Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin E for people with non-alcoholic fatty liver disease (Review)

Wen H, Deng H, Yang L, Li L, Lin J, Zheng P, Bjelakovic M, Ji G

Wen H, Deng H, Yang L, Li L, Lin J, Zheng P, Bjelakovic M, Ji G.
Vitamin E for people with non-alcoholic fatty liver disease.
Cochrane Database of Systematic Reviews 2024, Issue 10. Art. No.: CD015033.
DOI: 10.1002/14651858.CD015033.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Vitamin E for people with non-alcoholic fatty liver disease

Hongzhu Wen[1], Hongyong Deng[2], Lili Yang[3], Lujin Li[4], Jiang Lin[1], Peiyong Zheng[3], Milica Bjelakovic[5], Guang Ji[4]

[1]Department of Gastroenterology, Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China. [2]EBM Center of TCM, Shanghai University of Traditional Chinese Medicine, Shanghai, China. [3]Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China. [4]Shanghai University of Traditional Chinese Medicine, Shanghai, China. [5]Clinic of Gastroenterohepatology, University Clinical Centre Nis, Nis, Serbia

Contact: Guang Ji, jg@shutcm.edu.cn.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 10, 2024.

Citation: Wen H, Deng H, Yang L, Li L, Lin J, Zheng P, Bjelakovic M, Ji G. Vitamin E for people with non-alcoholic fatty liver disease. *Cochrane Database of Systematic Reviews* 2024, Issue 10. Art. No.: CD015033. DOI: 10.1002/14651858.CD015033.pub2.

ABSTRACT

Rationale

Non-alcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD), is the most common liver disease worldwide, affecting an estimated 3 in 10 people. The available treatment is far from optimal. Diet and lifestyle changes to promote weight loss and weight loss maintenance are the basic management of NAFLD, but these are difficult to achieve and maintain. Vitamin E has shown beneficial effects on oxidative stress, which plays a major role in the pathogenesis of NAFLD. However, there is uncertainty about the effects of vitamin E for people with NAFLD.

Objectives

To evaluate the beneficial and harmful effects of vitamin E alone, or vitamin E in combination with other vitamins or minerals, versus placebo or no intervention in people with NAFLD.

Search methods

We used recommended Cochrane search methods. The latest search was performed on 2 February 2024.

Eligibility criteria

We included randomised clinical trials that compared vitamin E alone, or in combination with other vitamins or minerals, at any dose, duration, and route of administration, versus placebo or no intervention, in people with NAFLD of any age, sex, or ethnic origin. We included participants with imaging techniques or histology-proven NAFLD and minimal alcohol intake, and participants with steatohepatitis who had liver biopsies.

Outcomes

Our critical outcomes were all-cause mortality, liver-related mortality, and serious adverse events. Our important outcomes were liver-related morbidity, health-related quality of life, non-serious adverse events, biochemical response, and imaging assessment of the degree of fatty liver.

Risk of bias

We used Cochrane's RoB 2 tool to assess risk of bias for each of the predefined outcomes.

Synthesis methods

We used standard Cochrane methods. We used GRADE to assess the certainty of evidence.

Included studies

We included 16 randomised clinical trials involving 1066 paediatric and adult participants with NAFLD. Experimental groups received vitamin E alone (14 trials) or vitamin E in combination with vitamin C (2 trials). Control groups received placebo in 13 trials and no intervention in three trials. Daily dosages of oral vitamin E ranged from 298 international units (IU) to 1000 IU. Co-interventions were lifestyle and low-calorie diet interventions in 13 trials, ursodeoxycholic acid in one trial, unchanged diet and physical activity in one trial, and baseline treatments for type 2 diabetes in one trial. Nine trials had more than two intervention groups, but we used only the groups in which vitamin E alone or vitamin E in combination with vitamin C were compared with placebo or no intervention. In total, 7.9% (84/1066) of participants dropped out. Follow-up ranged from 2 months to 24 months.

Synthesis of results

Vitamin E versus placebo or no intervention

The effects of vitamin E versus placebo or no intervention on all-cause mortality (risk ratio (RR) 3.45, 95% confidence interval (CI) 0.57 to 20.86; 3 trials, 351 participants; very low certainty evidence) and serious adverse events (RR 1.91, 95% CI 0.30 to 12.01; 2 trials, 283 participants; very low certainty evidence) are very uncertain. There were no data on liver-related mortality or liver-related morbidity. The effects of vitamin E versus placebo or no intervention on physical health-related quality of life (mean difference (MD) 0.74, 95% CI −0.52 to 2.01; 2 trials, 251 participants; higher scores indicate better quality of life; very low certainty evidence); psychosocial health-related quality of life (MD −0.57, 95% CI −4.11 to 2.97; 2 trials, 251 participants; higher scores indicate better quality of life; very low certainty evidence); and non-serious adverse events (RR 0.86, 95% CI 0.64 to 1.17; 2 trials, 283 participants; very low certainty evidence) are also very uncertain. There were no data on proportion of participants without a decrease in liver enzymes. Vitamin E likely slightly reduces serum alanine transaminase (ALT) (MD −9.29, 95% CI −13.69 to −4.89; 11 trials, 708 participants; moderate certainty evidence) and aspartate aminotransferase (AST) (MD −4.90, 95% CI −7.24 to −2.57; 11 trials, 695 participants; moderate certainty evidence) levels compared with placebo or no intervention. Vitamin E may slightly reduce serum alkaline phosphatase (ALP) levels (MD −5.21, 95% CI −9.88 to −0.54; 5 trials, 416 participants; very low certainty evidence), but the evidence is very uncertain.

Vitamin E plus vitamin C versus placebo

There were no data on all-cause mortality, liver-related mortality, serious adverse events, liver-related morbidity, health-related quality of life, and non-serious adverse events. The effects of vitamin E plus vitamin C on reducing serum ALT (MD −0.50, 95% CI −4.58 to 3.58; 2 trials, 133 participants; very low certainty evidence), AST (MD 0.09, 95% CI −3.39 to 3.57; 1 trial, 88 participants; very low certainty evidence), and gamma-glutamyl transferase (GGT) levels (MD 1.58, 95% CI −3.22 to 6.38; 1 trial, 88 participants; very low certainty evidence) are very uncertain.

We identified three ongoing trials, and six trials are awaiting classification.

Authors' conclusions

Given the very low certainty evidence, we do not know if long-term treatment (18 months to 24 months) with vitamin E administered alone affects all-cause mortality, serious adverse events, quality of life, or non-serious adverse events in people with NAFLD when compared with placebo or no intervention. We found no data on liver-related mortality, liver-related morbidity, or proportion of participants without a decrease in liver enzymes. Vitamin E likely reduces ALT and AST slightly when compared with placebo, but whether this has any impact on the clinical course in people with NAFLD is unknown.

The trials on vitamin E plus vitamin C did not report on all-cause mortality, liver-related mortality, serious adverse events, liver-related morbidity, health-related quality of life, or non-serious adverse events. Given the very low certainty evidence, we do not know the effects of vitamin E plus vitamin C on liver enzymes in people with NAFLD when compared with placebo.

Funding

Three trials disclosed no external funding. Five trials were industry funded. Five trials were funded by organisations with no vested interests. Three trials did not provide any information on clinical trial support or sponsorship.

Registration

Protocol: doi.org/10.1002/14651858.CD015033

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of vitamin E for non-alcoholic fatty liver disease?

Key messages

- It is unclear whether long-term treatment (18 months to 24 months) with vitamin E alone or in combination with vitamin C affects death due to any cause, serious unwanted effects, health-related quality of life, or non-serious unwanted effects when compared with placebo (dummy pill) or no treatment.
- Vitamin E alone probably reduces alanine transaminase and aspartate aminotransferase (liver enzyme) levels slightly.
- Further research is needed to increase our confidence in the evidence.

What is non-alcoholic fatty liver disease?

Non-alcoholic fatty liver disease, recently renamed 'metabolic dysfunction-associated steatotic liver disease', is a common condition that affects people who may drink little to no alcohol. It is caused by too much fat in the liver (steatosis). People with non-alcoholic fatty liver disease can experience weakness, pain, or discomfort in the upper right side of the tummy. The disease affects not only the liver, but it is also associated with a high risk of high blood sugar, heart disease, and kidney disease.

What did we want to find out?

We wanted to find out if vitamin E alone, or in combination with other vitamins or minerals, was better than placebo (dummy pill) or no treatment in improving outcomes such as death due to any cause, serious unwanted effects, quality of life, liver-related death, liver-related illness, and non-serious unwanted effects. We also wanted to know if this treatment improves liver enzymes and steatosis, which indicate good liver function.

What did we do?

We searched for studies that looked at vitamin E alone or in combination with other vitamins or minerals compared to placebo or no treatment in adults and children with non-alcoholic fatty liver disease. We compared and summarised the results of the trials and rated our confidence in the evidence based on factors such as study methods and sizes.

What did we find?

We found 16 studies including 1066 adults and children with non-alcoholic fatty liver disease. The studies were performed in countries around the world and lasted between two months and two years.

Evidence for the effect of vitamin E administered alone on death from any cause, serious unwanted effects, quality of life, and non-serious unwanted events is very uncertain. Vitamin E alone likely slightly reduces serum alanine transaminase and aspartate aminotransferase levels (enzymes found in the liver) when compared with placebo or no intervention. Vitamin E may slightly reduce serum alkaline phosphatase (another liver enzyme) levels, but the evidence is very uncertain.

Evidence for the effect of vitamin E in combination with vitamin C on liver enzyme levels is very uncertain. No trial looking at vitamin E in combination with vitamin C reported on death due to any cause, serious unwanted effects, quality of life, or non-serious unwanted effects.

The outcomes liver-related death, liver-related illness, and numbers of people without a decrease in serum liver enzymes were not reported in any included study.

What are the limitations of the evidence?

Our confidence in the evidence ranged from very low to moderate. In general, we have little confidence in the evidence because few studies provided information on outcomes we were interested in; results varied across studies; and many of the studies were small. Further research is likely to change our results.

How up-to-date is this evidence?

The evidence is current to 2 February 2024.

Summary of findings 1. Summary of findings table - Vitamin E compared with placebo or no intervention for people with NAFLD

Vitamin E compared with placebo or no intervention for people with NAFLD

Patient or population: people with NAFLD
Setting: outpatients
Intervention: vitamin E
Comparison: placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with vitamin E				
All-cause mortality follow-up: range 18 months to 24 months	Not pooled	Not pooled	Not pooled	351 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b]	There were no events in the placebo group. Causes of death were pneumonia and liver failure secondary to sepsis (1 person with fibrosis), suicide (1 person), and ischaemic and haemorrhagic stroke (2 people with non-alcoholic steatohepatitis).
Liver-related mortality - not reported	-	-	-	-	-	
Serious adverse events follow-up: mean 24 months	14 per 1000	**27 per 1000** (4 to 170)	**RR 1.91** (0.30 to 12.01)	283 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	Serious adverse events were mood alteration and suicide (1 trial), and cardiac ischaemia and liver dysfunction (1 trial).
Liver-related morbidity - not reported	-	-	-	-	-	
Health-related quality of life follow-up: mean 24 months	The mean health-related quality of life was **-0.3**	MD **0.74 higher** (0.52 lower to 2.01 higher)	-	251 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	Psychosocial health-related quality of life (MD -0.57, 95% CI -4.11 to 2.97; I^2 = 0%; 2 trials, 251 participants); higher scores indicate better quality of life.[c]
Non-serious adverse events (number of events)	567 per 1000	**488 per 1000** (363 to 664)	**RR 0.86** (0.64 to 1.17)	283 (2 RCTs)	⊕⊖⊖⊖ Very low[a,d]	

follow-up: mean 24 months						
Liver enzyme levels. Serum ALT follow-up: range 2 months to 24 months	The mean liver enzyme levels. Serum ALT was **-5.97** IU/L	MD **9.29 IU/L lower** (13.69 lower to 4.89 lower)	-	708 (11 RCTs)	⊕⊕⊕⊖ Moderate[a]	Eleven trials reported aspartate aminotransferase reduction (MD -4.9, 95% CI -7.24 to -2.57; 11 trials, 695 participants; moderate certainty evidence), and five trials reported alkaline phosphatase reduction (MD -5.21, 95% CI -9.88 to -0.54; 5 trials, 416 participants; very low certainty evidence) in the intervention groups versus control groups.[e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_451115499886960764.

[a] Downgraded one level for risk of bias: data were from trials with some concerns, i.e. at least one domain with some concerns.
[b] Downgraded three levels for imprecision: few events, 95% CIs were extremely wide and crossed the null effect.
[c] The mean value for health-related quality of life is from Sanyal 2010 trial, as this trial carries the greatest weight in the analysis.
[d] Downgraded two levels for imprecision: few events and 95% CIs crossed the null effect.
[e] The mean value of alanine transminase is from Pervez 2020 trial, as this trial carries the greatest weight in the analysis.

Summary of findings 2. Summary of findings table - Vitamin E plus vitamin C compared with placebo for people with NAFLD

Vitamin E plus vitamin C compared with placebo for people with NAFLD

Patient or population: people with NAFLD
Setting: outpatients
Intervention: vitamin E plus vitamin C
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants	Certainty of the evidence	Comments

	Risk with placebo	Risk with vitamin E plus vitamin C		(studies)	(GRADE)	
All-cause mortality - not reported	-	-	-	-	-	No data reported
Liver-related mortality - not reported	-	-	-	-	-	No data reported
Serious adverse events - not reported	-	-	-	-	-	No data reported
Liver-related morbidity - not reported	-	-	-	-	-	No data reported
Health-related quality of life - not reported	-	-	-	-	-	No data reported
Non-serious adverse events - not reported	-	-	-	-	-	No data reported
Liver enzyme levels. Serum ALT follow-up: range 6 months to 12 months	The mean liver enzyme levels. Serum ALT was **32.67** IU/L	MD **0.5 IU/L lower** (4.58 lower to 3.58 higher)	-	133 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	One trial reported aspartate aminotransferase levels (MD 0.09, 95% CI -3.39 to 3.57; 88 participants; very low certainty evidence), and one trial reported gamma-glutamyl transferase levels (MD 1.58, 95% CI -3.22 to 6.38; 88 participants; very low certainty evidence) in the intervention groups versus control groups.[c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_451134490528433331.

[a] Downgraded one level for risk of bias: data were from trials with some concerns, i.e. at least one domain with some concerns.
[b] Downgraded three levels for imprecision: few events, 95% CIs were extremely wide and crossed the null effect.
[c] The mean value of alanine transminase is from Nobili 2006 trial, as this trial carries the greatest weight in the analysis.

BACKGROUND

Description of the condition

Non-alcoholic fatty liver disease (NAFLD) is an overarching term that includes all disease grades and stages, and refers to a population in which ≥ 5% of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis (e.g. medications, starvation, monogenic disorders) in people without excessive alcohol intake (defined as less than 20 g/day for women and less than 30 g/day for men). The spectrum of disease includes non-alcoholic fatty liver (NAFL), characterised by macrovesicular hepatic steatosis that may be accompanied by mild inflammation, and non-alcoholic steatohepatitis (NASH), which is additionally characterised by the presence of inflammation and cellular injury (ballooning), with or without fibrosis. NASH may progress to cirrhosis, liver failure, and liver cancer [1].

Since June 2023, NAFLD has been replaced by the term 'metabolic dysfunction-associated steatotic liver disease' (MASLD) [2]. The diagnosis of the disease is no longer made by exclusion; the positive diagnostic criteria are in the presence of hepatic steatosis, with one or more of the five cardiometabolic risk factors:

- body mass index (BMI) ≥ 25 kg/m^2 (≥ 23 kg/m^2 for Asians) or waist circumference > 94 cm for males and > 80 cm for females or ethnicity adjusted;
- fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) or two-hour post-load glucose levels ≥ 7.8 mmol/L (≥ 140 mg/dL) or glycated haemoglobin ≥ 5.7% (39 mmol/L) or type 2 diabetes or treatment for type 2 diabetes;
- blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment;
- plasma triglycerides ≥ 1.70 mmol/L (150 mg/dL) or lipid-lowering treatment; and
- plasma high-density lipoprotein (HDL) cholesterol ≤ 1.0 mmol/L (40 mg/dL) for males and ≤ 1.3 mmol/L (50 mg/dL) for females or lipid-lowering treatment [2].

