLD was 1.34 in Adams 2005 and 1.47 in Bedogni 2007. Therefore, it is reasonable to expect a 20% relative reduction in mortality by intervention: even this will mean that mortality in NALFD is higher than in those without NAFLD. If we assumed a proportional hazards model, an alpha error of 0.5, power of 0.9, mortality of people who received standard care of 9% at 8 years, estimated 20% reduction in mortality by intervention, recruitment period of 3 years, and follow-up period of 8 years, one would need 3610 participants in each group before loss to follow-up (PS: power and sample size 3.1.6).

Clearly, such a trial will be expensive to conduct. Some recent and innovative trial designs may allow completion 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 that can be used for registry-based RCTs. Existing registries for NAFLD such as European NAFLD, European paediatric NAFLD, and the TARGET-NASH study register observational studies with bio-banking facilities (Barritt 2017; Mann 2018; Hardy 2020). Establishment of national research registries 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) such as Relton 2010 (although staged-informed consent in the design is less contentious in terms of ethical concerns in Young-Afat 2016 than the originally proposed design of cmRCT, whereby some participants did not know of their participation in an RCT such as Relton 2010). There are methodological differences in the way cmRCT is designed compared to the standard parallel RCT design, for example, sample size calculations in such cmRCTs need to take into account the proportion who consented to receive the intervention in addition to the attrition that is usually accounted for in the standard parallel RCT design (Reeves 2018). Furthermore, other than a certain proportion of participants allocated to the intervention group after consenting to undergo the intervention, the efficiency of the cmRCT is lost (Reeves 2018). Because of these methodological challenges, feasibility studies may be necessary to determine the optimal design of cmRCT. Some innovations such as follow-up based on national electronic health record data (participants should be consented for linking their details to national electronic health record data at the time they consent 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 health-related quality of life measured in a sample of participants, but there is no current evidence on the validity of these approaches nor on the biases in these approaches. Therefore, nesting methodological research projects within NAFLD trials can reveal the optimal trade-off between the most valid and the most efficient study designs in trials involving people with NAFLD.

Overall completeness and applicability of evidence

Trials included only people with NAFLD with and without non-alcoholic steatohepatitis (NASH). Therefore, the results of this review are applicable in people with NAFLD with or without NASH who are able to undergo these interventions. The results are not applicable in people who had previously undergone liver transplantation.

Different studies used different methods of diagnosis of NAFLD. Having consensus on minimum standards for definition of NAFLD in clinical trials can help with the applicability of evidence from future trials.

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

The review provides evidence only about what happens within the first 28 months and does not provide any information on what happens beyond 28 months.

Quality of the evidence

The overall certainty (quality) of evidence was low or very low for all clinical outcomes. One of the main reasons for this was high risk of bias in all trials. 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 context for interpretation of information. Randomisation can be performed by standard

methods, for example, by web-based central randomisation; an intention-to-treat analysis can be performed; and a protocol should be published prior to recruitment. Blinding of healthcare providers, participants, and outcome assessors is possible through use of an identical placebo. Another major reason for the decreased certainty of evidence is imprecision. Clinical events were extremely sparse, resulting in difficulty undertaking a formal analysis, or in the rare instance when formal analysis was possible, the credible intervals were extremely wide for most comparisons. The designs of ongoing trials suggest that this imprecision cannot be addressed by these trials. We used clinical outcomes; therefore, there is no issue of indirectness due to outcomes. There is 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 inconsistency because of sparse data and absence of direct and indirect estimates for the same comparison. Therefore, one cannot rule out inconsistency ('incoherence' according to GRADE terminology). There was no meaningful way to rank these studies (i.e. there was no specific change in risk of bias in the studies, in sample size, or in the control group used over time, noting that the first trial dates back to only 2000 and there is no evidence that any additional intervention works); we have completed a thorough search for studies on effectiveness. However, only 52 of 202 (25.7%) trials reported mortality; fewer trials reported other clinical outcomes, which would have been recorded in trials of this nature. Many of these outcomes were considered as core outcome measures (Clearfield 2021). We acknowledge there is no publication related to core outcomes, but we expect reporting of 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 National Institute for Health and Care Excellence Decision Support Unit (NICE DSU) guidance. In addition, we analysed by using the fixed-effect model and the random-effects model. These are the strengths of the review process. We excluded studies that compared variations in duration or dose in the different interventions. Hence, this review does not provide information on whether one variation is better than another. The potential effect modifiers in trials that reported them were broadly similar across comparisons. Therefore, concern about the transitivity assumption is low. We were unable to assess or report inconsistency, as no comparisons with direct and indirect comparisons were available for any of these outcomes. Therefore, concern about the transitivity assumption cannot be ruled out. However, this is only of academic interest because data are sparse.

Inclusion of indirect observational evidence could weaken our network meta-analysis, but this could also be viewed as a strength for assessing rare adverse events. It is well established that exclusion of non-randomised studies increases focus on potential benefits and reduces focus on risks of serious adverse events and risks of any adverse events. As stated in the protocol, we would have recommended a new systematic review of non-randomised studies for identifying true adverse event proportions and rates, but we do not recommend such a systematic review because of the findings of this review (i.e. there is uncertainty about whether any of the interventions improve clinical outcomes, and trials powered to measure such clinical outcomes are likely to identify the major harms that need to be considered in decision-making). A significant effort is required to identify non-randomised studies that report on harm. It is also challenging to assess risk of bias in these studies. As trials powered to measure clinical outcomes are likely to identify major harms that need to be considered in decision-making, a systematic review on adverse events from observational studies will likely be unnecessary.

Agreements and disagreements with other studies or reviews

This is the first network meta-analysis on the impact of nutritional supplementation on clinical outcomes in people with NAFLD. Therefore, we are 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 rather than surrogate outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence indicates considerable uncertainty about effects of nutritional supplementation compared to no nutritional supplementation on any clinical outcomes in people with non-alcohol-related fatty liver disease.

Implications for research

Further well-designed randomised clinical trials are necessary. Some aspects of the design of these randomised clinical trials are provided here.

Study design

Registry-based RCT or cmRCT.

Participants

People with NAFLD.

Intervention/control

Vitamin E, prebiotics/probiotics/synbiotics, polyunsaturated fatty acid (PUFA), no nutritional supplementation.

Outcomes

- *Primary outcome:* mortality
- *Secondary outcomes:* health-related quality of life, decompensated liver cirrhosis, liver transplantation, resource utilisation measures including costs of intervention, decreased healthcare utilisation
- *Minimum length of follow-up:* 8 years

Sample size

If we assumed a proportional hazards model, an alpha error of 0.5, power of 0.9, mortality of people who received standard care of 9% at 8 years, estimated 20% reduction in mortality by intervention, recruitment period of 3 years, and follow-up period of 8 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 cmRCTs.

Other aspects

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

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Danish State and the Copenhagen Trial Unit disclaimer

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REFERENCES

References to studies included in this review

Abdelmalek 2009 *{published data only}*

Abdelmalek MF, Sanderson SO, Angulo P, Soldevila-Pico C, Liu C, Peter J, et al. Betaine for nonalcoholic fatty liver disease: results of a randomized placebo-controlled trial. *Hepatology (Baltimore, Md.)* 2009;**50**(6):1818-26.

Abhari 2020 *{published data only}*

Abhari K, Saadati S, Yari Z, Hosseini H, Hedayati M, Abhari S, et al. The effects of bacillus coagulans supplementation in patients with non-alcoholic fatty liver disease: a randomized, placebo-controlled, clinical trial. *Clinical Nutrition ESPEN* 2020;**39**:53-60.

Afsharinasab 2020 *{published data only}*

Afsharinasab M, Mohammad-Sadeghipour M, Reza Hajizadeh M, Khoshdel A, Mirzaiey V, Mahmoodi M. The effect of hydroalcoholic berberis integerrima fruits extract on the lipid profile, antioxidant parameters and liver and kidney function tests in patients with nonalcoholic fatty liver disease. *Saudi Journal of Biological Sciences* 2020;**27**(8):2031-7.

Afzali 2020 *{published data only}*

Afzali N, Ebadi SS, Afzali H, Sharif MR, Vazirian M, Ebadi SA, et al. Effect of beta vulgaris extract on liver enzymes in patients with non-alcoholic fatty liver disease: a randomized clinical trial. *Hepatitis Monthly* 2020;**20**(7):1-8.

Ahn 2018 *{published data only}*

Ahn SB, Jun DW, Kim E, Oh H, Jeong JY, Sohn JH, et al. Change of microbiota in patients with improved fatty liver and obesity. *Journal of Hepatology* 2018;**68**(Suppl 1):S838-9.

Akbarzadeh 2015 *{published data only}*

Akbarzadeh Z, Nourian M, Askari G, Maracy MR, Rafiei R. The effect of psyllium on anthropometric measurements and liver enzymes in overweight or obese adults with nonalcoholic fatty liver disease (NAFLD). *Journal of Isfahan Medical School* 2015;**33**(355):1771-83.

Aliashrafi 2014 *{published data only}*

Aliashrafi S, Ebrahimi-Mameghani M, Kakaie F, Javadzadeh Y, Jafarabadi MA. The effect of microalgae chlorella vulgaris supplementation on inflammatory factors in non-alcoholic fatty liver disease: a double blind randomized clinical trial. *Journal of Mazandaran University of Medical Sciences* 2014;**24**(112):113-21.

Alisi 2014 *{published data only}*

Alisi A, Bedogni G, Baviera G, Giorgio V, Porro E, Paris C, et al. Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. *Alimentary Pharmacology & Therapeutics* 2014;**39**(11):1276-85.

Aller 2011 *{published data only}*

Aller R, De Luis DA, Izaola O, Conde R, Gonzalez Sagrado M, Primo D, et al. Effect of a probiotic on liver aminotransferases in nonalcoholic fatty liver disease patients: a double blind randomized clinical trial. *European Review for Medical and Pharmacological Sciences* 2011;**15**(9):1090-5.

Aller 2015 *{published data only}*

Aller R, Izaola O, Gomez S, Tafur C, Gonzalez G, Berroa E, et al. Effect of silymarin plus vitamin E in patients with non-alcoholic fatty liver disease. A randomized clinical pilot study. *European Review for Medical and Pharmacological Sciences* 2015;**19**(16):3118-24.

Amanat 2018 *{published data only}*

Amanat S, Eftekhari MH, Fararouei M, Bagheri Lankarani K, Massoumi SJ. Genistein supplementation improves insulin resistance and inflammatory state in non-alcoholic fatty liver patients: a randomized, controlled trial. *Clinical Nutrition* 2018;**37**(4):1210-5.

Amiri 2017 *{published data only}*

Amiri HL, Agah S, Azar JT, Hosseini S, Shidfar F, Mousavi SN. Effect of daily calcitriol supplementation with and without calcium on disease regression in non-alcoholic fatty liver patients following an energy-restricted diet: randomized, controlled, double-blind trial. *Clinical Nutrition* 2017;**36**(6):1490-7.

Amiri-Moghadam 2015 *{published data only}*

Amiri-Moghadam S, Nematy M, Eghtesadi S, Khalili M, Mojarrad M, Jazayeri S, et al. Effects of L-carnitine supplementation on body composition in patients with nonalcoholic steatohepatitis (NASH). *Current Topics in Nutraceutical Research* 2015;**13**(2):71-6.

Amirkhizi 2018 *{published data only}*

Amirkhizi F, Hamedi-Shahraki S, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. The effect of alpha-lipoic acid on liver function and metabolic markers in obese patients with non-alcoholic fatty liver disease: a double-blind randomized controlled trial. *Iranian Red Crescent Medical Journal* 2018;**20**(3):e65925.

* Amirkhizi F, Hamedi-Shahraki S, Hosseinpour-Arjmand S, Vaghef-Mehrabany E, Ebrahimi-Mameghani M. Effects of alpha-lipoic acid supplementation on oxidative stress status in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. *Iranian Red Crescent Medical Journal* 2018;**20**(9):e67615.

Argo 2015 *{published data only}*

Argo CK, Patrie JT, Lackner C, Henry TD, de Lange EE, Weltman AL, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. *Journal of Hepatology* 2015;**62**(1):190-7.

Asghari 2018 *{published data only}*

Asghari S, Rafraf M, Farzin L, Asghari-Jafarabadi M, Ghavami SM, Somi MH. Effects of pharmacologic dose of resveratrol supplementation on oxidative/antioxidative status biomarkers in nonalcoholic fatty liver disease patients: a

randomized, double-blind, placebo-controlled trial. *Advanced Pharmaceutical Bulletin* 2018;**8**(2):307-17.

Asgharian 2016 *{published data only}*

* Asgharian A, Askari G, Esmailzade A, Feizi A, Mohammadi V. The effect of symbiotic supplementation on liver enzymes, C-reactive protein and ultrasound findings in patients with non-alcoholic fatty liver disease: a clinical trial. *International Journal of Preventive Medicine* 2016;**7**:59.

Asgharian A, Mohammadi V, Gholi Z, Esmaillzade A, Feizi A, Askari G. The effect of synbiotic supplementation on body composition and lipid profile in patients with NAFLD: a randomized, double blind, placebo-controlled clinical trial study. *Iranian Red Crescent Medical Journal* 2017;**19**(4):e42902.

Ashraf 2017 *{published data only}*

Ashraf MS, Jamshed A, Alam SJ, Ahmed KF, Farhana Y. An open-label randomized clinical study to compare the effects of a nutritional supplement versus vitamin E on fibroscan score in nonalcoholic steatohepatitis patients. *Journal of Hepatology* 2017;**66**(1 Suppl 1):S426.

Askari 2014 *{published data only}*

Askari F, Rashidkhani B, Hekmatdoost A. Cinnamon may have therapeutic benefits on lipid profile, liver enzymes, insulin resistance, and high-sensitivity C-reactive protein in nonalcoholic fatty liver disease patients. *Nutrition Research* 2014;**34**(2):143-8.

Babaei 2020 *{published data only}*

Babaei A, Taghavi SA, Mohammadi A, Mahdiyar MA, Iranpour P, Ejtehadi F, et al. Comparison of the efficacy of oral fenugreek seeds hydroalcoholic extract versus placebo in nonalcoholic fatty liver disease; a randomized, triple-blind controlled pilot clinical trial. *Indian Journal of Pharmacology* 2020;**52**(2):86-93.

Bae 2015 *{published data only}*

Bae JC, Lee WY, Yoon KH, Park JY, Son HS, Han KA, et al. Improvement of nonalcoholic fatty liver disease with carnitine-orotate complex in type 2 diabetes (corona): a randomized controlled trial. *Diabetes Care* 2015;**38**(7):1245-52.

Bahrami 2020 *{published data only}*

Bahrami M, Cheraghpour M, Jafarirad S, Alavinejad P, Asadi F, Hekmatdoost A, et al. The effect of melatonin on treatment of patients with non-alcoholic fatty liver disease: a randomized double blind clinical trial. *Complementary Therapies in Medicine* 2020;**52**:102452.

Bakhshimoghaddam 2018 *{published data only}*

Bakhshimoghaddam F, Shateri K, Sina M, Hashemian M, Alizadeh M. Daily consumption of synbiotic yogurt decreases liver steatosis in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. *Journal of Nutrition* 2018;**148**(8):1276-84.

Barbakadze 2020 *{published data only}*

Barbakadze GG, Khachidze TG, Sulaberidze GT, Burnadze KG, Jebashvili MI. Role of vitamin E and vitamin C for the treatment of nonalcoholic steatohepatitis in non-diabetic patients. *Hepatology International* 2020;**14**:S312-3.

Barchetta 2016 *{published data only}*

* Barchetta I, Del Ben M, Angelico F, Di Martino M, Fraioli A, La Torre G, et al. No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *BMC Medicine* 2016;**14**:92.

EUCTR 2011-003010-17-IT. Randomized double-blind intervention trial to assess the efficacy of vitamin D3 supplementation vs placebo in reducing hepatic steato-inflammation and cardio-metabolic risk profile in patients affected by type 2 diabetes and non-alcoholic fatty liver disease (NAFLD/NASH). www.clinicaltrialsregister.eu/ctr-search/search?query=2011-003010-17 (first received 7 July 2011).

Basu 2012 *{published data only}*

* Basu P, James Shah N, Farhat S. Effect of vitamin E and alfa lipoic acid (ALA) in non-alcoholic fatty liver disease: a randomised placebo control open label prospective clinical trial: VAIN trial. *Gut* 2012;**61**:A204.

Basu PP, Krishnaswamy N, Nair T, Shah NJ, Farhat S. Effect of vitamin E and alfa lipoic acid (ALA) in non alcoholic fatty liver disease: a randomized placebo control open label prospective clinical trial - VAIN trial. *American Journal of Gastroenterology* 2011;**106**:S136-7.

Basu PP, Krishnaswamy N, Nair TJ, Shah NJ, Farhat S. Effect of vitamin E and alfa lipoic acid (ALA) in non alcoholic fatty liver disease: a randomized placebo control open label prospective clinical trial - VAIN trial. *Hepatology (Baltimore, Md)* 2011;**54**(4 Suppl):1145a.

Basu 2013 *{published data only}*

* Basu P, Mittimanj K, Shah NJ, Siriki R, Rahaman K, Atluri N, et al. Curcumin, anti-oxidant, and pioglitazone therapy with inclusion of vitamin E in non-alcoholic fatty liver disease - a randomized open label placebo controlled clinical prospective trial (captive). *Journal of Clinical and Experimental Hepatology* 2013;**3**(1 Suppl 1):S26-7.

Basu P, Shah NJ, Farhat S, Siriki R, Mittimanj K, Atluri S, et al. Curcumin, anti-oxidant, and pioglitazone therapy with inclusion of vitamin E in non alcoholic fatty liver disease - a randomized open label placebo controlled clinical prospective trial (captive). *Gut* 2013;**62**:A23.

Behrouz 2017 *{published data only}*

Behrouz V, Aryaeian N, Zahedi MJ, Jazayeri S. Effects of probiotic and prebiotic supplementation on metabolic parameters, liver aminotransferases, and systemic inflammation in nonalcoholic fatty liver disease: a randomized clinical trial. *Journal of Food Science* 2020;**85**(10):3611-7.

* Behrouz V, Jazayeri S, Aryaeian N, Zahedi MJ, Hosseini F. Effects of probiotic and prebiotic supplementation on leptin, adiponectin, and glycemic parameters in non-alcoholic fatty liver disease: a randomized clinical trial. *Middle East Journal of Digestive Diseases* 2017;**9**(3):150-7.

Bomhof 2018 *{published data only}*

Bomhof MR, Parnell JA, Ramay HR, Crotty P, Rioux KP, Probert CS, et al. Histological improvement of non-alcoholic steatohepatitis with a prebiotic: a pilot clinical trial. *European Journal of Nutrition* 2018;**19**:19.

Bonfrate 2015 *{published data only}*

Bonfrate L, Grattagliano I, Portincasa P. The efficacy of Eurosil 85-vit. E complex on metabolic profile in adults with non alcoholic fatty liver disease (NAFLD). A double-blind randomized placebo-controlled clinical study. *European Journal of Clinical Investigation* 2015;**45**:15.

Boonyagard 2016 *{published data only}*

Boonyagard S, Techathuvanan K. Impact of vitamin D replacement on liver enzymes in non-alcoholic fatty liver disease patients. *Hepatology (Baltimore, Md)* 2016;**63**(1 Suppl 1):542a.

Boonyagard 2020 *{published data only}*

Boonyagard S, Techathuvanan K. Impact of vitamin D replacement on liver enzymes in non-alcoholic fatty liver disease patients: a randomized, double-blind, placebo-controlled trial. *Chotmaihet Thangphaet [Journal of the Medical Association of Thailand]* 2020;**103**(12 Suppl 8):A105-12.

Boyraz 2015 *{published data only}*

Boyraz M, Pirgon O, Dundar B, Cekmez F, Hatipoglu N. Long-term treatment with n-3 polyunsaturated fatty acids as a monotherapy in children with nonalcoholic fatty liver disease. *Journal of Clinical Research in Pediatric Endocrinology* 2015;**7**(2):121-7.

Bril 2019 *{published data only}*

* Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2019;**42**(8):1481-8.

Bril F, Biernacki DM, Lomonaco R, Kalavalapalli S, Subbarayan SK, Lai J, et al. Role of vitamin E for the treatment of nonalcoholic steatohepatitis (NASH) in patients with t2dm-a randomized, controlled trial. *Diabetes* 2018;**67**(Suppl 1):A328-9.

Byrne 2014 *{published data only}*

Byrne CD, Scorletti E, Bhatia L, McCormick K, Clough G, Nash K, et al. Benefits of docosahexanoic acid tissue enrichment in nonalcoholic fatty liver disease: results from a randomised, double-blind, placebo-controlled study testing the effects of omega-3 fatty acid treatment. *Diabetes* 2014;**63**:a468.

Cai 2020 *{published data only}*

Cai GS, Su H, Zhang J. Protective effect of probiotics in patients with non-alcoholic fatty liver disease. *Medicine* 2020;**99**(32):e21464.

Celinski 2014 *{published data only}*

Celinski K, Konturek PC, Slomka M, Cichoz-Lach H, Brzozowski T, Konturek SJ, et al. Effects of treatment with melatonin and tryptophan on liver enzymes, parameters of fat metabolism and plasma levels of cytokines in patients with non-alcoholic fatty liver disease - 14 months follow-up. *Journal of Physiology and Pharmacology* 2014;**65**(1):75-82.

Cerletti 2020 *{published data only}*

Cerletti C, Colucci M, Storto M, Semeraro F, Ammollo CT, Incampo F, et al. Randomised trial of chronic supplementation with a nutraceutical mixture in subjects with non-alcoholic fatty liver disease. *British Journal of Nutrition* 2020;**123**(2):190-7.

Chachay 2014 *{published data only}*

Chachay VS, Macdonald GA, Martin JH, Whitehead JP, O'Moore-Sullivan TM, Lee P, et al. Resveratrol does not benefit patients with nonalcoholic fatty liver disease. *Clinical Gastroenterology and Hepatology* 2014;**12**(12):2092-103.e1-6.

Chan 2017 *{published data only}*

Chan WK, Mustapha NRN, Mahadeva S. Silymarin for the treatment of non-alcoholic steatohepatitis: interim analysis of a randomized, double-blind, placebo-controlled trial. *Journal of Gastroenterology and Hepatology* 2015;**30**:324-5.

Chan WK, Mustapha NRN, Mahadeva S. Silymarin improves fibrosis in non-alcoholic steatohepatitis. *Journal of Hepatology* 2016;**64**(2 Suppl 1):S225-6.

* Chan WK, Nik Mustapha NR, Mahadeva S. A randomized trial of silymarin for the treatment of nonalcoholic steatohepatitis. *Clinical Gastroenterology and Hepatology* 2017;**15**(12):1940-9.e8.

Chan WK, Nik Mustapha NR, Mahadeva S. Silymarin for the treatment of non-alcoholic steatohepatitis: interim analysis of a randomized, double-blind, placebo-controlled trial. *Journal of Hepatology* 2015;**62**:S269.

Chande 2006 *{published data only}*

Chande N, Laidlaw M, Adams P, Marotta P. Yo Jyo Hen Shi Ko (YHK) improves transaminases in nonalcoholic steatohepatitis (NASH): a randomized pilot study. *Digestive Diseases and Sciences* 2006;**51**(7):1183-9.

Chen 2008 *{published data only}*

Chen R, Guo Q, Zhu WJ, Xie Q, Wang H, Cai W. Therapeutic efficacy of omega-3 polyunsaturated fatty acid capsule in treatment of patients with non-alcoholic fatty liver disease. *World Chinese Journal of Digestology* 2008;**16**(18):2002-6.

Chen 2015a *{published data only}*

Chen SH, Zhao XL, Ran L, Wan J, Wang XF, Qin Y, et al. Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Digestive and Liver Disease* 2015;**47**(3):226-32.

Chen 2015b *{published data only}*

Chen SH, Zhao XL, Wan J, Ran L, Qin Y, Wang XF, et al. Dihydromyricetin improves glucose and lipid metabolism and exerts anti-inflammatory effects in nonalcoholic fatty liver disease: a randomized controlled trial. *Pharmacological Research* 2015;**99**:74-81.

Cheraghpour 2019 *{published data only}*

Cheraghpour M, Imani H, Ommi S, Alavian SM, Karimi-Shahrbabak E, Hedayati M, et al. Hesperidin improves hepatic steatosis, hepatic enzymes, and metabolic and inflammatory parameters in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled, double-blind clinical trial. *Phytotherapy Research* 2019;**33**(8):2118-25.

Chiou 2021 *{published data only}*

Chiou YL, Chyau CC, Li TJ, Kuo CF, Kang YY, Chen CC, et al. Hepatoprotective effect of Antrodia cinnamomea mycelium in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled trial. *Journal of the American College of Nutrition* 2021;**40**(4):349-57.

Chongsrisawat 2017 *{published data only}*

Chongsrisawat V, Poparn H, Chatrproedprai S, Sornsiri K, Treeprasertsuk S. Effect of pre/probiotic mixture in children with nonalcoholic fatty liver disease: a randomized controlled trial. *European Journal of Pediatrics* 2017;**176**(11):1486.

Chou 2006 *{published data only}*

Chou SC, Chen KW, Hwang JS, Lu WT, Chu YY, Lin JD, et al. The add-on effects of Gynostemma pentaphyllum on nonalcoholic fatty liver disease. *Alternative Therapies in Health and Medicine* 2006;**12**(3):34-9.

Climax 2020 *{published data only}*

Climax J, Newsome PN, Hamza M, Weissbach M, Coughlan D, Sattar N, et al. Effects of epeleuton, a novel synthetic second-generation n-3 fatty acid, on non-alcoholic fatty liver disease, triglycerides, glycemic control, and cardiometabolic and inflammatory markers. *Journal of the American Heart Association* 2020;**9**(16):e016334.

Dabbaghmanesh 2018 *{published data only}*

Dabbaghmanesh MH, Danafar F, Eshraghian A, Omrani GR. Vitamin D supplementation for the treatment of non-alcoholic fatty liver disease: a randomized double blind placebo controlled trial. *Diabetes and Metabolic Syndrome* 2018;**12**(4):513-7.

Dallio 2020 *{published data only}*

Dallio M, Masarone M, Gravina AG, Di Somma A, Romeo M, Tuccillo C, et al. Evaluation of the effect derived from silybin with vitamin D and vitamin E administration on clinical, metabolic, endothelial dysfunction, oxidative stress parameters and serological worsening markers in non-alcoholic fatty liver disease patients. *Digestive and Liver Disease* 2020;**52**(Suppl 2):S165.

Daneshi-Maskooni 2018 *{published data only}*

Daneshi-Maskooni M, Keshavarz SA, Qorbani M, Mansouri S, Alavian SM, Badri-Fariman M, et al. Green cardamom increases sirtuin-1 and reduces inflammation in overweight or obese patients with non-alcoholic fatty liver disease: a double-blind randomized placebo-controlled clinical trial. *Nutrition and Metabolism* 2018;**15**:63.

Dasarathy 2015 *{published data only}*

* Dasarathy S, Dasarathy J, Khiyami A, Yerian L, Hawkins C, Sargent R, et al. Double-blind randomized placebo-controlled clinical trial of omega 3 fatty acids for the treatment of diabetic patients with nonalcoholic steatohepatitis. *Journal of Clinical Gastroenterology* 2015;**49**(2):137-44.

Dasarathy S, Dasarathy J, Khiyami A, Yerian LM, Sargent R, Hawkins CA, et al. Randomized controlled trial of omega 3 fatty acids in the treatment of non-alcoholic steatohepatitis in type 2 diabetes mellitus. *Hepatology (Baltimore, Md)* 2013;**58**(4 Suppl 1):518a.

Della Corte 2012 *{published data only}*

Della Corte C, Alterio A, Papadatou B, Sartorelli MR, Comparcola D, Nobili V. Beneficial effect of dietary supplementation with glucomannan in children with NAFLD: preliminary results. *Digestive and Liver Disease* 2012;**44**:S289.

Della Corte 2016 *{published data only}*

Della Corte C, Carpino G, De Vito R, De Stefanis C, Alisi A, Cianfarani S, et al. Docosahexanoic acid plus vitamin D treatment improves features of NALFD in children with serum vitamin D deficiency: results from a single centre trial. *PLOS One* 2016;**11**(12):e0168216.

Deng 2005 *{published data only}*

Deng YQ, Fan XF, Li JP. The state of insulin resistance in patients with nonalcoholic fatty liver and the intervention with gankangyin. *Chinese Journal of Integrative Medicine* 2005;**11**(2):117-22.

Dufour 2006 *{published data only}*

Balmer ML, Siegrist K, Zimmermann A, Dufour JF. Effects of ursodeoxycholic acid in combination with vitamin E on adipokines and apoptosis in patients with nonalcoholic steatohepatitis. *Liver International* 2009;**29**(8):1184-8.

* Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, et al. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin E in nonalcoholic steatohepatitis. *Clinical Gastroenterology and Hepatology* 2006;**4**(12):1537-43.

Duseja 2019 *{published data only}*

* Duseja A, Acharya SK, Mehta M, Chhabra S, Shalimar, Rana S, et al. High potency multistrain probiotic improves liver histology in non-alcoholic fatty liver disease (NAFLD): a randomised, double-blind, proof of concept study. *BMJ Open Gastroenterology* 2019;**6**:e000315.

Duseja AK, Acharya SK, Mehta M, Chhabra S, Shalimar, Rana S, et al. Probiotic VSL#3 improves liver histology in patients with nonalcoholic fatty liver disease - a proof of concept study. *Hepatology (Baltimore, Md)* 2016;**64**(1 Suppl 1):596a.

Ebrahimi-Mameghani 2016 *{published data only}*

Ebrahimi-Mameghani M, Jamali H, Mahdavi R, Kakaei F, Abedi R, Kabir-Mamdooh B. Conjugated linoleic acid improves glycemic response, lipid profile, and oxidative stress in obese patients with non-alcoholic fatty liver disease: a randomized controlled clinical trial. *Croatian Medical Journal* 2016;**57**(4):331-42.

Ebrahimi-Mameghani 2017 *{published data only}*

Ebrahimi-Mameghani M, Sadeghi Z, Abbasalizad Farhangi M, Vaghef-Mehrabany E, Aliashrafi S. Glucose homeostasis, insulin resistance and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: beneficial effects of supplementation with microalgae chlorella vulgaris: a double-blind placebo-controlled randomized clinical trial. *Clinical Nutrition* 2017;**36**(4):1001-6.

Eghtesadi 2016 *{published data only}*

Eghtesadi S, Amiri Moghadam S, Nemati M, Khalili M, Mojarrad M, Jazayeri S, et al. Effects of L-carnitine supplementation on inflammatory factors and malondialdehyde in patients with nonalcoholic steatohepatitis (NASH). *Obesity Facts* 2016;**9**:184.

Ekhlasi 2016 *{published data only}*

* Ekhlasi G, Kolahdouz Mohammadi R, Agah S, Zarrati M, Hosseini AF, Arabshahi SS, et al. Do symbiotic and vitamin E supplementation have favorite effects in nonalcoholic fatty liver disease? A randomized, double-blind, placebo-controlled trial. *Journal of Research in Medical Sciences* 2016;**21**:106.

Ekhlasi G, Zarrati M, Agah S, Hosseini AF, Hosseini S, Shidfar S, et al. Effects of symbiotic and vitamin E supplementation on blood pressure, nitric oxide and inflammatory factors in non-alcoholic fatty liver disease. *Excli Journal* 2017;**16**:278-90.

Eriksson 2018 *{published data only}*

Eriksson JW, Lundkvist P, Jansson PA, Johansson L, Kvarnstrom M, Moris L, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. *Diabetologia* 2018;**61**(9):1923-34.

Eslamparast 2014 *{published data only}*

Eslamparast T, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *American Journal of Clinical Nutrition* 2014;**99**(3):535-42.

EUCTR 2008-008275-34-GB *{published data only}*

EUCTR 2008-008275-34-GB. The effect of omega-3 fatty acids on non-alcoholic fatty liver disease. www.clinicaltrialsregister.eu/ctr-search/trial/2008-008275-34/GB (first received 6 July 2009).

EUCTR 2009-017080-41-GB *{published data only}*

EUCTR 2009-017080-41-GB. A randomised, partially-blind, placebo-controlled, pilot, dose-ranging study to assess the effect of cannabidiol (CBD) on liver fat levels in subjects with fatty liver disease. www.clinicaltrialsregister.eu/ctr-search/search?query=2009-017080-41 (first received 17 March 2010).

Fabbrini 2010 *{published data only}*

Fabbrini E, Mohammed BS, Korenblat KM, Magkos F, McCrea J, Patterson BW, et al. Effect of fenofibrate and niacin on intrahepatic triglyceride content, very low-density lipoprotein kinetics, and insulin action in obese subjects with nonalcoholic fatty liver disease. *Journal of Clinical Endocrinology and Metabolism* 2010;**95**(6):2727-35.

Faghihzadeh 2015 *{published data only}*

Faghihzadeh F, Adibi P, Hekmatdoost A. The effects of resveratrol supplementation on cardiovascular risk factors in patients with non-alcoholic fatty liver disease: a randomised, double-blind, placebo-controlled study. *British Journal of Nutrition* 2015;**114**(5):796-803.

Famouri 2017a *{published data only}*

Famouri F, Shariat Z, Hashemipour M, Keikha M, Kelishadi R. Effects of probiotics on nonalcoholic fatty liver disease in obese children and adolescents. *Journal of Pediatric Gastroenterology and Nutrition* 2017;**64**(3):413-7.

Farhangi 2014 *{published data only}*

Farhangi MA, Alipour B, Jafarvand E, Khoshbaten M. Oral coenzyme q10 supplementation in patients with nonalcoholic fatty liver disease: effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress. *Archives of Medical Research* 2014;**45**(7):589-95.

Farsi 2016 *{published data only}*

Farsi F, Mohammadshahi M, Alavinejad P, Rezazadeh A, Zarei M, Engali KA. Functions of coenzyme q10 supplementation on liver enzymes, markers of systemic inflammation, and adipokines in patients affected by nonalcoholic fatty liver disease: a double-blind, placebo-controlled, randomized clinical trial. *Journal of the American College of Nutrition* 2016;**35**(4):346-53.

Farzin 2020 *{published data only}*

Farzin L, Asghari S, Rafraf M, Asghari-Jafarabadi M, Shirmohammadi M. No beneficial effects of resveratrol supplementation on atherogenic risk factors in patients with nonalcoholic fatty liver disease. *International Journal for Vitamin & Nutrition Research* 2020;**90**(3-4):279-89.

Fathi 2020 *{published data only}*

* Fathi M, Alavinejad P, Haidari Z, Amani R. The effect of zinc supplementation on steatosis severity and liver function enzymes in overweight/obese patients with mild to moderate non-alcoholic fatty liver following calorie-restricted diet: a double-blind, randomized placebo-controlled trial. *Biological Trace Element Research* 2020;**197**(2):394-404.

Fathi M, Alavinejad P, Haidari Z, Amani R. The effects of zinc supplementation on metabolic profile and oxidative stress in overweight/obese patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. *Journal of Trace Elements in Medicine & Biology* 2020;**62**:126635.

Fernandez-Travieso 2020 *{published data only}*

Fernandez-Travieso JC, Rodriguez-Perez I, Ruenes-Domech C, Illnait-Ferrer J, Fernandez-Dorta L, Mendoza-Castano S. Benefits of the therapy with abexol in patients with non-alcoholic fatty liver disease. *Gastroenterology Research* 2020;**13**(2):73-80.

Ferolla 2016 *{published data only}*

Ferolla SM, Couto CA, Armiliato GN, Silva LC, Lima EC, Lisboa QC, et al. Improvement in hepatic steatosis in nonalcoholic steatohepatitis in response to synbiotic supplementation. *Hepatology (Baltimore, Md)* 2015;**62**:1280a.

* Ferolla SM, Couto CA, Costa-Silva L, Armiliato GN, Pereira CA, Martins FS, et al. Beneficial effect of synbiotic supplementation on hepatic steatosis and anthropometric parameters but not on gut permeability in a population with nonalcoholic steatohepatitis. *Nutrients* 2016;**8**(7):28.

Ferro 2020 *{published data only}*

Ferro Y, Montalcini T, Mazza E, Foti D, Angotti E, Gliozzi M, et al. Randomized clinical trial: Bergamot citrus and wild cardoon reduce liver steatosis and body weight in non-diabetic individuals aged over 50 years. *Frontiers in Endocrinology* 2020;**11**:494.

Foroughi 2014 *{published data only}*

Foroughi M, Maghsoudi Z, Ghiasvand R, Iraj B, Askari G. Effect of vitamin D supplementation on C-reactive protein in patients with nonalcoholic fatty liver. *International Journal of Preventive Medicine* 2014;**5**(8):969-75.

Gavrilescu 2017 *{published data only}*

Gavrilescu O, Savin A, Chiosa AM, Dorobaf A, Mihai C. Effects of prebiotics on non-alcoholic fatty liver disease. *Journal of Gastrointestinal and Liver Diseases* 2017;**26**(Suppl 3):10-1.

Geier 2018 *{published data only}*

Geier A, Eichinger M, Stirnimann G, Semela D, Tay F, Seifert B, et al. Treatment of non-alcoholic steatohepatitis patients with vitamin D: a double-blinded, randomized, placebo-controlled pilot study. *Scandinavian Journal of Gastroenterology* 2018;**53**(9):1114-20.

Ghaffari 2018 *{published data only}*

Ghaffari A, Rafraf M, Navekar R, Asghari-Jafarabadi M. Effects of turmeric and chicory seed supplementation on antioxidant and inflammatory biomarkers in patients with non-alcoholic fatty liver disease (NAFLD). *Advances in Integrative Medicine* 2018;**5**(3):89-95.

Ghergherehchi 2013 *{published data only}*

Ghergherehchi R, Hazhir N, Gharehbaghi MM. Lifestyle intervention and vitamin E therapy in obese children with nonalcoholic fatty liver disease. *Journal of Comprehensive Pediatrics* 2013;**4**(1):62-5.

Gianturco 2013 *{published data only}*

Gianturco V, Troisi G, Bellomo A, Bernardini S, D'Ottavio E, Formosa V, et al. Impact of combined therapy with alpha-lipoic and ursodeoxycholic acid on nonalcoholic fatty liver disease: double-blind, randomized clinical trial of efficacy and safety. *Hepatology International* 2013;**7**(2):570-6.

Gomez 2009 *{published data only}*

Vilar Gomez E, Rodriguez De Miranda A, Gra Oramas B, Arus Soler E, Llanio Navarro R, Calzadilla Bertot L, et al. Clinical trial: a nutritional supplement viusid, in combination with diet and exercise, in patients with nonalcoholic fatty liver disease. *Alimentary Pharmacology & Therapeutics* 2009;**30**(10):999-1009.

Gonciarz 2012 *{published data only}*

Gonciarz M, Gonciarz Z, Bielanski W, Mularczyk A, Konturek PC, Brzozowski T, et al. The effects of long-term melatonin treatment on plasma liver enzymes levels and plasma concentrations of lipids and melatonin in patients with nonalcoholic steatohepatitis: a pilot study. *Journal of Physiology and Pharmacology* 2012;**63**(1):35-40.

Guo 2016 *{published data only}*

Guo W, Gao M-s, Li W, Peng C, Xie H-y, Tan Y. Effects of metformin combined with enteric bifid-triple viable capsule on nonalcoholic fatty liver disease. *Chinese Journal of New Drugs* 2016;**25**(4):439-42.

Harrison 2003 *{published data only}*

Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *American Journal of Gastroenterology* 2003;**98**(11):2485-90.

Hashemi 2009 *{published data only}*

Hashemi SJ, Hajiani E, Sardabi EH. A placebo-controlled trial of silymarin in patients with nonalcoholic fatty liver disease. *Hepatitis Monthly* 2009;**9**(4):265-70.

Heeboll 2016 *{published data only}*

Heeboll S, Kreuzfeldt M, Hamilton-Dutoit S, Poulsen MK, Stodkilde-Jorgensen H, Moller HJ, et al. Placebo-controlled, randomised clinical trial: high-dose resveratrol treatment for non-alcoholic fatty liver disease. *Scandinavian Journal of Gastroenterology* 2016;**51**(4):456-63.

Hong 2016 *{published data only}*

Hong M, Lee YH, Kim S, Suk KT, Bang CS, Yoon JH, et al. Anti-inflammatory and antifatigue effect of Korean red ginseng in patients with nonalcoholic fatty liver disease. *Journal of Ginseng Research* 2016;**40**(3):203-10.

Hong 2021 *{published data only}*

Hong JT, Lee MJ, Yoon SJ, Shin SP, Bang CS, Baik GH, et al. Effect of Korea red ginseng on nonalcoholic fatty liver disease: an association of gut microbiota with liver function. *Journal of Ginseng Research* 2021;**45**(2):316-24.

Hormoznejad 2020 *{published data only}*

Hormoznejad R, Mohammad Shahi M, Rahim F, Helli B, Alavinejad P, Sharhani A. Combined cranberry supplementation and weight loss diet in non-alcoholic fatty liver disease: a double-blind placebo-controlled randomized clinical trial. *International Journal of Food Sciences & Nutrition* 2020;**71**(8):991-1000.

Hoseini 2020 *{published data only}*

Hoseini Z, Behpoor N, Hoseini R. Co-treatment with vitamin D supplementation and aerobic training in elderly women with vitamin D deficiency and NAFLD: a single-blind controlled trial. *Hepatitis Monthly* 2020;**20**(2):e96437.

Hosseinabadi 2020 *{published data only}*

* Hosseinabadi S, Rafraf M, Asghari S, Asghari-Jafarabadi M, Vojouhi S. Effect of green coffee extract supplementation on serum adiponectin concentration and lipid profile in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. *Complementary Therapies in Medicine* 2020;**49**:102290.

Hosseinabadi S, Rafraf M, Mahmoodzadeh A, Asghari-Jafarabadi M, Asghari S. Effects of green coffee extract supplementation on glycemic indexes, leptin, and obesity values in patients with non-alcoholic fatty liver disease. *Journal of Herbal Medicine* 2020;**22**:100340.

Hosseini 2018 *{published data only}*

Hosseini SM, Aliashrafi S, Ebrahimi-Mameghani M. The effect of a single intramuscular injection of cholecalciferol on the serum levels of vitamin D, adiponectin, insulin resistance, and liver function in women with non-alcoholic fatty liver disease (NAFLD): a randomized, controlled clinical trial. *Iranian Red Crescent Medical Journal* 2018;**20**(10):e60746.

Hussain 2017 *{published data only}*

Hussain M, Habib Ur R, Akhtar L. Therapeutic benefits of green tea extract on various parameters in non-alcoholic fatty liver disease patients. *Pakistan Journal of Medical Sciences* 2017;**33**(4):931-6.

Illnait 2013 *{published data only}*

Illnait J, Rodriguez I, Mendoza S, Fernandez Y, Mas R, Miranda M, et al. Effects of d-002, a mixture of high molecular weight beeswax alcohols, on patients with nonalcoholic fatty liver disease. *Korean Journal of Internal Medicine* 2013;**28**(4):439-48.

Izadi 2021 *{published data only}*

Izadi F, Farrokhzad A, Tamizifar B, Tarrahi MJ, Entezari MH. Effect of sour tea supplementation on liver enzymes, lipid profile, blood pressure, and antioxidant status in patients with non-alcoholic fatty liver disease: a double-blind randomized controlled clinical trial. *Phytotherapy Research* 2021;**35**(1):477-85.

Jameshorani 2017 *{published data only}*

Jameshorani M, Rafiee E, Nayshaburi H, Kamali K. Treatment effects of probiotic in non alcoholic fatty liver disease. *Journal of Zanjan University of Medical Sciences and Health Services* 2017;**25**(109):23-35.

Janczyk 2015 *{published data only}*

Janczyk W, Lebensztejn D, Wierzbicka-Rucinska A, Mazur A, Neuhoff-Murawska J, Matusik P, et al. Omega-3 fatty acids therapy in children with nonalcoholic fatty liver disease: a randomized controlled trial. *Journal of Pediatrics* 2015;**166**(6):1358-63.e1-3.

Javadi 2017 *{published data only}*

Javadi L, Ghavami M, Khoshbaten M, Safaiyan A, Barzegari A, Gargari BP. The effect of probiotic and/or prebiotic on liver function tests in patients with nonalcoholic fatty liver disease: a double blind randomized clinical trial. *Iranian Red Crescent Medical Journal* 2017;**19**(4):e46017.

Javanmardi 2018 *{published data only}*

Javanmardi MA, Mohammad Shahi M, Seyedian SS, Haghighizadeh MH. Effects of phytosterol supplementation on serum levels of lipid profiles, liver enzymes, inflammatory markers, adiponectin, and leptin in patients affected by nonalcoholic fatty liver disease: a double-blind, placebo-controlled, randomized clinical trial. Journal of the American College of Nutrition 2018 May 16 [Epub ahead of print]. [DOI: 10.1080/07315724.2018.1466739]

Jazayeri-Tehrani 2019 *{published data only}*

Jazayeri-Tehrani SA, Rezayat SM, Mansouri S, Qorbani M, Alavian SM, Daneshi-Maskooni M, et al. Efficacy of nanocurcumin supplementation on insulin resistance, lipids, inflammatory factors and nesfatin among obese patients with non-alcoholic fatty liver disease (NAFLD): a trial protocol. *BMJ Open* 2017;**7**(7):e016914.

* Jazayeri-Tehrani SA, Rezayat SM, Mansouri S, Qorbani M, Alavian SM, Daneshi-Maskooni M, et al. Nano-curcumin improves glucose indices, lipids, inflammation, and nesfatin in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD): a double-blind randomized placebo-controlled clinical trial. *Nutrition & Metabolism* 2019;**16**:8.

Jeong 2017 *{published data only}*

Jeong JY, Sohn JH, Baek YH, Cho YK, Kim Y, Kim H. New botanical drug, hl tablet, reduces hepatic fat as measured by magnetic resonance spectroscopy in patients with nonalcoholic fatty liver disease: a placebo-controlled, randomized, phase II trial. *World Journal of Gastroenterology* 2017;**23**(32):5977-85.

Kanoni 2021 *{published data only}*

* Kanoni S, Kumar S, Amerikanou C, Kurth MJ, Stathopoulou MG, Bourgeois S, et al. Nutrigenetic interactions might modulate the antioxidant and anti-inflammatory status in mastiha-supplemented patients with NAFLD. *Frontiers in Immunology* 2021;**12**:683028.

NCT03135873. Mastiha treatment for obese with NAFLD diagnosis. clinicaltrials.gov/ct2/show/NCT03135873 (first posted 1 May 2017).

Kazemi 2020 *{published data only}*

Kazemi S, Shidfar F, Ehsani S, Adibi P, Janani L, Eslami O. The effects of sumac (Rhus coriaria l) powder supplementation in patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Complementary Therapies in Clinical Practice* 2020;**41**:101259.

Khoshbaten 2010b *{published data only}*

Khoshbaten M, Aliasgarzadeh A, Masnadi K, Tarzamani MK, Farhang S, Babaei H, et al. N-acetylcysteine improves liver function in patients with non-alcoholic fatty liver disease. *Hepatitis Monthly* 2010;**10**(1):12-6.

Khutsishvili 2020 *{published data only}*

Khutsishvili N. Prebiotics' plus probiotics' effect on the patients with nonalcoholic fatty liver disease. *Hepatology International* 2020;**14**:S329-30.

Kobyliak 2017 *{published data only}*

Kobyliak N, Abenavoli L, Falalyeyeva T, Mykhalchyshyn G, Boccuto L, Kononenko L, et al. Beneficial effects of probiotic combination with omega-3 fatty acids in NAFLD: a randomized clinical study. *Minerva Medica* 2018;**13**:13.

Kobyliak 2018 *{published data only}*

* Kobyliak N, Abenavoli L, Mykhalchyshyn G, Kononenko L, Boccuto L, Kyriienko D, et al. A multi-strain probiotic reduces the fatty liver index, cytokines and aminotransferase levels in NAFLD patients: evidence from a randomized clinical trial. *Journal of Gastrointestinal and Liver Diseases* 2018;**27**(1):41-9.

Kobyliak N, Bosak N, Falalyeyeva T, Beregova T, Bodnar P. Effect of a probiotic on fatty liver index and liver stiffness in NAFLD patients: randomized clinical trial. *Journal of Hepatology* 2017;**66**(1 Suppl 1):S426-7.

Kooshki 2020 *{published data only}*

Kooshki F, Moradi F, Karimi A, Niazkar HR, Khoshbaten M, Maleki V, et al. Chromium picolinate balances the metabolic and clinical markers in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. *European Journal of Gastroenterology & Hepatology* 2020;**14**:14.

Kugelmas 2003 *{published data only}*

Kugelmas M, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. *Hepatology (Baltimore, Md)* 2003;**38**(2):413-9.

Lavine 2011 *{published data only}*

Bell LN, Molleston JP, Lavine JE, Schwimmer JB, Murray KF, Rosenthal P, et al. Changes in adipose tissue insulin resistance correlate with changes in alt and lobular inflammation in children enrolled in the tonic trial. *Hepatology (Baltimore, Md)* 2011;**54**:711a.

* Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the tonic randomized controlled trial. *JAMA* 2011;**305**(16):1659-68.

Lewis 2018 *{published data only}*

Lewis JE, Atlas SE, Higuera OL, Fiallo A, Rasul A, Farooqi A, et al. Corrigendum to "The Effect of a Hydrolyzed Polysaccharide Dietary Supplement on Biomarkers in Adults with Nonalcoholic Fatty Liver Disease". *Evidence-Based Complementary and Alternative Medicine* 2020;**2020**:9575878.

* Lewis JE, Atlas SE, Higuera OL, Fiallo A, Rasul A, Farooqi A, et al. The effect of a hydrolyzed polysaccharide dietary supplement on biomarkers in adults with nonalcoholic fatty liver disease. *Evidence-Based Complementary and Alternative Medicine* 2018;**2018**:1751583.

Li 2010 *{published data only}*

Li L, Zhang XJ, Lan Y, Xu L, Zhang XZ, Wang HH. Treatment of non-alcoholic fatty liver disease by qianggan capsule ((sic)). *Chinese Journal of Integrative Medicine* 2010;**16**(1):23-7.

Li 2016 *{published data only}*

Li YH, Yang LH, Sha KH, Liu TG, Zhang LG, Liu XX. Efficacy of poly-unsaturated fatty acid therapy on patients with nonalcoholic steatohepatitis. *World Journal of Gastroenterology* 2016;**22**(22):7008-13.

Loguercio 2012 *{published data only}*

Loguercio C, Andreone P, Brisc C, Brisc MC, Bugianesi E, Chiaramonte M, et al. Silybin combined with phosphatidylcholine and vitamin E in patients with nonalcoholic fatty liver disease: a randomized controlled trial. *Free Radical Biology and Medicine* 2012;**52**(9):1658-65.

Magosso 2013 *{published data only}*

Magosso E, Ansari MA, Gopalan Y, Shuaib IL, Wong JW, Khan NA, et al. Tocotrienols for normalisation of hepatic echogenic response in nonalcoholic fatty liver: a randomised placebo-controlled clinical trial. *Nutrition Journal* 2013;**12**(1):166.

Malaguarnera 2010 *{published data only}*

Malaguarnera M, Gargante MP, Russo C, Antic T, Vacante M, Malaguarnera M, et al. L-carnitine supplementation to diet: a new tool in treatment of nonalcoholic steatohepatitis - a randomized and controlled clinical trial. *American Journal of Gastroenterology* 2010;**105**(6):1338-45.

Malaguarnera 2012 *{published data only}*

Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, et al. Bifidobacterium longum with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. *Digestive Diseases and Sciences* 2012;**57**(2):545-53.

Mansour 2020 *{published data only}*

Mansour A, Mohajeri-Tehrani MR, Karimi S, Sanginabadi M, Poustchi H, Enayati S, et al. Short term effects of coffee components consumption on gut microbiota in patients with non-alcoholic fatty liver and diabetes: a pilot randomized placebo-controlled, clinical trial. *Excli Journal* 2020;**19**:241-50.

Manzhalii 2017 *{published data only}*

Manzhalii E, Virchenko O, Falalyeyeva T, Beregova T, Stremmel W. Treatment efficacy of a probiotic preparation for non-alcoholic steatohepatitis: a pilot trial. *Journal of Digestive Diseases* 2017;**18**(12):698-703.

Martinez-Rodriguez 2014 *{published data only}*

Martínez-Rodríguez Leonardo A, Rojas Serrano J, Torre A. Siliphos selenium methionine alpha lipoic acid for non-alcoholic fatty liver disease: results of a pilot study. *Journal of Clinical & Experimental Pharmacology* 2014;**5**(1):1-5.

Miglio 2000 *{published data only}*

Miglio F, Rovati LC, Santoro A, Setnikar I. Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis - a double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. *Arzneimittel-Forschung-Drug Research* 2000;**50**(8):722-7.

Mofidi 2017 *{published data only}*

Mofidi F, Poustchi H, Yari Z, Nourinayyer B, Merat S, Sharafkhah M, et al. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. *British Journal of Nutrition* 2017;**117**(5):662-8.

Moradi 2020 *{published data only}*

* Moradi B, Rahmati-Ahmadabad S, Farzanegi P, Helalizadeh M, Azarbayjani MA. Effects of non-linear resistance training and curcumin supplementation on the liver biochemical markers levels and structure in older women with non-alcoholic fatty liver disease. *Journal of Bodywork and Movement Therapies* 2020;**24**(3):154-60.

Moradi F, Kooshki F, Nokhostin F, Khoshbaten M, Bazyar H, Pourghassem Gargari B. A pilot study of the effects of chromium picolinate supplementation on serum fetuin-a, metabolic and inflammatory factors in patients with nonalcoholic fatty liver disease: a double-blind, placebo-controlled trial. *Journal of Trace Elements in Medicine and Biology* 2021;**63**:126659.

Morvaridzadeh 2021 *{published data only}*

Morvaridzadeh M, Nachvak SM, Mohammadi R, Moradi S, Mostafai R, Pizarro AB, et al. Probiotic yogurt fortified with vitamin D can improve glycemic status in non-alcoholic fatty liver disease patients: a randomized clinical trial. *Clinical Nutrition Research* 2021;**10**(1):36-47.

Nabavi 2016 *{published data only}*

Nabavi S, Rafraf M, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. Effects of probiotic yogurt consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. *Journal of Dairy Science* 2014;**97**(12):7386-93.

* Nabavi S, Rafraf M, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. Probiotic yogurt improves body mass index and fasting insulin levels without affecting serum leptin and adiponectin levels in non-alcoholic fatty liver disease (NAFLD). *Journal of Functional Foods* 2015;**18**:684-91.

Nabavi S, Rafraf M, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. The effects of probiotic yogurt on metabolic factors in nonalcoholic fatty liver disease. *Scientific Journal of Kurdistan University of Medical Sciences* 2016;**20**(6):12-25.

Rafraf M, Nabavi S, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. Effect of probiotic yogurt on enzymes and ecogenicity of liver in individuals with non alcoholic fatty liver disease: a double-blind randomized controlled clinical trial. *Journal of Zanjan University of Medical Sciences and Health Services* 2015;**23**(99):25-38.

Rafraf M, Nabavi S, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi Rad M. The effect of probiotic and conventional yogurt consumption on anthropometric parameters in individuals with non-alcoholic fatty liver disease. *Journal of Babol University of Medical Sciences* 2014;**16**(9):55-62.

Naganuma 2016 *{published data only}*

Naganuma A, Ogawa Y, Hoshino T, Hatanaka T, Tanaka H, Inagawa M, et al. Effect of the medical walking and leucine enriched amino acid containing food for female nonalcoholic fatty liver disease: randomized controlled trial. *Clinical Nutrition* 2016;**35**:S62-3.

Navekar 2017 *{published data only}*

Navekar R, Rafraf M, Ghaffari A, Asghari-Jafarabadi M, Khoshbaten M. Turmeric supplementation improves serum glucose indices and leptin levels in patients with nonalcoholic fatty liver diseases. *Journal of the American College of Nutrition* 2017;**36**(4):261-7.

NCT00816465 *{published data only}*

NCT00816465. Safety and efficacy of Hoodia gordonii for treatment of non-alcoholic fatty liver disease (NAFLD). clinicaltrials.gov/ct2/show/NCT00816465 (first posted 1 January 2009).

NCT00845845 *{published data only}*

NCT00845845. Fish oil and diet for the treatment of non-alcoholic steatohepatitis (NASH). clinicaltrials.gov/ct2/show/NCT00845845 (first posted 18 February 2009).

NCT00941642 *{published data only}*

NCT00941642. Placebo controlled study using lovaza as treatment for non-alcoholic fatty liver disease. clinicaltrials.gov/ct2/show/NCT00941642 (first posted 17 July 2009).

NCT00977730 *{published data only}*

NCT00977730. The effect of protandim on non-alcoholic steatohepatitis. clinicaltrials.gov/ct2/show/NCT00977730 (first posted 16 September 2009).

NCT01083992 *{published data only}*

NCT01083992. Role of vitagliptin and vitamin D in the treatment of non-alcoholic fatty liver disease (NAFLD). clinicaltrials.gov/ct2/show/NCT01083992 (first posted 10 March 2010).

NCT01623024 *{published data only}*

NCT01623024. Effect on liver histology of vitamin D in patients with non-alcoholic steatohepatitis. clinicaltrials.gov/ct2/show/NCT01623024 (first posted 19 June 2012).

NCT02690792 *{published data only}*

NCT02690792. Effect of vitamin E on non-alcoholic fatty liver disease. clinicaltrials.gov/ct2/show/NCT02690792 (first posted 24 February 2016).

NCT04411862 *{published data only}*

NCT04411862. Efficacy of phosphatidylcholine in NAFLD. clinicaltrials.gov/show/NCT04411862 (first posted 2 June 2020).

Nelson 2009 *{published data only}*

Nelson JE, Maliken BD, Saunders C, Stevenson J, Richards T, Kowdley KV. A randomized, masked, controlled study of omega-3 polyunsaturated fatty acid vs monounsaturated fatty acid diet supplementation for the treatment of nonalcoholic fatty liver disease. *Gastroenterology* 2009;**136**(5):A847-8.

Nobili 2006 *{published data only}*

Mosca A, Crudele A, Smeriglio A, Braghini MR, Panera N, Comparcola D, et al. Antioxidant activity of hydroxytyrosol and vitamin E reduces systemic inflammation in children with paediatric NAFLD. *Digestive & Liver Disease* 2020;**12**:12.

Mosca A, Crudele A, Tozzi G, Alterio T, Smeriglio A, Trombetta D, et al. The anti-inflammatory effects of hydroxytyrosol and vitamin E on paediatric NAFLD. *Digestive and Liver Disease* 2020;**52**(Suppl 1):e42-e3.

* Nobili V, Manco M, Devito R, Ciampalini P, Piemonte F, Marcellini M. Effect of vitamin E on aminotransferase levels and insulin resistance in children with non-alcoholic fatty liver disease. *Alimentary Pharmacology & Therapeutics* 2006;**24**(11-12):1553-61.

Nobili V, Manco M, Devito R, Di Ciomm V, Comparcola D, Sartorelh MP, et al. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. *Hepatology (Baltimore, Md)* 2008;**48**(1):119-28.

Nobili V, Manco M, DeVito R, PietroBattista A, Comparcola D, Sartorelli MR, et al. Lifestyle intervention and antioxidants in children with nonalcoholic fatty liver disease: a randomized, controlled trial. *Gastroenterology* 2008;**134**(4):A781.

Nobili 2013 *{published data only}*

* Nobili V, Alisi A, Della Corte C, Rise P, Galli C, Agostoni C, et al. Docosahexaenoic acid for the treatment of fatty liver: randomised controlled trial in children. *Nutrition Metabolism and Cardiovascular Diseases* 2013;**23**(11):1066-70.

Nobili V, Bedogni G, Alisi A, Pietrobattista A, Rise P, Galli C, et al. Docosahexaenoic acid supplementation decreases liver fat content in children with non-alcoholic fatty liver disease: double-blind randomised controlled clinical trial. *Archives of Disease in Childhood* 2011;**96**(4):350-3.

Nogueira 2016 *{published data only}*

Nogueira MA, Oliveira CP, Alves VAF, Stefano JT, Rodrigues LSD, Torrinhas RS, et al. Omega-3 polyunsaturated fatty acids in treating non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled trial. *Clinical Nutrition* 2016;**35**(3):578-86.

Orang 2020 *{published data only}*

Orang Z, Mohsenpour MA, Mozaffari-Khosravi H. Effect of omega-3 fatty acid supplementation on inflammatory markers and insulin resistance indices in patient with type 2 diabetes and nonalcoholic fatty liver: a randomized double-blind clinical trial. *Obesity Medicine* 2020;**19**:100278.

Orr 2015 *{published data only}*

Orr DW, Murphy R. Prebiotic supplementation with inulin following metronidazole therapy achieves greater alt reduction in non-alcoholic fatty liver disease (NAFLD): a randomised double-blind placebo controlled trial. *Hepatology (Baltimore, Md)* 2015;**62**:1268a-9a.

Oscarsson 2018 *{published data only}*

Oscarsson J, Onnerhag K, Riserus U, Sunden M, Johansson L, Jansson PA, et al. Effects of free omega-3 carboxylic acids and fenofibrate on liver fat content in patients with hypertriglyceridemia and non-alcoholic fatty liver disease: a double-blind, randomized, placebo-controlled study. *Journal of Clinical Lipidology* 2018;**10**:10.

Pacifico 2015 *{published data only}*

Pacifico L, Bonci E, Di Martino M, Versacci P, Andreoli G, Silvestri LM, et al. A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease. *Nutrition Metabolism and Cardiovascular Diseases* 2015;**25**(8):734-41.

Palamaru 2017 *{published data only}*

Palamaru AL, Dranga M, Ungureanu I, Cucos A, Prelipcean CC. Vitamin E and non-alcoholic fatty liver disease. *Journal of Gastrointestinal and Liver Diseases* 2017;**26**(Suppl 3):28.

Panahi 2012 *{published data only}*

Panahi Y, Ghamarchehreh ME, Beiraghdar F, Zare R, Jalalian HR, Sahebkar A. Investigation of the effects of Chlorella vulgaris supplementation in patients with non-alcoholic fatty liver disease: a randomized clinical trial. *Hepato-Gastroenterology* 2012;**59**(119):2099-103.

Panahi 2016 *{published data only}*

* Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendia LE, Sahebkar A. Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: a randomized controlled trial. *Journal of Cardiovascular Pharmacology* 2016;**68**(3):223-9.

Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendia LE, Sahebkar A. Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: a randomized controlled trial. *Drug Research* 2017;**67**(4):244-51.

Parsi 2020 *{published data only}*

Parsi A, Torkashvand M, Hajiani E, Rahimlou M, Sadeghi N. The effects of Crocus sativus extract on serum lipid profile and liver enzymes in patients with non-alcoholic fatty liver disease: a randomized placebo-controlled study. *Obesity Medicine* 2020;**17**:100165.

Pasdar 2020 *{published data only}*

Pasdar Y, Oubari F, Zarif MN, Abbasi M, Pourmahmoudi A, Hosseinikia M. Effects of quercetin supplementation on hematological parameters in non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *Clinical Nutrition Research* 2020;**9**(1):11-9.

Pervez 2018 *{published data only}*

Pervez MA, Khan DA, Ijaz A, Khan S. Effects of delta-tocotrienol supplementation on liver enzymes, inflammation, oxidative stress and hepatic steatosis in patients with nonalcoholic fatty liver disease. *Turkish Journal of Gastroenterology* 2018;**29**(2):170-6.

Pervez 2020 *{published data only}*

Pervez MA, Khan DA, Slehria AUR, Ijaz A. Delta-tocotrienol supplementation improves biochemical markers of hepatocellular injury and steatosis in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled trial. *Complementary Therapies in Medicine* 2020;**52**:102494.