This differs from the diagnostic criteria of the NAFLD definition, but as analysis has demonstrated that 98% of the existing registry cohort of people with NAFLD would fulfil the new criteria for MASLD [3], those with the previous definition (NAFLD) can now be seen to be completely covered by the categories of MASLD and possible MASLD [2], and findings from older NAFLD studies remain valid under the new MASLD definition [4].

Liver biopsy is the current gold standard to evaluate hepatic fat, inflammation, and fibrosis in NAFLD, but as an invasive tool, it is not a viable tool for widespread NAFLD management. Thus, multiple surrogate markers have been studied, including clinical predictors, serum biomarkers, and imaging methods. Serum biomarkers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been shown to be elevated in people with NAFLD/NASH, although normal aminotransferase levels do not exclude the diagnosis of NASH [5]. Non-invasive imaging modalities used for NAFLD evaluation include B-mode ultrasonography (US), computed tomography (CT), magnetic resonance (MR) imaging, ultrasound elastography (USE), quantitative ultrasound-based techniques, magnetic resonance elastography (MRE), and magnetic resonance-based fat quantitation techniques [6].

NAFLD is now the most common form of chronic liver disease globally. Since the 1990s, the prevalence of NAFLD has more than doubled in adolescents and adults [7], and it is a cause of significant morbidity due to chronic liver disease [8, 9]. The worldwide prevalence of NAFLD is 30% and is rising rapidly according to a systematic review and meta-analysis collected from 1990 to 2019, that is, 3 in 10 people were affected by NAFLD worldwide [10]. For children and adolescents, trend analysis from 2000 to 2017 indicates an increasing global prevalence of paediatric NAFLD from 4.6% to 9.0% at a yearly increase of 0.26%, and the prevalence is predicted to reach 30.7% by 2040 [11]. NAFLD is associated with tremendous clinical, economic, and health-related quality of life burden [12]. Currently, NASH is the most rapidly growing indication for liver transplantation in the USA. Despite the resurgence in alcoholic liver disease, NASH remains the second leading indication for liver transplantation [13].

Causes of NAFLD include obesity, insulin resistance, hyperglycaemia or diabetes, and elevated blood lipids such as cholesterol and triglycerides. People with NAFLD are usually obese with diabetes mellitus and arterial hypertension [14, 15], and there is growing evidence that NAFLD is a multisystem disease, affecting extra-hepatic organs and increasing the risk of cardiovascular and cardiac diseases, and chronic kidney disease [16]. The pathophysiology underlying the disorder is also incompletely understood. So far, there are two well-accepted hypotheses: the 'two-hits' hypothesis [17] and the 'multiple parallel hits' hypothesis [18]. In both, oxidative stress is considered a key factor in the onset and development of NAFLD. Briefly, oxidative stress causes lipid peroxidation and activates inflammatory cytokines resulting in hepatocyte injury and inflammation in NASH. Furthermore, lipotoxicity of adipose tissue [19], gut microbiome and related metabolites [20, 21], and genetic pathways such as palatin like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), gene knock-out chain reaction (GKCR), membrane bound O-acyltransferase domain containing 7 (MBOAT7), and 17-beta dehydrogenase 13 (HSD17B13) [22] play crucial roles in the evolution of NAFLD.

The recommended treatments for NAFLD nowadays are lifestyle modifications, including weight reduction, a healthy diet, and regular physical activity. Though there are currently no US Food and Drug Administration (FDA)-approved medications for the treatment of NAFLD, drugs approved to treat associated comorbidities with potential benefit in NAFLD are recommended, for example semaglutide, liraglutide, or pioglitazone may be considered for type 2 diabetes mellitus in people with NASH, with pioglitazone contraindicated in people with New York Heart Association class III or IV heart failure [1, 23]. Despite recent progress, medicine for the treatment of NAFLD remains an unmet need. Vitamin E 800 international units (IU) per day has been suggested in selected individuals without diabetes [1]. It is notable that lifestyle modification is a basic treatment combined with these drugs.

Description of the intervention and how it might work

As oxidative stress is reported to be causative in NAFLD initiation and progression, antioxidant supplements may potentially protect cellular structures against damage from oxygen-free radicals and reactive products of lipid peroxidation. A number of antioxidants such as vitamin E [24, 25, 26], silymarin [27, 24], betaine [28], and N-acetylcysteine [29] are also being studied. A 2011 Cochrane review

also reported that antioxidant supplements might increase liver enzyme activity [30].

Vitamin E (α-tocopherol), a fat-soluble antioxidant, is the major type of lipid-soluble, chain-breaking antioxidant found in the human body. It occurs naturally in foods such as nuts, seeds, and leafy green vegetables. Vitamin E was first described in 1922 as a dietary factor essential to prevent foetal reabsorption in rats [31], and soon after it was identified as an antioxidant of polyunsaturated lipids. It was considered a cytoprotective factor with suggested roles in preventing inflammatory and degenerative processes of the liver during exposure to a range of xenobiotics, environmental pollutants, and dietary factors [32].

Recently, convincing evidence from animal studies found a preventive role of vitamin E in metabolic and inflammatory abnormalities associated with NAFLD, which was confirmed in clinical trials [33]. Since the 2000s, vitamin E has been studied in monotherapy or with other agents in many clinical trials to treat NAFLD [24, 34, 25, 26], and Sanyal and colleagues showed that vitamin E, but not pioglitazone, improved the histological features of NASH [26]. Results from these studies showed that vitamin E relieved NASH-associated injury and inflammation, decreased intrahepatic triglycerides, and improved lipid metabolism [35, 26]. However, a 2021 Cochrane network meta-analysis conducted by Komolafe and colleagues reported no effects of vitamin E on all clinical outcomes for people with NAFLD when compared to no additional intervention; the authors also reported that data were sparse [36].

The dosages of vitamin E used in studies range from 39 IU per day [37] to 1000 IU per day [38]; duration of administration ranged from one month [39] to 96 weeks [26]. However, high-dose vitamin E (400 IU per day or greater) might increase the risk of all-cause mortality [40, 41], bleeding [42], and prostate cancer [43].

Vitamin E improves the biochemistry and histology features of NAFLD; however, the mechanistic aspects that lie behind this remain elusive. One study reported that vitamin E decreased intrahepatic triglycerides by inhibiting hepatic de novo lipogenesis through its antioxidant activity [44], and other studies demonstrated that vitamin E attenuated NAFLD via multiple other mechanisms, including protecting cellular structures against damage from oxygen-free radicals; upregulation of superoxide dismutase activity; and downregulation of isoprostanes (an index of lipid peroxidation), malondialdehyde and genes related to inflammation, apoptosis, fibrosis, and leptin and adiponectin expression [45, 46, 47, 48, 49]. The results of these studies reflect the potential beneficial effects of vitamin E on inhibition of NAFLD progression.

Why it is important to do this review

The increased prevalence of NAFLD has become one of the most important global public health issues. Oxidative stress is one of the key factors in the onset and development of NAFLD. Therefore, antioxidant therapy could possibly be beneficial in the management of NAFLD. Vitamin E may improve liver function and histological changes in people with NAFLD [26].

A review addressing the effects of antioxidant supplements on people with NAFLD or NASH was published in 2007, and it has not been updated since [50]. That review concluded that antioxidant supplements other than vitamin E exerted a beneficial effect on the activity of alanine aminotransferase and on steatosis, but meta-analyses published in 2015 and 2019 reported that vitamin E had a beneficial effect on NAFLD [51, 52]. In addition, given the enormous amount of research being published on the topic of antioxidants, we decided to prepare a new review focusing on vitamin E in people with NAFLD. We use the updated Cochrane methodology during our review production, starting with its protocol [53].

OBJECTIVES

To evaluate the beneficial and harmful effects of vitamin E alone, or vitamin E in combination with other vitamins or minerals, versus placebo or no intervention in people with non-alcoholic fatty liver disease.

METHODS

The Methods section of the review has been updated since publication of the protocol.

For rare events such as the critical outcomes of all-cause mortality and serious adverse events, we presented the risk ratio, and used the Peto odds ratio in sensitivity analysis.

For the important outcome of biochemical response, we found no data on the proportion of participants without a decrease in liver enzymes. Fifteen out of the 16 included trials reported data on changes in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatases (ALP), and gamma-glutamyl transpeptidase (GGT) levels; as these results were within the scope of biochemical response, we reported them in our review.

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials, irrespective of language, publication status, trial design, or date of publication. We excluded studies labelled as 'quasi-randomised' (i.e. pseudo-randomised) because the method of allocation of participants is not truly random.

Types of participants

We included randomised clinical trials involving participants of any age, sex, or ethnic origin with NAFLD. Participants had imaging techniques or histology (evidence of histological damage on liver biopsy, including simple steatosis, fatty infiltration plus non-specific inflammation, steatohepatitis, fibrosis, and cirrhosis) showing hepatic steatosis or steatofibrosis (steatosis accompanied by fibrosis), with minimal alcohol intake: preferably a daily alcohol intake less than 20 g in women and less than 30 g in men. According to the new definition [2], minimal alcohol intake is a weekly intake of 140 g to 350 g for women and 210 g to 420 g for men (average daily 20 g to 50 g for women, 30 g to 60 g for men).

We excluded trials that included people with other causes of hepatic steatosis or steatofibrosis, including hepatitis B, hepatitis C, autoimmune hepatitis, and genetic liver diseases such as Wilson's disease and haemochromatosis. We excluded trials considering people with one or more causes commonly associated with secondary NAFLD (drugs, surgical procedures, and miscellaneous disorders such as abetalipoproteinaemia or hypobetalipoproteinaemia, partial lipodystrophy, environmental

toxins, or total parenteral nutrition). We excluded studies including people with NASH diagnosed by imaging only.

Types of interventions

Experimental intervention

- Vitamin E alone.
- Vitamin E in combination with other vitamins or minerals.

Vitamin E may have been administered at any dose, duration, route of administration, formulation, frequency, setting, and time of administration, regardless of who provided vitamin E.

Control intervention

- Placebo or no treatment.

Co-interventions were allowed if used equally in the experimental and control groups (e.g. regimens including reduced calorie intake, increased physical activity, or behaviour modification).

Outcome measures

We collected data for the time points used in the original trials. We performed our primary analyses using the outcome data from the longest follow-up time.

We planned to include trials irrespective of whether they had prespecified or reported on the outcomes listed below; however, we found no such trials.

Critical outcomes

- All-cause mortality.
- Liver-related mortality.
- Serious adverse events. We used the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event [54], that is any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We considered all other adverse events as non-serious adverse events.

Important outcomes

- Liver-related morbidity (gastrointestinal bleeding, ascites, hepatic encephalopathy, hepatorenal syndrome, jaundice).
- Health-related quality of life (HRQoL), measured with validated questionnaires (e.g. WHOQOL, EQ-5D, 36-item Short Form Health Survey (SF-36)).
- Non-serious adverse events as defined or reported by the trialists, and not included under the ICH Guidelines for serious adverse events [54].
- Biochemical response (proportion of people without a decrease in liver enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatases (ALP), and gamma-glutamyl transpeptidase (GGT)).
- Imaging assessment of degree of fatty liver at the end of follow-up, assessed by ultrasound, computed tomography, or magnetic resonance imaging [55, 56, 57]. The included trials mainly used ultrasound, and the findings are based on lipid accumulation in the liver. NAFLD sonographic features include increased echogenicity, hepatomegaly, and intrahepatic vascular blurring. This technique is qualitative, and there is a lack of sonographic criteria for different degrees of steatosis.

We contacted trial authors to enquire if outcomes were measured but not reported, or outcomes were not measured and therefore not reported. We also contacted trial authors to enquire about serious adverse events that were not reported in the primary or any other identified publication.

Search methods for identification of studies

To minimise bias in our search results, we followed the guidance in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* [58] and in PRISMA-S (PRISMA-S Checklist; [59]) to plan and describe the search process for the review. The Cochrane Hepato-Biliary Group Information Specialist developed the search strategies and performed the electronic searches. We imposed no restrictions on language of publication, date, or status.

Electronic searches

We searched the following databases.

- Cochrane Hepato-Biliary Group Controlled Trials Register via the Cochrane Register of Studies Web (2 February 2024)
- Cochrane Central Register of Controlled Trials (CENTRAL) (2024; Issue 2) in the Cochrane Library
- MEDLINE ALL Ovid (1946 to 2 February 2024)
- Embase Ovid (1974 to 2 February 2024)
- LILACS (Latin American and Caribbean Health Science Information database) (VHL Regional Portal; 1982 to 2 February 2024)
- Science Citation Index Expanded (Web of Science; 1900 to 2 February 2024)
- Conference Proceedings Citation Index-Science (Web of Science; 1990 to 2 February 2024).
- China National Knowledge Infrastructure (CNKI), Wanfang Data, and SinoMed (2 February 2024).

Supplementary material 1 provides the search strategies with the date range of the searches.

Searching other resources

We searched ClinicalTrials.gov (clinicaltrials.gov/), the European Medicines Agency (EMA; www.ema.europa.eu/ema/), the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp), the US Food and Drug Administration (FDA; www.fda.gov), as well as pharmaceutical company sources, reference lists of potentially eligible studies, and relevant reviews for ongoing or unpublished trials on 2 February 2024.

We contacted the authors of each included trial for information regarding unpublished trials. We searched the reference lists of identified trials for potentially eligible studies. None of the included trials had records of retractions or data corrections.

Data collection and analysis

Selection of studies

Two review authors (LLY and HZW) independently inspected citations from the searches and identified relevant records. One review author (HYD) independently re-inspected a random 20% sample of these records to ensure reliability. Where disputes arose, we acquired the full-text report for more detailed scrutiny. Three review authors (LLY, HZW, and MB) obtained and inspected full-text reports of the records meeting the review criteria. One review author (HYD) re-inspected a random 20% sample of the full-text reports to ensure reliable selection. We contacted the study authors for clarification to resolve discrepancies. We recorded the selection process in sufficient detail to complete a PRISMA 2020 flow diagram [60, 61].

For the reasons for exclusion of excluded studies, see Supplementary material 3 table. For characteristics of studies awaiting classification, see Supplementary material 4 table. For characteristics of ongoing studies, see Supplementary material 5 table.

We identified and collated multiple reports of the same trial under a single reference ID so that each trial, rather than each report, was the unit of interest in the review.

Data extraction and management

We used a data collection form for trial characteristics and outcome data that had been piloted on at least one trial in the review. Two review authors (HYD and LJL) extracted the following information from the included trials.

- Methods: trial registration, trial design, trial period, number of trial centres and location, trial setting, withdrawals/dropouts, and date of trial.
- Participants: mean age, age range, sex, diagnostic criteria, diagnostic methods, severity of condition, baseline liver function, smoking history, inclusion criteria and exclusion criteria.
- Intervention: intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: planned outcomes in the trial protocol, if available, for later comparison during risk of bias assessment.
- Time points of the outcome data.
- Notes: funding for trials, and notable conflicts of interest reported by the trial authors.

Two review authors (HYD and LJL) independently extracted outcome data from the included trials. We noted in the Supplementary material 2 table whether outcome data were not reported in a usable way. Any disagreements were resolved by consensus involving all review authors. We contacted the trial investigators in the case of inadequate information or discrepancies.

One review author (HZW) entered the data into the Supplementary material 2 table in RevMan software [62], and another review author (LLY) checked the data entry against the trial reports for accuracy.

For data only presented in figures, we extracted data using the open source software Plot Digitizer (plotdigitizer.sourceforge.net/).

Risk of bias assessment in included studies

Two review authors (PYZ and GJ) independently assessed risk of bias using the Cochrane RoB 2 tool (available at Risk of bias tools - Current version of RoB 2) and according to the *Cochrane Handbook for Systematic Reviews of Interventions* [63, 64, 65]. We assessed the effect of assignment to the intervention. We used the intention-to-treat (ITT) principle to assess the risk of bias domains whenever possible.

We assessed the following risk of bias domains [64, 66].

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of an outcome
- Bias in selection of the reported result

The signalling questions for these domains are shown in Supplementary material 9 [64]. The response options for the signalling questions are as follows.

- Yes
- Probably yes
- Probably no
- No
- No information

We judged overall risk of bias as follows.

- Low risk of bias: the trial is judged at low risk of bias for all domains for this result.
- Some concerns: the trial is judged to raise some concerns in at least one domain for this result, but is not at high risk of bias for any of the remaining domains.
- High risk of bias: the trial is judged at high risk of bias in at least one domain for this result, or the trial is judged to have some concerns for multiple domains such that our confidence in the result is substantially lowered.