Pezeshki 2016 *{published data only}*

Pezeshki A, Safi S, Feizi A, Askari G, Karami F. The effect of green tea extract supplementation on liver enzymes in patients

with nonalcoholic fatty liver disease. *International Journal of Preventive Medicine* 2016;**7**:28.

Poparn 2020 *{published data only}*

Poparn H, Chatrproedprai S, Treeprasertsuk S, Sonsiri K, Chongsrisawat V. Effect of synbiotic supplementation in children with nonalcoholic fatty liver disease: a randomized controlled trial. *Chotmaihet Thangphaet [Journal of the Medical Association of Thailand]* 2020;**103**(12):S99-104.

Poulos 2021 *{published data only}*

Poulos JE, Kalogerinis PT, Milanov V, Kalogerinis CT, Poulos EJ. The effects of vitamin E, silymarin and carnitine on the metabolic abnormalities associated with nonalcoholic liver disease. Journal of Dietary Supplements 2021 Jan 25 [Online ahead of print]. [DOI: 10.1080/19390211.2021.1874587]

Pour 2020 *{published data only}*

Pour FK, Aryaeian N, Mokhtare M, Mirnasrollahi Parsa RS, Jannani L, Agah S, et al. The effect of saffron supplementation on some inflammatory and oxidative markers, leptin, adiponectin, and body composition in patients with nonalcoholic fatty liver disease: a double-blind randomized clinical trial. *Phytotherapy Research* 2020;**34**(12):3367-78.

Qin 2015 *{published data only}*

Qin Y, Zhou Y, Chen SH, Zhao XL, Ran L, Zeng XL, et al. Fish oil supplements lower serum lipids and glucose in correlation with a reduction in plasma fibroblast growth factor 21 and prostaglandin e2 in nonalcoholic fatty liver disease associated with hyperlipidemia: a randomized clinical trial. *PLOS One* 2015;**10**(7):e0133496.

Rafie 2020 *{published data only}*

Rafie R, Hosseini SA, Hajiani E, Malehi AS, Mard SA. Effect of ginger powder supplementation in patients with non-alcoholic fatty liver disease: a randomized clinical trial. *Clinical and Experimental Gastroenterology* 2020;**13**:35-45.

Rahimlou 2016 *{published data only}*

Rahimlou M, Yari Z, Hekmatdoost A, Alavian SM, Keshavarz SA. Ginger supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *Hepatitis Monthly* 2016;**16**(1):e34897.

Rahmani 2016 *{published data only}*

Rahmani S, Asgary S, Askari G, Keshvari M, Hatamipour M, Feizi A, et al. Treatment of non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial. *Phytotherapy Research* 2016;**30**(9):1540-8.

Ruan 2010 *{published data only}*

Ruan JW, Yang J. Efficacy of silibin capsules in the treatment of metabolism syndrome-related fatty liver disease: an analysis of 30 cases. *World Chinese Journal of Digestology* 2010;**18**(29):3151-4.

Sadrkabir 2020 *{published data only}*

Sadrkabir M, Jahed S, Sadeghi Z, Isazadeh K. The effect of gerilact on non-alcoholic fatty liver disease. *Journal of Kerman University of Medical Sciences* 2020;**27**(1):82-90.

Sakpal 2017 *{published data only}*

Sakpal M, Mehta M, Duseja A, Bhadada S, Das A, Dhiman RK, et al. Vitamin D supplementation in patients with nonalcoholic fatty liver disease - a randomized controlled trial. *Indian Journal of Gastroenterology* 2015;**34**(1 Suppl 1):A106.

* Sakpal M, Satsangi S, Mehta M, Duseja A, Bhadada S, Das A, et al. Vitamin D supplementation in patients with nonalcoholic fatty liver disease: a randomized controlled trial. *JGH Open* 2017;**1**(2):62?7.

Sangouni 2020 *{published data only}*

* Sangouni AA, Azar MR, Alizadeh M. Effect of garlic powder supplementation on hepatic steatosis, liver enzymes and lipid profile in patients with non-alcoholic fatty liver disease: a double-blind randomised controlled clinical trial. *British Journal of Nutrition* 2020;**124**(4):450-6.

Sangouni AA, Mohammad Hosseini Azar MR, Alizadeh M. Effects of garlic powder supplementation on insulin resistance, oxidative stress, and body composition in patients with non-alcoholic fatty liver disease: a randomized controlled clinical trial. *Complementary Therapies in Medicine* 2020;**51**:102428.

Sanyal 2010 *{published data only}*

Bell LN, Wang J, Muralidharan S, Chalasani S, Fullenkamp AM, Wilson LA, et al. Relationship between adipose tissue insulin resistance and liver histology in nonalcoholic steatohepatitis: a pioglitazone versus vitamin E versus placebo for the treatment of nondiabetic patients with nonalcoholic steatohepatitis trial follow-up study. *Hepatology (Baltimore, Md)* 2012;**56**(4):1311-8.

Chalasani NP, Sanyal AJ, Kowdley KV, Robuck PR, Hoofnagle J, Kleiner DE, et al. Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis: Pivens trial design. *Contemporary Clinical Trials* 2009;**30**(1):88-96.

Hoofnagle JH, Van Natta ML, Kleiner DE, Clark JM, Kowdley KV, Loomba R, et al. Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. *Alimentary Pharmacology & Therapeutics* 2013;**38**(2):134-43.

* Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *New England Journal of Medicine* 2010;**362**(18):1675-85.

Sanyal 2014 *{published data only}*

Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology* 2014;**147**(2):377-84.e1.

Saxena 2013 *{published data only}*

Saxena A, Kaushik N, Vikram NK, Pandey RM, Misra A, Bhushan SM. Double-blind randomized placebo controlled clinical trial of herbal compound livomap (ma-579) in patients with non alcoholic fatty liver disease (NAFLD). *Journal of Ayurveda and Integrative Medicine* 2013;**4**:63.

Sayari 2018 *{published data only}*

Sayari S, Neishaboori H, Jameshorani M. Combined effects of synbiotic and sitagliptin versus sitagliptin alone in patients with nonalcoholic fatty liver disease. *Clinical and Molecular Hepatology* 2018;**24**(3):331-8.

Schattenberg 2017 *{published data only}*

Schattenberg JM, Schlegel L, Nier A, Huber Y, Galle PR, Bergheim I. Dietary counselling focusing only on fructose consumption improves hepatic inflammation in patients with NAFLD-A prospective, controlled, randomized open-label study (Nuces NASH). *Hepatology (Baltimore, Md)* 2017;**66**(Suppl 1):1106a-7a.

Scorletti 2014 *{published data only}*

Bhatia LS, Scorletti E, Shojaee-Moradie F, Umpleby M, Clough GF, Curzen NP, et al. High-dose n-3 fatty acid treatment in non-alcoholic fatty liver disease is independently associated with reduced hepatic steatosis and improved hepatic insulin sensitivity. *Diabetic Medicine* 2014;**31**:53.

Scorletti E, Bhatia B, McCormick KG, Clough GF, Nash K, Hodson L, et al. Potential benefits of purified long chain omega-3 fatty acid treatment in non-alcoholic fatty liver disease (NAFLD): a potential treatment for early NAFLD in metabolic syndrome and type 2 diabetes? Results from the Welcome study. *Diabetic Medicine* 2014;**31**:1.

* Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: results from the Welcome study. *Hepatology (Baltimore, Md)* 2014;**60**(4):1211-21.

Scorletti 2020 *{published data only}*

* Scorletti E, Afolabi PR, Calder PC, Byrne CD. Investigation of the effects of synbiotic treatment on gut microbiota composition in patients with non-alcoholic fatty liver disease and type 2 diabetes. *Diabetic Medicine* 2020;**37**(Suppl 1):55.

Scorletti E, Afolabi PR, Miles EA, Smith DE, Almehmadi A, Alshathry A, et al. Design and rationale of the Insyte study: a randomised, placebo controlled study to test the efficacy of a synbiotic on liver fat, disease biomarkers and intestinal microbiota in non-alcoholic fatty liver disease. *Contemporary Clinical Trials* 2018;**71**:113-23.

Scorletti E, Afolabi PR, Miles EA, Smith DE, Almehmadi A, Alshathry A, et al. Synbiotics alter fecal microbiomes, but not liver fat or fibrosis, in a randomized trial of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2020;**158**(6):1597-610.e7.

Sepideh 2016 *{published data only}*

Sepideh A, Karim P, Hossein A, Leila R, Hamdollah M, Mohammad EG, et al. Effects of multistrain probiotic supplementation on glycemic and inflammatory indices in patients with nonalcoholic fatty liver disease: a double-blind randomized clinical trial. *Journal of the American College of Nutrition* 2016;**35**(6):500-5.

Shahmohammadi 2017 *{published data only}*

Shahmohammadi HA, Hosseini SA, Hajiani E, Malehi AS, Alipour M. Effects of green coffee bean extract supplementation on patients with non-alcoholic fatty liver disease: a randomized clinical trial. *Hepatitis Monthly* 2017;**17**(4):e12299.

Sharifi 2014 *{published data only}*

Sharifi N, Amani R, Hajiani E, Cheraghian B. Does vitamin D improve liver enzymes, oxidative stress, and inflammatory biomarkers in adults with non-alcoholic fatty liver disease? A randomized clinical trial. *Endocrine* 2014;**47**(1):70-80.

Shavakhi 2013 *{published data only}*

Shavakhi A, Minakari M, Firouzian H, Assali R, Hekmatdoost A, Ferns G. Effect of a probiotic and metformin on liver aminotransferases in non-alcoholic steatohepatitis: a double blind randomized clinical trial. *International Journal of Preventive Medicine* 2013;**4**(5):531-7.

Soleimani 2020 *{published data only}*

Soleimani D, Paknahad Z, Askari G, Iraj B, Feizi A. Effect of garlic powder consumption on body composition in patients with nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. *Advanced Biomedical Research* 2016;**5**:2.

* Soleimani D, Paknahad Z, Rouhani MH. Therapeutic effects of garlic on hepatic steatosis in nonalcoholic fatty liver disease patients: a randomized clinical trial. *Diabetes, Metabolic Syndrome and Obesity Targets and Therapy* 2020;**13**:2389-97.

Soleimani 2021 *{published data only}*

Soleimani D, Rezaie M, Rajabzadeh F, Gholizadeh Navashenaq J, Abbaspour M, Miryan M, et al. Protective effects of propolis on hepatic steatosis and fibrosis among patients with nonalcoholic fatty liver disease (NAFLD) evaluated by real-time two-dimensional shear wave elastography: a randomized clinical trial. *Phytotherapy Research* 2021;**35**(3):1669-79.

Solhi 2014 *{published data only}*

Solhi H, Ghahremani R, Kazemifar AM, Yazdi ZH. Silymarin in treatment of non-alcoholic steatohepatitis: a randomized clinical trial. *Caspian Journal of Internal Medicine* 2014;**5**(1):9-12.

Somi 2014 *{published data only}*

Somi MH, Fatahi E, Panahi J, Havasian MR, Judaki A. Data from a randomized and controlled trial of l-carnitine prescription for the treatment for non- alcoholic fatty liver disease. *Bioinformation* 2014;**10**(9):575-9.

Song 2020 *{published data only}*

Song LH, Zhao XG, Ouyang PL, Guan Q, Yang L, Peng FJ, et al. Combined effect of n-3 fatty acids and phytosterol esters on alleviating hepatic steatosis in non-alcoholic fatty liver disease subjects: a double-blind placebo-controlled clinical trial. *British Journal of Nutrition* 2020;**123**(10):1148-58.

Spadaro 2008 *{published data only}*

Spadaro L, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona C, et al. Effects of n-3 polyunsaturated fatty acids in

subjects with nonalcoholic fatty liver disease. *Digestive and Liver Disease* 2008;**40**(3):194-9.

Tabatabaee 2017 *{published data only}*

Tabatabaee SM, Alavian SM, Ghalichi L, Miryounesi SM, Mousavizadeh K, Jazayeri S, et al. Green tea in non-alcoholic fatty liver disease: a double blind randomized clinical trial. *Hepatitis Monthly* 2017;**17**(12):e14993.

Taghvaei 2018 *{published data only}*

Taghvaei T, Akha O, Mouodi M, Fakheri HT, Kashi Z, Maleki I, et al. Effects of vitamin D supplementation on patients with non-alcoholic fatty liver disease (NAFLD). *Acta Medica Mediterranea* 2018;**34**(2):415-22.

Tan 2011 *{published data only}*

Tan HH, Low ASC, Lim KH, Wan WK, Goh BB, Wang YT, et al. A randomized, unblinded pilot trial of essential phospholipids in Chinese subjects with nonalcoholic fatty liver disease (NASH). *Journal of Gastroenterology and Hepatology* 2011;**26**:162.

Tobin 2018 *{published data only}*

Tobin D, Brevik-Andersen M, Qin Y, Innes JK, Calder PC. Evaluation of a high concentrate omega-3 for correcting the omega-3 fatty acid nutritional deficiency in non-alcoholic fatty liver disease (condin). *Nutrients* 2018;**10**(8):20.

Tutunchi 2020 *{published data only}*

* Tutunchi H, Naeini F, Saghafi-Asl M, Farrin N, Monshikarimi A, Ostadrahimi A. Effects of oleoylethanolamide supplementation on atherogenic indices and hematological parameters in patients with nonalcoholic fatty liver disease: a clinical trial. *Health Promotion Perspectives* 2020;**10**(4):373-82.

Tutunchi H, Ostadrahimi A, Saghafi-Asl M, Hosseinzadeh-Attar MJ, Shakeri A, Asghari-Jafarabadi M, et al. Oleoylethanolamide supplementation in obese patients newly diagnosed with non-alcoholic fatty liver disease: effects on metabolic parameters, anthropometric indices, and expression of ppar-alpha, ucp1, and ucp2 genes. *Pharmacological Research* 2020;**156**:104770.

Tutunchi H, Ostadrahimi A, Saghafi-Asl M, Roshanravan N, Shakeri-Bavil A, Asghari-Jafarabadi M, et al. Expression of NF-kappaB, IL-6, and IL-10 genes, body composition, and hepatic fibrosis in obese patients with NAFLD-combined effects of oleoylethanolamide supplementation and calorie restriction: a triple-blind randomized controlled clinical trial. *Journal of Cellular Physiology* 2021;**236**(1):417-26.

Uygun 2000 *{published data only}*

Uygun A, Kadayifci A, Bagci S, Erdil A, Deveci S, Saka M, et al. L-carnitine therapy in non-alcoholic steatohepatitis. *Turkish Journal of Gastroenterology* 2000;**11**(3):196-201.

Vajro 2011 *{published data only}*

Vajro P, Mandato C, Licenziati MR, Franzese A, Vitale DF, Lenta S, et al. Effects of Lactobacillus rhamnosus strain GG in pediatric obesity-related liver disease. *Journal of Pediatric Gastroenterology and Nutrition* 2011;**52**(6):740-3.

Wang 2008 *{published data only}*

Wang CL, Liang L, Fu JF, Zou CC, Hong F, Xue JZ, et al. Effect of lifestyle intervention on non-alcoholic fatty liver disease in Chinese obese children. *World Journal of Gastroenterology* 2008;**14**(10):1598-602.

Wang 2017 *{published data only}*

Wang X, Yao N. Effect of herb formula xiao-zhi-hua-xian-tang against nonalcoholic steatohepatitis with advanced fibrosis: a preliminary clinical study. *Hepatology International* 2017;**11**(1 Suppl 1):S939-40.

Wang 2018 *{published data only}*

* Wang W, Shi LP, Shi L, Xu L. [Efficacy of probiotics on the treatment of non-alcoholic fatty liver disease]. *Chinese Journal of Internal Medicine* 2018;**57**(2):101-6.

Wang W. Clinical observation on the treatment of nonalcoholic fatty liver with probiotics. *United European Gastroenterology Journal* 2017;**5**(5 Suppl 1):A163-4.

Wong 2013a *{published data only}*

Wong VW, Won GL, Chim AM, Chu WC, Yeung DK, Li KC, et al. Treatment of nonalcoholic steatohepatitis with probiotics. A proof-of-concept study. *Annals of Hepatology* 2013;**12**(2):256-62.

Wong 2013b *{published data only}*

Wong VWS, Wong GLH, Chan AWH, Chu WCW, Choi PCL, Chim AML, et al. Treatment of non-alcoholic steatohepatitis with Phyllanthus urinaria: a randomized trial. *Journal of Gastroenterology and Hepatology* 2013;**28**(1):57-62.

Yan 2015 *{published data only}*

Yan H, Xia M, Chang X, Bian H, Lin H, Zhang L, et al. Berberine vs. pioglitazone for treatment of nonalcoholic fatty liver disease and its associated impaired glucose metabolism. *Diabetes* 2014;**63**:A513-4.

Yan H, Xia M, Chang X, Bian H, Xu Q, Gao X, et al. Pioglitazone versus berberine for treatment of non-alcoholic fatty liver disease patients with impaired glucose regulation or type 2 diabetes mellitus. *Diabetologia* 2012;**55**:S36.

Yan H, Xia M, Chang X, Bian H, Zhang L, Lin H, et al. Berberine increases serum osteocalcin levels and improves early phase of insulin secretion in non-alcoholic fatty liver disease patients with impaired glucose metabolism. *Diabetologia* 2014;**57**(1 Suppl 1):S351.

* Yan HM, Xia MF, Wang Y, Chang XX, Yao XZ, Rao SX, et al. Efficacy of berberine in patients with non-alcoholic fatty liver disease. *PLOS One* 2015;**10**(8):e0134172.

Yari 2016 *{published data only}*

Yari Z, Rahimlou M, Eslamparast T, Ebrahimi-Daryani N, Poustchi H, Hekmatdoost A. Flaxseed supplementation in non-alcoholic fatty liver disease: a pilot randomized, open labeled, controlled study. *International Journal of Food Sciences and Nutrition* 2016;**67**(4):461-9.

Yari 2020 *{published data only}*

Yari Z, Cheraghpour M, Alavian SM, Hedayati M, Eini-Zinab H, Hekmatdoost A. The efficacy of flaxseed and hesperidin on non-alcoholic fatty liver disease: an open-labeled randomized controlled trial. *European Journal of Clinical Nutrition* 2021;**75**(1):99-111.

Youshari 2017 *{published data only}*

Youshari N, Mehrangiz, Mameghani E. The effect of oral β-glucan supplement on liver echogenicity and enzymes in non-alcoholic fatty liver disease treating with hypocaloric diet and vitamin E. *Iranian Journal of Basic Medical Sciences* 2017;**20**(Supp 1):82-3.

Zamani 2018 *{published data only}*

Zamani N, Shams M, Nimrouzi M, Zarshenas MM, Abolhasani Foroughi A, Fallahzadeh Abarghooei E, et al. The effects of Zataria multiflora boiss (Shirazi thyme) on nonalcoholic fatty liver disease and insulin resistance: a randomized double-blind placebo-controlled clinical trial. *Complementary Therapies in Medicine* 2018;**41**:118-23.

Zanko 2020 *{published data only}*

Mikolasevic I, Domislovic V, Trkulja V, Krznaric, Skenderevic N, Mijic A, et al. The efficacy of vitamin D supplementation on NAFLD: a randomized, double-blind, placebo-controlled 12- month trial on 311 patients. *Journal of Hepatology* 2020;**73**(Suppl 1):S447-8.

* Zanko VL, Domislovic V, Trkulja V, Krznaric-Zrnic I, Turk-Wensveen T, Krznaric Z, et al. Vitamin D for treatment of non-alcoholic fatty liver disease detected by transient elastography: a randomized, double-blind, placebo-controlled trial. *Diabetes Obesity & Metabolism* 2020;**22**(11):2097-106.

Zhang 2015 *{published data only}*

Zhang PW, Chen FX, Li D, Ling WH, Guo HH. A CONSORT-compliant, randomized, double-blind, placebo-controlled pilot trial of purified anthrocyanin in patients with nonalcoholic fatty liver disease. *Medicine* 2015;**94**(20):e758.

Zhu 2008 *{published data only}*

Zhu FS, Liu S, Chen XM, Huang ZG, Zhang DW. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. *World Journal of Gastroenterology* 2008;**14**(41):6395-400.

Zohrer 2017 *{published data only}*

Zohrer E, Alisi A, Jahnel J, Mosca A, Della Corte C, Crudele A, et al. Efficacy of docosahexaenoic acid-choline-vitamin E in paediatric NASH: a randomized controlled clinical trial. *Applied Physiology, Nutrition, and Metabolism* 2017;**42**(9):948-54.

References to studies excluded from this review

Abenavoli 2017 *{published data only}*

* Abenavoli L, Greco M, Milic N, Accattato F, Foti D, Gulletta E, et al. Effect of Mediterranean diet and antioxidant formulation in non-alcoholic fatty liver disease: a randomized study. *Nutrients* 2017;**9**(8):12.

Abenavoli L, Milic N, Larussa T, Suraci E, Imeneo M, Medic M, et al. Efficacy of Mediterranean diet and antioxidants in overweight patients with non-alcoholic fatty liver disease. *Digestive and Liver Disease* 2016;**48**:e130-1.

Akcam 2011 *{published data only}*

Akcam M, Boyaci A, Pirgon O, Kaya S, Uysal S, Dundar BN. Therapeutic effect of metformin and vitamin E versus prescriptive diet in obese adolescents with fatty liver. *International Journal for Vitamin and Nutrition Research* 2011;**81**(6):398-406.

Basu 2014 *{published data only}*

* Basu P, Shah NJ, Aloysius M. Berberine with alfa lipoic acid (ALA) in non alcoholic steato-hepatitis (NASH). A randomized double blinded placebo control trial. A clinical pilot - the Banish Trial. *Hepatology (Baltimore, Md)* 2014;**60**:624a.

Basu P, Shah NJ, Aloysius MM. Berberine with alfa lipoic acid (ALA) in non alcoholic steatohepatitis (NASH). A randomized double blinded placebo control trial. A clinical pilot - the Banish Trial. *Journal of the International Hepato Pancreato Biliary Association* 2015;**17**:43.

Basu PP, Aloysius MM, Shah NJ, Brown RS Jr. Berberine with alfa lipoic acid (ALA) in non alcoholic steatohepatitis (NASH). A randomized double blinded placebo control trial. A clinical pilot: the Banish Trial. *Hepatology International* 2014;**8**(1 Suppl 1):S10.

Chambers 2018 *{published data only}*

Chambers ES, Byrne CS, Rugyendo A, Morrison DJ, Preston T, Tedford C, et al. The effects of dietary supplementation with inulin and inulin-propionate ester on hepatic steatosis in adults with non-alcoholic fatty liver disease. *Diabetes, Obesity and Metabolism* 2018;**11**:11.

Chang 2014 *{published data only}*

Chang HC, Peng CH, Yeh DM, Kao ES, Wang CJ. Hibiscus sabdariffa extract inhibits obesity and fat accumulation, and improves liver steatosis in humans. *Food and Function* 2014;**5**(4):734-9.

Dela Cruz 2012 *{published data only}*

Dela Cruz R, Mappala HT. The efficacy of ursodeoxycholic acid, probiotics vs. diet and exercise in the treatment of NAFLD: an open-labelled prospective randomized trial. *Journal of Gastroenterology and Hepatology* 2012;**27**:223.

Ersoz 2005 *{published data only}*

Ersoz G, Gunsar F, Karasu Z, Akay S, Batur Y, Akarca US. Management of fatty liver disease with vitamin E and C compared to ursodeoxycholic acid treatment. *Turkish Journal of Gastroenterology* 2005;**16**(3):124-8.

Famouri 2017b *{published data only}*

Famouri F, Salehi MM, Rostampour N, Hashemi E, Shahsanaee A. The effect of silymarin on non-alcoholic fatty liver disease of children. *Journal of Herbmed Pharmacology* 2017;**6**(1):16-20.

Guo 2014 *{published data only}*

Guo H, Zhong R, Liu Y, Jiang X, Tang X, Li Z, et al. Effects of bayberry juice on inflammatory and apoptotic markers in young adults with features of non-alcoholic fatty liver disease. *Nutrition* 2014;**30**(2):198-203.

Hajiaghamohammadi 2012 *{published data only}*

Hajiaghamohammadi AA, Ziaee A, Oveisi S, Masroor H. Effects of metformin, pioglitazone, and silymarin treatment on non-alcoholic fatty liver disease: a randomized controlled pilot study. *Hepatitis Monthly* 2012;**12**(8):e6099.

Han 2014 *{published data only}*

Han Y, Shi JP, Ma AL, Xu Y, Ding XD, Fan JG. Randomized, vitamin E-controlled trial of bicyclol plus metformin in non-alcoholic fatty liver disease patients with impaired fasting glucose. *Clinical Drug Investigation* 2014;**34**(1):1-7.

Khoshbaten 2010a *{published data only}*

Khoshbaten M, Aliasgarzadeh A, Masnadi K, Farhang S, Tarzamani MK, Babaei H, et al. Grape seed extract to improve liver function in patients with nonalcoholic fatty liver change. *Saudi Journal of Gastroenterology* 2010;**16**(3):194-7.

Mahmoudi 2020 *{published data only}*

Mahmoudi L, Asadi S, Al-Mousavi Z, Niknam R. A randomized controlled clinical trial comparing calcitriol versus cholecalciferol supplementation to reduce insulin resistance in patients with non-alcoholic fatty liver disease. Clinical Nutrition 2020 Dec 8 [Online ahead of print]. [10.1016/j.clnu.2020.11.037]

NCT00820651 *{published data only}*

NCT00820651. Efficacy and safety of diamel in patients with nonalcoholic steatohepatitis. clinicaltrials.gov/ct2/show/NCT00820651 (first posted 12 January 2009).

NCT04281121 *{published data only}*

NCT04281121. Omega 3 supplementation in children with non alcoholic fatty liver. clinicaltrials.gov/show/NCT04281121 (first posted 24 February 2020).

Petyaev 2018 *{published data only}*

Petyaev IM, Dovgalevsky PY, Chalyk NE, Klochkov VA, Kyle NH, Bashmakov YK. Reduction of liver span and parameters of inflammation in nonalcoholic fatty liver disease patients treated with lycosome formulation of phosphatidylcholine: a preliminary report. *International Journal of Chronic Diseases Print* 2018;**2018**:4549614.

Podszun 2020 *{published data only}*

Podszun MC, Alawad AS, Lingala S, Morris N, Huang WA, Yang S, et al. Vitamin E treatment in NAFLD patients demonstrates that oxidative stress drives steatosis through upregulation of de-novo lipogenesis. *Redox Biology* 2020;**37**:101710.

Saarinen 2011 *{published data only}*

Saarinen M, Kotronen A, Yamaki G, Matsuzaki S, Mitsuya N, Tiihonen K. Effects of low dose betaine in subjects with mild fatty liver. *Annals of Nutrition and Metabolism* 2011;**58**:112.

Semiserin 2016 *{published data only}*

Semiserin VA, Karakozov AG, Malkuta MA, Zolotareva LA, Levchenko OB, Kalyagin IE, et al. [Evaluation of the efficiency of hepatoprotective monotherapy using succinic acid and methionine for nonalcoholic fatty liver disease at the stage of steatohepatitis]. *Terapevticheskii Arkhiv* 2016;**88**(2):58-63.

Singhal 2015 *{published data only}*

Singhal P, Nesari T, Gupta GS. Efficacy of herbomineral compounds and pathya (ayurvedic dietary regime and physical exercise) in the management of yakrt roga (non-alcoholic fatty liver disease). *Ancient Science of Life* 2015;**34**(4):216-22.

Zhang 2008 *{published data only}*

Zhang SJ, Chen ZX, Jiang KP, Cheng YH, Gu YL. The effect of quyuhuatantongluo decoction on the non-alcoholic steatohepatitis. *Complementary Therapies in Medicine* 2008;**16**(4):192-8.

References to ongoing studies

ChiCTR2000034740 *{published data only}*

ChiCTR2000034740. To explore the protective effect of Lycium barbarum polysaccharide combined with exercise intervention on nonalcoholic fatty liver disease based on gut microbiota: a randomized controlled trial. www.chictr.org.cn/hvshowproject.aspx?id=43624 (date of approval by ethics committee 25 July 2019).

ChiCTR2000035899 *{published data only}*

ChiCTR2000035899. Efficacy and safety of caffeic acid in nonalcoholic fatty liver disease. www.chictr.org.cn/hvshowproject.aspx?id=49625 (date of approval by ethics committee 14 August 2020).

CTRI/2020/05/025322 *{published data only}*

CTRI/2020/05/025322. Effect of herbal blend in non-alcoholic subjects with elevated fatty liver index. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=41930&EncHid=&userName=CTRI/2020/05/025322 (first registered 22 May 2020).

CTRI/2020/07/026362 *{published data only}*

CTRI/2020/07/026362. To evaluate the efficacy of sarvakalpa-ghan-vati in management of non-alcoholic liver disorder. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=44069&EncHid=&userName=2020/07/026362 (first registered 4 July 2020).

Han 2020 *{published data only}*

Han K, Kwon O, Park HJ, Jung SY, Yang C, Son CG. Effect of daesiho-tang on obesity with non-alcoholic fatty liver disease: a study protocol for a randomised, double-blind, placebo-controlled pilot trial. *Trials* 2020;**21**(1):128.

IRCT20131125015536N *{published data only}*

IRCT20131125015536N. Effects of naringenin supplement on non-alcoholic fatty liver disease. www.irct.ir/trial/49713 (first registered 6 August 2020).

IRCT20191009045043N *{published data only}*

IRCT20191009045043N. Investigation the effect of the sumac powder consumption on patients with non-alcoholic fatty liver. www.irct.ir/trial/43090 (first registered 20 January 2020).

IRCT20200304046692N *{published data only}*

IRCT20200304046692N. Evaluating the effect of spirulina in non-alcoholic fatty liver patient. www.irct.ir/trial/46330 (first registered 11 March 2020).

IRCT20200531047614N *{published data only}*

IRCT20200531047614N. Zinc supplementation in treatment of obese children and adolescents with nonalcoholic fatty liver disease. www.irct.ir/trial/48543 (first registered 19 June 2020).

Lambert 2015 *{published data only}*

Lambert JE, Parnell JA, Eksteen B, Raman M, Bomhof MR, Rioux KP, et al. Gut microbiota manipulation with prebiotics in patients with non-alcoholic fatty liver disease: a randomized controlled trial protocol. *BMC Gastroenterology* 2015;**15**:169.

NCT02289235 *{published data only}*

NCT02289235. The effects of ginger on nonalcoholic fatty liver disease. clinicaltrials.gov/ct2/show/NCT02289235 (first posted 13 November 2014).

NCT02642172 *{published data only}*

NCT02642172. Prebiotics in patients with non-alcoholic liver disease. clinicaltrials.gov/ct2/show/NCT02642172 (first posted 30 December 2015).

NCT02647294 *{published data only}*

NCT02647294. Polyunsaturated fatty acids in patients with NAFLD. clinicaltrials.gov/ct2/show/NCT02647294 (first posted 6 January 2016).

NCT02764047 *{published data only}*

NCT02764047. Probiotics in the treatment of NAFLD. clinicaltrials.gov/ct2/show/NCT02764047 (first posted 6 May 2016).

NCT03439917 *{published data only}*

NCT03439917. Effects of carnitine supplementation on liver and muscle. clinicaltrials.gov/ct2/show/NCT03439917 (first posted 20 February 2018).

NCT03467282 *{published data only}*

NCT03467282. Probiotics in NASH Patients - PROBILIVER TRIAL (NASH). clinicaltrials.gov/ct2/show/NCT03467282 (first posted 15 March 2018).

NCT04175392 *{published data only}*

NCT04175392. Effect of probiotics in non-alcoholic fatty liver disease and steatohepatitis. clinicaltrials.gov/ct2/show/NCT04175392 (first posted 25 November 2019).

NCT04193982 *{published data only}*

NCT04193982. An investigator initiated prospective, four arms randomized comparative study of efficacy and safety of saroglitazar, vitamin E and life style modification in patients with nonalcoholic fatty liver disease (NAFLD)/ non-alcoholic steatohepatitis (NASH). clinicaltrials.gov/ct2/show/NCT04193982 (first posted 11 December 2019).

NCT04198805 *{published data only}*

NCT04198805. Vitamin E and DHA-EE on NAFLD - randomized, double-blind, placebo-controlled, parallel-group clinical trial (PUVENAFLD). clinicaltrials.gov/ct2/show/NCT04198805 (first posted 13 December 2019).

NCT04330326 *{published data only}*

NCT04330326. Metabolic cofactor supplementation in obese patients with non-alcoholic fatty liver disease. clinicaltrials.gov/show/NCT04330326 (first posted 1 April 2020).

NCT04475276 *{published data only}*

NCT04475276. Effect of alpha lipoic acid on non-alcoholic fatty liver diseases. clinicaltrials.gov/show/NCT04475276 (first posted 17 July 2020).

NCT04555434 *{published data only}*

None of the outcomes of interest for this review will be reported in this trial. Effects of probiotics (P pentosaceus, l lactis or l helveticus) in NASH. clinicaltrials.gov/show/NCT04555434 (first posted 18 September 2020).

NCT04671186 *{published data only}*

NCT04671186. Role of probiotics in treatment of pediatric NAFLD patients by assessing with fibroscan. clinicaltrials.gov/show/NCT04671186 (first posted 17 December 2020).

NCT04704063 *{published data only}*

NCT04704063. A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of Tocovid Suprabio 200mg in non-alcoholic fatty liver (NAFL). clinicaltrials.gov/ct2/show/NCT04704063 (first posted 11 January 2021).

NCT04718051 *{published data only}*

NCT04718051. S.P.Pro liver powder is used to improve liver and metabolic indexes in people with non-alcoholic fatty liver disease. clinicaltrials.gov/ct2/show/NCT04718051 (first posted 22 January 2021).

Wicklow 2015 *{published data only}*

Wicklow B, Wittmeier K, Gw TJ, McGavock J, Robert M, Duhamel T, et al. Proposed trial: safety and efficacy of resveratrol for the treatment of non-alcoholic fatty liver disease (NAFLD) and associated insulin resistance in adolescents who are overweight or obese adolescents - rationale and protocol. *Biochemistry and Cell Biology* 2015;**93**(5):522-30.

Zang 2018 *{published data only}*

Zang S, Chen J, Song Y, Bai L, Chen J, Chi X, et al. Haptoglobin genotype and vitamin E versus placebo for the treatment of nondiabetic patients with nonalcoholic steatohepatitis in China: a multicenter, randomized, placebo-controlled trial design. *Advances in Therapy* 2018;**35**(2):218-31.

Additional references

Abdelmalek 2007

Abdelmalek MF, Diehl AM. Nonalcoholic fatty liver disease as a complication of insulin resistance. *Medical Clinics of North America* 2007;**91**(6):1125-49, ix.

Abenavoli 2013

Abenavoli L, Bellentani S. Milk thistle to treat non-alcoholic fatty liver disease: dream or reality? *Expert Review of Gastroenterology & Hepatology* 2013;**7**(8):677-9.

Abenavoli 2015

Abenavoli L, Greco M, Nazionale I, Peta V, Milic N, Accattato F, et al. Effects of Mediterranean diet supplemented with silybin-vitamin E-phospholipid complex in overweight patients with non-alcoholic fatty liver disease. *Expert Review of Gastroenterology & Hepatology* 2015;**9**(4):519-27.

Adams 2005

Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005;**129**(1):113-21.

Adorini 2012

Adorini L, Pruzanski M, Shapiro D. Farnesoid X receptor targeting to treat nonalcoholic steatohepatitis. *Drug Discovery Today* 2012;**17**(17-18):988-97.

Alberti 2009

Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;**120**(16):1640-5.

Al-Muzafar 2017

Al-Muzafar HM, Amin KA. Probiotic mixture improves fatty liver disease by virtue of its action on lipid profiles, leptin, and inflammatory biomarkers. *BMC Complementary and Alternative Medicine* 2017;**17**(1):43.

Angulo 2002

Angulo P. Nonalcoholic fatty liver disease. *New England Journal of Medicine* 2002;**346**(16):1221-31.

Angulo 2015

Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015;**149**(2):389-97.e10.

Anstee 2012

Anstee QM, Day CP. S-adenosylmethionine (SAMe) therapy in liver disease: a review of current evidence and clinical utility. *Journal of Hepatology* 2012;**57**(5):1097-109.

Ballestri 2016

Ballestri S, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *Journal of Gastroenterology and Hepatology* 2016;**31**(5):936-44.

Barritt 2017

Barritt AS 4th, Gitlin N, Klein S, Lok AS, Loomba R, Malahias L, et al. Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: the TARGET-NASH study. *Contemporary Clinical Trials* 2017;**61**:33-8.

Bedogni 2005

Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos Nutrition and Liver Study. *Hepatology (Baltimore, Md)* 2005;**42**(1):44-52.

Bedogni 2007

Bedogni G, Miglioli L, Masutti F, Castiglione A, Croce LS, Tiribelli C, et al. Incidence and natural course of fatty liver in the general population: the Dionysos Study. *Hepatology (Baltimore, Md)* 2007;**46**(5):1387-91.

Bernsmeier 2015

Bernsmeier C, Weisskopf DM, Pflueger MO, Mosimann J, Campana B, Terracciano L, et al. Sleep disruption and daytime sleepiness correlating with disease severity and insulin resistance in non-alcoholic fatty liver disease: a comparison with healthy controls. *PLOS One* 2015;**10**(11):e0143293.

Best 2018

Best LMJ, Freeman S, Sutton AJ, Hawkins N, Tsochatzis E, Gurusamy KS. Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2018, Issue 9. Art. No: CD013103. [DOI: 10.1002/14651858.CD013103]

Buzzetti 2016

Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism: Clinical and Experimental* 2016;**65**(8):1038-48.

Buzzetti 2021

Buzzetti E, Linden A, Best LMJ, Madden AM, Roberts D, Chase TJ G, et al. Lifestyle modifications for nonalcohol-related fatty liver disease: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2021, Issue 3. Art. No: CD013156. [DOI: 10.1002/14651858.CD013156.pub2]

Cerovic 2013

Cerovic I, Mladenovic D, Jesic R, Naumovic T, Brankovic M, Vucevic D, et al. Alcoholic liver disease/nonalcoholic fatty liver disease index: distinguishing alcoholic from nonalcoholic fatty liver disease. *European Journal of Gastroenterology & Hepatology* 2013;**25**(8):899-904.

Chaimani 2012

Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* 2012;**3**(2):161-76.

Chaimani 2013

Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLOS One* 2013;**8**(10):e76654.

Chalasani 2012

Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology (Baltimore, Md)* 2012;**55**(6):2005-23.

Chan 2013

Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013;**158**(3):200-7.

Cholankeril 2017

Cholankeril G, Wong RJ, Hu M, Perumpail RB, Yoo ER, Puri P, et al. Liver transplantation for nonalcoholic steatohepatitis in the US: temporal trends and outcomes. *Digestive Diseases and Sciences* 2017;**62**(10):2915-22.

Clearfield 2021

Clearfield E, Miller V, Nadglowski J, Barradas K, Al Naber J, Sanyal AJ, et al. coreNASH: multi-stakeholder consensus on core outcomes for decision making about nonalcoholic steatohepatitis treatment. Hepatology Communications 2021;**5**(5):774-85.

Cowie 2017

Cowie MR, Blomster JI, Curtis LH, Duclaux S, Ford I, Fritz F, et al. Electronic health records to facilitate clinical research. *Clinical Research in Cardiology* 2017;**106**(1):1-9.

Dam-Larsen 2005

Dam-Larsen S, Franzmann MB, Christoffersen P, Larsen K, Becker U, Bendtsen F. Histological characteristics and prognosis in patients with fatty liver. *Scandinavian Journal of Gastroenterology* 2005;**40**(4):460-7.

Dassanayake 2009

Dassanayake AS, Kasturiratne A, Rajindrajith S, Kalubowila U, Chakrawarthi S, De Silva AP, et al. Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. *Journal of Gastroenterology and Hepatology* 2009;**24**(7):1284-8.

Del Giovane 2013

Del Giovane C, Vacchi L, Mavridis D, Filippini G, Salanti G. Network meta-analysis models to account for variability in treatment definitions: application to dose effects. *Statistics in Medicine* 2013;**32**(1):25-39.

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**29**(7-8):932-44.

Dias 2012a

Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment, September 2011 (last updated April 2012). nicedsu.org.uk/wp-content/uploads/2016/03/TSD3-Heterogeneity.final-report.08.05.12.pdf (accessed 26 February 2021).

Dias 2012b

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 1: introduction to evidence synthesis for decision making, April 2011 (last updated April 2012). silo.tips/download/nice-dsu-technical-support-document-1-introduction-to-evidence-synthesis-for-dec (accessed 26 February 2021).

Dias 2014

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU technical support document 4: inconsistency in networks of evidence based on randomised controlled trials, May 2011 (last updated April 2014). nicedsu.org.uk/wp-content/uploads/2016/03/TSD4-Inconsistency.final_.15April2014.pdf (accessed 26 February 2021).

Dias 2016

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials, August 2011 (last updated September 2016). www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088912/pdf/PubMedHealth_PMH0088912.pdf (accessed 26 February 2021).

Edgeworth 1887

Edgeworth FY. On observations relating to several quantities. *Hermathena* 1887;**6**(13):285-79.

Ekstedt 2015

Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology (Baltimore, Md)* 2015;**61**(5):1547-54.

Eslam 2019

Eslam M, Sanyal AJ, George J. Toward more accurate nomenclature for fatty liver diseases. *Gastroenterology* 2019;**157**(3):590-3.

EuroQol 2018

EuroQol. EQ-5D Instruments | About EQ-5D, 2018. euroqol.org/eq-5d-instruments/ (accessed 26 February 2021).

Fleischman 2014

Fleischman MW, Budoff M, Zeb I, Li D, Foster T. NAFLD prevalence differs among Hispanic subgroups: the multi-ethnic study of atherosclerosis. *World Journal of Gastroenterology* 2014;**20**(17):4987-93.

Gurusamy 2019

Gurusamy K, Walmsley M, Davidson BR, Frier C, Fuller B, Madden A, et al. Top research priorities in liver and gallbladder disorders in the United Kingdom. BMJ Open 2019;**9**(3):e025045.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94.

Hardy 2020

Hardy T, Wonders K, Younes R, Aithal GP, Aller R, Allison M, et al. The European NAFLD Registry: a real-world longitudinal cohort study of nonalcoholic fatty liver disease. *Contemporary Clinical Trials* 2020;**98**:106175.

Hernaez 2011

Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology (Baltimore, Md)* 2011;**54**(3):1082-90.

Higgins 2003

Higgins JT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research edition)* 2003;**327**(7414):557-60.

Higgins 2011a

Higgins JT, Altman DG, Sterne JA (editors). Chapter 8. Assessing risk of bias in included studies. In: Higgins JT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Higgins 2011b

Higgins JT, Deeks JJ, Altman DG (editors). Chapter 16. Special topics in statistics. In: Higgins JT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org..

Higgins 2012

Higgins JT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98-110.

Houghton 2017

Houghton D, Thoma C, Hallsworth K, Cassidy S, Hardy T, Burt AD, et al. Exercise reduces liver lipids and visceral adiposity in patients with nonalcoholic steatohepatitis in a randomized controlled trial. *Clinical Gastroenterology and Hepatology* 2017;**15**(1):96-102.e3.

Hutton 2015

Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine* 2015;**162**(11):777-84.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice CFR & ICH Guidelines. Vol. **1**. Philadelphia (PA): Barnett International/PAREXEL, 1997.

Jackson 2014

Jackson D, Barrett JK, Rice S, White IR, Higgins JT. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine* 2014;**33**(21):3639-54.

James 2015

James S, Rao SV, Granger CB. Registry-based randomized clinical trials - a new clinical trial paradigm. *Nature Reviews. Cardiology* 2015;**12**(5):312-6.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9.

Koehler 2012

Koehler EM, Schouten JN, Hansen BE, van Rooij FJ, Hofman A, Stricker BH, et al. Prevalence and risk factors of non-alcoholic fatty liver disease in the elderly: results from the Rotterdam study. *Journal of Hepatology* 2012;**57**(6):1305-11.

Lazo 2013

Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. *American Journal of Epidemiology* 2013;**178**(1):38-45.

Li 2014

Li Z, Xue J, Chen P, Chen L, Yan S, Liu L. Prevalence of nonalcoholic fatty liver disease in mainland of China: a meta-analysis of published studies. *Journal of Gastroenterology and Hepatology* 2014;**29**(1):42-51.

Li 2015

Li YH, Yang LH, Sha KH, Liu TG, Zhang LG, Liu XX. Efficacy of poly-unsaturated fatty acid therapy on patients with nonalcoholic steatohepatitis. *World Journal of Gastroenterology* 2015;**21**(22):7008-13.

Lombardi 2017

Lombardi R, Onali S, Thorburn D, Davidson BR, Gurusamy KS, Tsochatzis E. Pharmacological interventions for non-alcohol related fatty liver disease (NAFLD). *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No: CD011640. [DOI: 10.1002/14651858.CD011640.pub2]

Lonardo 2015

Lonardo A, Bellentani S, Argo CK, Ballestri S, Byrne CD, Caldwell SH, et al. Epidemiological modifiers of non-alcoholic fatty liver disease: focus on high-risk groups. *Digestive and Liver Disease* 2015;**47**(12):997-1006.

Lu 2006

Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006;**101**(474):447-59.

Mann 2018

Mann JP, Vreugdenhil A, Socha P, Janczyk W, Baumann U, Rajwal S, et al. European Paediatric Non-Alcoholic Fatty Liver Disease registry (EU-PNAFLD): design and rationale. *Contemporary Clinical Trials* 2018;**75**:67-71.

Mills 2012

Mills EJ, Ioannidis JP, Thorlund K, Schünemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA* 2012;**308**(12):1246-53.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**(9128):609-13.

Nabavi 2014

Nabavi S, Rafraf M, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. Effects of probiotic yogurt consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. *Journal of Dairy Science* 2014;**97**(12):7386-93.

NCBI 2018

NCBI. Fatty liver. www.ncbi.nlm.nih.gov/mesh/68005234 (accessed 26 February 2021).

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

Nishioji 2015

Nishioji K, Sumida Y, Kamaguchi M, Mochizuki N, Kobayashi M, Nishimura T, et al. Prevalence of and risk factors for non-alcoholic fatty liver disease in a non-obese Japanese population, 2011-2012. *Journal of Gastroenterology* 2015;**50**(1):95-108.

OmniPage 18.0 [Computer program]

OmniPage 18.0. Nuance, 2011.

Ong 2008

Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *Journal of Hepatology* 2008;**49**(4):608-12.

Onnerhag 2014

Onnerhag K, Nilsson PM, Lindgren S. Increased risk of cirrhosis and hepatocellular cancer during long-term follow-up of patients with biopsy-proven NAFLD. *Scandinavian Journal of Gastroenterology* 2014;**49**(9):1111-8.

OpenBUGS 3.2.3 [Computer program]

Members of OpenBUGS project management group OpenBUGS. Members of OpenBUGS project management group, 2014.

Optum 2018

Optum. Patient-reported Outcomes | What We Do | SF Health Surveys | SF-36v2 Health Survey, 2018. www.qualitymetric.com/health-surveys/the-sf-36v2-health-survey/ (accessed 26 February 2021).

Park 2006

Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, et al. Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. *Journal of Gastroenterology and Hepatology* 2006;**21**(1 Pt 1):138-43.

Paschos 2012

Paschos P, Tziomalos K. Nonalcoholic fatty liver disease and the renin-angiotensin system: implications for treatment. *World Journal of Hepatology* 2012;**4**(12):327-31.

Piscaglia 2016

Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. *Hepatology (Baltimore, Md)* 2016;**63**(3):827-38.

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clinical research edition)* 2014;**349**:g5630.

Reeves 2018

Reeves D, Howells K, Sidaway M, Blakemore A, Hann M, Panagioti M, et al. The cohort multiple randomized controlled trial design was found to be highly susceptible to low statistical power and internal validity biases. *Journal of Clinical Epidemiology* 2018;**95**:111-9.

Relton 2010

Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ (Clinical research edition)* 2010;**340**:C1066. [PMID: 20304934]

Riley 2007

Riley P, O'Donohue J, Crook M. A growing burden: the pathogenesis, investigation and management of non-alcoholic fatty liver disease. *Journal of Clinical Pathology* 2007;**60**(12):1384-91.

Rinella 2015

Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015;**313**(22):2263-73.

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163-71.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**(2):80-97.

Savović 2012a

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**(35):1-82.

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429-38.

Savović 2018

Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JT, et al. Association between risk-of-bias assessments and results of randomized trials in Cochrane Reviews: the ROBES Meta-Epidemiologic Study. *American Journal of Epidemiology* 2018;**187**(5):1113-22.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12.

Schulz 2010

Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Annals of Internal Medicine* 2010;**152**(11):726-32.

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JT, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12. Interpreting results and drawing conclusions. In: Higgins JT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Severini 1993

Severini TA. Bayesian interval estimates which are also confidence intervals. *Journal of the Royal Statistical Society. Series B (Methodological)* 1993;**55**(2):533-40.

Shen 2014

Shen H, Shahzad G, Jawairia M, Bostick RM, Mustacchia P. Association between aspirin use and the prevalence of nonalcoholic fatty liver disease: a cross-sectional study from The Third National Health and Nutrition Examination Survey. *Alimentary Pharmacology & Therapeutics* 2014;**40**(9):1066-73.

Shojaee-Moradie 2016

Shojaee-Moradie F, Cuthbertson DJ, Barrett M, Jackson NC, Herring R, Thomas EL, et al. Exercise training reduces liver fat and increases rates of VLDL clearance but not VLDL production in NAFLD. *Journal of Clinical Endocrinology and Metabolism* 2016;**101**(11):4219-28.

Soderberg 2010

Soderberg C, Stal P, Askling J, Glaumann H, Lindberg G, Marmur J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology (Baltimore, Md)* 2010;**51**(2):595-602.

Sookoian 2011

Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology (Baltimore, Md)* 2011;**53**(6):1883-94.

Stata/SE 15.1 [Computer program]

Stata/SE. Version 15.1. Texas, USA: StataCorp LLC, 2016. www.stata.com/.

Tilg 2010

Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology (Baltimore, Md)* 2010;**52**(5):1836-46.

van Valkenhoef 2012

van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Research Synthesis Methods* 2012;**3**(4):285-99.

Wang 2016

Wang J, Li P, Jiang Z, Yang Q, Mi Y, Liu Y, et al. Diagnostic value of alcoholic liver disease (ALD)/nonalcoholic fatty liver disease (NAFLD) index combined with gamma-glutamyl transferase in differentiating ALD and NAFLD. *Korean Journal of Internal Medicine* 2016;**31**(3):479-87.

White 2012

White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clinical Gastroenterology and Hepatology* 2012;**10**(12):1342-59.e2.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical research edition)* 2008;**336**(7644):601-5.

Yepes-Nunez 2019

Yepes-Nunez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology* 2019;**115**:1-13.

Young-Afat 2016

Young-Afat DA, Verkooijen HA, van Gils CH, van der Velden JM, Burbach JP, Elias SG, et al. Brief report: staged-informed consent in the cohort multiple randomized controlled trial design. *Epidemiology (Cambridge, Mass)* 2016;**27**(3):389-92. [PMID: 27035689]

Zhang 2016

Zhang HJ, He J, Pan LL, Ma ZM, Han CK, Chen CS, et al. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: a randomized clinical trial. *JAMA Internal Medicine* 2016;**176**(8):1074-82.

CHARACTERISTICS OF STUDIES

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

Abdelmalek 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2003 to 2005 Number randomised: 55 Post-randomisation dropouts: 20 (36.4%) Revised sample size: 35 Reasons for post-randomisation dropouts: lack of compliance, did not receive treatment Average age, years: 47 Females: 35 (100.0%) NASH: 35 (100.0%) Diabetes mellitus: 18 (51.4%) Inclusion criteria: 1. Age 18 to 70. 2. Histological features of NASH. 3. Elevated ALT or AST ≥ 1.5× times normal on ≥ 2 different occasions within 6 months of enrolment. 4. Ethanol consumption < 20 g/d for females and < 30 g/d for males Exclusion criteria: 1. Pregnant women, lactating women. 2. ALT/AST > 5× normal. 3. Abnormal total bilirubin or albumin, prolonged PT, or platelets less than lower limit of normal. 4. Creatinine ≥ 1.5 mg/dL. 5. Creatine kinase ≥ 3× normal. 6. Drugs known to cause hepatosteatosis or therapy with drugs that may have potential benefit in treatment of NAFLD Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: amino acids (n = 17) Further details: betaine 20 g for 12 months Group 2: no active intervention (n = 18) Further details: placebo
Outcomes	Outcomes reported: fibrosis score, NAFLD activity score Follow-up, months: 12
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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

References to other published versions of this review

Gurusamy 2018

Gurusamy KS, Tsochatzis E, Madden AM. Nutritional supplementation for non-alcohol-related fatty liver disease: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2018, Issue 10. Art. No: CD013157. [DOI: 10.1002/14651858.CD013157]

* Indicates the major publication for the study

Abdelmalek 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: participants were excluded from analysis for reasons likely to be related to intervention and outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Abhari 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 53 Post-randomisation dropouts: 8 (15.1%) Revised sample size: 45 Reasons for post-randomisation dropouts: did not follow protocol Average age, years: 47 Females: 20 (44.4%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 18 to 75 years of age. 2. Presence of steatosis on FibroScan (controlled attenuation parameter (CAP) > 270 dB/m). 3. High concentration of liver enzyme ALT > 1.5× upper limit of normal. 4. No history of alcohol consumption. 5. No history of disease such as diabetes or severe hepatic disease (hepatitis B, C) or cirrhosis (according to gastroenterologist diagnosis). 6. Absence of antimicrobial medication within previous 3 months. 7. No history of weight loss or bariatric surgery in recent years Exclusion criteria: 1. Pregnancy or lactation. 2. Unexpected adverse effects. 3. Supplement intolerance Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 23) Further details: patients in the synbiotic group received 1 synbiotic capsule containing 10^9 spores of *B coagulans* (GBI-30) plus 0.4 g inulin per day Group 2: no active intervention (n = 22) Further details: patients in the placebo group received 1 capsule of placebo (maltodextrin), which apparently was similar to the synbiotic capsule in terms of size, colour, and shape of capsules
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 3

Abhari 2020 *(Continued)*

Notes	Source of funding (quote): "the study was supported by Shahid Beheshti University of Medical Science" Trial name/Trial registry number: IRCT20100524004010N23 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated by a statistician"
Allocation concealment (selection bias)	Low risk	Quote: "subjects and investigators were blind to the treatment assignment until the end of the study…placebo" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "subjects and investigators were blind to the treatment assignment until the end of the study…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "subjects and investigators were blind to the treatment assignment until the end of the study…placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts on the basis of not following the protocol. This was probably related to intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Afsharinasab 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 42 Post-randomisation dropouts: not stated Revised sample size: 42 Average age, years: 34 Females: 13 (31.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT). 2. Age range 20 to 45 years Exclusion criteria: 1. Patients using alcohol or daily Berberis. 2. Patients having allergy to Berberis and its compounds. 3. Patients with diabetes, high blood pressure, perceptual disorders, nephrotic syndrome, uremia ischaemic heart disease, chronic liver disease such as hepatitis. 4. Pregnancy or lactation Method for diagnosis of NAFLD: ultrasound

Afsharinasab 2020 *(Continued)*

Interventions	Group 1: other supplements (n = 21) Further details: experimental group received a gelatin capsule containing 750 mg hydroalcoholic extract of *Berberis integerrima* every 12 hours for 2 months. All patients in this study received metformin and vitamin E as standard treatment during the study Group 2: no active intervention (n = 21) Further details: control group received a gelatin capsule containing 750 mg cellulose every 12 hours for 2 months. All patients in this study received metformin and vitamin E as standard treatment during the study
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work was supported by the RUMS by the grant number P/31/1/2806" Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 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	Low risk	Quote: "double blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Afzali 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2018 to 2019 Number randomised: 120 Post-randomisation dropouts: 3 (2.5%) Revised sample size: 117 Reasons for post-randomisation dropouts: side effects and unusual values Average age, years: 47

Afzali 2020 *(Continued)*

	Females: 55 (47.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Age between 18 and 70 years. 2. Primary diagnosis of NAFLD. 3. Increased levels of liver enzymes (2 or 3× higher than normal) Exclusion criteria: 1. Patients with liver disease, including Wilson's disease, haemochromatosis, alcoholic fatty liver disease, autoimmune liver disease, or cirrhosis. 2. Pregnant and lactating women Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin E plus other antioxidants plus other supplements (n = 60) Further details: the *Beta vulgaris* group received vitamin E pearl (300 IU/twice daily), Livergol tablet (140 mg/d), and *Beta vulgaris* capsule (400 mg/d) for 6 months Group 2: vitamin E plus other antioxidants (n = 57) Further details: the placebo group received the same dosages of vitamin E pearl and Livergol tablet, but placebo capsules instead of *Beta vulgaris* capsules for the same amount of time
Outcomes	Outcomes reported: mortality, liver transplantation, decompensated cirrhosis Follow-up, months: 6
Notes	Source of funding (quote): "this study was supported by a teaching and research scholarship from the Faculty of Pharmacy of Tehran University of Medical Sciences" Trial name/Trial registry number: IRCT20121017011145N20 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the sequence of groups was drawn up by coin tossing"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts on the basis of adverse events and usual values; these were probably related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Ahn 2018

Study characteristics

Ahn 2018 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: South Korea Period of recruitment: not stated Number randomised: 68 Post-randomisation dropouts: not stated Revised sample size: 68 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = not stated) Further details: probiotics mixture consists of 6 kinds of probiotics (*Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus paracasei, Pediococcus pentosaceus, Bifidobacterium lactis, Bifidobacterium breve*) for 12 weeks Group 2: no active intervention (n = not stated) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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	Low risk	Quote: "double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Akbarzadeh 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2015 Number randomised: 80 Post-randomisation dropouts: 5 (6.3%) Revised sample size: 75 Reasons for post-randomisation dropouts: surgery, disliked the intervention, personal reasons Average age, years: 45 Females: 40 (53.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD diagnosed by physical examination and/or ALT > 40 and/or elastometry > 4 kPa in FibroScan Exclusion criteria: 1. Alcohol. 2. Pregnancy/Lactation. 3. Weight loss diet over previous 3 months. 4. Malignancy. 5. Medication affecting liver enzymes. 6. Multi-vitamin supplements, omega 3 supplements in last 3 months. 5. CLD except NAFLD Method for diagnosis of NAFLD: ultrasound plus/minus elastography plus/minus transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 38) Further details: psyllium 10 g daily for 10 weeks Group 2: no active intervention (n = 37) Further details: placebo Additional details: both groups received lifestyle interventions
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the present study was supported by Isfahan University of Medical Sciences, Isfahan, Iran" Trial name/Trial registry number: not stated Attempts were made to contact study 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	Low risk	Quote: "placebo-controlled, double-blind, randomized clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "placebo-controlled, double-blind, randomized clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Akbarzadeh 2015 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Aliashrafi 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2011 to 2012 Number randomised: 60 Post-randomisation dropouts: 5 (8.3%) Revised sample size: 55 Reasons for post-randomisation dropouts: discontinuation (3), pregnancy (1), travel (1) Average age, years: 37 Females: 25 (45.5%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Fatty liver on USS. 2. Aged 20 to 50. 3. BMI ≥ 30 Exclusion criteria: 1. Other liver diseases. 2. Those taking the following medications - hepatotoxic or lipid-lowering agent, metformin, antihypertensive, contraceptive, oestrogen Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: vitamin E plus other supplements (n = 29) Further details: four 300-mg tablets of *Chlorella vulgaris* per day for 8 weeks plus vitamin E 400 mg/d Group 2: vitamin E (n = 26) Further details: four placebos per day for 8 weeks, similar to *Chlorella vulgaris* tablets in colour and size, plus vitamin E 400 mg/d
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the authors would like to thanks Iranians Green Future Co. (Tehran, Iran) for providing C vulgaris tablets" Trial name/Trial registry number: IRCT201202233320N7 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated using a computer-generated random sequence into two groups"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomized placebo-controlled clinical trial. The placebo tablets were similar to C vulgaris tablets in color and size"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind randomized placebo-controlled clinical trial"

Aliashrafi 2014 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available; recruitment had commenced before the protocol was published, and several pre-defined primary outcomes were not reported
Other bias	Low risk	Comment: no other bias noted

Alisi 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2012 to 2013 Number randomised: 48 Post-randomisation dropouts: 4 (8.3%) Revised sample size: 44 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 11 Females: 20 (45.5%) NASH: 44 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Obese children with NAFLD Exclusion criteria: 1. Liver disease due to known other cause. 2. Use of NSAIDs, antibiotics, probiotics, or anti-secretory drugs capable of causing achlorhydria within 2 months preceding enrolment Method for diagnosis of NAFLD: clinical examination plus transaminases plus liver biopsy
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 22) Further details: probiotics (VSL #3) 1 sachet/d for 4 months Group 2: no active intervention (n = 22) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this study was funded by the Italian Ministry of Health (Fondi di Ricerca Corrente and 5*1000) to Prof. Valerio Nobili. Prof. Anania is supported by US Public Health Service Grant DK062092 and Departments of Veterans' Affairs Grant BX001746" Trial name/Trial registry number: NCT01650025 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a statistician blinded to participants' clinical data, and who did not perform the final analysis, generated the allocation sequence and randomly assigned participants to the VSL#3 or placebo group"

Alisi 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "a statistician blinded to participants' clinical data, and who did not perform the final analysis, generated the allocation sequence and randomly assigned participants to the VSL#3 or placebo group"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "parallel-arm double-blind RCT…only the statistician had access to the treatment codes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "parallel-arm double-blind RCT…only the statistician had access to the treatment codes"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Aller 2011

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: not stated Number randomised: 30 Post-randomisation dropouts: 2 (6.7%) Revised sample size: 28 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 47 Females: 8 (28.6%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Hep B/C, CMV, EBV. 2. Alcohol consumption. 3. Diabetes mellitus, impaired glucose tolerance. 4. Use of blood pressure-lowering medication or statins. 5. Hereditary defects. 6. Non-organ-specific autoantibodies Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 14) Further details: 500 million *Lactobacillus bulgaricus* and *Streptococcus thermophilus* organisms for 3 months Group 2: no active intervention (n = 14) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Aller 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomized clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Aller 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: not stated Number randomised: 36 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 36 Average age, years: 47 Females: 14 (38.9%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Hep B/C, CMV, EBV. 2. Alcohol consumption. 3. Diabetes mellitus, impaired glucose tolerance. 4. Use of blood pressure-lowering medication or statins. 5. Hereditary defects. 6. Non-organ-specific autoantibodies Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E plus other antioxidants (n = 18) Further details: silymarin plus vitamin E (Eurosil85®, MEDAS SL) 2 tablets/d for 3 months Group 2: no active intervention (n = 18) Further details: no treatment Additional details: both groups received lifestyle modification intervention

Aller 2015 *(Continued)*

Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), fibrosis score Follow-up, months: 3
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "all patients were randomized (table of numbers)"
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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Amanat 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 82 Post-randomisation dropouts: 4 (4.9%) Revised sample size: 78 Reasons for post-randomisation dropouts: missing samples Average age, years: 44 Females: 21 (26.9%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 18 to 69 years of age with steatosis grade ≥ 2 by USS Exclusion criteria: 1. Viral hepatitis, cirrhosis, or other CLD. 2. 5× increase in ALT. 3. Regular alcohol consumption. 4. Pregnancy. 5. Parenteral nutrition. 6. Lipid-lowering drugs or antidiabetic drugs Method for diagnosis of NAFLD: ultrasound

Amanat 2018 *(Continued)*

Interventions	Group 1: oestrogen (n = 37) Further details: 250 mg genistein in capsules once a day for 8 weeks Group 2: no active intervention (n = 41) Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 2
Notes	Source of funding (quote): "the trial was supported by a research funding (no. 94-7516) from SUMS, Iran (SUMS = Shiraz University of Medical Sciences)" Trial name/Trial registry number: IRCT20131213240NS Attempts were made to contact study 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 either genistein or placebo groups by a computer-generated random sequence"
Allocation concealment (selection bias)	Low risk	Quote: "eight-week double-blinded randomized controlled trial…participants, investigators and laboratory technicians were unaware of the participant's group allocation" Comment: both allocation concealment and blinding were achieved with use of a placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "eight-week double-blinded randomized controlled trial…participants, investigators and laboratory technicians were unaware of the participant's group allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "eight-week double-blinded randomized controlled trial…participants, investigators and laboratory technicians were unaware of the participant's group allocation"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Amiri 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2015 to 2016 Number randomised: 120 Post-randomisation dropouts: 10 (8.3%)

Amiri 2017 *(Continued)*

	Revised sample size: 110 Reasons for post-randomisation dropouts: lost to follow-up, non-compliant, discontinued intervention Average age, years: 42 Females: 28 (25.5%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD via USS. 2. BMI < 35. 3. Age 18 to 65. 4. Serum 25 (OH) D level < 15 ng/mL. 5. Iranian Exclusion criteria: 1. BMI < 25. 2. Lactating/pregnant. 3. Diagnosis of chronic disease including inflammatory disease, heart failure, liver failure, renal failure, cancer, acute myocardial infarction, diabetes, stroke, or serious injury. 4. Use of hepatotoxic drugs or multi-vitamin or antioxidant supplements within 3 months. 5. Smoking or alcohol consumption. 6. Malabsorption disease. 7. Hereditary liver disease. 8. Athlete Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin D (n = 74) Further details: 25 mcg calcitriol (37 patients also received calcium carbonate 500 mg, which was determined at random) for 12 weeks Group 2: no active intervention (n = 36) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors" Trial name/Trial registry number: IRC T201408312709N29 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible participants were randomly assigned by using a computer-generated random-numbers method by the project coordinator"
Allocation concealment (selection bias)	Low risk	Quote: "eligible participants were randomly assigned by using a computer-generated random-numbers method by the project coordinator"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, controlled, double-blind trial…products were administered by a blinded researcher assistant to blinded patients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, controlled, double-blind trial…products were administered by a blinded researcher assistant to blinded patients"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Amiri-Moghadam 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2013 to 2014 Number randomised: 72 Post-randomisation dropouts: 4 (5.6%) Revised sample size: 68 Reasons for post-randomisation dropouts: withdrew from the study Average age, years: 43 Females: not stated NASH: 68 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. ALT >3 times upper limit of normal and ultrasonography outcomes for diagnosis of NASH. 2. 18 to 65 years old. 3. BMI > 25 Exclusion criteria: 1. Smoking. 2. Pregnancy. 3. Use of insulin, blood lipid-lowering agents, or steroid drugs. 3. Hemochromatosis. 4. Wilson's disease. 5. Consumption of supplement in previous month. 6. Use of high doses of oestrogen. 7. Cushing's disease. 8. Hyperthyroidism. 9. Total parenteral nutrition in past 6 months Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: amino acids (n = 36) Further details: L-carnitine 2000 mg/d for 12 weeks Group 2: no active intervention (n = 32) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the study was supported by a grant (no. 19463) from Iran University of Medical Sciences, Tehran, Iran" Trial name/Trial registry number: not stated Attempts were made to contact study 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)	Low risk	Quote: "neither the researchers nor the patients were informed about the allocated group during the study" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomised double-blind placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomised double-blind placebo-controlled clinical trial"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Amiri-Moghadam 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Amirkhizi 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 5 (10.0%) Revised sample size: 45 Reasons for post-randomisation dropouts: discontinued treatment or withdrawal Average age, years: 40 Females: 22 (48.9%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Hepatic steatosis on USS. 2. BMI 30 to 40. 3. Age 20 to 50 years Exclusion criteria: 1. Pregnancy/Lactation. 2. Hormone therapy or use of oral contraceptive pill. 3. Chemotherapy in previous year. 4. Cardiovascular disease, hypertension, diabetes mellitus, thyroid disorders, or kidney dysfunction. 5. Viral hepatitis, cirrhosis, autoimmune hepatitis, or other hepatic disease. 6. Consumption of antioxidant supplements. 7. Use of lipid-lowering or antihypertensive medication. 8. Smoking. 9. Calorie-restricted diet Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin E plus other antioxidants (n = 23) Further details: vitamin E 400 mg plus 1200 mg alpha-lipoic acid per day for 12 weeks Group 2: vitamin E (n = 22) Further details: vitamin E 400 mg per day for 12 weeks
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "we thank the Research Vice-Chancellor and Nutrition Research Center of Tabriz University of Medical Sciences, Tabriz, Iran, for the financial support" Trial name/Trial registry number: IRCT201511143320N12 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random allocation software (RAS)"
Allocation concealment (selection bias)	Low risk	Quote: "once the random sequences were generated by the software, they were kept in a secure location and managed by a third party, who had no involvement in the study"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled randomized clinical trial"

Amirkhizi 2018 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind placebo-controlled randomized clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Argo 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2007 to 2010 Number randomised: 41 Post-randomisation dropouts: 7 (17.1%) Revised sample size: 34 Reasons for post-randomisation dropouts: cirrhosis (1), relocation (1), transportation difficulties (5) Average age, years: 47 Females: 21 (61.8%) NASH: 34 (100.0%) Diabetes mellitus: 11 (32.4%) Inclusion criteria: 1. Biopsies demonstrating steatohepatitis. 2. Ethanol < 30 g/d for males and < 20 g/d females Exclusion criteria: 1. Cirrhosis. 2. Secondary forms of steatohepatitis. 3. Treatment with thiazolidinediones. 4. Viral hepatitis or autoimmune metabolic liver disease Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: PUFA (n = 17) Further details: n-3 fish oil 3000 mg/d for 1 year Group 2: no active intervention (n = 17) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "study medication and identical appearing placebo was provided at no charge by Nordic Natural. RBC phospholipid profile was performed by Metametrix (www.metametrix.com)" Trial name/Trial registry number: NCT00681408 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "an independent biostatistician generated the randomization list which was confidentially forwarded to the investigational pharmacy"

Argo 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "an independent biostatistician generated the randomization list which was confidentially forwarded to the investigational pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not 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: 39 Females: 20 (33.3%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 20- to 60-year-olds. 2. BMI 25 to 35. 3. NAFLD Exclusion criteria: 1. Pregnant/lactating women. 2. Postmenopausal women. 3. Professional athletes. 4. Smoking. 5. Alcohol consumption. 6. Inherited liver disorders. 7. Liver disease, cardiovascular disease, kidney disease, gastrointestinal disease, diabetes mellitus, thyroid dysfunction, or malignancy. 8. Use of hepatotoxic drugs, steroids, or hormonal drugs Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 30) Further details: resveratrol 600 mg pure trans-resveratrol capsules for 12 weeks Group 2: no active intervention (n = 30) Further details: placebo capsules Additional details: another group not relevant to this review was excluded
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "we thank the Research Vice-Chancellor and Nutrition Research Center of Tabriz University of Medical Sciences, Tabriz, Iran, for the financial support" Trial name/Trial registry number: IRCT201511233664N16

Asghari 2018 *(Continued)*

Attempts were made to contact study 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)	Low risk	Quote: "an independent person not involved in the study process prepared both resveratrol and placebo bottles, and labeled them as A or B"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: an intention-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Asgharian 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2014 Number randomised: 80 Post-randomisation dropouts: 6 (7.5%) Revised sample size: 74 Reasons for post-randomisation dropouts: lost to follow up/poor compliance (4), unwilling (2) Average age, years: 47 Females: 55 (74.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. 18 to 60 years of age. 2. NAFLD. Exclusion criteria: 1. Other liver disease. 2. Inflammatory bowel disease. 3. Malignancy. 4. Pregnancy or lactation. 5. Use of corticosteroids, amiodarone, tamoxifen, cyclines, perhexiline, methotrexate, hydralazine, laxatives, or oral contraceptives; use of vitamin-mineral, antioxidant, or omega-3 supplement Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 38) Further details: 500-mg capsule (Familact, produced by Zisttakhmir Company) containing 7 species of probiotic bacteria (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacil-*

Asgharian 2016 *(Continued)*

	lus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophilus) and fructo-oligosaccharides. Capsule ingested once daily for 8 weeks Group 2: no active intervention (n = 36) Further details: placebo capsule (containing 120 mg starch) similar in shape and appearance to symbiotic capsule. Capsule ingested once daily for 8 weeks
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 2
Notes	Source of funding (quote): "financial support and sponsorship: Food Security Research Centre, School of Nutrition and Food Science, Isfahan University of Medical sciences, Isfahan, Iran" Trial name/Trial registry number: IRCT2013122811763N15 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomly allocated to two numerically equal groups from a `double-blind, 80-person` list, using a table of random digits"
Allocation concealment (selection bias)	Low risk	Quote: "the supplements and placebo tablets will be coded as A andB in similar packets by a person that will be unaware from goals of the study (quote from protocol)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, `double-blind, placebo-controlled` clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, `double-blind, placebo-controlled` clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	Low risk	Comment: all pre-defined outcomes in the protocol published before recruitment were reported
Other bias	Low risk	Comment: no other bias noted

Ashraf 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Bangladesh Period of recruitment: not stated Number randomised: 52 Post-randomisation dropouts: not stated Revised sample size: 52 Average age, years: 46 Females: 18 (34.6%) NASH: 52 (100.0%)

Ashraf 2017 *(Continued)*

	Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Patients with fibrotic NASH Exclusion criteria: 1. Diabetes. 2. Cirrhosis Method for diagnosis of NAFLD: elastography
Interventions	Group 1: vitamin C plus other antioxidants (n = 25) Further details: Viusid (Catalysis Laboratory, Madrid, Spain) is a nutritional supplement that contains activated glycyrrhizic acid, ascorbic acid, folic acid, and zinc. Patients were given Viusid 3 sachets daily for 3 months Group 2: vitamin E (n = 27) Further details: vitamin E 800 IU daily for 3 months Additional details: both groups received lifestyle intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Askari 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50

Askari 2014 *(Continued)*

	Post-randomisation dropouts: 5 (10.0%) Revised sample size: 45 Reasons for post-randomisation dropouts: did not complete study Average age, years: 45 Females: 24 (53.3%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD diagnosis in past 6 months. 2. 20 to 65 years old. 3. ALT < 60. 4. Evidence of fatty liver in USS with score ≥ 2 Exclusion: 1. No alcohol/drug abuse. 2. No chemotherapy in previous year. 3. No incidence of other acute or chronic liver disease, cirrhosis, biliary disease, autoimmune disease, or cancer. 4. Pregnancy/Lactation. 5. Diabetes. 6. Hyperlipidaemia. 7. Hypertension requiring medication. 8. Use of vitamin E or hepatotoxic drugs in last 6 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 23) Further details: cinnamon 1500 mg daily for 12 weeks Group 2: no active intervention (n = 22) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work was financially supported by the National Nutrition and Food Technology Research Institute" Trial name/Trial registry number: IRCT201207114010N9 Attempts were made to contact study 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)	Low risk	Quote: "in order to blind the study, supplement and placebo capsules were packaged by a third person who had no involvement in the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized double blinded, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double blinded, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Babaei 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2014 to 2017 Number randomised: 30 Post-randomisation dropouts: 6 (20.0%) Revised sample size: 24 Reasons for post-randomisation dropouts: intervention: discontinued due to GI upset (1), personal reasons (2), migration (1), loss to follow-up (2) Average age, years: 39 Females: 2 (8.3%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Age 18 to 70 years. 2. Increased ALT 1.5 to 10× upper normal values. 3. BMI 18.5 to 40 Exclusion criteria: 1. Diabetes (types 1 and 2). 2. Alcohol consumption > 1 unit per day for > 10 years. 3. Use of particular drugs (fatty liver control medication, glucose-lowering drugs, cholesterol-lowering drugs, antihypertensives, vitamin E, coenzyme Q10, corticosteroids, glucocorticoids, thyroxine) within past 4 months. 4. Use of hepatotoxic drugs within past 6 months. 5. Cancer or chemotherapy within 2 years. 6. Other liver disease, renal failure, chronic pancreatitis, uncontrolled hypertension, heart failure, coronary artery disease, hypothyroidism or hyperthyroidism, Cushing's syndrome, disorders of HPA axis. 7. Pregnant or lactating women Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 13) Further details: 1 g hydroalcoholic extract of Fenugreek (*Trigonella foenum-graecum*) seed capsules daily for 3 months Group 2: no active intervention (n = 11) Further details: placebo (rice flour) capsules daily for 3 months. Placebo capsules were the same as Fenugreek placebo in colour, package, shape, and size Additional details: both groups received lifestyle intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this article was supported financially by the Vice Chancellor for Research of Shiraz University of Medical Sciences (grant number: 92-01-21-6352)" Trial name/Trial registry number: NCT02303314 ; IRCT2013102015083N1 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization was done by blocked randomization method. A computer random number generator generated the sequence of permuted blocks"
Allocation concealment (selection bias)	Low risk	Quote: "randomized, placebo-controlled, pilot, triple-blind (participants, investigator, and outcomes assessor)" Comment: although the precise method was not reported, allocation was probably concealed by use of a placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants, investigators (the nurse who measures anthropometric variables and hepatologist who perform FibroScan), and the statistician who analyzed the data were all blinded to treatment allocation until the statistical analysis was complete…placebo"

Babaei 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "participants, investigators (the nurse who measures anthropometric variables and hepatologist who perform FibroScan), and the statistician who analyzed the data were all blinded to treatment allocation until the statistical analysis was complete…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but it is not clear whether recruitment had commenced before the protocol was published; adverse events, mortality, fatty liver resolution were not reported
Other bias	Unclear risk	Comment: there were baseline differences in important prognostic factors

Bae 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: South Korea Period of recruitment: 2011 to 2012 Number randomised: 78 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 78 Average age, years: 51 Females: 24 (30.8%) NASH: not stated Diabetes mellitus: 78 (100.0%) Inclusion criteria: 1. 20 to 70 years of age. 2. Known diabetes with previous type 2 diabetes diagnosis ≥ 3 months before screening. 3. Glycated haemoglobin > 6.4% or fasting plasma glucose 130 to 300 mg/dL at screening. 4. ALT 50 to 350 IU/L at screening Exclusion criteria: 1. Alcohol > 30 g/d in men, > 20 g/d in women. 2. Viral hepatitis, cirrhosis, platelets < 150,000/mm^3, or other liver disease. 3. Thiazolidinediones for treatment of diabetes or anti-obesity drug within 1 month before screening. 4. History of malignancy or severe heart disease. 5. Pregnancy/Lactation Method for diagnosis of NAFLD: CT scan
Interventions	Group 1: amino acids (n = 39) Further details: carnitine-orotate complex (824 mg, 3 times daily) for 12 weeks Group 2: no active intervention (n = 39) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), serious adverse events (number of events), any adverse events (number of people), any adverse events (number of events) Follow-up, months: 3
Notes	Source of funding (quote): "this study was funded by Celltrion Pharm (Seoul, Korea)" Trial name/Trial registry number: KCT0000505 Attempts were made to contact study authors in December 2020

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

Bae 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "the randomization sequence was produced by an independent clinical research organization (Medical Excellence, Seoul, Korea) and was computer-generated and stratified by sites with block sizes of four"
Allocation concealment (selection bias)	Low risk	Quote: "allocation concealment was implemented by use of sequentially numbered, opaque, and sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, controlled, double-blind trial…all patients and investigators were masked to the treatment assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, controlled, double-blind trial…all patients and investigators were masked to the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were included for analysis of adverse events
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Bahrami 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 5 (10.0%) Revised sample size: 45 Reasons for post-randomisation dropouts: discontinued, travel Average age, years: 40 Females: 14 (31.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Age ≥ 18. 2. Evidence of non-alcoholic fatty liver by ultrasound (steatosis score ≥ 1) and serum levels of alanine aminotransferase > 30 U/L for men and > 19 U/L for women Exclusion criteria: 1. Autoimmune disorders. 2. Liver and biliary tract disease. 3. Cardiovascular disease. 4. Diabetes mellitus. 5. Renal disease. 6. Metabolic disease. 7. Malignancy. 8. Hypothyroidism. 9. Cushing's syndrome. 10. Alcohol abuse and use of hepatotoxic drugs such as methotrexate, tamoxifen, amiodarone, and corticosteroids. 11. Pregnancy or lactation. 12. Night shift workers. 13. History of bariatric surgery during the last year Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 24) Further details: 6 mg melatonin daily, 1 hour before bedtime (each tablet contains 3 mg melatonin), for 12 weeks Group 2: no active intervention (n = 21) Further details: participants in the placebo group received matching placebo (with same shape and colour of melatonin tablets) at the same time. Starch was the main ingredient in the placebo

Bahrami 2020 *(Continued)*

Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 2.8
Notes	Source of funding (quote): "Hyperlipidemia Research Center, Ahvaz Jundishapur University of Medical Sciences (grant number: HLRC-9503)" Trial name/Trial registry number: IRCT2016061516123N8 Attempts were made to contact study authors in April 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	Quote: "sealed envelopes were used to allocate patients to treatment or placebo groups" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts related to discontinuation of treatment; it is not clear if this was related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: outcomes specified in pre-published protocol were not reported
Other bias	Low risk	Comment: no other bias noted

Bakhshimoghaddam 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2016 to 2017 Number randomised: 68 Post-randomisation dropouts: 8 (11.8%) Revised sample size: 60 Reasons for post-randomisation dropouts: lost-to follow-up, pregnant, taking excluded medication Average age, years: 40 Females: 52 (86.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Grade 1 to 3 fatty liver. 2. ≥ 18 years old Exclusion criteria: 1. Alcohol history > 10 g/d for women, ≥ 20 g/d for men. 2. Chronic viral hepatitis, autoimmune hepatitis, PBC, Wilson's disease, other liver disease. 3. Diabetes. 4. Impaired renal function.

Bakhshimoghaddam 2018 *(Continued)*

	5. Drugs affecting glucose and lipid metabolism and medications known to increase risk of NAFLD. 6. Preganancy/Lactation Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 32) Further details: 300 g synbiotic yogurt (*Bifidobacterium animalis* for 24 weeks) Group 2: no active intervention (n = 28) Further details: no active intervention Additional details: both groups received lifestyle advice; another group not relevant to this review was excluded
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 6
Notes	Source of funding (quote): "the study, funded by the Urmia University of Medical Sciences. The West Azarbaijan Pegah Dairy Company (Urmia, Iran) supplied the synbiotic and conventional yogurts (author replies)" Trial name/Trial registry number: IRCT2017020932417N2 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization lists were computer-generated by a statistician"
Allocation concealment (selection bias)	Low risk	Quote: "sequentially numbered, opaque, and sealed envelopes were used to conceal allocation" Comment: information from study author's email reply
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the radiologist, laboratory staff, and statistician were blinded to the intervention assignment until the end of the study" Comment: it is not clear whether healthcare professionals assessing adverse events were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Barbakadze 2020

Study characteristics

Barbakadze 2020 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: Georgia Period of recruitment: not stated Number randomised: 72 Post-randomisation dropouts: not stated Revised sample size: 72 Average age, years: not stated Females: not stated NASH: 72 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Elevated aminotransferase levels. 2. Drinking < 40 g alcohol/week. 3. NASH diagnosis Exclusion criteria: 1. Drinking ≥ 40 g alcohol/week Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E plus vitamin C (n = 52) Further details: vitamin E 800 mg/d plus vitamin C 500 mg/d Group 2: no active intervention (n = 20) Further details: did not receive any medical treatment
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 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: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Barchetta 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 65 Post-randomisation dropouts: 10 (15.4%) Revised sample size: 55 Reasons for post-randomisation dropouts: discontinued treatment, including for adverse event Average age, years: 59 Females: 21 (38.2%) NASH: not stated Diabetes mellitus: 55 (100.0%) Inclusion criteria: 1. 25 to 70 years old. 2. Diagnosis of type 2 diabetes mellitus. 3. Fatty liver on USS and confirmed on MRI in patients with suspected NAFLD (raised transaminase with no other cause of chronic liver disease) Exclusion criteria: 1. History of alcohol abuse (> 30 g/d men, > 20 g/d women). 2. Cirrhosis, viral hepatitis, autoimmune hepatitis, and other causes of liver disease. 3. Advanced renal failure. 4. Cancer. 5. Hyper/Hypoparathyroidism. 6. Previous 6 months' supplementation with vitamin D, calcium, multi-vitamins, agents affecting bone and calcium/vitamin D metabolism. 7. UV radiation exposure. 8. Pregnancy/Lactation Method for diagnosis of NAFLD: ultrasound plus MRI plus transaminases
Interventions	Group 1: vitamin D (n = 26) Further details: cholecalciferol (2000 IU/d) for 24 weeks Group 2: no active intervention (n = 29) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work was funded by research grants from the Sapienza University Ateneo Scientific Research (MGC, IB) and the Italian Minister of University and Research (MGC, MGB)" Trial name/Trial registry number: 2011-003010-17 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed by the statistician following acquisition of participants' informed consent, through a computer-generated and centrally administered procedure"
Allocation concealment (selection bias)	Low risk	Quote: "randomization was performed by the statistician following acquisition of participants' informed consent, through a computer-generated and centrally administered procedure"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a randomized, double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a randomized, double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Barchetta 2016 *(Continued)*

All outcomes

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Basu 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 155 Post-randomisation dropouts: not stated Revised sample size: 155 Average age, years: not stated Females: not stated NASH: 155 (100.0%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD, NASH. 2. BMI ≥ 28 to < 33 Exclusion criteria: 1. Normal antibodies for known liver disease. 2. Diabetes. 3. Viral hepatitis. 4. Hypo/Hyperthyroidism. 5. Syndrome with known insulin resistance. 6. Alcohol > 30 g/d. 7. Use of other medication including herbs and supplements Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E plus other antioxidants (n = 40) Further details: vitamin E 700 IU plus alfa lipoic acid 300 mg daily orally for 6 months Group 2: other antioxidants (n = 40) Further details: alfa lipoic acid 300 mg daily orally for 6 months Group 3: vitamin E (n = 40) Further details: vitamin E 700 IU daily orally for 6 months Group 4: no active intervention (n = 35) Further details: no intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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)	High risk	Quote: "open label"

Basu 2012 *(Continued)*

All outcomes		
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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Basu 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 60 Post-randomisation dropouts: not stated Revised sample size: 60 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Alcohol < 30 g/d Exclusion criteria: 1. HIV. 2. Medications causing fatty liver including herbal supplements. 3.Lipodystrophy. 4. Overt diabetes mellitus. 5. Pregnancy. 5. Hypersensitivity to study medications Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E plus other supplements (n = 20) Further details: vitamin E plus curcumin (no further details available, probably for 12 months) Group 2: vitamin E (n = 20) Further details: vitamin E (no further details available, probably for 12 months) Group 3: other supplements (n = 20) Further details: curcumin (no further details available, probably for 12 months) Additional details: another group not relevant to this review was excluded
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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

Basu 2013 *(Continued)*

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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Behrouz 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 111 Post-randomisation dropouts: 22 (19.8%) Revised sample size: 89 Reasons for post-randomisation dropouts: non-compliance (1), lost to follow-up (14), withdrew (1), travel (3), refused to give blood (2), pregnant (1) Average age, years: 38 Females: 26 (29.2%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. BMI 25 to 40. 2. 20 to 60 years old. 3. NAFLD diagnosis based on ALT > 1.5× upper limit and steatosis on USS > grade 2 Exclusion criteria: 1. Pregnancy/Lactation. 2. Consumption of omega-3 fatty acids and nutritional supplements in previous year. 3. Other acute and chronic liver disease, cirrhosis. 4. Coeliac disease. 5. Diabetes. 6. Hypertension, cardiovascular disease, kidney disease, or lung disease. 7. Alcohol abuse. 8. Antibiotic use over 1 week during the study. 9. Contraceptive pill, corticosteroid, NSAID, another drug. 9. Significant changes in recommended diet and daily physical activity Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 59) Further details: 1 Webber Naturals capsule (probiotic containing *Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium longum*, *Bifidobacterium breve*) or ORAFTI P95 (oligofructose) 16 g/d (prebiotic group) for 12 weeks Group 2: no active intervention (n = 30) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	No outcomes of interest were reported

Behrouz 2017 *(Continued)*

Notes	Source of funding (quote): "the present study was supported by a grant from Vice Chancellor for Research, Iran University of Medical Sciences, Tehran, Iran (no. 24996)" Trial name/Trial registry number: IRCT201410052394N13 Attempts were made to contact study 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	Low risk	Quote: "double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Bomhof 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Canada Period of recruitment: not stated Number randomised: 14 Post-randomisation dropouts: 1 (7.1%) Revised sample size: 13 Reasons for post-randomisation dropouts: inadequate liver biopsy Average age, years: 49 Females: 6 (46.2%) NASH: 13 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Liver biopsy-confirmed NASH (NAS ≥ 5). 2. ≥ 18 years old. 3. BMI > 25 (Caucasians), ≥ 23 (Asians). 4. Serum ALT ≥ 1.5 upper limit normal. 5. No changes to lipid-lowering or diabetic medication in last 3 months Exclusion criteria: 1. Alcohol > 20 g/d women, > 30 g/d men. 2. Alternate aetiology for liver disease. 3. Use of orlistat, liraglutide, prebiotic, probiotic, antibiotic in last 3 months Method for diagnosis of NAFLD: ultrasound plus transaminases

Bomhof 2018 *(Continued)*

Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 8) Further details: oligofructose (prebiotic 8 g/d for 12 weeks followed by 16 g/d for 24 weeks) Group 2: no active intervention (n = 5) Further details: placebo
Outcomes	Outcomes reported: NAFLD activity score Follow-up, months: 8
Notes	Source of funding (quote): "MRB was supported by Alberta Innovates Health Solutions (AIHS)" Trial name/Trial registry number: NCT03184376 Attempts were made to contact study 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)	Low risk	Quote: "participants were randomly assigned to one of two groups by a senior study investigator not involved in recruiting participants"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "placebo-controlled, randomized pilot trial…participants were blinded to the treatment allocation" Comment: it is not clear whether investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "placebo-controlled, randomized pilot trial…participants were blinded to the treatment allocation" Comment: it is not clear whether investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 participant was excluded because of inadequate liver biopsy; this is unlikely to be related to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Bonfrate 2015

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: not stated Revised sample size: 40 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD and metabolic abnormalities

Bonfrate 2015 *(Continued)*

	Exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E plus other antioxidants (n = not stated) Further details: Eurosil 85 complex (silybin-vit E complex) for 6 months Group 2: no active intervention (n = not stated) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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	Low risk	Quote: "double-blind randomized placebo-controlled clinical study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized placebo-controlled clinical study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Boonyagard 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Thailand Period of recruitment: 2015 Number randomised: 60 Post-randomisation dropouts: not stated Revised sample size: 60 Average age, years: not stated Females: not stated NASH: not stated

Boonyagard 2016 *(Continued)*

	Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD and vitamin D deficiency Exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin D (n = 30) Further details: vitamin D for 20 weeks (no further details) Group 2: no active intervention (n = 30) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Boonyagard 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Thailand Period of recruitment: 2015 to 2018 Number randomised: 63 Post-randomisation dropouts: 3 (4.8%) Revised sample size: 60 Reasons for post-randomisation dropouts: did not receive the intervention

Boonyagard 2020 *(Continued)*

	Average age, years: 54 Females: 31 (51.7%) NASH: not stated Diabetes mellitus: 24 (40.0%) Inclusion criteria: 1. Diagnosed NAFLD by ultrasonography. 2. Increased levels of alanine transaminase (ALT). 3. Serum vitamin D level < 30 ng/mL Exclusion criteria: 1. Alcohol consumption > 14 drinks/week in women, > 21 drinks/week in men. 2. Pregnancy and nursing. 3. Known hepatic disease such as hereditary haemochromatosis, Wilson's disease, and α1-antitrypsin deficiency. 4. History of jejunoileal bypass surgery or gastroplasty. 5. Using total parenteral nutrition in the past 6 months. 6. Taking potential hepatotoxic drugs such as high doses of synthetic oestrogens, methotrexate, amiodarone, or chloroquine. 7. History of hypothyroidism, Cushing's syndrome, renal failure, or kidney stones. 8. Serum calcium levels > 10.6 mg/dL and use of vitamin D, vitamin E, and calcium supplements during the last 6 months Method for diagnosis of NAFLD: ultrasonography and transaminases
Interventions	Group 1: vitamin D (n = 30) Further details: 40,000 IU vitamin D2 weekly for 5 months Group 2: no active intervention (n = 30) Further details: placebo
Outcomes	Outcomes reported: mortality, adverse events, liver transplantation, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma Follow-up, months: 5
Notes	Source of funding (quote): "we would like to thank Faculty of Medicine and Vajira Hospital, Navamindradhiraj University Research Fund for the funding support" Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "randomization and allocation were concealed from the researchers and participants until the statistical analysis was completed…placebo" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomization and allocation were concealed from the researchers and participants until the statistical analysis was completed…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomization and allocation were concealed from the researchers and participants until the statistical analysis was completed…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether these could be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Boyraz 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Turkey Period of recruitment: 2010 to 2012 Number randomised: 138 Post-randomisation dropouts: 30 (21.7%) Revised sample size: 108 Reasons for post-randomisation dropouts: did not complete the protocol Average age, years: 14 Females: 53 (49.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. BMI > 95th percentile for age and sex. 2. Persistently elevated serum aminotransferase levels. 3. Diffusely echogenic liver in imaging studies suggestive of fatty liver Exclusion criteria: 1. Viral hepatitis. 2. Alcohol consumption. 3. History of parenteral nutrition. 4. Use of drugs known to induce steatosis Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: PUFA (n = 56) Further details: Marincap (n3-PUFA) once daily for 12 months Group 2: no active intervention (n = 52) Further details: placebo Additional details: both groups received lifestyle intervention and advice (scheduled exercise and calorie restriction advice)
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "we had no source of funding" Trial name/Trial registry number: not stated Attempts were made to contact study 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: "double-blind…the radiologist was blinded to all clinical and biochemical characteristics of the subjects" Comment: although states double-blind, it appears that only outcome assessors were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind…the radiologist was blinded to all clinical and biochemical characteristics of the subjects" Comment: there were no clinical outcomes reported in this trial; therefore, radiologist blinding indicates outcome assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Boyraz 2015 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Bril 2019

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2010 to 2016 Number randomised: 68 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 68 Average age, years: 59 Females: 5 (7.4%) NASH: 68 (100.0%) Diabetes mellitus: 68 (100.0%) Inclusion criteria: 1. Diagnosis of type 2 diabetes mellitus. 2. Histologically confirmed NASH Exclusion criteria: 1. Other cause of chronic liver disease (e.g. viral hepatitis). 2. Alcohol abuse. 3. Type 1 diabetes mellitus. 4. Total parenteral nutrition within past 6 months. 5. Hepatotoxic drugs. 6. Severe osteoporosis Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E (n = 36) Further details: vitamin E 400 IU orally twice daily for 18 months Group 2: no active intervention (n = 32) Further details: placebo Additional details: both groups received lifestyle intervention; another group not relevant to this review was excluded
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), serious adverse events (number of events), any adverse events (number of events), fibrosis score Follow-up, months: 18
Notes	Source of funding (quote): "this work was supported by a U.S. Department of Veterans Affairs Merit Award" Trial name/Trial registry number: NCT01002547 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the computer-generated randomization and patient allocation were performed by the research pharmacist without any stratification and using a block factor of 4, which was unknown to investigators"
Allocation concealment (selection bias)	Low risk	Quote: "the computer-generated randomization and patient allocation were performed by the research pharmacist without any stratification and using a block factor of 4, which was unknown to investigators"

Bril 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Byrne 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: United Kingdom Period of recruitment: not stated Number randomised: 103 Post-randomisation dropouts: not stated Revised sample size: 103 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: PUFA (n = 51) Further details: Omacor (4 g/d) (n-3 fatty acid containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) for 15 to 18 months Group 2: no active intervention (n = 52) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "supported by: NIHR; Diabetes UK" Trial name/Trial registry number: not stated Attempts were made to contact study 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

Byrne 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomised double blind placebo controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomised double blind placebo controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Cai 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2017 to 2019 Number randomised: 140 Post-randomisation dropouts: not stated Revised sample size: 140 Average age, years: 48 Females: 55 (39.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. With or without abnormal indexes of liver function. 2. Diffuse fatty liver detected on ultrasound and NAFLD confirmed by ultrasound-guided biopsy. 3. Aged between 18 and 59 Exclusion criteria: 1. Other liver disease with definite aetiology, such as viral hepatitis. 2. Liver fibrosis or cirrhosis. 3. Use of drugs for weight loss, regulating glucose, lipid metabolism, or intestinal flora, and antibiotics in the past 3 months. 4. Autoimmune disease or other severely chronic co-morbidities. 5. Shedding criteria: could not tolerate diet and exercise therapy; failure to co-operate during intervention treatment as required; occurrence of other disease during intervention or follow-up Method for diagnosis of NAFLD: ultrasound and biopsy
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 70) Further details: live combined *Bifidobacterium, Lactobacillus,* and *Enterococcus* powder (Bifid Triple Viable) was given orally, 2 g/d Group 2: no active intervention (n = 70) Further details: no treatment Additional details: both groups received lifestyle modification intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated

Cai 2020 *(Continued)*

	Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random numbers table
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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Celinski 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Poland Period of recruitment: not stated Number randomised: 74 Post-randomisation dropouts: not stated Revised sample size: 74 Average age, years: 33 Females: 51 (68.9%) NASH: 18 (24.3%) Diabetes mellitus: 34 (45.9%) Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: amino acids plus PUFA (n = 51) Further details: tryptophan 1000 mg/d or melatonin 10 mg/d plus Essentiale forte (major component is PUFA) 3 tablets/d for 14 months Group 2: PUFA (n = 23) Further details: Essentiale forte (PUFA) 3 tablets/d for 14 months
Outcomes	No outcomes of interest were reported

Celinski 2014 *(Continued)*

Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Cerletti 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2015 to 2016 Number randomised: 126 Post-randomisation dropouts: 13 (10.3%) Revised sample size: 113 Reasons for post-randomisation dropouts: bone fracture (1), relocation (1), discontinued supplementation due to dermatitis (1), discontinued supplementation for faecal colour abnormality (green faeces) (1), unmotivated personal decision (9) Average age, years: 55 Females: 39 (34.5%) NASH: not stated Diabetes mellitus: 27 (23.9%) Inclusion criteria: 1. 18 to 80 years of age. 2. Mild or moderate hepatic steatosis on USS. 3. At least 1 of serum ALT/AST/GGT levels higher than normal Exclusion criteria: 1. Alcohol abuse history (> 210 g/week in men, > 140 g/week in women). 2. Drugs associated with hepatic steatosis. 3. Malnutrition. 4. Other liver disease. 5. Severe renal, cardiac, or respiratory failure. 6. Malignancy. 7. Intolerance to formulation. 8. Pregnancy, lactation Method for diagnosis of NAFLD: ultrasound plus transaminases

Cerletti 2020 *(Continued)*

Interventions	Group 1: control (n = 58) Further details: 2 capsules of control mixture once a day for 3 months. Comparator capsules (control) contained formulation excipients and the same amount of choline present in the active mixture (in the form of bitartrate salt) Group 2: other supplements (n = 55) Further details: 2 capsules of nutraceutical mixture once a day for 3 months. Study product was a mixture of active ingredients, formulated as soft gel capsules, each composed of fish oil containing 70% DHA (250 mg), phosphatidylcholine concentrated in sunflower oil (150 mg), silymarin (75 mg), choline bitartrate (35 mg), curcumin (35 mg), and D-α-tocopherol (10 mg), for a total of 830 mg. Total content of choline is 21.5 mg per capsule (43 mg/d) Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: any adverse events (number of people) Follow-up, months: 3
Notes	Source of funding (quote): "the present study was supported by the Italian Ministry of University and Research (MIUR, PON01_01226/1 - Decr. N.l/ Ric 18-1-2010)" Trial name/Trial registry number: NCT02369536 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the random allocation sequence to treatment was computer based per blocks of four or six subjects stratified for each recruiting centre; it was generated by the principal investigator (PI)'s statistician and forwarded to each recruitment centre"
Allocation concealment (selection bias)	Low risk	Quote: "the random allocation sequence was generated by the principal investigator (PI)'s statistician and forwarded to each recruitment centre. The doctor responsible for each recruitment centre enrolled participants and assigned them to interventions, according to the allocation sequence received by the PI of the trial"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomised, multicentre controlled trial…active and control capsules were identical for organoleptic properties and coded as A and B by the producer"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomised, multicentre controlled trial…active and control capsules were identical for organoleptic properties and coded as A and B by the producer"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	Low risk	Comment: all pre-defined outcomes in the protocol published before recruitment were reported
Other bias	Low risk	Comment: no other bias noted

Chachay 2014

Study characteristics

Chachay 2014 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: Australia Period of recruitment: 2011 to 2012 Number randomised: 20 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 20 Average age, years: 48 Females: 0 (0.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Male. 2. BMI > 25. 3. Waist circumference > 90 cm. 4. Hepatic steatosis on USS Exclusion: 1. Any known cause of steatosis (e.g. viral hepatitis). 2. Alcohol > 40 g/d. 3. Use of steatogenic medication. 4. Cirrhosis. 5. Type 2 diabetes mellitus. 6. History of chronic kidney disease or serious cardiovascular disorder Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 10) Further details: resveratrol 3000 mg daily for 8 weeks Group 2: no active intervention (n = 10) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 2
Notes	Source of funding: not stated Trial name/Trial registry number: ACTRN12612001135808 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "randomized, double-blind, placebo-controlled trial…participants and investigating staff were blinded to the randomization until completion of results analyses" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately

Chachay 2014 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Chan 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Malaysia Period of recruitment: 2012 to 2014 Number randomised: 99 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 99 Average age, years: 50 Females: 53 (53.5%) NASH: 99 (100.0%) Diabetes mellitus: 53 (53.5%) Inclusion criteria: 1. > 18 years old. 2. Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels ≥ 40 IU/L Exclusion criteria: 1. Cirrhosis. 2. Significant alcohol intake. 3. Medications causing hepatic steatosis. 4. Viral hepatitis or other cause of chronic liver disease. 5. Use of silymarin or other milk-thistle preparations, vitamin C, vitamin E, glutathione, alpha-tocopherol, or non-prescribed complementary alternative medications within the past 30 days Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: other antioxidants (n = 49) Further details: Silymarin 700 mg, 3 times daily, for 48 weeks Group 2: no active intervention (n = 50) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma, fibrosis score, NAFLD activity score Follow-up, months: 11
Notes	Source of funding (quote): "this study was funded by the University of Malaya Research Grant (Project Number: RG536-13HTM) and Meda Group" Trial name/Trial registry number: NCT02006498 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated table of random numbers was utilized"
Allocation concealment (selection bias)	Low risk	Quote: "the numbers were kept centrally at this institution's Clinical Investigation Center and released to a research assistant only after a subject was recruited into the study"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "randomized, double-blind, placebo-controlled study"

Chan 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Chande 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Canada Period of recruitment: 2003 to 2004 Number randomised: 8 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 8 Average age, years: 53 Females: 5 (62.5%) NASH: 8 (100.0%) Diabetes mellitus: 4 (50.0%) Inclusion criteria: 1. 18 to 75 years of age. 2. Minimum of 3 months elevated AST/ALT. 3. < 20 g alcohol/week. 4. Biopsy-proven NASH Exclusion criteria: 1. Other liver, gastrointestinal, renal, cardiovascular, neurological, or haematological disease or psychiatric disorder. 2. Pregnancy, breastfeeding, or lack of birth control. 3. Use of herbal/dietary supplements other than multi-vitamin/mineral formulations. 4. Any change in medication within 4 weeks. 5. Participation in clinical trial within 6 weeks Method for diagnosis of NAFLD: liver biopsy plus transaminases
Interventions	Group 1: other supplements (n = 5) Further details: YHK (500 mg 3 times daily) for 8 weeks. Yo Jyo Hen Shi Ko (YHK; Kyotsu Jigyo, Inc., Japan), which is derived from *Panax pseudoginseng*, *Eucommia ulmoides*, *Polygonati rhizoma*, and *Glycyrrhiza glabra* Group 2: no active intervention (n = 3) Further details: identical placebo for 8 weeks
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events), any adverse events (number of events), quality of life (maximal follow-up) Follow-up, months: 3
Notes	Source of funding (quote): "this study was funded by Kyotsu Jigyo, Inc., Japan" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020
Risk of bias	

Chande 2006 *(Continued)*

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: "masking: the YHK or identical placebo was prepackaged and coded prior to delivery to our research office, to ensure complete double-blinding of the study coordinator, investigators, and patients. The blinding code was not broken until all patients had completed the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Chen 2008

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 46 Post-randomisation dropouts: not stated Revised sample size: 46 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: clinical examination plus transaminases
Interventions	Group 1: PUFA (n = 30) Further details: omega-3 polyunsaturated fatty acid capsule (sea seal oil 4 g/d or 5 g/d decided randomly) for 24 weeks Group 2: no active intervention (n = 16) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated

Chen 2008 *(Continued)*

	Attempts were made to contact study 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	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Chen 2015a

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2012 to 2013 Number randomised: 60 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 60 Average age, years: 44 Females: 18 (30.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 20 to 60 years old. 2. 'Bright liver' on USS. 3. BMI 30:30. 4. Fasting blood glucose < 7.8 Exclusion criteria: 1. Known aetiology of chronic liver disease. 2. Liver/kidney dysfunction. 3. Malignant tumour. 4. Alcohol > 140 g/week male, > 70 g/week female. 5. Any medication over last 6 months altering glucose and lipid metabolism Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 30) Further details: resveratrol 300 mg twice daily for 3 months Group 2: no active intervention (n = 30) Further details: placebo

Chen 2015a *(Continued)*

Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 3
Notes	Source of funding (quote): "this study was supported by the National Natural Science Foundation of China (No. 30972469; No. 81273059), the Science and Technology Key Project Foundation of Chongqing (No. CSTC, 2011AB5040), and the National Science-Technology Support Plan Projects Foundation of China (No. 2012BAI35B02)" Trial name/Trial registry number: CHICTR-TRC12002378 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "an independent investigator determined whether a patient would be treated with either placebo or resveratrol according to a computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Quote: "an independent investigator determined whether a patient would be treated with either placebo or resveratrol according to a computer-generated randomization list"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Chen 2015b

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2012 to 2013 Number randomised: 60 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 60 Average age, years: 45 Females: 20 (33.3%) NASH: not stated Diabetes mellitus: 0 (0.0%)

Chen 2015b *(Continued)*

	Inclusion criteria: 1. 20 to 60 years. 2. 20 < BMI < 30. 3. Fasting blood glucose < 7.8. 4. No weight gain or loss over last 3 months. 5. No medical therapy Exclusion criteria: 1. Excessive alcohol. 2. Other liver disease. 3. Any medication that would influence glucose or lipid metabolism in the last 6 months. 4. Liver or kidney dysfunction. 5. Malignant tumour Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other antioxidants (n = 30) Further details: dihydromyricetin (DHM) 600 mg/d for 12 weeks. DHM capsules also contained pullulan and maltodextrin Group 2: no active intervention (n = 30) Further details: placebo capsules (containing only pullulan and maltodextrin) daily for 12 weeks. Placebo and DHM capsules were identically packaged Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of events), resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "this study was supported by the National Natural Science Foundation of China (No. 30972469; No. 81273059), the Science and Technology Key Project Foundation of Chongqing (No. CSTC, 2011AB5040), and the National Science-technology Support Plan Projects Foundation of China (No. 2012BAI35B02)" Trial name/Trial registry number: ChiCTR-TRC-12002377 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "an investigator who was not involved in the trial used Excel's random number generator to generate a number that would determine whether a patient would be treated with placebo or DHM"
Allocation concealment (selection bias)	Low risk	Quote: "an investigator who was not involved in the trial used Excel's random number generator to generate a number that would determine whether a patient would be treated with placebo or DHM. The placebo and DHM capsules were identically packaged"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Cheraghpour 2019

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2017 to 2018 Number randomised: 50 Post-randomisation dropouts: 1 (2.0%) Revised sample size: 49 Reasons for post-randomisation dropouts: discontinued study for personal reasons Average age, years: 47 Females: 25 (51.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 18 to 70 years. 2. CAP > 261 (≥ grade 2) on FibroScan Exclusion criteria: 1. Excessive alcohol consumption (> 10 g/d). 2. Liver cirrhosis, renal disease, cardiovascular disease, cancer, or diabetes. 3. Use of vitamin E, betaine, pioglitazone, rosiglitazone, pentoxifylline, or gemfibrozil. 4. Weight loss or bariatric surgery within past 6 months. 5. Pregnancy or breastfeeding Method for diagnosis of NAFLD: elastography
Interventions	Group 1: other antioxidants (n = 25) Further details: oral administration of 2 capsules of Hesperidin (each contains 500 mg) for 12 weeks Group 2: no active intervention (n = 24) Further details: 2 placebo (starch) capsules for 12 weeks. Capsules were similar in size and colour to intervention Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 3
Notes	Source of funding (quote): "no funding has been received for this research (author replies)" Trial name/Trial registry number: NCT03377140 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization lists were computer generated by a statistician and given to the interviewer"
Allocation concealment (selection bias)	Low risk	Quote: "an investigator who had no clinical involvement in the trial numbered bottles containing supplements and placebos and assigned the participants to the trial groups in accordance with the randomization list"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "subjects, investigators, and staff were blind to the treatment assignment until the end of the study…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "subjects, investigators, and staff were blind to the treatment assignment until the end of the study…placebo"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes

Cheraghpour 2019 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Unclear risk	Comment: there were baseline differences in important prognostic factors

Chiou 2021

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: 2015 to 2016 Number randomised: 42 Post-randomisation dropouts: 14 (33.3%) Revised sample size: 28 Reasons for post-randomisation dropouts: loss to follow-up or discontinued intervention Average age, years: 46 Females: 13 (46.4%) NASH: 28 (100%) Diabetes mellitus: not stated Inclusion criteria: 1. Adult human participants with NASH Exclusion criteria: 1. Patients with other forms of liver disease such as active hepatitis A, active hepatitis B, cirrhosis, hepatocellular carcinoma, haemochromatosis, anaemia, and alcoholic liver disease Method for diagnosis of NAFLD: not stated
Interventions	Group 1: other supplements (n = 15) Further details: participants were treated with 3 capsules per day containing 420 mg *Antrodia cinnamomea* Mycelium for 6 months Group 2: no active intervention (n = 24) Further details: participants received matching placebo capsules daily for 6 months Additional details: both groups received lifestyle modification
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the study was supported by the cooperative research projects of Hungkuang University and Kuang-Tien General Hospital (HK-102147)" Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 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	Low risk	Quote: "double-blind, placebo-controlled'

Chiou 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled'
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts, which probably were related to intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was not available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Chongsrisawat 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Thailand Period of recruitment: 2016 Number randomised: 37 Post-randomisation dropouts: not stated Revised sample size: 37 Average age, years: not stated Females: 12 (32.4%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Children with NAFLD Exclusion criteria: not stated Method for diagnosis of NAFLD: FibroScan
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 18) Further details: chicory inulin, *Lactobacillus acidophilus*, and *Bifidobacterium lactis* for 16 weeks Group 2: no active intervention (n = 19) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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)	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"

Chongsrisawat 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Chou 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: 2001 to 2002 Number randomised: 60 Post-randomisation dropouts: 4 (6.7%) Revised sample size: 56 Reasons for post-randomisation dropouts: withdrawal before trial medicine treatment began (i.e. within first 2 months) because patients could not make scheduled visits Average age, years: 43 Females: 4 (7.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. 20 years or over. 2. Fatty liver on USS. 3. Increased ALT > 36 or AST > 34 U/L Exclusion criteria: 1. Major cardiovascular disease. 2. Other liver disease. 3. Hypothyroidism. 4. Nephrotic syndrome. 5. Cushing's syndrome. 6. Use of medications such as diuretics, oestrogen, steroids, hyperglycaemia requiring oral hypoglycaemic agent or insulin, cancer treatment. 7. Pregnancy or lactation. 8. Immunosuppression Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 28) Further details: 80 mL *Gynostemma pentaphyllum* (GP) extraction taken 3 times daily after meals for 4 months Group 2: no active intervention (n = 28) Further details: placebo capsule with corn starch (500 mg) taken 3 times daily after meals for 4 months Additional details: both groups received lifestyle intervention
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events) Follow-up, months: 6
Notes	Source of funding (quote): "the authors would like to thank Chang Gung Memorial Hospital for its financial support (CMRP 841)" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020
Risk of bias	

Chou 2006 *(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	Quote: "a randomized, single-blind, controlled clinical trial. Although the GP bags and placebo capsules were different in appearance, the research subjects did not know whether they were taking GP or the placebo" Comment: only participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "a randomized, single-blind, controlled clinical trial. Although the GP bags and placebo capsules were different in appearance, the research subjects did not know whether they were taking GP or the placebo" Comment: only participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Climax 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2016 to 2019 Number randomised: 96 Post-randomisation dropouts: 3 (3.1%) Revised sample size: 93 Reasons for post-randomisation dropouts: not stated Average age, years: 48 Females: 31 (33.3%) NASH: not stated Diabetes mellitus: 25 (26.9%) Inclusion criteria: 1. Age 18 to 75 years. 2. NAFLD based on the presence of hepatic steatosis on imaging or histology in the absence of secondary causes. 3. BMI between 25.0 and 40.0 kg/m^2. 4. ALT ≥ 1.5 times the upper limit of normal and < 5 times the upper limit of normal Exclusion criteria: 1. Weight change > 5% in the 3 months before screening. 2. History of gastric bypass surgery. 3. History of or scheduled orthotopic liver transplant. 4. Haemoglobin A1C (HbA1c) ≥ 9%. 5. Decompensated or severe liver disease. 6. Requiring antihyperglycaemic treatment or lipid-lowering treatment and not on a stable dose for at least 3 months before screening. 7. Use of dietary supplements containing n-3 or n-6 fatty acids in the 4 weeks before baseline Method for diagnosis of NAFLD: imaging or histology and transaminases
Interventions	Group 1: PUFA (n = 63) Further details: Epeleuton (15-hydroxy eicosapentaenoic acid) 2 g/d or 1 g/d Group 2: no active intervention (n = 30)

Climax 2020 *(Continued)*

	Further details: placebo (light liquid paraffin) twice daily
Outcomes	Outcomes reported: adverse events (number of people) Follow-up, months: 4
Notes	Source of funding (quote): "this work was supported by Afimmune. Afimmune was involved in the design and conduct of the trial, collection, analysis, and interpretation of data; and preparation of this manuscript" Trial name/Trial registry number: NCT02941549 Attempts were made to contact study authors in April 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	Low risk	Quote: "double blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether these could be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: all pre-defined outcomes in the protocol published before recruitment were reported
Other bias	Low risk	Comment: no other bias noted

Dabbaghmanesh 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2011 to 2013 Number randomised: 106 Post-randomisation dropouts: 15 (14.2%) Revised sample size: 91 Reasons for post-randomisation dropouts: lost-to-follow-up (8), did not follow study protocol or discontinued drugs due to side effects (7) Average age, years: 45 Females: 54 (59.3%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 20 to 75 years old. 2. Hepatic steatosis on USS. 3. Vitamin D < 30 ng/mL

Dabbaghmanesh 2018 *(Continued)*

	Exclusion criteria: 1. Cirrhosis. 2. Viral hepatitis. 3. Alcohol > 10 g/d. 4. Other causes of chronic liver disease. 5. Cancer. 6. Hypercalciuria. 7. Pregnancy/Lactation. 8. Hypersensitivity to D3. 9. Use of oestrogen, tamoxifen, methotrexate, amiodarone, tetracycline, vitamin D, and calcium supplementation in last 6 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin D (n = 59) Further details: 50,000 U vitamin D3 (cholecalciferol) pearl per week or 0.25 mg calcitriol (1,25 dihydroxycholecalciferol) pearl per day for 12 weeks Group 2: no active intervention (n = 32) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this study was supported by a research grant from Shiraz University of Medical Sciences, Shiraz, Iran" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer based procedure"
Allocation concealment (selection bias)	Low risk	Quote: "treatments and placebo were provided in identical packages and were given to the participants by an educated person who was blinded to the drug and patients"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind, randomized, placebo controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind, randomized, placebo controlled trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: participants were excluded from analysis for reasons that are likely to be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Dallio 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated

Dallio 2020 *(Continued)*

	Number randomised: 90 Post-randomisation dropouts: not stated Revised sample size: 90 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin D plus vitamin E plus other antioxidants (n = 60) Further details: silybin with vitamin D and vitamin E (RealSIL 100D) Group 2: no active intervention (n = 30) Further details: not treated
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 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: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Daneshi-Maskooni 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran

Daneshi-Maskooni 2018 *(Continued)*

	Period of recruitment: 2016 to 2017 Number randomised: 92 Post-randomisation dropouts: 5 (5.4%) Revised sample size: 87 Reasons for post-randomisation dropouts: lost to follow-up, discontinued intervention Average age, years: 45 Females: 33 (37.9%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Age 30 to 60 years. 2. BMI 25 to 35 Exclusion criteria: 1. Alcohol use in past 12 months. 2. Other liver conditions. 3. Uncontrolled hypertension. 4. Pregnancy or lactation. 5. Professional athlete. 6. Use of ursodeoxycholic acid, probiotics, statins, and antihypertensives. 7. Antioxidant and vitamin supplements within past 3 months. 8. Weight loss over past 3 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 43) Further details: cardamom 1000 mg 3 times daily for 3 months Group 2: no active intervention (n = 44) Further details: placebo
Outcomes	Outcomes reported: any adverse events (number of people) Follow-up, months: 3
Notes	Source of funding (quote): "funding was supported by the Tehran University of Medical Sciences (Code: 30123-161-03-94)" Trial name/Trial registry number: IRCT2015121317254N4 Attempts were made to contact study 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)	Low risk	Quote: "both the subjects and investigators were blinded to the intervention allocation" Comment: although the precise method was not reported, allocation was probably concealed by use of a placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomized placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published: neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Dasarathy 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 37 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 37 Average age, years: 51 Females: 29 (78.4%) NASH: 37 (100.0%) Diabetes mellitus: 37 (100.0%) Inclusion criteria: 1. Established diagnosis of NASH. 2. NAFLD activity score ≥ 4 on biopsy performed within 6 months of entry into the study. 3. Adult patient. 4. Diabetic patient with at least moderate control of blood sugar (HbA1c < 8.5%) and stable antidiabetes regimen > 4 months Exclusion criteria: 1. Other liver disease. 2. Cirrhosis. 3. Alcohol > 30 g for males, > 20 g/d for females. 4. End-stage organ disease associated with diabetes or heart failure NYHA II to IV. Use of fish oil supplement in last 6 months. 5. Use of medication causing steatosis (i.e. vitamin E, thiazolidinedione, S-adenosyl methionine) Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: PUFA (n = 18) Further details: n3 fatty acid containing eicosapentaenoic acid 2160 mg and docosahexaenoic acid 1440 mg daily for 48 weeks Group 2: no active intervention (n = 19) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, fibrosis score, NAFLD activity score Follow-up, months: 11
Notes	Source of funding (quote): "research funding for the study was provided by the National Institutes of Health: U01061732 DK83414, CTSC grant, UL1TR000439. Douglas Laboratories and their Vice President Andrew Hoelpner assisted with providing the PUFA and placebo in a masked manner" Trial name/Trial registry number: NCT00323414 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized by the sealed envelope technique using a random numbers table"
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomized by the sealed envelope technique using a random numbers table" Comment: additional information about sealed envelope technique was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind randomized placebo controlled clinical trial"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double blind randomized placebo controlled clinical trial"

Dasarathy 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Della Corte 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: not stated Revised sample size: 40 Average age, years: 11 Females: 17 (42.5%) NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = not stated) Further details: glucomannan-enriched biscuits 5 g/d for 6 months Group 2: no active intervention (n = not stated) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT01553500 Attempts were made to contact study 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	Low risk	Quote: "masking: triple (participant, care provider, investigator) (Trial Registry information)"

Della Corte 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "masking: triple (participant, care provider, investigator) (Trial Registry information)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Della Corte 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2014 to 2015 Number randomised: 43 Post-randomisation dropouts: 2 (4.7%) Revised sample size: 41 Reasons for post-randomisation dropouts: refused end-of-study biopsy Average age, years: 13 Females: 23 (56.1%) NASH: 14 (34.1%) Diabetes mellitus: not stated Inclusion criteria: 1. 4 to 16 years old. 2. Liver biopsy consistent with NAFLD/NASH. 3. Decreased vitamin D levels < 20 ng/mL. 4. ALT < 10× upper limit of normal. 5. No lab/clinical signs of liver decompensation Exclusion: 1. Other causes of liver disease Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: PUFA plus vitamin D (n = 18) Further details: n3 fatty acid docosahexanoic acid (DHA) (500 mg) plus vitamin D (800 IU) for 24 weeks Group 2: no active intervention (n = 23) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT02098317 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated randomization sequence assigned participants in a 1:1 ratio to treatment with Vitamin D plus DHA (Treatment arm) or placebo (Placebo arm) (source: trial registry)"

Della Corte 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "a statistician, who was blinded to participants' clinical data and did not participate in patients' clinical care, generated the allocation sequence and assigned participants to their group (source: trial registry)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Deng 2005

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 96 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 96 Average age, years: 48 Females: 40 (41.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Diagnosis of NAFLD. 2. No bibulous history Exclusion criteria: 1. Hypertension, coronary heart disease, diabetes mellitus, other liver disease, or genetic disease. 2. Total parenteral nutrition Method for diagnosis of NAFLD: liver imaging and transaminases
Interventions	Group 1: other antioxidants (n = 48) Further details: silymarin 600 mg daily for 3 months Group 2: other supplements (n = 48) Further details: gankangyin (GKY) orally administered, 60 mL daily, for 3 months. GKY is a Chinese preparation composed of 8 traditional Chinese drugs, including cudweed 30 g, mung bean 25 g, bupleurum root 12 g, pinellia tuber 10 g, rhubarb root 3 g, laminaria 20 g, grossy privet fruit 20 g, *Gynostemma pentaphyllum* 30 g, with approximately fresh crude drugs 1.5 g per mL
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Deng 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized number derived by NDST software developed by Prof. Sun Rui-yuan"
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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Dufour 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Switzerland Period of recruitment: 1999 to 2002 Number randomised: 33 Post-randomisation dropouts: 12 (36.4%) Revised sample size: 21 Reasons for post-randomisation dropouts: non-compliant, personal reason, lost to follow-up, did not have follow-up liver biopsy Average age, years: 46 Females: 10 (47.6%) NASH: 27 (128.6%) Diabetes mellitus: 8 (38.1%) Inclusion criteria: 1. 18 to 75 years old. 2. Persistent ALT > 1.5 upper limit of normal for 6 months. 3. Alcohol < 40 g. 4. Liver biopsy < 6 months before enrolment with macrovesicular steatosis with > 10% of hepatocytes, hepatocellular injury, and lobular inflammation Exclusion criteria: 1. Other causes of chronic liver disease, decompensation, or cirrhosis. 2. Pregnancy/Lactation. 3. Drug inducing NASH. 4. Use of oral anticoagulation. Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E (n = 10) Further details: vitamin E 400 IU twice daily for 2 years Group 2: no active intervention (n = 11) Further details: placebo

Dufour 2006 *(Continued)*

Outcomes	Outcomes reported: fibrosis score, NAFLD activity score Follow-up, months: 24
Notes	Source of funding (quote): "tablets containing vitamin E (natural d-tocopherol) 400 IU and placebo tablets were provided by Antistress AG (Rapperswil, Switzerland)" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the pharmacy established before the start of the study a list randomly assigning each patient to…" Comment: although the precise method of generation of random sequence generation was not reported, the method of allocation concealment suggests that sequence generation was random
Allocation concealment (selection bias)	Low risk	Quote: "the medication was delivered by the pharmacy of the lead center (Inselspital, Bern) and shipped regularly to the patients, depending on their requirements…patients as well as their physicians were blinded to the treatment until completion of the whole study" Comment: both allocation concealment and blinding were achieved with use of a placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the medication was delivered by the pharmacy of the lead center (Inselspital, Bern) and shipped regularly to the patients, depending on their requirements…patients as well as their physicians were blinded to the treatment until completion of the whole study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the medication was delivered by the pharmacy of the lead center (Inselspital, Bern) and shipped regularly to the patients, depending on their requirements…patients as well as their physicians were blinded to the treatment until completion of the whole study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: participants were excluded from analysis for reasons that are likely to be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Duseja 2019

Study characteristics

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 39 Post-randomisation dropouts: 24 (61.5%) Revised sample size: 15

Duseja 2019 *(Continued)*

	Reasons for post-randomisation dropouts: did not undergo repeat liver biopsy (15); lost to follow-up (5); non-compliant (3), pregnant (1) Average age, years: 36 Females: 11 (73.3%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Age above 18 years. 2. Raised AST and ALT at least 1.5× normal for longer than 3 months. 3.No history of alcohol intake or < 20 g/d confirmed by at least 2 family members. 4. Negative viral markers for hepatitis C virus. 5. Negative autoimmune markers (antinuclear antibodies, anti-smooth muscle antibody, anti-liver kidney macrosomal antibody, anti-mitochondrial antibody, negative Kayser-Fleischer ring with normal ceruloplasmin, and normal iron studies). 6. Liver biopsy consistent with features of NAFLD Exclusion criteria: 1. Pregnant/lactating. 2. Diabetes mellitus. 3. Liver cirrhosis on imaging or liver biopsy. 4. Use of drugs that can cause NAFLD (e.g. corticosteroids, methotrexate, tamoxifen) Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: probiotics (n = 10) Further details: oral probiotic VSL#3 (2 capsules, 3 times daily; 675 billion CFU/d) for 1 year Group 2: no active intervention (n = 5) Further details: placebo Additional details: both groups received lifestyle modifications.
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), cirrhosis (number of people), resolution of fatty liver disease, NAFLD activity score Follow-up, months: 12
Notes	Source of funding (quote): "CD Pharma India Private Limited (New Delhi, India) funded the study and supplied the investigational drugs but did not participate in any part of the study" Trial name/Trial registry number: CTRI/2008/091/000074 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated randomization (source: trial registry)"
Allocation concealment (selection bias)	Low risk	Quote: "sequentially numbered, sealed, opaque envelopes (source: trial registry)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "prospective, double blind, placebo controlled, randomised"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "prospective, double blind, placebo controlled, randomised"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: participants were excluded from analysis for reasons that are likely to be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Ebrahimi-Mameghani 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2014 to 2015 Number randomised: 54 Post-randomisation dropouts: 16 (29.6%) Revised sample size: 38 Reasons for post-randomisation dropouts: discontinued intervention (8), travelling (3), not stated (5) Average age, years: 38 Females: 33 (86.8%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. 20 to 50 years old. 2. BMI 30 to 40. 3. Taking 400 IU vitamin E supplement daily Exclusion criteria: 1. Alcohol consumption. 2. Preganancy/Lactation. 3. Menopause. 4. Athlete. 5 Inflammatory conditions. 6. Family history of hyperlipidaemia. 7. Cardiovascular, lung, renal, or liver disease. 8. Other known liver disease. 9. Use of supplements in last 2 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: PUFA plus vitamin E (n = 19) Further details: 3 times 1000 mg softgel of conjugated linoleic acid plus 400 IU vitamin E for 8 weeks Group 2: vitamin E (n = 19) Further details: vitamin E 400 IU for 8 weeks Additional details: both groups received weight loss diet
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this study was supported by a research grant from Nutrition Research center, Tabriz University of Medical Sciences, Iran" Trial name/Trial registry number: IRCT2014020516491N1 Attempts were made to contact study 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: "the person who determined allocation sequence for the study and those who assigned participants were blinded" Comment: it is not clear how the random sequence was concealed
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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Ebrahimi-Mameghani 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Ebrahimi-Mameghani 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2011 to 2012 Number randomised: 70 Post-randomisation dropouts: 15 (21.4%) Revised sample size: 55 Reasons for post-randomisation dropouts: lost-to follow-up, discontinued intervention Average age, years: 37 Females: 25 (45.5%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD. 2. 20- to 50-year-olds Exclusion criteria: 1. Other causes of liver disease. 2. Use of hepatotoxic drug, antihypertensive medication, contraceptive, or oestrogen Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 29) Further details: *Chlorella vulgaris* four 300-mg tablets for 8 weeks Group 2: no active intervention (n = 26) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "also, the authors appreciate Iranians Green Future Co. (Tehran, Iran) for providing C vulgaris tablets" Trial name/Trial registry number: IRCT201202233320N7 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated random sequence"
Allocation concealment (selection bias)	Low risk	Quote: "a double-blind placebo-controlled randomized clinical trial…the study participants, investigators and the laboratory staff were all blinded to treatment assignment" Comment: allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a double-blind placebo-controlled randomized clinical trial"