The risk of bias assessment informs the GRADE approach for assessing the certainty of a body of evidence [67].

Our summary of findings tables (see Certainty of the evidence assessment) contain seven outcomes (i.e. all-cause mortality, liver-related mortality, serious adverse events, liver-related morbidity, health-related quality of life, non-serious adverse events, and biochemical response) for which we assessed the risk of bias at the longest follow-up time point.

Measures of treatment effect

We used Cochrane RevMan software [62].

Dichotomous/binary data

For dichotomous outcomes, we calculated and presented risk ratios (RR) with 95% confidence intervals (CIs). For binary data presented in the summary of findings tables, we calculated illustrative comparative risks where possible.

Continuous data

For continuous outcomes, we calculated and presented mean differences (MD) with 95% CI. We abstracted the MD and standard deviation (SD) between groups. If no SDs were available, we contacted the corresponding authors to obtain the missing data or imputed the data using the calculator provided in RevMan [62]. We estimated MD and its 95% CI when the trials measured the outcome of interest using the same tool; we estimated the standardised mean difference (SMD) and its 95% CI when the trials measured the same outcome in different ways. We interpreted SMDs as follows: SMD less than 0.40 for small intervention effects; SMD between 0.40 and 0.70 for moderate intervention effects; and SMD greater than 0.70 for large intervention effects [68]. Given that the SMD method does not correct for differences in direction of scale, if some scales increased with disease severity (e.g. a higher score indicates more severe condition) while others decreased (a higher score indicates less severe condition), we multiplied the mean values from one set of studies by –1 (or alternatively to subtract the mean from the maximum possible value for the scale) to ensure that all the scales pointed in the same direction, before standardisation [69].

For skewed data, we applied the following standards before inclusion.

For outcome data from studies with fewer than 200 participants:

- if a scale started from the number zero, we subtracted the lowest possible value from the mean, and divided this by the SD. When this value was lower than 1, we excluded the data. When this ratio was higher than 1 but below 2, we entered the data and tested whether their inclusion or exclusion changed the results substantially. Finally, if the ratio was larger than 2, we included the data because a skewness is less likely to be present [70];
- if a scale started from a positive value, we modified the calculation described above to take the scale's starting point into account. In these cases, skewness was present if 2 SD > (S – S_{min}), where S was the mean score and S_{min} was the minimum score [71].

For outcome data from trials with more than 200 participants, we entered all relevant data in the analysis irrespective of the above rules, as skewed data in large studies pose less of a problem.

Count data

When adverse events were recorded as count data, for the counts of common events such as nausea, diarrhoea, or vomiting, we treated the counts in the same way as continuous outcome data; for those counts of rare events, we treated the data as 'Poisson data', and calculated the rate ratio and presented the result in the Results section [72].

Unit of analysis issues

The unit of analysis was the participants with NAFLD as originally randomised to the trial groups. In trials with one experimental and one control parallel-group design, we compared the experimental intervention group versus the control group. In parallel-group trials with more than two intervention groups, we combined the vitamin E groups if possible and compared the combined group to the placebo or no-intervention group.

For analyses of cluster trials, we had planned to follow the formula in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [66]. After appropriate analyses, we would combine cluster-randomised trials with individually randomised trials using the generic inverse-variance method.

For cross-over trials, we planned to include only data from the first intervention period to avoid carry-over effects [66].

We listed all treatment arms in the Supplementary material 2 table, irrespective of whether they were used in the review.

Dealing with missing data

We contacted the original trial investigators of all 16 included trials to request missing outcome data. We investigated attrition bias (i.e. dropouts, losses to follow-up, and withdrawals). We performed an ITT analysis whenever possible [64]; otherwise, we performed a modified ITT analysis based on the trial authors' data. The modified ITT analysis adheres to the ITT principle, except that participants with missing outcome data are excluded [64].

For the critical outcomes, we included trial participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios [73].

- Extreme-case analysis favouring the experimental intervention ('best-worse' case scenario): none of the dropouts/participants lost from the experimental arm, but all the dropouts/participants lost from the control arm experienced the outcome, including all randomised participants in the denominator.
- Extreme-case analysis favouring the control intervention ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator.

We addressed the potential impact of missing data on the findings of the review in the Discussion section [72].

Reporting bias assessment

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of the results. These are described in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* [74]. We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We used funnel plots for outcomes where there were 10 or more trials. We did not use funnel plots where all trials were of similar sizes. We sought statistical advice on the interpretation of funnel plots when used.

We planned to perform adjusted rank correlation [75] and a regression asymmetry test [76] for detection of bias, and considered a P value less than 0.10 significant in these analyses.

Synthesis methods

Our primary analysis included all eligible trials where outcome data were provided. We used the random-effects model meta-analysis as our main analysis, according to Chapter 10 of *Cochrane Handbook for Systematic Reviews of Interventions* [72]. We presented all results with 95% CIs using RevMan software [62].

We planned to conduct meta-analysis only where it was meaningful to do so, as described in Chapter 12 (Table 12.1.a) of the *Cochrane Handbook for Systematic Reviews of Interventions* [77]. If meta-analysis was not possible, we would summarise the main findings and results of the included trials in a narrative format.

We investigated heterogeneity between trials by considering the I^2 statistic alongside the Chi^2 P value. We used a P value of 0.10 to determine statistical significance.

We interpreted the I^2 statistic as follows [72].

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Where we found considerable inconsistency, we attempted to determine the reasons for it by examining whether data had been entered correctly. We also attempted to inspect the graph visually and remove outlying trials to see if homogeneity was restored.

Where unanticipated clinical or methodological heterogeneity was obvious, we simply stated hypotheses regarding this for future reviews or versions of this review. We did not anticipate undertaking analyses relating to this.

Investigation of heterogeneity and subgroup analysis

We aimed to conduct the following subgroup analyses.

- Stages of NAFLD, NAFL compared to NASH (as NASH progresses from NAFL, the difference between the two can affect the outcomes of vitamin E treatment).
- Low-dose vitamin E (less than 400 IU per day) compared to high-dose vitamin E (400 IU per day or greater).
- Short-term treatment (less than one year) compared to long-term treatment (one year or more).
- Trials at low risk of bias or some concerns compared to trials at high risk of bias because trials at high risk of bias may overestimate beneficial intervention effects or underestimate harmful intervention effects.
- Trials at risk of for-profit support compared to trials without for-profit support because trials with for-profit support may overestimate beneficial intervention effects or underestimate harmful intervention effects [78].

We planned to perform subgroup analyses of the following outcomes.

- All-cause mortality
- Liver-related mortality
- Serious adverse events
- Liver-related morbidity
- HRQoL
- Proportion of people without a biochemical response
- Proportion of people without an imaging response

We used the formal test for subgroup interactions in RevMan [62]. For heterogeneous data, we planned to conduct a meta-regression between intervention effect and dose, or follow-up.

Equity-related assessment

We did not investigate equity-related characteristics in this review.

Sensitivity analysis

We planned to conduct the following sensitivity analyses for all outcomes.

- Excluding trials at high risk of bias.
- Conducting analyses using a fixed-effect model.
- Extreme-case analysis, favouring the experimental intervention (see Dealing with missing data).
- Extreme-case analysis, favouring the control intervention (see Dealing with missing data).
- Imputed values. We planned to exclude trials with imputed data, to assess the effects of including data from trials where we used imputed values. If there were substantial differences, we would not pool data from the excluded trials with the other trials contributing to the outcome and would present them separately.
- Assessment of imprecision with Trial Sequential Analysis. We planned to compare our GRADE assessment of imprecision with the Trial Sequential Analysis assessment of imprecision for our critical outcomes (i.e. all-cause mortality, liver-related mortality, and serious adverse events) [79, 80, 81].

Trial Sequential Analysis

We planned to use Trial Sequential Analysis on our critical outcomes to calculate the diversity-adjusted required information size (DARIS) and to reduce the risk of random errors due to sparse data and repetitive testing of accumulating data [82, 83, 84]. We calculated the DARIS using the following parameters for dichotomous outcomes [85]: the proportion of events in the control group estimated from the included trials; anticipated intervention effect (risk ratio reduction, RRR) of 20% based on the intervention effect suggested by trials at any risk of bias; alpha of 2.5% and a beta of 10% and diversity of the meta-analysis [81, 86].

We performed the meta-analyses sequentially by introducing trials in chronological order [86]. When more than one trial is published in one year, trials are added in alphabetical order, according to the name of the first author. On the basis of the required information size, we planned to construct the trial sequential monitoring boundaries for benefits, harms, and futility using the O'Brien-Fleming alpha-spending and beta-spending functions. If a trial sequential monitoring boundary is crossed before the required information size is reached, a sufficient level of evidence is attained, and the results of the meta-analysis may be considered conclusive, and no additional trials may be needed. Conversely, if a boundary is not crossed, the meta-analysis is inconclusive, and more trials may be needed to detect or reject a certain intervention effect. When the cumulative Z-curve crosses the futility boundaries, a sufficient level of evidence is reached that the two treatments do not differ in effect, and no additional trials may be needed. In all situations where no trial sequential monitoring boundaries are reached, further studies may be needed until the information size is reached, or until monitoring boundaries are crossed [79, 81].

In Trial Sequential Analysis where the cumulative Z-value does not cross the monitoring boundaries for benefit, harm, or futility, we planned to downgrade our assessment of imprecision by two levels

if the accrued number of participants was below 50% of the DARIS, and one level if it was between 50% and 100% of the DARIS [81]. We did not plan to downgrade for imprecision if the cumulative Z-value reached or crossed benefit, harm, futility, or DARIS [80, 81].

We performed this analysis with Trial Sequential Analysis software, version 0.9.5.10 beta [82, 83], using the random-effects model. However, as the monitoring boundaries were not crossed for the planned outcomes, and our result was similar to the GRADE assessment of imprecision, we did not present the Trial Sequential Analysis figures.

Certainty of the evidence assessment

We used the GRADE approach to interpret the findings of our review [68]. We used GRADEpro GDT software to create two summary of findings tables [87, 67], as both comparisons were clinically important. We used GRADE to assess the following outcomes: all-cause mortality, liver-related mortality, serious adverse events, liver-related morbidity, HRQoL, non-serious adverse events, and biochemical response. For each outcome, we provided the range of follow-up and the median.

Two review authors (HYD and LJL) performed the GRADE assessment based on the five GRADE considerations: risk of bias (we used the overall RoB 2 judgement to assess the methodological quality of trials), inconsistency of results (unexplained heterogeneity), indirectness of evidence (population, intervention, comparator, or outcome), imprecision of results (wide CIs), and publication bias. Any disagreements were resolved by consensus involving all review authors.

Regarding risk of bias, we used the overall risk of bias judgement to inform the GRADE assessment: 'low risk of bias' indicates 'no limitation' (no downgrading); 'some concerns' indicates either 'no limitation' or 'serious limitation' (certainty of evidence is downgraded one level); and 'high risk of bias' indicates either 'serious limitation' or 'very serious limitation' (certainty of evidence is downgraded two levels).

We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* [67]. We used the updated guidance on rating imprecision [88]. We calculated the optimal information size which helped us assess imprecision. We justified all decisions to downgrade the certainty of the evidence using footnotes, and made comments to aid the reader's understanding of the review where necessary.

We defined the levels of evidence as high, moderate, low, or very low following the 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.

We conducted the review according to our published protocol and have reported any deviations from it in the beginning of the Methods section.

Consumer involvement

No.

RESULTS

Description of studies

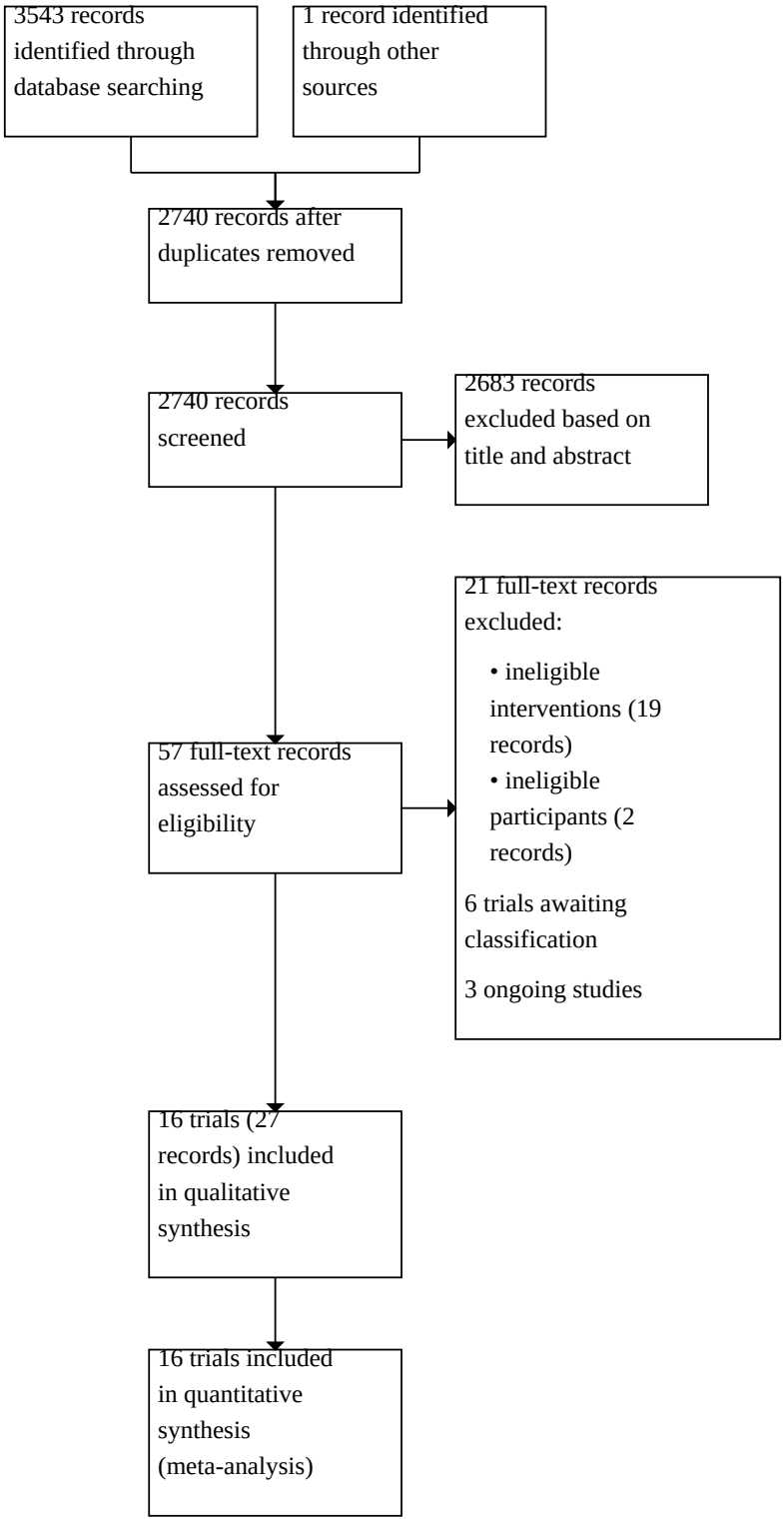
Results of the search

Our electronic searches dated 2 February 2024 identified 3543 references of possible interest: the Cochrane Hepato-Biliary Group Controlled Trials Register (107 records), CENTRAL (851 records), MEDLINE ALL Ovid (349 records), Embase Ovid (927 records), LILACS (24 records), Science Citation Index Expanded and Conference Proceedings Citation Index-Science (1022 records), CNKI (72 records), Wanfang Data (106 records), and SinoMed (85 records). We identified one additional reference by handsearching. After removal of 804 duplicate references, we screened 2740 references. We excluded 2683 clearly irrelevant records based on title and abstract and retrieved 57 full-text records for further assessment. We excluded 21 records (reasons for exclusion are provided in Supplementary material 3). Six trials are awaiting classification, and three trials are ongoing. We included a total of 16 trials (27 records) (Supplementary material 2).

None of the included trials had records of retractions or data corrections during the time of the review preparation.

The flow of references is shown in the PRISMA flowchart (Figure 1).

Figure 1. PRISMA flow diagram [60, 61]. Date of search 2 February 2024.



Included studies

We included 16 randomised clinical trials (Akcam 2011 [89]; Anushiravani 2019 [90]; Bril 2019 [91, 92]; Devarajan 2023 [93]; Dufour 2006 [94, 95]; Ekhlasi 2016 [96, 97]; Ghergherehchi 2013 [98]; Harrison 2003 [99]; Lavine 2011 [100]; Magosso 2013 [101]; Mir 2024 [102, 103]; Mohammadi 2022 [104]; Nobili 2006 [105, 106, 107]; Pervez 2020 [108, 109]; Sanyal 2010 [110, 111, 112, 113, 114]; Vajro 2004 [115]). The trials were published from 2003 to 2024.

All 16 trials used a parallel-group design, assessing in total two (Devarajan 2023; Ghergherehchi 2013; Harrison 2003; Magosso 2013; Nobili 2006; Pervez 2020; Vajro 2004), three (Akcam 2011; Bril 2019; Dufour 2006; Lavine 2011; Sanyal 2010), four (Ekhlasi 2016; Mir 2024; Mohammadi 2022), and five (Anushiravani 2019) intervention groups.

The trials were conducted in Iran (Anushiravani 2019; Ekhlasi 2016; Ghergherehchi 2013; Mohammadi 2022), the USA (Bril 2019; Harrison 2003; Lavine 2011; Sanyal 2010), Italy (Nobili 2006; Vajro 2004), Malaysia (Magosso 2013), Pakistan (Pervez 2020), Switzerland (Dufour 2006), India (Devarajan 2023; Mir 2024), and Turkey (Akcam 2011).

Two trials included outpatients (Akcam 2011; Anushiravani 2019); three trials were conducted in a clinic (Bril 2019; Ghergherehchi 2013; Mohammadi 2022); four trials were conducted at clinical centres (Dufour 2006; Ekhlasi 2016; Lavine 2011; Sanyal 2010); three trials were conducted in institutes (Harrison 2003; Pervez 2020; Vajro 2004); three trials were conducted at hospitals (Devarajan 2023; Nobili 2006; Mir 2024); and one trial included volunteers from a population-based study on the prevalence of NAFLD (Magosso 2013).

Participants

The 16 trials randomised a total of 1066 participants with NAFLD to vitamin E with or without vitamin C versus placebo or no intervention. The number of participants in the trials ranged from 28 to 167. Participants in five trials were with biopsy-proven NASH (Bril 2019; Dufour 2006; Ekhlasi 2016; Harrison 2003; Sanyal 2010), while participants in the remaining 11 trials were with NAFLD, with unknown stage.

Five trials included children and adolescents (Akcam 2011; Ghergherehchi 2013; Harrison 2003; Nobili 2006; Vajro 2004), while 11 trials included only adult participants (Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ekhlasi 2016; Harrison 2003; Magosso 2013; Mir 2024; Mohammadi 2022; Pervez 2020; Sanyal 2010).

One trial reported the baseline vitamin E status of participants as within normal limits (Vajro 2004). The remaining 15 trials did not report this information.

Experimental interventions

Vitamin E was administered alone in 14 trials (Akcam 2011; Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Lavine 2011; Magosso 2013; Mir 2024; Mohammadi 2022; Pervez 2020; Sanyal 2010; Vajro 2004), while vitamin E plus vitamin C was administered in two trials (Harrison 2003; Nobili 2006).

The daily dosages of vitamin E were measured in international units (IU) in 11 trials, ranging from 400 IU to 1000 IU (Akcam 2011; Anushiravani 2019; Bril 2019; Dufour 2006; Ekhlasi 2016; Harrison 2003; Lavine 2011; Mir 2024; Mohammadi 2022; Nobili 2006; Sanyal 2010), and in milligrams (mg) in five trials, ranging from 200 mg to 400 mg (Devarajan 2023; Ghergherehchi 2013; Magosso 2013; Pervez 2020; Vajro 2004). As 1 mg is equivalent to about 1.49 IU, the daily dosages of vitamin E ranged from 298 IU to 1000 IU in all 16 trials.

Six trials reported that the vitamin E was naturally made (i.e. extracted from plant oils) (Bril 2019; Dufour 2006; Lavine 2011; Mohammadi 2022; Pervez 2020; Sanyal 2010).

Control interventions

Thirteen trials used a placebo in the control group (Anushiravani 2019; Bril 2019; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Pervez 2020; Sanyal 2010; Vajro 2004), while the remaining three trials had a no-intervention control group (Akcam 2011; Devarajan 2023; Mir 2024).

The placebo was cornstarch in Ekhlasi 2016, sugar pill in Vajro 2004, and sucrose capsule in Pervez 2020. The remaining trials using placebo did not describe what it was made of (Anushiravani 2019; Bril 2019; Dufour 2006; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Sanyal 2010).

Co-interventions

Lifestyle (to increase physical activity including aerobic exercise like brisk walking, jogging, running, etc.) and diet (low-calorie diet) interventions were applied to all trial groups in 12 trials (Akcam 2011; Anushiravani 2019; Bril 2019; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Mir 2024; Mohammadi 2022; Nobili 2006; Pervez 2020; Sanyal 2010; Vajro 2004). The participants in Dufour 2006 were not actively asked to change their lifestyle or diet. Participants in Ekhlasi 2016 maintained unchanged dietary energy intake and physical activity throughout the trial. Participants in the Magosso 2013 trial were given no guidance about specific diets, but were advised about the overall health benefits of increased physical activity and a reduced-fat diet. Participants in the Devarajan 2023 trial had type 2 diabetes. They were asked to maintain diabetes treatments unchanged during the trial; treatments included oral hypoglycaemic agents and insulin.

One trial used ursodeoxycholic acid in both treatment groups (Dufour 2006).

Trials with more than two intervention groups

Five trials had three intervention groups (Akcam 2011; Bril 2019; Dufour 2006; Lavine 2011; Sanyal 2010); three trials had four groups (Ekhlasi 2016; Mir 2024; Mohammadi 2022); and one trial had five intervention groups (Anushiravani 2019). We analysed only the groups in which vitamin E alone or in combination with vitamin C was compared with placebo or no intervention. Information on the omitted experimental or control groups is provided in Supplementary material 2.

Dropouts

The number of dropouts in the included trials was 84 (7.9%) out of 1066 participants. There were no dropouts in six trials (Akcam 2011;

Anushiravani 2019; Ghergherehchi 2013; Mir 2024; Mohammadi 2022; Pervez 2020).

Follow-up

Follow-up ranged from 2 months to 24 months. Follow-up for all-cause mortality ranged from 18 months to 24 months (median 24 months). Follow-up for serious adverse events, HRQoL, and non-serious adverse events was 24 months. Follow-up ranged from 2 months to 24 months (median 6 months) for biochemical response and from 5 months to 24 months (median 6 months) for image response.

Outcomes

Three trials reported all-cause mortality (Bril 2019; Lavine 2011; Sanyal 2010). None of the included trials assessed liver-related mortality. Two trials assessed and reported HRQoL (Lavine 2011; Sanyal 2010). Two trials assessed and reported serious adverse events (Lavine 2011; Sanyal 2010). Three trials reported adverse events with details (Bril 2019; Lavine 2011; Sanyal 2010); eight trials reported zero adverse events (Akcam 2011; Anushiravani 2019; Devarajan 2023; Ekhlasi 2016; Magosso 2013; Nobili 2006; Pervez 2020; Vajro 2004); one trial reported "no significant side effects" without providing detailed information (Harrison 2003); one trial reported "the rates of adverse events were comparable between groups" without providing detailed information (Mir 2024); and three trials did not report data on adverse events (Dufour 2006; Ghergherehchi 2013; Mohammadi 2022). Fifteen trials reported biochemical response (Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Magosso 2013; Mir 2024; Mohammadi 2022; Nobili 2006; Pervez 2020; Sanyal 2010; Vajro 2004). The Akcam 2011 trial assessed biochemical response but did not report on it. Eight trials assessed and reported imaging assessment of fatty liver using ultrasound (Akcam 2011; Ghergherehchi 2013; Magosso 2013; Mir 2024; Mohammadi 2022; Nobili 2006; Pervez 2020; Vajro 2004). The Anushiravani 2019 trial assessed fatty liver but did not report on it.

Funding

Five trials were industry funded (Dufour 2006; Lavine 2011; Magosso 2013; Mohammadi 2022; Sanyal 2010). Five trials were funded through academic grants without financial support from a commercial entity (Anushiravani 2019; Bril 2019; Ekhlasi 2016; Ghergherehchi 2013; Pervez 2020). Three trials disclosed no external funding (Devarajan 2023; Harrison 2003; Mir 2024). Three trials provided no information on clinical trial support or sponsorship (Akcam 2011; Nobili 2006; Vajro 2004).

For details of the included studies, see Supplementary material 2.

Excluded studies

The reasons for exclusion of excluded studies are provided in Supplementary material 3. A summary is provided here.

- Reasons related to interventions or co-interventions, e.g. all groups used vitamin E (Abenavoli 2017 [116]; Afsharinasab 2020 [117]; Dallio 2020 [118]; Ebrahimi-Mameghani 2016 [119]; Ebrahimi-Mameghani 2017 [120]; Fouda 2021 [121]; Han 2014 [122]; Kugelmas 2003 [123]; Majnooni 2021 [124]; NCT04193982 [125]; NCT04781933 [126]; Palamaru 2017 [127]; Pervez 2022 [128]; Podszun 2020 [129]; Poulos 2022 [130]; Qin 2015 [131]; Wang 2008 [132]; Yoon 2021 [133]).
- Reasons related to participants, NASH was diagnosed on ultrasound or FibroScan only (Barbakadze 2020 [134]; Basu 2014 [135]).

Risk of bias in included studies

We assessed the risk of bias in our predefined outcomes with trial data (Supplementary material 6). Detailed risk of bias assessments are available on reasonable request.

Domain 1: bias arising from the randomisation process

All-cause mortality

We judged the risk of bias arising from the randomisation process to be low in the three trials reporting data on all-cause mortality (Bril 2019; Lavine 2011; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process.

Serious adverse events

We judged the risk of bias arising from the randomisation process to be low in the two trials reporting data on serious adverse events (Lavine 2011; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process.

Health-related quality of life

We judged the risk of bias arising from the randomisation process to be low in the two trials reporting data on health-related quality of life (Lavine 2011; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process.

Non-serious adverse events

We judged the risk of bias arising from the randomisation process to be low in the two trials reporting data on non-serious adverse events (Lavine 2011; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process.

Liver enzyme levels, serum ALT levels

We judged the risk of bias arising from the randomisation process to be low in 10 trials (Anushiravani 2019; Bril 2019; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Magosso 2013; Pervez 2020; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process. We judged the risk of bias arising from the randomisation process to be with some concerns in three trials because the authors reported only baseline characteristics of participants in the final analysis (Mohammadi 2022; Nobili 2006; Vajro 2004). Two of these trials did not provide details on how the random sequence was generated (Mohammadi 2022; Nobili 2006), and the trial by Vajro 2004 used sealed envelopes for the allocation of participants without a clear description of whether envelopes were sequentially numbered, opaque, or were only opened after they were irreversibly assigned to the participants.

Liver enzyme levels, serum AST levels

We judged the risk of bias arising from the randomisation process to be low in nine trials (Anushiravani 2019; Bril 2019; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Lavine 2011; Magosso 2013; Pervez 2020; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process. We judged the risk of bias arising from the randomisation process to be with some concerns in three trials (Devarajan 2023; Mohammadi 2022; Nobili 2006), as the authors reported only baseline characteristics of participants in the final analysis. The three trials did not provide details on how the random sequence was generated (Devarajan 2023; Mohammadi 2022; Nobili 2006).

Liver enzyme levels, serum ALP levels

We judged the risk of bias arising from the randomisation process to be low in the five trials reporting serum ALP levels (Ekhlasi 2016; Lavine 2011; Magosso 2013; Pervez 2020; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process.

Liver enzyme levels, serum GGT levels

We judged the risk of bias arising from the randomisation process to be low in three trials reporting serum GGT levels (Lavine 2011; Magosso 2013; Sanyal 2010), as they used random components in the sequence generation process, and there were no baseline differences to suggest problems with the randomisation process. We judged the risk of bias arising from the randomisation process to be some concerns in Nobili 2006 because the authors did not provide details on how the random sequence was generated.

Domain 2: bias due to deviations from intended interventions

All-cause mortality

We judged the risk of bias due to deviations from intended interventions to be low in the three trials reporting data on all-cause mortality (Bril 2019; Lavine 2011; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses.

Serious adverse events

We judged the risk of bias due to deviations from intended interventions to be low in the two trials reporting data on serious adverse events (Lavine 2011; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses.

Health-related quality of life

We judged the risk of bias due to deviations from intended interventions to be low in the two trials reporting data on health-related quality of life (Lavine 2011; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses.

Non-serious adverse events

We judged the risk of bias due to deviations from intended interventions to be low in the two trials reporting data on non-serious adverse events (Lavine 2011; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses.

Liver enzyme levels, serum ALT levels

We judged the risk of bias due to deviations from intended interventions to be low in five trials (Bril 2019; Ekhlasi 2016; Lavine 2011; Pervez 2020; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses. We judged the risk of bias due to deviations from intended interventions to be some concerns in eight trials (Anushiravani 2019; Dufour 2006; Ghergherehchi 2013; Harrison 2003; Magosso 2013; Mohammadi 2022; Nobili 2006; Vajro 2004): six of these trials did not report what analyses were applied (Anushiravani 2019; Dufour 2006; Ghergherehchi 2013; Harrison 2003; Mohammadi 2022; Nobili 2006); one trial was a single-blind trial using placebo as control (Vajro 2004); and one trial excluded participants with protocol violation (Magosso 2013).

Liver enzyme levels, serum AST levels

We judged the risk of bias due to deviations from intended interventions to be low in five trials (Bril 2019; Ekhlasi 2016; Lavine 2011; Pervez 2020; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses. We judged the risk of bias due to deviations from intended interventions to be some concerns in seven trials (Anushiravani 2019; Devarajan 2023; Dufour 2006; Ghergherehchi 2013; Magosso 2013; Mohammadi 2022; Nobili 2006): five of these trials did not report what analyses were applied (Anushiravani 2019; Dufour 2006; Ghergherehchi 2013; Mohammadi 2022; Nobili 2006); one trial was open-label (Devarajan 2023); and one trial excluded participants with protocol violation (Magosso 2013).

Liver enzyme levels, serum ALP levels

We judged the risk of bias due to deviations from intended interventions to be low in four trials (Ekhlasi 2016; Lavine 2011; Pervez 2020; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses. We judged the risk of bias due to deviations from intended interventions to be some concerns in one trial because participants with protocol violations were excluded (Magosso 2013).

Liver enzyme levels, serum GGT levels

We judged the risk of bias due to deviations from intended interventions to be low in two trials (Lavine 2011; Sanyal 2010), as they used randomised, double-blind, placebo-controlled designs to prevent the participants, carers, and people delivering the interventions from being aware of the assignment, and they employed ITT analyses. We judged the risk of bias due to deviations

from intended interventions to be some concerns in two other trials (Magosso 2013; Nobili 2006): the Magosso 2013 trial excluded participants with protocol violation, and the Nobili 2006 trial did not report what analyses were applied.