Ebrahimi-Mameghani 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a double-blind placebo-controlled randomized clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Eghtesadi 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 68 Post-randomisation dropouts: not stated Revised sample size: 68 Average age, years: not stated Females: not stated NASH: 68 (100.0%) Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: amino acids (n = 36) Further details: 2000 mg L-carnitine supplements for 12 weeks Group 2: no active intervention (n = 32) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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)	Low risk	Quote: "randomized double-blind placebo-controlled clinical trial"

Eghtesadi 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double-blind placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Ekhlasi 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2012 to 2013 Number randomised: 63 Post-randomisation dropouts: 3 (4.8%) Revised sample size: 60 Reasons for post-randomisation dropouts: did not receive allocated intervention or discontinued treatment Average age, years: not stated Females: 12 (20.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD plus raised ALT. 2. 25- to 64-year-olds. 3. BMI 25 to 35 Exclusion criteria: 1. Other causes of liver disease. 2. Alcohol consumption. 3. Cancer. 4. Cardiovascular disease. 5. Diabetes. 6. Pregnancy/Lactation. 7. Use of NSAIDs, antibiotics, or probiotic/food supplements Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics plus vitamin E (n = 15) Further details: synbiotics (Protexin; Probiotics International Ltd.; contained *Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus bulgaricus*, prebiotic (fructo-oligosaccharide), probiotic cultures (magnesium stearate), a vegetable capsule (hydroxypropyl methylcellulose)) twice daily plus vitamin E 400 IU daily for 8 weeks Group 2: vitamin E (n = 15) Further details: vitamin E 400 IU daily plus placebo for 8 weeks Group 3: prebiotics/probiotics/synbiotics (n = 15) Further details: synbiotics (Protexin) twice daily plus placebo for 8 weeks Group 4: no active intervention (n = 15) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work was supported by the Iran National Science Foundation" Trial name/Trial registry number: 201111082709N22 Attempts were made to contact study authors in December 2020

Ekhlasi 2016 *(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	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a randomized, `double-blind, placebo-controlled` trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a randomized, `double-blind, placebo-controlled` trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Eriksson 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Sweden Period of recruitment: 2015 Number randomised: 84 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 84 Average age, years: 66 Females: 25 (29.8%) NASH: not stated Diabetes mellitus: 84 (100.0%) Inclusion criteria: 1. Type 2 diabetes mellitus. 2. 40- to 75-year-olds. 3. Stable dose of metformin or sulfonylurea alone or in combination for at least 3 months. 4. Proton density fat fraction (PDFF) > 5.5% (as measured by MRI). 5. BMI 25 to 40 Exclusion criteria: 1. Use of SGLT2is, n-3 fatty acids, insulin, or glucagon-like peptide 1 receptor agonist. 2. Other liver disease, or renal disease. 3. Significant alcohol (> 14 drinks/week) Method for diagnosis of NAFLD: MRI
Interventions	Group 1: PUFA (n = 42) Further details: 4 g n3 carboxylic acids (OM-3CA capsules) for 12 weeks Group 2: no active intervention (n = 42) Further details: placebo Additional details: some participants in both groups also received dapagliflozin, an antidiabetic drug; this was decided randomly

Eriksson 2018 *(Continued)*

Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people) Follow-up, months: 3
Notes	Source of funding (quote): "the study was funded by AstraZeneca" Trial name/Trial registry number: NCT02279407 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a centralised system, which provided a randomisation code delivered by an external call centre"
Allocation concealment (selection bias)	Low risk	Quote: "a centralised system, which provided a randomisation code delivered by an external call centre"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a double-blind randomised placebo-controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a double-blind randomised placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Eslamparast 2014

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2012 Number randomised: 52 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 52 Average age, years: 46 Females: 27 (51.9%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD. 2. ALT > 60 Exclusion criteria: 1. Other causes of chronic liver disease. 2. Alcohol use. 3. Diabetes. 4. Hypothyroidism that is untreated. 5. Systemic disease. 6. Pregnancy/Lactation. 7. Lack of effective birth control in women of childbearing age Method for diagnosis of NAFLD: ultrasound plus transaminases

Eslamparast 2014 *(Continued)*

Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 26) Further details: synbiotics (Protexin; Probiotics International Ltd.; contained *Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus bulgaricus*, prebiotic (fructo-oligosaccharide), probiotic cultures (magnesium stearate), a vegetable capsule (hydroxypropyl methylcellulose)) for 28 weeks Group 2: no active intervention (n = 26) Further details: placebo Additional details: both groups received lifestyle modification advice
Outcomes	Outcomes reported: fibrosis score Follow-up, months: 7
Notes	Source of funding (quote): "Protexin Company, UK, provided the synbiotic supplements, and Nikan Teb Co provided the FibroScan machine" Trial name/Trial registry number: NCT01791959 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization lists were computer-generated by a statistician"
Allocation concealment (selection bias)	Low risk	Quote: "a randomized, double-blind, placebo-controlled pilot study…subjects, investigators, and staff were blind to the treatment assignment until the end of the study" Comment: allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a randomized, double-blind, placebo-controlled pilot study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a randomized, double-blind, placebo-controlled pilot study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: a multiple imputation procedure was performed based on multi-variate imputation by chained equations; however, values may not be missing at random, as people were excluded from analysis because of discontinued intervention or loss to follow-up
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

EUCTR 2008-008275-34-GB

Study characteristics

Methods	Randomised clinical trial

EUCTR 2008-008275-34-GB *(Continued)*

Participants	Country: UK Period of recruitment: 2010 to 2011 Number randomised: 50 Post-randomisation dropouts: 1 (2.0%) Revised sample size: 49 Reasons for post-randomisation dropouts: did not have NAFLD Average age, years: 53 Females: 23 (46.9%) NASH: not stated Diabetes mellitus: 16 (32.7%) Inclusion criteria: 1. Clinical diagnosis of NAFLD made by a gastroenterologist. 2. Fatty infiltration confirmed on ultrasound. 3. Abnormal serum liver function tests Exclusion criteria: 1. Any other established cause of chronic liver disease. 2. Severe heart failure (NYHA class IV). 3. Use of medication that could cause fatty liver (e.g. tamoxifen). 4. Use of anticoagulants (antiplatelets were permitted). 5. Current alcohol intake > 20 g/d for women, > 40 g/d for men. 6. Already taking fish oil. 7. Known allergy to fish oil. 8. Pregnancy/Lactation. 9. Younger than 18 years Method for diagnosis of NAFLD: clinical plus ultrasound plus abnormal serum LFTs
Interventions	Group 1: PUFA (n = 24) Further details: Omacor capsules, 4 g/d Group 2: no active intervention (n = 25) Further details: placebo capsules, 4 g/d
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people) Follow-up, months: 9
Notes	Source of funding (quote): "this trial was funded by The University of Edinburgh 'Liver Fund'. No external funding was applied for. No funding or support was received from the pharmaceutical industry" Trial name/Trial registry number: NCT01277237 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the medication was pre-packed and pack numbers were assigned at random by means of a computer generated list at Tayside Pharmaceuticals"
Allocation concealment (selection bias)	Low risk	Quote: "the study numbers were randomised and allocated by a randomised list generated by the labelling company (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants, radiologist, and investigators were blinded…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "participants, radiologist, and investigators were blinded…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there was one post-randomisation dropout unrelated to the intervention and to the outcome
Selective reporting (reporting bias)	Low risk	Comment: all pre-defined outcomes in the protocol published before recruitment were reported

EUCTR 2008-008275-34-GB *(Continued)*

Other bias	Low risk	Comment: no other bias noted

EUCTR 2009-017080-41-GB

Study characteristics

Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: not stated Number randomised: 25 Post-randomisation dropouts: not stated Revised sample size: 25 Average age, years: 46 Females: 13 (52.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 years or older. 2. Evidence of liver fat content ≥ 5% as measured by MRI/MRS scanning or biopsy within 2 months. 3. No changes in levels of exercise or diet for 4 weeks before the start of treatment Exclusion criteria: 1. Type 1/2 diabetes. 2. Use of recreational cannabis, medicinal cannabis, or cannabinoid medications (including Sativex) within 1 month before study entry. 3. History of alcohol or substance abuse, or epilepsy or recurrent seizures. 4. History of major depression. 5. Cardiac, renal, or hepatic impairment, or any other significant disease or disorder. 6. History of hepatitis B or C. 7. Genetic dyslipidaemia. 8. Hypersensitivity to cannabinoids or any excipients of the IMP(s). 9. Presence of any metal implants. 10. History of claustrophobia. 11. Female participants (or partners of male participants) of childbearing potential not using effective contraception. 12. Pregnant or lactating. 13. Weight > 150 kg Method for diagnosis of NAFLD: MRI/MRS scanning or liver biopsy
Interventions	Group 1: other supplements (n = 20) Further details: Cannabidiol Licaps® Size 00 hard gelatin capsules containing 100 mg of CBD dissolved in vehicle (Gelucire 44/14) Group 2: no active intervention (n = 5) Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), any adverse events (number of events) Follow-up, months: 2
Notes	Source of funding: not stated Trial name/Trial registry number: NCT01284634 Attempts were made to contact study authors in April 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

EUCTR 2009-017080-41-GB *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "quadruple blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "quadruple blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention-to-treat analysis was used
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but it is not clear whether recruitment had commenced before the protocol was published: neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Fabbrini 2010

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 18 Post-randomisation dropouts: not stated Revised sample size: 18 Average age, years: 42 Females: 12 (66.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Obese. 2. NAFLD Exclusion criteria: 1. Smokers. 2. Alcohol > 20 g/d. 3. Severe hypertriglyceridaemia. 4. Diabetes. 5. Other causes of chronic liver disease Method for diagnosis of NAFLD: not stated
Interventions	Group 1: amino acids (n = 9) Further details: nicotinic acid (Niaspan) titrated from 500 mg/week to final dose of 2000 mg/week during first 3 weeks for 8 weeks Group 2: no active intervention (n = 9) Further details: placebo Additional details: another group not relevant to this review was excluded
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "kindly provided by Abbott Laboratories. This study was supported by National Institutes of Health Grants DK 37948, DK 56341 (to Clinical Nutrition Research Unit), RR024992 (to Clinical and Translational Science Award), and RR-00954 (to Biomedical Mass Spectrometry Resource)" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020
Risk of bias	

Fabbrini 2010 *(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	Low risk	Quote: "subjects were randomly assigned in a double-blind fashion...randomized, placebo-controlled trial to evaluate the effect"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "subjects were randomly assigned in a double-blind fashion...randomized, placebo-controlled trial to evaluate the effect"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Faghihzadeh 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2013 to 2014 Number randomised: 50 Post-randomisation dropouts: 2 (4.0%) Revised sample size: 48 Reasons for post-randomisation dropouts: discontinued study, had excessive weight loss Average age, years: 45 Females: 15 (31.3%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD. 2. Raised ALT Exclusion criteria: 1. Viral hepatitis. 2. Alcohol use. 3. Other causes of chronic liver disease. 4. Diabetes. 5. Untreated hypothyroidism. 6. Pregnancy/Lactation. 7. Lack of effective birth control in women of childbearing age Method for diagnosis of NAFLD: ultrasound plus elastography plus transaminases
Interventions	Group 1: other supplements (n = 24) Further details: resveratrol 500 mg daily for 12 weeks Group 2: no active intervention (n = 24) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people), resolution of fatty liver disease Follow-up, months: 3

Faghihzadeh 2015 *(Continued)*

Notes	Source of funding (quote): "this work was financially supported by the Iran National Science Foundation (A. H., grant number 90008014), and the National Nutrition and Food Technology Research Institute (A. H., grant number 046468)" Trial name/Trial registry number: IRCT201202014010N7 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "stratified randomisation lists were computer generated by a statistician and given to the investigator, while the supplements were masked as A product or B product"
Allocation concealment (selection bias)	Low risk	Quote: "stratified randomisation lists were computer generated by a statistician and given to the investigator, while the supplements were masked as A product or B product"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomised double-blinded placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomised double-blinded placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Famouri 2017a

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2014 Number randomised: 64 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 64 Average age, years: 13 Females: 32 (50.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. 10 to 18 years old. 2. BMI > 85th percentile. 3. NAFLD Exclusion criteria: 1. Alcohol use. 2. Long-term medication use. 3. Other chronic liver disease Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 32)

Famouri 2017a *(Continued)*

	Further details: probiotic capsule (containing *Lactobacillus acidophilus* ATCC B3208, *Bifidobacterium lactis* DSMZ 32269, *Bifidobacterium bifidum* ATCC SD6576, *Lactobacillus rhamnosus* DSMZ 21690) for 12 weeks Group 2: no active intervention (n = 32) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: mortality at maximal follow-up, resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "the study was conducted as a part of a thesis, funded by Isfahan University of Medical Sciences" Trial name/Trial registry number: IRCT2013100414882N1 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "random allocation of patients to 2 groups was performed by sequentially numbered containers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized triple-blind trial. An assistant performed randomization, so the group allocation was blinded for the investigators and participants"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized triple-blind trial. An assistant performed randomization, so the group allocation was blinded for the investigators and participants"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Farhangi 2014

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 44 Post-randomisation dropouts: 3 (6.8%) Revised sample size: 41 Reasons for post-randomisation dropouts: withdrawal, adverse event, travel Average age, years: 42 Females: 10 (24.4%)

Farhangi 2014 *(Continued)*

	NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD. 2. Aged 20 to 50 years for women, 20 to 65 years for men Exclusion criteria: 1. History of excessive alcohol (< 30 g/d men, < 20 g/d women). 2. Cirrhosis, hepatitis B/C, or other chronic liver disease. 3. Diabetes. 4. Gastrointestinal disease. 5. Rheumatoid arthritis, heart failure, or renal disease. 6. Use of antioxidants and omega 3 supplements Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other antioxidants (n = 20) Further details: coenzyme Q10 100 mg/d for 4 weeks Group 2: no active intervention (n = 21) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "we thank research undersecretary of Tabriz University of Medical Sciences for financial support" Trial name/Trial registry number: IRCT201305254105N12 Attempts were made to contact study 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	Low risk	Quote: "randomized double-blind placebo controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double-blind placebo controlled trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: participants were excluded from analysis for reasons that are likely to be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Farsi 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated

Farsi 2016 *(Continued)*

	Number randomised: 42 Post-randomisation dropouts: 1 (2.4%) Revised sample size: 41 Reasons for post-randomisation dropouts: discontinued intervention Average age, years: not stated Females: 13 (31.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD. 2. Absence of alcohol consumption Exclusion criteria: 1. History of chronic liver disease. 2. Renal failure, gastrointestinal disease. 3. Use of vitamin supplements, anticoagulant medication, hepatotoxic drugs. 4. Alcohol consumption. 5. Diabetes Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: other antioxidants (n = 20) Further details: coenzyme Q10 100 mg/d for 12 weeks Group 2: no active intervention (n = 21) Further details: placebo
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "financial support was provided by Ahvaz Jundishapur University of Medical Sciences" Trial name/Trial registry number: IRCT2013071313984N1 Attempts were made to contact study 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	Low risk	Quote: "randomized double-blind placebo controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double-blind placebo controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Farzin 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: not stated Revised sample size: 50 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: other supplements (n = 25) Further details: resveratrol 600 mg daily for 12 weeks Group 2: no active intervention (n = 25) Further details: placebo daily for 12 weeks
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: IRCT201511233664N16 Attempts were made to contact study authors in April 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	Low risk	Quote: "double blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Fathi 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2018 to 2019 Number randomised: 56 Post-randomisation dropouts: 6 (10.7%) Revised sample size: 50 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 40 Females: 18 (36.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD participants. 2. Overweight or obese (body mass index (BMI) between 25 and 35 kg/m^2). 3. Aged 18 to 65 years. 4. Abdominal obesity (waist circumference (WC) > 80 cm for women, > 94 cm for men) Exclusion criteria: 1. Highly physically active (> 3 hours/week). 2. Grade 3 NAFLD. 3. Smoking. 4. Pregnant or lactating women. 5. Chronic disease such as diabetes, major cardiovascular disease, cancer, hepatic or kidney dysfunction, hypothyroidism or hyperthyroidism, malabsorption disorders. 6. Taking medication that may interfere with zinc function. 7. Not taking more than 10% of zinc supplement. 8. Using dietary supplements or adhering to special diets or heavy physical activity programmes over past 3 months. 9. History of regular alcohol drinking over past 3 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 25) Further details: 220 mg zinc gluconate (as 30 mg elemental zinc) supplement per day for 12 weeks Group 2: no active intervention (n = 25) Further details: placebo daily for 12 weeks Additional details: all participants also followed a weight-loss calorie-restricted diet for 12 weeks
Outcomes	Outcome reported: resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "the study was funded by a research grant from Iran National Science Foundation (INSF) (Grant Number 97014520)" Trial name/Trial registry number: IRCT 20181005041238N1 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed according to the blocked randomization schedule with a block size of 4 subjects provided by the computer"
Allocation concealment (selection bias)	Low risk	Quote: "allocation concealment was conducted to decrease the possible bias. For this purpose, the tablets containers were coded by the producing company" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind…placebo"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double blind…placebo"

Fathi 2020 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts related to loss to follow-up; it is not clear whether these were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Fernandez-Travieso 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Cuba Period of recruitment: not stated Number randomised: 100 Post-randomisation dropouts: not stated Revised sample size: 100 Average age, years: 53 Females: 54 (54.0%) NASH: not stated Diabetes mellitus: 22 (22.0%) Inclusion criteria: 1. Both sexes. 2. Aged between 25 and 70 years. 3. History of liver enzyme elevation, obesity or overweight, diabetes, or dyslipidaemia, or with ultrasound history of liver disease due to non-alcoholic fat deposition Exclusion criteria: 1. Current alcohol consumption. 2. Hepatitis C and B virus infection. 3. Autoimmune liver disease, haemochromatosis, hepatotoxicity, human immunodeficiency virus (HIV), secondary cause of NAFLD, cirrhosis. 4. Pregnant or nursing. 5. Uncompensated diabetic patients. 6. Treatment that could influence liver function Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 50) Further details: Abexol tablets 100 mg/d for 6 months Group 2: no active intervention (n = 50) Further details: placebo tablets twice daily for 6 months
Outcomes	Outcomes reported: any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding (quote): "this study was support by the National Centre for Scientific Research, as part of its research-development projects" Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was computer generated using blocks and 1/1 randomization"

Fernandez-Travieso 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "identical coded packages…placebo" Comment: both allocation concealment and blinding were achieved with use of identical coded packages
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: double-blind…placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: double-blind…placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Ferolla 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: 2014 to 2015 Number randomised: 50 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 50 Average age, years: 57 Females: 38 (76.0%) NASH: 50 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. NASH confirmed on biopsy (NAS ≥ 3) Exclusion criteria: 1. Other causes of liver disease. 2. Evidence of decompensated liver disease. 3. Contraindication to MRI examination Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 27) Further details: 5 g of synbiotic Fiber Mais Flora (Nestlé Health Science), which consisted of 4 g of dietary fibre (partially hydrolysed guar gum and inulin) and 1×10^8 CFU of *L reuteri*, twice daily for 3 months Group 2: no active intervention (n = 23) Further details: no treatment Additional details: both groups received nutritional advice
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of events) Follow-up, months: 3
Notes	Source of funding: not stated Trial name/Trial registry number: not stated

Ferolla 2016 *(Continued)*

Attempts were made to contact study 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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Ferro 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2019 Number randomised: 102 Post-randomisation dropouts: 16 (15.7%) Revised sample size: 86 Reasons for post-randomisation dropouts: personal reasons, health reasons, work reasons Average age, years: 51 Females: 33 (38.4%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Liver steatosis. 2. Not taking nutraceuticals, supplements, or functional food Exclusion criteria: 1. Past and current alcohol abuse (> 20 g of alcohol per day). 2. Chronic hepatitis B and/or C virus infection. 3. Allergies to cardoon, artichoke, or maize. 4. Triglyceride concentration > 250 mg/dL. 5. Diabetes. 6. Autoimmune or cholestatic liver disease. 7. Liver cirrhosis. 8. Pregnancy. 9. Nephrotic syndrome, chronic renal failure. 10. Gastroesophageal reflux. 11. Cancer. 12. Taking amiodarone, antiretroviral agents, corticosteroids, methotrexate, tamoxifen, or valproate. 13. Recent initiation of lipid-lowering drugs (less than 6 weeks) Method for diagnosis of NAFLD: elastography
Interventions	Group 1: other supplements (n = 45)

Ferro 2020 *(Continued)*

	Further details: Bergamot and wild cardoon nutraceutical capsule 300 mg/d for 12 weeks (capsule contained a combination product with bergamot polyphenolic fraction (BPF) and wild-type *Cynara cardunculus* extract (CyC) plus excipients including PUFA and a mixture of bergamot pulp and albedo derivative (registered Patents RM2008A000615, PCT/IB2009/055061, and 102017000040866) (batch number 18R049, expiration date 10/2020)) Group 2: no active intervention (n = 41) Further details: placebo capsule daily for 12 weeks (placebo contained maltodextrin plus excipients including PUFA and a mixture of bergamot pulp and albedo derivative (batch number 18R050, expiration date 10/2020))
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this study was funded by Italian Ministry of University and Research, grant number: Nutramed Project, PON 03PE000_78_1" Trial name/Trial registry number: ISRCTN12833814 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random numbers were used for the simple randomization of subjects"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: double-blind…placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: double-blind…placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts related to personal reasons, health reasons, and work reasons - it is not clear whether they were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Foroughi 2014

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

Foroughi 2014 *(Continued)*

	Average age, years: 49 Females: 31 (51.7%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD on USS Exclusion criteria: 1. Acute illness. 2. Chronic kidney disease. 3. Hyperparathyroid, hypoparathyroid. 4. Coronary heart disease. 5. Other chronic liver disease. 6. Pregnancy. 7. Taking drugs affecting ALT including metformin Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin D (n = 30) Further details: vitamin D 50,000 IU weekly for 10 weeks Group 2: no active intervention (n = 30) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 2
Notes	Source of funding (quote): "source of support: nil" Trial name/Trial registry number: not stated Attempts were made to contact study 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	Low risk	Quote: "randomized double-blind placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double-blind placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Gavrilescu 2017

Study characteristics

Methods	Randomised clinical trial

Gavrilescu 2017 *(Continued)*

Participants	Country: Romania Period of recruitment: 2015 to 2016 Number randomised: 42 Post-randomisation dropouts: not stated Revised sample size: 42 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = not stated) Further details: prebiotic supplements for 24 weeks Group 2: no active intervention (n = not stated) Further details: no treatment Additional details: both groups received lifestyle modification
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Geier 2018

Study characteristics

Geier 2018 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: Switzerland Period of recruitment: not stated Number randomised: 20 Post-randomisation dropouts: 2 (10.0%) Revised sample size: 18 Reasons for post-randomisation dropouts: missing values Average age, years: not stated Females: not stated NASH: 18 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Increased alanine aminotransferase (ALT) level (≥ 1.2-fold ULN). 2. Histological diagnosis of NASH diagnosed according to SAF score obtained within 18 months preceding entry. 3. Decreased 25-OH vitamin D level (< 30 µg/L). 4. Non-excessive alcohol consumption (< 21 standard drinks on average per week in males, < 14 standard drinks on average per week in females) Exclusion criteria: 1. Cirrhosis. 2. HCV RNA positivity. 3. HBs antigen positivity. 4. Other liver disease including autoimmune hepatitis, hereditary haemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease. 5. Drug-induced fatty liver disease. 6. Serious disease limiting life expectancy. 7. Pregnant or breastfeeding. 8. Intention to become pregnant during the course of the study, or childbearing potential in women who were not using safe contraception Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin D (n = 8) Further details: vitamin D 2100 IU once daily for 48 weeks Group 2: no active intervention (n = 10) Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events), any adverse events (number of events) Follow-up, months: 11
Notes	Source of funding (quote): "the study medication (vitamin D3 2100 IU daily) and placebo were produced and provided by Antistress AG, Rapperswil-Jona, Switzerland" Trial name/Trial registry number: NCT01571063 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization on day 0 (stratified for the presence of diabetes, block size 10, not stratified by center) was performed by the Cantonal Pharmacy Zurich before starting the 48 week treatment period" Comment: although the precise method of generation of random sequence generation was not reported, the method of allocation concealment suggests that sequence generation was random
Allocation concealment (selection bias)	Low risk	Quote: "randomization on day 0 (stratified for the presence of diabetes, block size 10, not stratified by center) was performed by the Cantonal Pharmacy Zurich before starting the 48 week treatment period"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blinded, randomized, placebo-controlled pilot study"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blinded, randomized, placebo-controlled pilot study"

Geier 2018 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Ghaffari 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 92 Post-randomisation dropouts: 7 (7.6%) Revised sample size: 85 Reasons for post-randomisation dropouts: discontinuation of intervention, lack of compliance, transport difficulties Average age, years: 41 Females: 46 (54.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD diagnosis confirmed by gastroenterologist Exclusion criteria: 1. Thyroid disorder. 2. Cancer. 3. Biliary and kidney stones. 4. Viral hepatitis plus other hepatic disease. 5. Post-menopausal. 6. Pregnant or breastfeeding Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 64) Further details: turmeric (3 g/d) and/or chicory seeds (9 g/d) for 12 weeks Group 2: no active intervention (n = 21) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: IRCT201406183664N12 Attempts were made to contact study 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)	Low risk	Quote: "turmeric capsules and chicory seed powder were delivered in identical packs for all patients by a coworker who did not involve in project"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind, randomized controlled clinical trial…placebo"

Ghaffari 2018 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomized controlled clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Ghergherehchi 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2008 to 2009 Number randomised: 33 Post-randomisation dropouts: not stated Revised sample size: 33 Average age, years: 7 Females: 15 (45.5%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. BMI > 97th percentile for age and sex. 2. ALT/AST > 1.5× normal. 3. Signs of hepatic steatosis on USS Exclusion criteria: 1. Other causes of liver disease. 2. Drugs causing steatosis Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: vitamin E (n = 17) Further details: vitamin E 400 mg/d for 6 months Group 2: no active intervention (n = 16) Further details: placebo Additional details: both groups underwent lifestyle intervention (exercise and low-calorie diet)
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this study is funded by Tabriz University of Medical Sciences" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients were randomized into two groups by a person who was not aware of the main objective by using software Random List"
Allocation concealment (selection bias)	Low risk	Quote: "eligible patients were randomized into two groups by a person who was not aware of the main objective by using software Random List"

Ghergherehchi 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind placebo study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind placebo study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Gianturco 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 200 Post-randomisation dropouts: 4 (2.0%) Revised sample size: 196 Reasons for post-randomisation dropouts: onset of diabetes Average age, years: 62 Females: 92 (46.9%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Histologically confirmed NAFLD Exclusion criteria: 1. Hepatitis B/C. 2. Gallstones. 3. Alcohol consumption. 4. Renal failure. 5. Diabetes Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: other antioxidants (n = 104) Further details: alpha-lipoic acid 400 mg/d for 12 months Group 2: no active intervention (n = 92) Further details: placebo Additional details: both groups received hypocaloric diet. A proportion of patients in each group received ursodeoxycholic acid; this was decided randomly
Outcomes	Outcomes reported: fibrosis score, NAFLD activity score Follow-up, months: 12
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

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

Gianturco 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "computerized random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "they were prepared in bottles and consecutively numbered for each patient, according to the randomization schedule. Each patient was assigned an order number and received the capsules in the corresponding bottle"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Gomez 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Cuba Period of recruitment: 2007 Number randomised: 60 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 60 Average age, years: 47 Females: 26 (43.3%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 18- to 70-year-olds. 2. Absence of significant alcohol history < 20 g/week. 3. Histological diagnosis of NASH Exclusion criteria: 1. Any other form of liver disease. 2. Positive screening for viral hepatitis B and C. 3. Pregnancy or lactation. 4. Decompensated cirrhosis. 5. Presence of secondary causes of NAFLD such as medications that induce steatosis (corticosteroids, oestrogens, methotrexate, amiodarone, tamoxifen, and calcium channel blockers). 6. Gastrointestinal bypass surgery. 7. Pharmacological treatment with some potential benefit for NAFLD, including ursodeoxycholic acid, vitamin E, betaine, pioglitazone, rosiglitazone, metformin, pentoxifylline, or gemfibrozil. 8. Use of cholesterol-lowering statin drugs within the 6-month period before enrolment. 9. Fasting glucose levels < 250 mg⁄dL (13.3 mmol⁄L). 10. Contraindication to liver biopsy. 11. Severe or morbid obesity (body mass index ≥ 35 kg⁄m^2). 12. Concomitant disease with reduced life expectancy. 13. Severe psychiatric condition and drug dependence Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin C plus other antioxidants (n = 30) Further details: 3 Viusid oral sachets (50 g) daily for 24 weeks Group 2: no active intervention (n = 30) Further details: no treatment

Gomez 2009 *(Continued)*

	Additional details: both groups received hypocaloric diet and exercise
Outcomes	Outcomes reported: mortality at maximal follow-up, fibrosis score, NAFLD activity score Follow-up, months: 6
Notes	Source of funding (quote): "supported in part by a grant from Catalysis Laboratories, Spain" Trial name/Trial registry number: NCT00509418 Attempts were made to contact study 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)	Low risk	Quote: "it was performed by a health worker experienced in randomization techniques who was not involved in the evaluation or treatment of the participants. The physicians, study coordinators and patients did not have access to the randomization scheme"
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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Gonciarz 2012

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Poland Period of recruitment: 2008 to 2010 Number randomised: 45 Post-randomisation dropouts: 3 (6.7%) Revised sample size: 42 Reasons for post-randomisation dropouts: not stated Average age, years: 41 Females: 16 (38.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NASH on liver biopsy. 2. Alcohol < 20 g/d. 3. Elevated aminotransferases Exclusion criteria: 1. Other causes of liver disease. 2. On supplements containing antioxidants

Gonciarz 2012 *(Continued)*

	Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: other antioxidants (n = 30) Further details: melatonin 5 mg twice daily for 24 weeks Group 2: no active intervention (n = 12) Further details: placebo Additional details: both groups received lifestyle intervention comprising exercise and diet
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work is supported by grant No K/PBW/000495 from the Polish Ministry of Science and Higher Education" Trial name/Trial registry number: not stated Attempts were made to contact study 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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Guo 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2011 to 2013 Number randomised: 88 Post-randomisation dropouts: 4 (4.5%) Revised sample size: 84 Reasons for post-randomisation dropouts: poor compliance/did not complete experimental protocol (2), diarrhoea/flatulence/nausea (1), lost to follow up (1)

Guo 2016 *(Continued)*

	Average age, years: 50 Females: 35 (41.7%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. 18 to 70 years old. 2. No lipid-lowering drugs used in past 3 months Exclusion criteria: 1. Viral hepatitis. 2. Drug-induced liver disease. 3. Total parenteral nutrition. 4. Hepatolenticular degeneration. 5. Autoimmune liver disease. 6. Excessive alcohol consumption (male weekly > 140 g, female weekly > 70 g). 7. Cardiac, liver, or renal insufficiency (GFR < 60 mL/min). 8. Hypertension, coronary heart disease, or pulmonary disease. 9. Pregnant and lactating women. 10. Psychiatric patients Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 42) Further details: routine treatment of diet, exercise, and metformin combined with enteric bifid-triple viable capsule (*Bifidobacterium:* 1260 mg per day) for 8 weeks Group 2: no active intervention (n = 42) Further details: routine treatment of diet, exercise, and metformin plus dimethicone (20 mg/kg/d) for 8 weeks Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people), adverse events (number of people) Follow-up, months: 2
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Harrison 2003

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2000 to 2002 Number randomised: 49 Post-randomisation dropouts: 4 (8.2%) Revised sample size: 45 Reasons for post-randomisation dropouts: did not want biopsy or moved away Average age, years: 51 Females: 25 (55.6%) NASH: 45 (100.0%) Diabetes mellitus: 19 (42.2%) Inclusion criteria: 1. Clinical and histological diagnosis of NASH. 2. > 18 years old. 3. Liver biopsy in past 6 months for elevated aminotransferases. 4. Well-compensated liver disease. 5. Hb > 12 g/dL in women, > 13 g/dL in men. 6. WCC > 3000 mm^3, neutrophils > 15,000, platelets > 70,000, and creatinine < 1.4 mg/dL Exclusion criteria: 1. Other causes of chronic liver disease. 2. Drugs causing steatohepatitis (e.g. tamoxifen, steroids, amiodarone). 3. Prior surgery such as gastroplasty, jejunoileal or jejunocolic bypass. 4. Decompensated liver disease. 5. Pregnancy. 6. Total parenteral nutrition in last 6 months. 7. Previous transplant. 8. Alcohol consumption > 10 g/d Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E plus vitamin C (n = 23) Further details: vitamin E 1000 IU plus vitamin C 1000 mg daily for 6 months Group 2: no active intervention (n = 22) Further details: placebo
Outcomes	Outcomes reported: fibrosis score Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization table"
Allocation concealment (selection bias)	Low risk	Quote: "this randomization table was kept by the pharmacy where the vitamins or placebo were to be obtained by the patient"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "prospective, double-blind, randomized, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "prospective, double-blind, randomized, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Harrison 2003 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Hashemi 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2007 to 2008 Number randomised: 100 Post-randomisation dropouts: not stated Revised sample size: 100 Average age, years: 39 Females: 43 (43.0%) NASH: 100 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Sonographic evidence of fatty liver. 2. ALT > 1.2× normal. 3. Exclusion of other chronic liver disease. 4. Suggestive histological evidence of NASH or strong risk factors such as type 2 diabetes or BMI > 30 Exclusion criteria: 1. Alcohol > 20 g/d. 2. Drugs causing fatty liver disease. 3. Severe comorbid medical condition Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: other antioxidants (n = 50) Further details: silymarin 280 mg for 24 weeks Group 2: no active intervention (n = 50) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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

Hashemi 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Heeboll 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Denmark Period of recruitment: 2011 to 2014 Number randomised: 28 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 28 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. BMI ≥ 25 kg/m^2. 2. ALT > 70 in men, > 45 in women. 3. At least 1 element of metabolic syndrome Exclusion criteria: 1. Type 2 diabetes mellitus. 2. Severe systemic or malignant disease Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 15) Further details: resveratrol 1.5 g daily for 6 months Group 2: no active intervention (n = 13) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), any adverse events (number of events), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 6
Notes	Source of funding (quote): "resveratrol was provided by Evolva SA (Basel, Switzerland), free of charge" Trial name/Trial registry number: NCT01464801 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a block randomization of four was generated (using www.randomization.com)"
Allocation concealment (selection bias)	Low risk	Quote: "a block randomization of four was generated (using www.randomization.com), by the hospital pharmacist at study start. Study medication was administered as tablets in sealed, sequentially numbered containers"

Heeboll 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "prospective, placebo-controlled, randomised and double-blind clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "prospective, placebo-controlled, randomised and double-blind clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Hong 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2011 to 2012 Number randomised: 80 Post-randomisation dropouts: 14 (17.5%) Revised sample size: 66 Reasons for post-randomisation dropouts: did not complete full therapy (inadequate data, patient refusal) Average age, years: 49 Females: 10 (15.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Fatty liver disease. 2. AST ≥ 50 or ALT ≥ 50 Exclusion: 1. Other causes of liver disease (e.g. viral hepatitis, autoimmune hepatitis, haemochromatosis). 2. Pancreatitis. 3. Cancer. 4. Drug-induced liver injury. Method for diagnosis of NAFLD: not stated
Interventions	Group 1: other supplements plus other antioxidants (n = 35) Further details: Korean red ginseng (3000 mg/d) plus *Silybum marianum* (Legalon) capsule (450 mg/d) for 3 weeks Group 2: other antioxidants (n = 31) Further details: *Silybum marianum* (Legalon) capsule (450 mg/d) plus placebo for 3 weeks Additional details: both groups received lifestyle intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this research was supported by a grant from the Korea Society of Ginseng funded by Korea Ginseng Corporation (Korean Red Ginseng; 2011)" Trial name/Trial registry number: NCT02331589 Attempts were made to contact study authors in December 2020
Risk of bias	

Hong 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed using a computerized procedure"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "a single-blind, randomized, controlled clinical trial" Comment: not clear who were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a single-blind, randomized, controlled clinical trial" Comment: not clear whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Hong 2021

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Korea Period of recruitment: 2017 to 2018 Number randomised: 94 Post-randomisation dropouts: 7 (7.4%) Revised sample size: 87 Reasons for post-randomisation dropouts: patient refusal, loss to follow-up Average age, years: 50 Females: 35 (40.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥ 50 IU/L. 2. Fatty liver disease in abdominal ultrasound. 3. Older than 20 years Exclusion criteria: 1. Excessive alcohol drinking (male > 60 g/week, female > 40 g/week). 2. Virus-related hepatitis, alcohol-induced hepatitis, autoimmune disease, haemochromatosis, infiltrative liver disease. 3. Pancreas problem. 4. Drug-related liver injury. 5. Cancer Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: other supplements (n = 43) Further details: Korean red ginseng (KRG, ginsenosides Rg1þRb1þRg3 4.5 mg/g; 2000 mg/d) and milk-thistle dried extracts powder (450 mg/d) for 30 days Group 2: no active intervention (n = 44) Further details: placebo capsules (cellulose) and milk-thistle dried extracts powder (450 mg/d) daily for 30 days. Placebos were of the same size and shape as the KRG capsule powder Additional details: all patients were educated about diet and exercise according to recommendations

Hong 2021 *(Continued)*

Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this research was supported by Hallym University ResearchFund, the Korea Society of Ginseng funded by Korea Ginseng Corporation (Korea Red Ginseng; 2016), the Basic Science ResearchProgram through the National Research Foundation of Korea (NRF)funded by the Ministry of Education, Science and Technology (NRF-2018M3A9F3020956 and NRF-2019R1I1A3A01060447) and Hallym University Research Fund 2018 (HURF-2018-67)" Trial name/Trial registry number: NCT03945123 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computerized procedure was used for the randomization"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: an identical placebo was used, but there is no mention about blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: an identical placebo was used, but there is no mention about blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts related to patient refusal, follow-up loss, and other reasons - it is not clear whether they were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Hormoznejad 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 9 (18.0%) Revised sample size: 41 Reasons for post-randomisation dropouts: not taking tablets regularly, weight-loss diet Average age, years: 42 Females: 18 (43.9%) NASH: not stated Diabetes mellitus: 0 (0.0%)

Hormoznejad 2020 *(Continued)*

	Inclusion criteria: 1. 18 years of age or older. 2. BMI 25 kg/m^2 - upper limit wrongly stated in the text. 3. Confirmed NAFLD (grade of steatosis ≥ 2 at ultrasonography) Exclusion criteria: 1. History of significant alcohol intake (> 10 mL/d for women, 20 mL/d for men). 2. Smoking habits. 3. Other liver disease; other cardiovascular, respiratory, or kidney disorder; malignancy. 4. Diabetes mellitus. 5. Pregnancy or breastfeeding. 6. Medication in previous 6 months. 7. Supplementation with antioxidants or vitamins. 8. Weight loss over the past 3 months. 9. Metabolism or endocrine disorder Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 20) Further details: cranberry tablets (2 tablets daily) for 12 weeks. Each tablet contained 144 mg of Vaccinium macrocarpon extract with ≥ 36 mg proanthrocyanidine (equal to 13 g dried cranberry fruit); composition of the remaining 144 mg was unknown Group 2: no active intervention (n = 21) Further details: placebo tablets twice daily for 12 weeks. Placebo tablets contained 288 mg of starch and were similar in colour, size, and weight to cranberry tablets Additional details: all participants were on a hypocaloric diet of 500 to 1000 kcal under estimated energy requirements
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "this work was financially supported by a Vice-Chancellor for Research Affairs of Ahvaz Jundishapur University of Medical Sciences from [grant number NRC-9718]" Trial name/Trial registry number: IRCT20150124020765N2 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients were block randomised based on gender and body mass index (BMI), then using a randomisation number table, they were assigned to receive either cranberry or placebo tablets for 12 weeks"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts that probably were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Hoseini 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age, years: 62 Females: 40 (100.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Alcohol consumption > 20 g/d. 2. Viral and autoimmune hepatitis. 3. Haemochromatosis. 4. Drug-induced liver disease. 5. Excessive weight loss. 6. Surgical treatment for obesity. 7. Pursuing physical activity programmes 6 months before the intervention. 8. Wilson's disease. 9. Coeliac disease Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin D (n = 20) Further details: 50,000 units of vitamin D supplement once per week at the beginning of the week Group 2: no active intervention (n = 20) Further details: received placebo weekly, with the same shape, colour, smell, and taste Additional details: 50% of participants in each group received aerobic training (factorial trial design)
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the authors declare that the research did not receive any financial grants" Trial name/Trial registry number: IRCT20190423043359N1 Attempts were made to contact study authors in April 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: "single blind" Comment: states single-blind, but it is not clear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single blind" Comment: states single-blind, but it is not clear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported

Hoseini 2020 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Hosseinabadi 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2016 Number randomised: 48 Post-randomisation dropouts: 4 (8.3%) Revised sample size: 44 Reasons for post-randomisation dropouts: discontinued intervention Average age, years: 41 Females: 21 (47.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD. 2. Aged 20 to 60 years. 3. Body mass index (BMI) ranging from 25 to 35 kg/m^2 Exclusion criteria: 1. Pregnant, breastfeeding, post menopause. 2. Professional athlete. 3. Known documented liver disease (such as hepatitis B, hepatitis C, and biliary disease). 4. Inherited disorder affecting liver (iron and copper storage disease). 5. History of diagnosed cardiovascular, kidney, diabetes, gastrointestinal, pulmonary, autoimmune disease, thyroid dysfunction, or cancer. 6. Recent surgery. 7. Use of alcohol and cigarettes, nutritional supplements, or weight-loss diet within past 3 months. 8. Use of medications such as corticosteroids, hepatotoxic agent, anticoagulant, antidiuretic, or lipid-lowering drug Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 21) Further details: green coffee extract group received 2 capsules per day (each contained 200 mg GCE) for 8 weeks. GCE capsules were purchased from Bonyan Salamat Kasra Co., Tehran, Iran, and were provided by the hydro-alcoholic extraction of green coffee beans. They contained 50% (100 mg) CGA (chlorogenic acids) as the main ingredient and < 2% caffeine Group 2: no active intervention (n = 23) Further details: placebo capsules contained starch and were similar in taste and appearance to GCE capsules
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 2
Notes	Source of funding (quote): "Research Vice-Chancellor of Tabriz University of Medical Sciences,Tabriz, Iran" Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 2021

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the sequence of the randomization was generated using random allocation software"
Allocation concealment (selection bias)	Low risk	Quote: "the medication boxes were labeled as A and B and the researchers and participants were blinded to the allocation until the statistical analyses were completed"

Hosseinabadi 2020 *(Continued)*

		Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts because the intervention was discontinued. It is not clear whether these were related to the intervention and to the outcome
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Hosseini 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2015 to 2016 Number randomised: 82 Post-randomisation dropouts: 7 (8.5%) Revised sample size: 75 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 34 Females: 75 (100.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Women. 2. 18 to 50 years old. 3. BMI 25 to 40 kg/m^2. 3. NAFLD confirmed on USS. 4. Vitamin D insufficiency (serum 25(OH)D < 30 ng/mL). 5. Not taking any dietary supplements including calcium and vit D over last 6 months Exclusion criteria: 1. Renal, hepatic, other endocrine disorder; malignancy. 2. Pregnancy/Lactation. 3. Alcohol consumption. 4. Menopause condition. 5. Receiving medications influencing vit D metabolism or insulin Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin D (n = 37) Further details: a single intramuscular injection of 600,000 IU of cholecalciferol Group 2: no active intervention (n = 38) Further details: no treatment
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this study was supported by Research Vice Chancellor of Tabriz University of Medical Sciences" Trial name/Trial registry number: IRCT201503163320N10 Attempts were made to contact study authors in December 2020

Hosseini 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer Random Allocation Software, version 1"
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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Hussain 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2016 Number randomised: 80 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 80 Average age, years: 27 Females: 26 (32.5%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 20 to 55 years old. 2. BMI ≥ 27. 3. Elevated aminotransferases. 4. USS with fatty liver grading 1, 2, or 3 Exclusion criteria: 1. Alcohol and drug abuse. 2. Smoking. 3. Pregnancy/Lactation. 4. Diabetes, 5, Hypothyroid. 6. Biliary disease. 7. Autoimmune disease. 8. Drug-induced hepatitis. 9. Chronic kidney disease. 10. Cardiac disease. 11. Decompensated liver disease or other cause of chronic liver disease Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: other supplements (n = 40) Further details: green tea extract 500 mg twice daily for 12 weeks Group 2: no active intervention (n = 40) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up

Hussain 2017 *(Continued)*

	Follow-up, months: 3
Notes	Source of funding (quote): "Grant Support & Financial Disclosures: none" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random numbers generated by computer for each subject"
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	Quote: "the imaging study of fatty liver was done by experienced radiologist who was blinded to the all data of patients" Comment: it is not clear whether outcome assessors of remaining outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Illnait 2013

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Cuba Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 50 Average age, years: 55 Females: 27 (54.0%) NASH: not stated Diabetes mellitus: 7 (14.0%) Inclusion criteria: 1. 25 to 70 years old. 2. Prior diagnosis of NAFLD and/or persistent increase in liver enzymes without excessive alcohol ingestion (< 70 g female, 40 g male) Exclusion criteria: 1. Overuse of alcohol. 2. Other cause of chronic liver disease. 3. Uncontrolled diabetes. 4. Pregnancy/Lactation. 5. Lack of effective birth control in women of childbearing age. 6. Unstable angina, MI, stroke, or any other serious adverse event within 3 months prior to study. 7. Any other treatment that could influence liver function

Illnait 2013 *(Continued)*

	Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 25) Further details: bees wax D-002 (100 mg/d) for 24 weeks Group 2: no active intervention (n = 25) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "treatments were given in identical coded packages accordingly"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Izadi 2021

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2018 Number randomised: 70 Post-randomisation dropouts: 9 (12.9%) Revised sample size: 61 Reasons for post-randomisation dropouts: personal reasons (7), travel (1), discontinued intervention (1) Average age, years: 43

Izadi 2021 *(Continued)*

	Females: 25 (41.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Diagnosis of NAFLD according to ultrasound (patients with grade 1 to 3) and serum alanine aminotransferase (ALT) > 30 IU/L for men, > 19 IU/L for women. 2. 20 to 55 years of age. 3. Body mass index (BMI) > 25 and < 40 kg/m^2. 3. Lack of history of alcohol consumption. 4. No evidence of any other acute or chronic disorder of the liver (hepatitis B, C, etc.), nor biliary disease, autoimmune disease, cancer, or inherited disorders affecting the liver Exclusion criteria: 1. Any allergic reaction to sour tea supplement. 2. Use of antioxidant drugs or any other supplements/drugs that could interfere with the study objectives within 3 months. 3. Weight loss > 10% during the study period. 4. Breastfeeding or pregnant. 5. Irregular use of capsules (consuming < 80% of capsules delivered to participants during the study) Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: other supplements (n = 30) Further details: 1 capsule of sour tea powder (450-mg capsule containing ≥ 250 mg of anthocyanin) daily for 8 weeks. *Hibiscus sabdariffa L* was obtained from a local market in 2018 and was scientifically identified by M. Kamalinejad Group 2: no active intervention (n = 31) Further details: 1 placebo capsule (pure microcrystalline cellulose) daily for 8 weeks. Placebo was indistinguishable in colour, shape, size, and packaging from sour tea capsules Additional details: all participants were advised to maintain their usual diet and physical activity during the intervention period
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events) Follow-up, months: 2
Notes	Source of funding (quote): "the authors would like to thank the Isfahan University of Medical Sciences for financial support" Trial name/Trial registry number: IRCT20140208016529N3 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization lists were computer-generated by a statistician"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all participants, the physician, and the laboratory personnel were blind to the intervention type…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all participants, the physician, and the laboratory personnel were blind to the intervention type…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts because the intervention was discontinued. it is not clear whether these were related to the intervention and to the outcome
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported

Izadi 2021 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Jameshorani 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 90 Post-randomisation dropouts: not stated Revised sample size: 90 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 45) Further details: 500 mg/d Familact (duration not stated) Group 2: no active intervention (n = 45) Further details: no treatment Additional details: both groups received diet and exercise interventions
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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

Jameshorani 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Janczyk 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Poland Period of recruitment: 2008 to 2011 Number randomised: 76 Post-randomisation dropouts: 12 (15.8%) Revised sample size: 64 Reasons for post-randomisation dropouts: withdrawn consent (1), personal reasons (2), contact lost (3), withdrawn by parents/patients (6) Average age, years: 13 Females: 11 (17.2%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. 5 to 19 years old. 2. Overweight or obesity (according to BMI). 3. ALT ≥ 1.3× upper limit of normal. 4. Hyperechogenic liver on USS or liver histology consistent with NAFLD/NASH Exclusion criteria: 1. Significant alcohol consumption history. 2. Other cause of chronic liver disease. 3. Diabetes. 4. Hypothyroidism. 5. Vitamin E treatment. 6. Use of statins, ursodeoxycholic acid, probiotics, metformin within 3 months. 7. History of total parenteral nutrition Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: PUFA (n = 30) Further details: omega-3 fatty acid (docosahexaenoic acid and eicosapentaenoic acid, 450 to 1300 mg/d) for 24 weeks Group 2: no active intervention (n = 34) Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding (quote): "omega-3 and placebo capsules were manufactured and blinded by Nepentes S.A. and Hasco-Lek Polska S.A." Trial name/Trial registry number: NCT01547910 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer statistical software StatsDirect version 2.7.9 (StatsDirect Ltd., England, UK); the list of random treatment assignments was generated"
Allocation concealment (selection bias)	Low risk	Quote: "investigators sent randomization requests by fax to the central randomization center (CRC) responsible for the process of randomization"

Janczyk 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "multicenter, randomized, double-blind, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "multicenter, randomized, double-blind, placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available (recruitment was completed at the time of protocol publication); adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Javadi 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2013 to 2014 Number randomised: 84 Post-randomisation dropouts: 9 (10.7%) Revised sample size: 75 Reasons for post-randomisation dropouts: personal reasons, hepatitis, diabetes Average age, years: 42 Females: 15 (20.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD. 2. 20 to 60 years of age. 3. ALT/AST higher than normal range Exclusion criteria: 1. Cardiovascular, thyroid, kidney, autoimmune disease. 2. Other cause of chronic liver disease. 3. Use of vitamin supplements. 4. Alcohol. 5. Pregnant/Lactating Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 56) Further details: probiotic capsules (*Bifidobacterium longum* and *Lactobacillus acidophilus*: 2×10^7 CFU/d) and/or prebiotic inulin high performance 10 g/d for 3 months Group 2: no active intervention (n = 19) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the study was granted by nutrition research center, Tabriz University of Medical Sciences, Iran" Trial name/Trial registry number: IRCT201301223140N6 Attempts were made to contact study authors in December 2020

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

Javadi 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Low risk	Quote: "to ensure blinding, the allocation was performed by an investigator with no clinical involvement in the study, and the main investigator and statistical data analyst, is the same one, remained blinded to the participant group until the end of the analysis"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind, placebo-control clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind, placebo-control clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Javanmardi 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 42 Post-randomisation dropouts: 4 (9.5%) Revised sample size: 38 Reasons for post-randomisation dropouts: personal reasons Average age, years: 44 Females: 21 (55.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD on USS Exclusion criteria: 1. Liver transplant. 2. Smoking. 3. Alcohol consumption. 4. Use of drugs such as amiodarone, steroids, tamoxifen, prexillin, methotrexate. 5. Rapid weight loss. 6. Heart failure. 7. Thyroid disease. 8. Renal disease. 10. Other aetiology of chronic liver disease Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 19) Further details: 1.6-g phytosterol supplement daily for 8 weeks Group 2: no active intervention (n = 19) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated

Javanmardi 2018 *(Continued)*

Trial name/Trial registry number: IRCT2017011531958N1
Attempts were made to contact study 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	Low risk	Quote: "randomized, double-blind, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Jazayeri-Tehrani 2019

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 84 Post-randomisation dropouts: not stated Revised sample size: 84 Average age, years: 42 Females: 38 (45.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. 25 to 50 years old. 2. BMI 25 to 35 Exclusion criteria: 1. Alcohol intake during previous year. 2. Other liver condition, secondary NAFLD. 3. Uncontrolled hypertension. 4. Pregnancy, lactation. 5. Professional athlete. 6. Use of statins, ursodeoxycholic acid, probiotics, antihypertensive, curcumin-interactive drugs, multi-vitamin/mineral/antioxidant supplements over past 3 months. 7. Weight loss over past 3 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 42) Further details: two 40-mg capsules/d of nano-curcumin (supplied by Exir-Nano-Sina Company) after meals for 3 months Group 2: no active intervention (n = 42)

Jazayeri-Tehrani 2019 *(Continued)*

	Further details: two 40-mg capsules/d of placebo (supplied by Exir-Nano-Sina Company) after meals for 3 months. Capsules were similar in shape, size, and colour to nano-curcumin capsules Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 3
Notes	Source of funding (quote): "the trial funding was supported by Tehran University of Medical Sciences (grant no. 31581)" Trial name/Trial registry number: IRCT2016071915536N3 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "double-blind, randomized, placebo-controlled clinical trial. Subjects were divided into two equal groups by the block randomization method, carried out by an assistant" Comment: although the precise method of generation of random sequence generation was not reported, the method of allocation concealment suggests that sequence generation was random
Allocation concealment (selection bias)	Low risk	Quote: "double-blind, randomized, placebo-controlled clinical trial. Intervention allocation blinding was performed for both participants and investigators before the beginning, kept during the intervention, and opened after the data analysis by a field worker"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled clinical trial. Intervention allocation blinding was performed for both participants and investigators before the beginning, kept during the intervention, and opened after the data analysis by a field worker"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: an intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Comment: a published protocol was available, but it is not clear whether recruitment had commenced before the protocol was published; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Unclear risk	Comment: there were baseline differences in important prognostic factors

Jeong 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: South Korea

Jeong 2017 *(Continued)*

	Period of recruitment: 2013 to 2015 Number randomised: 74 Post-randomisation dropouts: 1 (1.4%) Revised sample size: 73 Reasons for post-randomisation dropouts: withdrawing during the study (1) Average age, years: 42 Females: 14 (19.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 19 to 75 years. 2. USS features of NAFLD. 3. AST or ALT above upper normal limits Exclusion criteria: 1. AST/ALT > 2. 2. Type 1 diabetes. 3. Other liver disease. 4. Excessive alcohol consumption. 5. Use of steatogenic medication within past 3 months. 5. Serious underlying disease. 6. Bariatric surgery within past 6 months. 7. Contraindication to magnetic resonance spectroscopy. 8. Pregnancy, breastfeeding. 9. Hypersensitivity to *Magnolia officinalis* Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: other supplements (n = 45) Further details: high-dose (400 mg) or low-dose (133.4 mg) HL tablet daily for 12 weeks. HL tablet is a new botanical drug extracted from *Magnolia officinalis* (MO) Group 2: no active intervention (n = 23) Further details: placebo daily for 12 weeks
Outcomes	Outcomes reported: any adverse events (number of people), any adverse events (number of events) Follow-up, months: 3
Notes	Source of funding: not stated Trial name/Trial registry number: NCT02491905 Attempts were made to contact study 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	Low risk	Quote: "double-blind, placebo controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo controlled"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: protocol was published after trial had ended; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Kanoni 2021

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: multi-centric (Europe) Period of recruitment: 2017 to 2019 Number randomised: 98 Post-randomisation dropouts: 11 (11.2%) Revised sample size: 87 Reasons for post-randomisation dropouts: lost to follow-up (11) Average age, years: 49 Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Men and women, aged 18 to 67 years. 2. Body mass index (BMI) ≥ 30 kg/m^2. 3. Established NAFLD/NASH based on sensitive LiverMultiScan magnetic resonance imaging (MRI) technique Exclusion criteria: 1. Hepatotoxic medication. 2. Concomitant liver disease. 3. Decompensated diabetes mellitus. 4. Thyroid disease, hypopituitarism, Cushing's syndrome, alcohol abuse or drug addiction, systemic disease, pregnancy, lactation, vegan or lacto- and ovo-lactovegetarianism, psychiatric or mental disorder. 5. Recent loss of body weight or current diet. 6. Any use of antioxidant-phytochemical-rich supplement, prebiotics, or probiotics. 7. Change in drug treatment, antibiotic treatment during or before screening Method for diagnosis of NAFLD: magnetic resonance imaging
Interventions	Group 1: other antioxidants (n = 35) Further details: Mastiha 0.35 g capsules thrice daily for 6 months Group 2: no active intervention (n = 52) Further details: placebo daily for 6 months
Outcomes	Outcomes reported: any adverse events Follow-up, months: 6
Notes	Source of funding: European Union's Horizon 2020 research and innovation programme MAST4HEALTH Trial name/Trial registry number: NCT03135873

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	Low risk	Quote: "all participants and researchers were blinded to the treatment allocation...double-blind, placebo controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all participants and researchers were blinded to the treatment allocation...double-blind, placebo controlled"

Kanoni 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: protocol was published after trial had started; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Kazemi 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 84 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 84 Average age, years: 42 Females: 46 (54.8%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Age range 20 to 60 years. 2. Body mass index (BMI) between 25 and 30 kg/m². 3. No evidence of secondary causes for steatosis, including history of alcohol use, haemochromatosis, or Wilson's disease; history of using hepatotoxic drugs (methotrexate, amiodarone, tamoxifen, corticosteroids, valproate, and antiviral drugs); history of hepatitis C and known autoimmune disease. 3. Not affected by chronic or acute liver disorder; coeliac disease; diabetes; cancer; thyroid disorder; cardiovascular, renal, or pulmonary disease; inflammatory disease; or autoimmune disease. 5. No history of smoking. 6. Not taking any antioxidant supplements over previous 1 month. 7. Not using any medication including weight-loss, glucose-lowering, and anti-inflammatory drugs. 8. Not following weight-loss diet over previous 3 months. 9. Not pregnant or breastfeeding Exclusion criteria: 1. Intolerance to sumac and/or placebo supplements or reporting any unexpected adverse effects. 2. Weight loss > 10% of baseline weight during the trial. 3. Low compliance with supplements, defined as consuming < 80% of supplements by the end of the trial. 4. Presence of any illness that requires special treatment during the study. 5. Unwillingness to continue co-operation Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 40) Further details: 1 capsule containing 500 mg sumac powder, 4 times a day (preferably after each meal), for 12 weeks Group 2: no active intervention (n = 40) Further details: received equal amounts of placebo capsule containing dextrin for the same period Additional details: all patients in sumac and placebo groups received a 500-kcal deficit diet plan, which comprised 55% to 65% of calories from carbohydrate, 20% to 30% from fat, and 10% to 15% from protein
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work was financially supported by Vice Chancellor for Research, Iran University of Medical Sciences, Tehran, Iran" Trial name/Trial registry number: IRCT201701162709N39 Attempts were made to contact study authors in April 2021
Risk of bias	

Kazemi 2020 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "performed using software-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Khoshbaten 2010b

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2008 Number randomised: 30 Post-randomisation dropouts: not stated Revised sample size: 30 Average age, years: 43 Females: 19 (63.3%) NASH: not stated Diabetes mellitus: 3 (10%) Inclusion criteria: 1. Ongoing NAFLD Exclusion criteria: 1. History of alcohol consumption or use of medications known to precipitate steatohepatitis, lipid-reducing agents, ursodeoxycholic acid, or vitamin supplements in the 6 months before the study Method for diagnosis of NAFLD: ultrasound or raised transaminases
Interventions	Group 1: other antioxidants (n = 15) Further details: N-acetyl cysteine 600 mg BD for 3 months Group 2: vitamin C (n = 15) Further details: vitamin C 1000 mg BD for 3 months
Outcomes	Outcomes reported: any adverse events

Khoshbaten 2010b *(Continued)*

	Follow-up, months: 3
Notes	Source of funding: Drug Applied Research Center at Tabriz University of Medical Sciences Trial name/Trial registry number: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients would pick up a ticket from a box containing mixed labels of two different treatments, twenty from each category"
Allocation concealment (selection bias)	Low risk	Quote: "patients would pick up a ticket from a box containing mixed labels of two different treatments, twenty from each category"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "liver hemodynamics, the grade of steatosis and the size of the spleen were measured by the same radiologist, blinded to the treatment method of the patients" Comment: no information on whether participants or healthcare providers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "liver hemodynamics, the grade of steatosis and the size of the spleen were measured by the same radiologist, blinded to the treatment method of the patients" Comment: there was no information on whether outcome assessors for adverse events were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Khutsishvili 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Georgia Period of recruitment: not stated Number randomised: 79 Post-randomisation dropouts: 6 (7.6%) Revised sample size: 73 Reasons for post-randomisation dropouts: not stated Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD. 2. Alcohol intake < 30 g/d Exclusion criteria: not stated

Khutsishvili 2020 *(Continued)*

	Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 35) Further details: mixture of 6 probiotic agents (*Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus fermentum, Lactobacillus plantarum, Lactobacillus acidophilus, E coli M-17*) and an auxiliary prebiotic component: fructo-oligosaccharide 50 mg Group 2: no active intervention (n = 38) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in April 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: there were post-randomisation dropouts; reasons for post-randomisation dropouts were not reported
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Kobyliak 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: not stated Period of recruitment: not stated Number randomised: 48 Post-randomisation dropouts: not stated Revised sample size: 48 Average age, years: not stated Females: not stated

Kobyliak 2017 *(Continued)*

	NASH: not stated Diabetes mellitus: 48 (100.0%) Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics plus PUFA (n = not stated) Further details: Symbiter omega (combination of probiotic biomass supplemented with flax and wheat germ oil (250 mg of each)) for 8 weeks Group 2: no active intervention (n = not stated) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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	Low risk	Quote: "we studied, in double-blind single center RCT…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "we studied, in double-blind single center RCT…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Kobyliak 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Ukraine Period of recruitment: not stated Number randomised: 58 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 58