Domain 3: bias due to missing outcome data

All-cause mortality

We judged the risk of bias due to missing outcome data to be some concerns in the three trials reporting data on all-cause mortality (Bril 2019; Lavine 2011; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Serious adverse events

We judged the risk of bias due to missing outcome data to be some concerns in the two trials reporting data on serious adverse events (Lavine 2011; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Health-related quality of life

We judged the risk of bias due to missing outcome data to be some concerns in the two trials reporting data on health-related quality of life (Lavine 2011; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Non-serious adverse events

We judged the risk of bias due to missing outcome data to be some concerns in the two trials reporting data on non-serious adverse events (Lavine 2011; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Liver enzyme levels, serum ALT levels

We judged the risk of bias due to missing outcome data to be low in eight trials (Anushiravani 2019; Ekhlasi 2016; Ghergherehchi 2013; Harrison 2003; Mohammadi 2022; Nobili 2006; Pervez 2020; Vajro 2004), as four of the trials reported no missing data and included all participants in data analyses (Anushiravani 2019; Ghergherehchi 2013; Mohammadi 2022; Pervez 2020), and the remaining four trials reported one or two missing data in the treatment or control groups, but the numbers and reasons for missing data between groups were comparable (Ekhlasi 2016; Harrison 2003; Nobili 2006; Vajro 2004). We judged the risk of bias due to missing outcome data to be some concerns in five trials (Bril 2019; Dufour 2006; Lavine 2011; Magosso 2013; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Liver enzyme levels, serum AST levels

We judged the risk of bias due to missing outcome data to be low in seven trials (Anushiravani 2019; Devarajan 2023; Ekhlasi 2016; Ghergherehchi 2013; Mohammadi 2022; Nobili 2006; Pervez 2020), as four of the trials reported no missing data and included all participants in data analyses (Anushiravani 2019; Ghergherehchi 2013; Mohammadi 2022; Pervez 2020), and the remaining three trials reported one or two missing data in the treatment or control groups, but the numbers and reasons for missing data between groups were comparable (Devarajan 2023; Ekhlasi 2016; Nobili 2006). We judged the risk of bias due to missing outcome data to be some concerns in five trials (Bril 2019; Dufour 2006; Lavine 2011; Magosso 2013; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Liver enzyme levels, serum ALP levels

We judged the risk of bias due to missing outcome data to be low in two trials (Ekhlasi 2016; Pervez 2020), as the trial by Pervez 2020 reported no missing data and included all participants in data analyses, and the trial by Ekhlasi 2016 reported one missing data in both treatment and control groups, but the numbers and reasons for missing data between groups were comparable. We judged the risk of bias due to missing outcome data to be some concerns in three trials (Lavine 2011; Magosso 2013; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Liver enzyme levels, serum GGT levels

We judged the risk of bias due to missing outcome data to be low in one trial (Nobili 2006), as the trial reported two missing data in the control group and no missing data in the treatment group, but the numbers and reasons for missing data between groups were comparable. We judged the risk of bias due to missing outcome data to be some concerns in three trials (Lavine 2011; Magosso 2013; Sanyal 2010), as there were imbalances between numbers or reasons for missing data in these trials, meaning that missingness could be related to the true outcome in these trials.

Domain 4: bias in measurement of the outcome

All-cause mortality

We judged the risk of bias in measurement of the outcome to be low in the three trials reporting data on all-cause mortality (Bril 2019; Lavine 2011; Sanyal 2010), as it was a prespecified outcome; comparable methods of outcome measurement were used; and outcome assessors were blinded to intervention status.

Serious adverse events

We judged the risk of bias in measurement of the outcome to be low in the two trials reporting data on serious adverse events (Lavine 2011; Sanyal 2010), as it was a prespecified outcome; comparable methods of outcome measurement were used; and outcome assessors were blinded to intervention status.

Health-related quality of life

We judged the risk of bias in measurement of the outcome to be low in the two trials reporting data on health-related quality of life (Lavine 2011; Sanyal 2010), as it was a prespecified outcome; comparable methods of outcome measurement were used; and outcome assessors were blinded to intervention status.

Non-serious adverse events

We judged the risk of bias in measurement of the outcome to be low in the two trials reporting data on non-serious adverse

events (Lavine 2011; Sanyal 2010), as it was a prespecified outcome; comparable methods of outcome measurement were used; and outcome assessors were blinded to intervention status.

Liver enzyme levels, serum ALT levels

We judged the risk of bias in measurement of the outcome to be low in the 13 trials reporting data on serum ALT levels (Anushiravani 2019; Bril 2019; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Pervez 2020; Sanyal 2010; Vajro 2004), as it was a prespecified outcome; comparable methods of outcome measurement were used; and the outcome did not involve judgement.

Liver enzyme levels, serum AST levels

We judged the risk of bias in measurement of the outcome to be low in the 12 trials reporting data on serum AST levels (Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Pervez 2020; Sanyal 2010), as it was a prespecified outcome; comparable methods of outcome measurement were used; and the outcome did not involve judgement.

Liver enzyme levels, serum ALP levels

We judged the risk of bias in measurement of the outcome to be low in the five trials reporting data on serum ALP levels (Ekhlasi 2016; Lavine 2011; Magosso 2013; Pervez 2020; Sanyal 2010), as it was a prespecified outcome; comparable methods of outcome measurement were used; and the outcome did not involve judgement.

Liver enzyme levels, serum GGT levels

We judged the risk of bias in measurement of the outcome to be low in the four trials reporting data on serum GGT levels (Lavine 2011; Magosso 2013; Nobili 2006; Sanyal 2010), as it was a prespecified outcome; comparable methods of outcome measurement were used; and the outcome did not involve judgement.

Domain 5: bias in selection of the reported result

All-cause mortality

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in two trials reporting data on all-cause mortality (Bril 2019; Lavine 2011), as no previously published protocol was available for these trials.

Serious adverse events

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in one trial reporting data on serious adverse events (Lavine 2011), as no previously published protocol was available.

Health-related quality of life

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in one trial reporting data on health-related quality of life (Lavine 2011), as no previously published protocol was available.

Non-serious adverse events

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in one trial reporting data on non-serious adverse events (Lavine 2011), as no previously published protocol was available.

Liver enzyme levels, serum ALT levels

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in 12 trials reporting data on ALT levels (Anushiravani 2019; Bril 2019; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Pervez 2020; Vajro 2004), as no previously published protocol was available for these trials.

Liver enzyme levels, serum AST levels

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in 11 trials reporting data on AST levels (Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Pervez 2020), as no previously published protocol was available for these trials.

Liver enzyme levels, serum ALP levels

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in four trials reporting data on ALP levels (Ekhlasi 2016; Lavine 2011; Magosso 2013; Pervez 2020), as no previously published protocol was available for these trials.

Liver enzyme levels, serum GGT levels

We judged the risk of bias in selection of the reported result to be low in one trial (Sanyal 2010), as the analysis plan was published before unblinded outcome data were available to the trialists. We judged the risk of bias in selection of the reported result to be some concerns in three trials reporting data on GGT levels (Lavine 2011; Magosso 2013; Nobili 2006), as no previously published protocol was available for these trials.

Overall risk of bias judgement

All-cause mortality

We judged the overall risk of bias to be some concerns in the three trials reporting data on all-cause mortality (Bril 2019; Lavine 2011; Sanyal 2010), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Serious adverse events

We judged the overall risk of bias to be some concerns in the two trials reporting data on serious adverse events (Lavine 2011; Sanyal 2010), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Health-related quality of life

We judged the overall risk of bias to be with some concerns in the two trials reporting on health-related quality of life (Lavine 2011; Sanyal 2010), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Non-serious adverse events

We judged the overall risk of bias to be some concerns in the two trials reporting data on non-serious adverse events (Lavine 2011; Sanyal 2010), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Liver enzyme levels, serum ALT levels

We judged the overall risk of bias to be some concerns in the 13 trials reporting data on serum ALT levels (Anushiravani 2019; Bril 2019; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Harrison 2003; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Pervez 2020; Sanyal 2010; Vajro 2004), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Liver enzyme levels, serum AST levels

We judged the overall risk of bias to be some concerns in the 12 trials reporting data on serum AST levels (Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Lavine 2011; Magosso 2013; Mohammadi 2022; Nobili 2006; Pervez 2020; Sanyal 2010), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Liver enzyme levels, serum ALP levels

We judged the overall risk of bias to be some concerns in the five trials reporting data on serum ALP levels (Ekhlasi 2016; Lavine 2011; Magosso 2013; Pervez 2020; Sanyal 2010), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Liver enzyme levels, serum GGT levels

We judged the overall risk of bias to be some concerns in the four trials reporting data on serum GGT levels (Lavine 2011; Magosso 2013; Nobili 2006; Sanyal 2010), as we judged these trials to raise some concerns in at least one domain, but not to be at high risk of bias for any domain for this outcome.

Synthesis of results

Vitamin E compared with placebo or no intervention for people with NAFLD

See: Summary of findings 1

Critical outcomes

All-cause mortality

Three trials (351 participants) reported mortality at maximal follow-up of 18 months to 24 months (Bril 2019; Lavine 2011; Sanyal 2010). Causes of death were pneumonia and liver failure secondary to sepsis in a participant who had fibrosis in the Sanyal 2010 trial, suicide in the Lavine 2011 trial, and ischaemic and haemorrhagic stroke in two participants who had NASH in the Bril 2019 trial.

The effect of vitamin E on all-cause mortality (risk ratio (RR) 3.45, 95% confidence interval (CI) 0.57 to 20.86; I^2 = 0%; 3 trials, 351 participants, very low certainty evidence; Analysis 1.1) versus placebo or no intervention is very uncertain. Two trials included participants with biopsy-proven NASH (Bril 2019; Sanyal 2010), and one trial included participants with NAFLD (Sanyal 2010). Participants received vitamin E 400 IU twice daily in the Lavine 2011 and Bril 2019 trials, and vitamin E 800 IU daily in the Sanyal 2010 trial.

An insufficient number of trials precluded subgroup analysis.

Sensitivity analysis

- Fixed-effect meta-analysis showed a similar result to the random-effects model (RR 3.49, 95% CI 0.58 to 21.04; P = 0.97; I^2 = 0%; 3 trials, 351 participants); the Peto odds ratio (OR) method also showed a similar result (Peto OR 7.07, 95% CI 0.99 to 50.66; P = 1.00; I^2 = 0%; 3 trials, 351 participants).
- Best-worst-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group survived, and all those with missing outcome data in the control group died, vitamin E decreased all-cause mortality compared with placebo (RR 0.14, 95% CI 0.05 to 0.39; I^2 = 0%; 3 trials, 351 participants; Analysis 1.2).
- Worst-best-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group died, and all those with missing outcome data in the control group survived, vitamin E increased all-cause mortality compared with placebo (RR 14.07, 95% CI 2.73 to 72.57; I^2 = 0%; 3 trials, 351 participants; Analysis 1.3).
- Risk of bias. We judged the overall risk of bias in all trials reporting on this outcome to be some concerns, thereby precluding a sensitivity analysis excluding trials at high risk of bias.

Liver-related mortality

No trials reported liver-related mortality.

Serious adverse events (number of events)

We planned to classify adverse events as serious adverse events and non-serious adverse events following the definitions in the ICH Guidelines (54). One trial did not classify adverse events

in conformity with our protocol [136]. The trial authors stated: "vitamin E was well-tolerated overall, without significant adverse events", and they reported adverse events in affected parts of the body: cardiovascular adverse events, gastrointestinal adverse events, respiratory adverse events, and others (Bril 2019). Two trials reported serious adverse events (Lavine 2011; Sanyal 2010): mood alteration and suicide in the Lavine 2011 trial, and cardiac ischaemia and liver dysfunction in the Sanyal 2010 trial.

The effect of vitamin E versus placebo on serious adverse events is very uncertain (RR 1.91, 95% CI 0.30 to 12.01; I^2 = 18%; 2 trials, 283 participants; very low certainty evidence; Analysis 1.5).

An insufficient number of trials precluded subgroup analysis.

Sensitivity analysis

- Fixed-effect meta-analysis showed a similar result to the random-effects model (RR 2.19, 95% CI 0.50 to 9.62; I^2 = 18%; 2 trials, 283 participants); the Peto OR method also showed a similar result (Peto OR 2.39, 95% CI 0.53 to 10.66; P = 0.19; I^2 = 41%; 2 trials, 283 participants).
- Best-worst-case scenario analysis. When we assumed that none of the participants lost to follow-up in the experimental intervention group had serious adverse events, and all those with missing outcomes in the control group had serious adverse events, vitamin E decreased the risk of serious adverse events compared with placebo (RR 0.21, 95% CI 0.08 to 0.54; I^2 = 0%; 2 trials, 283 participants; Analysis 1.6).
- Worst-best-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group had serious adverse events, and none of those with missing outcomes in the control group had serious adverse events, vitamin E increased the risk of serious adverse events compared with placebo (RR 6.63, 95% CI 1.80 to 24.51; I^2 = 0%; 2 trials, 283 participants; Analysis 1.7).
- Risk of bias. We judged the overall risk of bias in all trials reporting on this outcome to be some concerns, thereby precluding a sensitivity analysis excluding trials at high risk of bias.

Important outcomes

Liver-related morbidity

No trials reported liver-related morbidity, such as gastrointestinal bleeding, ascites, hepatic encephalopathy, hepatorenal syndrome, or jaundice.

Health-related quality of life (HRQoL)

Two trials (251 participants) reported HRQoL (Lavine 2011; Sanyal 2010), with increasing scores indicating better quality of life. Sanyal 2010 included participants with biopsy-proven NASH, and Lavine 2011 included participants with NAFLD without stage information. Both trials used a vitamin E dosage of 800 IU. The Lavine 2011 trial reported final scores, while the Sanyal 2010 trial reported changes from baseline. Lavine 2011 used the Pediatric Quality of Life Inventory to assess quality of life (scores range from 0 to 100, with increasing scores indicating better quality of life). Sanyal 2010 used the 36-Item Short-Form Health Survey (SF-36) to assess quality of life (scores range from 0 to 100, with higher scores representing better health).

The effect of vitamin E versus placebo or no intervention on HRQoL, including physical health (mean difference (MD) 0.74, 95% CI −0.52 to 2.01; I^2 = 0%; 2 trials, 251 participants; very low certainty evidence; Analysis 1.9) and psychosocial health (MD −0.57, 95% CI −4.11 to 2.97; I^2 = 0%; 2 trials, 251 participants; very low certainty evidence; Analysis 1.10) is very uncertain.

An insufficient number of trials precluded subgroup analysis.

Sensitivity analysis

- Fixed-effect meta-analysis on HRQoL showed similar results to the random-effects model for both physical health (MD 0.74, 95% CI −0.52 to 2.01; I^2 = 0%; 2 trials, 251 participants) and psychosocial health (MD −0.57, 95% CI −4.11 to 2.97; I^2 = 0%; 2 trials, 251 participants).
- Risk of bias. We judged the overall risk of bias in all trials reporting on this outcome to be some concerns, thereby precluding a sensitivity analysis excluding trials at high risk of bias.

Non-serious adverse events

Seven trials (356 participants) reported zero adverse events in the groups included in this review (Akcam 2011; Anushiravani 2019; Devarajan 2023; Ekhlasi 2016; Magosso 2013; Pervez 2020; Vajro 2004), and three trials (136 participants) did not report on this outcome (Dufour 2006; Ghergherehchi 2013; Mohammadi 2022). Three trials (351 participants) reported adverse events with detailed information (Bril 2019; Lavine 2011; Sanyal 2010). The Bril 2019 trial reported adverse events, but the authors did not define whether an adverse event was serious or not, and the total number of events exceeded the number of participants in each group, that is, 32 participants had 39 adverse events in the placebo group, and 36 participants had 49 adverse events in the vitamin E group. These adverse events were atypical chest pain or epigastralgia, arrhythmia, diarrhoea/constipation, ALT/AST elevations, upper respiratory infection, sinusitis, bronchitis, and others. Adverse events reported in the Sanyal 2010 trial were hepatotoxicity, cataract, fracture, gastroenteritis, gout, infection, and others. Adverse events reported in the Lavine 2011 trial were pain, syncope, and unspecified adverse events. We included two trials in the meta-analysis on non-serious adverse events (Lavine 2011; Sanyal 2010). The vitamin E dosage was 800 IU, and follow-up time was 24 months in both trials.

The effect of vitamin E on non-serious adverse events versus placebo or no intervention is very uncertain (RR 0.86, 95% CI 0.64 to 1.17; I^2 = 40%; 2 trials, 283 participants; very low certainty evidence; Analysis 1.11) (rate ratio 0.88, 95% CI 0.46 to 1.68; P = 0.689).

An insufficient number of trials precluded subgroup analysis.

Sensitivity analysis

- Fixed-effect meta-analysis showed similar results to the random-effects model (RR 0.89, 95% CI 0.72 to 1.10; I^2 = 40%; 2 trials, 283 participants).
- Best-worst-case scenario analysis. When we assumed that none of the participants lost to follow-up in the experimental intervention group had adverse events, and all those with missing outcomes in the control group had adverse events, we found a similar result (RR 0.67, 95% CI 0.42 to 1.05; I^2 = 77%; 2 trials, 283 participants; Analysis 1.12).

- Worst-best-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group had adverse events, and none of those with missing outcomes in the control group had adverse events, we found a similar result (RR 1.04, 95% CI 0.85 to 1.26; I^2 = 0%; 2 trials, 283 participants; Analysis 1.13).
- Risk of bias. We judged the overall risk of bias in all trials reporting on this outcome to be some concerns, thereby precluding a sensitivity analysis excluding trials at high risk of bias.

Biochemical response

No trials reported the proportion of participants without a decrease in liver enzymes, such as ALT, AST, ALP, and GGT.

Thirteen trials (826 participants) reported biochemical indices of serum ALT, AST, ALP, and GGT levels (Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ekhlasi 2016; Ghergherehchi 2013; Lavine 2011; Magosso 2013; Mir 2024; Mohammadi 2022; Pervez 2020; Sanyal 2010; Vajro 2004). Six trials reported final scores (Anushiravani 2019; Bril 2019; Devarajan 2023; Dufour 2006; Ghergherehchi 2013; Mohammadi 2022), while the remaining seven trials reported changes from baseline for these serum liver enzymes (Ekhlasi 2016; Lavine 2011; Magosso 2013; Mir 2024; Pervez 2020; Sanyal 2010; Vajro 2004). The Mir 2024 trial reported changes in ALT levels from baseline by regression analysis, and we could not use these data. The Devarajan 2023 trial reported ALT and GGT levels in median (min, max), as these data were significantly skewed away from normality, so we excluded these data.

Serum ALT levels (MD −9.29, 95% CI −13.69 to −4.89; I^2 = 75%; 11 trials, 708 participants; moderate certainty evidence; Analysis 1.14) and AST levels (MD −4.90, 95% CI −7.24 to −2.57; I^2 = 31%; 11 trials, 695 participants; moderate certainty evidence; Analysis 1.15) are likely slightly lower in the vitamin E group compared with the control group receiving placebo or no intervention. Serum ALP levels may be slightly lower in the vitamin E group compared with the control group receiving placebo or no intervention, but the evidence is very uncertain (MD −5.21, 95% CI −9.88 to −0.54; I^2 = 53%; 5 trials, 416 participants; very low certainty evidence; Analysis 1.16). The effect of vitamin E versus placebo or no intervention on reducing GGT levels is very uncertain (MD −3.47, 95% CI −11.42 to 4.47; I^2 = 44%; 3 trials, 315 participants; very low certainty evidence; Analysis 1.17).

Subgroup analyses

- Stages of NAFLD (NAFL compared to NASH). This analysis was not possible as no trial included participants with NAFL.
- Dosages of vitamin E (<400 IU compared to ≥ 400 IU). The test for these subgroup differences indicated no statistically significant subgroup effect (ALT: P = 0.27; AST: P = 0.43), suggesting that daily dosage of vitamin E in comparison with placebo or no intervention does not modify the effect of vitamin E on reducing biochemical indices. However, as only one trial contributed data to the <400 IU subgroup, the analysis may not be able to detect subgroup differences. Furthermore, there was substantial unexplained heterogeneity between trials in the ≥ 400 IU subgroup (I^2 = 77%) for ALT levels. The validity of the treatment effect estimate for this subgroup is therefore uncertain, as individual trial results are inconsistent (Analysis 3.2; Analysis 3.5). An insufficient number of trials precluded subgroup analysis for ALP and GGT levels.
- Treatment time (<1 year compared to ≥ 1 year). The test for these subgroup differences indicated no statistically significant subgroup effect (ALT: P = 0.08; AST: P = 0.38), suggesting that treatment time does not modify the effect of vitamin E on reducing biochemical indices. However, there was substantial unexplained heterogeneity between trials within each of these subgroups (≥ 1 year: I^2 = 78%; <1 year: I^2 = 68%) for ALT levels. The validity of the treatment effect estimate for each subgroup is therefore uncertain, as individual trial results are inconsistent (Analysis 3.1; Analysis 3.4). An insufficient number of trials precluded subgroup analysis for ALP and GGT levels.
- Risk of bias (low risk of bias/some concerns compared to high risk of bias). This analysis was not possible as all trials had some concerns.
- Support (with for-profit support compared to without for-profit support). The test for these subgroup differences indicated no statistically significant subgroup effect (ALT: P = 0.13; AST: P = 0.40), suggesting that the type of support does not modify the effect of vitamin E in comparison with placebo or no intervention on reducing biochemical indices. However, as a smaller number of trials (< 5) contributed data to the for-profit subgroup than to the without-for-profit subgroup, the analysis may not be able to detect subgroup differences. Furthermore, there was substantial unexplained heterogeneity between trials in the for-profit subgroup for ALT (I^2 = 83%). The validity of the treatment effect estimate for each subgroup is therefore uncertain, as individual trial results are inconsistent (Analysis 3.3; Analysis 3.6). An insufficient number of trials precluded subgroup analysis for ALP and GGT levels.

Sensitivity analysis

- Fixed-effect meta-analyses showed similar results to the random-effects model on biochemical responses.
- Risk of bias. We judged the overall risk of bias in all trials reporting on this outcome to be some concerns, thereby precluding a sensitivity analysis excluding trials at high risk of bias.

Imaging response

Six trials (334 participants) reported imaging (ultrasound) response (Akcam 2011; Ghergherehchi 2013; Magosso 2013; Mohammadi 2022; Pervez 2020; Vajro 2004). The effect of vitamin E versus placebo or no intervention on reducing steatosis in ultrasound (RR 0.82, 95% CI 0.66 to 1.00; I^2 = 29%; 4 trials, 236 participants; Analysis 1.18) and on proportion of participants without a normal ultrasound (RR 0.87, 95% CI 0.66 to 1.13; I^2 = 63%; 4 trials, 256 participants; Analysis 1.21) is unclear.

The Akcam 2011 trial stated NAFLD was assessed according to the hyperechogenicity of the liver tissue, the discrepancy between the liver and diaphragm, and visibility of vascular structures. The ultrasonographic criteria of liver-kidney echo discrepancy, echo penetration into the deep portion of the liver, and clarity of liver blood vessel structures were used to diagnose fatty liver in the Vajro 2004 trial. The remaining four trials did not state or provide sufficient detail on how liver steatosis was measured by ultrasound.

An insufficient number of trials precluded subgroup analysis.

Sensitivity analysis

- Fixed-effect meta-analysis compared with the random-effects model analysis showed different results for vitamin E reducing steatosis on ultrasound imaging (RR 0.76, 95% CI 0.63 to 0.92; I^2 = 29%; 4 trials, 236 participants) and for the proportion of participants without a normal ultrasound (RR 0.83, 95% CI 0.71 to 0.97; I^2 = 63%; 4 trials, 256 participants).
- Best-worst-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group had reduced steatosis on ultrasound, and all those with missing outcomes in the control group did not have a reduction on ultrasound, we found a similar result (RR 0.73, 95% CI 0.50 to 1.05; I^2 = 77%; 4 trials, 236 participants; Analysis 1.19). When we assumed that all participants lost to follow-up in the experimental intervention group had a normal ultrasound, and all those with missing outcomes in the control group did not have a normal ultrasound, we found a similar result (RR 0.70, 95% CI 0.37 to 1.32; I^2 = 90%; 4 trials, 256 participants; Analysis 1.22).
- Worst-best-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group did not have a reduction on ultrasound, and all those with missing outcomes in the control group had reduced steatosis on ultrasound, we found a similar result (RR 0.89, 95% CI 0.76 to 1.05; I^2 = 7%; 4 trials, 236 participants; Analysis 1.20). When we assumed that all participants lost to follow-up in the experimental intervention group did not have a normal ultrasound result, and all those with missing outcomes in the control group had a normal ultrasound result, we found a similar result (RR 0.96, 95% CI 0.73 to 1.25; I^2 = 57%; 4 trials, 256 participants; Analysis 1.23).
- Risk of bias. We judged the overall risk of bias in all trials reporting on this outcome to be some concerns, thereby precluding a sensitivity analysis excluding trials at high risk of bias.

Vitamin E plus vitamin C compared with placebo for people with NAFLD

See: Summary of findings 2

Critical outcomes

All-cause mortality

No trials reported data on all-cause mortality.

Liver-related mortality

No trials reported data on liver-related mortality.

Serious adverse events

No trials reported data on serious adverse events.

Important outcomes

Liver-related morbidity

No trials reported data on liver-related morbidity.

Health-related quality of life (HRQoL)

No trials reported data on HRQoL.

Non-serious adverse events

One trial reported "no significant side effects" (Harrison 2003), and the other trial reported no side effects or adverse events (Nobili 2006).

Biochemical response

No trials reported the proportion of participants without a decrease in liver enzymes, such as ALT, AST, ALP, and GGT.

Two trials (139 participants) reported final scores of ALT, AST, and GGT (Harrison 2003; Nobili 2006), for a follow-up of six months (Harrison 2003) and 12 months (Nobili 2006).

The effect of vitamin E plus vitamin C versus placebo on reducing ALT levels (MD −0.50, 95% CI −4.58 to 3.58; I^2 = 0%; 2 trials, 133 participants; very low certainty evidence; Analysis 2.7), AST levels (MD 0.09, 95% CI −3.39 to 3.57; 1 trial, 88 participants; very low certainty evidence; Analysis 2.8), and GGT levels (MD 1.58, 95% CI −3.22 to 6.38; 1 trial, 88 participants; very low certainty evidence; Analysis 2.9) is very uncertain.

An insufficient number of trials precluded subgroup analysis.

Sensitivity analysis

- Fixed-effect meta-analysis showed the same results as random-effects meta-analysis for ALT levels (MD −0.50, 95% CI −4.58 to 3.58; I^2 = 0%; 2 trials, 133 participants), AST levels (MD 0.09, 95% CI −3.39 to 3.57; 1 trial, 88 participants), and GGT levels (MD 1.58, 95% CI −3.22 to 6.38; 1 trial, 88 participants).
- Risk of bias. We judged the overall risk of bias in all trials reporting on this outcome to be some concerns, thereby precluding a sensitivity analysis excluding trials at high risk of bias.

Imaging response

One trial (88 participants) reported imaging (ultrasound) response during a follow-up of 12 months (Nobili 2006).

The effect of vitamin E plus vitamin C versus placebo on reducing steatosis in ultrasound (RR 1.91, 95% CI 0.79 to 4.64; 1 trial, 88 participants; Analysis 2.10) and on the proportion of participants without a normal ultrasound (RR 0.96, 95% CI 0.87 to 1.05; 1 trial, 88 participants; Analysis 2.13) is unclear.

An insufficient number of trials precluded subgroup analysis.

Sensitivity analysis

- As there was only one trial, we did not perform a fixed-effect meta-analysis as the result would not change.
- Best-worst-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group had reduced steatosis in ultrasound, and all those with missing outcomes in the control group did not have a reduction in ultrasound, we found a similar result (RR 1.50, 95% CI 0.68 to 3.32; P = 0.32; 1 trial, 90 participants; Analysis 2.11). When we assumed that all participants lost to follow-up in the experimental intervention group had a normal ultrasound, and all those with missing outcomes in the control group did not have a normal ultrasound, we found a similar result (RR 1.00, 95% CI 0.90 to 1.12; 1 trial, 90 participants; Analysis 2.14).

- Worst-best-case scenario analysis. When we assumed that all participants lost to follow-up in the experimental intervention group did not have a reduction in ultrasound, and all those with missing outcomes in the control group had reduced steatosis in ultrasound, we found a similar result (RR 2.00, 95% CI 0.82 to 4.86; P = 0.13; 1 trial, 90 participants; Analysis 2.12). When we assumed that all participants lost to follow-up in the experimental intervention group did not have a normal ultrasound, and all those with missing outcomes in the control group had a normal ultrasound, we found a similar result (RR 1.05, 95% CI 0.92 to 1.20; P = 0.13; 1 trial, 90 participants; Analysis 2.15).
- Risk of bias. Only one trial reported image response, thereby precluding sensitivity analysis excluding trials at high risk of bias.

Reporting biases

Analyses 1.14 and 1.15 included more than 10 trials, so we created two funnel plots (Figure 2; Figure 3). We deemed the risk of publication bias to be low.

Figure 2. The risk of publication bias is low.

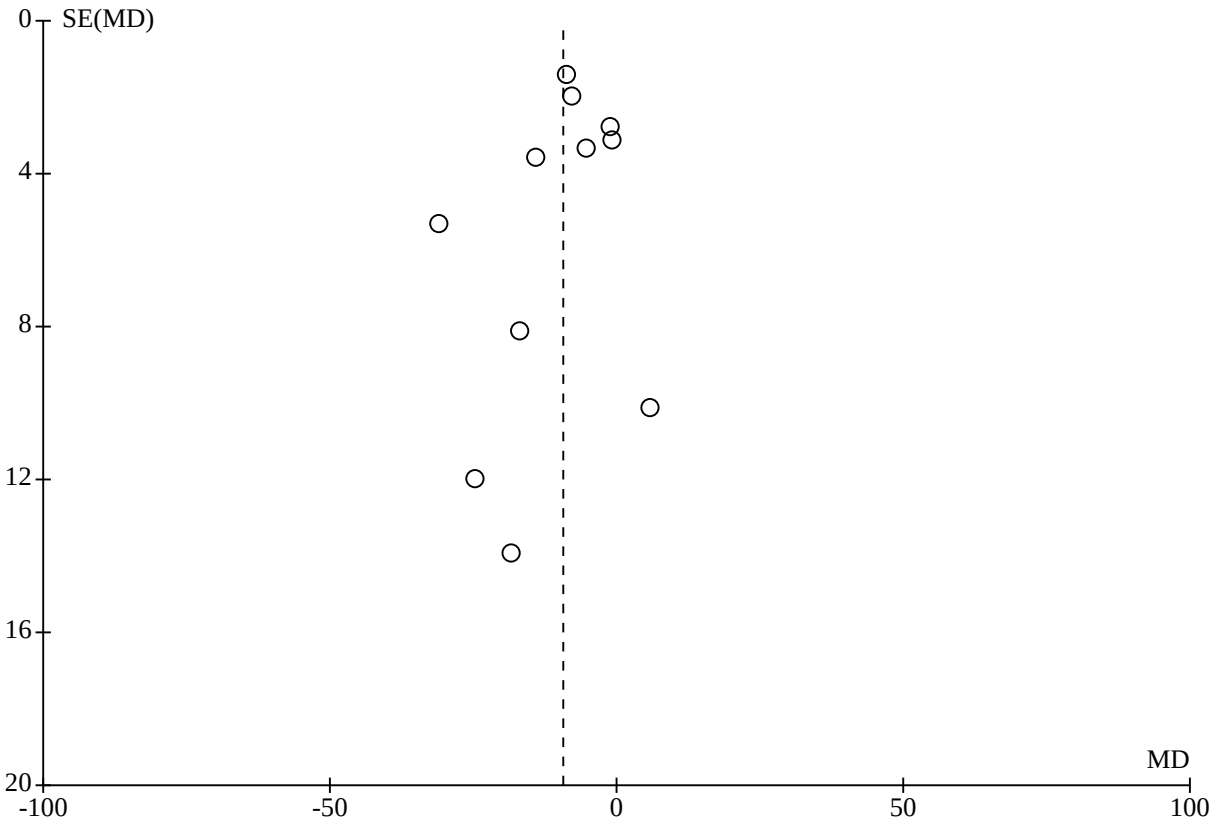
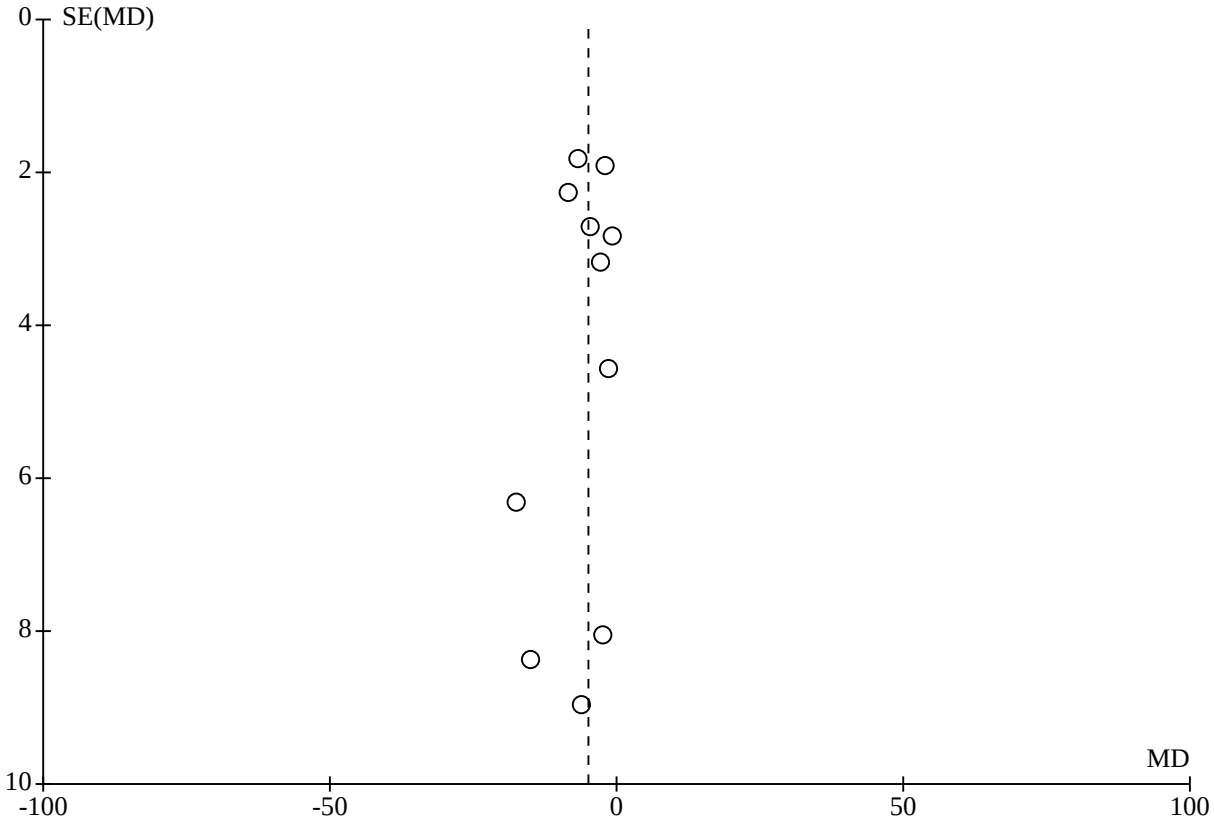


Figure 3. The risk of publication bias is low.