Kobyliak 2018 *(Continued)*

	Average age, years: 55 Females: not stated NASH: not stated Diabetes mellitus: 58 (100.0%) Inclusion criteria: 1. Aged 18 to 65 years. 2. BMI ≥ 25. 3. Diagnosed with NAFLD. 4. Type 2 diabetes mellitus treated with diet and exercise alone or metformin, sulphonylureas, or insulin. 5. AST/ALT ≤ 3× upper limit of normal Exclusion criteria: 1. Alcohol > 20 g/d in women, > 30 g/d in men. 2. Other cause of chronic liver disease. 3. Prebiotic/probiotic supplement in last 3 months. 4. Uncontrolled cardiovascular or respiratory disease, active malignancy, or chronic infection. 5. Use of vitamin E, omega-3 fatty acid, or medication with evidence for effects on NAFLD. 6. Presence of active infection. 7. Pregnancy/Lactation Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: no active intervention (n = 28) Further details: 1 sachet (10 grams) of placebo per day for 8 weeks. Placebo sachets were identical with similar organoleptic characteristics (e.g. taste, appearance) to probiotic sachets Group 2: prebiotics/probiotics/synbiotics (n = 30) Further details: 1 sachet (10 grams) of Symbiter (concentrated biomass of 14 probiotic bacteria genera: *Lactobacillus* + *Lactococcus* (6×10^{10} CFU/g), *Bifidobacterium* (1×10^{10}/g), *Propionibacterium* (3×10^{10}/g), *Acetobacter* (1×10^{6}/g)) per day for 8 weeks
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 2
Notes	Source of funding (quote): "the multiprobiotic "Symbiter" was supplied by the Scientific and Production Company "O.D. Prolisok" (Kyiv, Ukraine)" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated list"
Allocation concealment (selection bias)	Low risk	Quote: "the study pharmacist gave the sachets to the participants according to their group assignment and was responsible for the delivery of the blinded supplements"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind treatment…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind treatment…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Kooshki 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2018 to 2019 Number randomised: 46 Post-randomisation dropouts: 3 (6.5%) Revised sample size: 43 Reasons for post-randomisation dropouts: refusal of treatment (2), withdrawal (1) Average age, years: 39 Females: 17 (39.5%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Women aged 20 to 50 years (pre-menopause) or men aged 20 to 65 years. 2. BMI 25 to 40. Exclusion criteria: 1. Alcohol consumption. 2. Renal disease. 3. Thyroid disorder. 4. Statin consumption. 5. Diabetes mellitus. 6. Hepatitis C and B. 7. Hereditary liver disease. 8. Pregnancy, lactation. 9. Being in weight loss programme during past 12 weeks. 10. Taking dietary supplements such as vitamins, minerals, fibre, and omega-3 in the past 12 weeks. 11. Doing professional sports Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 22) Further details: 200 µg tablets of chromium picolinate 2 times per day after a meal for 12 weeks (tablets produced by 21st Century HealthCare, Inc., Tempe, Arizona, USA) Group 2: no active intervention (n = 21) Further details: placebo tablets 2 times per day after a meal for 12 weeks (placebo tablets with corn starch prepared in Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, and similar in size and colour to CrPic tablets)
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "also, we would like to thank the Nutrition Research Center, Tabriz University of Medical Sciences, and Tabriz, Iran, for providing our study grant" Trial name/Trial registry number: IRCT20100123003140N15 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "using the blocked randomization method through RAS software"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled"

Kooshki 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts because the intervention was discontinued. It is not clear whether these were related to the intervention and to the outcome
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Kugelmas 2003

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 16 Post-randomisation dropouts: not stated Revised sample size: 16 Average age, years: 48 Females: 9 (56.3%) NASH: 16 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 65 years. 2. Diagnosis of NASH with liver biopsy consistent with NASH. 3. No more than 1 drink/week in past 6 months and no history of alcohol abuse Exclusion criteria: 1. Other cause of chronic liver disease. 2. Decompensated liver disease. 3. Ongoing total parenteral nutrition. 4. HIV. 5. Previous vitamin E replacement in last 3 months Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E (n = 9) Further details: 800 IU of vitamin E daily for 12 weeks Group 2: no active intervention (n = 7) Further details: no treatment Additional details: both groups received dietary intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "supported by National Institutes of Health grants MO1RR02602, AA00297(to D.B.H.), AA014185(D.B.H.), AA01762 (to C.J.M.), and AA10496(to C.J.M.); a Kentucky Science and Engineering Foundation grant; and the Department of Veterans Affairs" Trial name/Trial registry number: not stated Attempts were made to contact study 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

Kugelmas 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "in a single-blinded fashion (principal investigator was blinded)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "in a single-blinded fashion (principal investigator was blinded)" Comment: it is not clear whether the principal investigator was also the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Lavine 2011

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2005 to 2010 Number randomised: 116 Post-randomisation dropouts: 19 (16.4%) Revised sample size: 97 Reasons for post-randomisation dropouts: did not have liver biopsy Average age, years: 13 Females: 33 (34.0%) NASH: 49 (50.5%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Aged 8 to 17 years. 2. NAFLD. 3. Perisistently raised ALT. 4. Liver biopsy < 6 months before randomisation Exclusion criteria: 1. Diabetes. 2. Cirrhosis. 3. Viral hepatitis. 4. Alchol use. 5. Other cause of chronic liver disease. 6. Pregnancy. 7. Inborn error in metabolism Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E (n = 50) Further details: vitamin E 800 IU for 96 weeks Group 2: no active intervention (n = 47) Further details: placebo Additional details: another group not relevant to this review was excluded
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), any adverse events (number of events), fibrosis score, NAFLD activity score Follow-up, months: 28
Notes	Source of funding (quote): "multiple authors received consulting fees from many pharmaceutical industries" Trial name/Trial registry number: TONIC TRIAL/00063635 Attempts were made to contact study authors in December 2020
Risk of bias	

Lavine 2011 *(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	Low risk	Quote: "randomized, double-blind, double-dummy, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, double-dummy, placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Lewis 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2016 to 2017 Number randomised: 23 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 23 Average age, years: 54 Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged > 18 years. 2. Confirmed NAFLD. 3. Stable medication Exclusion criteria: 1. Allergy to rice, rice bran, mushrooms, or related food product. 2. Gastrointestinal disorder with uncertain absorption. 3. Use of lipid-lowering agent 3 months before the study. 4. Immunomodulator use. 5. Active chemotherapy. 6. Anaemia. 7. Pregnancy/Attempting conception. 8. Previous dietary supplements. 9. Use of similar polysaccharide formula within 2 weeks before the study Method for diagnosis of NAFLD: not stated
Interventions	Group 1: polysaccharides (n = 12) Further details: rice bran arabinoxylan compound 1 gram/d for 90 days Group 2: no active intervention (n = 11) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma

Lewis 2018 *(Continued)*

	Follow-up, months: 3
Notes	Source of funding (quote): "John E. Lewis has been paid by Daiwa Pharmaceutical to speak at international conferences and write articles on health and wellness for their website" Trial name/Trial registry number: NCT02568787 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using a random permutations table created by the principal investigator"
Allocation concealment (selection bias)	Low risk	Quote: "all subjects and investigators were blinded to the treatment condition and remained blinded until after data analysis" Comment: allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all subjects and investigators were blinded to the treatment condition and remained blinded until after data analysis…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all subjects and investigators were blinded to the treatment condition and remained blinded until after data analysis…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Li 2010

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2007 to 2008 Number randomised: 88 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 88 Average age, years: 46 Females: 33 (37.5%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 65 years. 2. NAFLD Exclusion criteria: 1. Other liver disease. 2. Severe dysfunction of heart, liver, kidney; cancer, or other severe disease. 3. Total parenteral nutrition. 4. Simultaneously receiving drug treatments that could influence trial results

Li 2010 *(Continued)*

	Method for diagnosis of NAFLD: CT scan
Interventions	Group 1: phospholipid (n = 43) Further details: polyene phosphatidylcholine capsule (PPC) (trade name: Essential, product of Sanofi-Aventis Pharmaceutical Co., Ltd., 1 capsule containing 228 mg of PPC), which was given as 2 capsules (456 mg) each time, 3 times a day, for 6 months Group 2: other supplements (n = 45) Further details: Qianggan Capsule (QGC), a product of Shijiazhuang Dongfang Pharmaceutical Co., Ltd., which was given as 3 capsules in the morning, 3 at noon, and 4 in the evening, with a 1-day pause after every 6 days, for 6 months (QGC consists of 16 Chinese drugs, namely, *Radix Astragali, Radix Salviae miltiorrhizae, Radix Angelicae sinensis, Radix Paeoniae alba, Radix Curcumae, Radix Codonopsis, Rhizoma Polygonati, Rhizoma Alismatis, Radix Rehmanniae, Rhizoma Dioscoreae, Fructus Crataegi, Massa Fermentata Medicinalis, Herba Artemisiae scopariae, Radix Gentianae Macrophyllae, Radix Isatidis, Radix Glycyrrhizae*)
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events), any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "they were assigned, depending on the randomized digital table, to two groups"
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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Li 2016

Study characteristics

Methods	Randomised clinical trial

Li 2016 *(Continued)*

Participants	Country: China Period of recruitment: not stated Number randomised: 78 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 78 Average age, years: 52 Females: 8 (10.3%) NASH: 78 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Pathological diagnosis of NASH Exclusion criteria: 1. Alcohol consumption > 20 g/week. 2. Medication cause of steatohepatitis. 3. Other chronic liver disease Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: PUFA (n = 39) Further details: 50 mL PUFA with 1:1 ratio of EHA and DHA into daily diet for 6 months Group 2: no active intervention (n = 39) Further details: no treatment Additional details: both groups received lifestyle modification (exercise) advice
Outcomes	Outcomes reported: mortality at maximal follow-up, fibrosis score Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: "not blinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "not blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Loguercio 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2005 to 2008 Number randomised: 179 Post-randomisation dropouts: 41 (22.9%) Revised sample size: 138 Reasons for post-randomisation dropouts: prematurely withdrawn because of physician's decision (5), patient's decision (21), adverse events (10), other (5) Average age, years: 42 Females: 17 (12.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Histologically documented liver steatosis or steatohepatitis diagnosed within 12 months. 2. Aged 18 to 65 years. 3. Persistent increase ≥ 1 plasma aminotransferase and or ALT and or GGT within 6 months Exclusion criteria: 1. Pregnancy. 2. Viral hepatitis (except hep C virus-positive patients with NAFLD with prior HCV treatment failure). 3. Cirrhosis. 4. Other major disease including type 1 diabetes. 5. Daily alcohol ≥ 20 g Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: phospholipids plus vitamin E plus other antioxidants (n = 69) Further details: Realsil (RA) (active components: silybin 94 mg, phosphatidylcholine 194 mg, vitamin E acetate 50% (α-tocopherol 30 mg) 89.28 mg) oral, twice daily, for 12 months Group 2: no active intervention (n = 69) Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people), resolution of fatty liver disease, NAFLD activity score Follow-up, months: 12
Notes	Source of funding (quote): "this study was funded by a grant from the Istituto Biochimico Italiano, Lorenzini S.p.a., Italy" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer program"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "multicenter, phase III, double-blind clinical trial…patients and investigators were blinded to treatment until trial completion"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "multicenter, phase III, double-blind clinical trial…patients and investigators were blinded to treatment until trial completion"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: participants were excluded from analysis for reasons that are likely to be related to the intervention and to outcomes

Loguercio 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Magosso 2013

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Malaysia Period of recruitment: 2008 to 2009 Number randomised: 87 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 87 Average age, years: 51 Females: 53 (60.9%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged ≥ 35 years old. 2. Mild untreated hypercholesterolaemia (5.2 to 6.2 for total cholesterol, 2.6 to 4.2 for LDL). 3. USS proven NAFLD Exclusion criteria: 1. Alcohol > 20 g/d and/or history of abuse or excessive intake of alcohol. 2. ALT/AST > 3x upper limit normal. 3. Antihyperlipidaemic medications in last 3 months. 4. Vitamin E intake. 5. Previous cardiovascular event or hepatitis Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin E (n = 43) Further details: 61.5 mg, 112.8 mg, and 25.7 mg for alpha-, gamma-, and delta-tocotrienol, respectively, and 61.1 mg for alpha-tocopherol (total: 200 mg)/d for 1 year Group 2: no active intervention (n = 44) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 12
Notes	Source of funding (quote): "JW Wong, BH Ng & E Magosso own shares of Hovid" Trial name/Trial registry number: NCT00753532 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated random allocation sequence"
Allocation concealment (selection bias)	Low risk	Quote: "the researcher (WJW) who generated the random allocation sequence and assigned participants was blinded to subjects' clinical data and was independent from the persons who enrolled participants"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "researchers and volunteers were blinded to the assigned treatment" Comment: it is not clear whether participants were blinded

Magosso 2013 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "researchers and volunteers were blinded to the assigned treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Malaguarnera 2010

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2004 to 2006 Number randomised: 80 Post-randomisation dropouts: 6 (7.5%) Revised sample size: 74 Reasons for post-randomisation dropouts: did not receive liver biopsy or had normalisation of ALT Average age, years: 48 Females: 34 (45.9%) NASH: 74 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Other cause of liver disease. 2. Significant alcohol consumption (>10 g/d female, > 20 g/d male). 3. Pregnancy. 4. Use of calcium channel blockers, oestrogens, methotrexate, amiodarone, steroids, chloroquine. 5. History of treatment with lipid-lowering agents. 6. Hypothyroidism. 7. Cushing's syndrome Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: amino acids (n = 36) Further details: 1 g carnitine twice daily for 24 weeks Group 2: no active intervention (n = 38) Further details: no treatment Additional details: both groups received dietary intervention
Outcomes	Outcomes reported: any adverse events (number of people), fibrosis score, NAFLD activity score Follow-up, months: 6
Notes	Source of funding (quote): "financial support: none" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

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

Malaguarnera 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Quote: "all drugs and placebos were identical in appearance, and neither investigators nor patients were informed of the selected agent until the end of the study phase"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all drugs and placebos were identical in appearance, and neither investigators nor patients were informed of the selected agent until the end of the study phase"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all drugs and placebos were identical in appearance, and neither investigators nor patients were informed of the selected agent until the end of the study phase"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Malaguarnera 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2003 to 2006 Number randomised: 66 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 66 Average age, years: 47 Females: 33 (50.0%) NASH: 66 (100.0%) Diabetes mellitus: 11 (16.7%) Inclusion criteria: 1. NASH. 2. Aged 30 to 65 years Exclusion criteria: 1. Other cause of liver disease. 2. No liver biopsy. 3. Treatment with metformin, vitamin E, thiazolidinedione before enrolment. 4. Prior surgical procedures (e.g. jejunoileal or jejunocolic bypass, gastroplasty). 5. Decompensated liver disease. 6. Pregnancy/Lactation. 7. Use of calcium channel blocker drugs, synthetic oestrogens, methotrexate, amiodarone steroids, chloroquine. 8. History of alcohol consumption > 10 g/d for females and > 20 g/d for males. 9. History of use of lipid-lowering agents. 10. Hypothyroidism. 11. Cushing's syndrome Method for diagnosis of NAFLD: ultrasound plus transaminases plus liver biopsy
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 34) Further details: oral sachet of *Bifidobacterium longum* with fructo-oligosaccharides for 24 weeks Group 2: no active intervention (n = 32) Further details: placebo Additional details: both groups received lifestyle intervention

Malaguarnera 2012 *(Continued)*

Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), fibrosis score, NAFLD activity score Follow-up, months: 6
Notes	Source of funding (quote): "this study was supported by a grant from the Regional Health Department for Sicily (Ric. Fin. 2007)" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "neither investigators nor patients were informed of the selected agent until the end of the study phase" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind treatment…neither investigators nor patients were informed of the selected agent until the end of the study phase" Comment: it is not clear how this was achieved as a placebo was not used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind treatment…neither investigators nor patients were informed of the selected agent until the end of the study phase"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Mansour 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 26 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 26 Average age, years: 45 Females: 5 (19.2%) NASH: not stated Diabetes mellitus: 26 (100.0%)

Mansour 2020 *(Continued)*

	Inclusion criteria: 1. Diabetes type 2. 2. Evidence of hepatic steatosis ≥ grade 2 in USS exam and steatosis ≥ grade 2 in Fibroscan exam (controlled attenuation parameter (CAP) score > 263) Exclusion criteria: 1. Professional athlete. 2. Taking any medication other than oral diabetes drugs. 3. Viral hepatitis. 4. Alcohol use. 5. Hepatic cirrhosis. 6. Other causes of chronic liver disease. 7. Hypothyroidism. 8. Renal, intestinal, and cardiovascular disorders. 9. Body mass index (BMI) > 35 kg/m^2. 10. On a special diet. 11. Any change in hypoglycaemic medications. 12. Psychiatric disorders impairing patient's ability to provide written informed consent. 13. Pregnancy, lactation Method for diagnosis of NAFLD: ultrasound and elastography
Interventions	Group 1: other supplements (n = 20) Further details: 200 mg caffeine or 200 mg chlorogenic acid or both (factorial trial design) for 12 weeks Group 2: no active intervention (n = 6) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 3
Notes	Source of funding (quote): "the study was supported by National Institute for Medical Research Development (NIMAD) to AH with grant number of 963356" Trial name/Trial registry number: NCT02929901 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization lists were computer generated by a statistician"
Allocation concealment (selection bias)	Low risk	Quote: "the supplements were concealed by the production company and revealed to us after the study results analysed (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "subjects, investigators, and staff were blinded to the treatment assignment until the end of the study…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "subjects, investigators, and staff were blinded to the treatment assignment until the end of the study…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Manzhalii 2017

Study characteristics

Manzhalii 2017 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: Ukraine Period of recruitment: not stated Number randomised: 75 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 75 Average age, years: 44 Females: 48 (64.0%) NASH: 75 (100.0%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NASH (based on USS detection of steatosis and elevated GGT > 45 and ALT > 40 and valid Fibroscan results). 2. Aged 30 to 60 years Exclusion criteria: 1. Other cause of chronic liver disease. 2. Alcohol > 40 g/d male, > 20 g/d female. 3. BMI > 30. 4. Diabetes. 5. Hypertriglycerides. 6. Pregnant/lactating. 7. Severe comorbidities Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	roup 1: prebiotics/probiotics/synbiotics (n = 38) Further details: probiotic cocktail (LBSF; Lactiale; Farmak, Kiev, Ukraine, containing *L casei, L rhamnosus, L bulgaris, B longum,* and *S thermophilus* (10^8 bacteria/capsule in total) as well as fructo-oligosaccharides), once daily for 12 weeks Group 2: no active intervention (n = 37) Further details: no treatment Additional details: both groups received low-calorie diet
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 3
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "closed envelop drawing"
Allocation concealment (selection bias)	Low risk	Quote: "closed envelop drawing"
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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported

Manzhalii 2017 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Martinez-Rodriguez 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Mexico Period of recruitment: 2013 to 2014 Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age, years: 47 Females: 26 (65.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD. 2. Aged ≥ 18 years. 3. Pre-diabetes, metabolic syndrome Exclusion criteria: 1. Significant alcohol consumption. 2. Other chronic liver disease. 3. Use of multi-vitamins within past 3 months. 4. Allergy to excipients used in study Method for diagnosis of NAFLD: ultrasound plus liver biopsy
Interventions	Group 1: other supplements (n = 20) Further details: orally administered selenium 15 mcg-methionine 3 mg-alpha lipoic acid 200 mg (SSMAL), every alternate day, for 24 weeks Group 2: no active intervention (n = 20) Further details: no additional supplementation Additional details: both groups received lifestyle advice and metformin
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: NCT01650181 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "we used www.randomization.com in order to assign participants to each arm"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "during data collection researchers did not have access to the randomization codes or statistical summaries of follow-up data" Comment: although study authors state double-blind, the method was not reported, as there is no mention of use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "during data collection researchers did not have access to the randomization codes or statistical summaries of follow-up data" Comment: although study authors state double-blind, the method was not reported, as there is no mention of use of placebo

Martinez-Rodriguez 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: a published protocol was available, but it is not clear whether recruitment had commenced before the protocol was published; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Miglio 2000

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 191 Post-randomisation dropouts: not stated Revised sample size: 191 Average age, years: 59 Females: 57 (29.8%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged > 18 years. 2. Liver enlargement and hepatic steatosis ascertained on USS Exclusion criteria: 1. History of past/present alcohol abuse. 2. Other cause of chronic liver disease Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: amino acids plus vitamin C (n = 96) Further details: Letepar (betaine glucuronate 150 mg, diethanolamine glucuronate 30 mg, nicotinamide ascorbate 20 mg) twice daily for 8 weeks Group 2: no active intervention (n = 95) Further details: placebo Additional details: both groups received dietary advice
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 2
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "double-blind, placebo-controlled" Comment: allocation concealment and blinding were achieved with use of placebo

Miglio 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Mofidi 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 8 (16.0%) Revised sample size: 42 Reasons for post-randomisation dropouts: lost to follow-up, travel Average age, years: 45 Females: 19 (45.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD. 2. Aged > 18 years. 3. BMI ≤ 25. 4. Lack of history of alcohol consumption Exclusion criteria: 1. Other cause of liver disease. 2. Use of antibiotics, probiotic supplements, and/or hepatotoxic medicine within 6 months. 3. Pregnant/breastfeeding. 4. > 10% body weight loss during the study Method for diagnosis of NAFLD: elastography plus transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 21) Further details: synbiotic supplement (Protexin; Probiotics International Ltd.; containing 200 million bacteria of 7 strains (*Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus bulgaricus*) and prebiotic (125 mg fructo-oligosaccharide) and probiotic cultures (magnesium stearate (source: mineral and vegetable) and a vegetable capsule (hydroxypropylmethyl cellulose)), twice daily, for 28 weeks Group 2: no active intervention (n = 21) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people) Follow-up, months: 7
Notes	Source of funding (quote): "Protexin Company, UK, provided the synbiotics supplements" Trial name/Trial registry number: NCT02530138 Attempts were made to contact study authors in December 2020

Mofidi 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization lists will be computer-generated by a statistician"
Allocation concealment (selection bias)	Low risk	Quote: "double-blind, placebo-controlled, clinical trial" Comment: allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled, clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled, clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but it is not clear whether recruitment had commenced before the protocol was published; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Moradi 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 45 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 45 Average age, years: 65 Females: 45 (100.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Obese. 2. Elderly. 3. Female. 4. Fatty liver disease confirmed by ultrasonography Exclusion criteria: 1. Addiction to smoking. 2. Alcohol abuse. 3. Regular physical exercise in the last 6 months. 4. Lung disease, kidney disease, cardiovascular disease, liver transplantation, high blood pressure, chronic disorder. 5. Special medications such as statins, oestrogen intake, additive effects on insulin sensitivity, hepatotoxic medication intake. 6. Special dietary programme. 7. Allergy to curcumin. 8. A cancer record. 9. Other supplements Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 22) Further details: 1 curcumin capsule (curcumin 80 mg as Nanomicelle, produced by Minoo Pharmaceutical Co.) per day for 12 weeks

Moradi 2020 *(Continued)*

	Group 2: no active intervention (n = 23) Further details: placebo daily for 12 weeks. Additional details: 50% of both groups received lifestyle intervention of non-linear resistance training (factorial trial design)
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "funding: none" Trial name/Trial registry number: IRCT20190103042219N1 Attempts were made to contact study authors in April 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: "the participants were identified using the codes instead of their actual names. A third party was asked to classify the participants randomly, using the (labelled) codes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind...placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind...placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Morvaridzadeh 2021

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 104 Post-randomisation dropouts: 16 (15.4%) Revised sample size: 88 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 40 Females: 41 (46.6%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD. 2. Aged 25 to 55 years. 3. Mild to moderate fatty liver

Morvaridzadeh 2021 *(Continued)*

	Exclusion criteria: 1. Any supplements and medications within 6 weeks. 2. Sensitive to yoghurt consumption. 3. Other chronic disease such as chronic heart, lung, kidney problems or cancer Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics plus vitamin D (n = 44) Further details: 100 g probiotic yoghurt fortified with vitamin D every day for 12 weeks Group 2: prebiotics/probiotics/synbiotics (n = 44) Further details: 100 g probiotic yoghurt every day for 12 weeks
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the Research Council approved this study of Kermanshah University of Medical Sciences" Trial name/Trial registry number: IRCT20131022015111N3 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using random numbers table"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind...placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind...placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts because of loss to follow-up; it is not clear whether these were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Nabavi 2016

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 72 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 72 Average age, years: 43

Nabavi 2016 *(Continued)*

	Females: 37 (51.4%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD. 2. Aged 23 to 60 years. 3. BMI 25 to 40 Exclusion criteria: 1. Kidney disease. 2. Other type of liver disease. 3. Inflammatory intestinal disease. 4. Immunodeficiency disease. 5. Use of tobacco or alcohol. 6. Nutritional supplements in previous 3 weeks. 7. Use of cholesterol-lowering medications, oestrogen, progesterone, or diuretics. 8. Pregnant/breastfeeding. 9. Consumption of probiotic yoghurt or any other probiotic products in last 2 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 36) Further details: 300 g/d of probiotic yoghurt for 8 weeks Group 2: no active intervention (n = 36) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 2
Notes	Source of funding (quote): "Pegah Dairy Industries Co. (Tabriz, Iran) for supplying the probiotic and conventional yoghurts" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the random sequence was generated by study statistician using random allocation software"
Allocation concealment (selection bias)	Low risk	Quote: "probiotic and conventional yogurt containers were identical looking…assignment of groups was covered from the investigators and the subjects"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized double-blind controlled clinical trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double-blind controlled clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Naganuma 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Japan Period of recruitment: not stated Number randomised: 20 Post-randomisation dropouts: not stated Revised sample size: 20 Average age, years: not stated Females: 20 (100.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD. 2. ALT ≥ 40. 3. Female Exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: amino acids (n = 10) Further details: 3 g leucine enriched amino acid-containing food for 3 months Group 2: no active intervention (n = 10) Further details: no treatment Additional details: both groups received lifestyle intervention
Outcomes	Outcomes reported: serious adverse events (number of people) Follow-up, months: 3
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Navekar 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 46 Post-randomisation dropouts: 4 (8.7%) Revised sample size: 42 Reasons for post-randomisation dropouts: personal reasons Average age, years: 41 Females: 24 (57.1%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Males aged 20 to 60 years, females aged 20 to 50 years. 2. BMI 24.9 to 40. 3. NAFLD Exclusion: 1. Diabetes. 2. Alcohol consumption. 3. Liver transplantation. 4. Liver disorders (hepatitis B or C, liver infection, etc.). 5. Biliary disease or presence of gallstones. 6. Inherited disorders affecting liver (iron storage disease, etc.). 7. Autoimmune disease. 8. Cancer. 9. Anaemia. 10. Medication (e.g. hypoglycaemics, dietary supplements). Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 21) Further details: turmeric capsules 3 g/d for 12 weeks Group 2: no active intervention (n = 21) Further details: placebo
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "we thank the Research Vice-Chancellor of Tabriz University of Medical Sciences, Tabriz, Iran, for the financial support" Trial name/Trial registry number: IRCT201406183664N12 Attempts were made to contact study 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	Low risk	Quote: "double-blind randomized controlled clinical trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized controlled clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Navekar 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

NCT00816465

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Israel Period of recruitment: 2009 to 2010 Number randomised: 20 Post-randomisation dropouts: not stated Revised sample size: 20 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 65 years. 2. Biopsy-proven NASH with score ≥ 4. 3. Altered glucose metabolism, including diabetes (non-treated, or treated with up to 2 drugs (not including insulin) without any change in medication 2 months before enrolment), impaired fasting glucose or impaired glucose tolerance, HbA1C between 5.5% and 14% Exclusion criteria: not stated Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: other supplements (n = not stated) Further details: oral administration of 1 tablet of Hoodia gordoni extract per day Group 2: no active intervention (n = not stated) Further details: oral placebo pill
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT00816465 Attempts were made to contact study 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	Low risk	Quote: "masking: quadruple (participant, care provider, investigator, outcomes assessor)…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "masking: quadruple (participant, care provider, investigator, outcomes assessor)…placebo"

NCT00816465 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

NCT00845845

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2006 to 2009 Number randomised: 9 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 9 Average age, years: not stated Females: 4 (44.4%) NASH: 9 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. ≥ 18 years old. 2. NASH on liver biopsy within 6 months. 3. Laboratory parameters of decompensated liver disease (bilirubin < 2 mg/dL, stable normal albumin, prothrombin time < 3 seconds prolonged). 4. Serum creatinine < 1.5× upper limit of normal. 5. Diabetic patients stable on oral meds or with < 10% change in insulin dose over past 2 months. 6. Normal TSH or FTI. 7. Hep C antibody negative, HBsAg seronegative, ANA < 1:320 Exclusion criteria: 1. Alcohol use exceeding 10 to 20 g/d during past 6 months. 2. Other cause of liver disease, cirrhosis. 3. Use of medication associated with NASH within 6 months. 5. Use of NSAIDs, fibrates, or warfarin within 1 month. 6. Uncontrolled diabetes, insulin-dependent diabetes. 7. History of small bowel resection. 8. Substance abuse within past 6 months. 9. Chemotherapy within 6 months. 10. Taking metformin. 11. Unstable thyroid function. 12. Pregnancy, breastfeeding. 13. Transplant recipient. 14. Use of oral supplements of vitamin E within 1 month Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: PUFA (n = 3) Further details: participants received 4 mg daily of omega-3-acid ethyl esters (Lovaza) for 24 weeks Group 2: no active intervention (n = 6) Further details: participants received daily placebo for 24 weeks Additional details: both groups received dietary advice
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events), adverse events (number of people), adverse events (number of events) Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: NCT00845845 Attempts were made to contact study authors in December 2020

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

NCT00845845 *(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	Low risk	Quote: "study design - masking: quadruple…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "study design - masking: quadruple…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although some participants were lost to follow-up, all randomised participants were included in the analysis
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

NCT00941642

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: not stated Revised sample size: 40 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged > 18 years. 2. Abnormal liver enzymes 3. NAFLD or NASH on biopsy Exclusion criteria: not stated Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: no active intervention (n = not stated) Further details: placebo Group 2: PUFA (n = not stated) Further details: Lovaza (fish oil supplement) 4 g daily for minimum 48 weeks
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT00941642 Attempts were made to contact study authors in December 2020
Risk of bias	

NCT00941642 *(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	Quote: "masking: single (participant)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "masking: single (participant)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

NCT00977730

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2008 to 2011 Number randomised: 70 Post-randomisation dropouts: not stated Revised sample size: 70 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 years and over. 2. ALT above normal limits. 3. Evidence of steatohepatitis on liver biopsy Exclusion criteria: 1. Other liver disease. 2. Excess alcohol ingestion. 3. Low platelets or high INR. 4. Stage III or IV fibrosis on baseline liver biopsy. 5. Diabetes mellitus. 6. History of gastrointestinal bypass surgery. 7. Use of certain drugs (corticosteroids, high-dose oestrogens, methotrexate, tetracycline, amiodarone, statins, antidiabetic drugs, herbal or non-prescription medications). 8. Major systemic illness. 9. Substance abuse. 10. Pregnancy. 11. Hepatocellular carcinoma. 12. Creatinine > 1.5 mg/dL in men, > 1.3 mg/dL in women. 13. Abnormal TSH, bilirubin > 2.0, AST or ALT > 3× upper limits of normal, sodium < 130, haematocrit < 35 Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: other antioxidants plus other supplements (n = not stated) Further details: 1× 675-mg capsule Protandim per day for 12 months. Protandim is a nutritional supplement composed of the following 5 botanical extracts: Bacopa Moniera extract, Milk Thistle extract, Ashwagandha powder, Green tea, and Turmeric extract

NCT00977730 *(Continued)*

	Group 2: no active intervention (n = not stated) Further details: 1 sugar pill per day
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT00977730 Attempts were made to contact study 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	Low risk	Quote: "masking: triple (participant, investigator, outcomes assessor)…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "masking: triple (participant, investigator, outcomes assessor)…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

NCT01083992

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Israel Period of recruitment: not stated Number randomised: not stated Post-randomisation dropouts: not stated Revised sample size: 0 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 65 years. 2. Men and women with NAFLD per USS. 3. Increased ALT level. 4. Hepatomegaly. 5. Liver biopsy within 2 years Exclusion criteria: 1. Other liver disease (HBV, HCV). 2. Hepatocellular carcinoma. 3. Decompensated liver disease. 4. Use of steroids

NCT01083992 *(Continued)*

	Method for diagnosis of NAFLD: liver biopsy plus transaminases plus ultrasound
Interventions	Group 1: no active intervention (n = not stated) Further details: no intervention Group 2: vitamin D (n = not stated) Further details: vitamin D (no further details) Additional details: both groups received vitagliptin
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

NCT01623024

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 200 Post-randomisation dropouts: not stated Revised sample size: 200 Average age, years: not stated Females: not stated NASH: 200 (100.0%)

NCT01623024 *(Continued)*

	Diabetes mellitus: not stated Inclusion criteria: 1. Aged > 18 years. 2. Histological diagnosis of possible or definitive NASH according to Kleiner score within 6 months Exclusion criteria: not stated Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: no active intervention (n = not stated) Further details: only lifestyle advice Group 2: vitamin D (n = not stated) Further details: vitamin D 20,000 IU/week for 96 weeks Additional details: both groups received lifestyle advice
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT01623024 Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

NCT02690792

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2009 to 2016 Number randomised: 70 Post-randomisation dropouts: not stated

NCT02690792 *(Continued)*

	Revised sample size: 70 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E (n = not stated) Further details: vitamin E 200 IU/capsule; 2 capsules each morning and 2 capsules each evening for 4 months Group 2: no active intervention (n = not stated) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT02690792 Attempts were made to contact study 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	Low risk	Quote: "masking: quadruple (participant, care provider, investigator, outcomes assessor)…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "masking: quadruple (participant, care provider, investigator, outcomes assessor)…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

NCT04411862

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Egypt Period of recruitment: 2016 to 2019

NCT04411862 *(Continued)*

	Number randomised: 100 Post-randomisation dropouts: not stated Revised sample size: 100 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Fatty liver upon USS/CT/MRI. 2. Increased alanine aminotransferase (ALT). 3. Homeostasis model assessment-insulin resistance (HOMA IR) score > 3. 4. Presence of liver steatosis or stiffness measured by transient elastography. 5. ≥ 1 of the following metabolic comorbidities: hypertension, type 2 diabetes mellitus, overweight/obesity (BMI > 27 kg/m^2), serum cholesterol > 200 mg/dL Exclusion criteria: 1. Evidence of alcoholic or chronic liver disease. 2. Hepatocellular carcinoma. 3. Autoimmune hepatitis. 4. End-stage liver disease. 5. Treatment with other hepatoprotectants. 6. Other concomitant EPL within 30 days. 7. Pregnancy or lactation Method for diagnosis of NAFLD: ultrasound, or CT, or MRI
Interventions	Group 1: phospholipids (n = 50) Further details: dietary supplement: 2.1 g phosphatidylcholine daily Group 2: no active intervention (n = 50) Further details: no additional dietary supplement Additional details: both groups received lifestyle behavioural modification and health education by a clinical pharmacist
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: NCT04411862 Attempts were made to contact study authors in April 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	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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Nelson 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: not stated Period of recruitment: not stated Number randomised: 15 Post-randomisation dropouts: not stated Revised sample size: 15 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: MUFA (n = not stated) Further details: monounsaturated fatty acids (MUFA; i.e. safflower oil) for 8 weeks Group 2: PUFA (n = not stated) Further details: omega-3 polyunsaturated fatty acids (PUFA; i.e. fish oil) for 8 weeks
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Nobili 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2003 to 2005 Number randomised: 90 Post-randomisation dropouts: 2 (2.2%) Revised sample size: 88 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 12 Females: 60 (68.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Otherwise healthy biopsy-proven NAFLD children. 2. Aged 3 to 18 years Exclusion criteria: 1. Hepatic virus infection. 2. Alcohol consumption. 3. Parenteral nutrition. 4. Steatosis-inducing drugs. 5. Other known chronic liver disease Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E plus vitamin C (n = 45) Further details: alpha-tocopherol 600 IU/d plus ascorbic acid 500 mg/d for 12 months Group 2: no active intervention (n = 43) Further details: placebo Additional details: both groups received balanced calorie diet and physical exercise
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 12
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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)	Low risk	Quote: "double-blind placebo study" Comment: allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind placebo study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind placebo study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Nobili 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Nobili 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 60 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 60 Average age, years: 12 Females: 35 (58.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged < 18 years. 2. Persistently elevated ALT ≥ 40. 3. Diffusely hyperechogenic liver. 4. Liver biopsy consistent with NAFLD Exclusion criteria: 1. Viral liver disease. 2. Autoimmune liver disease. 3. Wilson's disease. 4. α-1-antitrypsin deficiency. 5. Coeliac disease. 6. Alcohol consumption. 7. Parenteral nutrition. 8. Use of drugs known to induce fatty liver. 9. Previous use of N3-LCPUFA Method for diagnosis of NAFLD: ultrasound plus liver biopsy
Interventions	Group 1: PUFA (n = 40) Further details: DHA supplementation (250 mg/d and 500 mg/d) for 24 months Group 2: no active intervention (n = 20) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: mortality at maximal follow-up, resolution of fatty liver disease Follow-up, months: 24
Notes	Source of funding (quote): "the study was supported by the 'Bambino Gesù' Children Hospital" Trial name/Trial registry number: NCT0885313 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Quote: "a statistician, who did not perform the final analysis, generated the allocation sequence and assigned participants to the treatment groups"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants, investigators and outcome assessors were blinded to the treatment for all the duration of the study…placebo"

Nobili 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "participants, investigators and outcome assessors were blinded to the treatment for all the duration of the study…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Nogueira 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: not stated Number randomised: 60 Post-randomisation dropouts: 10 (16.7%) Revised sample size: 50 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 53 Females: 49 (98.0%) NASH: 60 (120.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Proven histological diagnosis of NASH Exclusion criteria: 1. Other chronic liver disease. 2. Substance abuse. 3. Use of hepatotoxic drugs. 4. Allergy or food intolerance Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: PUFA (n = 27) Further details: 3 capsules of 0.315 g omega-3 PUFAs (64% alphalinolenic (ALA), 16% eicosapentaenoic (EPA), and 21% docosahexaenoic (DHA) acids) per day for 6 months Group 2: no active intervention (n = 23) Further details: placebo
Outcomes	Outcomes reported: fibrosis score, NAFLD activity score Follow-up, months: 6
Notes	Source of funding (quote): "omega-3 and placebo capsules were provided by Amway (USA)" Trial name/Trial registry number: ID01992809 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "generated by computer"

Nogueira 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "this independent dietician, investigators and clinical staff remained blinded to each study participant's assignment until the end of the statistical analysis phase of the trial" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Orang 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 48 Post-randomisation dropouts: 4 (8.3%) Revised sample size: 44 Reasons for post-randomisation dropouts: lost to follow-up (2), discontinued intervention (2) Average age, years: 48 Females: 31 (70.5%) NASH: not stated Diabetes mellitus: 44 (100.0%) Inclusion criteria: 1. Adults. 2. Type 2 diabetes mellitus. 3. NAFLD Exclusion criteria: 1. Any kind of malignancy. 2. Renal, heart, thyroid, or haemorrhagic disease. 3. Use of insulin or omega-3 supplement in previous 3 months. 4. Use of alcohol. 5. Diagnosis of hepatitis B or C Method for diagnosis of NAFLD: not stated
Interventions	Group 1: PUFA (n = 22) Further details: omega-3 consumed as 2 capsules per day, each containing 1000 mg of omega-3, for 12 weeks Group 2: no active intervention (n = 22) Further details: 2 capsules of placebo (edible paraffin oil) per day for 12 weeks
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "Nutrition and Food Security Research Center of Shahid Sadoughi University of Medical Sciences funded this research. The corresponding author, Mozaffari-hassan, is an academ-

Orang 2020 *(Continued)*

	ic member of Shahid Sadoughi University of Medical Sciences, and the others were master science students. Authors of the presents study have no conflict of interests to declare" Trial name/Trial registry number: IRCT2017103030489N2 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using computer generated random number"
Allocation concealment (selection bias)	Low risk	Quote: "random allocation remains blind until the beginning of study and, in order to blinding both participants and personnel for the type of capsules, the factory made both omega-3 and placebo capsules with a same appearances and packed in similar package, named as A and B, and was not revealed after the analyzing data" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts because the intervention was discontinued. it is not clear whether these were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Orr 2015

Study characteristics

Methods	Randomised clinical trial
Participants	Country: New Zealand Period of recruitment: not stated Number randomised: not stated Post-randomisation dropouts: not stated Revised sample size: 0 Average age, years: 50 Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = not stated)

Orr 2015 *(Continued)*

	Further details: inulin (4 g) sachets twice daily for 12 weeks Group 2: no active intervention (n = not stated) Further details: placebo Additional details: another group not relevant to this review was excluded
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: ANZCTR-12613001002774 Attempts were made to contact study 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	Low risk	Quote: "double-blind, placebo controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo controlled"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Oscarsson 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Sweden Period of recruitment: not stated Number randomised: 51 Post-randomisation dropouts: 5 (9.8%) Revised sample size: 46 Reasons for post-randomisation dropouts: adverse events (3); patients withdrew due to going abroad (2) Average age, years: 60 Females: 21 (45.7%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Aged 40 to 75 years. 2. BMI 25 to 40. 3. Serum TG > 1.7. 4. Liver PDFF > 5.5%

Oscarsson 2018 *(Continued)*

	Exclusion criteria: 1. History of hepatic disease. 2. Inability to undergo MRI scanning. 3. Significant alcohol intake Method for diagnosis of NAFLD: liver MRI
Interventions	Group 1: PUFA (n = 23) Further details: 4 g omega 3 fatty acid (Epanova; EPA (500 to 600 mg/g), DHA (150 to 250 mg/g), and docosapentaenoic acid (10 to 80 mg/g)) for 12 weeks Group 2: no active intervention (n = 23) Further details: placebo Additional details: another group not relevant to this review was excluded
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), hepatocellular carcinoma Follow-up, months: 3
Notes	Source of funding (quote): "the EFFECT I study was funded by AstraZeneca" Trial name/Trial registry number: EFFECT 1 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated numbers"
Allocation concealment (selection bias)	Low risk	Quote: "centralized randomization system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomized, placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the participant flow was not clear (i.e. it is not clear whether participants who were withdrawn were included for the outcomes)
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Pacifico 2015

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2012 to 2014

Pacifico 2015 *(Continued)*

	Number randomised: 58 Post-randomisation dropouts: 7 (12.1%) Revised sample size: 51 Reasons for post-randomisation dropouts: lost to follow-up, MRI not available Average age, years: 11 Females: 21 (41.2%) NASH: 33 (64.7%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Aged < 18 years. 2. BMI > 85th percentile. 3. Persistently elevated ALT. 4. MRI-diagnosed NAFLD Exclusion criteria: 1. Hepatic viral infection and other secondary cause of steatosis. 2. Smoking. 3. Renal disease. 4. Alcohol intake. 5. Total parenteral nutrition. 6. Hepatotoxic medications. 7. Type 1 or 2 diabetes Method for diagnosis of NAFLD: liver biopsy plus MRI
Interventions	Group 1: PUFA (n = 25) Further details: docosahexaenoic acid (DHA) supplementation 250 mg/d for 6 months Group 2: no active intervention (n = 26) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this study was funded by the Sapienza University of Rome (Progetti di Ricerca Universitaria 2011e2012)" Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a randomization list (in a 1:1 ratio to treatment with DHA or placebo) was generated by an independent statistician who was blinded to participants' clinical data and did not perform the final analysis"
Allocation concealment (selection bias)	Unclear risk	Quote: "all participants and research staff were blind to the group assignment" Comment: allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled randomized trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled randomized trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Palamaru 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Romania Period of recruitment: 2016 to 2017 Number randomised: 40 Post-randomisation dropouts: not stated Revised sample size: 40 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E (n = 20) Further details: vitamin E supplements Group 2: no active intervention (n = 20) Further details: no additional supplements Additional details: both groups received lifestyle intervention (i.e. diet and exercise)
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Panahi 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2009 Number randomised: 76 Post-randomisation dropouts: 22 (28.9%) Revised sample size: 54 Reasons for post-randomisation dropouts: not stated Average age, years: 49 Females: not stated NASH: not stated Diabetes mellitus: 11 (20.4%) Inclusion criteria: 1. Sonographic evidence of fatty liver disease Exclusion criteria: 1. Alcohol intake. 2. Cirrhosis and other forms of chronic liver disease. 3. Hepatitis (autoimmune, viral, iatrogenic). 4. Surgery Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin E plus other supplements (n = 21) Further details: *Chlorella vulgaris* extract (Algomed: 1200 mg/d) plus vitamin E (200 mg/d) for 3 months Group 2: vitamin E (n = 33) Further details: vitamin E (200 mg/d) for 3 months Additional details: both groups received metformin
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work was financially supported by a grant from the Baqiyatallah University of Medical Sciences (Tehran, Iran)" Trial name/Trial registry number: not stated Attempts were made to contact study 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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Panahi 2012 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Panahi 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 102 Post-randomisation dropouts: 15 (14.7%) Revised sample size: 87 Reasons for post-randomisation dropouts: discontinued intervention because of perception of lack of effect Average age, years: 46 Females: 36 (41.4%) NASH: not stated Diabetes mellitus: 21 (24.1%) Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Pregnancy/breastfeeding. 2. Alcohol consumption. 3. Smoking. 4. Hepatotoxic drugs. 5. Hepatitis. 6. Coronary, renal, pulmonary, and thyroid disease Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 44) Further details: curcumin (1000 mg/d in 2 divided doses) for 8 weeks Group 2: no active intervention (n = 43) Further details: no treatment Additional details: both groups received dietary and lifestyle advice
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "the authors are grateful for the supports provided by the Baqiyatallah University of Medical Sciences (Tehran, Iran) and Indena SpA (Milan, Italy)" Trial name/Trial registry number: IRCT2015122525641N2 Attempts were made to contact study 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

Panahi 2016 *(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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Parsi 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 60 Post-randomisation dropouts: not stated Revised sample size: 60 Average age, years: 35 Females: 27 (45.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Liver ultrasonography (steatosis score ≥ 1). 2. Serum levels of ALT > 19 U/L for women, 30 U/L for men. 3. Aged 20 to 60 years. 4. BMI ranging from 24.9 to 40 kg/m^2 Exclusion criteria: 1. Other cause of fatty liver such as alcohol consumption. 2. Use of drugs that may have potential benefit for treatment of NAFLD such as vitamin E, metformin, pentoxifylline, and rosiglitazone. 3. Pregnant and lactating woman. 4. Renal, liver, heart, pituitary, thyroid, or psychiatric disorder. 5. Weight loss > 10% of initial body weight during the intervention. 6. Taking a probiotic, multi-vitamin-mineral, or antioxidant supplement during past 3 months. 7. Not taking more than 10% of supplements at any follow-up visit Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: other supplements (n = 30) Further details: saffron (containing 15 mg Crocin) supplement daily for 8 weeks Group 2: no active intervention (n = 30) Further details: Identical-appearing placebo capsules (starch) once daily for 8 weeks
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "this work was financially supported by Alimentary Tract Research Center, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Grant Number: RDC-9612)" Trial name/Trial registry number: IRCT20180513039634N Attempts were made to contact study authors in April 2021

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

Parsi 2020 *(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	Low risk	Quote: "double-blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Pasdar 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2017 Number randomised: 90 Post-randomisation dropouts: 12 (13.3%) Revised sample size: 78 Reasons for post-randomisation dropouts: unwillingness to continue (7), non-adherence (3), travel (2) Average age, years: 45 Females: 50 (64.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. 18 to 65 years old. 2. NAFLD as approved by ultrasonography. 3. Body mass index between 25 and 40 kg/m^2 Exclusion criteria: 1. History of alcohol abuse. 2. Acute or chronic disease such as liver disorder (hepatitis B and C), Wilson's disease, cirrhosis, autoimmune disease, and thyroid disorder. 3. Previous exposure to pesticides and insecticides. 4. Taking steatogenic medications, which potentially interact with quercetin (anticoagulant agents, inhibitors of CYP3A4, etc.) Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 39) Further details: quercetin (Sigma Q4951 ≥ 95% purity; Sigma-Aldrich, St. Louis, Missouri, USA); each patient received 250-mg capsules twice daily Group 2: no active intervention (n = 39) Further details: placebo (Avicel PH101; Sigma-Aldrich) produced at same size, colour, and smell as quercetin capsules. Each patient received 250-mg capsules twice daily
Outcomes	No outcomes of interest were reported

Pasdar 2020 *(Continued)*

Notes	Source of funding: not stated Trial name/Trial registry number: IRCT2016060628299N1 Attempts were made to contact study authors in April 2021

Risk of bias

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)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts, some of which seem to be related to the intervention
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Pervez 2018

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2015 to 2016 Number randomised: 71 Post-randomisation dropouts: 7 (9.9%) Revised sample size: 64 Reasons for post-randomisation dropouts: withdrew consent, lost to follow-up Average age, years: 44 Females: 35 (54.7%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Chronic hepatitis B/C. 2. Alcoholic liver disease. 3. Autoimmune disease. 4. Hepatotoxic medication Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin E (n = 31) Further details: oral delta-tocotrienol 300 mg twice daily for 12 weeks Group 2: no active intervention (n = 33)

Pervez 2018 *(Continued)*

	Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "this study is funded by the Armed Forces Institute of Pathology, Rawalpindi and Higher Education Commission, Government of Pakistan, Islamabad" Trial name/Trial registry number: not stated Attempts were made to contact study 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)	Low risk	Quote: "the same opaque capsules containing either δ-tocotrienol or placebo (sucrose) were administered to the patients by a research assistant blinded to the contents of the capsules"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled pilot study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled pilot study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Pervez 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2015 to 2016 Number randomised: 71 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 71 Average age, years: 44 Females: 37 (52.1%) NASH: not stated Diabetes mellitus: not stated

Pervez 2020 *(Continued)*

	Inclusion criteria: 1. Aged 20 to 70 years. 2. Ultrasound-proven fatty liver, fatty liver index (FLI) ≥ 6018, and mild to moderate persistent elevation of alanine transaminase (ALT) and aspartate transaminase (AST) (i.e. not greater than 4 times the upper limit of 42 IU/L and 37 IU/L, respectively) Exclusion criteria: 1. Viral hepatitis B and C. 2. Alcoholic liver disease. 3. Autoimmune hepatitis, haemochromatosis, Wilson's disease. 4. Malignancy. 5. Cardiovascular, respiratory, and kidney disorders. 6. Pregnancy or lactation. 7. History of using hepatotoxic and lipid-lowering drugs and herbal or vitamin supplements. 8. History of average alcohol consumption > 30 g/d in men, > 20 g/d in women, in past 3 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin E (n = 35) Further details: tocotrienol group received two 300-mg tocotrienol capsules per day. Tocotrienol capsules were manufactured by American River Nutrition, Inc., Hadley, MA. USA. Tocotrienol was extracted from annatto bean; each capsule contained 90% δ-tocotrienol and 10% γ- tocotrienol Group 2: no active intervention (n = 36) Further details: placebo group received two 50-mg sucrose capsules per day. Placebo and tocotrienol capsules were identical in size, colour, and consistency to ensure blinding of patients
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding (quote): "this work was financially supported by Higher EducationCommission, Government of Pakistan Islamabad" Trial name/Trial registry number: SLCTR/2015/023 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized to receive δ-tocotrienol or placebo through the simple randomization technique by a person not involved in the study" Comment: further details were not available
Allocation concealment (selection bias)	Low risk	Quote: "randomized to receive δ-tocotrienol or placebo through the simple randomization technique by a person not involved in the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both the patients and investigators were blinded to treatment allocation…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "both the patients and investigators were blinded to treatment allocation…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: an intention-to-treat analysis was used
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Pezeshki 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2013 to 2014 Number randomised: 80 Post-randomisation dropouts: 9 (11.3%) Revised sample size: 71 Reasons for post-randomisation dropouts: discontinued treatment Average age, years: not stated Females: 39 (54.9%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 20 to 50 years. 2. BMI ≥ 30. 3. NAFLD Exclusion criteria: 1. Other liver disease (Wilson's, autoimmune, haemochromatosis, viral infection). 2. Alcoholic liver disease. 3. Hepatotoxic medication Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: other supplements (n = 35) Further details: green tea extract (GTE) 500 mg/d for 90 days Group 2: no active intervention (n = 36) Further details: placebo
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: Protexin Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a random number between 0.0 and 0.99 was generated by the computer for each subject"
Allocation concealment (selection bias)	Low risk	Quote: "by a research assistant blinded to the contents in the capsules"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled, randomized clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled, randomized clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Poparn 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Thailand Period of recruitment: 2016 Number randomised: 37 Post-randomisation dropouts: 0 (0%) Revised sample size: 37 Average age (years): 12 Females: 25 (67.6%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Children. 2. NAFLD defined by CAP value > 225 dB/m by Fibroscan Exclusion criteria: 1. Children with metabolic liver disease. 2. Viral hepatitis. 3. Wilson's disease. 4. Autoimmune hepatitis. 5. Hepatotoxic drug exposure. 6. Alcohol consumption Method for diagnosis of NAFLD: FibroScan
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 18) Further details: a powder mixture containing 2.24 grams chicory inulin, 1.5×10^9 colony-forming units of *Lactobacillus acidophilus* and *Bifidobacterium lactis* in each sachet for 16 weeks Group 2: no active intervention (n = 19) Further details: indistinguishable placebo for 16 weeks
Outcomes	Outcomes reported: mortality, serious adverse events (number of people), any adverse events (number of people), liver transplantation, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma Follow-up, months: 3
Notes	Source of funding (quote): "this study was supported by the Ratchadaphiseksomphot Fund, Faculty of Medicine, Chulalongkorn University (RA59/030)" Trial name/Trial registry number: TCTR20170128001 Attempts were made to contact study authors in April 2021

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "by generating random allocation sequence using computer software" (author replies)
Allocation concealment (selection bias)	Low risk	Quote: "the company allocated synbiotics and placebo, which were packed in indistinguishable sachets to the recruiter (concealed allocation)" (author replies)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts

Poparn 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Poulos 2021

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 27 Post-randomisation dropouts: 2 (7.4%) Revised sample size: 25 Reasons for post-randomisation dropouts: lost to follow-up Average age, years: 56 Females: 19 (76.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria. 1. ≥ 18 years of age. 2. Clinical or radiological evidence of NAFLD established by liver biopsy or radiographic studies revealing hepatic steatosis. 3. Metabolic syndrome. 4. Elevated AST/ALT in the absence of any other metabolic, viral, or autoimmune aetiology. 5. Negative urine pregnancy test (for females of childbearing potential) Exclusion criteria: 1. History of having received any investigational drug within 3 months. 2. History of a medical condition associated with chronic liver disease other than NAFLD. 3. Baseline increased risk for anaemia or anaemia would be medically problematic. 4. History of severe psychiatric disease, including psychosis and/or severe depression, characterised by a suicide attempt, hospitalisation for psychiatric disease, or a period of disability due to psychiatric disease. 5. Positive test at screening for hepatitis A, B, C, or HIV/AIDS. 6. Pregnant or breastfeeding. 7. Type 1 or 2 diabetes with HbA1C > 8.5% at screening. 8. History or other evidence of chronic pulmonary disease associated with functional limitation. 9. Uncontrolled seizure disorder. 10. Poorly controlled thyroid function. 11. Bleeding disorder, or anticoagulant use. 12. Poorly controlled hypertension. 13. Evidence of active or suspected cancer, or history of malignancy within last 2 years, except those with basal cell carcinoma that has been excised and cured Method for diagnosis of NAFLD: liver biopsy or radiographic studies plus transaminases
Interventions	Group 1: amino acids plus vitamin E plus other antioxidants (n = 14) Further details: drug compound consisted of a pill containing vitamin E 200 IU, silymarin 750 mg, and *L carnitine* 1 gram (EuroMED USA, Inc.). Silymarin was 80% silybin Group 2: no active intervention (n = 11) Further details: placebo consisted of rice flour containing 32 calories per dose and 0.77 net carbs/g
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "Biovil Corporation" Trial name/Trial registry number: NCT01511523 Attempts were made to contact study authors in April 2021

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

Poulos 2021 *(Continued)*

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 because of loss to follow-up. it is not clear whether these were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Pour 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2016 to 2017 Number randomised: 76 Post-randomisation dropouts: not stated Revised sample size: 76 Average age, years: 43 Females: 33 (43.4%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Chronic liver disease such as viral hepatitis. 2. Diabetes mellitus. 3. Infection. 4. Cancer. 5. Autoimmune disease. 6. Inherited disorder affecting the liver condition (storage disorders of iron, copper, and others). 7. Acute cardiovascular, respiratory, and kidney disorders. 8. Hypertension. 9. Hypothyroidism. 10. Any disorder that affects weight (hyperprolactinaemia, Cushing's syndrome). 11. Pregnant or lactating women. 12. Use of hepatotoxic medication. 13. Alcohol use. 14. Taking any medication or on strict diet to lose weight in the past 3 months. 15. Taking lipid-lowering drugs or antidiabetic drugs, vitamins, or any antioxidant supplements. 16. Therapy with approved medicine that may have potential benefit for treatment of NAFLD (i.e. vitamin E, betaine, pioglitazone, milk thistle, thiazolidinedione, anti-TNF-α, UDCA, SAM-E). 17. Consuming < 80% of tablets at any follow-up visit Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 38) Further details: 1 tablet containing 100 mg saffron per day Group 2: no active intervention (n = 38) Further details: placebo - similar shape and size tablets containing 100 mg maltodextrin Additional details: both groups were given a healthy diet and physical activity advice
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people)

Pour 2020 *(Continued)*

	Follow-up, months: 3
Notes	Source of funding (quote): "this work was financially supported by the Iran University of Medical Sciences (IUMS)" Trial name/Trial registry number: IRCT number: 201705309472N13 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the participants were randomly assigned into two groups by a computer-generated random sequence"
Allocation concealment (selection bias)	Low risk	Quote: "a statistical advisor who did not involved in the study encoded unique codes on the identical boxes, which was generated by the software"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomization and assignment of the participants into the groups (allocation) were hidden from both the researchers and the patients until the final analyses were completed…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomization and assignment of the participants into the groups (allocation) were hidden from both the researchers and the patients until the final analyses were completed…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: an intention-to-treat analysis was performed
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Qin 2015

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2012 to 2013 Number randomised: 80 Post-randomisation dropouts: 10 (12.5%) Revised sample size: 70 Reasons for post-randomisation dropouts: loss to follow-up Average age, years: 45 Females: 19 (27.1%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Steady BMI between 20 and 30 over past 3 months. 2. No excessive alcohol consumption Exclusion criteria: 1. Viral hepatitis, autoimmune hepatitis, or other liver disease. 2. Use of medication or dietary supplement over past 6 months that could influence NAFLD. 3. Gastrointestinal disease, severe chronic disease, kidney dysfunction, or malignant tumour. 4. Acute or chronic infectious disease. 5. Any surgical procedure

Qin 2015 *(Continued)*

	Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: PUFA plus vitamin E (n = 36) Further details: fish oil (182 mg EPA and 129 mg DHA, in addition to vitamin E) 4 g/d for 3 months Group 2: no active intervention (n = 34) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 3
Notes	Source of funding: not stated Trial name/Trial registry number: ChiCTR-TRC12002380 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomized sequence was produced by a randomization protocol using the IBM SPSS Statistics 19.0 (IBM, Japan) system"
Allocation concealment (selection bias)	Low risk	Quote: "the information of randomization was sealed until the end of the study" Comment: allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomized clinical trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, randomized clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Rafie 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 4 (8.0%)

Rafie 2020 *(Continued)*

	Revised sample size: 46 Reasons for post-randomisation dropouts: discontinued intervention (2), received supplementary (2) Average age, years: 49 Females: 26 (56.5%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 20 to 70 years. 2. 24.9 < BMI < 35.19. 3. High levels of liver enzymes (> 30 U/L in men, > 19 U/L in women) Exclusion criteria: 1. Alcohol > 20 g per day. 2. Taking drugs with liver toxicity such as calcium channel blockers, methotrexate, NSAIDs, oestrogens, progesterones, immunosuppressants, diuretics, and corticosteroids. 3. Liver disorder other than NAFLD (e.g. hereditary haemochromatosis, Wilson's disease, cirrhosis, hepatitis C, hepatitis B, autoimmune hepatitis). 4. Diabetes and other metabolic disease. 5. History of disease such as Cushing's syndrome, hypothyroidism, heart failure, renal failure, and renal stones. 6. Weight loss medication. 7. Any supplement in last 6 months. 8. History of gastric bypass surgery. 9. Severe weight loss during last 6 months. 10. Receiving hormone therapy Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: other supplements (n = 23) Further details: 500 mg ginger rhizome powder capsules; 3 capsules daily Group 2: no active intervention (n = 23) Further details: 3 capsules 500 mg of placebo that were apparently similar to the ginger supplement. Placebo containing wheat flour was prepared in the same form and colour as a ginger supplement at Pharmacy Faculty Lab of Ahvaz Jundishapur University of Medical Sciences Additional details: patients in both groups were advised to receive a diet with energy balanced, according to guidelines published by the North American Association, and all patients were asked to exercise at least 3 times a week for 30 minutes a day
Outcomes	Outcomes reported: any adverse events (number of people) Follow-up, months: 3
Notes	Source of funding (quote): "this study was supported by the Vice Chancellor for research affairs of Ahvaz Jundishapur University of Medical Sciences" Trial name/Trial registry number: IRCT2016042827652N1 Attempts were made to contact study authors in April 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: "before the beginning of the study, the cans containing the capsules were coded by a person other than the researcher, in the form of B and A, to ensure that the researchers did not know the type of capsules received by each group (given the double-blindness of the study)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomized clinical trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether these were related to the intervention and to outcomes

Rafie 2020 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Rahimlou 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 6 (12.0%) Revised sample size: 44 Reasons for post-randomisation dropouts: willingness to continue, immigration Average age, years: 45 Females: 24 (54.5%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Presence of steatosis on Fibroscan Exclusion criteria: 1. Chronic liver disease. 2. Diabetes mellitus. 3. Cancer. 4. Inherited disorder of liver. 5. Untreated hypothyroidism. 6. Alcohol use.7. Weight loss surgery. 8. Pregnancy/Lactation Method for diagnosis of NAFLD: elastography plus transaminases
Interventions	Group 1: other supplements (n = 23) Further details: ginger supplement 2 g/d for 12 weeks Group 2: no active intervention (n = 21) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people) Follow-up, months: 3
Notes	Source of funding (quote): "we thank green plants of life pharmaceutics Co. for providing ginger and placebo capsules and all participants that contributed to this study" Trial name/Trial registry number: NCY02535195 Attempts were made to contact study authors in December 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "statistician and participants, project managers and employees at the clinic were completely unaware (blind) about the intervention and control groups… identical placebos" Comment: both allocation concealment and blinding were achieved with use of placebo

Rahimlou 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Rahmani 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 80 Post-randomisation dropouts: 3 (3.8%) Revised sample size: 77 Reasons for post-randomisation dropouts: adverse events Average age, years: 48 Females: 42 (54.5%) NASH: not stated Diabetes mellitus: not stated Inclusion: criteria: 1. Diagnosis of NAFLD according to liver ultrasound Exclusion holiday: 1. Pregnancy/breastfeeding. 2. NAFLD secondary to alcohol. 3. Smoking. 4. Hepatotoxic medication. 5. Hepatitis Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 37) Further details: curcumin (500 mg/d equivalent to 70 mg curcumin) for 8 weeks Group 2: no active intervention (n = 40) Further details: placebo
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 2
Notes	Source of funding (quote): "this study was financially supported by the Isfahan University of Medical Sciences (Isfahan, Iran). The financial support provided by the Iran National Science Foundation (INSF) is also gratefully acknowledged" Trial name/Trial registry number: IRCT2014110511763N18 Attempts were made to contact study authors in December 2020

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

Rahmani 2016 *(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	Low risk	Quote: "randomized double-blind placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double-blind placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons which may be related to the intervention and the outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available: adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Ruan 2010