DISCUSSION

Summary of main results

The evidence for the effect of vitamin E alone or vitamin E combined with vitamin C on all-cause mortality, serious adverse events, HRQoL, non-serious adverse events, and ultrasound changes is very uncertain. There were no data on liver-related mortality or liver-related morbidity. Regarding the effect of vitamin E on biochemical response, there were no data on the proportion of participants without a decrease in liver enzymes. Vitamin E likely slightly reduces serum ALT and AST levels. The evidence for the effect of vitamin E alone or combined with vitamin C on reducing serum ALP and GGT levels is very uncertain.

The results of our systematic review should be interpreted cautiously because the overall risk of bias for the outcomes investigated and reported in the included trials was some concerns, and we found significant heterogeneity in the analyses of biochemical indices. Furthermore, the numbers of participants and trials that provided the data for our critical outcomes were low, which adds to the risk of both type I and type II errors.

Limitations of the evidence included in the review

We used GRADEpro GDT to construct summary of findings tables. We calculated the optimal information size when rating imprecision with Trial Sequential Analysis. The certainty of evidence was very low for mortality, serious adverse events, HRQoL, and non-serious adverse events. The certainty of evidence was moderate for biochemical changes to serum ALT and AST levels, and heterogeneity was substantial for serum ALT levels. The certainty of evidence was very low for biochemical changes to serum ALP and GGT levels. The overall risk of bias for the outcomes investigated and reported in the included trials was some concerns.

We include all eligible randomised clinical trials up to 2 February 2024. We found 16 randomised trials involving 1066 participants. We found significant heterogeneity in the analyses of biochemical indices, which decreases the precision and power of our analyses. Our analyses revealed that outcome reporting was missing in 7.9% of trial participants. Accordingly, our 'best-worst-case' and 'worst-best-case' analyses on all-cause mortality and serious adverse events revealed quite different results. Although these extreme sensitivity analyses are unlikely scenarios, they reveal how missing numbers of participants can substantially change findings from showing benefit to showing a null effect, or possibly even a harmful effect. We therefore advise critical evaluation of the evidence. Regarding ultrasound response, the fixed-effect model result showed narrower CIs, while the random-effects model showed wider CIs and included the null value of 1. We, therefore, also advise critical evaluation of the evidence.

For the outcomes serious adverse events, HRQoL, non-serious adverse events, and ultrasound response, we were unable to perform subgroup analyses according to stages of NAFLD (NAFL compared to NASH), daily dosages of vitamin E (< 400 IU compared to ≥ 400 IU), treatment time (< 1 year compared to ≥ 1 year), and support (with for-profit support compared to without

for-profit support). Regarding biochemical indices, we detected no statistically significant subgroup differences, suggesting that vitamin E dosage, treatment time, and for-profit support do not modify the effect of vitamin E on reducing biochemical indices when compared to placebo or no intervention. However, trials and participants contributing data to each subgroup were not equal, meaning that the analysis may not be able to detect subgroup differences. Furthermore, there was substantial unexplained heterogeneity between trials within some subgroups. The validity of the treatment effect estimate for this subgroup is therefore uncertain, as individual trial results are inconsistent.

The findings of this review were limited because the numbers of trials and participants were small; data on some outcomes in subgroup analyses were based on one trial only; and there were no data on liver-related mortality, liver-related morbidity, and proportion of participants without a decrease in liver enzymes.

The certainty of the evidence for the clinically relevant outcomes was mainly very low, indicating that further research is likely to have an important impact on our confidence in the estimate of effect.

Limitations of the review processes

Certain limitations of this review warrant consideration. As with all systematic reviews, our findings and interpretations are limited by the certainty and quantity of the available evidence on the effects of vitamin E alone or in combination with other vitamins or minerals on NAFLD. The duration of the intervention and follow-up were short in some trials, making it difficult to establish the certainty of the effects of vitamin E. It should be noted that liver-related complications due to NAFLD are expected to develop over 8 to 28 years [36]. None of the included trials assessed the effect of vitamin E on the different types of NAFLD, given that NAFL is a more benign condition, and people with NASH are at risk of progression from fibrosis to cirrhosis and development of hepatocellular carcinoma.

There are currently no validated surrogate outcome measures in hepatology, and the usage of non-validated surrogate outcomes may lead to misleading conclusions. Most of the included trials examined normal levels or decrease of biochemical indices and liver steatosis as surrogate outcomes for successful treatment. However, these outcomes do not definitively mean significant improvement in clinical outcomes. Furthermore, the included trials mainly used sonography to evaluate liver steatosis, but this technique is qualitative, and sonographic criteria for different degrees of steatosis are lacking. Most trials did not clearly state how liver steatosis was measured, which could have influenced our results.

The overall risk of bias for the outcomes investigated and reported in the included trials was some concerns.

Insufficient information precluded some of our preplanned subgroup and sensitivity analyses (which were underpowered).

Another limitation is that it was not possible to investigate whether reduction in the biochemical and ultrasound indices was a consequence of controlled adherence to diet and lifestyle modifications, as only one trial reported the relationship between biochemical and ultrasound changes and low-calorie diet adherence.

Agreements and disagreements with other studies or reviews

We found seven reviews that reported the efficacy of vitamin E in NAFLD [137, 51, 138, 139, 52, 140, 141].

A 2020 review by Abdel-Maboud and colleagues assessed the efficacy of vitamin E, alone or combined, on clinical outcomes in people with NAFLD and included 15 randomised trials involving 1317 participants [137]. We included eight of these trials in our review; the remaining seven trials did not fulfil our inclusion criteria as four trials used vitamin E plus other medicines as an experimental intervention; data on vitamin E plus vitamin C versus placebo were not accessible in one trial; lifestyle interventions between groups were different in one trial; and one trial was an extension of a trial already included in our review.

A 2019 review by Amanullah and colleagues assessed the efficacy of vitamin E on clinical outcomes of people with NAFLD and included nine randomised trials involving 889 participants [51]. We included six of these trials in our review; the remaining three trials did not fulfil our inclusion criteria as one trial used silymarin plus vitamin E as an experimental intervention; one trial used atorvastatin plus vitamins E and C as an experimental intervention; and one trial was a post hoc analysis of a trial already included in our review.

A 2022 review by Karedath and colleagues assessed the efficacy of vitamin E treatment compared with other treatments in people with NAFLD and included nine randomised trials involving 569 participants [138]. We included six of these trials in our review; the remaining three trials did not fulfil our inclusion criteria as one trial used silymarin plus vitamin E as an experimental intervention; lifestyle interventions differed between groups in one trial; and one trial was an extension of a trial already included in our review.

A 2021 review by Lin and colleagues assessed the efficacy of vitamin E on clinical outcomes of people with NAFLD and included 10 studies involving 625 participants [139]. We included five of these trials in our review; the remaining five studies did not fulfil our inclusion criteria as one study was not a randomised trial; one trial used vitamin E plus other medicines as an experimental intervention; lifestyle interventions differed between groups in one trial; and two trials were extensions of a trial already included in our review.

A 2015 review by Sato and colleagues assessed the efficacy of vitamin E on liver function and histology in people with NAFLD/NASH and included five randomised trials involving 401 participants [52]. We included all five of these trials in our review.

A 2021 review by Vadarlis and colleagues assessed the effects of vitamin E on biochemical and histological parameters in adults with NAFLD and included eight randomised trials involving 923 participants [140]. We included seven of these trials in our review; the remaining one trial diagnosed the NASH participants by ultrasound and therefore did not fulfil our inclusion criteria.

A 2023 review by Vogli and colleagues assessed the effects of vitamin E on biochemical parameters in people with NAFLD and included 12 studies involving 794 participants [141]. We included nine of these studies; the remaining three studies did not fulfil our inclusion criteria as one study was not a randomised trial; lifestyle

interventions differed between groups in one trial; and NASH was diagnosed by ultrasound in one trial.

Our results are consistent with the six reviews that found that vitamin E reduced levels of ALT and AST [28, 51, 138, 52, 140, 141]. Regarding ALP, the Sato and colleagues' review found a reduction based on two trials [52], and our review found similar results based on very low certainty evidence. The Lin and colleagues' review found that vitamin E had no effect on ALT, AST, and GGT [139]. One Cochrane review reported that vitamin E might increase enzyme levels [50], while our review found a different result. None of the seven reviews reported results on all-cause mortality, liver-related mortality, serious adverse events, liver-related morbidity, HRQoL, non-serious adverse events, or imaging response.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence for the effects of vitamin E, administered alone, in people with non-alcoholic fatty liver disease (NAFLD) (metabolic dysfunction-associated steatotic liver disease (MASLD)) on clinical outcomes such as all-cause mortality, serious adverse events, health-related quality of life, and non-serious adverse events is very uncertain. Vitamin E likely slightly reduces serum alanine aminotransferase (ALT) and aspartate transaminase (AST) levels. It also may slightly reduce alkaline phosphatases (ALP) levels, although the evidence is very uncertain. Vitamin E may or may not affect gamma-glutamyl transpeptidase (GGT) levels, and steatosis diagnosed on ultrasound. None of the trials reported on liver-related mortality, liver-related morbidity, or proportion of participants without a decrease in liver enzymes.

The evidence for the effects of vitamin E plus vitamin C in people with NAFLD (MASLD) on liver enzyme levels and steatosis diagnosed on ultrasound is very uncertain. None of the trials reported on all-cause mortality, liver-related mortality, serious adverse events, liver-related morbidity, health-related quality of life, non-serious adverse events, or proportion of participants without a decrease in liver enzymes.

The decision for a person with NAFLD (MASLD) to start vitamin E therapy, in the absence of diet and lifestyle change, should balance the benefits and disadvantages, and integrate the person's values and preferences. Lifestyle modifications were a co-intervention in 12 out of the 16 trials.

Implications for research

More evidence is needed before any conclusions can be drawn on the safety and effect of vitamin E alone or in combination with vitamin C in people with NAFLD (MASLD), as the certainty of the evidence was generally very low, and there was significant heterogeneity in some analyses. More randomised clinical trials assessing any relationship between vitamin E effect and adherence to lifestyle modification would seem appropriate. The effect of vitamin E on health-related quality of life also deserves further investigation. Future trials should be designed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (www.spirit-statement.org) and reported according to the CONSORT statement (www.consortstatement.org).

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD015033.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Risk of bias

Supplementary material 7 Analyses

Supplementary material 8 Data package

Supplementary material 9 Descriptions of the bias domains in RoB 2 tool for randomised trials

ADDITIONAL INFORMATION

Acknowledgements

Special thanks to Dimitrinka Nikolova and Sarah Louise Klingenberg from the Cochrane Hepato-Biliary Group (CHBG), Rachel Richardson and Emma Axon in the Cochrane Central Executive Team, and Jian Gao Fan and Yi Wen Shi in Xin Hua Hospital for their unlimited help in preparing this review.

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the CHBG through its investment in the Copenhagen Trial Unit, Centre for Clinical Intervention Research, the Capital Region, Rigshospitalet, Copenhagen, Denmark. Disclaimer: the views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

The following people from the Cochrane Hepato-Biliary Editorial Team conducted the editorial process for this review.

- Sign-off Editor (final editorial decision): Christian Gluud, Co-ordinating Editor, Denmark
- Contact Editor (provided editorial decision): Rosa Simonetti, Italy
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the review): Dimitrinka Nikolova, Denmark
- Peer reviewers (provided clinical and content review comments): Goran Bjelakovic, Serbia; Stefano Bellentani, Switzerland; Azita Hekmatdoost, Iran; Mark Aninakwah Asante, Denmark
- Rachel Richardson, Associate Editor, Evidence Production and Methods Department, Cochrane, UK; Emma Axon, Evidence Synthesis Methodology Editor, Methods Support Unit, Evidence Production and Methods Directorate, Cochrane Central Executive Team, UK

Cochrane Central Executive Team.

- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service

Contributions of authors

HW: formulated the research question; collected, entered, analysed, and interpreted data; assisted with GRADE assessment; wrote the review with suggestions from team members.

HD: extracted data, rated the certainty of the evidence, assisted with data synthesis, interpreted results, commented on the review.

LY: collected data, assisted with data entry, commented on the review.

LL: extracted data, rated the certainty of the evidence, commented on the review.

JL: assisted with Background description, interpreted results, commented on the review.

PZ: assessed risk of bias, commented on the review.

MB: collected data, interpreted results, commented on the review.

GJ: formulated the research question, assessed risk of bias, assisted with writing the review, commented on the review.

All authors approved the review for publication.

Declarations of interest

HW: none

HD: none

LY: none

LL: none

JL: none

PZ: none

MB: none

GJ: none

Sources of support

Internal sources

- EBM Center of TCM, Shanghai University of Traditional Chinese Medicine, Shanghai, China

  Support to HD
- Shanghai University of Traditional Chinese Medicine, Shanghai, China

  Support to JL and GJ
- Clinic of Gastroenterohepatology, University Clinical Centre Nis, Nis, Serbia

  Support to MB
- Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

  Support to LY and PZ
- Department of Gastroenterology, Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

  Support to HW and JL

External sources

- National Natural Science Foundation of China (No. 82174250, 81703986, 81704018, 81873254, 81873183), China Clinical Research Plan of SHDC (No 16CR4024A), ChinaZY (2018-2020)-FWTX-4018, and ChinaZY (2018 2020) CCCX-2002-01, China, China

  Provided funds for the preparation, drafting, revision, and publication of the review as gold open access. The funding is non-commercial granting from the government, and it had no role in the design, conduct, or publication of the review.
- Cochrane Hepato-Biliary Group Editorial Team, Denmark

  Provided guidance to authors during the entire review process. CHBG editorial staff ran the peer-review process.

History

Protocol first published: Issue 5, 2022

Registration and protocol

Wen H, Deng H, Yang L, Li L, Lin J, Zheng P, Ji G. Vitamin E for people with non-alcoholic fatty liver disease (Protocol). Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD015033. DOI: 10.1002/14651858.CD015033.

Data, code and other materials

Supplementary material 7, Supplementary material 8.

REFERENCES

1. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;**77**(5):1797-835.

2. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al; NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Journal of Hepatology* 2023;**23**:S0168-8278.

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

4. Song SJ, Lai JC, Wong GL, Wong VW, Yip TC. Can we use old NAFLD data under the new MASLD definition? *Journal of Hepatology* 2024;**80**(2):e54-6.