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: china Period of recruitment: 2008 to 2009 Number randomised: 60 Post-randomisation dropouts: not stated Revised sample size: 60 Average age, years: not stated Females: 12 (20.0%) NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: other antioxidants (n = 30) Further details: silymarin 70 mg 3 times a day for 24 weeks Group 2: no active intervention (n = 30) Further details: no treatment Additional details: both groups received lifestyle intervention
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020
Risk of bias	

Ruan 2010 *(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	Quote: "open, randomized, controlled clinical study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open, randomized, controlled clinical study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Sadrkabir 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 67 Post-randomisation dropouts: 6 (9.0%) Revised sample size: 61 Reasons for post-randomisation dropouts: none referred to receive treatment (3), cut of treatment (3) Average age, years: 44 Females: 21 (34.4%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged > 18 years. 2. Newly diagnosed NAFLD, grade 2 and 3 fatty liver, treatment naïve Exclusion criteria: 1. Digestive disease. 2. Diabetes. 3. Rheumatoid arthritis, other rheumatological disease treated with immunosuppressive drugs, 4. Cholestatic liver disease, advanced liver disease. 5. Heart failure, thyroid and kidney diseases. 6. Any cause of chronic liver disease other than NAFLD, such as positive test for hepatitis B, hepatitis C, and autoimmune hepatitis. 7. History of cancer and drug treatment. 8. Antibiotic use in the past 2 weeks. 9. Use of vitamin supplemental antioxidant, fibre, and omega-3 in 3 weeks before and during study, pregnancy or lactation, contraceptive use, liver transplantation, and alcohol consumption in the 3 months before the study Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 33)

Sadrkabir 2020 *(Continued)*

	Further details: 2 capsules of 500 mg of GeriLact for 60 days. GeriLact was used in this study as a symbiotic product in capsule form (*lactobacilli, cassia, acidophilous, langburoum, bifidobacterial,* and *streptococcus* along with prebiotics (fructolucosaccharide) Group 2: no active intervention (n = 28) Further details: placebo for 60 days Additional details: diet and exercise recommendations for both groups
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "funder: vice chancellor for research, Ardabil University of Medical Sciences" Trial name/Trial registry number: IRCT2017102537007N1 Attempts were made to contact study authors in April 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: placebo was used, but there is no mention about blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo was used, but there is no mention about blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether these were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Sakpal 2017

Study characteristics

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 81 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 81 Average age, years: 38 Females: 26 (32.1%) NASH: not stated Diabetes mellitus: 13 (16.0%) Inclusion criteria: 1. Aged over 12 years. 2. Ultrasound showing features of steatosis

Sakpal 2017 *(Continued)*

	Exclusion criteria: 1. Pregnancy. 2. Drug intake likely to cause NAFLD. 3. Extensive small bowel resection Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: vitamin D (n = 51) Further details: a single intramuscular injection of 600,000 IU of cholecalciferol Group 2: no active intervention (n = 30) Further details: no treatment Additional details: both groups received lifestyle modifications
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Sangouni 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2018 Number randomised: 90 Post-randomisation dropouts: 2 (2.2%) Revised sample size: 88

Sangouni 2020 *(Continued)*

	Reasons for post-randomisation dropouts: undergoing surgery (1), lost to follow-up (1) Average age, years: 45 Females: 31 (35.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Patients with grade 1 to 3 fatty liver. 2. Aged ≥ 18 years Exclusion criteria: 1. History of alcohol abuse (average daily alcohol consumption ≥ 10 g for women, ≥ 20 g for men). 2. Viral hepatitis. 3. Liver cancer, other liver disease. 4. Diabetes mellitus. 5. Untreated hypothyroidism. 6. Mental disease. 7. Kidney disease. 8. Pregnancy, lactation. 9. Low blood pressure, taking blood pressure-lowering medications. 10. Allergic to garlic. 11. Unwilling to continue the study. Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 45) Further details: 400 mg garlic powder tablets (each coated tablet contained 1.5 mg allicin, approximately 2 g of fresh garlic) 4 times daily. Garlic and placebo tablets were manufactured at Amin Pharmaceutical Company Group 2: no active intervention (n = 43) Further details: placebo tablets (each 400-mg coated tablet contained starch) 4 times daily. Placebo and garlic powder tablets had similar appearance Additional details: the usual treatment for all patients consisted of prescribing milk thistle tablets and recommending weight loss without offering any method
Outcomes	Outcomes reported: serious adverse events (number of people) Follow-up, months: 3
Notes	Source of funding (quote): "we would like to express our gratitude towards the Urmia University of Medical Sciences, for the facilities and financial support" Trial name/Trial registry number: IRCT20170206032417N4 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation lists were computer-generated by a statistician"
Allocation concealment (selection bias)	Low risk	Quote: "patients, researcher, laboratory staff and statistician were blinded to the study groups until the end of the study…placebo" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patients, researcher, laboratory staff and statistician were blinded to the study groups until the end of the study…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients, researcher, laboratory staff and statistician were blinded to the study groups until the end of the study…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether these were related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Sanyal 2010

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2005 to 2007 Number randomised: 167 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 167 Average age, years: 46 Females: 148 (88.6%) NASH: 167 (100.0%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Definitive or possible steatohepatitis (histologically) Exclusion criteria: 1. Alcohol consumption (> 30 g/d for men, > 20 g/d for women for at least 3 consecutive months over past 5 years. 2. Cirrhosis 3. Hepatitis C or other liver disease. 4. Heart failure (NYHA Class II to IV). 5. Drugs causing steatohepatitis Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: vitamin E (n = 84) Further details: vitamin E 800 IU daily for 96 weeks Group 2: no active intervention (n = 83) Further details: placebo Additional details: another group not relevant to this review was excluded
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of events), decompensation (number of events), cirrhosis (number of people), resolution of fatty liver disease, fibrosis score, NAFLD activity score Follow-up, months: 28
Notes	Source of funding (quote): "several authors received consulting fees" Trial name/Trial registry number: NCT00063622 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the randomization plan was prepared and administered centrally by the Data Coordinating Center"
Allocation concealment (selection bias)	Low risk	Quote: "the randomization plan was prepared and administered centrally by the Data Coordinating Center"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "multi-center, randomized, placebo-controlled, double-masked, double-dummy clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "multi-center, randomized, placebo-controlled, double-masked, double-dummy clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts

Sanyal 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the protocol was published after recruitment was completed; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Sanyal 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2011 to 2012 Number randomised: 243 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 243 Average age, years: 49 Females: 148 (60.9%) NASH: 243 (100.0%) Diabetes mellitus: 85 (35.0%) Inclusion criteria: 1. Biopsy-confirmed NASH Exclusion criteria: 1. Cirrhosis. 2. Decompensated liver disease with ascites. 3. Encephalopathy or variceal haemorrhage. 4. ALT > 300 IU/L. 5. Pregnancy or lactation. 6. Serum creatinine > 2 mg/dL. 7. Symptomatic coronary, peripheral, or neurovascular disease. 8. Symptomatic heart failure (NYHA Class II or higher). 9. Prolonged QTC. 9. Respiratory disease requiring oxygen therapy. 10. History of cerebral or retinal haemorrhage or known bleeding disorder Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: PUFA (n = 168) Further details: ethyl-eicosapentaenoic acid 1800 mg or 2700 mg (randomly chosen) for 12 months Group 2: no active intervention (n = 75) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of events), fibrosis score, NAFLD activity score Follow-up, months: 12
Notes	Source of funding: not stated Trial name/Trial registry number: NCT01154985 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "interactive voice-response system" Comment: although the precise method of random sequence generation was not reported, the method of allocation concealment suggests that the sequence generation was random
Allocation concealment (selection bias)	Low risk	Quote: "interactive voice-response system"

Sanyal 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "prospective, double-blind, randomized, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "prospective, double-blind, randomized, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Saxena 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 58 Post-randomisation dropouts: 8 (13.8%) Revised sample size: 50 Reasons for post-randomisation dropouts: reasons not stated and breakdown of dropouts in each group not given Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD on USS with/without persistent elevation of serum ALT or AST. 2. Negative viral markers Exclusion criteria: not stated Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 26) Further details: patients received an herbal compound MA 579 (Livomap), 2 tablets twice daily for 4 months Group 2: no active intervention (n = 24) Further details: patients received placebo, 2 tablets twice daily for 4 months Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events), any adverse events (number of people), any adverse events (number of events) Follow-up, months: 4
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020
Risk of bias	

Saxena 2013 *(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	Low risk	Quote: "double-blind randomized placebo controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized placebo controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Sayari 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2015 to 2017 Number randomised: 140 Post-randomisation dropouts: 2 (1.4%) Revised sample size: 138 Reasons for post-randomisation dropouts: loss to follow-up (1), refusal to continue (1) Average age, years: 43 Females: 55 (39.9%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 60 years. 2. BMI from 25 to 29.9. 3. Impaired fasting blood glucose and/or impaired oral glucose tolerance test. 4. New cases of NAFLD Exclusion criteria: 1. Other liver disease. 2. Alcohol consumption > 10 g/d in women, > 20 g/d in men. 3. Presence of kidney disease, thyroid disorder, immunodeficiency disease, heart failure, on cholesterol-lowering medication. 4. Pregnancy, breastfeeding Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 70) Further details: synbiotic (500 mg) once daily for 16 weeks. Each synbiotic capsule (Familakt) contained 109 colony-forming units (CFUs) of 7 strains of friendly bacteria (*Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophilus*) and prebiotic (fructo-oligosaccharide) and probiotic cultures (magnesium stearate (source: mineral and vegetable), and a vegetable capsule (hydroxypropyl methylcellulose))

Sayari 2018 *(Continued)*

	Group 2: no active intervention (n = 68) Further details: placebo (maltodextrin) once daily for 16 weeks Additional details: both groups received lifestyle advice and sitagliptin
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: ZMDRC approval number: A-12-500-13 Attempts were made to contact study 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	Low risk	Quote: "randomized, double blind trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double blind trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution 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 dropouts: 0 (0.0%) Revised sample size: 29 Average age, years: 48 Females: 19 (65.5%) NASH: 29 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Histologically confirmed NASH or a combination of M30 levels above 200 U/L and hepatic steatosis on ultrasound. 2. Aged 18 to 75 years Method for diagnosis of NAFLD: ultrasound plus M30 (biomarker of liver injury) or liver biopsy

Schattenberg 2017 *(Continued)*

Interventions	Group 1: no active intervention (n = 14) Further details: no additional supplementation Group 2: prebiotics/probiotics/synbiotics (n = 15) Further details: *Lactobacillus casei*Shirota plus 2.1 g soluble fibre twice daily (LcS) for 12 weeks Additional details: both groups received dietary advice
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people) Follow-up, months: 3
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 Attempts were made to contact study 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 another intervention (which was excluded from this review), it is not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "blinded lab analysis (author replies)" Comment: assessors of clinical outcomes were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Scorletti 2014

Study characteristics

Methods	Randomised clinical trial
Participants	Country: United Kingdom Period of recruitment: 2010 to 2011 Number randomised: 103 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 103 Average age, years: 51

Scorletti 2014 *(Continued)*

	Females: 43 (41.7%) NASH: not stated Diabetes mellitus: 10 (9.7%) Inclusion criteria: 1. Aged > 18 years. 2. Recent histological diagnosis of NAFLD or steatosis diagnosed by ultrasound/CT/MRI in context of diabetes and/or metabolic syndrome Exclusion criteria: 1. Other cause of liver disease (e.g. viral hepatitis, Wilson's disease). 2. Alcohol consumption (> 35 units/week for women, > 50 units/week for men). 3. Decompensated acute or chronic liver disease. 4. Cirrhosis. 5. Pregnancy or breastfeeding. 6. Hypersensitivity to Omacar or soya Method for diagnosis of NAFLD: liver biopsy or USS/CT/MRI
Interventions	Group 1: PUFA (n = 51) Further details: 4 g/d purified long chain omega-3 fatty acids (Omacor; DHA plus EPA) for 15 to 18 months Group 2: no active intervention (n = 52) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 15 to 18
Notes	Source of funding (quote): "Omacor and placebo were provided by Pronova Biopharma through Abbott Laboratories, Southampton, UK" Trial name/Trial registry number: NCT00760513 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerized block randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomised according to standardized procedures (computerized block randomisation) by a research pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomised double blind placebo controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomised double blind placebo controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Scorletti 2020

Study characteristics

Scorletti 2020 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: not stated Number randomised: 104 Post-randomisation dropouts: 15 (14.4%) Revised sample size: 89 Reasons for post-randomisation dropouts: claustrophobia (5), family circumstances (1), personal circumstances (2), relocation (2), non-compliance (2), taken over 3 courses of antibiotics (3) Average age, years: 51 Females: 31 (34.8%) NASH: not stated Diabetes mellitus: 33 (37.1%) Inclusion criteria: 1. Diagnosis of liver fat on normal clinical grounds with either histologic confirmation of NAFLD or imaging evidence of liver fat with exclusion of other liver conditions causing liver fat accumulation. 2. Alcohol consumption of < 14 units/week for women and < 21 units/week for men Exclusion criteria: 1. Abdominal surgery. 2. Three or more courses of broad-spectrum antibiotics in the previous year that may change gut microbiota. 3. Consumption of probiotic foods or supplements within the 2 months preceding enrolment Method for diagnosis of NAFLD: liver biopsy or imaging evidence of liver fat
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 45) Further details: synbiotic treatment, which consisted of fructo-oligosaccharides 4 g twice a day (2 sachets a day, stirred into a cold drink) plus *Bifidobacterium animalis* subspecies *lactis* BB-12 at a minimum of 10 billion colony-forming units/day (1 capsule a day) for 10 to 14 months Group 2: no active intervention (n = 44) Further details: placebo, which consisted of 4 g twice a day of maltodextrin (1 capsule a day plus 2 sachets a day, stirred into a cold drink) for 10 to 14 months
Outcomes	Outcomes reported: mortality, liver transplantation, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, fibrosis score Follow-up, months: 12
Notes	Source of funding (quote): "the synbiotic and placebo were provided at no cost by Chr. Hansen Holding. Chr. Hansen had no input into any aspect of study design or conduct of the trial. Furthermore, Chr. Hansen will have no input into data analysis or subsequent reporting of the trial results. The INSYTE trial was funded by the National Institute for Heath Research Southampton Biomedical Research Centre and JKS is Funded by the Wellcome Trust (Grant Number 206453/Z/17/Z)" Trial name/Trial registry number: NCT01680640 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "according to a list generated by the BRC Statistics and Data Management group" (author replies)
Allocation concealment (selection bias)	Low risk	Quote: "by a person from within University Hospital Southampton or the University of Southampton who was not connected to the INSYTE study" (author replies)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind phase 2 trial…placebo"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind phase 2 trial…placebo"

Scorletti 2020 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts - differentially more in the intervention group; some are likely to be related to the intervention
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Sepideh 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2013 Number randomised: 50 Post-randomisation dropouts: 8 (16.0%) Revised sample size: 42 Reasons for post-randomisation dropouts: withdrew Average age, years: 45 Females: 14 (33.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 65 years. 2. NAFLD Exclusion: 1. Other cause of liver disease (e.g. Wilson's disease, viral hepatitis, autoimmune disease). 2. Pregnancy or lactation. 3. Cardiovascular or kidney disease, haemochromatosis, or immunodeficiency. 4. Antibiotics, probiotics, NSAIDs, or medicinal plant use in previous 2 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 21) Further details: 2 capsules/d probiotic (Lactocare) for 8 weeks Group 2: no active intervention (n = 21) Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people) Follow-up, months: 2
Notes	Source of funding: not stated Trial name/Trial registry number: IRCT2012122911920N1 Attempts were made to contact study 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)	Low risk	Quote: "the placebo and probiotic were packaged in identical sealed boxes, identified by a code number only"

Sepideh 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomized clinical trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Shahmohammadi 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 44 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 44 Average age, years: 43 Females: 22 (50.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Age > 20 years. 2. NAFLD Exclusion criteria: 1. Hepatotoxic drugs. 2. Other forms of liver disease (e.g. viral hepatitis). 3. Metabolic disease (e.g. diabetes). 4. Pregnancy or lactation. 5. HRT. 6. Other supplements in previous 6 months. 7. Bariatric surgery Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 22) Further details: green coffee bean extract 1 g/d for 8 weeks Group 2: no active intervention (n = 22) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 2
Notes	Source of funding (quote): "this work was financially supported by Vice-Chancellor for Research Affairs of Ahvaz Jundishapur University of Medical Sciences" Trial name/Trial registry number: IRCT2016030626941N1 Attempts were made to contact study authors in December 2020

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

Shahmohammadi 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "a person, who was not aware of the nature of the trial, packed the supplements and placebo capsules in numbered bottles based on the list. The other person who was not aware of random sequences allocated the patients to the numbered bottles"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "parallel, double-blind, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "parallel, double-blind, placebo-controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Sharifi 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2012 to 2013 Number randomised: 60 Post-randomisation dropouts: 7 (11.7%) Revised sample size: 53 Reasons for post-randomisation dropouts: discontinued intervention, personal reasons Average age, years: 42 Females: 27 (50.9%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 70 years. 2. Serum ALT > 19 U/L for women, 30 U/L for men Exclusion criteria: 1. Alcohol consumption > 20 g/d. 2. Pregnancy or lactation. 3. Other forms of hepatic disease (e.g. haemochromatosis). 4. History of bypass surgery. 5. Total parenteral nutrition in past 6 months. 6. Hepatotoxic drugs. 7. Intake of vitamin D/E or calcium in past 6 months Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: vitamin D (n = 27) Further details: 50,000 IU vitamin D3 (D-Vitin) every 14 days for 4 months Group 2: no active intervention (n = 26) Further details: placebo
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 4

Sharifi 2014 *(Continued)*

Notes	Source of funding (quote): "this work was financially supported by a Grant (No. RDC-9105) from Vice-Chancellor for Research Affairs of Jundishapur University of Medical Sciences and approved by the Research Institute for Infectious Diseases of the Digestive System, Jundishapur University of Medical Sciences, Ahvaz, Iran" Trial name/Trial registry number: IRCT2012071810333N1 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "an investigator with no clinical involvement in the trial packed the supplements and placebos in numbered bottles based on the random list. The other person, who was not involved in the trial and not aware of random sequences, assigned the patients to the numbered bottles of pearls"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "parallel, double-blind, placebo-controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "parallel, double-blind, placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Shavakhi 2013

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2010 to 2012 Number randomised: 70 Post-randomisation dropouts: 7 (10.0%) Revised sample size: 63 Reasons for post-randomisation dropouts: loss to follow-up, personal reasons Average age, years: 40 Females: 31 (49.2%) NASH: 63 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 75 years. 2. NAFLD

Shavakhi 2013 *(Continued)*

	Exclusion criteria: 1. Other causes of liver disease (e.g. autoimmune hepatitis). 2. Insulin-dependent diabetes mellitus. 3. Pregnancy or lactation. 4. Impaired renal function. 5. Heart failure. 6. Hepatocellular carcinoma. 7. Hepatotoxic drugs Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: no active intervention (n = 32) Further details: placebo tablets (similar in shape and appearance to Protexin) Group 2: prebiotics/probiotics/synbiotics (n = 31) Further details: probiotic (Protexin; made by Science and Nature in Balance Co., UK; contained *Lactobacillus acidophilus* 1×10^8 CFUs, *Lactobacillus casei*5×10^8 CFUs, *Lactobacillus rhamnosus* 7.5×10^7 CFUs, *Lactobacillus bulgaricus* 1.5×10^8 CFUs, *Bifidobacterium breve* 5×10^7 CFUs, *Bifidobacterium longum* 2.5×10^7 CFUs, *Streptococcus thermophilus* 5×10^7 CFUs, fructo-oligosaccharides 350 mg), 2 tablets per day for 6 months Additional details: both groups received metformin
Outcomes	Outcomes reported: mortality at maximal follow-up, resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding (quote): "source of support: Isfahan University of Medical Science Vice Chancellery for Research" Trial name/Trial registry number: not stated Attempts were made to contact study 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	Low risk	Quote: "randomized double-blind clinical trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized double-blind clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Soleimani 2020

Study characteristics

Methods	Randomised clinical trial

Soleimani 2020 *(Continued)*

Participants	Country: Iran Period of recruitment: not stated Number randomised: 110 Post-randomisation dropouts: 12 (10.9%) Revised sample size: 98 Reasons for post-randomisation dropouts: lost to follow-up (4), withdrawn (8) Average age, years: 44 Females: 64 (65.3%) NASH: not stated Diabetes mellitus: 26 (26.5%) Inclusion criteria: 1. Aged between 20 and 70 years. 2. ALT and/or AST > 40 U/L. 3. Evidence of hepatic steatosis on USS Exclusion criteria: 1. Weight management programme during last 3 months. 2. Other cause of hepatic steatosis such as alcohol consumption. 3. Hypothyroidism. 4. Hepatotoxic drug or corticosteroid consumption. 5. Pregnancy, lactation. 6. Any change in drugs during the study period Method for diagnosis of NAFLD: ultrasound and transaminases
Interventions	Group 1: other supplements (n = 47) Further details: enteric-coated garlic powder supplement at a dose of 400 mg (equal to 1.5 mg allicin) 2 times daily for 15 weeks Group 2: no active intervention (n = 51) Further details: garlic-like placebo (microcrystalline cellulose) supplement for 15 weeks
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 4
Notes	Source of funding (quote): "the financial support provided by Isfahan University of Medical Sciences, Isfahan, Iran. The funder is not involved in the study design, data analysis and interpretation, or writing of the manuscript" Trial name/Trial registry number: IRCT2014110819853N1 Attempts were made to contact study authors in April 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: "the treatment assignment was concealed from the patients, investigators, staff, radiologist, and hepatologist throughout the study…placebo" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the treatment assignment was concealed from the patients, investigators, staff, radiologist, and hepatologist throughout the study…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the treatment assignment was concealed from the patients, investigators, staff, radiologist, and hepatologist throughout the study…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether these were related to the intervention and to outcomes

Soleimani 2020 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Soleimani 2021

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2018 Number randomised: 54 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 54 Average age, years: 42 Females: 16 (29.6%) NASH: not stated Diabetes mellitus: 3 (5.6%) Inclusion criteria: 1. Aged 18 to 60 years. 2. New diagnosis of hepatic steatosis with elastography technique Exclusion criteria: 1. History of alcohol abuse. 2. Presence of secondary cause of hepatic steatosis (such as hepatitis B and C virus, autoimmune hepatitis, haemochromatosis, coeliac disease, hypopituitarism, hypothyroidism, Wilson's disease, abetalipoproteinaemia, or corticosteroid medication). 3. Confounding concomitant drug use (vitamin E, thiazolidinediones, glucagon-like peptide-1 analogs, exogenous insulin, or ursodeoxycholic acid). 4. Pregnancy, lactation. 5. Aadverse reactions to honey bee products. 6. Poor compliance with trial treatment (< 80% were withdrawn from the trial during the follow-up period) Method for diagnosis of NAFLD: elastography
Interventions	Group 1: other supplements (n = 27) Further details: patients in the propolis group received poplar propolis tablet (450 mg containing 250 mg of freeze-dried ethanolic extract of Iranian propolis and 200 mg of microcrystalline cellulose) twice daily for 4 months. Each propolis tablet contains 90 mg gallic acid equivalent and 67 mg flavonoids Group 2: no active intervention (n = 27) Further details: propolis-like placebo tablet (442 mg of microcrystalline cellulose and 8 mg of various artificial food dyes) for 4 months Additional details: all patients were advised to follow an energy-restricted diet (~ 250 kcal) containing 30% calories from fat, 52% from carbohydrate, and 18% from protein, along with 150 minutes/week of moderate-intensity exercise such as walking and cycling
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of events), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), hepatocellular carcinoma Follow-up, months: 4
Notes	Source of funding (quote): "financial support was provided by Mashhad University of Medical Sciences, Mashhad, Iran. The funder was not involved in the study design, data analysis and interpretation, or writing of the manuscript" Trial name/Trial registry number: IRCT20180824040857N1 Attempts were made to contact study authors in April 2021

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

Soleimani 2021 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization sequence"
Allocation concealment (selection bias)	Low risk	Quote: "the allocation sequence was concealed through consecutively numbered, opaque, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "except for the study pharmacist, who provided a randomization list and sequentially numbered drug containers according to it, other investigators and all patients were blinded from the study-group assignment. The placebo tablet was identical in terms of shape, color, size, odor, and weight to the propolis tablet. All tablets were dispensed in similar containers"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "except for the study pharmacist, who provided a randomization list and sequentially numbered drug containers according to it, other investigators and all patients were blinded from the study-group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: an intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Solhi 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 80 Post-randomisation dropouts: 16 (20.0%) Revised sample size: 64 Reasons for post-randomisation dropouts: did not participate in follow-up Average age, years: 27 Females: 16 (25.0%) NASH: 64 (100.0%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NASH confirmed on ultrasound. 2. Persistent elevation in ALT/AST > 1.2× ULN in previous 6 months Exclusion criteria: 1. Other liver disease (e.g. autoimmune hepatitis). 2. Diabetes. 3. Severe cardiac, renal, or pulmonary disease. 4. Pregnancy. 5. Alcohol consumption > 20 g daily or substance abuse. 6. Hepatotoxic drugs Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: other antioxidants (n = 33) Further details: silymarin (Livergol) 210 mg/d orally for 8 weeks Group 2: no active intervention (n = 31) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	No outcomes of interest were reported

Solhi 2014 *(Continued)*

Notes	Source of funding (quote): "the project has been performed under financial support of research department of Arak's university of medical sciences, Arak, Iran" Trial name/Trial registry number: IRCT201202159018N1 Attempts were made to contact study 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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Somi 2014

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2012 to 2014 Number randomised: 80 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 80 Average age, years: 41 Females: 14 (17.5%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD on ultrasound Exclusion criteria: 1. Diabetic patients. 2. Other cause of raised liver enzymes (e.g. Wilson's disease). 3. Hepatotoxic drugs. 4. Excessive alcohol consumption Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: amino acids (n = 40) Further details: L-carnitine 500 mg twice daily for 24 weeks Group 2: no active intervention (n = 40)

Somi 2014 *(Continued)*

	Further details: no treatment
Outcomes	Outcomes reported: mortality at maximal follow-up, resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: N11RCT201102235893 Attempts were made to contact study 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: "sonography of patients in each group was done by radiologist who was not aware of biochemical liver tests, with Siemens G40 and pruvconex, and 3.46 MHz frequency after 8 hours fasting" Comment: no clinical outcomes were reported in this trial; therefore, radiologist blinding indicates outcome assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Song 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2018 Number randomised: 96 Post-randomisation dropouts: 21 (21.9%) Revised sample size: 75 Reasons for post-randomisation dropouts: withdrawal from study because of business trips, poor compliance Average age, years: 46 Females: 8 (10.7%) NASH: not stated Diabetes mellitus: not stated

Song 2020 *(Continued)*

	Inclusion criteria: 1. Adult participants (aged 30 to 67 years). 2. Average liver:spleen attenuation ratio ≤ 1.2 or liver attenuation ≤ 52 Hounsfield units, as determined by non-enhanced computerised tomography. 3. Dyslipidaemia (TC ≥ 5.2 mmol/l, LDL cholesterol ≥ 3.36 mmol/L, or TAG ≥ 1.7 mmol/L). 4. Overweight (BMI ≥ 24 kg/m^2) Exclusion criteria: 1. Pregnancy. 2. Cardiovascular disease, cancer, disability, diabetes mellitus. 3. Excessive alcohol consumption (≥ 30 g/d for men, ≥ 20 g/d for women). 4. Hepatitis B or C or other liver disease. 5. Use of hypoglycaemic or lipid-regulating drugs (statins, fibrates) or other drugs that may impact glucose and lipid metabolism. 6. Intolerable adverse events from soya milk products. 8. Disease that impacts the participant's metabolism. 9. Hyperthyroidism, mental disorder, or disease associated with serious dysfunction of the heart, liver, or kidney Method for diagnosis of NAFLD: CT scan plus abnormal serum lipid profile or high BMI
Interventions	Group 1: other supplements (n = 16) Further details: phytosterol esters (PS)-enriched soyamilk powder containing 3.3 g of PS (Vegapure 67 WDP, equivalent to 2.5 g phytosterol in free form) and placebo capsules (vegetable oil blend: 30% palmitic acid, 40% oleic acid, and 20% linoleic acid obtained by blending rapeseed, sunflower and palm oils). Intervention lasted for 12 weeks Group 2: PUFA plus other supplements (n = 17) Further details: PS-enriched soyamilk powder containing 3.3 g of PS plus fish oil capsules containing highly concentrated EPA and DHA (450 mg EPA plus 1500 mg DHA). Intervention lasted for 12 weeks Group 3: PUFA (n = 21) Further details: fish oil capsules containing highly concentrated EPA and DHA (PronovaPure 150:500TG, 450 mg EPA þ 1500 mg DHA) and placebo soyamilk powder. Intervention lasted for 12 weeks Group 4: no active intervention (n = 21) Further details: placebo soyamilk and placebo capsule for 12 weeks Additional details: no dietary intervention management was performed in the interest of achieving high compliance and isolating the effects of supplements used in the trial. Participants were not encouraged to specifically modify their lifestyles (including dietary habits) but were instructed to refrain from consuming supplements or other products claimed to reduce blood cholesterol
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events), any adverse events (number of people), any adverse events (number of events) Follow-up, months: 3
Notes	Source of funding (quote): "the authors gratefully acknowledge the kindly provider of intervention and placebo products by company of Yanling Natural Hygiene Sdn. Bhd" Trial name/Trial registry number: ChiCTR1800014419 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was conducted using computer-generated random numbers by a trained staff member at the physical examination centre"
Allocation concealment (selection bias)	Low risk	Quote: "all participants, care providers and outcome assessors were blinded to the treatment allocations…placebo" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all participants, care providers and outcome assessors were blinded to the treatment allocations…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all participants, care providers and outcome assessors were blinded to the treatment allocations…placebo"

Song 2020 *(Continued)*

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

Spadaro 2008

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: 4 (10.0%) Revised sample size: 36 Reasons for post-randomisation dropouts: loss to follow-up, non-compliance Average age, years: 51 Females: 17 (47.2%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Previous PUFA therapy within 3 months. 2. Inflammatory disease (e.g. IBD, autoimmune disease). 3. Malignancy. 4. Pregnancy Method for diagnosis of NAFLD: ultrasound plus transaminases
Interventions	Group 1: PUFA (n = 18) Further details: polyunsaturated fatty acid 2 g/d for 6 months Group 2: no active intervention (n = 18) Further details: no treatment Additional details: both groups received modified diet
Outcomes	Outcomes reported: resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random sampling numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: this information was not available

Spadaro 2008 *(Continued)*

All outcomes		
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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Tabatabaee 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 67 Post-randomisation dropouts: 22 (32.8%) Revised sample size: 45 Reasons for post-randomisation dropouts: did not receive allocated intervention, lost to follow-up, discontinued intervention Average age, years: 40 Females: 40 (88.9%) NASH: not stated Diabetes mellitus: 14 (31.1%) Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Iron deficiency anaemia. 2. Green tea allergy. 3. Alcohol consumption (> 20 g daily). 4. Other liver disorder (e.g. autoimmune hepatitis). 5. Pregnancy or lactation Method for diagnosis of NAFLD: ultrasound, elastography, or liver biopsy
Interventions	Group 1: other supplements (n = 21) Further details: green tea 550 mg daily for 3 months Group 2: no active intervention (n = 24) Further details: placebo Additional details: both groups received lifestyle advice
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: IRCT201404332365N8 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "list already generated using a random number sequence"

Tabatabaee 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "only the main researcher had access to this list and could detect if a certain participant was receiving supplements or placebo"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind clinical trial…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind clinical trial…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Taghvaei 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age, years: 43 Females: 20 (50.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Liver cirrhosis. 2. Pregnancy or lactation. 3. Alcohol consumption. 4. Drug abuse. 5. Use of vitamins in past 6 months. 7. Diabetes mellitus. 8. Chronic kidney disease. 9. Hypercalcaemia. 10. End-stage heart and lung disease. 11. Use of hepatotoxic medication Method for diagnosis of NAFLD: elastography plus transaminases
Interventions	Group 1: vitamin D (n = 20) Further details: 50,000 IU vitamin D3 weekly for 12 weeks Group 2: no active intervention (n = 20) Further details: no further details
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: IRCT2015102624725N1 Attempts were made to contact study authors in December 2020
Risk of bias	

Taghvaei 2018 *(Continued)*

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	Unclear risk	Quote: "randomized, double-blind, parallel-group, clinical trial" Comment: no placebo was used; therefore, it is not clear how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "randomized, double-blind, parallel-group, clinical trial" Comment: no placebo was used; therefore, it is not clear how blinding was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Tan 2011

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 15 Post-randomisation dropouts: not stated Revised sample size: 15 Average age, years: 46 Females: 1 (6.7%) NASH: 15 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Biopsy-proven NASH Exclusion criteria: not stated Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: phospholipids (n = 10) Further details: essential phospholipids 1800 mg/d for 6 months Group 2: no active intervention (n = 5) Further details: no treatment Additional details: both groups received lifestyle intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

Tan 2011 *(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	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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Tobin 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2015 to 2017 Number randomised: 176 Post-randomisation dropouts: 9 (5.1%) Revised sample size: 167 Reasons for post-randomisation dropouts: intervention: non-compliance (2), refusal to continue (4), loss to follow-up (3) Average age, years: 55 Females: 87 (52.1%) NASH: 0 (0.0%) Diabetes mellitus: 62 (37.1%) Inclusion criteria: 1. Aged ≥ 18 years. 2. < 1 year suspected NAFLD. 3. Non-smoker. 4. BMI 18 to 39.9. 5. On statin medication > 1 month stable dose Exclusion criteria: 1. NASH diagnosis. 2. Bilirubin > 2× upper limit of normal. 3. Other liver disease. 4. Pancreatitis. 5. Medication known to cause liver damage. 6. History of bariatric surgery. 7. Significant or rapid weight loss within 6 months. 8. Cancer. 9. Significant cardiovascular, gastrointestinal, renal, pulmonary, hepatic, biliary, or endocrine disease. 10. Significant alcohol consumption. 11. Use of any medicine or supplement that may affect NAFLD or lipid metabolism. 12. Use of anticoagulants. 13. Pregnancy, breastfeeding. 14. Sensitivity to study medication Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: MUFA (n = 86)

Tobin 2018 *(Continued)*

	Further details: 3 placebo (olive oil) capsules per day for 24 weeks. Placebo capsules were identical in size and appearance to MF4637 and contained 1 g of olive oil Group 2: PUFA (n = 81) Further details: omega-3 concentrate MF4637, 3 capsules daily, for 24 weeks. Omega-3 fatty acid medical food (MF4637; BASF AS, Lysaker, Norway) was provided as soft gel capsules, with each 1-gram capsule containing marine-sourced EPA and DHA as ethyl esters (460 mg and 380 mg, respectively) Additional details: both groups received lifestyle advice
Outcomes	No outcomes of interest were reported
Notes	Source of funding (quote): "funding: this study was funded by BASF AS. Conflicts of Interest: D.T. and Y.Q. are employees of BASF AS; M.B.A. is a former employee of BASF AS; P.C.C. is an advisor to BASF AS" Trial name/Trial registry number: NCT02923804 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization numbers corresponding to predetermined intervention were assigned in a sequential manner to each subject via an Interactive Voice/Web Response System"
Allocation concealment (selection bias)	Low risk	Quote: "each participant was centrally randomized. Randomization numbers corresponding to predetermined intervention were assigned in a sequential manner to each subject via an Interactive Voice/Web Response System"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the investigational products were administered in a double-blinded fashion…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the investigational products were administered in a double-blinded fashion…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	High risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published; adverse events, mortality, fatty liver resolution were not reported
Other bias	Unclear risk	Comment: there were baseline differences in important prognostic factors

Tutunchi 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2019 Number randomised: 76 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 76

Tutunchi 2020 *(Continued)*

	Average age, years: 41 Females: 36 (47.4%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Obese. 2. Newly diagnosed NAFLD. 3. Body mass index (BMI) 30 to 40 kg/m^2. 4. Aged 21 to 59 years Exclusion criteria: 1. Liver disease such as hepatitis, cirrhosis, biliary disorder, inherited disorder affecting the liver. 2. Diabetes, hypertension, cardiovascular disorder, kidney dysfunction, thyroid problem, gastrointestinal disorder, pulmonary and autoimmune disease, malignancy, recent surgery. 3. Alcoholic, smoker, tobacco consumer. 4. Pregnancy or lactation. 5. Weight-loss programme within 3 months prior to the study. 6. Use of lipid-lowering drugs, weight loss drugs, corticosteroids, hepatotoxic drugs, anticoagulants, antidiuretics, multi-vitamins, minerals, and any dietary supplements during past 3 months Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 38) Further details: 2 capsules of oleoylethanolamide per day for 12 weeks. OEA capsules contained 125 mg OEA Group 2: no active intervention (n = 38) Further details: 2 capsules of placebo per day for 12 weeks. Placebo capsules contained 125 mg starch and were similar in appearance, size, and colour to OEA capsules Additional details: all patients were given weight loss diet and physical activity recommendations
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events), resolution of fatty liver disease Follow-up, months: 3
Notes	Source of funding (quote): "the study was financially supported by the Nutrition Research Center of Tabriz University of Medical Sciences, and Iran National Science Foundation (INSF)" Trial name/Trial registry number: IRCT20110530006652N2 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients were randomized to receive either OEA or placebo for 12 weeks based on the random block procedure developed by random allocation software"
Allocation concealment (selection bias)	Low risk	Quote: "the random sequence was administered by an independent third investigator who was not aware of the study clinical process until the outcome data collection was completed"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both OEA and placebo capsules were labeled as A or B, and the investigators, participants, and the statistician were blinded to the drug allocation until the end of the analysis"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "both OEA and placebo capsules were labeled as A or B, and the investigators, participants, and the statistician were blinded to the drug allocation until the end of the analysis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: an intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported

Tutunchi 2020 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Uygun 2000

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Turkey Period of recruitment: not stated Number randomised: 133 Post-randomisation dropouts: 32 (24.1%) Revised sample size: 101 Reasons for post-randomisation dropouts: did not complete the protocol Average age, years: not stated Females: 29 (28.7%) NASH: 101 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Elevated ALT levels. 2. NASH. 3. No other liver disease Exclusion criteria: not stated Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: amino acids (n = 78) Further details: carnitine 1 to 3 g/d for 6 months Group 2: no active intervention (n = 23) Further details: no treatment Additional details: both groups received lifestyle intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes

Uygun 2000 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Vajro 2011

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 20 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 20 Average age, years: 11 Females: 2 (10.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. BMI > 95th percentile for age and sex. 2. NAFLD Exclusion criteria: 1. Other cause of transaminitis (e.g. viral hepatitis, alcohol abuse, drug toxicity). 2. Antibiotic use Method for diagnosis of NAFLD: elastography plus transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 10) Further details: probiotic *Lactobacillus rhamnosus* strain GG (12 billion CFUs/d) for 8 weeks Group 2: no active intervention (n = 10) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 2
Notes	Source of funding (quote): "this work was partly funded by the Italian Ministry of University and Research (MIUR) PRIN 2005" Trial name/Trial registry number: not stated Attempts were made to contact study 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" Comment: further information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled pilot study"

Vajro 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled pilot study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were 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: 0 (0.0%) Revised sample size: 57 Average age, years: 14 Females: 18 (31.6%) NASH: 57 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. Aged 10 to 17 years. 2. Obesity. 3. NAFLD Exclusion criteria: 1. History of alcohol intake. 2. Positive markers for other liver disease (e.g. hepatitis) Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E (n = 19) Further details: vitamin E 100 mg/d for 1 month Group 2: no active intervention (n = 38) Further details: no treatment Additional details: another group not relevant to this review was excluded
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: not stated
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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

Wang 2008 *(Continued)*

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	Quote: "all patients underwent an ultrasonographic study of the liver performed by one operator who was blinded to the groups" Comment: not clear whether remaining outcomes were measured by blinded outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Wang 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: not stated Number randomised: 36 Post-randomisation dropouts: not stated Revised sample size: 36 Average age, years: 41 Females: 13 (36.1%) NASH: 36 (100.0%) Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. NASH with advanced fibrosis Exclusion criteria: 1. Other liver disease. 2. Diabetes. 3. Pregnancy. 4. Breastfeeding Method for diagnosis of NAFLD: elastography
Interventions	Group 1: other supplements (n = 24) Further details: Xiao-Zhi-Hua-Xian-Tang (XZHXT), a traditional Chinese medicine herbal formulation (Lotus Leaf, Semen Coicis) 3 times daily Group 2: no active intervention (n = 12) Further details: no supplementation Additional details: both groups received lifestyle intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Wang 2017 *(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: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Wang 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2010 to 2015 Number randomised: 200 Post-randomisation dropouts: not stated Revised sample size: 200 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: phospholipids (n = 50) Further details: polyene phosphatidylcholine 456 mg 3 times daily for 1 month Group 2: prebiotics/probiotics/synbiotics (n = 150) Further details: 2 live combined *Bifidobacterium, Lactobacillus,* and *Enterococcus* powder or 2 live combined *Bacillus subtilis* and *Enterococcus* or 4 live combined bacteria for 1 month
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020
Risk of bias	

Wang 2018 *(Continued)*

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	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: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Wong 2013a

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2009 Number randomised: 20 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 20 Average age, years: 49 Females: 7 (35.0%) NASH: 20 (100.0%) Diabetes mellitus: 7 (35.0%) Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Viral hepatitis. 2. Liver decompensation. 3. ALT > 10× upper limit of normal. 4. Malignancy. 5. Use of steroids or methotrexate in past 6 months Method for diagnosis of NAFLD: liver biopsy plus transaminases
Interventions	Group 1: prebiotics/probiotics/synbiotics (n = 10) Further details: Lepicol probiotic formula 1 sachet twice daily for 6 months. Lepicol probiotic formula contained *Lactobacillus plantarum, Lactobacillus deslbrueckii, Lactobacillus acidophilus, Lactobacillus rhamnosus,* and *Bifidobacterium bifidum* Group 2: no active intervention (n = 10) Further details: no treatment
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people) Follow-up, months: 6

Wong 2013a *(Continued)*

Notes	Source of funding (quote): "the work described in this paper was partially supported by the direct grant of The Chinese University of Hong Kong (Ref 2010.1.042)" Trial name/Trial registry number: NCT00870012 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated list"
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed envelopes" Comment: further 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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Wong 2013b

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2010 to 2011 Number randomised: 60 Post-randomisation dropouts: not stated Revised sample size: 60 Average age, years: 51 Females: 27 (45.0%) NASH: 60 (100.0%) Diabetes mellitus: 23 (38.3%) Inclusion criteria: 1. Histology-proven NASH. 2. Aged 18 to 70 years Exclusion criteria: 1. Other liver disease. 2 Significant alcohol consumption. 3. Liver decompensation. 4. Type 1 diabetes. 5. Malignancy Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: other supplements (n = 40)

Wong 2013b *(Continued)*

	Further details: *Phyllanthus urinaria* 1 g (2 tablets) 3 times daily for 24 weeks. Each *Phyllanthus* tablet contained 400 mg of *Phyllanthus urinaria* together with inactive ingredients of microcrystalline cellulose, hydroxypropylmethylcelllose, and magnesium stearate Group 2: no active intervention (n = 20) Further details: Phyllanthus-like placebo, 2 tablets, 3 times daily, for 24 weeks Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of people), resolution of fatty liver disease, fibrosis score, NAFLD activity score Follow-up, months: 6
Notes	Source of funding (quote): "the Phyllanthus tablets and placebo were provided by Hepaguard Company Limited, Hong Kong" Trial name/Trial registry number: NCT01210989 Attempts were made to contact study 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 through the use of a computer-generated list of random numbers in blocks of 6"
Allocation concealment (selection bias)	Low risk	Quote: "study medications were stored in consecutively numbered, sealed bottles and the preparation was done at a separate office"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the hepatologists, pathologists, nurses and patients were all blinded to the treatment assignment…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the hepatologists, pathologists, nurses and patients were all blinded to the treatment assignment…placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: an intention-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Yan 2015

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2008 to 2011 Number randomised: 124 Post-randomisation dropouts: 16 (12.9%) Revised sample size: 108 Reasons for post-randomisation dropouts: discontinued intervention, lost to follow-up

Yan 2015 *(Continued)*

	Average age, years: 52 Females: 54 (50.0%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Hepatitis B/C. 2. Hepatotoxic drugs. 3. Alcohol consumption (> 10 g/d for women, > 20 g/d for men) Method for diagnosis of NAFLD: magnetic resonance spectroscopy
Interventions	Group 1: other supplements (n = 55) Further details: berberine 0.5 mg, 3 times daily for 16 weeks Group 2: no active intervention (n = 53) Further details: no treatment Additional details: both groups received lifestyle intervention; another group not relevant to this review was excluded
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of events) Follow-up, months: 4
Notes	Source of funding (quote): "this work was supported by grants from the Major State Basic Research Development Program of China (2012CB524906 to Gao X.; http// www.973.gov.cn/Default_3.aspx), National Natural Science Foundation of China (81270933 to Gao X.), Major State Basic Research Development Program of China (2011CB504004 to Gao X.), the Science and Technology Commission of Shanghai Municipality" Trial name/Trial registry number: NCT00633282 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
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: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported
Other bias	Low risk	Comment: no other bias noted

Yari 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 50 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 50 Average age, years: 45 Females: 23 (46.0%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Aged 18 to 70 years. 2. NAFLD Exclusion criteria: 1. Allergy to nuts, flaxseed, or sesame seeds. 2. Excessive alcohol use. 3. Cardiovascular disease. 4. Cancer. 5. Diabetes mellitus. 6. Therapy that may benefit NAFLD (e.g. vitamin E). 7. Weight loss in past 6 months. 8. Pregnancy or lactation Method for diagnosis of NAFLD: elastography
Interventions	Group 1: PUFA (n = 25) Further details: flaxseed (milled) 30 g/d for 12 weeks Group 2: no active intervention (n = 25) Further details: no treatment Additional details: both groups received lifestyle modification
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up, months: 3
Notes	Source of funding (quote): "this study was supported by a grant from the National Nutrition and Food Technology Research Institute of the ShahidBeheshti University and the Digestive Disease Research Center of the Shariati Hospital" Trial name/Trial registry number: NCT02395900 Attempts were made to contact study 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 labeled"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open labeled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts

Yari 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Yari 2020

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2018 to 2019 Number randomised: 100 Post-randomisation dropouts: 8 (8.0%) Revised sample size: 92 Reasons for post-randomisation dropouts: loss to follow-up Average age, years: 45 Females: 44 (47.8%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. Aged 18 to 70 years. 2. BMI between 25 and 40. 3. > 37% hepatic fat content (CAP ≥ 260, grade ≥ 2) Exclusions criteria: 1. Alcohol consumption > 10 g/d (women), > 20 g/d (men). 2. Other liver disease. 3. Athlete. 4. Pregnancy, lactation. 5. Taking hypoglycaemic, lipid-regulating, anti-inflammatory medications, drugs, or herbal supplements affecting liver function. 6. Presence of gastrointestinal, cardiac, renal, pulmonary, autoimmune, thyroid disease; severe metabolic abnormalities. 7. History of weight loss surgery or concurrent weight-reduction programme Method for diagnosis of NAFLD: elastography
Interventions	Group 1: other supplements (n = 24) Further details: 30 g whole brown milled flaxseed powder daily for 12 weeks Group 2: other antioxidants plus other supplements (n = 25) Further details: combination of 1 g hesperidin and 30 g flaxseed daily for 12 weeks Group 3: other antioxidants (n = 22) Further details: 1 g hesperidin supplementation daily for 12 weeks Group 4: no active intervention (n = 21) Further details: control reference group had not undertaken any intervention Additional details: both groups received lifestyle advice
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), resolution of fatty liver disease, hepatocellular carcinoma Follow-up, months: 3
Notes	Source of funding (quote): "funded by the University (author replies)" Trial name/Trial registry number: NCT03734510 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the random allocations were carried out using a random numbers table"

Yari 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "it was concealed by a third person" (author replies)
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 it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	Low risk	Comment: a published protocol was available, but recruitment had commenced before the protocol was published; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Unclear risk	Comment: there were baseline differences in important prognostic factors

Youshari 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: not stated Number randomised: 41 Post-randomisation dropouts: not stated Revised sample size: 41 Average age, years: not stated Females: not stated NASH: not stated Diabetes mellitus: not stated Inclusion and exclusion criteria: not stated Method for diagnosis of NAFLD: not stated
Interventions	Group 1: vitamin E plus other supplements (n = 20) Further details: 3 grams of oats beta-glucan daily for 8 weeks plus vitamin E (no further details) Group 2: vitamin E (n = 21) Further details: 3 grams of maltodextrin as placebo daily for 8 weeks plus vitamin E (no further details) Additional details: both groups received lifestyle intervention
Outcomes	No outcomes of interest were reported
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study authors in December 2020

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

Youshari 2017 *(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	Low risk	Quote: "randomized, double-blind, parallel, placebo-controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind, parallel, placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; adverse events, mortality, fatty liver resolution were not reported
Other bias	Low risk	Comment: no other bias noted

Zamani 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Iran Period of recruitment: 2017 Number randomised: 90 Post-randomisation dropouts: 5 (5.6%) Revised sample size: 85 Reasons for post-randomisation dropouts: immigration (2), use of some drugs (2), missed follow-up (1) Average age, years: 39 Females: 24 (28.2%) NASH: not stated Diabetes mellitus: 0 (0.0%) Inclusion criteria: 1. Aged 18 to 65 years. 2. BMI 18 to 36. 3. Fatty liver on USS. 4. ALT ≥ 1.5× upper limit of normal Exclusion criteria: 1. Pregnancy, lactation. 2. Alcohol consumption. 3. Diabetes mellitus. 4. Sensitivity to ZM or thyme. 5. Other liver disease. 6. Malignancy. 7. Use of hepatotoxic drugs within past 6 months. 8. Use of drugs with effects on biochemical tests of the study within previous 3 months (e.g. metformin, vitamin E, oral contraceptive pills, omega-3, statins, glucocorticoids). 8. Hypothyroidism and hyperthyroidism. 9. Renal insufficiency Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 45) Further details: *Zataria multiflora Boiss* (Lamiaceae) is an herbal plant (ZM, Shirazi thyme). Patients in the treatment group received 4 capsules (each containing 350 mg ZM) daily for a period of 12 weeks Group 2: no active intervention (n = 40) Further details: in the control group, patients received identical placebo (wheat flour) capsules, 4 capsules daily for a period of 12 weeks. Each placebo capsule contained 350 mg wheat flour including 35 mg of ZM aerial part powder (to improve blindness regarding taste and aroma)

Zamani 2018 *(Continued)*

	Additional details: both groups received dietary advice
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), hepatocellular carcinoma Follow-up, months: 3
Notes	Source of funding (quote): "this study was supported by Shiraz University Medical Sciences (Grant No. 94-7648) as part of a PhD thesis" Trial name/Trial registry number: NCT02983669 Attempts were made to contact study authors in December 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated into treatment and placebo groups by block randomization which was generated by a computer as a non-stratified list"
Allocation concealment (selection bias)	Low risk	Quote: "randomized double-blind placebo-controlled clinical trial. Both the participants and investigators were blind to the intervention and placebo groups" Comment: although the precise method was not reported, allocation was probably concealed by use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both the participants and investigators were blind to the intervention and control groups…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "both the participants and investigators were blind to the intervention and control groups…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether these were related to the intervention or to outcomes
Selective reporting (reporting bias)	Low risk	Comment: all pre-defined outcomes in the protocol published before recruitment were reported
Other bias	Unclear risk	Comment: there were baseline differences in important prognostic factors

Zanko 2020

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Croatia Period of recruitment: 2015 to 2019 Number randomised: 311 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 311 Average age, years: 65 Females: 133 (42.8%)

Zanko 2020 *(Continued)*

	NASH: not stated Diabetes mellitus: 171 (55.0%) Inclusion criteria: 1. Aged ≥ 18 years. 2. Irrespective of serum vitamin D levels. 3. NAFLD confirmed by ultrasound and transient elastography (TE) with CAP ≥ 238 dB/m. 4. Positively excluded other cause of chronic liver disease. 5. Metabolic syndrome Exclusion criteria: 1. Significant alcohol consumption (> 30 g/d in men, 20 g/d in women). 2. Presence of autoimmune, viral, or other metabolic chronic liver disease. 3. Pregnancy. 4. Right-sided heart failure. 5 Malignancy. 6. Ascites. 7. Jejunoileal bypass or extensive small bowel resection or total parenteral nutrition. 8. Clinical, laboratory, and imaging features of liver cirrhosis. 9. Consumption of drugs that might induce hepatic steatosis (e.g. corticosteroids, high-dose oestrogen, methotrexate, amiodarone) during the 9 pre-study months. 10. Inability of reliable TE measurement (TE failure; including inadequate results) at pre-study screening Method for diagnosis of NAFLD: ultrasound plus transient elastography
Interventions	Group 1: vitamin D (n = 201) Further details: vitamin D3 oral solution (cholecalciferol 1000 IU/d; delivered as 5 drops, 200 IU each) for 12 months Group 2: no active intervention (n = 110) Further details: matching placebo (containing vehicles: castor oil, purified water, and methylparaben preservative) for 12 months Additional details: dietary and physical activity measures that were in place before the trial; continued as usual throughout the trial
Outcomes	Outcomes reported: serious adverse events (number of people), serious adverse events (number of events) Follow-up, months: 12
Notes	Source of funding (quote): "the authors declare that there was no financial support for this study" Trial name/Trial registry number: NCT04038853 Attempts were made to contact study authors in April 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple randomization was implemented using a random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "the randomization list was kept in a sealed envelope by a staff member not participating in patient recruitment and follow-up. The same person dispensed the allocated treatments, which were labelled at the hospital pharmacy to contain only the patient code"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial. At scheduled visits, investigators were unaware of the assigned treatment and had no information about the serum vitamin D3 levels"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial. At scheduled visits, investigators were unaware of the assigned treatment and had no information about the serum vitamin D3 levels"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no previously published protocol was available; neither mortality nor fatty liver resolution was reported

Zanko 2020 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Zhang 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2013 Number randomised: 74 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 74 Average age, years: 46 Females: 35 (47.3%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Cirrhosis. 2. Viral hepatitis. 3. Cardiovascular disease. 4. Cancer. 5. Excessive alcohol consumption. 6. Hepatotoxic drugs Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: other supplements (n = 37) Further details: purified anthocyanin (biolink) 320 mg/d for 12 weeks Group 2: no active intervention (n = 37) Further details: placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), liver transplantation at maximal follow-up, decompensation (number of people), cirrhosis (number of people), hepatocellular carcinoma, fibrosis score Follow-up, months: 3
Notes	Source of funding (quote): "this work was funded by grants from the National Basic Research Program (973 Program, 2012CB517506), National Natural Science Foundation (81372994, 81172655), and Guangdong Industry-University Research Foundation (2013B090600138)" Trial name/Trial registry number: NCT01940263 Attempts were made to contact study 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: "scheduled participants were consecutively assigned by a medical technologist, who was unaware of enrolment status, to treatment codes that corresponded to labels on otherwise identical concealed containers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, randomized study…placebo"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind, randomized study…placebo"

Zhang 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Zhu 2008

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2006 to 2008 Number randomised: 144 Post-randomisation dropouts: 10 (6.9%) Revised sample size: 134 Reasons for post-randomisation dropouts: did not complete protocol Average age, years: 45 Females: 37 (27.6%) NASH: not stated Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Alcohol excess. 2. Other cause of liver disease (e.g. viral hepatitis). 3. Pregnancy and breastfeeding. 4. Hepatotoxic medication Method for diagnosis of NAFLD: ultrasound
Interventions	Group 1: PUFA (n = 66) Further details: omega-3 fatty acids, 2 g from seal oils (Shanghai Hengsheng Biology & Medicine Co. Ltd., Shanghai, China), 3 times daily for 24 weeks Group 2: no active intervention (n = 68) Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people), resolution of fatty liver disease Follow-up, months: 6
Notes	Source of funding: not stated Trial name/Trial registry number: not stated Attempts were made to contact study 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

Zhu 2008 *(Continued)*

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	Quote: "ultrasound scans were performed by a trained operator who was blind to the treatment of participants" Comment: it is not clear whether outcome assessors of remaining outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	Low risk	Comment: no previously published protocol was available; adverse events and either mortality or fatty liver resolution or both were reported
Other bias	Low risk	Comment: no other bias noted

Zohrer 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 43 Post-randomisation dropouts: 3 (7.0%) Revised sample size: 40 Reasons for post-randomisation dropouts: did not complete the study Average age, years: 13 Females: 16 (40.0%) NASH: 40 (100.0%) Diabetes mellitus: not stated Inclusion criteria: 1. NAFLD Exclusion criteria: 1. Other cause of liver disease (e.g. autoimmune hepatitis). 2. Parenteral nutrition. 3. Previous gastrointestinal surgery. 4. Use of NSAIDs, antibiotics, probiotics within 2 months Method for diagnosis of NAFLD: liver biopsy
Interventions	Group 1: phospholipids plus PUFA plus vitamin E (n = 20) Further details: docosahexaenoic acid, choline, and vitamin E (DHA-CHO-VE) (Pro DHA Steatolip Plus) for 6 months Group 2: no active intervention (n = 20) Further details: placebo Additional details: both groups received lifestyle intervention.
Outcomes	Outcomes reported: serious adverse events (number of people), any adverse events (number of events) Follow-up, months: 12
Notes	Source of funding (quote): "we thank DMF Dietetic Metabolic Food (Italy) who provided Pro DHA Steatolip Plus with verified composition and indistinguishable placebo" Trial name/Trial registry number: NCT01934777 Attempts were made to contact study authors in December 2020
Risk of bias	

Zohrer 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "children were randomized by computer"
Allocation concealment (selection bias)	Low risk	Quote: "children were randomized by computer" Comment: both allocation concealment and blinding were achieved with use of placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patients and investigators were blinded before and after intervention assignment…placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients and investigators were blinded before and after intervention assignment…placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: participants were excluded from analysis for reasons that may be related to the intervention and to outcomes
Selective reporting (reporting bias)	High risk	Quote: "however, we underline that the current primary endpoint differs from that in the protocol submitted to ClinicalTrials.gov because liver biopsy at 12 months in the placebo group was not performed for ethical reasons"
Other bias	Low risk	Comment: no other bias noted

ALT: alanine aminotransferase.
AST: aspartate aminotransferase.
BMI: body mass index.
CAP: controlled attenuation parameter.
CLD: chronic lung disease.
CMV: cytomegalovirus.
DHA: docosahexaenoic acid.
EBV: Epstein-Barr virus.
EPA: eicosapentaenoic acid.
HbA1c: glycosylated haemoglobin.
HPA: hypothalamic-pituitary-adrenal.
LFT: liver function test.
MUFA: monounsaturated fatty acid.
NAFLD: non-alcohol-related fatty liver disease.
NASH: non-alcoholic steatohepatitis.
NSAID: non-steroidal anti-inflammatory drug.
NYHA: New York Heart Association.
PDFF: proton density fat fraction.
PT: prothrombin time.
PUFA: polyunsaturated fatty acid.
RCT: randomised controlled trial.
SAM-E: S-adenosyl methionine.
TG: triglyceride.
TNF: tumour necrosis factor.
TSH: thyroid-stimulating hormone.
UDCA: ursodeoxycholic acid.
USS: ultrasound scan.

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

Study	Reason for exclusion
Abenavoli 2017	Study authors used systematic sampling method. Although they mention the word "randomisation", they also state: "the control group (Group C), [which] refused any pharmacological and/or nutritional treatment, was also studied" (in an earlier report)
Akcam 2011	Comparison of nutritional supplementation with pharmacological intervention or lifestyle intervention
Basu 2014	Interventions were not reported clearly enough to assess whether this trial is eligible for the review (i.e. it is not clear what intervention and control were)
Chambers 2018	Comparison of a polysaccharide with a non-nutritional supplement
Chang 2014	Not clear whether participants had NAFLD
Dela Cruz 2012	Comparison of nutritional supplementation with pharmacological intervention and lifestyle intervention
Ersoz 2005	Comparison of nutritional supplementation with pharmacological intervention
Famouri 2017b	Quasi-randomised study (alternation)
Guo 2014	In this cross-over study, cross-over was at 4 weeks, with no outcomes available prior to cross-over; therefore, the RCT will not meet objectives of this Review
Hajiaghamohammadi 2012	Comparison of nutritional supplementation with pharmacological intervention
Han 2014	Only 1 of the groups received metformin, a pharmacological intervention (i.e. unequal co-interventions)
Khoshbaten 2010a	Comparison of nutritional supplementation with lifestyle intervention
Mahmoudi 2020	Comparison of variations in same treatment node
NCT00820651	Comparison of nutritional supplementation with lifestyle intervention
NCT04281121	In this study, which is available only from a trial register, although study authors state that allocation is random, they also state "single group assignment", and the description of interventions is identical
Petyaev 2018	Comparison of different formulations of supplement (i.e. comparison of variations in treatment node)
Podszun 2020	Comparison of variations in same treatment node
Saarinen 2011	Not clear whether participants had NAFLD
Semiserin 2016	Not clear whether this was an RCT
Singhal 2015	Although study authors state "randomly divided", they also state "retrospective…study"
Zhang 2008	Comparison with nutritional supplementation with pharmacological intervention

NAFLD: non-alcohol-related fatty liver disease.

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

ChiCTR2000034740

Study name	ChiCTR2000034740
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplement vs no active intervention (placebo)
Outcomes	No outcomes of interest will be measured in this trial
Starting date	August 2020
Contact information	Gao Lulu (gaolu755243@163.com)
Notes	

ChiCTR2000035899

Study name	ChiCTR2000035899
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplement vs no active intervention (placebo)
Outcomes	No outcomes of interest will be measured in this trial
Starting date	October 2020
Contact information	Chen Yuanwen (chenyuanwen@xinhuamed.com.cn)
Notes	

CTRI/2020/05/025322

Study name	CTRI/2020/05/025322
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplement vs no active intervention (placebo)
Outcomes	No outcomes of interest will be measured in this trial
Starting date	June 2020

CTRI/2020/05/025322 *(Continued)*

Contact information	Mr Krishna Chaitanya (highaspirer@gmail.com)
Notes	

CTRI/2020/07/026362

Study name	CTRI/2020/07/026362
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplement vs no active intervention (placebo)
Outcomes	No outcomes of interest will be measured in this trial
Starting date	July 2020
Contact information	Dr Gyanendra Datta Shukla (dr.gdshukla@gmail.com)
Notes	

Han 2020

Study name	KCT0003554
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplements vs no active intervention (placebo)
Outcomes	Change in liver fat
Starting date	March 2019
Contact information	Changsop Yang (yangunja@kiom.re.kr)
Notes	

IRCT20131125015536N

Study name	IRCT20131125015536N
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplements vs no active intervention (placebo)

IRCT20131125015536N *(Continued)*

Outcomes	No outcomes of interest will be measured in this trial
Starting date	October 2020
Contact information	Mohammad Javad Hosseinzadeh (mhosseinzadeh@tums.ac.ir)
Notes	

IRCT20191009045043N

Study name	IRCT20191009045043N
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplements vs no active intervention (placebo)
Outcomes	No outcomes of interest will be measured in this trial
Starting date	January 2020
Contact information	Mohsen Mohit (mohsen.mohit20@yahoo.com)
Notes	

IRCT20200304046692N

Study name	IRCT20200304046692N
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplements vs no active intervention (placebo)
Outcomes	Change in liver fat
Starting date	December 2019
Contact information	Reza Barati-Boldaji (reza93barati@gmail.com)
Notes	

IRCT20200531047614N

Study name	IRCT20200531047614N
Methods	Randomised clinical trial

IRCT20200531047614N *(Continued)*

Participants	People with NAFLD
Interventions	Other supplements vs no active intervention (placebo)
Outcomes	Change in liver fat
Starting date	May 2020
Contact information	Mohammad Rajabi (rajabi-m@kaums.ac.ir)
Notes	

Lambert 2015

Study name	NCT02568605
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Prebiotics/Probiotics/Synbiotics vs no active intervention (placebo)
Outcomes	Quality of life, change in liver fat
Starting date	May 2015
Contact information	Raylene A. Reimer (reimer@ucalgary.ca)
Notes	

NCT02289235

Study name	NCT02289235
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplements (ginger) vs no active intervention (placebo)
Outcomes	Change in liver fat
Starting date	May 2019
Contact information	Mesbah Shams (Internal Medicine & Endocrinology, Shiraz University of Medical Sciences)
Notes	

NCT02642172

Study name	NCT02642172
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Prebiotics/Probiotics/Synbiotics vs no active intervention (placebo)
Outcomes	Change in liver fat
Starting date	January 2016
Contact information	Yaakov Maor (NCT02642172; %20PN-837-CTIL,%20Prebiotics%20in%20Patients%20With%20Non-alcoholic%20Liver%20Disease" type="EXTERNAL">yaakovma1@clalit.org.il)
Notes	

NCT02647294

Study name	NCT02647294
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	PUFA vs no active intervention (placebo)
Outcomes	Change in liver fat, liver fibrosis
Starting date	February 2016
Contact information	Radan Bruha (General University Hospital in Prague)
Notes	

NCT02764047

Study name	NCT02764047
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Prebiotics/Probiotics/Synbiotics vs no active intervention (placebo)
Outcomes	Liver fibrosis
Starting date	January 2015
Contact information	Gabriela Z Port (NCT02764047; %20852.771,%20Probiotics%20in%20the%20Treatment%20of%20NAFLD" type="EXTERNAL">gabriela.port@hotmail.com)

NCT02764047 *(Continued)*

Notes	

NCT03439917

Study name	NCT03439917
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Amino acids (carnitine) vs no active intervention (placebo)
Outcomes	No outcomes of interest for this review will be reported in this trial
Starting date	April 2018
Contact information	Guru Aithal (University of Nottingham)
Notes	

NCT03467282

Study name	NCT03467282
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Prebiotics/Probiotics/Synbiotics vs no active intervention (placebo)
Outcomes	Liver fibrosis
Starting date	November 2017
Contact information	Valesca Dall Alba (Hospital de Clinicas de Porto Alegre)
Notes	

NCT04175392

Study name	PRONE Study
Methods	Randomised clinical trial
Participants	People with NAFLD and NASH
Interventions	Prebiotics/Probiotics/Synbiotics vs no active intervention (placebo)
Outcomes	Liver fibrosis

NCT04175392 *(Continued)*

Starting date	January 2021
Contact information	Mark Anthony Raphael (mark.raphael@beaumont.org)
Notes	

NCT04193982

Study name	NCT04193982
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Vitamin E vs no active intervention
Outcomes	No outcomes of interest for this review will be reported in this trial
Starting date	January 2021
Contact information	Mithun Sharma (drmithunsharma@gmail.com)
Notes	

NCT04198805

Study name	PUVENAFLD
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Vitamin E vs PUFA vs Vitamin E plus PUFA vs no active intervention
Outcomes	Health-related quality of life
Starting date	January 2020
Contact information	Stacey Richardson (stlyrich@iu.edu)
Notes	

NCT04330326

Study name	NCT04330326
Methods	Randomised clinical trial
Participants	People with NAFLD

NCT04330326 *(Continued)*

Interventions	Other supplement vs no active intervention
Outcomes	Change in liver fat
Starting date	July 2019
Contact information	Mujdat Zeybel (mzeybel@kuh.ku.edu.tr)
Notes	

NCT04475276

Study name	NCT04475276
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other antioxidants vs no active intervention
Outcomes	Change in fat
Starting date	August 2020
Contact information	Monalisa Jena (drmonalisajena@gmail.com)
Notes	

NCT04555434

Study name	NCT04555434
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Prebiotics/Probiotics/Synbiotics vs no active intervention (placebo)
Outcomes	No outcomes of interest for this review will be reported in this trial
Starting date	October 2019
Contact information	Ki Tae Suk (ktsuk@hallym.ac.kr)
Notes	

NCT04671186

Study name	NCT04671186

NCT04671186 *(Continued)*

Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Prebiotics/Probiotics/Synbiotics vs no active intervention
Outcomes	Change in liver fat
Starting date	September 2020
Contact information	Kanya Ahuja (kahuja3@northwell.edu)
Notes	

NCT04704063

Study name	NCT04704063
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Vitamin E vs no active intervention
Outcomes	Change in liver fat
Starting date	January 2021
Contact information	Siok Yee Chan (sychan@usm.my)
Notes	

NCT04718051

Study name	NCT04718051
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplements vs no active intervention
Outcomes	No outcomes of interest for this review will be reported in this trial
Starting date	January 2021
Contact information	Ming Shun Wu (vw1017@gmail.com)
Notes	

Wicklow 2015

Study name	INSYTE study
Methods	Randomised clinical trial
Participants	People with NAFLD
Interventions	Other supplements (resveratrol) vs no active intervention (placebo)
Outcomes	No outcomes of interest for this review will be reported in this trial
Starting date	December 2013
Contact information	Brandy Wicklow (bwicklow@hsc.mb.ca)
Notes	

Zang 2018

Study name	NCT02962297
Methods	Randomised clinical trial
Participants	People with NASH
Interventions	Vitamin E vs no active intervention (placebo)
Outcomes	Liver fibrosis, NAFLD activity scores
Starting date	December 2016
Contact information	Junping Shi (davidshi0571@126.com)
Notes	

NAFLD: non-alcohol-related fatty liver disease.
NASH: non-alcoholic steatohepatitis.
PUFA: polyunsaturated fatty acid.

ADDITIONAL TABLES

Table 1. Summary of characteristics of included studies

Features	Summary
Participant characteristics	Mean or median age in trials ranged from 7 to 66 years in trials that reported this information (Miglio 2000; Harrison 2003; Kugelmas 2003; Deng 2005; Chande 2006; Chou 2006; Dufour 2006; Nobili 2006; Spadaro 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Gomez 2009; Hashemi 2009; Fabbrini 2010; Khoshbaten 2010b; Li 2010; Malaguarnera 2010; Sanyal 2010; Aller 2011; Lavine 2011; Tan 2011; Vajro 2011; Della Corte 2012; Gonciarz 2012; Loguercio 2012; Malaguarnera 2012; Panahi 2012; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Shavakhi 2013; Wong 2013a; Wong 2013b; Aliashrafi 2014; Alisi 2014; Askari 2014; Celinski 2014; Chachay 2014; Eslamparast 2014; Farhangi 2014; Foroughi 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Solhi 2014; Somi 2014; Akbarzadeh 2015; Aller 2015; Amiri-Moghadam 2015;

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

Argo 2015; Bae 2015; Boyraz 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Orr 2015; Pacifico 2015; Qin 2015; Yan 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Della Corte 2016; Ebrahimi-Mameghani 2016; Ferolla 2016; Guo 2016; Hong 2016; Li 2016; Nabavi 2016; Nogueira 2016; Panahi 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Amiri 2017; Ashraf 2017; Behrouz 2017; Chan 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Hussain 2017; Javadi 2017; Jeong 2017; Manzhalii 2017; Mofidi 2017; Navekar 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Tabatabaee 2017; Wang 2017; Zohrer 2017; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Bomhof 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Ghaffari 2018; Hosseini 2018; Javanmardi 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Sayari 2018; Taghvaei 2018; Tobin 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afsharinasab 2020; Afzali 2020; Babaei 2020; Bahrami 2020; Boonyagard 2020; Cai 2020; Cerletti 2020; Climax 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hoseini 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020; Mansour 2020; Moradi 2020; Orang 2020; Parsi 2020; Pasdar 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Chiou 2021; Hong 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Poulos 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB)

In 9 trials, all participants were females (Abdelmalek 2009; Panahi 2012; Amiri-Moghadam 2015; Orr 2015; Hosseini 2018; Kobyliak 2018; Lewis 2018; Hoseini 2020; Moradi 2020). In 1 trial, all participants were males (Chachay 2014). In the remaining 154 trials that reported information on gender of participants, the proportion of females ranged from 6.7% to 98% (Miglio 2000; Harrison 2003; Kugelmas 2003; Deng 2005; Chande 2006; Chou 2006; Dufour 2006; Nobili 2006; Spadaro 2008; Wang 2008; Zhu 2008; Gomez 2009; Hashemi 2009; Fabbrini 2010; Li 2010; Khoshbaten 2010b; Malaguarnera 2010; Sanyal 2010; Aller 2011; Lavine 2011; Tan 2011; Vajro 2011; Della Corte 2012; Gonciarz 2012; Loguercio 2012; Malaguarnera 2012; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Shavakhi 2013; Wong 2013a; Wong 2013b; Aliashrafi 2014; Alisi 2014; Askari 2014; Celinski 2014; Eslamparast 2014; Farhangi 2014; Foroughi 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Solhi 2014; Somi 2014; Akbarzadeh 2015; Aller 2015; Argo 2015; Bae 2015; Boyraz 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Pacifico 2015; Qin 2015; Yan 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Della Corte 2016; Ebrahimi-Mameghani 2016; Ferolla 2016; Guo 2016; Hong 2016; Li 2016; Nabavi 2016; Nogueira 2016; Panahi 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Amiri 2017; Ashraf 2017; Behrouz 2017; Chan 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Hussain 2017; Javadi 2017; Jeong 2017; Manzhalii 2017; Mofidi 2017; Navekar 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Tabatabaee 2017; Wang 2017; Zohrer 2017; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Bomhof 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Ghaffari 2018; Javanmardi 2018; Oscarsson 2018; Pervez 2018; Sayari 2018; Taghvaei 2018; Tobin 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afsharinasab 2020; Afzali 2020; Babaei 2020; Bahrami 2020; Boonyagard 2020; Cai 2020; Cerletti 2020; Climax 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020; Mansour 2020; Orang 2020; Parsi 2020; Pasdar 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Chiou 2021; Hong 2021; Izadi 2021; Morvaridzadeh 2021; Poulos 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB)

A total of 44 trials reported the proportion of participants who had NASH: in 1 trial, no participants had NASH (Tobin 2018); in 39 trials, all participants had NASH (Uygun 2000; Harrison 2003; Kugelmas 2003; Chande 2006; Dufour 2006; Wang 2008; Abdelmalek 2009; Hashemi 2009; Malaguarnera 2010; Sanyal 2010; Tan 2011; Basu 2012; Malaguarnera 2012; Shavakhi 2013; Wong 2013a; Wong 2013b; Alisi 2014; Sanyal 2014; Solhi 2014; Amiri-Moghadam 2015; Argo 2015; Dasarathy 2015; Eghtesadi 2016; Ferolla 2016; Li 2016; Nogueira 2016; Ashraf 2017; Chan 2017; Manzhalii 2017; Schattenberg 2017; Wang 2017; Zohrer 2017; Bomhof 2018; Geier 2018; Bril 2019; Barbakadze 2020; Chiou 2021; NCT00845845; NCT01623024); in the remaining 4 trials, the proportion of participants who had NASH ranged from 24.3% to 64.7% (Lavine 2011; Celinski 2014; Pacifico 2015; Della Corte 2016)

In all, 90 trials reported the proportion of participants who had diabetes mellitus: in 53 trials, no participants had diabetes mellitus (Deng 2005; Gomez 2009; Fabbrini 2010; Sanyal 2010; Aller 2011; Lavine 2011; Vajro 2011; Basu 2012; Gianturco 2013; Askari 2014; Eslamparast 2014; Farhangi 2014;

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

	Martinez-Rodriguez 2014; Solhi 2014; Somi 2014; Aller 2015; Chen 2015a; Chen 2015b; Faghihzadeh 2015; Janczyk 2015; Pacifico 2015; Ekhlasi 2016; Farsi 2016; Heeboll 2016; Rahimlou 2016; Yari 2016; Ashraf 2017; Behrouz 2017; Hussain 2017; Manzhalii 2017; Navekar 2017; Shahmohammadi 2017; Wang 2017; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Dabbaghmanesh 2018; Hosseini 2018; Oscarsson 2018; Taghvaei 2018; Zamani 2018; Cheraghpour 2019; Duseja 2019; Abhari 2020; Afsharinasab 2020; Babaei 2020; Fathi 2020; Ferro 2020; Hormoznejad 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020); in 9 trials, all participants had diabetes mellitus (Bae 2015; Dasarathy 2015; Barchetta 2016; Kobyliak 2017; Eriksson 2018; Kobyliak 2018; Bril 2019; Mansour 2020; Orang 2020); in the remaining 28 trials, the proportion of participants who had diabetes mellitus ranged from 5.6% to 55.0% (Harrison 2003; Chande 2006; Dufour 2006; Abdelmalek 2009; Khoshbaten 2010b; Malaguarnera 2012; Panahi 2012; Illnait 2013; Wong 2013a; Wong 2013b; Celinski 2014; Sanyal 2014; Scorletti 2014; Argo 2015; Panahi 2016; Chan 2017; Sakpal 2017; Tabatabaee 2017; Tobin 2018; Boonyagard 2020; Cerletti 2020; Climax 2020; Fernandez-Travieso 2020; Scorletti 2020; Soleimani 2020; Zanko 2020; Soleimani 2021; EUCTR 2008-008275-34-GB) The method of diagnosis of NAFLD included biopsy, transaminases, and imaging methods including ultrasound, elastography, CT examination, or a combination of these methods. The method of diagnosis used in each study is available in Table 2 and under Characteristics of included studies
Interventions compared	Interventions compared in these 202 trials included amino acids, amino acids plus PUFA, amino acids plus vitamin C, amino acids plus vitamin E plus other antioxidants, oestrogen, MUFA, other antioxidants, other antioxidants plus other supplements, other supplements, other supplements plus other antioxidants, phospholipids, phospholipids plus PUFA plus vitamin E, phospholipids plus vitamin E plus other antioxidants, polysaccharides, prebiotics/probiotics/synbiotics plus vitamin E, prebiotics/probiotics/synbiotics, prebiotics/probiotics/synbiotics plus PUFA, prebiotics/probiotics/synbiotics plus vitamin D, PUFA, PUFA plus other supplements, PUFA plus vitamin D, PUFA plus vitamin E, vitamin C, vitamin C plus other antioxidants, vitamin D, vitamin D plus vitamin E plus other antioxidants, vitamin E, vitamin E plus other antioxidants, vitamin E plus other antioxidants plus other supplements, vitamin E plus other supplements, vitamin E plus vitamin C, and no active intervention
Trials reporting outcomes	A total of 115 trials (7732 participants) reported 1 or more outcomes for this review (Miglio 2000; Harrison 2003; Chande 2006; Chou 2006; Dufour 2006; Nobili 2006; Spadaro 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Gomez 2009; Khoshbaten 2010b; Li 2010; Malaguarnera 2010; Ruan 2010; Sanyal 2010; Lavine 2011; Vajro 2011; Loguercio 2012; Malaguarnera 2012; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Wong 2013a; Wong 2013b; Chachay 2014; Eslamparast 2014; Foroughi 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Somi 2014; Aller 2015; Bae 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Qin 2015; Yan 2015; Zhang 2015; Asgharian 2016; Farsi 2016; Ferolla 2016; Guo 2016; Heeboll 2016; Li 2016; Nabavi 2016; Naganuma 2016; Nogueira 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Chan 2017; Famouri 2017a; Hussain 2017; Jeong 2017; Manzhalii 2017; Mofidi 2017; Navekar 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Zohrer 2017; Amanat 2018; Asghari 2018; Bakhshimoghaddam 2018; Bomhof 2018; Daneshi-Maskooni 2018; Eriksson 2018; Geier 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Taghvaei 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Bahrami 2020; Boonyagard 2020; Cerletti 2020; Climax 2020; Fathi 2020; Fernandez-Travieso 2020; Hormoznejad 2020; Hosseinabadi 2020; Mansour 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Izadi 2021; Kanoni 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00845845)
Follow-up	The follow-up period in trials ranged from 1 to 28 months. In 104 trials, follow-up was less than 3 months (Miglio 2000; Kugelmas 2003; Deng 2005; Chande 2006; Nelson 2009; Fabbrini 2010; Khoshbaten 2010b; Aller 2011; Vajro 2011; Panahi 2012; Aliashrafi 2014; Askari 2014; Chachay 2014; Farhangi 2014; Foroughi 2014; Solhi 2014; Aller 2015; Amiri-Moghadam 2015; Bae 2015; Chen 2015a; Chen 2015b; Faghihzadeh 2015; Orr 2015; Qin 2015; Zhang 2015; Asgharian 2016; Ebrahimi-Mameghani 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Ferolla 2016; Guo 2016; Hong 2016; Nabavi 2016; Naganuma 2016; Panahi 2016; Pezeshki 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Amiri 2017; Ashraf 2017; Behrouz 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Hussain 2017; Javadi 2017; Jeong 2017; Kobyliak 2017; Manzhalii 2017; Navekar 2017; Schattenberg

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

	2017; Shahmohammadi 2017; Tabatabaee 2017; Youshari 2017; Amanat 2018; Amirkhizi 2018; Asghari 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Ghaffari 2018; Hosseini 2018; Javanmardi 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Wang 2018; Zamani 2018; Cheraghpour 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afsharinasab 2020; Babaei 2020; Bahrami 2020; Cai 2020; Cerletti 2020; Fathi 2020; Ferro 2020; Hormoznejad 2020; Hoseini 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020; Mansour 2020; Moradi 2020; Orang 2020; Parsi 2020; Pasdar 2020; Poparn 2020; Pour 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Song 2020; Tutunchi 2020; Yari 2020; Hong 2021; Izadi 2021; Morvaridzadeh 2021; EUCTR 2009-017080-41-GB; NCT00816465); in 92 trials, follow-up was between 3 months and 28 months (Uygun 2000; Harrison 2003; Chou 2006; Dufour 2006; Nobili 2006; Chen 2008; Spadaro 2008; Zhu 2008; Abdelmalek 2009; Gomez 2009; Hashemi 2009; Li 2010; Malaguarnera 2010; Ruan 2010; Sanyal 2010; Lavine 2011; Tan 2011; Basu 2012; Della Corte 2012; Gonciarz 2012; Loguercio 2012; Malaguarnera 2012; Basu 2013; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Wong 2013a; Wong 2013b; Alisi 2014; Byrne 2014; Celinski 2014; Eslamparast 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Somi 2014; Akbarzadeh 2015; Argo 2015; Bonfrate 2015; Boyraz 2015; Dasarathy 2015; Janczyk 2015; Pacifico 2015; Yan 2015; Barchetta 2016; Boonyagard 2016; Della Corte 2016; Heeboll 2016; Li 2016; Nogueira 2016; Chan 2017; Chongsrisawat 2017; Gavrilescu 2017; Mofidi 2017; Palamaru 2017; Sakpal 2017; Wang 2017; Zohrer 2017; Ahn 2018; Bakhshimoghaddam 2018; Bomhof 2018; Geier 2018; Sayari 2018; Taghvaei 2018; Tobin 2018; Bril 2019; Duseja 2019; Afzali 2020; Barbakadze 2020; Boonyagard 2020; Climax 2020; Dallio 2020; Fernandez-Travieso 2020; Pervez 2020; Scorletti 2020; Soleimani 2020; Zanko 2020; Chiou 2021; Kanoni 2021; Poulos 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; NCT00845845; NCT00977730; NCT01083992; NCT02690792; NCT04411862); follow-up was not reported in 6 trials (Wang 2008; Jameshorani 2017; Farzin 2020; Khutsishvili 2020; NCT00941642; NCT01623024)
Funding	The source of funding for 41 trials was industrial organisations that would benefit from study results (Chande 2006; Dufour 2006; Gomez 2009; Fabbrini 2010; Sanyal 2010; Lavine 2011; Magosso 2013; Wong 2013b; Aliashrafi 2014; Eslamparast 2014; Scorletti 2014; Argo 2015; Bae 2015; Dasarathy 2015; Janczyk 2015; Heeboll 2016; Hong 2016; Nabavi 2016; Nogueira 2016; Panahi 2016; Rahimlou 2016; Chan 2017; Ebrahimi-Mameghani 2017; Mofidi 2017; Schattenberg 2017; Zohrer 2017; Bomhof 2018; Eriksson 2018; Geier 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Tobin 2018; Duseja 2019; Cerletti 2020; Climax 2020; Scorletti 2020; Song 2020; Hong 2021; Poulos 2021; EUCTR 2009-017080-41-GB); 87 trials were funded by neutral organisations that have no vested interests in results of the study (Kugelmas 2003; Chou 2006; Khoshbaten 2010b; Malaguarnera 2010; Gonciarz 2012; Loguercio 2012; Malaguarnera 2012; Panahi 2012; Ghergherehchi 2013; Nobili 2013; Shavakhi 2013; Alisi 2014; Askari 2014; Byrne 2014; Farhangi 2014; Foroughi 2014; Sharifi 2014; Solhi 2014; Akbarzadeh 2015; Amiri-Moghadam 2015; Boyraz 2015; Chen 2015a; Chen 2015b; Faghihzadeh 2015; Pacifico 2015; Yan 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Ebrahimi-Mameghani 2016; Ekhlasi 2016; Farsi 2016; Rahmani 2016; Yari 2016; Amiri 2017; Behrouz 2017; Famouri 2017a; Hussain 2017; Javadi 2017; Navekar 2017; Shahmohammadi 2017; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Hosseini 2018; Pervez 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afsharinasab 2020; Afzali 2020; Babaei 2020; Bahrami 2020; Boonyagard 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hoseini 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020; Mansour 2020; Moradi 2020; Orang 2020; Parsi 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Soleimani 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Chiou 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Soleimani 2021; EUCTR 2008-008275-34-GB); the source of funding for the remaining 74 trials was unclear (Miglio 2000; Uygun 2000; Harrison 2003; Deng 2005; Nobili 2006; Chen 2008; Spadaro 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Hashemi 2009; Nelson 2009; Li 2010; Ruan 2010; Aller 2011; Tan 2011; Vajro 2011; Basu 2012; Della Corte 2012; Basu 2013; Gianturco 2013; Illnait 2013; Saxena 2013; Wong 2013a; Celinski 2014; Chachay 2014; Martinez-Rodriguez 2014; Sanyal 2014; Somi 2014; Aller 2015; Bonfrate 2015; Orr 2015; Qin 2015; Boonyagard 2016; Della Corte 2016; Eghtesadi 2016; Ferolla 2016; Guo 2016; Li 2016; Naganuma 2016; Pezeshki 2016; Sepideh 2016; Ashraf 2017; Chongsrisawat 2017; Gavrilescu 2017; Jameshorani 2017; Jeong 2017; Kobyliak 2017; Manzhalii 2017; Palamaru 2017; Sakpal 2017; Tabatabaee 2017; Wang 2017; Youshari 2017; Ahn 2018; Ghaffari 2018; Javanmardi 2018; Sayari 2018; Taghvaei 2018; Wang 2018; Barbakadze 2020; Cai 2020; Dallio 2020; Farzin 2020; Khutsishvili 2020; Pasdar 2020; NCT00816465; NCT00845845; NCT00941642; NCT00977730; NCT01083992; NCT01623024; NCT02690792; NCT04411862)

MUFA: monounsaturated fatty acid.
NAFLD: non-alcohol-related fatty liver disease.
PUFA: polyunsaturated fatty acid.

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

Study name	Intervention 1 (number of participants) vs intervention 2 (number of participants)	NASH	Diabetes mellitus	Supplementary lifestyle modification	Method of diagnosis of NAFLD	Period of recruitment	Follow-up in months	Risk of bias
Afshari-nasab 2020	Other supplements (n = 21) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	2	High
Asghari 2018	Other supplements (n = 30) vs No active intervention (n = 30)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	2.8	Low
Askari 2014	Other supplements (n = 23) vs No active intervention (n = 22)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Not stated	Not stated	2.8	High
Babaei 2020	Other supplements (n = 13) vs No active intervention (n = 11)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2014-2017	3	High
Bahrami 2020	Other supplements (n = 24) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	2.8	High
Cerletti 2020	Other supplements (n = 55) vs No active intervention (n = 58)	Not stated	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound + transaminases	2015-2016	3	High
Chachay 2014	Other supplements (n = 10) vs No active intervention (n = 10)	Not stated	Not stated	Not stated	Ultrasound	2011-2012	1.8	High
Chande 2006	Other supplements (n = 5) vs No active intervention (n = 3)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy + transaminases	2003-2004	2.8	High
Chen 2015a	Other supplements (n = 30) vs No active intervention (n = 30)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2012-2013	3	High

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

Chiou 2021	Other supplements (n = 15) vs No active intervention (n = 13)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Not stated	2015-2016	6	High
Chou 2006	Other supplements (n = 28) vs No active intervention (n = 28)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	2001-2002	6	High
Daneshi-Maskooni 2018	Other supplements (n = 43) vs No active intervention (n = 44)	Not stated	Not stated	Not stated	Ultrasound	2016-2017	3	High
Ebrahimi-Mameghani 2017	Other supplements (n = 29) vs No active intervention (n = 26)	Not stated	Not stated	Not stated	Ultrasound	2011-2012	1.8	High
EUCTR 2009-017080-41-GB	Other supplements (n = 20) vs No active intervention (n = 5)	Not stated	Not stated	Not stated	MRI, MRS, or biopsy	Not stated	2	High
Faghihzadeh 2015	Other supplements (n = 24) vs No active intervention (n = 24)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound + elastography + transaminases	2013-2014	2.8	High
Farzin 2020	Other supplements (n = 25) vs No active intervention (n = 25)	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	High
Fathi 2020	Other supplements (n = 25) vs No active intervention (n = 25)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2018-2019	2.8	High
Fernandez-Travieso 2020	Other supplements (n = 50) vs No active intervention (n = 50)	Not stated	Participants with and without diabetes mellitus	Not stated	Ultrasound	Not stated	6	High
Ferro 2020	Other supplements (n = 45) vs No active intervention (n = 41)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2019	2.8	High

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

Ghaffari 2018	Other supplements (n = 64) vs No active intervention (n = 21)	Not stated	Not stated	Not stated	Ultrasound	Not stated	2.8	High
Heeboll 2016	Other supplements (n = 15) vs No active intervention (n = 13)	Participants with and without NASH	No participants had diabetes mellitus	Not stated	Ultrasound	2011-2014	6	Low
Hong 2021	Other supplements (n = 43) vs No active intervention (n = 44)	Not stated	Not stated	Not stated	Ultrasound	2017-2018	0.9	High
Hormoznejad 2020	Other supplements (n = 20) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	2.8	High
Hosseinabadi 2020	Other supplements (n = 21) vs No active intervention (n = 23)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2016	1.8	High
Hussain 2017	Other supplements (n = 40) vs No active intervention (n = 40)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2016	2.8	High
Illnait 2013	Other supplements (n = 25) vs No active intervention (n = 25)	Not stated	Participants with and without diabetes mellitus	Not stated	Ultrasound	Not stated	5.5	High
Izadi 2021	Other supplements (n = 30) vs No active intervention (n = 31)	Not stated	Not stated	Not stated	Ultrasound	2018	1.8	High
Javanmardi 2018	Other supplements (n = 19) vs No active intervention (n = 19)	Not stated	Not stated	Not stated	Ultrasound	Not stated	1.8	High
Jazayeri-Tehrani 2019	Other supplements (n = 42) vs No active intervention (n = 42)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	Not stated	3	High
Jeong 2017	Other supplements (n = 45) vs No active intervention (n = 23)	Not stated	Not stated	Not stated	Ultrasound	2013-2015	2.8	High

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

Kazemi 2020	Other supplements (n = 40) vs No active intervention (n = 40)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	2.8	High
Kooshki 2020	Other supplements (n = 22) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2018-2019	2.8	High
Mansour 2020	Other supplements (n = 20) vs No active intervention (n = 6)	Not stated	All participants had diabetes mellitus only	Not stated	Ultrasound	Not stated	2.8	Low
Martinez-Rodriguez 2014	Other supplements (n = 20) vs No active intervention (n = 20)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound + liver biopsy	2013-2014	5.5	High
Moradi 2020	Other supplements (n = 22) vs No active intervention (n = 23)	Not stated	Not stated	50% of participants (factorial trial design)	Ultrasound	Not stated	2.8	High
Navekar 2017	Other supplements (n = 21) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	2.8	High
NCT00816465	Other supplements (n = not stated) vs No active intervention (n = not stated)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	2009-2010	2	High
Panahi 2016	Other supplements (n = 44) vs No active intervention (n = 43)	Not stated	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	Not stated	1.8	High
Parsi 2020	Other supplements (n = 30) vs No active intervention (n = 30)	Not stated	Not stated	Not stated	Ultrasound and liver enzymes	Not stated	1.8	High
Pasdar 2020	Other supplements (n = 39) vs No active intervention (n = 39)	Not stated	Not stated	Not stated	Ultrasound	2017	2.8	High

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

Pezeshki 2016	Other supplements (n = 35) vs No active intervention (n = 36)	Not stated	Not stated	Not stated	Ultrasound + transaminases	2013-2014	3	High
Rahimlou 2016	Other supplements (n = 23) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Elastography + transaminases	Not stated	2.8	High
Rahmani 2016	Other supplements (n = 37) vs No active intervention (n = 40)	Not stated	Not stated	Not stated	Ultrasound	Not stated	1.8	High
Sangouni 2020	Other supplements (n = 45) vs No active intervention (n = 43)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2018	2.8	High
Saxena 2013	Other supplements (n = 26) vs No active intervention (n = 24)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	Not stated	3.9	High
Shahmohammadi 2017	Other supplements (n = 22) vs No active intervention (n = 22)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	Not stated	1.8	High
Soleimani 2020	Other supplements (n = 47) vs No active intervention (n = 51)	Not stated	Participants with and without diabetes mellitus	Not stated	Ultrasound	Not stated	3.5	High
Soleimani 2021	Other supplements (n = 27) vs No active intervention (n = 27)	Not stated	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Elastography technique	2018	4	Low
Song 2020	Other supplements (n = 16) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	CT scan + abnormal serum lipid profile or high BMI	2018	2.8	High

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

Tabatabaee 2017	Other supplements (n = 21) vs No active intervention (n = 24)	Not stated	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound, elastography, or liver biopsy	Not stated	3	High
Tutunchi 2020	Other supplements (n = 38) vs No active intervention (n = 38)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2019	2.8	Low
Wang 2017	Other supplements (n = 24) vs No active intervention (n = 12)	All participants had NASH	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Elastography	Not stated	5.5	High
Wong 2013b	Other supplements (n = 40) vs No active intervention (n = 20)	All participants had NASH	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Liver biopsy	2010-2011	5.5	Low
Yan 2015	Other supplements (n = 55) vs No active intervention (n = 53)	Not stated	Not stated	All participants had supplementary lifestyle modification	MRS	2008-2011	3.7	High
Yari 2020	Other supplements (n = 24) vs No active intervention (n = 21)	Not stated	Not stated	All participants had supplementary lifestyle modification	Elastography	2018-2019	2.8	High
Zamani 2018	Other supplements (n = 45) vs No active intervention (n = 40)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2017	2.8	High
Zhang 2015	Other supplements (n = 37) vs No active intervention (n = 37)	Not stated	Not stated	Not stated	Ultrasound	2013	2.8	Low
Abhari 2020	Prebiotics/Probiotics/Synbiotics (n = 23) vs No active intervention (n = 22)	Not stated	No participants had diabetes mellitus	Not stated	Not stated	Not stated	2.8	High

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

Ahn 2018	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Not stated	Not stated	Not stated	Not stated	Not stated	8	High
Akbarzadeh 2015	Prebiotics/Probiotics/Synbiotics (n = 38) vs No active intervention (n = 37)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound ± elastography ± transaminases	2015	6.3	High
Alisi 2014	Prebiotics/Probiotics/Synbiotics (n = 22) vs No active intervention (n = 22)	All participants had NASH	Not stated	Not stated	Clinical examination + transaminases + liver biopsy	2012-2013	4	High
Aller 2011	Prebiotics/Probiotics/Synbiotics (n = 14) vs No active intervention (n = 14)	Not stated	No participants had diabetes mellitus	Not stated	Liver biopsy	Not stated	3	High
Guo 2016	Prebiotics/Probiotics/Synbiotics (n = 42) vs No active intervention (n = 42)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	2011-2013	1.8	High
Asgharian 2016	Prebiotics/Probiotics/Synbiotics (n = 38) vs No active intervention (n = 36)	Participants with and without NASH	Not stated	Not stated	Ultrasound	2014	1.8	High
Bakhshimoghaddam 2018	Prebiotics/Probiotics/Synbiotics (n = 32) vs No active intervention (n = 28)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2016-2017	5.5	High
Behrouz 2017	Prebiotics/Probiotics/Synbiotics (n = 59) vs No active intervention (n = 30)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound and ALT	Not stated	2.8	High
Bomhof 2018	Prebiotics/Probiotics/Synbiotics (n = 8) vs No active intervention (n = 5)	All participants had NASH	Participants with and with-	Not stated	Ultrasound + transaminases	Not stated	8.3	High

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

			out diabetes mellitus					
Cai 2020	Prebiotics/Probiotics/Synbiotics (n = 70) vs No active intervention (n = 70)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound and biopsy	2017-2019	3	High
Chongsrisawat 2017	Prebiotics/Probiotics/Synbiotics (n = 18) vs No active intervention (n = 19)	Not stated	Not stated	Not stated	FibroScan	2016	3.7	High
Della Corte 2012	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Not stated	Not stated	Not stated	Not stated	Not stated	6	High
Duseja 2019	Prebiotics/Probiotics/Synbiotics (n = 10) vs No active intervention (n = 5)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Biopsy	Not stated	12	High
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics (n = 15) vs No active intervention (n = 15)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2012-2013	1.8	High
Eslamparast 2014	Prebiotics/Probiotics/Synbiotics (n = 26) vs No active intervention (n = 26)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound + transaminases	2012	6.5	High
Famouri 2017a	Prebiotics/Probiotics/Synbiotics (n = 32) vs No active intervention (n = 32)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	2014	2.8	High
Ferolla 2016	Prebiotics/Probiotics/Synbiotics (n = 27) vs No active intervention (n = 23)	All participants had NASH	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Liver biopsy	2014-2015	3	High
Gavrilescu 2017	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Not stated	Not stated	All participants had supplementary lifestyle modification	Not stated	2015-2016	5.5	High

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

Jameshorani 2017	Prebiotics/Probiotics/Synbiotics (n = 45) vs No active intervention (n = 45)	Not stated	Not stated	All participants had supplementary lifestyle modification	Not stated	Not stated	Not stated	High
Javadi 2017	Prebiotics/Probiotics/Synbiotics (n = 56) vs No active intervention (n = 19)	Not stated	Not stated	Not stated	Ultrasound	2013-2014	3	High
Khutsishvili 2020	Prebiotics/Probiotics/Synbiotics (n = 35) vs No active intervention (n = 38)	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	High
Kobyliak 2018	Prebiotics/Probiotics/Synbiotics (n = 30) vs No active intervention (n = 28)	Not stated	All participants had diabetes mellitus only	Not stated	Ultrasound	Not stated	1.8	Low
Malaguarnera 2012	Prebiotics/Probiotics/Synbiotics (n = 34) vs No active intervention (n = 32)	All participants had NASH	Both	All participants had supplementary lifestyle modification	Ultrasound + transaminases	2003-2006	5.5	High
Manzhalii 2017	Prebiotics/Probiotics/Synbiotics (n = 38) vs No active intervention (n = 37)	All participants had NASH	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound + transaminases	Not stated	2.8	High
Mofidi 2017	Prebiotics/Probiotics/Synbiotics (n = 21) vs No active intervention (n = 21)	Not stated	Not stated	All participants had supplementary lifestyle modification	Elastography + transaminases	Not stated	6.5	High
Nabavi 2016	Prebiotics/Probiotics/Synbiotics (n = 36) vs No active intervention (n = 36)	Not stated	Not stated	Not stated	Ultrasound	Not stated	1.8	Low
Orr 2015	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Not stated	Not stated	Not stated	Not stated	Not stated	2.8	High
Poparn 2020	Prebiotics/Probiotics/Synbiotics (n = 18) vs No active intervention (n = 19)	Not stated	Not stated	Not stated	Fibroscan	2016	2.8	Low
Sadrkabir 2020	Prebiotics/Probiotics/Synbiotics (n = 33) vs No active intervention (n = 28)	Not stated	No participants had diabetes mellitus	All participants had supplemen-	Ultrasound	Not stated	2	High

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

				tary lifestyle modification				
Sayari 2018	Prebiotics/Probiotics/Synbiotics (n = 70) vs No active intervention (n = 68)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound + transaminases	2015-2017	3.7	High
Schattenberg 2017	Prebiotics/Probiotics/Synbiotics (n = 15) vs No active intervention (n = 14)	All participants had NASH	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound + M30 (biomarker of liver injury) or liver biopsy	Not stated	3	High
Scorletti 2020	Prebiotics/Probiotics/Synbiotics (n = 45) vs No active intervention (n = 44)	Not stated	Participants with and without diabetes mellitus	Not stated	biopsy or imaging evidence of liver fat	Not stated	12	High
Sepideh 2016	Prebiotics/Probiotics/Synbiotics (n = 21) vs No active intervention (n = 21)	Not stated	Not stated	Not stated	Ultrasound	2013	1.8	High
Shavakhi 2013	Prebiotics/Probiotics/Synbiotics (n = 31) vs No active intervention (n = 32)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	2010-2012	6	High
Vajro 2011	Prebiotics/Probiotics/Synbiotics (n = 10) vs No active intervention (n = 10)	Not stated	No participants had diabetes mellitus	Not stated	Elastography + transaminases	Not stated	1.8	High
Wong 2013a	Prebiotics/Probiotics/Synbiotics (n = 10) vs No active intervention (n = 10)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy + transaminases	2009	6	High
Argo 2015	PUFA (n = 17) vs No active intervention (n = 17)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	2007-2010	12	High

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

Boyraz 2015	PUFA (n = 56) vs No active intervention (n = 52)	Not stated	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound + transaminases	2010-2012	12	High
Byrne 2014	PUFA (n = 51) vs No active intervention (n = 52)	Not stated	Not stated	Not stated	Not stated	Not stated	16.5	High
Chen 2008	PUFA (n = 30) vs No active intervention (n = 16)	Participants with and without NASH	Not stated	Not stated	Clinical examination + transaminases	Not stated	5.5	High
Climax 2020	PUFA (n = 63) vs No active intervention (n = 30)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Imaging or histology	2016-2019	3.7	High
Dasarathy 2015	PUFA (n = 18) vs No active intervention (n = 19)	All participants had NASH	All participants had diabetes mellitus only	Not stated	Liver biopsy	Not stated	11.1	High
Eriksson 2018	PUFA (n = 42) vs No active intervention (n = 42)	Not stated	All participants had diabetes mellitus only	Not stated	MRI	2015	2.8	Low
EUCTR 2008-008275-34-GB	PUFA (n = 24) vs No active intervention (n = 25)	Not stated	Participants with and without diabetes mellitus	Not stated	Clinical + ultrasound + abnormal LFTs	2010-2011	9	Low
Janczyk 2015	PUFA (n = 30) vs No active intervention (n = 34)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2008-2011	5.5	High
Li 2016	PUFA (n = 39) vs No active intervention (n = 39)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	6	High
NCT00845845	PUFA (n = 3) vs No active intervention (n = 6)	All participants had NASH	Participants with and with-	All participants had supplemen-	Liver biopsy	2006-2009	5.5	High

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

			out diabetes mellitus	tary lifestyle modification				
NCT00941642	PUFA (n = not stated) vs No active intervention (n = not stated)	Participants with and without NASH	No participants had diabetes mellitus	Not stated	Liver biopsy	Not stated	Not stated	High
Nobili 2013	PUFA (n = 40) vs No active intervention (n = 20)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	Not stated	24	High
Nogueira 2016	PUFA (n = 27) vs No active intervention (n = 23)	All participants had NASH	Not stated	Not stated	Liver biopsy	Not stated	6	High
Orang 2020	PUFA (n = 22) vs No active intervention (n = 22)	Not stated	All participants had diabetes mellitus only	Not stated	Not stated	Not stated	2.8	High
Oscarsson 2018	PUFA (n = 23) vs No active intervention (n = 23)	Not stated	No participants had diabetes mellitus	Not stated	Liver MRI	Not stated	2.8	High
Pacifico 2015	PUFA (n = 25) vs No active intervention (n = 26)	Not stated	No participants had diabetes mellitus	Not stated	Liver biopsy	2012-2014	6	High
Sanyal 2014	PUFA (n = 168) vs No active intervention (n = 75)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	2011-2012	12	Low
Scorletti 2014	PUFA (n = 51) vs No active intervention (n = 52)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	2010-2011	15	High
Song 2020	PUFA (n = 21) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	CT scan + abnormal serum lipid profile or high BMI	2018	2.8	High

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

Spadaro 2008	PUFA (n = 18) vs No active intervention (n = 18)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound + transaminases	Not stated	6	High
Yari 2016	PUFA (n = 25) vs No active intervention (n = 25)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Elastography	Not stated	2.8	High
Zhu 2008	PUFA (n = 66) vs No active intervention (n = 68)	Not stated	Not stated	Not stated	Ultrasound	2006-2008	5.5	High
Song 2020	PUFA (n = 21) vs Other supplements (n = 16)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	CT scan + abnormal serum lipid profile or high BMI	2018	2.8	High
Basu 2012	Vitamin E (n = 40) vs No active intervention (n = 35)	All participants had NASH	No participants had diabetes mellitus	Not stated	Not stated	Not stated	6	High
Bril 2019	Vitamin E (n = 36) vs No active intervention (n = 32)	All participants had NASH	All participants had diabetes mellitus only	All participants had supplementary lifestyle modification	Liver biopsy	2010-2016	18	Low
Dufour 2006	Vitamin E (n = 10) vs No active intervention (n = 11)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	1999-2002	24	High
Ekhlasi 2016	Vitamin E (n = 15) vs No active intervention (n = 15)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2012-2013	1.8	High
Gherghere-hchi 2013	Vitamin E (n = 17) vs No active intervention (n = 16)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound + transaminases	2008-2009	6	High

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

Kugelmas 2003	Vitamin E (n = 9) vs No active intervention (n = 7)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	2.8	High
Lavine 2011	Vitamin E (n = 50) vs No active intervention (n = 47)	Participants with and without NASH	No participants had diabetes mellitus	Not stated	Liver biopsy	2005-2010	27.7	High
Magosso 2013	Vitamin E (n = 43) vs No active intervention (n = 44)	Not stated	Not stated	Not stated	Ultrasound	2008-2009	12	High
NCT02690792	Vitamin E (n = not stated) vs No active intervention (n = not stated)	Not stated	Not stated	Not stated	Not stated	2009-2016	4	High
Palamaru 2017	Vitamin E (n = 20) vs No active intervention (n = 20)	Not stated	Not stated	All participants had supplementary lifestyle modification	Not stated	2016-2017	5.5	High
Pervez 2018	Vitamin E (n = 31) vs No active intervention (n = 33)	Not stated	Not stated	Not stated	Ultrasound	2015-2016	2.8	High
Pervez 2020	Vitamin E (n = 35) vs No active intervention (n = 36)	Not stated	Not stated	Not stated	Ultrasound	2015-2016	5.5	High
Sanyal 2010	Vitamin E (n = 84) vs No active intervention (n = 83)	All participants had NASH	No participants had diabetes mellitus	Not stated	Liver biopsy	2005-2007	27.7	Low
Wang 2008	Vitamin E (n = 19) vs No active intervention (n = 38)	All participants had NASH	Not stated	Not stated	Not stated	Not stated	Not stated	High
Basu 2013	Vitamin E (n = 20) vs Other supplements (n = 20)	Not stated	Not stated	Not stated	Not stated	Not stated	12	High
Ekhlasi 2016	Vitamin E (n = 15) vs Prebiotics/Probiotics/Synbiotics (n = 15)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2012-2013	1.8	High

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

Amiri 2017	Vitamin D (n = 74) vs No active intervention (n = 36)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2015-2016	2.8	High
Barchetta 2016	Vitamin D (n = 26) vs No active intervention (n = 29)	Not stated	All participants had diabetes mellitus only	Not stated	Ultrasound + MRI + transaminases	Not stated	5.5	High
Boonyagard 2016	Vitamin D (n = 30) vs No active intervention (n = 30)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	2015	4.6	High
Boonyagard 2020	Vitamin D (n = 30) vs No active intervention (n = 30)	Not stated	Participants with and without diabetes mellitus	Not stated	Ultrasonography and increased levels of alanine transaminase	2015-2018	5	High
Dabbaghmanesh 2018	Vitamin D (n = 59) vs No active intervention (n = 32)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2011-2013	2.8	High
Foroughi 2014	Vitamin D (n = 30) vs No active intervention (n = 30)	Not stated	Not stated	Not stated	Ultrasound	Not stated	2.3	High
Geier 2018	Vitamin D (n = 8) vs No active intervention (n = 10)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	Not stated	11.1	High
Hoseini 2020	Vitamin D (n = 20) vs No active intervention (n = 20)	Not stated	Not stated	50% of participants (factorial trial design)	Not stated	Not stated	1.8	High
Hosseini 2018	Vitamin D (n = 37) vs No active intervention (n = 38)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2015-2016	1	High

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

NCT01083992	Vitamin D (n = not stated) vs No active intervention (n = not stated)	Not stated	Not stated	All participants had supplementary lifestyle modification	Liver biopsy + elevated enzymes	Not stated	6	High
NCT01623024	Vitamin D (n = not stated) vs No active intervention (n = not stated)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	Not stated	High
Sakpal 2017	Vitamin D (n = 51) vs No active intervention (n = 30)	Participants with and without NASH	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	Not stated	6	High
Sharifi 2014	Vitamin D (n = 27) vs No active intervention (n = 26)	Not stated	Not stated	Not stated	Ultrasound	2012-2013	4	High
Taghvaei 2018	Vitamin D (n = 20) vs No active intervention (n = 20)	Not stated	No participants had diabetes mellitus	Not stated	Elastography + transaminases	Not stated	6	High
Zanko 2020	Vitamin D (n = 201) vs No active intervention (n = 110)	Not stated	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound and transient elastography	2015-2019	12	High
Basu 2012	Other antioxidants (n = 40) vs No active intervention (n = 35)	All participants had NASH	No participants had diabetes mellitus	Not stated	Not stated	Not stated	6	High
Chan 2017	Other antioxidants (n = 49) vs No active intervention (n = 50)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	2012-2014	11.1	Low
Chen 2015b	Other antioxidants (n = 30) vs No active intervention (n = 30)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2012-2013	2.8	Low

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

Cheraghpour 2019	Other antioxidants (n = 25) vs No active intervention (n = 24)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Elastography	2017-2018	2.8	High
Farhangi 2014	Other antioxidants (n = 20) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	0.9	High
Farsi 2016	Other antioxidants (n = 20) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	Not stated	2.8	High
Gianturco 2013	Other antioxidants (n = 104) vs No active intervention (n = 92)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	12	High
Gonciarz 2012	Other antioxidants (n = 30) vs No active intervention (n = 12)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	2008-2010	8.3	High
Hashemi 2009	Other antioxidants (n = 50) vs No active intervention (n = 50)	All participants had NASH	Not stated	Not stated	Ultrasound + transaminases	2007-2008	5.5	High
Kanoni 2021	Other antioxidants (n = 35) vs No active intervention (n = 52)	Participants with and without NASH	Not stated	Not stated	Magnetic resonance imaging	2017-2019	6	High
Ruan 2010	Other antioxidants (n = 30) vs No active intervention (n = 30)	Not stated	Not stated	All participants had supplementary lifestyle modification	Not stated	2008-2009	5.5	High
Solhi 2014	Other antioxidants (n = 33) vs No active intervention (n = 31)	All participants had NASH	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Elastography + transaminases	Not stated	1.8	High
Yari 2020	Other antioxidants (n = 22) vs No active intervention (n = 21)	Not stated	Not stated	All participants had supplemen-	Elastography	2018-2019	2.8	High

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

				tary lifestyle modification				
Deng 2005	Other antioxidants (n = 48) vs Other supplements (n = 48)	Not stated	No participants had diabetes mellitus	Not stated	Not stated	Not stated	3	High
Basu 2012	Other antioxidants (n = 40) vs Vitamin E (n = 40)	All participants had NASH	No participants had diabetes mellitus	Not stated	Not stated	Not stated	6	High
Khoshbaten 2010b	Other antioxidants (n = 15) vs Vitamin C (n = 15)	Not stated	Participants with and without diabetes mellitus	Not stated	Ultrasound or transaminases	2008	3	High
Yari 2020	Other antioxidants (n = 22) vs Other supplements (n = 24)	Not stated	Not stated	All participants had supplementary lifestyle modification	Elastography	2018-2019	2.8	High
Abdelmalek 2009	Amino acids (n = 17) vs No active intervention (n = 18)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	2003-2005	12	High
Amiri-Moghadam 2015	Amino acids (n = 36) vs No active intervention (n = 32)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Ultrasound + transaminases	2013-2014	2.8	High
Bae 2015	Amino acids (n = 39) vs No active intervention (n = 39)	Not stated	All participants had diabetes mellitus only	Not stated	CT scan	2011-2012	2.8	Low
Eghtesadi 2016	Amino acids (n = 36) vs No active intervention (n = 32)	All participants had NASH	Not stated	Not stated	Not stated	Not stated	2.8	High
Fabbrini 2010	Amino acids (n = 9) vs No active intervention (n = 9)	Not stated	No participants had diabetes mellitus	Not stated	Not stated	Not stated	1.8	High

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

Malaguarnera 2010	Amino acids (n = 36) vs No active intervention (n = 38)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	2004-2006	5.5	High
Naganuma 2016	Amino acids (n = 10) vs No active intervention (n = 10)	Not stated	Not stated	All participants had supplementary lifestyle modification	Not stated	Not stated	3	High
Somi 2014	Amino acids (n = 40) vs No active intervention (n = 40)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	2012-2014	5.5	High
Uygun 2000	Amino acids (n = 78) vs No active intervention (n = 23)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	12	High
Aller 2015	Vitamin E plus other antioxidants (n = 18) vs No active intervention (n = 18)	Participants with and without NASH	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	3	High
Basu 2012	Vitamin E plus other antioxidants (n = 40) vs No active intervention (n = 35)	All participants had NASH	No participants had diabetes mellitus	Not stated	Not stated	Not stated	6	High
Bonfrate 2015	Vitamin E plus other antioxidants (n = not stated) vs No active intervention (n = not stated)	Not stated	Participants with and without diabetes mellitus	Not stated	Not stated	Not stated	6	High
Amirkhizi 2018	Vitamin E plus other antioxidants (n = 23) vs Vitamin E (n = 22)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	2.8	High
Basu 2012	Vitamin E plus other antioxidants (n = 40) vs Vitamin E (n = 40)	All participants had NASH	No participants had diabetes mellitus	Not stated	Not stated	Not stated	6	High

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

Basu 2012	Vitamin E plus other antioxidants (n = 40) vs Other antioxidants (n = 40)	All participants had NASH	No participants had diabetes mellitus	Not stated	Not stated	Not stated	6	High
NCT04411862	Phospholipids (n = 50) vs No active intervention (n = 50)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound, CT, MRI	2016-2019	6	High
Tan 2011	Phospholipids (n = 10) vs No active intervention (n = 5)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	6	High
Li 2010	Phospholipids (n = 43) vs Other supplements (n = 45)	Not stated	Not stated	Not stated	CT scan	2007-2008	6	High
Wang 2018	Phospholipids (n = 50) vs Prebiotics/Probiotics/Synbiotics (n = 150)	Not stated	Not stated	Not stated	Not stated	2010-2015	1	High
Basu 2013	Vitamin E plus other supplements (n = 20) vs Other supplements (n = 20)	Not stated	Not stated	Not stated	Not stated	Not stated	12	High
Aliashrafi 2014	Vitamin E plus other supplements (n = 29) vs Vitamin E (n = 26)	Not stated	Not stated	Not stated	Ultrasound + transaminases	2011-2012	1.8	High
Basu 2013	Vitamin E plus other supplements (n = 20) vs Vitamin E (n = 20)	Not stated	Not stated	Not stated	Not stated	Not stated	12	High
Panahi 2012	Vitamin E plus other supplements (n = 21) vs Vitamin E (n = 33)	Participants with and without NASH	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2009	3	High
Youshari 2017	Vitamin E plus other supplements (n = 20) vs Vitamin E (n = 21)	Not stated	Not stated	All participants had supplementary lifestyle modification	Not stated	Not stated	1.8	High
Barbakadze 2020	Vitamin E plus vitamin C (n = 52) vs No active intervention (n = 20)	All participants had NASH	Not stated	Not stated	Not stated	Not stated	12	High

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

Harrison 2003	Vitamin E plus vitamin C (n = 23) vs No active intervention (n = 22)	All participants had NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	2000-2002	6	High
Nobili 2006	Vitamin E plus vitamin C (n = 45) vs No active intervention (n = 43)	Participants with and without NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	2003-2005	12	High
Pour 2020	Other supplements (n = 38) vs No active intervention (n = 38)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2016-2017	2.8	High
Rafie 2020	Other supplements (n = 23) vs No active intervention (n = 23)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	High levels of liver enzymes (> 30 U/L in men, > 19 U/L in women), ultrasound, and 24.9 < BMI < 35.19	Not stated	2.8	High
Nelson 2009	MUFA (n = not stated) vs PUFA (n = not stated)	Not stated	Not stated	Not stated	Not stated	Not stated	1.8	High
Tobin 2018	MUFA (n = 86) vs PUFA (n = 81)	No participants had NASH	Participants with and without diabetes mellitus	All participants had supplementary lifestyle modification	Ultrasound	2015-2017	5.5	High
NCT00977730	Other antioxidants plus other supplements (n = not stated) vs No active intervention (n = not stated)	All participants had NASH	No participants had diabetes mellitus	Not stated	Liver biopsy	2008-2011	12	High
Yari 2020	Other antioxidants plus other supplements (n = 25) vs No active intervention (n = 21)	Not stated	Not stated	All participants had supplementary lifestyle modification	Elastography	2018-2019	2.8	High

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

Yari 2020	Other antioxidants plus other supplements (n = 25) vs Other supplements (n = 24)	Not stated	Not stated	All participants had supplementary lifestyle modification	Elastography	2018-2019	2.8	High
Yari 2020	Other antioxidants plus other supplements (n = 25) vs Other antioxidants (n = 22)	Not stated	Not stated	All participants had supplementary lifestyle modification	Elastography	2018-2019	2.8	High
Qin 2015	PUFA plus vitamin E (n = 36) vs No active intervention (n = 34)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	2012-2013	3	High
Gomez 2009	Vitamin C plus other antioxidants (n = 30) vs No active intervention (n = 30)	Not stated	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Liver biopsy	2007	5.5	High
Ebrahimi-Mameghani 2016	PUFA plus vitamin E (n = 19) vs Vitamin E (n = 19)	Not stated	Not stated	All participants had supplementary lifestyle modification	Ultrasound	2014-2015	1.8	High
Ashraf 2017	Vitamin C plus other antioxidants (n = 25) vs Vitamin E (n = 27)	All participants had NASH	No participants had diabetes mellitus	All participants had supplementary lifestyle modification	Elastography	Not stated	3	High
Miglio 2000	Amino acids plus vitamin C (n = 96) vs No active intervention (n = 95)	Not stated	Both	All participants had supplementary lifestyle modification	Ultrasound	Not stated	1.8	High
Celinski 2014	Amino acids plus PUFA (n = 51) vs PUFA (n = 23)	Participants with and without NASH	Participants with and without diabetes mellitus	Not stated	Liver biopsy	Not stated	14	High
Poulos 2021	Amino acids plus vitamin E plus other antioxidants (n = 14) vs No active intervention (n = 11)	Not stated	Not stated	Not stated	Liver biopsy or radiographic	Not stated	4.1	High

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

					studies + liver enzymes			
Amanat 2018	Estrogen (n = 37) vs No active intervention (n = 41)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound	Not stated	1.8	High
Zohrer 2017	Phospholipids plus PUFA plus vitamin E (n = 20) vs No active intervention (n = 20)	All participants had NASH	Not stated	All participants had supplementary lifestyle modification	Liver biopsy	Not stated	12	High
Loguercio 2012	Phospholipids plus vitamin E plus other antioxidants (n = 69) vs No active intervention (n = 69)	Participants with and without NASH	Not stated	Not stated	Liver biopsy	2005-2008	12	High
Hong 2016	Other supplements plus other antioxidants (n = 35) vs Other antioxidants (n = 31)	Not stated	Not stated	All participants had supplementary lifestyle modification	Not stated	2011-2012	0.7	High
Lewis 2018	Polysaccharides (n = 12) vs No active intervention (n = 11)	Not stated	Both	Not stated	Not stated	2016-2017	3	Low
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics plus vitamin E (n = 15) vs No active intervention (n = 15)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2012-2013	1.8	High
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics plus vitamin E (n = 15) vs Prebiotics/Probiotics/Synbiotics (n = 15)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2012-2013	1.8	High
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics plus vitamin E (n = 15) vs Vitamin E (n = 15)	Not stated	No participants had diabetes mellitus	Not stated	Ultrasound + transaminases	2012-2013	1.8	High
Kobyliak 2017	Prebiotics/Probiotics/Synbiotics plus PUFA (n = not stated) vs No active intervention (n = not stated)	Not stated	All participants had diabetes mellitus only	Not stated	Not stated	Not stated	1.8	High
Song 2020	PUFA plus other supplements (n = 17) vs No active intervention (n = 21)	Not stated	No participants had diabetes mellitus	All participants had supplemen-	CT scan + abnormal serum lipid	2018	2.8	High

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

				tary lifestyle modification	profile or high BMI			
Mor-varidzadeh 2021	Prebiotics/Probiotics/Synbiotics plus vitamin D (n = 44) vs Prebi-otics/Probiotics/Synbiotics (n = 44)	Not stated	Not stated	Not stated	Ultrasound	Not stated	2.8	High
Song 2020	PUFA plus other supplements (n = 17) vs Other supplements (n = 16)	Not stated	No participants had diabetes mellitus	All participants had supplemen-tary lifestyle modification	CT scan + abnormal serum lipid profile or high BMI	2018	2.8	High
Song 2020	PUFA plus other supplements (n = 17) vs PUFA (n = 21)	Not stated	No participants had diabetes mellitus	All participants had supplemen-tary lifestyle modification	CT scan + abnormal serum lipid profile or high BMI	2018	2.8	High
Della Corte 2016	PUFA plus vitamin D (n = 18) vs No active intervention (n = 23)	Participants with and without NASH	Not stated	Not stated	Liver biopsy	2014-2015	12	High
Dallio 2020	Vitamin D plus vitamin E plus other antioxidants (n = 60) vs No active in-tervention (n = 30)	Not stated	Not stated	Not stated	Not stated	Not stated	6	High
Afzali 2020	Vitamin E plus other antioxidants plus other supplements (n = 60) vs Vitamin E plus other antioxidants (n = 57)	Not stated	Not stated	Not stated	Ultrasound	2018-2019	6	High

ALT: alanine aminotransferase.
BMI: body mass index.
LFT: liver function test.
MUFA: monounsaturated fatty acid.
NASH: non-alcoholic steatohepatitis.
PUFA: polyunsaturated fatty acid.