5. Ballestri S, Nascimbeni F, Romagnoli D, Lonardo A. The independent predictors of non-alcoholic steatohepatitis and its individual histological features: insulin resistance, serum uric acid, metabolic syndrome, alanine aminotransferase and serum total cholesterol are a clue to pathogenesis and candidate targets for treatment. *Hepatology Research* 2016;**46**:1074–87.

6. Li Q, Dhyani M, Grajo JR, Sirlin C, Samir AE. Current status of imaging in nonalcoholic fatty liver disease. *World Journal of Hepatology* 2018;**10**(8):530-42.

7. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. *Lancet* 2021;**397**(10290):2212-24. [DOI: 10.1016/S0140-6736(20)32511-3]

8. Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. *Journal of Pediatrics* 2013;**162**:496-500.

9. Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic fatty liver disease: a pathogenic duo. *Endocrine Reviews* 2013;**34**:84-129.

10. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology* 2023;**77**(4):1335-47.

11. Li J, Ha A, Rui F, Zou B, Yang H, Xue Q, et al. Meta-analysis: global prevalence, trend and forecasting of non-alcoholic fatty liver disease in children and adolescents, 2000-2021. *Alimentary Pharmacology & Therapeutics* 2022;**56**(3):396-406.

12. Younossi ZM, Henry L, Bush H, Mishra A. Clinical and economic burden of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Clinical Liver Disease* 2018;**22**(1):1-10.

13. 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.

14. Lonardo A, Nascimbeni F, Mantovani A, Targher G. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? *Journal of Hepatology* 2018;**68**(2):335-52.

15. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. *Nature Reviews Gastroenterology & Hepatology* 2017;**14**(1):32-42.

16. Byrne CD, Targher G. NAFLD: a multisystem disease. *Journal of Hepatology* 2015;**62**(1 Suppl):S47-64.

17. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology* 1998;**114**:842-5.

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

19. Azzu V, Vacca M, Virtue S, Allison M, Vidal-Puig A. Adipose tissue-liver cross talk in the control of whole-body metabolism: implications in non-alcoholic fatty liver disease. *Gastroenterology* 2020;**158**(7):1899-912.

20. Chu H, Duan Y, Yang L, Schnabl B. Small metabolites, possible big changes: a microbiota-centered view of non-alcoholic fatty liver disease. *Gut* 2019;**68**:359-70.

21. Mehal WZ, Loomba R. The intestinal microbiome, plasma metabolome, and liver transcriptome: a conspiracy driving hepatic steatosis. *Hepatology* 2019;**70**:741-4.

22. Sookoian S, Pirola CJ, Valenti L, Davidson NO. Genetic pathways in nonalcoholic fatty liver disease: insights from systems biology. *Hepatology* 2020;**72**(1):330-46.

23. Leung PB, Davis AM, Kumar S. Diagnosis and management of nonalcoholic fatty liver disease. *JAMA* 2023;**330**(17):1687-8.

24. Aller R, Izaola O, Gómez S, Tafur C, González 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**:3118-24.

25. 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**:1553-61.

26. 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.

27. 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):E870.

28. 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* 2009;**50**:1818-26.

29. 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**:12-6.

30. Bjelakovic G, Gluud LL, Nikolova D, Bjelakovic M, Nagorni A, Gluud C. Antioxidant supplements for liver diseases. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No: CD007749. [DOI: 10.1002/14651858.CD007749.pub2]

31. Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science* 1922;**56**(1458):650-1.

32. Niki E, Traber MG. A history of vitamin E. *Annals of Nutrition and Metabolism* 2012;**61**(3):207-12.

33. Galli F, Azzi A, Birringer M, Cook-Mills JM, Eggersdorfer M, Frank J, et al. Vitamin E: emerging aspects and new directions. *Free Radical Biology & Medicine* 2017;**102**:16-36.

34. Basu PP, Shah NJ, Aloysius MM, Brown RS Jr. Effect of vitamin E and alpha lipoic acid in nonalcoholic fatty liver disease: a randomized, placebo-controlled, open-label, prospective clinical trial (VAIN trial). *Open Journal of Gastroenterology* 2014;**4**(5):199-207.

35. 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.

36. Komolafe O, Buzzetti E, Linden A, Best LMJ, Madden AM, Roberts D, et al. Nutritional supplementation for nonalcohol-related fatty liver disease: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No: CD013157. [DOI: 10.1002/14651858.CD013157.pub2]

37. Zöhrer 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.

38. 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.

39. 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.

40. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 2007;**297**:842-57.

41. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all cause mortality. *Annals of Internal Medicine* 2005;**142**:37-46.

42. Wittlin L, Logomarsino JV. Therapeutic effects of vitamin E supplementation in liver diseases and transplantation. *Journal of Gastroenterology and Hepatology* 2014;**3**(6):1095-102.

43. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011;**306**:1549-56.

44. 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.

45. Iida C, Fujii K, Koga E, Washino Y, Kitamura Y, Ichi I, et al. Effect of alpha-tocopherol on carbon tetrachloride intoxication in the rat liver. *Archives of Toxicology* 2009;**83**(5):477-83.

46. Nan YM, Wu WJ, Fu N, Liang BL, Wang RQ, Li LX, et al. Antioxidants vitamin E and 1-aminobenzotriazole prevent experimental non-alcoholic steatohepatitis in mice. *Scandinavian Journal of Gastroenterology* 2009;**44**(9):1121-31.

47. Shen XH, Tang QY, Huang J, Cai W. Vitamin E regulates adipocytokine expression in a rat model of dietary-induced obesity. *Experimental Biology and Medicine* 2010;**235**(1):47-51.

48. Sutherland WH, Manning PJ, Walker RJ, de Jong SA, Ryalls AR, Berry EA. Vitamin E supplementation and plasma 8-isoprostane and adiponectin in overweight subjects. *Obesity* 2007;**15**(2):386-91.

49. Yoshida Y, Hayakawa M, Habuchi Y, Itoh N, Niki E. Evaluation of lipophilic antioxidant efficacy in vivo by the biomarkers hydroxyoctadecadienoic acid and isoprostane. *Lipids* 2007;**42**(5):463-72.

50. Lirussi F, Azzalini L, Orando S, Orlando R, Angelico F. Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No: CD004996. [DOI: 10.1002/14651858.CD004996.pub3]

51. Amanullah I, Khan YH, Anwar I, Gulzar A, Mallhi TH, Raja AA. Effect of vitamin E in non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials. *Postgraduate Medical Journal* 2019;**95**:601-11.

52. Sato K, Gosho M, Yamamoto T, Kobayashi Y, Ishii N, Ohashi T, et al. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Nutrition* 2015;**31**(7-8):923-30.

53. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

54. International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH). ICH Harmonised Guideline. Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2). database.ich.org/sites/default/files/E6_R2_Addendum.pdf (accessed 5 October 2023).

55. Poonam M, Zobair M. Abdominal ultrasound for diagnosis of nonalcoholic fatty liver disease (NAFLD). *American Journal of Gastroenterology* 2007;**102**:2716-7.

56. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002;**123**:745-50.

57. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *Journal of Hepatology* 2009;**51**(3):433-5.

58. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

59. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al; PRISMA-S Group. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Systematic Reviews* 2021;**10**(1):39.

60. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)* 2021;**372**:n71.

61. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ (Clinical Research Ed.)* 2021;**372**:n160.

62. Review Manager (RevMan). Version 8.1.1. The Cochrane Collaboration, 2024. Available at revman.cochrane.org.

63. Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

64. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

65. Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)* 2019;**366**:l4898.

66. Higgins JP, Eldridge S, Li T editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

67. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

68. Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

69. Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

70. Altman DG, Bland JM. Detecting skewness from summary information. *British Medical Journal* 1966;**313**(7066):1200.

71. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 1987;**13**(2):261-76.

72. Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

73. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ (Clinical Research Ed.)* 1999;**319**(7211):670-4.

74. Page MJ, Higgins JP, Sterne JA. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

75. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;**50**(4):1088-101.

76. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629-34.

77. McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

78. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No: MR000033. [DOI: 10.1002/14651858.MR000033.pub3]

79. Castellini G, Bruschettini M, Gianola S, Gluud C, Moja L. Assessing imprecision in Cochrane systematic reviews: a comparison of GRADE and Trial Sequential Analysis. *Systematic Reviews* 2018;**7**:110.

80. Gartlehner G, Nussbaumer-Streit B, Wagner G, Patel S, Swinson-Evans T, Dobrescu A, et al. Increased risks for random errors are common in outcomes graded as high certainty of evidence. *Journal of Clinical Epidemiology* 2019;**106**:50-9.

81. Jakobsen J, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**:120.

82. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User Manual for Trial Sequential Analysis (TSA); 2nd edition. Copenhagen Trial Unit, 2017. Available from ctu.dk/tsa/learn-more (accessed 5 October 2023).

83. TSA - Trial Sequential Analysis. Version 0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, 2021. Available at www.ctu.dk/tsa/downloads.aspx.

84. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial Sequential Analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75.

85. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in a random-effects meta-analysis. *BMC Medical Research Methodology* 2009;**9**:86.

86. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39.

87. GRADEpro GDT. Version accessed 17 July 2024. Hamilton (ON): McMaster University (developed by Evidence Prime), 2024. Available at gradepro.org.

88. Zeng L, Brignardello-Petersen R, Hultcrantz M, Mustafa RA, Murad MH, Iorio A, et al. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach. *Journal of Clinical Epidemiology* 2022;**150**:216-24.

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

90. Anushiravani A, Haddadi N, Pourfarmanbar M, Mohammadkarimi V. Treatment options for nonalcoholic fatty liver disease: a double-blinded randomized placebo-controlled trial. *European Journal of Gastroenterology & Hepatology* 2019;**31**(5):613-7.

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

92. 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):1223-P.

93. Devarajan A, Jayashankar LK, Arun P, Barman MH, Barman H, Kumpatla S, et al. Effect of tocotrienol on liver enzymes, fatty liver and liver stiffness in people with type 2 diabetes and NAFLD: a pilot study based on biochemical and transient elastography parameters. *Journal of the Indian Medical Association* 2023;**121**:14-8.

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

95. 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.

96. 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.

97. 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 : Experimental and Clinical Sciences* 2017;**16**:278-90.

98. 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.

99. 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.

100. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al; Nonalcoholic Steatohepatitis Clinical Research Network. 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.

101. 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.

102. Mir B, Sharma B, Sharma R, Bodh V, Chauhan A, Majeed T. A prospective randomized comparative four arm intervention study of efficacy and safety of saroglitazar and vitamin E in patients with non-alcoholic fatty liver disease. *Journal of Clinical and Experimental Hepatology* 2024;**14**(5):101398. [PMID: 38628977]

103. Mir B, Sharma B, Sharma R, Bodh V, Chauhan A. A prospective randomized comparative four arm intervention study of efficacy and safety of saroglitazar and vitamin E in patients with non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis - an interim analysis. *Indian Journal of Gastroenterology* 2023;**42**:S52.

104. Hajiagha Mohammadi AA, Khajeh Jahromi S, Ahmadi Gooraji S, Bastani A. Comparison of the therapeutic effects of melatonin, metformin and vitamin E on non-alcoholic fatty liver disease: a randomized clinical trial. *Journal of Advances in Medical and Biomedical Research* 2022;**30**(140):232-40.

105. 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.

106. 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 and Liver Disease* 2021;**53**(9):1154-8.

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

108. 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.

109. 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.

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

111. Chalasani NP, Sanyal AJ, Kowdley KV, Robuck PR, Hoofnagle J, Kleiner DE, et al; NASH CRN Research Group. 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.

112. Gawrieh S, Wilson LA, Yates KP, Cummings OW, Vilar-Gomez E, Ajmera V, et al. Relationship of ELF and PIIINP with liver histology and response to vitamin E or pioglitazone in the PIVENS Trial. *Hepatology Communications* 2021;**5**(5):786-97.

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

114. Bell LN, Wang J, Muralidharan S, Chalasani S, Fullenkamp AM, Wilson LA, et al; Nonalcoholic Steatohepatitis Clinical Research Network. 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* 2012;**56**(4):1311-8.

115. Vajro P, Mandato C, Franzese A, Ciccimarra E, Lucariello S, Savoia M, et al. Vitamin E treatment in pediatric obesity-related liver disease: a randomized study. *Journal of Pediatric Gastroenterology and Nutrition* 2004;**38**(1):48-55.

116. 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):870.

117. 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.

118. Federico A, Dallio M, Masarone M, Gravina AG, Di Sarno R, 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 nonalcoholic fatty liver disease patients. *Oxidative Medicine and Cellular Longevity* 2019;**2019**:8742075.

119. 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.

120. 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.

121. Fouda A, Abdelaziz AE, Hussien M, Ali AA, Abdelkawy KS, Elbarbry F. A randomized controlled trial comparing the effects of vitamin E, ursodeoxycholic acid and pentoxifylline on Egyptian non-alcoholic steatohepatitis patients. *European Review for Medical and Pharmacological Sciences* 2021;**25**(23):7449-59.

122. 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.

123. 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* 2003;**38**(2):413-9.

124. Majnooni MB, Ataee M, Bahrami G, Heydarpour F, Aneva IY, Farzaei MH, et al. The effects of co-administration of artichoke leaf extract supplementation with metformin and vitamin E in patients with nonalcoholic fatty liver disease: a randomized clinical trial. *Phytotherapy Research* 2021;**35**(11):6324-34.

125. 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).

126. NCT04781933. Interest in "Combo" (a Combination of Dietary Supplements Including Probiotics) in NASH Improvement (ICAN). clinicaltrials.gov/ct2/show/NCT04781933 (first posted 4 March 2021).

127. 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.

128. Pervez MA, Khan DA, Mirza SA, Slehria AU, Nisar U, Aamir M. Comparison of delta-tocotrienol and alpha-tocopherol effects on hepatic steatosis and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: a randomized double-blind active-controlled trial. *Complementary Therapies in Medicine* 2022;**70**:102866.

129. 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.

130. 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* 2022;**19**(3):287-302.

131. 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.

132. 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.

133. Yoon S, Lee H, Ji SC, Yoon SH, Cho JY, Chung JY. Pharmacokinetics and pharmacodynamics of ursodeoxycholic acid in an overweight population with abnormal liver function. *Clinical Pharmacology in Drug Development* 2021;**10**(1):68-77.

134. Barbakadze G, Khachidze T, Sulaberidze G, Burnadze K, Jebashvili M. Comparative analysis of efficiency of ursodeoxycholic acid and combination of vitamin E and vitamin C in treatment of non-diabetic nonalcoholic steatohepatitis. *Georgian Medical News* 2019;**288**:81-5.

135. Basu P, Shah N, Aloysius M, Brown R Jr. Effect of vitamin E and alpha lipoic acid in nonalcoholic fatty liver disease: a randomized, placebo-controlled, open-label, prospective clinical trial (VAIN trial). *Open Journal of Gastroenterology* 2014;**4**:199-207.

136. Wen H, Deng H, Yang L, Li L, Lin J, Zheng P, et al. Vitamin E for people with non-alcoholic fatty liver disease. *Cochrane Database of Systematic Reviews* 2022, Issue 5. Art. No: CD015033. [DOI: 10.1002/14651858.CD015033]

137. Abdel-Maboud M, Menshawy A, Menshawy E, Emara A, Alshandidy M, Eid M. The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Therapeutic Advances in Gastroenterology* 2020;**13**:1756284820974917.

138. Karedath J, Javed H, Ahsan Talpur F, Lal B, Kumari A, Kivan H, et al. Effect of vitamin E on clinical outcomes in patients with non-alcoholic fatty liver disease: a meta-analysis. *Cureus* 2022;**14**(12):e32764.

139. Lin M, Zeng H, Deng G, Lei J, Li J. Vitamin E in paediatric non-alcoholic fatty liver disease: a meta-analysis. *Clinics and Research in Hepatology and Gastroenterology* 2021;**45**(3):101530.

140. Vadarlis A, Antza C, Bakaloudi DR, Doundoulakis I, Kalopitas G, Samara M, et al. Systematic review with meta-analysis: the effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease. *Journal of Gastroenterology and Hepatology* 2021;**36**(2):311-9.

141. Vogli S, Naska A, Marinos G, Kasdagli MI, Orfanos P. The effect of vitamin E supplementation on serum aminotransferases in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. *Nutrients* 2023;**15**(17):3733.