Table 3. Summary of risk of bias

Domain	Classification
Allocation (selection bias)	A total of 106 trials were at low risk of selection bias due to lack of random sequence generation (Miglio 2000; Harrison 2003; Deng 2005; Dufour 2006; Spadaro 2008; Khoshbaten 2010b; Li 2010; Malaguarnera 2010; Sanyal 2010; Aller 2011; Loguercio 2012; Malaguarnera 2012; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Wong 2013a; Wong 2013b; Aliashrafi 2014; Alisi 2014; Chachay 2014; Eslamparast 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Aller 2015; Argo 2015; Bae 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Pacifico 2015; Qin 2015; Yan 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Della Corte 2016; Heeboll 2016; Hong 2016; Nabavi 2016; Nogueira 2016; Pezeshki 2016; Rahimlou 2016; Amiri 2017; Chan 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Hussain 2017; Manzhalii 2017; Mofidi 2017; Shahmohammadi 2017; Tabatabaee 2017; Zohrer 2017; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Dabbaghmanesh 2018; Eriksson 2018; Geier 2018; Hosseini 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Taghvaei 2018; Tobin 2018; Wang 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afzali 2020; Babaei 2020; Boonyagard 2020; Cai 2020; Cerletti 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020; Mansour 2020; Orang 2020; Pasdar 2020; Poparn 2020; Pour 2020; Sangouni 2020; Scorletti 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Hong 2021; Izadi 2021; Morvaridzadeh 2021; Soleimani 2021; EUCTR 2008-008275-34-GB); the remaining 96 trials, which did not provide sufficient information, were at unclear risk of selection bias due to lack of random sequence generation (Uygun 2000; Kugelmas 2003; Chande 2006; Chou 2006; Nobili 2006; Chen 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Gomez 2009; Hashemi 2009; Nelson 2009; Fabbrini 2010; Ruan 2010; Lavine 2011; Tan 2011; Vajro 2011; Basu 2012; Della Corte 2012; Gonciarz 2012; Panahi 2012; Basu 2013; Saxena 2013; Shavakhi 2013; Askari 2014; Byrne 2014; Celinski 2014; Farhangi 2014; Foroughi 2014; Solhi 2014; Somi 2014; Akbarzadeh 2015; Amiri-Moghadam 2015; Bonfrate 2015; Boyraz 2015; Orr 2015; Boonyagard 2016; Ebrahimi-Mameghani 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Ferolla 2016; Guo 2016; Li 2016; Naganuma 2016; Panahi 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Ashraf 2017; Behrouz 2017; Chongsrisawat 2017; Gavrilescu 2017; Jameshorani 2017; Javadi 2017; Jeong 2017; Kobyliak 2017; Navekar 2017; Palamaru 2017; Sakpal 2017; Schattenberg 2017; Wang 2017; Youshari 2017; Ahn 2018; Bomhof 2018; Daneshi-Maskooni 2018; Ghaffari 2018; Javanmardi 2018; Pervez 2018; Sayari 2018; Afsharinasab 2020; Bahrami 2020; Barbakadze 2020; Climax 2020; Dallio 2020; Farzin 2020; Hoseini 2020; Khutsishvili 2020; Moradi 2020; Parsi 2020; Pervez 2020; Rafie 2020; Sadrkabir 2020; Soleimani 2020; Chiou 2021; Kanoni 2021; Poulos 2021; EUCTR 2009-017080-41-GB; NCT00816465; NCT00845845; NCT00941642; NCT00977730; NCT01083992; NCT01623024; NCT02690792; NCT04411862) In all, 94 trials were at low risk of selection bias due to lack of allocation concealment (Miglio 2000; Harrison 2003; Chande 2006; Dufour 2006; Nobili 2006; Gomez 2009; Khoshbaten 2010b; Malaguarnera 2010; Sanyal 2010; Malaguarnera 2012; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Wong 2013b; Alisi 2014; Askari 2014; Chachay 2014; Eslamparast 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Amiri-Moghadam 2015; Argo 2015; Bae 2015; Chen 2015a; Chen 2015b; Faghihzadeh 2015; Janczyk 2015; Pacifico 2015; Qin 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Della Corte 2016; Heeboll 2016; Nabavi 2016; Nogueira 2016; Pezeshki 2016; Rahimlou 2016; Sepideh 2016; Amiri 2017; Chan 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Javadi 2017; Manzhalii 2017; Mofidi 2017; Shahmohammadi 2017; Tabatabaee 2017; Zohrer 2017; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Bomhof 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Geier 2018; Ghaffari 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Tobin 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Babaei 2020; Boonyagard 2020; Cerletti 2020; Fathi 2020; Fernandez-Travieso 2020; Hosseinabadi 2020; Mansour 2020; Moradi 2020; Orang 2020; Pervez 2020; Pour 2020; Rafie 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Yari 2020; Zanko 2020; Soleimani 2021; EUCTR 2008-008275-34-GB); the remaining 108 trials, which did not provide sufficient information, were at unclear risk of selection bias due to lack of allocation concealment (Uygun 2000; Kugelmas 2003; Deng 2005; Chou 2006; Chen 2008; Spadaro 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Hashemi 2009; Nelson 2009; Fabbrini 2010; Li 2010; Ruan 2010; Aller 2011; Lavine 2011; Tan 2011; Vajro 2011; Basu 2012; Della Corte 2012; Gonciarz 2012; Loguercio 2012; Panahi 2012; Basu 2013; Saxena 2013; Shavakhi 2013; Wong 2013a; Aliashrafi 2014; Byrne 2014; Celinski 2014; Farhangi 2014; Foroughi 2014; Martinez-Ro-

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

	driguez 2014; Solhi 2014; Somi 2014; Akbarzadeh 2015; Aller 2015; Bonfrate 2015; Boyraz 2015; Dasarathy 2015; Orr 2015; Yan 2015; Boonyagard 2016; Ebrahimi-Mameghani 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Ferolla 2016; Guo 2016; Hong 2016; Li 2016; Naganuma 2016; Panahi 2016; Rahmani 2016; Yari 2016; Ashraf 2017; Behrouz 2017; Chongsrisawat 2017; Gavrilescu 2017; Hussain 2017; Jameshorani 2017; Jeong 2017; Kobyliak 2017; Navekar 2017; Palamaru 2017; Sakpal 2017; Schattenberg 2017; Wang 2017; Youshari 2017; Ahn 2018; Hosseini 2018; Javanmardi 2018; Sayari 2018; Taghvaei 2018; Wang 2018; Afsharinasab 2020; Afzali 2020; Bahrami 2020; Barbakadze 2020; Cai 2020; Climax 2020; Dallio 2020; Farzin 2020; Ferro 2020; Hormoznejad 2020; Hoseini 2020; Kazemi 2020; Khutsishvili 2020; Kooshki 2020; Parsi 2020; Pasdar 2020; Poparn 2020; Sadrkabir 2020; Chiou 2021; Hong 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Poulos 2021; EUCTR 2009-017080-41-GB; NCT00816465; NCT00845845; NCT00941642; NCT00977730; NCT01083992; NCT01623024; NCT02690792; NCT04411862)
Blinding (performance bias and detection bias)	A total of 138 trials were at low risk of performance bias as participants and healthcare providers were blinded (Miglio 2000; Harrison 2003; Chande 2006; Dufour 2006; Nobili 2006; Chen 2008; Abdelmalek 2009; Fabbrini 2010; Malaguarnera 2010; Sanyal 2010; Aller 2011; Lavine 2011; Vajro 2011; Della Corte 2012; Loguercio 2012; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Wong 2013b; Aliashrafi 2014; Alisi 2014; Askari 2014; Byrne 2014; Chachay 2014; Eslamparast 2014; Farhangi 2014; Foroughi 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Akbarzadeh 2015; Amiri-Moghadam 2015; Argo 2015; Bae 2015; Bonfrate 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Orr 2015; Pacifico 2015; Qin 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Della Corte 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Heeboll 2016; Nabavi 2016; Nogueira 2016; Pezeshki 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Amiri 2017; Behrouz 2017; Chan 2017; Chongsrisawat 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Javadi 2017; Jeong 2017; Kobyliak 2017; Mofidi 2017; Navekar 2017; Shahmohammadi 2017; Tabatabaee 2017; Youshari 2017; Zohrer 2017; Ahn 2018; Amanat 2018; Amirkhizi 2018; Asghari 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Geier 2018; Ghaffari 2018; Javanmardi 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Sayari 2018; Tobin 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afsharinasab 2020; Afzali 2020; Babaei 2020; Bahrami 2020; Boonyagard 2020; Cerletti 2020; Climax 2020; Farzin 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020; Mansour 2020; Moradi 2020; Orang 2020; Parsi 2020; Pasdar 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Zanko 2020; Chiou 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00816465; NCT00845845; NCT00977730; NCT02690792); 46 trials, which did not provide sufficient information, were at unclear risk of performance bias (Uygun 2000; Deng 2005; Spadaro 2008; Wang 2008; Zhu 2008; Gomez 2009; Hashemi 2009; Nelson 2009; Khoshbaten 2010b; Li 2010; Tan 2011; Gonciarz 2012; Malaguarnera 2012; Magosso 2013; Wong 2013a; Celinski 2014; Martinez-Rodriguez 2014; Solhi 2014; Somi 2014; Aller 2015; Boyraz 2015; Boonyagard 2016; Ebrahimi-Mameghani 2016; Ferolla 2016; Guo 2016; Hong 2016; Naganuma 2016; Panahi 2016; Gavrilescu 2017; Hussain 2017; Jameshorani 2017; Palamaru 2017; Sakpal 2017; Wang 2017; Bomhof 2018; Hosseini 2018; Taghvaei 2018; Wang 2018; Barbakadze 2020; Cai 2020; Dallio 2020; Hoseini 2020; Khutsishvili 2020; Sadrkabir 2020; Hong 2021; Poulos 2021); the remaining 18 trials were at high risk of performance bias as it is clear that either participants or healthcare providers or both were not blinded (Kugelmas 2003; Chou 2006; Ruan 2010; Basu 2012; Panahi 2012; Basu 2013; Yan 2015; Li 2016; Yari 2016; Ashraf 2017; Manzhalii 2017; Schattenberg 2017; Bakhshimoghaddam 2018; Yari 2020; NCT00941642; NCT01083992; NCT01623024; NCT04411862) In all, 142 trials were at low risk of detection bias (Miglio 2000; Harrison 2003; Chande 2006; Dufour 2006; Nobili 2006; Chen 2008; Abdelmalek 2009; Fabbrini 2010; Malaguarnera 2010; Sanyal 2010; Aller 2011; Lavine 2011; Vajro 2011; Della Corte 2012; Loguercio 2012; Malaguarnera 2012; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Wong 2013b; Aliashrafi 2014; Alisi 2014; Askari 2014; Byrne 2014; Chachay 2014; Eslamparast 2014; Farhangi 2014; Foroughi 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Somi 2014; Akbarzadeh 2015; Amiri-Moghadam 2015; Argo 2015; Bae 2015; Bonfrate 2015; Boyraz 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Orr 2015; Pacifico 2015; Qin 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Della Corte 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Heeboll 2016; Nabavi 2016; Nogueira 2016; Pezeshki 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Amiri 2017; Behrouz 2017; Chan 2017; Chongsrisawat 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Javadi 2017; Jeong 2017; Kobyliak 2017; Mofidi 2017; Navekar

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

	2017; Shahmohammadi 2017; Tabatabaee 2017; Youshari 2017; Zohrer 2017; Ahn 2018; Amanat 2018; Amirkhizi 2018; Asghari 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Geier 2018; Ghaffari 2018; Javanmardi 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Sayari 2018; Tobin 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Afsharinasab 2020; Afzali 2020; Babaei 2020; Bahrami 2020; Boonyagard 2020; Cerletti 2020; Climax 2020; Farzin 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hosseinabadi 2020; Kazemi 2020; Kooshki 2020; Mansour 2020; Moradi 2020; Orang 2020; Parsi 2020; Pasdar 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Zanko 2020; Chiou 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00816465; NCT00845845; NCT00977730; NCT02690792); 44 trials, which did not provide sufficient information, were at unclear risk of detection bias (Uygun 2000; Kugelmas 2003; Deng 2005; Spadaro 2008; Wang 2008; Zhu 2008; Gomez 2009; Hashemi 2009; Nelson 2009; Khoshbaten 2010b; Li 2010; Tan 2011; Gonciarz 2012; Wong 2013a; Celinski 2014; Martinez-Rodriguez 2014; Solhi 2014; Aller 2015; Boonyagard 2016; Ebrahimi-Mameghani 2016; Ferolla 2016; Guo 2016; Hong 2016; Naganuma 2016; Panahi 2016; Gavrilescu 2017; Hussain 2017; Jameshorani 2017; Palamaru 2017; Sakpal 2017; Wang 2017; Bakhshimoghaddam 2018; Bomhof 2018; Hosseini 2018; Taghvaei 2018; Wang 2018; Barbakadze 2020; Cai 2020; Dallio 2020; Hoseini 2020; Khutsishvili 2020; Sadrkabir 2020; Hong 2021; Poulos 2021); the remaining 16 trials were at high risk of detection bias as it is clear that outcome assessors were not blinded (Chou 2006; Ruan 2010; Basu 2012; Panahi 2012; Basu 2013; Yan 2015; Li 2016; Yari 2016; Ashraf 2017; Manzhalii 2017; Schattenberg 2017; Yari 2020; NCT00941642; NCT01083992; NCT01623024; NCT04411862)
Incomplete outcome data (attrition bias)	A total of 60 trials were at low risk of attrition bias as there were no post-randomisation dropouts or an intention-to-treat analysis was used (Deng 2005; Chande 2006; Wang 2008; Gomez 2009; Li 2010; Sanyal 2010; Vajro 2011; Malaguarnera 2012; Illnait 2013; Magosso 2013; Nobili 2013; Wong 2013a; Wong 2013b; Chachay 2014; Foroughi 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Somi 2014; Aller 2015; Bae 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Zhang 2015; Ferolla 2016; Heeboll 2016; Li 2016; Nabavi 2016; Yari 2016; Chan 2017; Famouri 2017a; Hussain 2017; Manzhalii 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Asghari 2018; Bomhof 2018; Eriksson 2018; Kobyliak 2018; Lewis 2018; Taghvaei 2018; Bril 2019; Jazayeri-Tehrani 2019; Afsharinasab 2020; Hoseini 2020; Kazemi 2020; Mansour 2020; Moradi 2020; Parsi 2020; Pervez 2020; Poparn 2020; Pour 2020; Tutunchi 2020; Zanko 2020; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00845845); 129 trials were at unclear risk of attrition bias (Miglio 2000; Uygun 2000; Harrison 2003; Kugelmas 2003; Chou 2006; Nobili 2006; Chen 2008; Spadaro 2008; Zhu 2008; Hashemi 2009; Nelson 2009; Fabbrini 2010; Khoshbaten 2010b; Malaguarnera 2010; Ruan 2010; Aller 2011; Lavine 2011; Tan 2011; Basu 2012; Della Corte 2012; Gonciarz 2012; Panahi 2012; Basu 2013; Ghergherehchi 2013; Gianturco 2013; Saxena 2013; Shavakhi 2013; Aliashrafi 2014; Alisi 2014; Askari 2014; Byrne 2014; Celinski 2014; Eslamparast 2014; Sharifi 2014; Solhi 2014; Akbarzadeh 2015; Amiri-Moghadam 2015; Argo 2015; Bonfrate 2015; Boyraz 2015; Faghihzadeh 2015; Janczyk 2015; Orr 2015; Pacifico 2015; Qin 2015; Yan 2015; Asgharian 2016; Barchetta 2016; Boonyagard 2016; Della Corte 2016; Ebrahimi-Mameghani 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Guo 2016; Hong 2016; Naganuma 2016; Nogueira 2016; Panahi 2016; Pezeshki 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Amiri 2017; Ashraf 2017; Behrouz 2017; Chongsrisawat 2017; Ebrahimi-Mameghani 2017; Gavrilescu 2017; Jameshorani 2017; Javadi 2017; Jeong 2017; Kobyliak 2017; Mofidi 2017; Navekar 2017; Palamaru 2017; Tabatabaee 2017; Wang 2017; Youshari 2017; Zohrer 2017; Ahn 2018; Amanat 2018; Amirkhizi 2018; Bakhshimoghaddam 2018; Daneshi-Maskooni 2018; Geier 2018; Ghaffari 2018; Hosseini 2018; Javanmardi 2018; Oscarsson 2018; Pervez 2018; Sayari 2018; Tobin 2018; Wang 2018; Zamani 2018; Cheraghpour 2019; Babaei 2020; Bahrami 2020; Barbakadze 2020; Boonyagard 2020; Cai 2020; Cerletti 2020; Climax 2020; Dallio 2020; Farzin 2020; Fernandez-Travieso 2020; Ferro 2020; Hosseinabadi 2020; Khutsishvili 2020; Kooshki 2020; NCT04411862; Orang 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Soleimani 2020; Song 2020; Yari 2020; Hong 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Poulos 2021; NCT00816465; NCT00941642; NCT00977730; NCT01083992; NCT01623024; NCT02690792), as it is not clear whether there were post-randomisation dropouts or whether post-randomisation dropouts were related to outcomes (if there were post-randomisation dropouts); the remaining 13 trials were at high risk of attrition bias (Dufour 2006; Abdelmalek 2009; Loguercio 2012; Farhangi 2014; Dabbaghmanesh 2018; Duseja 2019; Abhari 2020; Afzali 2020; Fathi 2020; Hormoznejad 2020; Pasdar 2020; Scorletti 2020; Chiou 2021), as post-randomisation dropouts probably were related to the intervention and to outcomes

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

Selective reporting (reporting bias)	In all, 48 trials were at low risk of selective outcome reporting bias (Nobili 2006; Zhu 2008; Li 2010; Sanyal 2010; Vajro 2011; Loguercio 2012; Malaguarnera 2012; Magosso 2013; Wong 2013a; Wong 2013b; Martinez-Rodriguez 2014; Sanyal 2014; Aller 2015; Bae 2015; Chen 2015b; Faghihzadeh 2015; Janczyk 2015; Zhang 2015; Asgharian 2016; Ferolla 2016; Heeboll 2016; Nabavi 2016; Chan 2017; Manzhalii 2017; Schattenberg 2017; Asghari 2018; Bakhshimoghaddam 2018; Eriksson 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Zamani 2018; Bril 2019; Cheraghpour 2019; Duseja 2019; Jazayeri-Tehrani 2019; Abhari 2020; Boonyagard 2020; Cerletti 2020; Climax 2020; Fernandez-Travieso 2020; Mansour 2020; Poparn 2020; Tutunchi 2020; Yari 2020; Soleimani 2021; EUCTR 2008-008275-34-GB), as important clinical outcomes expected to be reported in such trials were reported; the remaining 154 trials were at high risk of selective outcome reporting bias (Miglio 2000; Uygun 2000; Harrison 2003; Kugelmas 2003; Deng 2005; Chande 2006; Chou 2006; Dufour 2006; Chen 2008; Spadaro 2008; Wang 2008; Abdelmalek 2009; Gomez 2009; Hashemi 2009; Nelson 2009; Fabbrini 2010; Khoshbaten 2010b; Malaguarnera 2010; Ruan 2010; Aller 2011; Lavine 2011; Tan 2011; Basu 2012; Della Corte 2012; Gonciarz 2012; Panahi 2012; Basu 2013; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Aliashrafi 2014; Alisi 2014; Askari 2014; Byrne 2014; Celinski 2014; Chachay 2014; Eslamparast 2014; Farhangi 2014; Foroughi 2014; Scorletti 2014; Sharifi 2014; Solhi 2014; Somi 2014; Akbarzadeh 2015; Amiri-Moghadam 2015; Argo 2015; Bonfrate 2015; Boyraz 2015; Chen 2015a; Dasarathy 2015; Orr 2015; Pacifico 2015; Qin 2015; Yan 2015; Barchetta 2016; Boonyagard 2016; Della Corte 2016; Ebrahimi-Mameghani 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Guo 2016; Hong 2016; Li 2016; Naganuma 2016; Nogueira 2016; Panahi 2016; Pezeshki 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Amiri 2017; Ashraf 2017; Behrouz 2017; Chongsrisawat 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Gavrilescu 2017; Hussain 2017; Jameshorani 2017; Javadi 2017; Jeong 2017; Kobyliak 2017; Mofidi 2017; Navekar 2017; Palamaru 2017; Sakpal 2017; Shahmohammadi 2017; Tabatabaee 2017; Wang 2017; Youshari 2017; Zohrer 2017; Ahn 2018; Amanat 2018; Amirkhizi 2018; Bomhof 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Geier 2018; Ghaffari 2018; Hosseini 2018; Javanmardi 2018; Sayari 2018; Taghvaei 2018; Tobin 2018; Wang 2018; Afsharinasab 2020; Afzali 2020; Babaei 2020; Bahrami 2020; Barbakadze 2020; Cai 2020; Dallio 2020; Farzin 2020; Fathi 2020; Ferro 2020; Hormoznejad 2020; Hoseini 2020; Hosseinabadi 2020; Kazemi 2020; Khutsishvili 2020; Kooshki 2020; Moradi 2020; Orang 2020; Parsi 2020; Pasdar 2020; Pervez 2020; Pour 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Zanko 2020; Chiou 2021; Hong 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Poulos 2021; EUCTR 2009-017080-41-GB; NCT00816465; NCT00845845; NCT00941642; NCT00977730; NCT01083992; NCT01623024; NCT02690792; NCT04411862), as outcomes were changed from the protocol published prior to recruitment without sufficient justification, or trials did not report reasonably expected clinical outcomes, if no protocol was published prior to recruitment
Other potential sources of bias	A total of 196 trials were at low risk of other bias (Miglio 2000; Uygun 2000; Harrison 2003; Kugelmas 2003; Deng 2005; Chande 2006; Chou 2006; Dufour 2006; Nobili 2006; Chen 2008; Spadaro 2008; Wang 2008; Zhu 2008; Abdelmalek 2009; Gomez 2009; Hashemi 2009; Nelson 2009; Fabbrini 2010; Khoshbaten 2010b; Li 2010; Malaguarnera 2010; Ruan 2010; Sanyal 2010; Aller 2011; Lavine 2011; Tan 2011; Vajro 2011; Basu 2012; Della Corte 2012; Gonciarz 2012; Loguercio 2012; Malaguarnera 2012; Panahi 2012; Basu 2013; Ghergherehchi 2013; Gianturco 2013; Illnait 2013; Magosso 2013; Nobili 2013; Saxena 2013; Shavakhi 2013; Wong 2013a; Wong 2013b; Aliashrafi 2014; Alisi 2014; Askari 2014; Byrne 2014; Celinski 2014; Chachay 2014; Eslamparast 2014; Farhangi 2014; Foroughi 2014; Martinez-Rodriguez 2014; Sanyal 2014; Scorletti 2014; Sharifi 2014; Solhi 2014; Somi 2014; Akbarzadeh 2015; Aller 2015; Amiri-Moghadam 2015; Argo 2015; Bae 2015; Bonfrate 2015; Boyraz 2015; Chen 2015a; Chen 2015b; Dasarathy 2015; Faghihzadeh 2015; Janczyk 2015; Orr 2015; Pacifico 2015; Qin 2015; Yan 2015; Zhang 2015; Asgharian 2016; Barchetta 2016; Boonyagard 2016; Della Corte 2016; Ebrahimi-Mameghani 2016; Eghtesadi 2016; Ekhlasi 2016; Farsi 2016; Ferolla 2016; Guo 2016; Heeboll 2016; Hong 2016; Li 2016; Nabavi 2016; Naganuma 2016; Nogueira 2016; Panahi 2016; Pezeshki 2016; Rahimlou 2016; Rahmani 2016; Sepideh 2016; Yari 2016; Amiri 2017; Ashraf 2017; Behrouz 2017; Chan 2017; Chongsrisawat 2017; Ebrahimi-Mameghani 2017; Famouri 2017a; Gavrilescu 2017; Hussain 2017; Jameshorani 2017; Javadi 2017; Jeong 2017; Kobyliak 2017; Manzhalii 2017; Mofidi 2017; Navekar 2017; Palamaru 2017; Sakpal 2017; Schattenberg 2017; Shahmohammadi 2017; Tabatabaee 2017; Wang 2017; Youshari 2017; Zohrer 2017; Ahn 2018; Amanat 2018; Amirkhizi 2018; Asghari 2018; Bakhshimoghaddam 2018; Bomhof 2018; Dabbaghmanesh 2018; Daneshi-Maskooni 2018; Eriksson 2018; Geier 2018; Ghaffari 2018; Hosseini 2018; Javanmardi 2018; Kobyliak 2018; Lewis 2018; Oscarsson 2018; Pervez 2018; Sayari 2018; Taghvaei 2018; Wang 2018; Bril 2019; Duseja 2019; Abhari 2020; Afsharinasab 2020; Afzali 2020; Bahrami 2020; Bar-

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

	bakadze 2020; Boonyagard 2020; Cai 2020; Cerletti 2020; Climax 2020; Dallio 2020; Farzin 2020; Fathi 2020; Fernandez-Travieso 2020; Ferro 2020; Hormoznejad 2020; Hoseini 2020; Hosseinabadi 2020; Kazemi 2020; Khutsishvili 2020; Kooshki 2020; Mansour 2020; Moradi 2020; Orang 2020; Parsi 2020; Pasdar 2020; Pervez 2020; Poparn 2020; Pour 2020; Rafie 2020; Sadrkabir 2020; Sangouni 2020; Scorletti 2020; Soleimani 2020; Song 2020; Tutunchi 2020; Zanko 2020; Chiou 2021; Hong 2021; Izadi 2021; Kanoni 2021; Morvaridzadeh 2021; Poulos 2021; Soleimani 2021; EUCTR 2008-008275-34-GB; EUCTR 2009-017080-41-GB; NCT00816465; NCT00845845; NCT00941642; NCT00977730; NCT01083992; NCT01623024; NCT02690792; NCT04411862); the remaining 6 trials were at unclear risk of other bias (Tobin 2018; Zamani 2018; Cheraghpour 2019; Jazayeri-Tehrani 2019; Babaei 2020; Yari 2020), as there were baseline differences in important prognostic factors

Table 4. Risk of bias (ordered by comparison)

Study name	Intervention 1 (number of participants) vs intervention 2 (number of participants)	Sequence generation	Allocation concealment	Blinding of patients and healthcare providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Other bias	Overall risk of bias
Afshari-nasab 2020	Other supplements (n = 21) vs No active intervention (n = 21)	Unclear	Unclear	Low	Low	Low	High	Low	High
Asghari 2018	Other supplements (n = 30) vs No active intervention (n = 30)	Low	Low	Low	Low	Low	Low	Low	Low
Askari 2014	Other supplements (n = 23) vs No active intervention (n = 22)	Unclear	Low	Low	Low	Unclear	High	Low	High
Babaei 2020	Other supplements (n = 13) vs No active intervention (n = 11)	Low	Low	Low	Low	Unclear	High	Unclear	High
Bahrami 2020	Other supplements (n = 24) vs No active intervention (n = 21)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Cerletti 2020	Other supplements (n = 55) vs No active intervention (n = 58)	Low	Low	Low	Low	Unclear	Low	Low	High
Chachay 2014	Other supplements (n = 10) vs No active intervention (n = 10)	Low	Low	Low	Low	Low	High	Low	High
Chande 2006	Other supplements (n = 5) vs No active intervention (n = 3)	Unclear	Low	Low	Low	Low	High	Low	High
Chen 2015a	Other supplements (n = 30) vs No active intervention (n = 30)	Low	Low	Low	Low	Low	High	Low	High
Chiou 2021	Other supplements (n = 15) vs No active intervention (n = 13)	Unclear	Unclear	Low	Low	High	High	Low	High
Chou 2006	Other supplements (n = 28) vs No active intervention (n = 28)	Unclear	Unclear	High	High	Unclear	High	Low	High
Daneshi-Maskooni 2018	Other supplements (n = 43) vs No active intervention (n = 44)	Unclear	Low	Low	Low	Unclear	High	Low	High

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

Ebrahimi-Mameghani 2017	Other supplements (n = 29) vs No active intervention (n = 26)	Low	Low	Low	Low	Unclear	High	Low	High
EUCTR 2009-017080-41-GB	Other supplements (n = 20) vs No active intervention (n = 5)	Unclear	Unclear	Low	Low	Low	High	Low	High
Faghihzadeh 2015	Other supplements (n = 24) vs No active intervention (n = 24)	Low	Low	Low	Low	Unclear	Low	Low	High
Farzin 2020	Other supplements (n = 25) vs No active intervention (n = 25)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Fathi 2020	Other supplements (n = 25) vs No active intervention (n = 25)	Low	Low	Low	Low	High	High	Low	High
Fernandez-Travieso 2020	Other supplements (n = 50) vs No active intervention (n = 50)	Low	Low	Low	Low	Unclear	Low	Low	High
Ferro 2020	Other supplements (n = 45) vs No active intervention (n = 41)	Low	Unclear	Low	Low	Unclear	High	Low	High
Ghaffari 2018	Other supplements (n = 64) vs No active intervention (n = 21)	Unclear	Low	Low	Low	Unclear	High	Low	High
Heeboll 2016	Other supplements (n = 15) vs No active intervention (n = 13)	Low	Low	Low	Low	Low	Low	Low	Low
Hong 2021	Other supplements (n = 43) vs No active intervention (n = 44)	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High
Hormoznejad 2020	Other supplements (n = 20) vs No active intervention (n = 21)	Low	Unclear	Low	Low	High	High	Low	High
Hosseinabadi 2020	Other supplements (n = 21) vs No active intervention (n = 23)	Low	Low	Low	Low	Unclear	High	Low	High
Hussain 2017	Other supplements (n = 40) vs No active intervention (n = 40)	Low	Unclear	Unclear	Unclear	Low	High	Low	High

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

Illnait 2013	Other supplements (n = 25) vs No active intervention (n = 25)	Low	Low	Low	Low	Low	High	Low	High
Izadi 2021	Other supplements (n = 30) vs No active intervention (n = 31)	Low	Unclear	Low	Low	Unclear	High	Low	High
Javanmardi 2018	Other supplements (n = 19) vs No active intervention (n = 19)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Jazayeri-Tehrani 2019	Other supplements (n = 42) vs No active intervention (n = 42)	Low	Low	Low	Low	Low	Low	Unclear	High
Jeong 2017	Other supplements (n = 45) vs No active intervention (n = 23)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Kazemi 2020	Other supplements (n = 40) vs No active intervention (n = 40)	Low	Unclear	Low	Low	Low	High	Low	High
Kooshki 2020	Other supplements (n = 22) vs No active intervention (n = 21)	Low	Unclear	Low	Low	Unclear	High	Low	High
Mansour 2020	Other supplements (n = 20) vs No active intervention (n = 6)	Low	Low	Low	Low	Low	Low	Low	Low
Martinez-Rodriguez 2014	Other supplements (n = 20) vs No active intervention (n = 20)	Low	Unclear	Unclear	Unclear	Low	Low	Low	High
Moradi 2020	Other supplements (n = 22) vs No active intervention (n = 23)	Unclear	Low	Low	Low	Low	High	Low	High
Navekar 2017	Other supplements (n = 21) vs No active intervention (n = 21)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
NCT00816465	Other supplements (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Panahi 2016	Other supplements (n = 44) vs No active intervention (n = 43)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High

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

Parsi 2020	Other supplements (n = 30) vs No active intervention (n = 30)	Unclear	Unclear	Low	Low	Low	High	Low	High
Pasdar 2020	Other supplements (n = 39) vs No active intervention (n = 39)	Low	Unclear	Low	Low	High	High	Low	High
Pezeshki 2016	Other supplements (n = 35) vs No active intervention (n = 36)	Low	Low	Low	Low	Unclear	High	Low	High
Rahimlou 2016	Other supplements (n = 23) vs No active intervention (n = 21)	Low	Low	Low	Low	Unclear	High	Low	High
Rahmani 2016	Other supplements (n = 37) vs No active intervention (n = 40)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Sangouni 2020	Other supplements (n = 45) vs No active intervention (n = 43)	Low	Low	Low	Low	Unclear	High	Low	High
Saxena 2013	Other supplements (n = 26) vs No active intervention (n = 24)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Shahmohammadi 2017	Other supplements (n = 22) vs No active intervention (n = 22)	Low	Low	Low	Low	Low	High	Low	High
Soleimani 2020	Other supplements (n = 47) vs No active intervention (n = 51)	Unclear	Low	Low	Low	Unclear	High	Low	High
Soleimani 2021	Other supplements (n = 27) vs No active intervention (n = 27)	Low	Low	Low	Low	Low	Low	Low	Low
Song 2020	Other supplements (n = 16) vs No active intervention (n = 21)	Low	Low	Low	Low	Unclear	High	Low	High
Tabatabaee 2017	Other supplements (n = 21) vs No active intervention (n = 24)	Low	Low	Low	Low	Unclear	High	Low	High
Tutunchi 2020	Other supplements (n = 38) vs No active intervention (n = 38)	Low	Low	Low	Low	Low	Low	Low	Low
Wang 2017	Other supplements (n = 24) vs No active intervention (n = 12)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High

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

Wong 2013b	Other supplements (n = 40) vs No active intervention (n = 20)	Low	Low	Low	Low	Low	Low	Low	Low
Yan 2015	Other supplements (n = 55) vs No active intervention (n = 53)	Low	Unclear	High	High	Unclear	High	Low	High
Yari 2020	Other supplements (n = 24) vs No active intervention (n = 21)	Low	Low	High	High	Unclear	Low	Unclear	High
Zamani 2018	Other supplements (n = 45) vs No active intervention (n = 40)	Low	Low	Low	Low	Unclear	Low	Unclear	High
Zhang 2015	Other supplements (n = 37) vs No active intervention (n = 37)	Low	Low	Low	Low	Low	Low	Low	Low
Abhari 2020	Prebiotics/Probiotics/Synbiotics (n = 23) vs No active intervention (n = 22)	Low	Low	Low	Low	High	Low	Low	High
Ahn 2018	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Akbarzadeh 2015	Prebiotics/Probiotics/Synbiotics (n = 38) vs No active intervention (n = 37)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Alisi 2014	Prebiotics/Probiotics/Synbiotics (n = 22) vs No active intervention (n = 22)	Low	Low	Low	Low	Unclear	High	Low	High
Aller 2011	Prebiotics/Probiotics/Synbiotics (n = 14) vs No active intervention (n = 14)	Low	Unclear	Low	Low	Unclear	High	Low	High
Guo 2016	Prebiotics/Probiotics/Synbiotics (n = 42) vs No active intervention (n = 42)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Asgharian 2016	Prebiotics/Probiotics/Synbiotics (n = 38) vs No active intervention (n = 36)	Low	Low	Low	Low	Unclear	Low	Low	High
Bakhshi-moghaddam 2018	Prebiotics/Probiotics/Synbiotics (n = 32) vs No active intervention (n = 28)	Low	Low	High	Unclear	Unclear	Low	Low	High
Behrouz 2017	Prebiotics/Probiotics/Synbiotics (n = 59) vs No active intervention (n = 30)	Unclear	Unclear	Low	Low	Unclear	High	Low	High

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

Bomhof 2018	Prebiotics/Probiotics/Synbiotics (n = 8) vs No active intervention (n = 5)	Unclear	Low	Unclear	Unclear	Low	High	Low	High
Cai 2020	Prebiotics/Probiotics/Synbiotics (n = 70) vs No active intervention (n = 70)	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High
Chongsri-sawat 2017	Prebiotics/Probiotics/Synbiotics (n = 18) vs No active intervention (n = 19)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Della Corte 2012	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Duseja 2019	Prebiotics/Probiotics/Synbiotics (n = 10) vs No active intervention (n = 5)	Low	Low	Low	Low	High	Low	Low	High
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics (n = 15) vs No active intervention (n = 15)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Eslamparast 2014	Prebiotics/Probiotics/Synbiotics (n = 26) vs No active intervention (n = 26)	Low	Low	Low	Low	Unclear	High	Low	High
Famouri 2017a	Prebiotics/Probiotics/Synbiotics (n = 32) vs No active intervention (n = 32)	Low	Low	Low	Low	Low	High	Low	High
Ferolla 2016	Prebiotics/Probiotics/Synbiotics (n = 27) vs No active intervention (n = 23)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	High
Gavrilescu 2017	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Jameshorani 2017	Prebiotics/Probiotics/Synbiotics (n = 45) vs No active intervention (n = 45)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Javadi 2017	Prebiotics/Probiotics/Synbiotics (n = 56) vs No active intervention (n = 19)	Unclear	Low	Low	Low	Unclear	High	Low	High
Khutsishvili 2020	Prebiotics/Probiotics/Synbiotics (n = 35) vs No active intervention (n = 38)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Kobyliak 2018	Prebiotics/Probiotics/Synbiotics (n = 30) vs No active intervention (n = 28)	Low	Low	Low	Low	Low	Low	Low	Low

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

Malaguarnera 2012	Prebiotics/Probiotics/Synbiotics (n = 34) vs No active intervention (n = 32)	Low	Low	Unclear	Low	Low	Low	Low	High
Manzhalii 2017	Prebiotics/Probiotics/Synbiotics (n = 38) vs No active intervention (n = 37)	Low	Low	High	High	Low	Low	Low	High
Mofidi 2017	Prebiotics/Probiotics/Synbiotics (n = 21) vs No active intervention (n = 21)	Low	Low	Low	Low	Unclear	High	Low	High
Nabavi 2016	Prebiotics/Probiotics/Synbiotics (n = 36) vs No active intervention (n = 36)	Low	Low	Low	Low	Low	Low	Low	Low
Orr 2015	Prebiotics/Probiotics/Synbiotics (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Poparn 2020	Prebiotics/Probiotics/Synbiotics (n = 18) vs No active intervention (n = 19)	Low	Low	Low	Low	Low	Low	Low	Low
Sadrkabir 2020	Prebiotics/Probiotics/Synbiotics (n = 33) vs No active intervention (n = 28)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Sayari 2018	Prebiotics/Probiotics/Synbiotics (n = 70) vs No active intervention (n = 68)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Schattenberg 2017	Prebiotics/Probiotics/Synbiotics (n = 15) vs No active intervention (n = 14)	Unclear	Unclear	High	High	Low	Low	Low	High
Scorletti 2020	Prebiotics/Probiotics/Synbiotics (n = 45) vs No active intervention (n = 44)	Low	Low	Low	Low	High	High	Low	High
Sepideh 2016	Prebiotics/Probiotics/Synbiotics (n = 21) vs No active intervention (n = 21)	Unclear	Low	Low	Low	Unclear	High	Low	High
Shavakhi 2013	Prebiotics/Probiotics/Synbiotics (n = 31) vs No active intervention (n = 32)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Vajro 2011	Prebiotics/Probiotics/Synbiotics (n = 10) vs No active intervention (n = 10)	Unclear	Unclear	Low	Low	Low	Low	Low	High
Wong 2013a	Prebiotics/Probiotics/Synbiotics (n = 10) vs No active intervention (n = 10)	Low	Unclear	Unclear	Unclear	Low	Low	Low	High

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

Argo 2015	PUFA (n = 17) vs No active intervention (n = 17)	Low	Low	Low	Low	Unclear	High	Low	High
Boyraz 2015	PUFA (n = 56) vs No active intervention (n = 52)	Unclear	Unclear	Unclear	Low	Unclear	High	Low	High
Byrne 2014	PUFA (n = 51) vs No active intervention (n = 52)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Chen 2008	PUFA (n = 30) vs No active intervention (n = 16)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Climax 2020	PUFA (n = 63) vs No active intervention (n = 30)	Unclear	Unclear	Low	Low	Unclear	Low	Low	High
Dasarathy 2015	PUFA (n = 18) vs No active intervention (n = 19)	Low	Unclear	Low	Low	Low	High	Low	High
Eriksson 2018	PUFA (n = 42) vs No active intervention (n = 42)	Low	Low	Low	Low	Low	Low	Low	Low
EUCTR 2008-008275-34 GB	PUFA (n = 24) vs No active intervention (n = 25)	Low	Low	Low	Low	Low	Low	Low	Low
Janczyk 2015	PUFA (n = 30) vs No active intervention (n = 34)	Low	Low	Low	Low	Unclear	Low	Low	High
Li 2016	PUFA (n = 39) vs No active intervention (n = 39)	Unclear	Unclear	High	High	Low	High	Low	High
NCT00845845	PUFA (n = 3) vs No active intervention (n = 6)	Unclear	Unclear	Low	Low	Low	High	Low	High
NCT00941642	PUFA (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	High	High	Unclear	High	Low	High
Nobili 2013	PUFA (n = 40) vs No active intervention (n = 20)	Low	Low	Low	Low	Low	High	Low	High
Nogueira 2016	PUFA (n = 27) vs No active intervention (n = 23)	Low	Low	Low	Low	Unclear	High	Low	High

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

Orang 2020	PUFA (n = 22) vs No active intervention (n = 22)	Low	Low	Low	Low	Unclear	High	Low	High
Oscarsson 2018	PUFA (n = 23) vs No active intervention (n = 23)	Low	Low	Low	Low	Unclear	Low	Low	High
Pacifico 2015	PUFA (n = 25) vs No active intervention (n = 26)	Low	Low	Low	Low	Unclear	High	Low	High
Sanyal 2014	PUFA (n = 168) vs No active intervention (n = 75)	Low	Low	Low	Low	Low	Low	Low	Low
Scorletti 2014	PUFA (n = 51) vs No active intervention (n = 52)	Low	Low	Low	Low	Low	High	Low	High
Song 2020	PUFA (n = 21) vs No active intervention (n = 21)	Low	Low	Low	Low	Unclear	High	Low	High
Spadaro 2008	PUFA (n = 18) vs No active intervention (n = 18)	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High
Yari 2016	PUFA (n = 25) vs No active intervention (n = 25)	Unclear	Unclear	High	High	Low	High	Low	High
Zhu 2008	PUFA (n = 66) vs No active intervention (n = 68)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Song 2020	PUFA (n = 21) vs Other supplements (n = 16)	Low	Low	Low	Low	Unclear	High	Low	High
Basu 2012	Vitamin E (n = 40) vs No active intervention (n = 35)	Unclear	Unclear	High	High	Unclear	High	Low	High
Bril 2019	Vitamin E (n = 36) vs No active intervention (n = 32)	Low	Low	Low	Low	Low	Low	Low	Low
Dufour 2006	Vitamin E (n = 10) vs No active intervention (n = 11)	Low	Low	Low	Low	High	High	Low	High
Ekhlasi 2016	Vitamin E (n = 15) vs No active intervention (n = 15)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Gherghere-hchi 2013	Vitamin E (n = 17) vs No active intervention (n = 16)	Low	Low	Low	Low	Unclear	High	Low	High

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

Kugelmas 2003	Vitamin E (n = 9) vs No active intervention (n = 7)	Unclear	Unclear	High	Unclear	Unclear	High	Low	High
Lavine 2011	Vitamin E (n = 50) vs No active intervention (n = 47)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Magosso 2013	Vitamin E (n = 43) vs No active intervention (n = 44)	Low	Low	Unclear	Low	Low	Low	Low	High
NCT02690792	Vitamin E (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Palamaru 2017	Vitamin E (n = 20) vs No active intervention (n = 20)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Pervez 2018	Vitamin E (n = 31) vs No active intervention (n = 33)	Unclear	Low	Low	Low	Unclear	Low	Low	High
Pervez 2020	Vitamin E (n = 35) vs No active intervention (n = 36)	Unclear	Low	Low	Low	Low	High	Low	High
Sanyal 2010	Vitamin E (n = 84) vs No active intervention (n = 83)	Low	Low	Low	Low	Low	Low	Low	Low
Wang 2008	Vitamin E (n = 19) vs No active intervention (n = 38)	Unclear	Unclear	Unclear	Unclear	Low	High	Low	High
Basu 2013	Vitamin E (n = 20) vs Other supplements (n = 20)	Unclear	Unclear	High	High	Unclear	High	Low	High
Ekhlasi 2016	Vitamin E (n = 15) vs Prebiotics/Probiotics/Synbiotics (n = 15)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Amiri 2017	Vitamin D (n = 74) vs No active intervention (n = 36)	Low	Low	Low	Low	Unclear	High	Low	High
Barchetta 2016	Vitamin D (n = 26) vs No active intervention (n = 29)	Low	Low	Low	Low	Unclear	High	Low	High
Boonyagard 2016	Vitamin D (n = 30) vs No active intervention (n = 30)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High

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

Boonyagard 2020	Vitamin D (n = 30) vs No active intervention (n = 30)	Low	Low	Low	Low	Unclear	Low	Low	High
Dabbagh-manesh 2018	Vitamin D (n = 59) vs No active intervention (n = 32)	Low	Low	Low	Low	High	High	Low	High
Foroughi 2014	Vitamin D (n = 30) vs No active intervention (n = 30)	Unclear	Unclear	Low	Low	Low	High	Low	High
Geier 2018	Vitamin D (n = 8) vs No active intervention (n = 10)	Low	Low	Low	Low	Unclear	High	Low	High
Hoseini 2020	Vitamin D (n = 20) vs No active intervention (n = 20)	Unclear	Unclear	Unclear	Unclear	Low	High	Low	High
Hosseini 2018	Vitamin D (n = 37) vs No active intervention (n = 38)	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High
NCT01083992	Vitamin D (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	High	High	Unclear	High	Low	High
NCT01623024	Vitamin D (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	High	High	Unclear	High	Low	High
Sakpal 2017	Vitamin D (n = 51) vs No active intervention (n = 30)	Unclear	Unclear	Unclear	Unclear	Low	High	Low	High
Sharifi 2014	Vitamin D (n = 27) vs No active intervention (n = 26)	Low	Low	Low	Low	Unclear	High	Low	High
Taghvaei 2018	Vitamin D (n = 20) vs No active intervention (n = 20)	Low	Unclear	Unclear	Unclear	Low	High	Low	High
Zanko 2020	Vitamin D (n = 201) vs No active intervention (n = 110)	Low	Low	Low	Low	Low	High	Low	High
Basu 2012	Other antioxidants (n = 40) vs No active intervention (n = 35)	Unclear	Unclear	High	High	Unclear	High	Low	High
Chan 2017	Other antioxidants (n = 49) vs No active intervention (n = 50)	Low	Low	Low	Low	Low	Low	Low	Low

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

Chen 2015b	Other antioxidants (n = 30) vs No active intervention (n = 30)	Low	Low	Low	Low	Low	Low	Low	Low
Cheraghpour 2019	Other antioxidants (n = 25) vs No active intervention (n = 24)	Low	Low	Low	Low	Unclear	Low	Unclear	High
Farhangi 2014	Other antioxidants (n = 20) vs No active intervention (n = 21)	Unclear	Unclear	Low	Low	High	High	Low	High
Farsi 2016	Other antioxidants (n = 20) vs No active intervention (n = 21)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Gianturco 2013	Other antioxidants (n = 104) vs No active intervention (n = 92)	Low	Low	Low	Low	Unclear	High	Low	High
Gonciarz 2012	Other antioxidants (n = 30) vs No active intervention (n = 12)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Hashemi 2009	Other antioxidants (n = 50) vs No active intervention (n = 50)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Kanoni 2021	Other antioxidants (n = 35) vs No active intervention (n = 52)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Ruan 2010	Other antioxidants (n = 30) vs No active intervention (n = 30)	Unclear	Unclear	High	High	Unclear	High	Low	High
Solhi 2014	Other antioxidants (n = 33) vs No active intervention (n = 31)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Yari 2020	Other antioxidants (n = 22) vs No active intervention (n = 21)	Low	Low	High	High	Unclear	Low	Unclear	High
Deng 2005	Other antioxidants (n = 48) vs Other supplements (n = 48)	Low	Unclear	Unclear	Unclear	Low	High	Low	High
Basu 2012	Other antioxidants (n = 40) vs Vitamin E (n = 40)	Unclear	Unclear	High	High	Unclear	High	Low	High
Khoshbaten 2010b	Other antioxidants (n = 15) vs Vitamin C (n = 15)	Low	Low	Unclear	Unclear	Unclear	High	Low	High

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

Yari 2020	Other antioxidants (n = 22) vs Other supplements (n = 24)	Low	Low	High	High	Unclear	Low	Unclear	High
Abdelmalek 2009	Amino acids (n = 17) vs No active intervention (n = 18)	Unclear	Unclear	Low	Low	High	High	Low	High
Amiri-Moghadam 2015	Amino acids (n = 36) vs No active intervention (n = 32)	Unclear	Low	Low	Low	Unclear	High	Low	High
Bae 2015	Amino acids (n = 39) vs No active intervention (n = 39)	Low	Low	Low	Low	Low	Low	Low	Low
Eghtesadi 2016	Amino acids (n = 36) vs No active intervention (n = 32)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Fabbrini 2010	Amino acids (n = 9) vs No active intervention (n = 9)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Malaguarnera 2010	Amino acids (n = 36) vs No active intervention (n = 38)	Low	Low	Low	Low	Unclear	High	Low	High
Naganuma 2016	Amino acids (n = 10) vs No active intervention (n = 10)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Somi 2014	Amino acids (n = 40) vs No active intervention (n = 40)	Unclear	Unclear	Unclear	Low	Low	High	Low	High
Uygun 2000	Amino acids (n = 78) vs No active intervention (n = 23)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Aller 2015	Vitamin E plus other antioxidants (n = 18) vs No active intervention (n = 18)	Low	Unclear	Unclear	Unclear	Low	Low	Low	High
Basu 2012	Vitamin E plus other antioxidants (n = 40) vs No active intervention (n = 35)	Unclear	Unclear	High	High	Unclear	High	Low	High
Bonfrate 2015	Vitamin E plus other antioxidants (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Amirkhizi 2018	Vitamin E plus other antioxidants (n = 23) vs Vitamin E (n = 22)	Low	Low	Low	Low	Unclear	High	Low	High

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

Basu 2012	Vitamin E plus other antioxidants (n = 40) vs Vitamin E (n = 40)	Unclear	Unclear	High	High	Unclear	High	Low	High
Basu 2012	Vitamin E plus other antioxidants (n = 40) vs Other antioxidants (n = 40)	Unclear	Unclear	High	High	Unclear	High	Low	High
NCT04411862	Phospholipids (n = 50) vs No active intervention (n = 50)	Unclear	Unclear	High	High	Unclear	High	Low	High
Tan 2011	Phospholipids (n = 10) vs No active intervention (n = 5)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Li 2010	Phospholipids (n = 43) vs Other supplements (n = 45)	Low	Unclear	Unclear	Unclear	Low	Low	Low	High
Wang 2018	Phospholipids (n = 50) vs Prebiotics/Probiotics/Synbiotics (n = 150)	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High
Basu 2013	Vitamin E plus other supplements (n = 20) vs Other supplements (n = 20)	Unclear	Unclear	High	High	Unclear	High	Low	High
Aliashrafi 2014	Vitamin E plus other supplements (n = 29) vs Vitamin E (n = 26)	Low	Unclear	Low	Low	Unclear	High	Low	High
Basu 2013	Vitamin E plus other supplements (n = 20) vs Vitamin E (n = 20)	Unclear	Unclear	High	High	Unclear	High	Low	High
Panahi 2012	Vitamin E plus other supplements (n = 21) vs Vitamin E (n = 33)	Unclear	Unclear	High	High	Unclear	High	Low	High
Youshari 2017	Vitamin E plus other supplements (n = 20) vs Vitamin E (n = 21)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Barbakadze 2020	Vitamin E plus vitamin C (n = 52) vs No active intervention (n = 20)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Harrison 2003	Vitamin E plus vitamin C (n = 23) vs No active intervention (n = 22)	Low	Low	Low	Low	Unclear	High	Low	High
Nobili 2006	Vitamin E plus vitamin C (n = 45) vs No active intervention (n = 43)	Unclear	Low	Low	Low	Unclear	Low	Low	High

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

Pour 2020	Other supplements (n = 38) vs No active intervention (n = 38)	Low	Low	Low	Low	Low	High	Low	High
Rafie 2020	Other supplements (n = 23) vs No active intervention (n = 23)	Unclear	Low	Low	Low	Unclear	High	Low	High
Nelson 2009	MUFA (n = not stated) vs PUFA (n = not stated)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Tobin 2018	MUFA (n = 86) vs PUFA (n = 81)	Low	Low	Low	Low	Unclear	High	Unclear	High
NCT00977730	Other antioxidants plus other supplements (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Yari 2020	Other antioxidants plus other supplements (n = 25) vs No active intervention (n = 21)	Low	Low	High	High	Unclear	Low	Unclear	High
Yari 2020	Other antioxidants plus other supplements (n = 25) vs Other supplements (n = 24)	Low	Low	High	High	Unclear	Low	Unclear	High
Yari 2020	Other antioxidants plus other supplements (n = 25) vs Other antioxidants (n = 22)	Low	Low	High	High	Unclear	Low	Unclear	High
Qin 2015	PUFA plus vitamin E (n = 36) vs No active intervention (n = 34)	Low	Low	Low	Low	Unclear	High	Low	High
Gomez 2009	Vitamin C plus other antioxidants (n = 30) vs No active intervention (n = 30)	Unclear	Low	Unclear	Unclear	Low	High	Low	High
Ebrahimi-Mameghani 2016	PUFA plus vitamin E (n = 19) vs Vitamin E (n = 19)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Ashraf 2017	Vitamin C plus other antioxidants (n = 25) vs Vitamin E (n = 27)	Unclear	Unclear	High	High	Unclear	High	Low	High
Miglio 2000	Amino acids plus vitamin C (n = 96) vs No active intervention (n = 95)	Low	Low	Low	Low	Unclear	High	Low	High
Celinski 2014	Amino acids plus PUFA (n = 51) vs PUFA (n = 23)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High

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

Poulos 2021	Amino acids plus vitamin E plus other antioxidants (n = 14) vs No active intervention (n = 11)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Amanat 2018	Oestrogen (n = 37) vs No active intervention (n = 41)	Low	Low	Low	Low	Unclear	High	Low	High
Zohrer 2017	Phospholipids plus PUFA plus vitamin E (n = 20) vs No active intervention (n = 20)	Low	Low	Low	Low	Unclear	High	Low	High
Loguercio 2012	Phospholipids plus vitamin E plus other antioxidants (n = 69) vs No active intervention (n = 69)	Low	Unclear	Low	Low	High	Low	Low	High
Hong 2016	Other supplements plus other antioxidants (n = 35) vs Other antioxidants (n = 31)	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High
Lewis 2018	Polysaccharides (n = 12) vs No active intervention (n = 11)	Low	Low	Low	Low	Low	Low	Low	Low
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics plus vitamin E (n = 15) vs No active intervention (n = 15)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics plus vitamin E (n = 15) vs Prebiotics/Probiotics/Synbiotics (n = 15)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Ekhlasi 2016	Prebiotics/Probiotics/Synbiotics plus vitamin E (n = 15) vs Vitamin E (n = 15)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Kobyliak 2017	Prebiotics/Probiotics/Synbiotics plus PUFA (n = not stated) vs No active intervention (n = not stated)	Unclear	Unclear	Low	Low	Unclear	High	Low	High
Song 2020	PUFA plus other supplements (n = 17) vs No active intervention (n = 21)	Low	Low	Low	Low	Unclear	High	Low	High
Morvaridzadeh 2021	Prebiotics/Probiotics/Synbiotics plus vitamin D (n = 44) vs Prebiotics/Probiotics/Synbiotics (n = 44)	Low	Unclear	Low	Low	Unclear	High	Low	High

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

Song 2020	PUFA plus other supplements (n = 17) vs Other supplements (n = 16)	Low	Low	Low	Low	Unclear	High	Low	High
Song 2020	PUFA plus other supplements (n = 17) vs PUFA (n = 21)	Low	Low	Low	Low	Unclear	High	Low	High
Della Corte 2016	PUFA plus vitamin D (n = 18) vs No active intervention (n = 23)	Low	Low	Low	Low	Unclear	High	Low	High
Dallio 2020	Vitamin D plus vitamin E plus other antioxidants (n = 60) vs No active intervention (n = 30)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Afzali 2020	Vitamin E plus other antioxidants plus other supplements (n = 60) vs Vitamin E plus other antioxidants (n = 57)	Low	Unclear	Low	Low	High	High	Low	High

MUFA: monounsaturated fatty acid.
PUFA: polyunsaturated fatty acid.

Table 5. Model fit

Serious adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	64.08	61.87	-
DIC	77.42	77.42	-
pD	13.35	15.55	-
Serious adverse events (number of events)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	15.77	-	-
DIC	19.51	-	-
pD	3.734	-	-
Any adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	216.2	215	-
DIC	253.5	255.3	-
pD	37.23	40.3	-
Any adverse events (number of events)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	188.3	188.3	-
DIC	206.1	206.2	-
pD	17.85	17.9	-
Resolution of fatty liver	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	-	255.6	-
DIC	-	297.8	-
pD	-	42.19	-
Fibrosis score	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	-24.08	-29.64	-
DIC	2.946	1.69	-
pD	27.03	31.33	-

Table 5. Model fit *(Continued)*

Non-alcohol-related fatty liver disease (NAFLD) activity score	Fixed-effect model	Random-effects model	Inconsistency model
Dbar	12.7	5.971	-
DIC	35.64	33.69	-
pD	22.93	27.72	-

Dbar: posterior mean of deviance.
DIC: deviance information criteria.
pD: effective number of parameters or leverage.

Table 6. Effect estimates

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

The table provides the effect estimates of each pairwise comparison for the different outcomes: odds ratios for serious adverse events (number of people) and adverse events (number of people), rate ratios for serious adverse events (number of people) and adverse events (number of people), mean differences for fibrosis and non-alcohol-related fatty liver disease activity scores, and hazard ratios for all other outcomes. The top half of the table indicates effect estimates from direct comparisons. The bottom half of the table indicates effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A vs 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 (i.e. it provides the odds A/odds B). If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. But this gives odds B/odds A. As we are interested in odds A/odds B, take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. 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. 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 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.

Table 7. Sensitivity analysis (worst-best and best-worst scenario analysis)

Any adverse events (number of people)
Other supplements vs No active intervention
main analysis: no evidence of difference between groups (OR 1.33, 95% CrI 0.78 to 2.26)
best-worst analysis: no evidence of difference between groups (OR 0.75, 95% CrI 0.47 to 1.18)
worst-best analysis: higher in other supplements than in no active intervention (OR 2.11, 95% CrI 1.30 to 3.46)
Prebiotics/Probiotics/Synbiotics vs No active intervention
main analysis: no evidence of difference between groups (OR 0.67, 95% CrI 0.30 to 1.46)
best-worst analysis: lower in prebiotics/probiotics/synbiotics than in no active intervention (OR 0.27, 95% CrI 0.12 to 0.56)
worst-best analysis: no evidence of difference between groups (OR 1.53, 95% CrI 0.77 to 3.11)
Vitamin E vs No active intervention
main analysis: no evidence of difference between groups (OR 0.83, 95% CrI 0.36 to 1.91)
best-worst analysis: lower in vitamin E than in no active intervention (OR 0.41, 95% CrI 0.19 to 0.87)
worst-best analysis: no evidence of difference between groups (OR 1.70, 95% CrI 0.79 to 3.71)
Prebiotics/Probiotics/Synbiotics vs Other supplements
main analysis: no evidence of difference between groups (OR 0.50, 95% CrI 0.19 to 1.29)
best-worst analysis: lower in prebiotics/probiotics/synbiotics than in other supplements (OR 0.37, 95% CrI 0.15 to 0.86)
worst-best analysis: no evidence of difference between groups (OR 0.72, 95% CrI 0.32 to 1.68)
Amino acids vs Other supplements
main analysis: no evidence of difference between groups (OR 0.46, 95% CrI 0.18 to 1.14)
best-worst analysis: lower in amino acids than in other supplements (OR 0.29, 95% CrI 0.12 to 0.71)

Table 7. Sensitivity analysis (worst-best and best-worst scenario analysis) *(Continued)*

worst-best analysis: no evidence of difference between groups (OR 0.80, 95% CrI 0.33 to 1.96)
Other antioxidants vs Prebiotics/Probiotics/Synbiotics
main analysis: no evidence of difference between groups (OR 2.51, 95% CrI 0.72 to 9.04)
best-worst analysis: no evidence of difference between groups (OR 1.09, 95% CrI 0.33 to 3.71)
worst-best analysis: higher in other antioxidants than in prebiotics/probiotics/synbiotics (OR 6.11, 95% CrI 1.80 to 21.87)
Amino acids plus vitamin C vs Prebiotics/Probiotics/Synbiotics
main analysis: no evidence of difference between groups (OR 2.66, 95% CrI 0.72 to 10.61)
best-worst analysis: no evidence of difference between groups (OR 1.15, 95% CrI 0.33 to 4.32)
worst-best analysis: higher in amino acids plus vitamin C than prebiotics/probiotics/synbiotics (OR 6.49, 95% CrI 1.82 to 25.51)
Other antioxidants vs Vitamin E
main analysis: no evidence of difference between groups (OR 2.02, 95% CrI 0.56 to 7.40)
best-worst analysis: no evidence of difference between groups (OR 0.99, 95% CrI 0.28 to 3.48)
worst-best analysis: higher in other antioxidants than in vitamin E (OR 4.13, 95% CrI 1.17 to 14.37)
Amino acids plus vitamin C vs Vitamin E
main analysis: no evidence of difference between groups (OR 2.14, 95% CrI 0.56 to 8.74)
best-worst analysis: no evidence of difference between groups (OR 1.04, 95% CrI 0.28 to 4.05)
worst-best analysis: higher in amino acids plus vitamin C than in vitamin E (OR 4.34, 95% CrI 1.20 to 17.65)
Phospholipids versus Other antioxidants
main analysis: no evidence of difference between groups (OR 0.22, 95% CrI 0.02 to 1.56)
best-worst analysis: lower in phospholipids than in other antioxidants (OR 0.12, 95% CrI 0.01 to 0.88)
worst-best analysis: no evidence of difference between groups (OR 0.35, 95% CrI 0.03 to 2.45)
Oestrogen vs Amino acids
main analysis: no evidence of difference between groups (OR 1.85, 95% CrI 0.04 to 80.56)
best-worst analysis: no evidence of difference between groups (OR 1.65, 95% CrI 0.04 to 71.74)
worst-best analysis: higher in oestrogen than in amino acids (OR 12.32, 95% CrI 1.34 to 391.90)
Amino acids plus vitamin C vs Phospholipids
main analysis: no evidence of difference between groups (OR 4.89, 95% CrI 0.64 to 53.57)
best-worst analysis: no evidence of difference between groups (OR 3.04, 95% CrI 0.40 to 33.08)
worst-best analysis: higher in amino acids plus vitamin C than in phospholipids (OR 8.70, 95% CrI 1.17 to 95.77)
Resolution of fatty liver
Vitamin E vs Prebiotics/Probiotics/Synbiotics
main analysis: no evidence of difference between groups (HR 0.46, 95% CrI 0.19 to 1.15)
worst-best analysis: no evidence of difference between groups (HR 0.83, 95% CrI 0.30 to 2.34)
best-worst analysis: lower in vitamin E than in prebiotics/probiotics/synbiotics (HR 0.38, 95% CrI 0.15 to 0.97)

CrI: credible interval.
OR: odds ratio.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL), in the Cochrane Library	Issue 2, 2021	#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

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		#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
MEDLINE Ovid	January 1947 to 25 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

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		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 25 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. 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.

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		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) and Conference Proceedings Citation Index-Science (Web of Science)	January 1945 to 25 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
ClinicalTrials.gov	25 February 2021	Fatty Liver, Nonalcoholic | Phase 2, 3, 4

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European Medicines Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	25 February 2021	"Fatty liver"

Footnote: This is a common search strategy that was used for this lifestyle interventions review (Buzzetti 2021).

Appendix 2. Abbreviations

AminoAcids: amino acids
Amino acids+PUFA: amino acids plus polyunsaturated fatty acids
Amino acids+VitC: amino acids plus vitamin C
CT scan: computerised tomography scan
Oestrogen: oestrogen
MRS: magnetic resonance spectroscopy
MRI: magnetic resonance imaging
MUFA: monounsaturated fatty acids
NAFLD: non-alcohol-related fatty liver disease
NASH: non-alcohol-related steatohepatitis
NoActiveIntervention: no active intervention
OtherAntioxidants: other antioxidants
OtherAntiOx: other antioxidants
OtherAntioxidants+OtherSupplements: other antioxidants plus other supplements
OtherAntiOx+OtherSupp: other antioxidants plus other supplements
OtherSupplements: other supplements
OtherSupp: other supplements
Phospholipids: phospholipids
Phospholipids+PUFA+VitE: phospholipids plus polyunsaturated fatty acids plus vitamin E
Phospholipids+PUFA+VitE+OtherAntioxidants+OtherSupplements: phospholipids plus polyunsaturated fatty acids plus vitamin E plus other antioxidants plus other supplements
Phospholipids+PUFA+VitE+OtherAntiOx+OtherSupp: phospholipids plus PUFA plus vitamin E plus other antioxidants plus other supplements
Phospholipids+VitE+OtherAntioxidants: phospholipids plus vitamin E plus other antioxidants
Phospholipids+VitE+OtherAntiOx: phospholipids plus vitamin E plus other antioxidants
Polysaccharides: polysaccharides
Prebiotics_probiotics_synbiotics+PUFA: prebiotics/probiotics/synbiotics plus polyunsaturated fatty acids
Prebiotics_probiotics_synbiotics+VitE: prebiotics/probiotics/synbiotics plus vitamin E
Prebiotics_Probiotics_Synbiotics: prebiotics/probiotics/synbiotics
PreProSynbiotics+PUFA: prebiotics/probiotics/synbiotics plus PUFA
PreProSynbiotics+VitE: prebiotics/probiotics/synbiotics plus vitamin E
PreProSynbiotics: prebiotics/probiotics/synbiotics
PUFA: polyunsaturated fatty acids
PUFA+VitD: polyunsaturated fatty acids plus vitamin D
PUFA+VitE: polyunsaturated fatty acids plus vitamin E
VitC+OtherAntioxidants: vitamin C plus other antioxidants
VitC+OtherAntiOx: vitamin C plus other antioxidants
VitC+VitE: vitamin C plus vitamin E
VitD: vitamin D
VitE: vitamin E
VitE+OtherAntioxidants: vitamin E plus other antioxidants
VitE+OtherAntiOx: vitamin E plus other antioxidants
VitE+OtherSupplements: vitamin E plus other supplements
VitE+OtherSupp: vitamin E plus other supplements

Appendix 3. Data

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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 protocol for publication.

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

Review

Co-ordinating the review: KG.
Study selection: KG, OK, EB.
Data extraction: KG, OK, AL, DR, TC, LB.
Writing the review: KG.
Providing advice on the review: SF, AJS, NC, EJM, MC, CP, BRD, ET.
Securing funding for the review: KG.

All review authors approved the review for publication.

DECLARATIONS OF INTEREST

None known for any of the review 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 clarified that we did not include trials in which participants without NAFLD were included and no separate data were available on those with NAFLD
- We excluded a trial that included NAFLD patients with chronic kidney disease because this trial does not address the objectives of this systematic review, which refers to people with NAFLD but not with specifically chronic kidney disease
- We have provided additional details on how we constructed the treatment nodes and what we considered a 'decision set'
- We have revised outcomes based on feedback from patients and the public representative for this project, an online survey about outcomes promoted through the Cochrane Consumer Network, and the coreNASH project (Clearfield 2021). This resulted in the addition of liver-related mortality and the MELD score
- We have provided further details on how we translated non-English articles
- 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 in the beginning of the 'Study design' section that we will exclude quasi-randomised studies
- We removed the 'For profit' bias from risk of bias domains as per the guidance of Cochrane Network editors

- We did not perform Trial Sequential Analysis (TSA) because the risk of false-positive results with Bayesian meta-analysis is usually less than or at least equivalent to TSA
- We used the latest guidance from the GRADE Working Group - Yepes-Nunez 2019 - rather than previous guidance - Puhan 2014 - in 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 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 misinterpretation of results. We have highlighted this clearly within the text of the review, along with reasons for not presenting them

NOTES

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